Review

Role of Platelets and Antiplatelet Therapy in Cardiovascular Disease

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Platelets have a key role in normal hemostasis and in the pathogenesis of atherothrombotic events, such as acute coronary syndrome. Following plaque rupture, platelets adhere to the subendothelial matrix, become activated and then aggregate to form a prothrombotic surface that promotes clot formation and subsequently vascular occlusion. Multiple pathways are involved in platelet activation, including those activated by adenosine diphosphate (ADP), thromboxane A2, epinephrine, serotonin, collagen, and thrombin. Currently, two groups of inhibitors of platelet activation are approved for clinical use in patients with acute coronary syndromes: cyclooxygenase-1 inhibitors, namely aspirin, and oral ADP receptor antagonists such as clopidogrel. These agents have shown improved short- and long-term clinical outcomes but are associated with increased bleeding risk, and the rates of recurrent ischemic events remain high. These considerations underscore the need for novel antiplatelet agents that can provide greater reduction in recurrent atherothrombotic events without increasing the risk of bleeding. Several novel antiplatelet agents are currently under clinical development, such as more potent ADP receptor antagonists and protease-activated receptor-1 antagonists. This article provides an overview of the basic principles of platelet biology and the current status of knowledge on available oral antiplatelet therapy, as well as those under clinical development.


Key words; Platelet, Atherothrombosis, Antiplatelet therapy

Introduction

Platelets have a key role in normal hemostasis and in the pathogenesis of atherothrombotic disease. Platelets provide an initial hemostasis plug of vascular injury and take part in pathophysiological thrombosis, which in turn precipitates myocardial infarction (MI), stroke, and peripheral vascular occlusions. Antiplatelet agents have thus impacted outcomes of cardiovascular disease processes; however, because both pathological and physiological functions of platelets are due to the same mechanism, it is difficult to separate the therapeutic benefits from harmful effects. The ultimate goal of new antiplatelet strategies is to increase efficacy without losing safety. The objectives of this manuscript are to review the role of platelets in protective hemostasis and pathogenic thrombosis, and to provide a general overview of current antiplatelet agents and novel agents under clinical development.

Overview of the Role of Platelets in Primary Hemostasis and Atherothrombosis

Platelet plug formation at sites of vascular injury occurs in 3 stages: 1) initiation phase involving platelet adhesion, 2) extension phase that includes activation, additional recruitment, and aggregation, 3) perpetuation phase characterized by platelet stimulation and stabilization of clot. Circulating platelets are quiescent under normal circumstances and do not bind to the intact endothelium; however, endothelial damage following injury leads to the exposure of circulating platelets to the subendothelial extracellular matrix and triggers platelet recruitment and adhesion. In the initial phase of primary hemostasis, the tethering of platelets at sites of vascular injury is mediated by the glycoprotein (GP) Ib-IX-V receptor
complex, which binds von Willebrand factor. Subendothelial collagen exposed by damaged vessel engages platelets via GPVI and GPIa/IIa receptors. These interactions allow the arrest and activation of adherent platelets. In the extension phase, additional platelets are recruited and activated via soluble agonists. These platelet-activating factors include adenosine diphosphate (ADP), thromboxane A\(_2\) (TXA\(_2\)). In parallel, tissue factor (TF) locally triggers thrombin formation, which also contributes to platelet activation via binding to the platelet protease-activated receptor (PAR)-1. (Adapted from Varga-Szabo et al. Arterioscler Thromb Vasc Biol 2008.)

![Diagram of platelet activation and aggregation](image)

**Fig. 1.** Platelet activation and aggregation. The interaction between von Willebrand factor (vWF) and the platelet receptor glycoprotein (GP) Ib-V-IX mediates platelet tethering to the subendothelium at sites of injury. GPVI binds collagen with low affinity. This triggers intracellular signals that shift platelet integrins to a high affinity state and induce the release of the secondary mediators adenosine diphosphate (ADP) and thromboxane A\(_2\) (TXA\(_2\)). In parallel, tissue factor (TF) locally triggers thrombin formation, which also contributes to platelet activation via binding to the platelet protease-activated receptor (PAR)-1. (Adapted from Varga-Szabo et al. Arterioscler Thromb Vasc Biol 2008.)
thrombin concentrations). Thrombin facilitates the production of fibrin from fibrinogen, contributing to the formation and stabilization of the hemostatic plug\(^9\). The final common pathway is activation of the integrin GP\(\text{IIb/IIIa}\), which allows binding to fibrinogen with high affinity, leading to platelet aggregates\(^9\). In the perpetuation phase, the platelet-rich thrombus and coagulation cascade reinforce one another and culminate in the generation of a stable platelet-fibrin-rich plug at sites of injury. Exaggerated platelet activation can lead to pathological thrombosis. These platelet-rich, white thrombi are typically not completely occlusive and are often associated with non-ST elevation (NSTE) acute coronary syndromes (ACS)\(^9\). Progression to completely occlusive thrombus mediated by the coagulation cascade involves the formation of a fibrin-rich, red clot superimposed on the underlying platelet-rich, white thrombus, and is usually found in ST elevation (STE) ACS patients.

