New Directions in Antiplatelet Therapy

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Atherosclerosis is a chronic inflammatory process that is known to be the underlying cause of coronary artery disease (CAD).[1] In addition to being the first step of primary hemostasis, platelets play a pivotal role in the thrombotic process that follows rupture, fissure, or erosion of an atherosclerotic plaque.[2] 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) cycloxigenase-1 (COX-1) inhibitor: aspirin, (2) adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonists: ticlopidine, clopidogrel, prasugrel, and ticagrelor, and (3) glycoprotein IIb/IIIa inhibitors (GPI): abciximab, eptifibatide, and tirofiban.[3–6] GPIs currently are available 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 $P2Y_{12}$ 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 currently approved antiplatelet agents in the setting of ACS and PCI, as well as on emerging agents that are in clinical development (Figure 1). Other antiplatelet drugs that are available for clinical use, such as pentoxifylline, cilostazol, and dypirimidamole, but do not have an approved indication for patients with ACS or undergoing PCI, as well as advances in anticoagulant therapy, will not be discussed.

Currently Approved Agents

Aspirin

Aspirin exerts its action through an irreversible blockade of COX-1, the enzyme that catalyzes the synthesis of thromboxane A_2 (TXA_2) from arachidonic acid through selective acetylation of a serine residue at position 529 (Ser529). TXA_2 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.[7]

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.[8–10] 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.[10] 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.[11] 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).[11] 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).[12–16]

Received January 9, 2012; accepted April 19, 2012.

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(*Circ Cardiovasc Interv*. 2012;5:433-445.)

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org DOI: 10.1161/CIRCINTERVENTIONS.111.966176

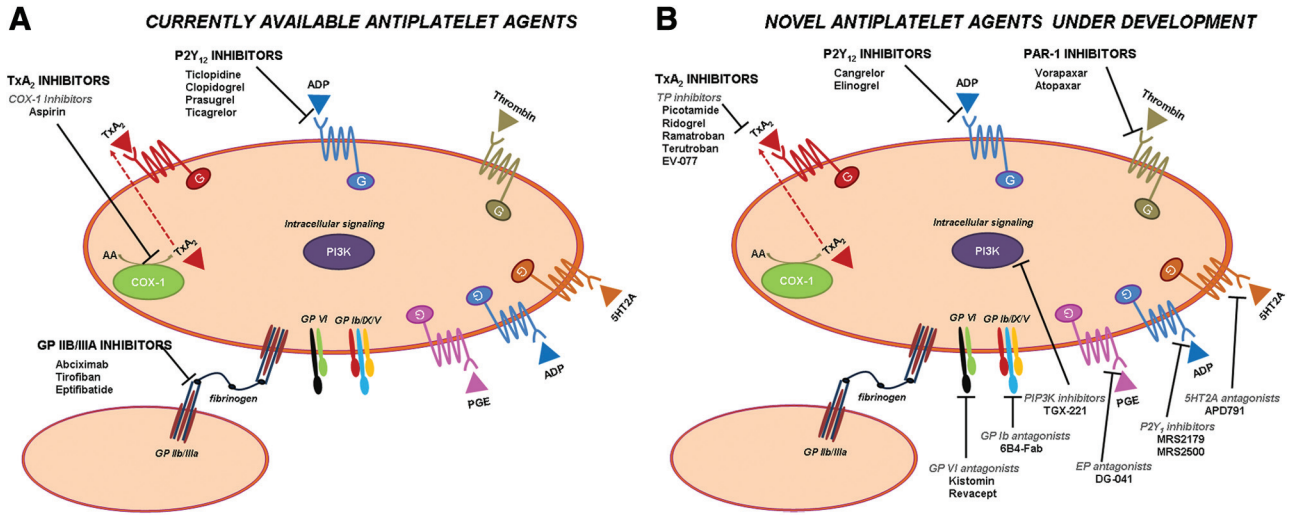

Figure 1. Sites of action of antiplatelet agents. **A**, Currently available agents for acute coronary syndromes or percutaneous coronary intervention. **B**, Novel antiplatelet agents under development. 5HT2A indicates serotonine; AA, arachidonic acid; ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; EP, prostaglandin receptor; G, g-protein; GP, glycoprotein; PG, prostaglandin; PAR-1, platelet protease-activated receptor-1; PI3K, phosphatidylinositol 3-kinase; TP, thromboxane receptor; TxA_2, thromboxane A_2.

