Update on Antithrombotic Therapy

Combination Antithrombotic Therapies

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Atherothrombosis is the major pathophysiological process responsible for the occurrence of severe ischemic events in patients with cardiovascular diseases. In the United States, atherothrombosis strongly influenced mortality in 2004: One in 2.8 deaths was due to CVD, 1 in 5 deaths to coronary heart disease, and 1 in 17 deaths to stroke. Because cardiovascular disease is a progressive and systemic disease, long-term antithrombotic therapies that effectively target the entire arterial vasculature and modulate the key components responsible for thrombus generation are essential to improve patient outcomes. Because platelet activation is determined by multiple receptor-mediated signaling pathways, clinical studies have evaluated the efficacy of multidrug administration in the prevention of atherothrombotic complications. The major concern with these therapies is the critical balance between anti-ischemic effect and bleeding risk. This review summarizes our understanding of the role of combination antiplatelet therapies in the treatment and prevention of atherothrombosis.

Pathophysiology of Atherothrombosis

Platelet activation and aggregation play a pivotal role in the generation of occlusive thrombus at the site of coronary arterial plaque rupture. In addition, platelets influence various endothelial and inflammatory responses during the initiation and progression of atherosclerosis. Under normal conditions, anucleate circulating platelets are in a quiescent state. Healthy vascular endothelium prevents adhesion and activation of platelets by producing antithrombotic factors such as CD39 (ectoADPase), prostaglandins, nitric oxide, heparin, matrix metalloproteinase-9, protein S, and thrombomodulin. Endothelial activation and denudation and frank atherosclerotic plaque rupture expose the subendothelial matrix and release prothrombotic factors during acute coronary syndromes (ACS) and percutaneous interventions. These processes result in localized platelet adhesion and platelet activation. After adhesion to the exposed subendothelial matrix, platelets are activated by shear and the soluble agonists thromboxane A2 (TxA2), ADP, and thrombin. TxA2 is produced from arachidonic acid, which originates from membrane phospholipids and binds to Tx receptors; ADP is secreted from dense granules and binds to P2Y12 and P2Y1 receptors. These 2 secondary agonists, through an autocrine and paracrine fashion, produce sustained activation of glycoprotein IIb/IIIa receptors, leading to stable platelet-rich thrombus generation. The ADP-P2Y12 interaction contributes most to ADP-induced aggregation measured by conventional aggregometry. Platelet activation also results in the membrane exposure of phosphatidyl serine, providing binding sites for coagulation factors. The coagulation process results in the generation of thrombin and subsequent platelet-fibrin clot formation. Endogenous phosphodiesterase (PDE) activity that affects intraplatelet cAMP levels also modulates platelet function (the Figure). Finally, isoprostanes derived from membrane arachidonic acid through peroxidation have been shown to induce platelet aggregation by activating the receptor for TxA2. Inhibition of PDE and cyclooxygenase (COX) may play a more important role in the treatment of peripheral and cerebrovascular disease, whereas antiplatelet therapy with clopidogrel and aspirin is the cornerstone of ACS and poststent treatment. Finally, the relative contribution of each pathway (ADP-platelet, TxA2-platelet, thrombin-platelet, aggregation, and PDE activity) to the development of thrombus formation in the individual patient is unknown. Therefore, despite immense research, determination of the optimal antiplatelet and antithrombotic therapy remains an elusive goal. The side effects observed during contemporary antithrombotic therapy may be related in part to the uniform dosing regimens used that ignore the inherent variability in the antiplatelet and antithrombotic response.

Aspirin

Aspirin is the primary component of combination antiplatelet therapy. The antiplatelet effect of aspirin is attributed primarily to the irreversible inhibition of platelet COX-1 by acetylation of serine residue 529, resulting in a downstream reduction in the synthesis of TxA2 and consequent TxA2-induced platelet activation/aggregation. However, recent studies indicate that the antiplatelet effect of aspirin may also involve inhibition of pathways distinct from COX-1 (non-COX-1 pathways). In addition, aspirin is known to reduce thrombin generation, to enhance fibrin clot permeability and clot lysis, and to promote nitric oxide production in platelets. Aspirin also has antiinflammatory properties that may enhance its antithrombotic effect.

Recent pharmacodynamic studies have demonstrated that low-dose aspirin has variable effects in inhibiting platelet non–COX-1 pathways. The term “aspirin nonresponsiveness...
or resistant” has been used to describe selected patients, especially high-risk patients and diabetics, exhibiting high platelet function as measured by assays that are nonspecific in their assessment of COX-1 activity. Ischemic event recurrence is also higher in patients found to be aspirin resistant by COX-1–nonspecific assays. The dose dependence of aspirin in the inhibition of non–COX-1 pathways suggests that selected patients require a dose of 81 mg to achieve an optimal antiplatelet effect. However, this observation conflicts with the results of meta-analyses demonstrating no conclusive clinical benefits of high-dose aspirin therapy.

Aspirin Dose and Bleeding
In a recent meta-analysis of randomized controlled trials of low-dose aspirin (75 to 325 mg/d), aspirin treatment was associated with a 0.13% absolute increase in any major bleeding and a 0.12% increase in major gastrointestinal bleeding compared with placebo in cardiovascular disease patients. There was an increased relative risk (RR) of major bleeding (RR, 1.71; 95% confidence interval [CI], 1.41 to 2.08), major gastrointestinal bleeding (RR, 2.07; 95% CI, 1.61 to 2.66), and intracranial bleeding (RR, 1.65; 95% CI, 1.06 to 2.59). No difference in bleeding was observed in patients treated with 75 to 162.5 mg/d versus >162.5 to 325 mg/d.