### Overview of Antiplatelet Therapy

The mechanisms by which antiplatelet drugs interfere with platelet function involve targeting enzymes or receptors that are critical for the synthesis or action of important mediators of these functional responses\(^9\). Current and investigational oral antiplatelet therapies target key pathways of platelet activation. This review focuses on the currently available antiplatelet agents and novel agents under clinical development, including inhibitors of the TXA\(_2\) pathway, P2Y\(_{12}\) receptor, PAR-1, phosphodiesterase, or GP\(\text{IIb/IIIa}\) inhibitors.

#### Inhibitors of TXA\(_2\) Pathway

Aspirin irreversibly inhibits COX-1 by acetylating serine 529, thereby inhibiting the production of TXA\(_2\), a promoter of platelet aggregation, and prostaglandin I\(_1\), a potent inhibitor of platelet aggregation and powerful vasodilator, in platelets and vascular endothelial cells, respectively\(^11\). Of note, in the absence of protein synthesis in platelets, TXA\(_2\) inhibition persists for the lifetime of the platelet compared with vascular endothelial cells, which recover COX-1 activity shortly after exposure to aspirin. For over 50 years, aspirin has been the foundation of antiplatelet therapy, and it remains so today. In high-risk patients, aspirin reduces vascular death by \(-15\%\) and non-fatal vascular events by \(-30\%\) as evidenced by meta-analysis of over 100 randomized trials\(^11\). Aspirin may also be of benefit in the primary prevention of cardiovascular events, but the effect is more modest and its recommendation in this setting is highly debated due to the fact that ischemic benefit may be offset by bleeding complications\(^12\). Although aspirin is a cost-effective therapy, a considerable number of patients who take aspirin continue to experience atherothrombotic complications, especially high-risk patients, such as those presenting with an ACS or undergoing percutaneous coronary intervention (PCI).

Despite its universal use, the optimal dose of aspirin for efficacy and safety remains unclear. Previous studies have suggested that aspirin \(\geq 300\) mg is similar to aspirin 75-100 mg/day for the prevention of major vascular events, but that higher doses increase the risk of bleeding complications\(^13\). Recently, the CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention) trial, a randomized head-to-head comparison of higher dose (\(\geq 300\) mg/day) versus low-dose (75-81 mg/day) aspirin in patients with ACS demonstrated similar outcomes for efficacy, without a difference in the risk of major bleeding complications\(^13\).

#### Inhibitors of P2Y\(_{12}\) Receptor

P2Y\(_{12}\) receptor antagonists include ticlopidine, clopidogrel, prasugrel, and ticagrelor (Table 1), and other compounds under late-stage development (cangrelor, elinogrel)\(^2\). Ticlopidine, clopidogrel, and prasugrel represent 3 generations of thienopyridines that selectively and irreversibly inhibit the P2Y\(_{12}\) receptor. Other new reversible P2Y\(_{12}\) inhibitors are currently at different stages of clinical development, including those which reversibly inhibit the P2Y\(_{12}\) receptor available for oral (ticagrelor recently approved), intravenous (cangrelor; under phase III investigation), or both oral and intravenous (elinogrel; recently completed phase II investigation) routes of administration\(^2\).

