# Current Options in Oral Antiplatelet Strategies During Percutaneous Coronary Interventions

Udaya S. Tantry, PhD, Paul A. Gurbel, MD

Sinai Center for Thrombosis Research, Sinai Hospital of Baltimore, Baltimore, MD

*Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor blocker is the standard of care to prevent recurrent ischemic event occurrence in patients undergoing percutaneous intervention. Glycoprotein IIb/IIIa receptor inhibitors are used in addition to DAPT in the highest-risk clinical settings. The persistent occurrence of ischemic events in the presence of DAPT and the irrefutable demonstration of clopidogrel response variability are two potent arguments against the widely practiced nonselective or "one-size-fits-all" strategy of administering clopidogrel therapy and provides a strong rationale for monitoring clopidogrel therapy. New, potent $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor are associated with greater platelet inhibition, faster onset of action, and better overall clinical outcomes compared with clopidogrel, but are associated with more non–surgery-related bleeding than clopidogrel. The inhibition of the platelet thrombin receptor may provide additional benefits in attenuating ischemic event occurrence in selected high-risk patients treated with DAPT.*
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Percutaneous coronary intervention (PCI) has revolutionized the treatment of patients with coronary artery disease (CAD) and ischemic complications. The occurrence of acute ischemic events in CAD patients is primarily attributed to thrombus development at the site of plaque rupture, leading to a severe flow-limiting stenosis or complete occlusion of the coronary artery. In addition, downstream embolization of thrombotic material from the lesion contributes significantly to the pathophysiology underlying acute coronary syndromes (ACS). Moreover, percutaneous balloon angioplasty and coronary arterial stenting cause

extreme vessel wall injury and rupture atherosclerotic plaques; in fact, these procedures are among the most potent thrombogenic stimuli delivered to an arterial vessel wall.[1] After injury, the subendothelial matrix is exposed and platelet adhesion is promoted. Platelets are activated by the binding of collagen and von Willebrand factor (vWF) to specific membrane receptors. Thrombin generated by exposed tissue factor is also a major platelet agonist. Following platelet activation by these primary agonists, two important secondary agonists are released from platelets: thromboxane $A_2$ ($TxA_2$) and adenosine diphosphate (ADP). Cyclooxygenase (COX)-1 converts arachidonic acid (originating from platelet membrane phospholipids) to prostaglandin (PG) $H_2$, and $PGH_2$ is subsequently converted to $TxA_2$ by platelet Tx synthase. ADP is secreted from platelet dense granules.[2,3] Although $TxA_2$ and ADP act synergistically during platelet aggregation, the ADP–$P2Y_{12}$ receptor interaction plays a central role in sustaining the activation of glycoprotein (GP) IIb/IIIa receptors by amplifying the response to agonists leading to stable platelet-rich thrombus generation at the site of vessel wall injury.[1] Therefore, simultaneous inhibition of the COX-1 pathway by aspirin and the $P2Y_{12}$–ADP interaction by $P2Y_{12}$ receptor blockers has been shown to be effective in reducing the incidence of ischemic event occurrence in a wide range of ACS trials and also in elective patients treated with stents[2] (Figure 1). Given the pivotal role of the platelet in ischemic event occurrence during and after PCI, optimization of antiplatelet therapy in both the periprocedural and long-term settings is of great importance.[2]