Thienopyridines
Because ADP plays a critical role in the amplification of platelet aggregation and the genesis of a stable occlusive thrombus, the inhibition of ADP-induced platelet activation was an early focus of alternative antiplatelet treatment. Moreover, drug intolerance, gastrointestinal bleeding, and treatment failure associated with aspirin therapy also stimulated the development of new antiplatelet agents. Thienopyridines are prodrugs that require metabolic activation by the cytochrome P450 pathway. The active metabolite forms a disulfide bond with the P2Y12 receptor, rendering the receptor unable to bind ADP and thus attenuating the subsequent response of the platelet to ADP.

Aspirin Monotherapy Versus Thienopyridine Monotherapy
Ticlopidine was the first thienopyridine to be widely used clinically. In the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine treatment (500 mg daily) was superior to aspirin (1300 mg QD) in reducing nonfatal stroke or death at 3 years (17% versus 19%; RR reduction [RRR], 12%; P=0.048) in patients with previous stroke. In the Ticlopidine Versus Aspirin After Myocardial Infarction (STAMI) trial, 1470 patients with acute myocardial infarction (MI) treated with thrombolysis received either aspirin (160 mg QD) or ticlopidine (500 mg QD) therapy. In that trial, there was no difference between the 2 treatment arms in primary combined end point of death, recurrent MI, stroke, or angina. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, aspirin (325 mg QD) was compared with clopidogrel therapy (75 mg/d) in patients at risk for ischemic events, and an RRR of 8.7% was observed in clopidogrel-treated patients in the composite end point of MI, ischemic stroke, or vascular death (the Table). Most of the benefit was observed in patients with peripheral arterial...
### Important Clinical Trials Evaluating Clinical Efficacy of Clopidogrel and Aspirin Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Protocol</th>
<th>End Points</th>
<th>Outcome</th>
<th>Safety Outcome</th>
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<tr>
<td>CAPRIE17</td>
<td>Symptomatic atherosclerotic disease (19 185)</td>
<td>75 mg CLP vs 325 mg ASA for median of 1.9 y</td>
<td>First occurrence of IS, MI, or vascular death</td>
<td>RRR=8.7%; 95% CI=0.3–16.5; P=0.043</td>
<td>No significant difference in rate of a bleeding disorder (9.28% vs 9.27%); ASA recipients had a greater rate of GI bleeding (2.66% vs 1.9%; P&lt;0.05)</td>
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<tr>
<td>CURE27</td>
<td>ACS (12 562)</td>
<td>300 mg LD+75 mg/d CLP vs placebo+75–325 mg ASA for 3 to 12 mo</td>
<td>CV death, nonfatal MI, or stroke</td>
<td>RR=0.8; 95% CI=0.72–0.90; P=0.001</td>
<td>Significant increase in major bleeding (RR=1.38; 95% CI=1.13–1.67; P=0.0001) and minor bleeding (RR=2.12; 95% CI=1.75–2.56; P=0.001)</td>
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<tr>
<td>PCI-CURE28</td>
<td>PCI (2658)</td>
<td>CLP vs placebo+ASA</td>
<td>CV death, nonfatal MI, or stroke</td>
<td>4.5% vs 6.5%; RRR=30%; P=0.003</td>
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<tr>
<td>CREDO29</td>
<td>Symptomatic CAD patients (n=2116) undergoing PCI with and without stenting</td>
<td>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</td>
<td>28-d CV death, MI, and urgent vessel revascularization; 1-y CV death, MI, and stroke; safety end point: modified TIMI major, minor, or insignificant</td>
<td>28-d outcome (RRR=18.5%; 95% CI=–4.2–41.8; P=0.23); patients with CLP LD &gt;6 h before PCI (RRR=38.6%; 95% CI=–1.6–62.9; P=0.051); 1-year outcome (RRR=26.9%; 95% CI=3.9–44; P=0.02)</td>
<td>A trend toward increased major bleeding with CLP (8.8% vs 6.7%; P=0.07)</td>
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<tr>
<td>CLARITY-TIMI 2830</td>
<td>Patients within 12 h of STEMI receiving lytic therapy (3491)</td>
<td>300 mg LD+75 mg MD CLP or placebo+ASA+heparin</td>
<td>Occluded infarct artery, death, or recurrent MI (before angiography)</td>
<td>RRR=36%; 95% CI=0.53–0.76; P&lt;0.001</td>
<td>TIMI-defined major bleeding and intracranial hemorrhage and TIMI minor bleedings were not statistically different</td>
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<tr>
<td>PCI-CLARITY31</td>
<td>Patients treated with PCI (1863)</td>
<td>Same as above</td>
<td>30-d CV death, recurrent MI, or recurrent ischemia leading to urgent revascularization</td>
<td>RR=0.80; 96% CI=0.65–0.97; P=0.03</td>
<td>No significant difference in composite of all transfused, fatal, or cerebral bleedings (0.58% vs 0.55%; P=0.59), but CLP increased minor bleeding (3.6% vs 3.1%; P=0.005)</td>
</tr>
<tr>
<td>COMMIT32</td>
<td>STEMI patients within 24 h of symptom onset (45 852)</td>
<td>72 mg/d CLP+162 mg/d ASA+metoprolol vs 162 mg/d ASA+metoprolol for 4 wk</td>
<td>Death, infarction, or stroke</td>
<td>OR=0.91; 95% CI=0.87–0.99; P=0.03</td>
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<tr>
<td>CHARISMA34</td>
<td>Documented CAD, CVD, or PAD or ≥3 atherothrombotic risk factors (15 603)</td>
<td>75–162 mg ASA+75 mg CLP vs 75–162 mg/ d ASA+placebo–media for 28 mo</td>
<td>Primary end point of first occurrence of MI, IS, or vascular death; secondary end point of hospitalization for UA, TIA, or revascularization procedure</td>
<td>Primary end point: RR=0.93; 95% CI=0.83–1.05; P=0.22; secondary end point: RR=0.92; 95% CI=0.85–0.995; P=0.004</td>
<td>Increase in severe bleeding according GUSTO definition (RR=1.25; 95% CI=0.97–1.61; P=0.09) and rate moderate bleeding (RR=1.62; 95% CI=1.27–2.08; P=0.001)</td>
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<td>Posthoc analysis of CHARISMA35</td>
<td>Patients with documented prior MI, IS, or symptomatic PAD</td>
<td>75–162 mg ASA+75 mg CLP vs 75–162 mg/d ASA+placebo</td>
<td>Same as above</td>
<td>RRR=17%; 95% CI=4–28; P=0.01</td>
<td>Nonsignificant increase in severe bleeding (RR=1.11; 95% CI=0.81–1.57; P=0.509)</td>
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<td>MATCH37</td>
<td>Recent history of IS and TIA and previous MI, angina, DM, or symptomatic PAD (7599)</td>
<td>75 mg/d CLP vs 75 mg/d CLP+75 mg/d ASA for 18 mo</td>
<td>IS, MI, vascular death, or rehospitalization for acute ischemic event</td>
<td>RRR=6.5%; 95% CI=–4.6–16.3; P=0.244</td>
<td>More common major (2% vs 1%) and life-threatening (3% vs 1%) bleedings with CLP+ASA</td>
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CLP indicates clopidogrel; ASA, aspirin; IS, ischemic stroke; GI, gastrointestinal; LD, loading dose; CV, cardiovascular; CAD, coronary artery disease; CVD, CV disease; PAD, peripheral vascular disease; US, unstable angina; and DM, diabetes mellitus.