$P2Y_{12}$ Receptor Antagonists

Adenosine diphosphate exerts its effects on platelets via the $P2Y_1$ and $P2Y_{12}$ receptors. Although both receptors are needed for aggregation, activation of the $P2Y_{12}$ pathway plays the principal role, leading to sustained platelet aggregation and stabilization of the platelet aggregate.[17] $P2Y_{12}$ 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 $P2Y_{12}$ 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 on 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 $P2Y_{12}$ platelet receptor. Due to the irreversible blockade of the $P2Y_{12}$ 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 (NSTEACS), 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 $P2Y_{12}$ 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 $P2Y_{12}$ Antagonists

	Clopidogrel	Prasugrel	Ticagrelor
2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction[3]	*Class I; Level of Evidence A* 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	*Class I; Level of Evidence B* 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	Not FDA approved or marketed at the time of writing of Guidelines
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention[4]	*Class I; Level of Evidence B** Clopidogrel 600 mg (ACS and non-ACS patients) followed by 75 mg daily for at least 12 months	*Class I; Level of Evidence B** Prasugrel 60 mg (ACS patients) followed by 10 mg daily for at least 12 months	*Class I; Level of Evidence B** Ticagrelor 180 mg (ACS patients) followed by 90 mg twice daily for at least 12 months
2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[5]	*Class I; Level of Evidence A* Clopidogrel (300-mg LD, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel. A 600-mg LD (or a supplementary 300-mg dose at PCI following an initial 300-mg LD) is recommended for patients scheduled for an invasive strategy: Class I; Level of Evidence B. A higher MD of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding: Class IIa; Level of Evidence B	*Class I; Level of Evidence B* Prasugrel (60-mg LD, 10-mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications	*Class I; Level of Evidence B* Ticagrelor (180-mg LD, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic 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).
2010 ESC/EACTS/EAPCI Guidelines on myocardial revascularization[6]	*Elective PCI: Class I; Level of Evidence A* *NSTE-ACS: Class I; Level of Evidence B* *STEMI: Class I; Level of Evidence C* Elective PCI: Pretreatment with 300 mg loading dose >6 h before PCI (or 600 mg >2 h before): Class I;Level of Evidence C NSTE-ACS: 600-mg LD as soon as possible: Class I; Level of Evidence C STEMI: 600-mg LD as soon as possible. Primarily if more efficient antiplatelet agents are contraindicated.	*NSTE-ACS: Class IIa; Level of Evidence B* *STEMI: Class I; Level of Evidence B* Prasugrel 60-mg LD followed by 10-mg daily dose Guidelines specify: "Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available"	*NSTE-ACS: Class I; Level of Evidence B* *STEMI: Class I; Level of Evidence B* Ticagrelor 180-mg LD followed 90 mg twice daily) Guidelines specify: "Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available"

*General recommendation: A loading dose of a $P2Y_{12}$ 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.[10] 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 ration [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.[30]

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.[31] 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 metabolizers.[29] However, to date none of these strategies have shown to have an impact on clinical outcomes in large-scale studies. This includes using prasugrel among 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