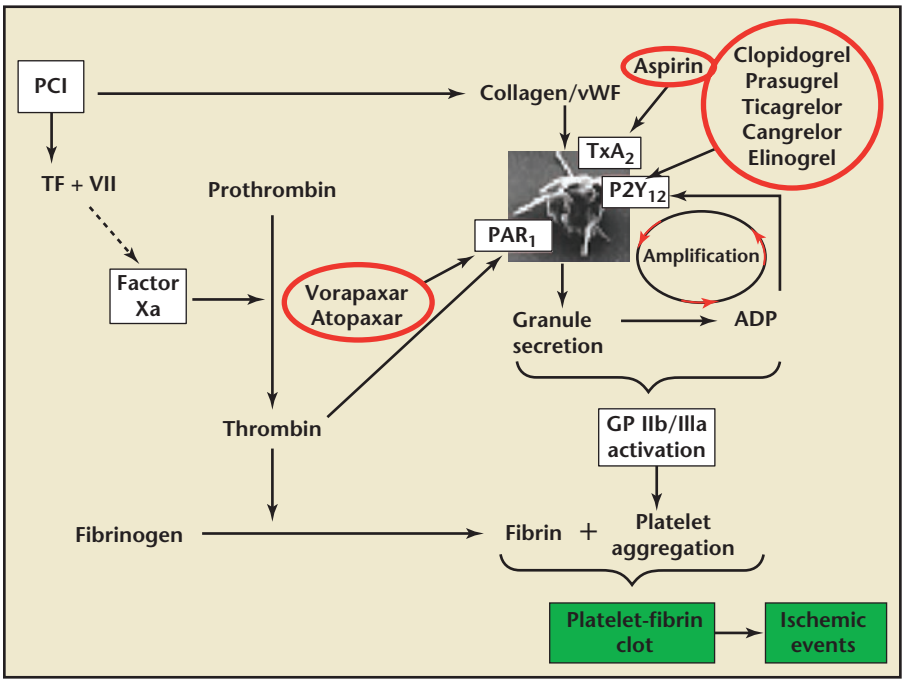


**Figure 1.** *Options in oral antiplatelet therapy during PCI. ADP, adenosine diphosphate; GP, glycoprotein; $PAR_1$, protease-activated receptor-1; PCI, percutaneous coronary intervention; TF, tissue factor; $TxA_2$, thromboxane $A_2$; vWF, von Willebrand factor.*

## Aspirin

Aspirin remains the bedrock of both periprocedural and long-term (ie, lifelong) antiplatelet therapy in patients treated with PCI. The antithrombotic property of aspirin is primarily attributed to irreversible acetylation of the platelet COX-1 enzyme. Subsequently, the generation of $TxA_2$ and $TxA_2$-induced platelet aggregation is inhibited.[3] A meta-analysis of secondary prevention studies in post-myocardial infarction (MI) patients showed significant reductions in serious vascular events (21%), nonfatal MI (29%), coronary heart disease-related death (13%), vascular death (13%), and major coronary events (20%) in patients treated with aspirin.[4]

The optimal aspirin dose remains controversial. In a meta-analysis, similar clinical efficacy was observed with daily aspirin doses between 75 and 1500 mg. However, there was a 50% reduction in efficacy with doses $< 75$ mg.[5] In the recent Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial, patients with ACS were randomly assigned in a $2 \times 2$ factorial design to high- versus low-dose clopidogrel regimens and high- versus low-dose aspirin regimens. There were no significant differences in the 30-day outcome of cardiovascular death, MI, or stroke, and no differences in major bleeding between 75 to 100 mg and 300 to 325 mg daily aspirin regimens. Interestingly, the lowest event rate in the PCI cohort

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was observed in patients who were treated with double-dose clopidogrel and high-dose aspirin (3.5% for high-dose aspirin + double-dose clopidogrel; 4.8% for high-dose aspirin + standard-dose clopidogrel; 4.2% for low-dose aspirin + standard-dose clopidogrel).[6]

The recommended aspirin maintenance doses are listed in Table 1. The most common side effect of aspirin treatment is gastrointestinal intolerance.[2] In patients who are allergic to aspirin or who cannot tolerate aspirin, clopidogrel treatment is recommended. There is a strong rationale for concomitant use of aspirin even if other antithrombotic drugs, such as clopidogrel or warfarin, are administered. Withdrawal or discontinuation of aspirin has been associated with recurrent ischemic event occurrence, including stent thrombosis. Concomitant administration of nonsteroidal anti-inflammatory drugs (NSAIDs) with aspirin should be avoided, if possible, because NSAIDs (particularly ibuprofen) affect the access of aspirin to its binding site within COX-1. Either alternative NSAIDs or administration of ibuprofen should be delayed at least 30 minutes after immediate-release aspirin administration or at least 8 hours before aspirin administration. It has been suggested that selected patients with conditions associated with high platelet reactivity, such as ACS and diabetes, may require higher doses of aspirin.[2]

## Aspirin Resistance

A major controversy associated with aspirin therapy is resistance. Aspirin therapy at 81 to 325 mg/d is associated with more than 90% inhibition of COX-1 as indicated by serum $TxB_2$ levels and supported by low levels of