disease. Although the overall safety profile was similar between the 2 groups, the aspirin-treated group had a greater rate of gastrointestinal bleeding (2.66% versus 1.99; RR, 1.34; 95% CI, 1.11 to 1.61; P<0.05). Subgroup analysis revealed that clopidogrel reduced the risk of acute MI (~19%) more significantly than aspirin in both low- and high-risk patients. On the basis of the favorable results of the CAPRIE trial, the US Food and Drug Administration...
(FDA) approved the use of a 75-mg daily dose of clopidogrel for patients with a history of recent heart attack, recent stroke, or established peripheral arterial disease.

**Thienopyridine Plus Aspirin: Stenting**

Given the important contributions of P2Y12 and COX-1 to the amplification of platelet aggregation mediated by ADP and TxA2, respectively, it was hypothesized that simultaneous inhibition of both pathways would provide a superior antithrombotic effect compared with single pathway inhibition. Nonhuman primate investigations using exteriorized arteriovenous shunts treated with metallic endovascular stents demonstrated the enhanced antithrombotic effect of clopidogrel with the addition of aspirin. Subsequent investigations in human volunteers treated with aspirin and clopidogrel similarly demonstrated the synergistic effect of dual antiplatelet therapy compared with aspirin monotherapy in a perfusion chamber assay measuring ex vivo thrombus formation. However, the results of large-scale clinical trials of dual antiplatelet therapy confirmed what was expected from the laboratory observations and changed the treatment paradigm for many cardiovascular disease states. In these trials, thienopyridines added to aspirin therapy demonstrated the potent effect in the inhibition of ischemic events across the spectrum of cardiovascular disease settings.

In the Stent Anticoagulation Restenosis Study (STARS), a significant decrease in the combined end point of death, MI, acute MI, angiographically evident thrombosis, and revascularization of the target vessel within 30 days was observed in patients undergoing stenting randomized to aspirin plus ticlopidine therapy (0.55%) compared with aspirin therapy alone (3.6%) and aspirin plus warfarin therapy (2.7%; \( P<0.001 \) for the comparison of all groups). This important trial led the way for dual antiplatelet therapy to become the standard of care in patients undergoing coronary arterial stenting. Other studies of ticlopidine plus aspirin versus aspirin plus anticoagulation demonstrated concordant effects. All of these studies influenced a change in the antithrombotic treatment paradigm, and dual antiplatelet therapy became the standard of care for the poststenot patient. However, unfavorable side effects (neutropenia, bone marrow aplasia, and thrombotic thrombocytopenic purpura) were associated with ticlopidine treatment, which led to the development of the second-generation thienopyridine, clopidogrel.

In the Clopidogrel Aspirin Stent Interventional Cooperative Study (CLASSICS), the safety of clopidogrel was compared with that of ticlopidine after successful coronary stenting. Treatment with clopidogrel 75 mg QD with or without a loading dose was associated with fewer major bleeding complications, less neutropenia, less thrombocytopenia, and early discontinuation of study drug because of noncardiac adverse events (4.6% versus 9.1%; \( P=0.005 \)). Similar recurrent ischemic event rates were observed between groups. The results of CLASSICS influenced the nearly uniform use of clopidogrel as the thienopyridine of choice that continues today.