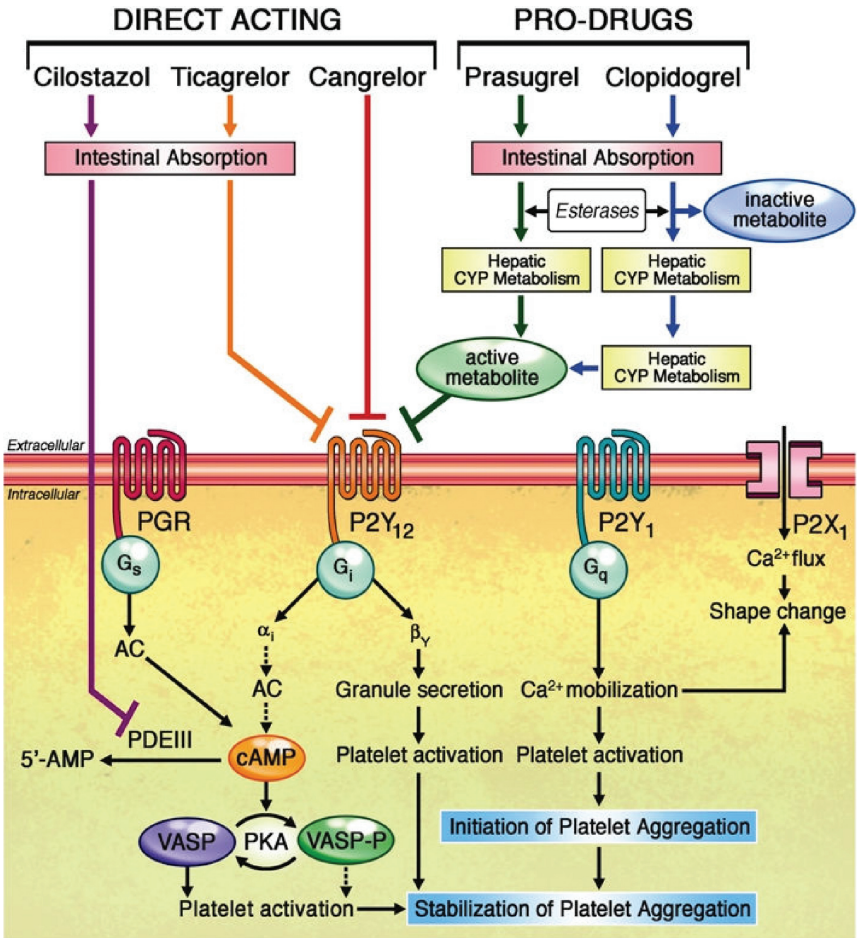

Figure 2. Schematic of different therapeutic options for inhibition of platelet $P2Y_{12}$ receptor. Clopidogrel is a prodrug, which, after intestinal absorption, undergoes metabolization in the liver through a double oxidation process mediated by several cytochrome P450 (CYP) isoforms to finally generate an active metabolite that inhibits platelet activation and aggregation processes through irreversible blockade of the $P2Y_{12}$ receptor. Approximately 85% of clopidogrel is hydrolyzed prehepatically by esterases into an inactive compound, thus, only 15% is available for hepatic metabolism. Prasugrel, like clopidogrel, is also an oral prodrug with a similar intestinal absorption process. However, in contrast to clopidogrel, esterases are part of prasugrel's activation pathway, and prasugrel is oxidized more efficiently to its active metabolite via a single CYP-dependent step. Direct-acting antiplatelet agents (cangrelor, ticagrelor, and cilostazol) have reversible effects and do not require hepatic metabolism for achieving pharmacodynamic activity. Ticagrelor and cilostazol are orally administered and, after intestinal absorption, inhibit platelet activation by direct blockade of the $P2Y_{12}$ receptor and PDE-III, respectively. Cangrelor is intravenously administered, and directly inhibits the $P2Y_{12}$ receptor, bypassing intestinal absorption. Genetic polymorphisms of target proteins/enzymes (intestine, liver, and platelet membrane) modulating clopidogrel-mediated platelet inhibition do not affect the pharmacodynamic activity of prasugrel, cilostazol, ticagrelor, and cangrelor, which ultimately inhibit platelet activation and aggregation processes by modulating intraplatelet levels of cAMP and VASP-P. Solid black arrows indicate activation. Dotted black arrows indicate inhibition. AC indicates adenylyl cyclase; ADP, adenosine diphosphate; ATP, adenosine triphosphate; PDE-III, phosphodiesterase III; PGE1, prostaglandin E1; PKA, protein kinases; VASP-P, phosphorylation of vasodilator-stimulated phosphoprotein. Reproduced with permission from Angiolillo DJ, Ueno M. Optimizing platelet inhibition in clopidogrel poor metabolizers: therapeutic options and practical considerations. *JACC Cardiovasc Interv*. 2011;4:411–414.

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 $P2Y_{12}$ 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