**Table 1**
**2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With UA/NSTEMI**

| Drug | Initial Medical Treatment | Pts Received Initial Medical Treatment | Pts Did Not Receive Initial Medical Treatment | After PCI | At Hospital Discharge |
|---|---|---|---|---|---|
| Aspirin | 162-325 mg nonenteric formulation, orally or chewed | No additional treatment | 162-325 mg nonenteric formulation, orally or chewed | 162-325 mg/d should be given for at least 1 mo after BMS implantation, 3 mo after SES implantation, and 6 mo after PES implantation, after which chronic aspirin should be continued indefinitely at a dose of 75-162 mg/d | 162-325 mg/d should be given for at least 1 mo after BMS implantation, 3 mo after SES implantation, and 6 mo after PES implantation, after which chronic aspirin should be continued indefinitely at a dose of 75-162 mg/d |
| Clopidogrel | 300-600 mg oral LD; 75 mg/d oral MD | A second LD of 300 mg orally may be given to supplement a prior LD of 300 mg | 300-600 mg oral LD; 75 mg/d for at least 1 mo and ideally up to 1 y for BMS; 75 mg/d for at least 1 y (in pts not at high risk of bleeding) for DES | 300-600 mg oral LD; 75 mg/d for at least 1 mo and ideally up to 1 y for BMS; 75 mg/d for at least 1 y (in pts not at high risk of bleeding) for DES | |
| Prasugrel | | | 60-mg LD promptly and no later than 1 h after PCI | 10 mg for at least 12 mo (in pts who are not at high risk of bleeding) | |

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BMS, bare-metal stent; DES, drug-eluting stent; LD, loading dose; MD, maintenance dose; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; pts, patients; SES, sirolimus-eluting stent; UA, unstable angina.

Reprinted with permission from Wright RS et al.[2]

arachidonic acid-induced platelet aggregation. Therefore, the prevalence of aspirin resistance as measured by COX-1 activity is < 10%.[7] However, higher prevalences of aspirin resistance reported in the literature may be due to analyses by laboratory methods affected by non–COX-1 pathways.[3,7] In addition, noncompliance, concomitant administration of NSAIDs, and conditions such as diabetes or postsurgery complications can all influence the prevalence of aspirin resistance. Currently, laboratory assessment of aspirin resistance or the alteration of aspirin therapy based on laboratory findings is not recommended.[3]

In stable CAD patients treated with aspirin it was reported that high platelet reactivity to arachidonic acid, identified by the VerifyNow P2Y12 Assay® (Accumetrics, San Diego, CA), was also accompanied by increased reactivity to other important platelet agonists as measured by aggregometry independent of fibrinogen and vWF levels. These observations suggested that the VerifyNow P2Y12 Assay may identify a generalized high platelet reactivity phenotype, and it may prove useful for the identification of patients at increased risk for thrombotic events.[8] In support of these findings, Lev and colleagues[9] reported that the prevalence of aspirin resistance was approximately 13% in elective PCI patients treated with dual antiplatelet therapy (DAPT) and that approximately 50% of these aspirin- resistant patients were also resistant to clopidogrel.[9] Similarly, in a subanalysis of the Do Point-of-Care Platelet Function Assays Predict Clinical Outcomes in Clopidogrel Pre-Treated Patients Undergoing Elective PCI (POPULAR) study, on-treatment platelet reactivity was measured in parallel by ADP- and arachidonic acid-induced light transmittance aggregometry (n = 921) and VerifyNow ($P2Y_{12}$ and aspirin assays; n = 422) in patients on DAPT undergoing elective stent implantation.[10] The prevalence of dual antiplatelet resistance varied between 14.7% and 26.9%, depending on the platelet function test used, and dual antiplatelet resistance was highly associated with the occurrence of an adverse clinical outcome. Taken together, the above studies suggest that a generalized high platelet reactivity phenotype indicated by the VerifyNow P2Y12 Assay is an important indicator of risk in the PCI patient. Two meta analyses have demonstrated an association between aspirin responsiveness according to various methodologies and clinical outcomes[11,12]; future studies may provide further clarification regarding the role of measuring aspirin responsiveness in clinical practice.