**Clopidogrel Plus Aspirin and Versus Aspirin Monotherapy**

**Acute Coronary Syndromes**

The major clinical trials evaluating the efficacy and safety of dual antiplatelet with clopidogrel and aspirin versus aspirin monotherapy in ACS are summarized in the Table. The first large-scale trial was the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. Dual antiplatelet therapy of clopidogrel (300-mg loading dose followed by 75 mg/d) and aspirin (75 to 325 mg/d) in patients with unstable angina and non–ST-elevation acute MI (NSTEMI) was associated with a superior reduction in 9-month cardiovascular mortality, nonfatal MI, and stroke across a broad range of risk groups. In a subset analysis of the CURE study (PCI-CURE), there was a reduction in the risk of MI before percutaneous coronary intervention (PCI) and cardiovascular death or MI 4 weeks after PCI in patients receiving clopidogrel and aspirin pretreatment for up to 10 days and continuing on long-term treatment. The results of the CURE trial strongly influenced cardiologists to adopt the strategy of a 300-mg clopidogrel loading dose during PCI in all patients as the standard of care. This strategy was approved by the FDA for the treatment of patients with ACS. In the Clopigadrel for the Reduction of Events During Observation (CREDO) trial, there was a significantly reduced risk of adverse ischemic events with long-term clopidogrel therapy. However, substantial benefits of a prestent clopidogrel loading dose (300 mg) were seen only when administered >6 hours before PCI.

The Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 study investigated the efficacy of a 300-mg clopidogrel load/75 mg QD administered to patients within 12 hours of onset of an STEMI treated with fibrinolytic therapy. Clopidogrel therapy was associated with a 20% reduction (\( P=0.03 \)) in the composite end point of cardiovascular death, reinfarction, or recurrent ischemia requiring urgent revascularization at 30 days. The PCI-CLARITY study examined 57% of the patients from CLARITY-TIMI 28 who underwent PCI and showed that clopidogrel pretreatment was also 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 glycoprotein IIb/IIIa inhibitor treatment or a loading dose of open-label clopidogrel at the time of PCI. It is also interesting that patients who were pretreated with a daily dose of 75 mg clopidogrel and received an additional loading dose of 300 mg at the time of PCI had the maximum protection against death, reinfarction, or stroke.

In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trial of acute STEMI patients, adjunctive clopidogrel therapy was associated with a modest but significant RRR in the primary end point of death, reinfarction, or stroke at hospital discharge and was not associated with an increased risk of major bleeding. The benefit of clopidogrel therapy was observed within the first 24 hours.
Primary and Secondary Prevention

In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, the efficacy and safety of long-term treatment with clopidogrel (75 mg QD) in addition to aspirin (75 to 162 mg QD) were compared with aspirin monotherapy (75 to 162 mg QD) in patients at high risk for cardiovascular events. Overall, there was a nonsignificant decrease in the primary end point of first occurrence of MI, stroke, or cardiovascular death, and a significant decrease in the secondary end point of hospitalization for unstable angina, transient ischemic attack (TIA), or a revascularization procedure (RR, 0.92; 95% CI, 0.85 to 0.995; \( P = 0.04 \)) in patients treated with dual antiplatelet therapy compared with aspirin monotherapy. At the same time, dual antiplatelet therapy was associated with a marginal increase in the primary safety end point of severe bleeding and a significant increase in the rate of moderate bleeding compared with aspirin monotherapy according to the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) definition. In the predefined subgroup of patients with clinically evident atherothrombosis (symptomatic group), there was a statistically significant decrease in the primary end point observed with dual antiplatelet therapy compared with aspirin monotherapy but not in a subgroup of patients with multiple risk factors (asymptomatic group). In that analysis, moderate bleeding was increased nonsignificantly in asymptomatic patients but significantly in symptomatic patients \( (P < 0.001) \).34 In another subgroup analysis of patients with documented prior MI, ischemic stroke, or symptomatic peripheral arterial disease (CAPRIE-like cohort), there was a significant reduction in the primary end point of cardiovascular death, MI, or stroke (hazard ratio [HR], 0.83; 95% CI, 0.72 to 0.96; \( P = 0.01 \)) associated with long-term clopidogrel plus aspirin treatment. Although there was no significant difference in the rate of severe bleeding, moderate bleeding was significantly increased with clopidogrel plus aspirin treatment \( (HR, 1.60; 95\% \text{ CI}, 1.16 \text{ to } 2.20; P = 0.0004) \).35

Finally, a meta-analysis of 5 randomized trials (CURE, CREDO, CLARITY, COMMIT, and CHARISMA) in 79,624 patients demonstrated that the incidence of all-cause mortality was 6.3% in the aspirin plus clopidogrel group versus 6.7% in the aspirin group (odds ratio [OR], 0.94; 95% CI, 0.89 to 0.99; \( P = 0.026 \)). The incidence of MI was 2.7% and 3.3% (OR, 0.82; 95% CI, 0.75 to 0.89; \( P < 0.0001 \)) and of stroke was 1.2% and 1.4% (OR, 0.82; 95% CI, 0.73 to 0.93; \( P = 0.002 \)) in the clopidogrel plus aspirin versus aspirin group, respectively. Similarly, the incidence of major bleeding was 1.6% and 1.3% (OR, 1.26; 95% CI, 1.11 to 1.41; \( P < 0.0001 \)) and of fatal bleeding was 0.28% and 0.27% (OR, 1.04; 95% CI, 0.76 to 1.43; \( P = 0.79 \)) in the aspirin plus clopidogrel versus aspirin group alone, respectively.36

Clopidogrel Plus Aspirin Versus Clopidogrel Monotherapy: TIA and Stroke

In the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) trial, there was no additional value of adding aspirin to clopidogrel in patients with a recent history of TIA or ischemic stroke who had >1 additional cardiovascular risk factor (ie, history of MI, angina, peripheral arterial disease, or diabetes mellitus; RRR, 6.4%); 95% CI, 4.6 to 16.3; \( P = 0.24 \)). However, significantly higher life-threatening bleeding (3% versus 1%; \( P < 0.0001 \)), specifically intracranial hemorrhage, was observed with clopidogrel therapy.37

Thus, a clear net benefit of dual antiplatelet therapy was observed in a wide range of patients with ACS and in patients undergoing coronary stenting as a secondary prevention strategy. However, current data do not support its use in the primary prevention or treatment of cerebrovascular disease.