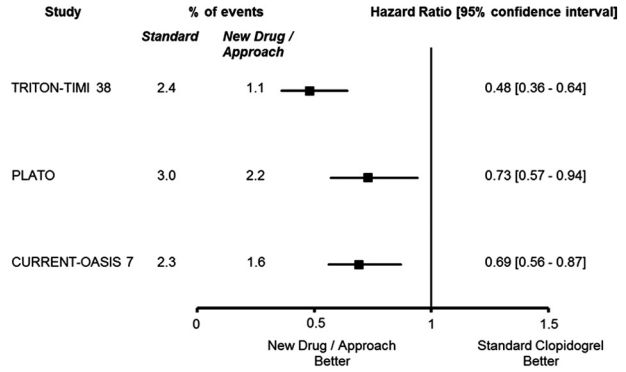

Figure 3. Efficacy in reducing the rates of definite and probable stent thrombosis of new drugs/approaches tested in large-scale clinical trials. The data presented represents the rates of definite and probable stent thrombosis in the cohort of patients undergoing stent placement in these studies. The TRITON-TIMI 38 trial compared prasugrel (60 mg loading dose followed by a 10 mg maintenance dose) versus standard clopidogrel therapy (300 mg loading dose followed by 75 mg daily maintenance dose) in patients with moderate to high risk acute coronary syndrome (ACS) undergoing percutaneous coronary intervention, with up to 15 months follow-up. The PLATO trial compared ticagrelor (180 mg loading dose followed by 90 mg twice daily) with clopidogrel (300 to 600 mg loading dose followed by 75 mg daily), with up to 12 months follow-up. The CURRENT-OASIS 7 trial evaluated 30 days outcomes comparing high (600 mg loading dose, then 150 mg once a day for 7 days, followed by 75 mg daily) versus standard (300 mg loading dose followed by 75 mg daily) clopidogrel dosing in ACS patients scheduled to undergo angiography within 72 hours of hospital arrival.

stroke over a follow-up period of 15 months, occurred in 9.9% of patients treated with prasugrel and in 12.1% of patients treated with clopidogrel, thus resulting in a significant 19% relative reduction with prasugrel (HR, 0.81 [0.73–0.90]; $P<0.001$). This benefit was hampered by an increased risk of TIMI major non-coronary artery bypass graft (CABG) related bleeding (2.4% versus 1.8%; $P=0.03$), including fatal bleeding (0.4% versus 0.1%; HR, 4.19 [1.58–11.11]; $P=0.002$), which occurred mostly in the maintenance phase of prasugrel treatment.[36] A prespecified net clinical benefit analysis (a composite of the rates of death from any cause, nonfatal MI, nonfatal stroke, and non–CABG- related TIMI major hemorrhage) was performed and a significant net clinical benefit was associated with prasugrel therapy despite the excess in bleeding (12.2% versus 13.9%; HR, 0.87 [0.79–0.95]; $P=0.004$). The clinical benefit of prasugrel was driven largely by a marked reduction in nonfatal MI, approximately 40% of which were periprocedural. In addition, a significant 52% reduction of the rates of definite or probable stent thrombosis was achieved with prasugrel compared with clopidogrel (1.13% versus 2.35%; HR, 0.48 [0.36–0.84]; $P<0.0001$).[37] A comparison of the efficacy of new antiplatelet strategies in the reduction of stent thrombosis is shown in Figure 3. Such benefit was both early (<30 days) and late (up to 15 months) and irrespective of stent type (bare metal or drug-eluting). Importantly, certain subgroups appeared to benefit the most from the use of prasugrel, such as patients with diabetes mellitus and those with STEMI, in whom there was a greater ischemic benefit without an increase in major bleeding complications.[38,39] In addition, in patients with an 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 in 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=10 300) 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 (NCT00699998). 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 cyclopentyltriazolopyrimidine, 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 18 624 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

Table 2. Pivotal Clinical Trials Evaluating the Efficacy of Dual Antiplatelet Therapy With Aspirin and an Orally Administered $P2Y_{12}$ Receptor Inhibitor

Study	N	Study Drugs	Setting	Primary End Point	Results*
CURE[22]	12 562	Aspirin+clopidogrel vs aspirin	UA/NSTEMI	Cardiovascular death, nonfatal MI, or stroke at 1 y	9.3% vs 11.4% RR = 0.80 [0.72–0.90]
CREDO[23]	2116	Aspirin+clopidogrel vs aspirin	Elective PCI	Death, MI, or stroke at 1 y	8.5% vs 11.5% RRR = 26.9% [3.9%–44.4%]
COMMIT[24]	45 852	Aspirin+clopidogrel vs aspirin	Acute MI (93% STEMI)	Death, reinfarction, or stroke at discharge or 28 d	9.2% vs 10.1% OR = 0.91 [0.86–0.97]
CLARITY[25]	3491	Aspirin+clopidogrel vs aspirin	STEMI with fibrinolysis	Occluded infarct-related artery on angiography or death or recurrent MI before angiography	15.0% vs 21.7% OR = 0.64 [0.53–0.76]
CURRENT OASIS-7[10]	25 086	Aspirin+clopidogrel (double dose for 1 wk) vs aspirin+clopidogrel (standard dose)	ACS patients referred for an invasive strategy	Cardiovascular death, MI, or stroke at 30 d	4.2% vs 4.4% HR = 0.94 [0.83–1.06]
TRITON-TIMI 38[35]	13 608	Aspirin+prasugrel vs aspirin+clopidogrel	ACS patients undergoing PCI	Cardiovascular death, nonfatal MI, or nonfatal stroke	9.9% vs 12.1% HR = 0.81 [0.7–0.90]
PLATO[44]	18 624	Aspirin+ticagrelor vs aspirin+clopidogrel	ACS patients	Death from vascular causes, MI, or stroke	10.2% vs 12.3% HR = 0.84 [0.77–0.92]

*Results are expressed as % of events and association measure [95% confidence interval].