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## Clopidogrel

Clopidogrel is the most widely studied $P2Y_{12}$ receptor blocker in patients undergoing PCI (Table 2). In the PCI-Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) study, a subset analysis of the CURE trial involving 2658 patients, pretreatment with clopidogrel for a median of 6 days before PCI was associated with a 30% relative risk reduction (RRR) in the cumulative incidence of cardiovascular death, MI, or urgent target vessel revascularization at 28 days and a 31% RRR in 1-year cardiovascular death or MI.[13] In the Clopidogrel for Reduction of Events During Observation (CREDO) trial involving patients undergoing elective PCI, the combined benefit of pretreatment and prolonged clopidogrel therapy up to 1 year was associated with a 26.9% RRR in the combined primary endpoint of death, MI, and stroke compared with treatment with aspirin alone ($P = .02$).[14] The results of PCI-CURE and CREDO trials supported a long-term strategy of $P2Y_{12}$ blockade on top of COX-1 blockade. At least 1 year of DAPT is now the standard of care for the ACS patient and following drug-eluting stent implantation.

The PCI-Clopidogrel as Adjunctive Reperfusion Therapy (PCI-CLARITY) study examined 57% of the patients with ST-segment elevation MI (STEMI) from the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial who underwent PCI and showed that clopidogrel pretreatment was associated with a 46% reduction in the odds of cardiovascular death, recurrent MI, or stroke within 30 days with no significant increase in the incidence of bleeding complications. This benefit was observed regardless of GP IIb/IIIa inhibitor treatment or a loading dose of open-label clopidogrel at the time of PCI.[15]

Pharmacodynamic studies indicated that a 300-mg clopidogrel loading dose was associated with a slow onset of action and wide response variability. Importantly, an absence of inhibition (resistance, based on 5 μM ADP-induced aggregation) was demonstrated at 24 hours and 5 days following nonemergent coronary stenting in 31% of patients; it was

**Table 2**
**Randomized Trials of Antiplatelet Therapy in PCI Patients**

| Trial | Study Population | Treatment | Endpoints | Results |
|---|---|---|---|---|
| PCI-CURE[13] | 2658 non-STEMI pts | Pts pretreated with ASA and CLP for a median of 6 d before PCI, and for a median of 10 d overall; 300 mg LD + 75 mg/d CLP vs placebo + 75-325 mg ASA for 3-12 mo | CV death, nonfatal MI, or stroke | 30 d: 4.5% vs 6.4 (RRR = 30%; *P* = .003) |
| CREDO[14] | 2116 elective PCI pts | 300 mg CLP vs placebo; 75 mg/d CLP + 325/d ASA for 28 d; 75 mg CLP or placebo + 81-325 mg ASA for 12 mo | 28 d CV death, MI, and urgent vessel revascularization; 1 y CV death, MI, and stroke | 28 d: (RRR = 18.5%; *P* = .23); pts with CLP LD > 6 h before PCI (RRR = 38.6%; *P* = .051); 1 y: (RRR = 26.9%; *P* = .02); a trend toward increased major bleeding with CLP (8.8% vs 6.7%; *P* = .07) |
| PCI-CLARITY[15] | 1863 pts within 12 h of STEMI receiving lytic therapy | 300 mg LD + 75 mg MD CLP or placebo + ASA + fibrinolytic + heparin | 30 d CV death, recurrent MI, or stroke | 3.6% vs 6.2% (RRR = 46%; *P* = .008) |
| CURRENT-OASIS 7[6] | 25,086 ACS pts scheduled for PCI | CLP = double dose (600 mg + 150 mg/d for 7 d + 75 mg/d) vs (300 mg LD + 75 mg/d) SD ASA = high dose (300-325 mg/d) vs low dose (75-100 mg/d) | 30 d CV death, MI, or stroke | CLP = 3.9% vs 4.5%, adjusted HR 0.86 (*P* = .039); ASA = 4.1% vs 4.2% (*P* = .76) |
| TRITON-TIMI 38[21] | 13,068 ACS pts scheduled for PCI | PRS = 60 mg LD/10 mg/d; CLP = 300 mg LD + 75 mg/d for 6-15 mo | CV death, nonfatal MI, or nonfatal stroke | 9.9% vs 12.1% (RRR = 19%; *P* < .001); major bleeding = 2.4% vs 1.8% (*P* = .03) |
| PLATO-Invasive[25] | 13,408 ACS pts | TIG = 180 mg LD + 90 mg bid or CLP = 300-600 mg LD + 75 mg/d for 6-12 mo | CV death, MI, or stroke | 9.0% vs 10.7% (RRR = 16%; *P* = .0025) |
| CHAMPION-PCI[26] | 8716 ACS pts | CANG vs 600 mg CLP administered before PCI | 48 h death from any cause, MI, or ischemia-driven revascularization | 7.5% vs 1% (*P* = .59); major bleeding = 3.6% vs 2.9% (OR, 1.26; *P* = .06) |
| CHAMPION-PLATFORM[27] | 5362 ACS pts who had not been treated with CLP | CANG or placebo at the time of PCI, followed by 600 mg CLP | 48 h death, MI, or ischemia-driven revascularization | 7.0% vs 8.0% (*P* = .17) |