Limitations of Clopidogrel Plus Aspirin

Early pharmacodynamic studies evaluating the antiplatelet response during clopidogrel and aspirin therapy, especially in patients undergoing stenting treated with a 300-mg loading dose and a 75-mg maintenance dose of clopidogrel, revealed various limitations: a delayed antiplatelet response and overall modest degree of platelet inhibition (≈30% to 50%), normally distributed response variability, nonresponsiveness in a substantial percentage of patients, and irreversible platelet inhibition and interindividual variability in the recovery of platelet function that may affect the outcomes of patients needing urgent surgery with exposure to an unpredictable risk of bleeding and ischemia. The prevalence of clopidogrel resistance varies from ≈8% to 30% and is dependent on dose and time of measurement in relation to dosing.38 In addition, various methods, including point-of-care methods reflecting P2Y12 reactivity, have been used to measure clopidogrel responsiveness. Although a good correlation has been demonstrated among these methods, measurement of vasodilator-stimulated phosphoprotein phosphorylation assay by flow cytometry has been considered by some investigators to be the most specific method to indicate P2Y12 reactivity.39,40 More recently described limitations include potentially important drug-drug interactions, interactions with cigarette smoking, and the influence of CYP450 genotype. Numerous reports associate the occurrence of post-PCI ischemic events, including stent thrombosis, with clopidogrel nonresponsiveness indicated by high on-treatment platelet reactivity.40

Clopidogrel is metabolized in a 2-step process. The thienopyridine ring of clopidogrel is oxidized to 2-oxo-clopidogrel, which is subsequently hydrolyzed to a highly labile active metabolite, R-130964.41 It has been reported that CYP2C19, CYP1A2, and CYP2B6 participate the first step, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A participate in the second step.42

In the Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE) study, the effects of higher loading doses were investigated. An increase in the clopidogrel loading dose from 300 to 600 mg increased platelet inhibition. However, 900 mg did not result in further suppression of ADP-induced platelet aggregation and was associated with a reduced increase in plasma concentration of the active metabolite. These data suggest that intestinal absorption limited the amount of the 900-mg
load accessible to the liver for conversion to the active metabolite.43 Similarly, only a moderate and nonsignificant increase in antiplatelet effects was observed after a 900-mg clopidogrel loading dose compared with 600 mg in the Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis (ALBION) study.44

Multiple lines of evidence strongly suggest that insufficient active metabolite generation is the primary explanation for clopidogrel response variability and nonresponsiveness.45 Variable levels of active metabolite generation after clopidogrel administration have been attributed to variability in intestinal absorption influenced by polymorphism of an ABCB1 gene that encodes p-glycoprotein. Moreover, the ABCB1 gene variant has been identified with decreased clopidogrel active metabolite generation and a 70% relative increased risk of 1-year cardiovascular events.46,47 Functional variability in P450 isoenzyme activity has also been associated with variable levels of active metabolite generation. In earlier studies, coadministration of lipophilic statins (which compete with clopidogrel for CYP3A4) such as atorvastatin or simvastatin has been shown to attenuate the antiplatelet effect of clopidogrel in pharmacodynamic studies.48 However, this interaction has not been proven to affect clinical outcomes significantly in patients treated with dual antiplatelet therapy. However, a trend toward a better clinical outcome in patients coadministered clopidogrel and non–CYP3A4-metabolized statins compared with CYP3A4-metabolized statins has been demonstrated in some retrospective analyses.49

Similar to statins, various proton pump inhibitors (PPIs), frequently used with clopidogrel and aspirin, are also metabolized by CYP450 isoenzymes. In a randomized controlled study involving patients undergoing stenting, coadministration of omeprazole with aspirin and clopidogrel significantly reduced the antiplatelet effect of clopidogrel as measured by the vasodilator-stimulated phosphoprotein phosphorylation assay.50 Coadministration of clopidogrel with PPIs, especially CYP2C19-metabolized PPIs such as omeprazole, lansoprazole, and rabeprazole, has been shown to be associated with reduced clinical efficacy in some but not all retrospective analyses.51,52 At this time, there is no conclusive evidence that PPIs influence clopidogrel metabolism and attenuate the clinical benefits of clopidogrel treatment. However, it has been recommended by some that PPIs be used in patients administered clopidogrel only when there are solid clinical indications.