UA indicates unstable angina; NSTEMI, non–ST-elevation myocardial infarction; MI, myocardial infarction; RR, relative risk; PCI, percutaneous coronary intervention; RRR, relative risk reduction; STEMI, ST-elevation myocardial infarction; OR, odds ratio; ACS, acute coronary syndromes; HR, hazard ratio.

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,[45] 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.[51] 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 NSTEACS, such as a dose with elevated troponin levels, and STEMI.[52,53] 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.[54] 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 benefit has been demonstrated in a number of clinical settings of patients undergoing PCI, including in NSTEACS as demonstrated in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and ISAR-REACT-4 (Intracoronary Stenting and Antithrombotic: Regimen Rapid Early Action for Coronary Treatment 4) trials,[55,56] as well as in STEMI undergoing primary PCI as demonstrated in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials,[57] which also showed a mortality benefit.

Most recently 2 studies provided new insights on the use of intracoronary abciximab in patients with STEMI undergoing primary PCI. The prospective, randomized AIDA STEMI (Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction) trial showed that intracoronary as compared with intravenous abciximab did not result in a difference in the combined end point of death, reinfarction, or congestive heart failure in patients with STEMI (n=2065) undergoing primary PCI, although it did not raise any safety concerns and showed reduced rates of congestive heart failure with the intracoronary route. The INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction) trial was a 2x2 factorial design study that showed that in patients with large anterior STEMI (n=452) presenting early after symptom onset (<4 hours) and undergoing primary PCI with bivalirudin as anticoagulant, infarct size at 30 days was significantly reduced by intracoronary bolus of abciximab delivered locally to the infarct lesion site but not by manual aspiration thrombectomy.[58]

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 CABG. 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 picotamide (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).[59,60] Some of these agents have been tested in clinical settings. In a randomized trial of patients with diabetes mellitus and peripheral artery disease (PAD), picotamide reduced long term overall mortality, but not major cardiovascular events, compared with aspirin.[61] Ridogrel failed to show any benefit over aspirin as adjunct therapy to thrombolysis in patients with acute MI.[62] Terutroban (S18886) is a novel oral, selective, and reversible TP antagonist, which has shown an excellent safety profile in patients with stable PAD.[63] However, terutroban failed to meet the primary end point of noninferiority compared with aspirin in a cohort of patients with cerebrovascular disease.[64] 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

Table 3. Pharmacological Properties of Currently Approved and Investigational $P2Y_{12}$ Inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor*	Elinogrel*
Group	Thienopyridine	Thienopyridine	CPTP	ATP analog	Quinazolinedione
Administration	Oral	Oral	Oral (bid)	IV	IV and oral
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible	Reversible
Onset of action	2–8 h	30 min–4 h	30 min– 2 h	Seconds	Seconds
Offset of action	7–10 d	7–10 d	3–5 d	~60 min	50 min (IV) 12 h (oral)
CYP drug interactions	Yes	No	Yes	No	No

*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.

triphosphate analog, which reversibly and directly, thus, not needing any biotransformation, inhibits the $P2Y_{12}$ 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 4μk/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 MI definition (P=0.646). However, with the use of the universal definition, the primary end point was decreased with cangrelor (odds ratio [OR], 0.82 [0.68–0.99]; P=0.037). Stent thrombosis was reduced from 0.4% to 0.2% (OR, 0.44 [0.22–0.87]; P=0.018). Major bleeding and transfusions were not increased with cangrelor.[68] Based on this evidence, another randomized large scale phase III clinical trial, the CHAMPION-PHOENIX (NCT01156571), is currently ongoing to evaluate efficacy and safety of cangrelor compared with standard of care patients undergoing PCI. Thus, the potential role of cangrelor in reducing ischemic events in PCI patients remains to be determined.