ACS, acute coronary syndrome; ASA, aspirin; bid, twice daily; CANG, cangrelor; CHAMPION, Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; CLP, clopidogrel; CREDO, Clopidogrel for Reduction of Events During Observation; CURRENT-OASIS, Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes; CV, cardiovascular; HR, hazard ratio; LD, loading dose; MD, maintenance dose; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PCI-CLARITY, PCI-Clopidogrel as Adjunctive Reperfusion Therapy; PCI-CURE, PCI-Clopidogrel in Unstable Angina to Prevent Recurrent Events; PLATO, Platelet Inhibition and Patient Outcomes; PRS, prasugrel; Pts, patients; RRR, relative risk reduction; SD, standard dose; STEMI, ST-segment elevation myocardial infarction; TIG, ticagrelor; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction.

15% at 30 days.[16] In multiple studies of patients undergoing PCI, high on-treatment platelet reactivity (HTPR) was associated with an increased risk of ischemic event occurrence. Further studies demonstrated that a 600-mg clopidogrel load was associated with greater platelet inhibition.[17]

In the CURRENT-OASIS 7 trial of patients with ACS there were no benefit of double-dose clopidogrel (600 mg day 1, 150 mg days 2-7, followed by 75 mg/d) in the overall population (n = 25,086) compared with standard-dose clopidogrel (300 mg day 1 followed by 75 mg/d).[18] However, in an analysis of patients who underwent PCI (n = 17,263), double-dose clopidogrel therapy was associated with a 14% reduction in the rate of the primary outcome and a 46% reduction in the secondary outcome of definite stent thrombosis. In addition, more major bleeding (1.6% vs 1.1%, hazard ratio [HR] 1.41, 95% confidence interval [CI], 1.09-1.83; $P$ = .009) was seen in the group treated with double-dose clopidogrel in the PCI cohort.[7]

In the Gauging Responsiveness With a VerifyNow Assay-Impact on Thrombosis and Safety (GRAVITAS) trial, patients with HTPR undergoing elective coronary artery stenting were treated with either a 600-mg extra loading dose followed by twice the standard dose of clopidogrel maintenance therapy or standard-dose clopidogrel therapy for 6 months. High-dose clopidogrel treatment was ineffective in reducing the 6-month composite ischemic event occurrence (cardiovascular death, nonfatal MI, and stent thrombosis); both HTPR groups had an unexpectedly low event rate (2.3%).[19] These data suggested that high-dose clopidogrel is not an optimal strategy to combat HTPR and that more potent $P2Y_{12}$ receptors may provide a better option, particularly in high-risk patients undergoing coronary artery stenting.[20]

Currently available evidence supports the concept of a threshold for on-treatment platelet reactivity to ADP in patients treated with DAPT that may be used to stratify patient risk for ischemic/thrombotic events following PCI, including stent thrombosis. In a recent white paper, it was stated that platelet function testing may be considered in determining an antiplatelet strategy in patients with a history of stent thrombosis and in patients prior to undergoing high-risk PCI. Similarly, in the 2011 American College of Cardiology Foundation/American Heart Association (AHA) Focused Update Incorporated Into the American College of Cardiology/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction, the Class IIb recommendation for personalized antiplatelet therapy states that platelet function testing to determine platelet inhibitory response in patients with unstable angina/non-STEMI (or after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management (Class IIb, Level of Evidence B).[2]