Cigarette smoking has been reported to induce CYP1A2 activity, thereby potentially affecting clopidogrel metabolism. In the CREDO trial, a larger reduction in clinical events occurred in patients receiving clopidogrel who were smokers compared with nonsmokers receiving clopidogrel treatment.53 A recent retrospective analysis of patients undergoing elective stenting treated with clopidogrel and aspirin reported that current smokers had greater platelet inhibition and a lower aggregation than nonsmokers. This effect was more pronounced in patients who smoked more than half a pack of cigarettes per day.54 In the CLARITY-TIMI 28 trial, clopidogrel was more effective in reducing the rate of 30-day cardiovascular death, MI, or urgent revascularization in patients smoking ≥19 cigarettes a day compared with patients who did not.55 Impaired clopidogrel responsiveness has also been associated with coadministration of calcium channel blockers that are metabolized by CYP3A4 isoenzymes.56

In addition to the variability in CYPP450 isoenzyme function induced by external influences, a link between reduced clopidogrel antiplatelet response, reduced clinical efficacy, and genetic polymorphisms of genes encoding for specific CYP isoenzymes has been reported. Most studies have highlighted the influence of a single nucleotide polymorphism in the gene encoding CYP2C19 on clopidogrel responsiveness, which results in the production of a loss-of-function isoenzyme, CYP2C19*2.57–60 However, a conclusive association between the CYP2C19*2 genetic polymorphism (pharmacogenetic measurement), suboptimal active metabolite generation (pharmacokinetic measurement), decreased clopidogrel responsiveness as measured by a platelet function assay (pharmacodynamic measurement), and poorer clinical outcomes has not yet been confirmed in a single study.

**Overcoming Clopidogrel Nonresponsiveness**

**Higher Doses**

Treatment with a 600-mg load has been used to overcome nonresponsiveness associated with the 300-mg load and is now the standard of care in most centers. This shift in dosing was based on pharmacodynamic studies that demonstrated a greater antiplatelet effect associated with the 600-mg dose. In addition, a 600-mg load is associated with a faster onset of action, less response variability, and less resistance.61,62 The ceiling effect of the antiplatelet response associated with the 600-mg loading dose has been addressed by the administration of repeated 600-mg loading doses of at time intervals of 24 hours (up to a total of 2400 mg) until the desired platelet reactivity is reached. This dosing strategy has been demonstrated to be effective in >80% of patients with high platelet reactivity after a single 600-mg loading dose as measured by vasodilator-stimulated phosphoprotein phosphorylation. This strategy also was associated with reduced postprocedural ischemic event occurrence, including stent thrombosis.63,64 In another study, a loading dose of 600 mg overcame less platelet inhibition after a 300-mg loading dose that was associated with the CYP2C19*2 polymorphism.65

Similarly, a meta-analysis demonstrated that the 600-mg clopidogrel loading dose was associated with a lower rate of 1-month cardiovascular death or nonfatal MI (OR, 0.54; 95% CI, 0.32 to 0.90; P=0.02) but no increase in major (OR, 1.88; 95% CI, 0.24 to 14.8; P=0.55) or minor (OR, 0.99; 95% CI, 0.49 to 2.0; P=0.98) bleeding compared with a 300-mg loading dose.66 The antiplatelet effect of a 150-mg maintenance dose has been compared with the standard 75-mg maintenance dose in small studies. Modestly greater overall inhibition was reported; however, some patients had persistent high platelet reactivity.67,68 Conclusive data on the antiplatelet efficacy of 75- versus 150-mg clopidogrel maintenance doses and associated clinical outcomes (bleeding and ischemia) are not yet available. The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to
Assess Strategies in Ischemic Syndromes (CURRENT/OASIS) 7 study enrolled ≈25,000 patients with ACS who were then randomized to treatment with either a 600-mg loading dose of clopidogrel followed by 150-mg maintenance dose for 7 days or a 300-mg load followed by a 75-mg maintenance dose. Patients were also randomized in a 2 × 2 factorial fashion to low (75 to 100 mg QD) or high (300 to 325 mg QD) aspirin dosing from day 2 to 30. The OASIS 7 study will be large enough to determine whether the greater antiplatelet effects observed after the 600-mg load and 150-mg maintenance dose observed in ex vivo studies actually translate into a superior clinical effect in the treatment of ACS patients.60 The primary efficacy outcome is a composite of cardiovascular death, MI, or stroke up to day 30. The results of OASIS 7 will be reported at the 2009 European Society of Cardiology Congress.

Prasugrel Plus Aspirin Versus Clopidogrel Plus Aspirin

The third-generation thienopyridine, prasugrel, was developed to overcome the limitations of clopidogrel and is the most recent FDA-approved thienopyridine for the treatment of ACS managed by PCI. Phase I and II studies demonstrated that prasugrel treatment was associated with a rapid onset of action and superior active metabolite generation resulting from efficient conversion of the prodrug to the intermediate metabolite by plasma esterases and 1-step rapid and efficient conversion by multiple CYP450 isoenzymes. These metabolic properties result in less response variability, a lower prevalence of nonresponsiveness, and greater inhibition of ADP-induced platelet aggregation by prasugrel compared with clopidogrel.60 Moreover, the potential influence of functional variability at the CYP450 level induced by statins and PPIs and genetic variability associated with loss-of-function single-nucleotide polymorphisms were not observed during prasugrel treatment. Owing to superior pharmacokinetics and pharmacodynamics and the apparent absence of genetic influences, prasugrel treatment in phase II clinical studies resulted in a rapid onset of action and greater platelet inhibition. A similar safety end point (TIMI major or minor bleeding events) and a trend to better efficacy compared with clopidogrel in the phase II Joint Utilization of Medications to Block Platelets Optimally (JUMBO) TIMI trial supported further study in a phase III investigation.71,72