Ticlopidine is a first-generation thienopyridine that is metabolized by the hepatic cytochrome P450 (CYP) system\(^3\). Ticlopidine is given orally twice a day and was the first approved P2Y\(_{12}\) antagonist. In the TASS (Ticlopidine Aspirin Stroke Study), ticlopidine was superior to aspirin for prevention of the primary endpoint, nonfatal stroke or death\(^19\). Furthermore, landmark clinical trials demonstrated that, in patients undergoing coronary stenting, better clinical outcomes were achieved with the combined use of aspirin and ticlopidine than aspirin alone or aspirin plus warfarin\(^15\); however, there are two limitations with the use of ticlopidine: its safety profile, such as neutropenia, thrombotic thrombocytopenic purpura, and rash\(^19\), and its inability to induce platelet inhibition rapidly. Ticlopidine has been largely replaced in clinical practice by clopidogrel, which has the same benefi-
cial properties as ticlopidine but without its limitations.

Clopidogrel is a second-generation thienopyridine that is also metabolized by CYP in the liver and is given orally once daily. Clopidogrel was first studied in a large group of patients with a history of ischemic stroke, prior MI, and symptomatic atherosclerotic peripheral arterial disease (PAD) in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Recurrent Ischemic Events) trial. This study demonstrated a significant, albeit marginal, benefit of clopidogrel over aspirin. Furthermore, clopidogrel has provided clinical benefits in dual antiplatelet therapy (aspirin plus clopidogrel) in patients with NSTE-ACS, as in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, STE-ACS, COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) and CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy trial), and in patients undergoing (PCI) as in PCI-CURE, PCI-CLARITY and CREDO (Clopidogrel for the Reduction of Events During Observation trial). However, in patients with established vascular disease, the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial demonstrated that the combination of aspirin and clopidogrel was not significantly more effective than aspirin alone in reducing the rate of MI, stroke or death from cardiovascular causes, and caused more bleeding. In a post-hoc subgroup analysis of the CHARISMA population, patients with documented prior MI, stroke, or symptomatic PAD appeared to derive significant benefit from dual antiplatelet therapy (8.8% vs 7.3%; \( p = 0.01 \)). Of note, the greatest benefit was observed in patients with prior MI (\( n = 3846 \)), in whom there was a 23% relative risk reduction in the event rate (\( p = 0.031 \)). Despite the fact that aspirin plus clopidogrel therapy resulted in a significant benefit, a considerable number of patients continued to experience cardiovascular events, which may in part be due to the substantial interindividual variation in platelet response to clopidogrel.

The relatively slow onset of action and limited potency of clopidogrel in its approved regimen has stimulated a number of studies evaluating higher doses of clopidogrel that can act more rapidly and more effectively. Most recently, the CURRENT-OASIS 7 trial evaluated the efficacy and safety of a double dose versus standard dose of clopidogrel in patients with

### Table 1. FDA-approved oral antiplatelet agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Frequency</th>
<th>Limitations</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1</td>
<td>Direct acting, irreversible</td>
<td>Daily</td>
<td>Weak antiplatelet agent</td>
<td>Approved 1988</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>P2Y₁₂</td>
<td>Pro-drug, irreversible</td>
<td>Twice daily</td>
<td>More side effects than clopidogrel</td>
<td>Approved 1991</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>P2Y₁₂</td>
<td>Pro-drug, irreversible</td>
<td>Daily</td>
<td>Inter-individual variability in response</td>
<td>Approved 1997</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>P2Y₁₂</td>
<td>Pro-drug, irreversible</td>
<td>Daily</td>
<td>Higher risk of bleeding than clopidogrel</td>
<td>Approved 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindicated in patients with a prior stroke or TIA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not recommended for patients aged over 75 years old</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>P2Y₁₂</td>
<td>Direct acting, reversible</td>
<td>Twice daily</td>
<td>Dyspnea in 13.8% of patients, and ventricular pauses</td>
<td>Approved 2010</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>cGMP</td>
<td>Pro-drug, reversible</td>
<td>Two or three times daily</td>
<td>Benefit is most evident in combination with low-dose aspirin</td>
<td>Approved 1961</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>PDEⅢ</td>
<td>Pro-drug, reversible</td>
<td>Twice daily</td>
<td>Side effects lead to discontinuation of the drug in -15% of patients</td>
<td>Approved 1998</td>
</tr>
</tbody>
</table>

cGMP, cyclic-3', 5'-guanosine monophosphate; COX-1, cyclooxygenase 1; FDA, US Food and Drug Administration; PDE, phosphodiesterase; TIA, transient ischemic attack
ACS. There was no significant difference in the primary endpoint (composite of cardiovascular death, MI or stroke) at 30 days between patients with ACS receiving a double dose versus standard dose of clopidogrel. However, in patients who underwent PCI, double-dose clopidogrel was associated with a significant 42% relative reduction in definite stent thrombosis (ST) versus the standard dose regimen. There was a modest excess in CURRENT-defined major bleeds but no difference in Thrombolysis in Myocardial Infarction (TIMI) major bleeds, intracranial hemorrhage, fatal bleeds, or coronary artery bypass graft-related bleeds between the double-dose and standard-dose clopidogrel regimen.