Cangrelor may still have a role, due to its pharmacological properties, as a bridging strategy in the setting of patients requiring surgery but who require treatment with a $P2Y_{12}$ inhibitor to prevent thrombotic complications, such as in ACS patients or those treated with drug-eluting stents. The BRIDGE (Maintenance of platelet inhiBition with cangreloR after dIscontinuation of thienopyriDines in patients undergoing surGEry) trial was a prospective, randomized double-blind, placebo-controlled, multicenter trial in patients (n=210) with an ACS or treated with a coronary stent on a thienopyridine awaiting CABG to receive either placebo or cangrelor at a dose (0.75 μg/kg/min) identified in dose-finding phase of the trial.[69] Therefore, cangrelor may represent a future option for bridging therapy in patients with ACS or treated with coronary stents who require surgery.

Elinogrel is a novel direct-acting agent that reversibly inhibits the $P2Y_{12}$ receptor and provides a high degree of platelet inhibition with rapid onset and offset of action.[70] Elinogrel has the important feature of having both oral and intravenous ways of administration. A comparison of pharmacological properties of $P2Y_{12}$ antagonists is provided in Table 3. The phase II INNOVATE-PCI (A Randomized, Double-Blind, Active-Controlled Trial to Evaluate Intravenous and Oral PRT060128, a Selective and Reversible P2Y12 Inhibitor, versus Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-Urgent PCI) trial (NCT00751231) has evaluated clinical efficacy, biological activity, tolerability, and safety of elinogrel in patients undergoing nonurgent PCI, testing 3 different doses (oral 50, 100, and 150 mg twice daily for 120 days, following an intravenous bolus of 80 mg), compared with clopidogrel. This trial provided promising results of elinogrel in terms of platelet inhibition, as both intravenous and oral dosing achieved greater and more rapid platelet inhibition than clopidogrel, and safety, as no significant increase in major bleedings was found.[71,72] A safety concern was the presence of elevated liver enzymes in 4.0% and 4.8% of the elinogrel 100 mg and 150 mg twice daily arms, respectively, mostly within the first 60 days, compared with 1% in the clopidogrel group. Phase III clinical evaluation of elinogrel is still pending.

Protease-Activated Receptor-1 Inhibitors

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor represents the current standard of care for patients with ACS or undergoing PCI. However, aspirin and $P2Y_{12}$ inhibitors target the TXA_2 and ADP $P2Y_{12}$ 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).[73] 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.[74]

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 2°P (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.[75] 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]; $P=0.07$).[75] In TRA 2°P-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.[76]

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.[77,78] However, dose-dependent QTc prolongation without apparent complications and transient elevation in liver transaminases were observed with the highest doses of atopaxar.[77,78] Parallel findings were found in another phase II study performed in Japanese patients with ACS or high risk CAD.[79] 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).[59,80] 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.[29] 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.[35,44] However, because there is some overlapping in the recommendations of currently available guidelines,[3–6] 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 $P2Y_{12}$ 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 antithrombotic 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.[81]

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

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

	Platelet Function Testing	Genetic Testing
2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction[3]	*Class IIb; Level of Evidence B* 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.	*Class IIb; Level of Evidence C* Genotyping for a CYP2C19 loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on clopidogrel therapy might be considered if results of testing may alter management.
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention[4]	*Class IIb; Level of Evidence C* 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.	*Class IIb; Level of Evidence C* Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g., prasugrel or ticagrelor) might be considered.
	Class III; Level of Evidence C The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.	*Class III; Level of Evidence C* The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.
2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation[5]	*Class IIb; Level of Evidence B* Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.	*Class IIb; Level of Evidence B* Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.
2010 ESC/EACTS/EAPCI Guidelines on myocardial revascularization[6]	No recommendation	No recommendation

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

despite compliance with clopidogrel therapy, have represented very important advancements in our field.[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.[82,83] 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).[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

Dominick J. Angiolillo (corresponding author) reports receiving honoraria for lectures from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly Co., Daiichi Sankyo, Inc., and Astra Zeneca, consulting fees from Bristol Myers Squibb, Sanofi-Aventis, Eli Lilly Co, Daiichi Sankyo, Inc., The Medicines Company, Portola, Novartis, Medicure, Accumetrics, Arena Pharmaceutical, Astra Zeneca, Merck, Evolva, and Abbott Vascular, and research grants from Bristol Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly Co., Daiichi Sankyo, Inc., The Medicines Company, Portola, Accumetrics, Schering-Plough, Astra-Zeneca, and Eisai.

José Luis Ferreiro reports honoraria for lectures from Eli Lilly Co., Daiichi Sankyo, Inc., and Astra Zeneca.

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KEY WORDS: acute coronary syndrome ■ antiplatelet therapy ■ percutaneous transluminal coronary angioplasty ■ pharmacology ■ platelets