## Prasugrel

Prasugrel, the third-generation thienopyridine, is associated with greater active metabolite generation, a more rapid onset of action, less response variability, a lower prevalence of nonresponsiveness, and greater inhibition of ADP-induced platelet aggregation compared with clopidogrel. Moreover, carriage of *CYP2C19* loss-of-function alleles did not significantly influence active metabolite generation or pharmacodynamic effects during prasugrel therapy, whereas carriage negatively influenced both of these effects during clopidogrel therapy. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, patients with ACS undergoing PCI treated with prasugrel (60 mg load + 10 mg/d maintenance) plus aspirin (75-162 mg/d) had a 19% reduction (9.9% vs 12.1%, HR, 0.81; $P$ = .0004) in the primary composite endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke at a median 14.5-month follow-up when compared with patients treated with clopidogrel (300 mg load + 75 mg/d maintenance) plus aspirin. However, prasugrel therapy was associated with a significantly increased occurrence of key safety endpoint of TIMI major bleeding not related to coronary artery bypass graft (CABG; 2.4% vs 1.8%; $P$ = .03). A maintenance dose to 5 mg has been approved by the US Food and Drug Administration (FDA) for patients < 60 kg. These patients are at increased risk of bleeding during therapy with the standard prasugrel maintenance dose. It is important to note that the effectiveness and safety of the 5-mg dose has never been confirmed in a prospective trial. Prasugrel is contraindicated in patients with active pathologic bleeding or a history of transient

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ischemic attack or stroke. In patients aged ≥ 75 years, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding. It is recommended not to start prasugrel therapy in patients likely to undergo urgent CABG. When possible, prasugrel should be discontinued at least 7 days before any surgery. Finally, in 80% of patients in the TRITON-TIMI 38 trial without the three demographic characteristics specified above, prasugrel treatment was associated with a significant net clinical benefit. Another important finding of TRITON-TIMI 38 trial was a 52% reduction in the occurrence of stent thrombosis in the prasugrel-treated group and a marked reduction in the primary endpoint in patients with diabetes that was not associated with a bleeding hazard. The benefit of prasugrel was also marked in patients presenting with STEMI.[21]

## Ticagrelor

Ticagrelor, a cyclopentyl triazolopyrimidine derivative, is a new oral, reversibly binding, direct-acting $P2Y_{12}$ inhibitor. Ticagrelor therapy has been associated with a much more rapid onset of action, a greater level of inhibition that persisted during maintenance therapy, and a more rapid offset of pharmacodynamic action when compared with clopidogrel.[22]

The Platelet Inhibition and Patient Outcomes (PLATO) trial was a randomized, multicenter, double-blind study designed to evaluate the efficacy of ticagrelor (180-mg load + 90 mg twice daily maintenance) compared with clopidogrel (300-600 mg load + 75 mg/d maintenance) for the prevention of vascular events and death in patients with ACS treated with a broad spectrum of therapies. The primary efficacy endpoint of the trial was significantly reduced by ticagrelor compared with clopidogrel at 30 days (4.8% vs 5.4%; $P = .045$) and the superiority of ticagrelor was maintained throughout 12 months with a 16% RRR (9.8% vs 11.7%, respectively; $P < .001$). Between ticagrelor- and clopidogrel-treated patients, there were no differences in the primary safety endpoint of major bleeding rate as defined by either the study protocol (ticagrelor 11.6% vs clopidogrel 11.2%; $P = .43$) or TIMI criteria (7.9% vs 7.7%; $P = .57$); there was also no difference in the rates of CABG-related bleeding. The most remarkable observation of the PLATO trial was a significant and consistent reduction in mortality. Ventricular pauses of at least 3 seconds and dyspnea were more common during ticagrelor therapy compared with clopidogrel, and increases in serum uric acid and creatinine were also observed.[24] Although major bleeding did not differ between groups in the overall population, non–CABG-related TIMI major bleeding and PLATO major bleeding were greater in the ticagrelor group. Among the 72.0% of patients in the PLATO trial managed with an invasive strategy, ticagrelor therapy was associated with a 16.0% reduction in the 1-year primary composite endpoint compared with clopidogrel therapy (9.0% vs 10.7%; $P = .002$) and there was no difference in the rates of total major bleeding (11.6% vs 11.5%; $P = .88$) or severe bleeding, as defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO), (3.2% vs 2.9%; $P = .37$). Furthermore, all-cause mortality (3.9% vs 5.0%; $P = .013$) and MI (5.3% vs 6.6%; $P = .0023$) were reduced by ticagrelor versus clopidogrel, respectively. Finally, the ticagrelor benefit remained significant irrespective of the total clopidogrel loading dose received either before randomization or 24 hours following study enrollment. Both primary efficacy endpoint events, as well as stent thrombosis, were significantly reduced by ticagrelor whether subjects received a $> 600$ mg or $< 600$ mg clopidogrel loading dose within 24 hours before or after study enrollment.[25]