In the phase III A Comparison of CS-747 and Clopidogrel in Acute Coronary Syndrome Subjects Who Are to Undergo Percutaneous Coronary Intervention (TRITON-TIMI) 38 trial, prasugrel (60 mg/10 mg) plus aspirin treatment (75 to 162 mg QD) was associated with a 19% reduction (9.9% versus 12.1%; HR, 0.81; P = 0.0004) in the primary composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke at a median 14.5-month follow-up compared with clopidogrel (300 mg/75 mg) plus aspirin treatment in patients with ACS (unstable angina/NSTEMI and STEMI) undergoing planned PCI. The TRITON trial was a landmark investigation supporting the concept that superior P2Y12 inhibition is associated with superior attenuation of thrombotic complications in ACS patients treated with PCI. Thienopyridine pretreatment before coronary artery anatomy determination was allowed only in the STEMI patients. The reduction in primary end point was attributed mainly to a 26% reduction in nonfatal MI (P < 0.001) that was most marked in the first 30 days. It has also been speculated that use of the 300-mg loading dose of clopidogrel was an unfair bias against it because it has been shown in ex vivo studies that a 600-mg load is associated with a superior antiplatelet profile (more rapid, less variable, less resistant). However, there are no conclusive data that a 600-mg load provides a clinical outcome superior to that of the 300-mg load (see CURRENT/OASIS 7 study). In addition, the secondary end point of urgent target vessel revascularization was reduced by 34%. However, these benefits were associated with significantly increased key safety end points of TIMI major bleeding, including life-threatening and fatal bleeding in patients treated with prasugrel (2.4% versus 1.8%; P = 0.03). Moreover, patients >75 years of age and weighing <60 kg had no net clinical benefit, and it has been suggested that these patients need a lower maintenance dose of prasugrel. Patients with prior cardiovascular accident/TIA exhibited an adverse net benefit profile; therefore, the FDA has recommended that prasugrel be contraindicated among the these patients. Finally, in 80% of patients in TRITON without the features specified above, prasugrel treatment was associated with a net clinical benefit. Another important finding of TRITON-TIMI 38 trial was a 52% reduction in the occurrence of stent thrombosis with prasugrel treatment and a reduction in the primary end point in diabetics that were not associated with a bleeding hazard.73 The benefit of prasugrel treatment among patients undergoing PCI may vary over time. Among patients with STEMI treated with PCI, the maximum difference between clopidogrel and prasugrel in the reduction of primary end point was achieved at 18 days after PCI and sustained through 450 days, but there were no additional reductions. Concomitantly, a sustained reduction in the primary end point was demonstrated among patients with NSTEMI through 450 days.74 Another group is made up of patients who need to undergo urgent coronary artery bypass graft surgery after PCI. A significant increase in coronary artery bypass graft surgery TIMI major bleeding occurred among patients treated with prasugrel (13.4%) compared with clopidogrel (3.2%; HR, 4.73; 95% CI, 1.9 to 11.2; P < 0.0001).71 It was reported that the antithrombotic effect of clopidogrel was reduced in patients with the CYP2C19*2 polymorphism, whereas the outcome of patients treated with prasugrel did not differ between wild type and carriers of the allele in a substudy of TRITON-TIMI 38.59,76

Ticagrelor Plus Aspirin Versus Clopidogrel Plus Aspirin

Thienopyridines are irreversible P2Y12 receptor blockers. Accordingly, recovery of baseline platelet function after cessation of thienopyridine therapy is prolonged and variable because it is dependent on the production of new platelets. Ticagrelor (AZD6140), an investigational cyclopentyltriazolo-pyrimidine derivative, is a new oral, reversible, direct-acting P2Y12 inhibitor. Unlike the permanent structural change in the P2Y12 receptor that occurs after thienopyridine active metabolite binding, ticagrelor reversibly binds to the P2Y12 receptor.77 By causing an extracellular structural change in the P2Y12 receptor, thienopyridines prevent ADP
binding permanently. However, ticagrelor acts through an allosteric modulation site and exhibits a conformational change in the receptor by binding independently of ADP. Therefore, ticagrelor allows ADP to bind to the P2Y12 receptor but prevents the receptor signaling induced by ADP. The reversible antiplatelet effect of ticagrelor or any other reversible P2Y12 may be advantageous in clinical scenarios requiring rapid reversal of the antiplatelet effect. The direct action of ticagrelor also obviates any potential influence of the CYP450 pathway on the antiplatelet response.

An experimental model of thrombosis and bleeding has demonstrated a more narrow therapeutic window associated with clopidogrel treatment compared with ticagrelor at doses achieving 90% inhibition of thrombosis. These observations may have important clinical implications because they imply a lower bleeding risk at an equivalent antithrombotic level during treatment with ticagrelor compared with clopidogrel.

Ticagrelor is a more potent P2Y12 inhibitor than clopidogrel and is associated with less response variability. Phase I and II studies demonstrated an association between the pharmacokinetic and pharmacodynamic properties of ticagrelor and a rapid onset of action. The Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs. Clopidogrel in NSTEMI (DISPERSE-2) studied non–ST-elevation ACS patients and demonstrated greater and more consistent platelet inhibition (>50% mean inhibition of ADP-induced platelet aggregation reached within 2 hours after a 180-mg loading dose compared with ∼10% after a 300-mg clopidogrel loading dose) and an overall similar tolerance profile and similar bleeding rates compared with clopidogrel treatment. Moreover, a moderate and nonsignificant decrease in MI was reported compared with clopidogrel treatment. However, ticagrelor therapy was associated with a higher prevalence of dyspnea than clopidogrel. The mechanism of this side effect remains unclear. In the Study of Platelet Inhibition and Patient Outcomes (PLATO), ticagrelor (180-mg loading dose, 90-mg BID maintenance) was compared with clopidogrel (300-mg loading dose, 75-mg QD maintenance with an additional 300 mg allowed before PCI) in the treatment of ACS patients. This study differs from TRITON by enrolling not only clopidogrel-naïve but also clopidogrel-pretreated patients. The results of PLATO were reported at the 2009 European Society of Cardiology Congress.