Prasugrel, a third-generation thienopyridine, was approved in 2009 in both the United States and Europe (Table 1). Prasugrel has shown more potent inhibition of platelet aggregation and a more consistent platelet response than standard- and high-dose clopidogrel. TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) showed prasugrel to be superior to standard-dose clopidogrel in reducing ischemic events in patients with ACS scheduled for PCI, although prasugrel was associated with a significantly higher risk of major bleeding events; however, patients with stroke or TIA had net clinical harm from prasugrel and those ≥75 years old or who weighed <60 kg had no net benefit. Prasugrel demonstrated the greatest benefit among patients with DM and those presenting with STEMI undergoing primary PCI in whom there were no differences in major bleeding complications.

Ticagrelor, a cyclo-pentyltriazolo-primidine and a direct and reversible P2Y₁₂ antagonist, has recently received favorable reports from drug-regulating authorities in the United States and Europe (Table 1). Like prasugrel, ticagrelor acts more rapidly and is a more potent inhibitory of platelets than clopidogrel and did not significantly increase major bleeding compared with clopidogrel in phase II studies; however, the occurrence of dyspnea and ventricular pause were greater, in an apparently dose dependent manner, in patients receiving ticagrelor than in patients receiving clopidogrel in these studies. The PLATO (Platelet Inhibition and Patient Outcomes) trial randomized 18,624 ACS patients to receive ticagrelor or clopidogrel. The overall trial demonstrated a significant reduction in the primary endpoint a composite of death from vascular causes, MI, or stroke at 12 months with ticagrelor, without an increase in overall major bleeding although non-surgical bleeding was significantly increased to a similar extent than that observed with prasugrel and there was a higher rate of drug discontinuation due to dyspnea. Interestingly, ticagrelor was associated with a significant reduction in overall and cardiovascular mortality, which has been potentially attributed to its off-target effects.

Cangrelor is a reversible, potent, competitive inhibitor of the P2Y₁₂ receptor, which is administered by intravenous infusion and rapidly achieves near complete inhibition of ADP-induced platelet aggregation. Two large-scale randomized trials forming part of the CHAMPION (Cangrelor versus standard tHerapy to Achieve optimal Management of Platelet Inhibition) clinical trial program were conducted: CHAMPION-PCI and CHAMPION-PLATFORM; however, these studies were stopped early owing to lack of efficacy. Cangrelor is still being studied in two trials: as a bridge for patients on clopidogrel who need to terminate treatment before surgery (BRIDGE; NCT00767507) and comparing cangrelor to clopidogrel standard therapy in patients who require PCI (CHAMPION PHOENIX; NCT01156571).

Elinogrel (PRT060128) is a reversible, potent, competitive inhibitor of the P2Y₁₂ receptor with fast onset and offset of action that can be administered by both oral and intravenous routes and rapidly achieves near complete platelet inhibition (Table 2). Elinogrel has more rapid and potent platelet inhibition, even is subjects with low responsiveness to clopidogrel. The phase II INNOVATE-PCI (INtravenous and Oral administration of PRT060128 to eVAluate Tolerability and Efficacy in non-urgent PCI patients) trial was designed to evaluate the clinical efficacy, safety, and tolerability of IV and oral elinogrel in the

### Table 2. Investigated antiplatelet agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Administration</th>
<th>Frequency</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cangrelor</td>
<td>P2Y₁₂</td>
<td>Direct acting, reversible</td>
<td>Intravenous</td>
<td>Bolus and infusion</td>
<td>Phase III</td>
</tr>
<tr>
<td>Elinogrel</td>
<td>P2Y₁₂</td>
<td>Direct acting, reversible</td>
<td>Intravenous and oral</td>
<td>Twice daily</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vorapaxar (SCH 530348)</td>
<td>PAR-1</td>
<td>Competitive, Reversible</td>
<td>Oral</td>
<td>Daily</td>
<td>Phase III</td>
</tr>
<tr>
<td>Atopaxar (E5555)</td>
<td>PAR-1</td>
<td>Competitive, Reversible</td>
<td>Oral</td>
<td>Daily</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