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Ticagrelor therapy has also been associated with greater platelet inhibition compared with clopidogrel in both clopidogrel responders and nonresponders. Ticagrelor was extremely effective in reducing the prevalence of high platelet reactivity within 30 minutes of administration.[23]

## Cangrelor

Cangrelor, an adenosine triphosphate (ATP) analogue, exhibits pharmacodynamic characteristics that are very appealing to the interventional cardiologist. Cangrelor is a potent (> 90% inhibition), parenteral, direct-acting, reversible, $P2Y_{12}$ inhibitor with very rapid onset and offset pharmacodynamics (within minutes). In the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI trial conducted in patients undergoing PCI, there was no difference in the primary endpoint (a composite of death, MI, or ischemia-driven revascularization at 48 hours) between cangrelor and clopidogrel administrations (7.5% vs 7.1%, odds ratio = 1.05; $P = .59$) and also no statistically significant difference in the rate of stent thrombosis at 48 hours or in the combined

ischemic endpoint at 30 days.[26] In the CHAMPION-PLATFORM trial, there was a nonsignificant 13% RRR in the cumulative incidence of death, MI, or ischemia-driven revascularization at 48 hours, and a significant reduction in the secondary endpoints of all-cause death and stent thrombosis associated with cangrelor infusion compared with placebo in patients (n = 5326) with non–ST-elevation ACS who had undergone diagnostic angiography.[27]

## Elinogrel

Elinogrel is a direct-acting, reversible $P2Y_{12}$ receptor antagonist. It is a first-in-class sulfonylurea that may be administered either intravenously or orally. Platelet inhibition by elinogrel occurs irrespective of clopidogrel response status and genotype.[28] The choice of both parenteral and oral administration may facilitate a smooth transition from immediate to long-term therapy. In the recent phase II Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Nonurgent PCI Patients (INNOVATE-PCI) trial, parenteral and oral elinogrel administration were associated with more rapid and greater platelet inhibition compared with standard doses of clopidogrel. Bleeding and ischemic event occurrence appeared similar between treatment strategies.[29] A larger investigation of elinogrel is planned in high-risk CAD patients.

## Thrombin Receptor Antagonists

The inhibition of the thrombin-protease-activated receptor 1 ($PAR_1$) interaction may provide additional benefits in attenuating ischemic event occurrence in selected high-risk patients treated with DAPT. Two major $PAR_1$ blockers are under investigation: vorapaxar and atopaxar. These agents are associated with selective and marked inhibition of thrombin-induced platelet activation and aggregation.[30] In a randomized, double-blind, placebo-controlled, dose-ranging phase II study, patients undergoing nonurgent PCI or coronary angiography with planned PCI were treated with vorapaxar or matching placebo in addition to aspirin plus clopidogrel. Vorapaxar was not associated with an increase in the primary endpoint of clinically significant TIMI major or minor bleeding compared with placebo (2.8% vs 3.3%; $P = .77$). In addition, there was a nonsignificant reduction in the secondary efficacy endpoint of 60-day death or major cardiovascular events (32% overall) and a 41% overall reduction in MI compared with placebo. Moreover, the 40-mg vorapaxar loading dose was associated with a more pronounced reduction in major cardiovascular events and MI (46% and 52%, respectively).[31] However, the recent recommendations of the combined Data and Safety Monitoring Board for the two phase III vorapaxar studies were to 1) discontinue the drug and to close out the ACS (Thrombin Receptor Antagonist for Clinical Events Reduction [TRACER]) trial, and 2) to discontinue therapy in patients with stroke enrolled in the secondary prevention trial (TRA-2P) because of concerns regarding intracranial bleeding. The decisions suggest that the data from phase II did not reveal important limitations of long-term potent $PAR_1$ inhibitor therapy. In phase II studies it was demonstrated that atopaxar was associated with significantly reduced early ischemia on Holter monitoring without a significant increase in major or minor bleeding in patients with ACS and in patients with CAD. In patients with high-risk CAD, atopaxar was associated with marked inhibition of thrombin receptor-activating peptide-stimulated platelet aggregation, more minor bleeding, and numerically fewer ischemic events, although further studies are warranted to confirm these findings.[32,33]

## Cilostazol

Cilostazol is a quinolone derivative that inhibits phosphodiesterase-3 in both platelet and vascular smooth muscle cells, thus increasing cyclic adenosine monophosphate levels. In addition, cilostazol inhibits adenosine reuptake and may potentiate the inhibitory effect of adenosine in vivo.[34] It is believed that these properties may be important in explaining the enhancement of PI when added to clopidogrel and aspirin therapy. In patients undergoing stenting with high platelet reactivity after a 300-mg clopidogrel loading dose, the addition of cilostazol to 75 mg/d of clopidogrel for 30 days was associated with a lower prevalence of high platelet reactivity compared with patients treated with 150 mg/d of clopidogrel.[35] In a recent retrospective study involving 4203 patients with STEMI who underwent primary PCI, triple antiplatelet therapy was associated with a significant reduction in in-hospital mortality but a similar incidence of major bleeding

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events. In addition, there was a significant reduction in the 8-month incidence of cardiac and total death and total major adverse cardiac events with triple antiplatelet therapy compared with DAPT.[36] At this time, cilostazol is approved by the FDA only for treatment of intermittent claudication.

## Conclusions

Despite well established clinical benefits in patients with high-risk CAD, clopidogrel therapy is also associated with numerous limitations, including resistance and response variability, HTPR associated with increased risk for ischemic event occurrence, influences of genotype and concomitant pharmacotherapy on pharmacodynamic effects, and slow onset of effect and irreversible inhibition.[4,7] The new $P2Y_{12}$ inhibitors overcome many of these limitations and are definite advancements in the pharmacotherapy for the PCI patient. However, their use is also associated with limitations. Importantly, both prasugrel and ticagrelor are associated with more non-CABG bleeding than clopidogrel. Moreover, despite the advances in DAPT, recurrent ischemic event occurrences (~ 10% incidence) remain high. Novel antiplatelet agents targeting the platelet thrombin receptor, $PAR_1$, are in development and may enhance the antithrombotic efficacy of DAPT with aspirin and $P2Y_{12}$ receptor blockers in the selected PCI patient. Moreover, clopidogrel is clearly pharmacodynamically effective in the majority of patients (at least two-thirds of the PCI population). Therefore, it may be cost effective to personalize antiplatelet therapy based on platelet function testing and/or genotyping to identify patients who are not responsive to clopidogrel, at which time an informed decision can be made about institution of therapy with one of the new more effective $P2Y_{12}$ blockers.[2] In light of Plavix (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership) losing patent protection in May 2012, the cost effectiveness of a personalized antiplatelet strategy may be significant. ■

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## Main Points

- Ischemic event occurrence following percutaneous coronary intervention (PCI) is critically dependent on platelet activation and aggregation.
- Dual antiplatelet therapy (DAPT) is the standard of care in PCI patients.
- Clopidogrel therapy is associated with numerous limitations: a delayed onset of action, irreversible binding, and an unpredictable pharmacodynamic effect; a substantial proportion of patients exhibit resistance (no measurable platelet inhibition) or high on-treatment platelet reactivity, which has been associated with higher post-PCI ischemic event occurrence.
- Both of the new $P2Y_{12}$ inhibitors, prasugrel (an irreversible, third-generation thienopyridine) and ticagrelor (a reversibly binding, direct-acting agent), are associated with a faster onset of action, greater platelet inhibition, and lower on-treatment platelet reeactivity than clopidogrel. However, increased coronary artery bypass graft (CABG) and non–CABG-related major bleeding were associated with prasugrel therapy and increased non–CABG-related bleeding was associated with ticagrelor.
- The inhibition of the thrombin-protease-activated receptor-1 interaction may provide additional benefits in attenuating ischemic event occurrence in selected high-risk patients treated with DAPT.

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