PAR, protease-activated receptor
setting of non-urgent PCI. Results from the INNOVATE-PCI trial were presented at the European Society of Cardiology Congress 2010 (Stockholm, Sweden), showing that patients treated with elinogrel 100 mg and 150 mg twice daily had greater platelet inhibition than those treated with clopidogrel, with those receiving 150 mg elinogrel having greater platelet inhibition. There were no differences in major or minor bleeding, or bleeding requiring medical attention among those treated with elinogrel and those treated with clopidogrel. The study was underpowered for ischemic endpoints. Phase III investigations are currently being designed.

**PAR-1 Inhibitors**

Selective inhibition of the principal protease-activated receptor (PAR)-1 for thrombin, the most potent platelet activator, represents a promising novel strategy to reduce ischemic events without increasing the risk of bleeding. Two PAR-1 receptor antagonists are currently being tested in clinical trials, vorapaxar (SCH 530348) and atopaxar (E5555) (Table 2). Both have demonstrated antiplatelet effects without increasing bleeding times in pre-clinical trials. The safety and efficacy of vorapaxar have already been tested in various Phase II trials, including the TRAPCI (Thrombin Receptor Antagonist for Cardiovascular Event Reduction in Percutaneous Coronary Interventions), which was designed to evaluate the safety and tolerability of treatment with vorapaxar when used in combination with the standard of care therapy in patients scheduled to undergo non-urgent PCI. Patients (n = 1030) were randomized to oral vorapaxar or placebo in a 3:1 ratio on top of standard antithrombotic therapy, including aspirin, clopidogrel, and the anticoagulant of choice. No significant increase was observed in TIMI major and minor bleeding (primary endpoint) with vorapaxar vs standard of care (2.8% vs 3.3%; p = 0.58). Although the study was not specifically powered to evaluate efficacy, there was a trend toward a lower rate of death and major adverse cardiac events (MACE), including MI in the vorapaxar-treated group compared with the placebo-treated group. Encouraging data from phase II trials have led to the initiation of two large phase III trials. The TRA-CER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) will evaluate vorapaxar in approximately 10,000 patients with NSTEMI. On the other hand, the TRA 2° P-TIMI 50 (Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) will recruit approximately 27,000 patients with prior MI, stroke or PAD. The other member of the thrombin receptor antagonist group, atopaxar, was evaluated in two phase II trials, J-LANCELOT (Japanese lessons from Antagonizing the Cellular Effects Of Thrombin) and LANCELOT. These trials were designed to evaluate the safety and tolerability of atopaxar in ACS and CAD patients as their primary objective. The results of these trials have been recently reported and overall show that atopaxar was not associated with any increase in serious bleeding events in both ACS and CAD patients, although there was a significant dose-dependent increase in liver function abnormalities and QTcF elongation with atopaxar.

**Phosphodiesterase Inhibitors**

Dipyridamole is a pyrimidopyrimidine derivative with antiplatelet and vasodilator properties. The antiplatelet effects of dipyridamole have been reported to be due to several mechanisms, including inhibition of the cyclic guanosine monophosphate (cGMP) phosphodiesterase (PDE) type V enzyme. A pivotal study, ESPS-2 (European Stroke Prevention Study), showed that aspirin plus dipyridamole was significantly more effective than aspirin alone in secondary prevention of stroke (relative risk reduction 23.1%; p = 0.006) and conveyed a similarly low risk of severe bleeding (1.6% vs 1.2%). Moreover, meta-analysis of 7 randomized trials was consistent with the ESPS-2 results. ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial) demonstrated that the incidence rate of the composite primary outcome (nonfatal MI, nonfatal stroke, vascular death, or major bleeding complication) was significantly lower in patients receiving aspirin plus dipyridamole than in those using aspirin alone (12.7% vs 15.7%, respectively; hazard ratio 0.80; 95% confidence interval 0.66-0.98); however, aspirin plus dipyridamole was not superior to clopidogrel in the treatment of recurrent stroke in the recently completed PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial.

Cilostazol, a selective PDE type III (PDE III) inhibitor, increases cAMP levels in platelets, endothelial and smooth muscle cells, having vasodilatory and antiplatelet properties and was approved by the FDA in 1998 for the treatment of symptoms of intermittent claudication. Cilostazol also has been shown to prevent the recurrence of cerebral infarction and the progression of symptomatic intracranial arterial stenosis. Recent studies have shown that the addition of cilostazol to dual antiplatelet therapy (triple antiplatelet therapy) is associated with a reduced risk of stent thrombosis, restenosis and major adverse car-
# Table 3. Pivotal Clinical trial of P2Y₁₂ receptor antagonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Event rate (active vs control)</th>
<th>Safety (active vs control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel vs ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPRIE</td>
<td>19,185</td>
<td>Previous stroke, MI or symptomatic PAD</td>
<td>Ischemic stroke, MI, or vascular death at 1 year</td>
<td>5.3% vs 5.8% (p = 0.043)</td>
<td>No major differences</td>
</tr>
<tr>
<td>Clopidogrel + ASA vs ASA</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>CURE</td>
<td>12,562</td>
<td>NSTEMI ACS Unstable angina</td>
<td>CV death, nonfatal MI, and stroke at 1 year</td>
<td>9.3% vs 11.4% (p &lt; 0.001)</td>
<td>Major bleeding occurred significantly more often in clopidogrel group. 3.7% vs 2.7% (p = 0.001)</td>
</tr>
<tr>
<td>CREDO</td>
<td>2,116</td>
<td>ACS with PCI</td>
<td>CV death, MI, or stroke at 1 year</td>
<td>8.5% vs 11.5% (p = 0.02)</td>
<td>Clopidogrel group has a trend toward an increase in major bleeding. 8.8% vs 6.7% (p = 0.07)</td>
</tr>
<tr>
<td>CLARITY</td>
<td>3,491</td>
<td>STEMI*</td>
<td>Occluded infarct-related artery, death or recurrent MI before angiography</td>
<td>15.0% vs 21.7% (p &lt; 0.001)</td>
<td>No difference in the rate of major bleeding. 1.9% vs 1.7% (p = 0.8)</td>
</tr>
<tr>
<td>COMMIT</td>
<td>45,852</td>
<td>STEMI</td>
<td>CV death, reinfarction, or stroke at 28 days</td>
<td>9.2% vs 10.1% (p = 0.002)</td>
<td>No difference in the rate of fatal bleeding. 0.32% vs 0.32% (p = 0.92)</td>
</tr>
<tr>
<td>CHARISMA</td>
<td>15,603</td>
<td>CVD or multiple risk factors</td>
<td>MI, stroke, or CV death at 28 months</td>
<td>6.8% vs 7.3% (p = 0.22)</td>
<td>Clopidogrel group has a trend toward an increase in severe bleeding. 1.7% vs 1.3% (p = 0.09)</td>
</tr>
<tr>
<td>Double-dose clopidogrel + ASA vs standard dose clopidogrel</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CURRENT-OASIS 7</td>
<td>25,087</td>
<td>ACS with planned early invasive management</td>
<td>CV death, MI, or stroke at 30 days</td>
<td>4.2% vs 4.4% (p = 0.37)</td>
<td>No difference in the rate of major bleeding. 2.3% vs 2.3% (p = 0.90)</td>
</tr>
<tr>
<td>Prasugrel + ASA vs Clopidogrel + ASA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TRITON</td>
<td>12,608</td>
<td>ACS</td>
<td>CV death, nonfatal MI, or nonfatal stroke at 15 months</td>
<td>9.9% vs 12.1% (p = 0.001)</td>
<td>Major bleeding occurred significantly more often in prasugrel group. 2.4% vs 1.8% (p = 0.03)</td>
</tr>
<tr>
<td>Ticagrelor + ASA vs Clopidogrel + ASA</td>
<td></td>
<td></td>
<td>CV death, MI, or stroke at 30 days</td>
<td>9.8% vs 11.7% (p &lt; 0.001)</td>
<td>No difference in the rate of major bleeding. 11.6% vs 11.2% (p = 0.43)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; MI, myocardial infarction; PAD, peripheral artery disease; ASA, aspirin; NSTEMI, non-ST-segment elevation MI; CV, cardiovascular; STEMI, ST elevation MI; CVD, CV disease; CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Recurrent Ischemic Events; CURE: Clopidogrel in Unstable angina to prevent Recurrent Events; CREDO: Clopidogrel for the Reduction of Events During Observation; CLARITY: Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT: Clopidogrel and Metoprolol in Myocardial Infarction Trial; CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance; CURRENT-OASIS 7: Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Intervention; TRITON: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; PLATO: Platelet Inhibition and Patient Outcomes.

*Patients received a fibrinolytic agent.

Clopidogrel was given as a loading dose of 300 mg then 75 mg maintenance dose in CURE, CREDO, CLARITY, CHARISMA, and TRITON. Clopidogrel 75 mg maintenance dose was administered in CAPRIE and COMMIT.

In CURRENT-OASIS 7, double-dose clopidogrel was defined as a 600 mg loading dose and 150 mg maintenance dose for 7 days, followed by 75 mg. Standard-dose clopidogrel was defined as a 300 mg loading dose, followed by 75 mg maintenance dose.

In TRITON, prasugrel was given as a loading dose of 60 mg, then 10 mg maintenance dose.

In PLATO, ticagrelor was given as a 180 mg loading dose, then 90 mg twice maintenance dose. Clopidogrel was given as a 300-600 mg loading dose, then 75 mg maintenance dose.
diac events without increased bleeding complications, even in patients undergoing PCI with drug-eluting stents (DES)\textsuperscript{72-73}. Pharmacodynamic studies showed that adjunctive cilostazol therapy resulted in greater platelet inhibition than dual antiplatelet therapy\textsuperscript{76, 77}. Interestingly, cilostazol has been shown to be particularly effective in diabetic patients\textsuperscript{78-80}. Moreover, recent studies have shown that adjunctive cilostazol to dual antiplatelet therapy after PCI can achieve greater platelet inhibition than high maintenance-dose clopidogrel of 150 mg daily\textsuperscript{76}, even in patients with the CYP2C19 mutant allele\textsuperscript{77}. The most common side effects include headache, tachycardia, palpitations, soft stools and diarrhea. Previous studies reported that the rate of drug discontinuation was approximately 15\%\textsuperscript{73, 78}. Cilostazol should be avoided in patients with congestive heart failure of any severity because of increased mortality risk\textsuperscript{81, 82}.

### Glycoprotein IIb/IIIa Inhibitors

Targeting the final common pathway of platelet activation, the GPIIb/IIIa receptor, by intravenous administration has been shown to reduce ischemic events in ACS patients undergoing PCI; however, GPIIb/IIIa inhibitors are associated with an increased risk of bleeding. In contrast, oral administration of GPIIb/IIIa inhibitors has failed to demonstrate any benefit\textsuperscript{83}. Three parenteral GPIIb/IIIa inhibitors, abciximab, eptifibatide, and tirofiban, are currently available; therefore, these drugs are only administered within the hospital setting and are indicated for use in high-risk ACS patients undergoing PCI\textsuperscript{84}. Eptifibatide and tirofiban reversibly and competitively bind to the GPIIb/IIIa receptor, whereas abciximab irreversibly binds to the GPIIb/IIIa receptor and blocks the binding of fibrinogen and other adhesion molecules\textsuperscript{85}.

### Conclusions and Future Direction

Platelets play a central role in cardiovascular thrombosis, underscoring the importance of antiplatelet therapy, particularly for secondary prevention of atherothrombotic events; however, recurrent event rates remain considerably high with currently available antiplatelet treatment regimens. These findings may be in part attributed to suboptimal platelet inhibition. Numerous antiplatelet drugs are currently under clinical development. Ongoing clinical studies will provide insights into strategies that will maximize the efficacy and safety of antithrombotic treatment regimens in patients with atherothrombotic disease manifestations.

### Conflicts of Interest

Dominick J Angiolillo:
- Honoraria/Lectures: Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly and Company; Daiichi Sankyo, Inc.
- Honoraria/Advisory board: Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly and Company; Daiichi Sankyo, Inc.; Astra Zeneca; The Medicines Company; Portola Pharmaceuticals; Novartis; Arena Pharmaceuticals; Evolva Pharmaceuticals; Merck
- Research Grants: GlaxoSmithKline; Otsuka; Accumetrics; Eli Lilly and Company; Daiichi Sankyo, Inc.; The Medicines Company; AstraZeneca; Eisai; Portola Pharmaceutical; Schering-Plough; Johnson and Johnson.

Masafumi Ueno, Murali Kodali, Antonio Tello-Montoliu: No conflicts of interest to report

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