Elinogrel Plus Aspirin Versus Clopidogrel Plus Aspirin

Elinogrel (PRT060128) is an investigational, direct-acting, reversible P2Y12 receptor inhibitor that has both oral and parenteral formulations. Phase I single-ascending-dose studies in healthy subjects have demonstrated a high-level inhibition of ADP-induced platelet aggregation after either single oral dose or intravenous bolus administration. A recent study demonstrated that high platelet reactivity accompanying standard maintenance clopidogrel (75 mg QD) and aspirin therapy (81 mg QD) in stable coronary artery disease patients is rapidly and reversibly overcome by a single 60-mg oral dose of elinogrel. The strong antiplatelet effect of elinogrel was demonstrated by concordant results from multiple assays measuring P2Y12 receptor reactivity. Platelet inhibition occurred within 4 hours of drug administration, the earliest time point evaluated, and nearly complete platelet function recovery occurred within 24 hours. The Intravenous and Oral Administration of PRT060128 to Evaluate Tolerability and Efficacy in Non-Urgent PCI Patients (INNOVATE-PCI) trial is an ongoing ascending-dose study comparing the tolerability and efficacy of elinogrel and clopidogrel in patients undergoing nonurgent PCI.

Cilostazol Plus Clopidogrel Plus Aspirin Versus Clopidogrel Plus Aspirin

Cilostazol is a quinolone derivative that inhibits the PDE3 enzyme in both platelet and vascular smooth muscle cells similar to dipyridamole, thus increasing cAMP levels. It is believed that this property may be important in explaining the enhancement of platelet inhibition when added to clopidogrel and aspirin therapy. It has been shown that cilostazol treatment has antiproliferative effects on vascular smooth muscle cells and reduces the rate of hyperplasia after balloon angioplasty and bare metal stent implantation compared with aspirin and thienopyridines. In addition, cilostazol has an additive inhibitory effect on platelet p-selectin expression when administered with aspirin and clopidogrel therapy.

It was concluded by a meta-regression analysis of available studies that cilostazol plus aspirin and clopidogrel plus aspirin were statistically indistinguishable from ticlopidine plus aspirin in the prevention of 30-day major cardiac events after coronary stenting. However, drug dosing was not uniform in the studies included in this analysis. Although the cilostazol group was limited by the overall sample size, the OR for the comparison of cilostazol plus aspirin versus clopidogrel plus aspirin was 0.69 (95% CI, 0.42 to 1.12). In a randomized study of 689 patients, it was also reported that the incidence of 30-day major cardiovascular events and stent thrombosis did not differ between patients treated with cilostazol plus aspirin and those treated with clopidogrel plus aspirin. From this observation and a subsequent meta-analysis, it was proposed that cilostazol can be used as an alternative to thienopyridine therapy (clopidogrel or ticlopidine) to prevent short-term poststenting complications, including stent thrombosis. Subsequently, a small study reported greater inhibition of ADP-induced platelet aggregation and a lower prevalence of low responsiveness with triple antiplatelet therapy compared with dual antiplatelet therapy. In patients undergoing stenting with high platelet reactivity (>50% 5 μmol/L ADP–induced platelet aggregation) after a 300-mg clopidogrel loading dose, the addition of cilostazol to 75 mg QD clopidogrel for 30 days was associated with a lower prevalence of high platelet reactivity compared with patients treated with 150 mg QD clopidogrel. Triple antiplatelet therapy has been shown to reduce in-stent late loss at 6 months after drug-eluting stent implantation, the occurrence of target lesion revascularization, and major cardiac adverse events in patients with long lesions (≥25 mm) compared with dual antiplatelet therapy. Similarly significant reductions in in-stent (P=0.025) and in-segment (P=0.031) late loss and 9-month target vessel revascularization (P=0.034) were demonstrated in diabetic patients treated with triple antiplatelet therapy.
therapy compared with dual antiplatelet therapy after drug-eluting stent implantation.95

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 events. In addition, there was a significant reduction in the 8-month incidence of cardiac death (adjusted OR, 0.52; 95% CI, 0.32 to 0.84), total death (adjusted OR, 0.60; 95% CI, 0.41 to 0.89; \(P=0.01\)), and total major adverse cardiac events (adjusted OR, 0.74; 95% CI, 0.58 to 0.95; \(P=0.019\)) with triple antiplatelet therapy compared with dual antiplatelet therapy. Moreover, these benefits were more pronounced in older (>65 years of age), female, and diabetic patients.96 In a prospective randomized study of ACS patients undergoing stenting, triple therapy was associated with a significantly lower incidence of the composite of 1-year cardiac death, nonfatal MI, stroke, or target vessel revascularization (10.3% versus 15.1%; \(P=0.011\)) but similar bleeding events compared with dual antiplatelet therapy.97 At this time, cilostazol is approved by the FDA only for treatment of intermittent claudication.

**Thrombin Receptor Blockade Plus Clopidogrel Plus Aspirin Versus Clopidogrel Plus Aspirin**

Despite the proven clinical benefits associated with dual antiplatelet therapy compared with aspirin monotherapy in the treatment of high-risk coronary artery disease patients, recurrent ischemic events are seen in a significant percentage of patients during long-term follow-up. This observation highlights an unmet need in the treatment of the patient at highest risk. For example, in the TRITON trial, there was an \(\approx 10\%\) treatment failure rate (ischemic event occurrence) in theprasugrel arm despite the superior inhibition compared with clopidogrel as demonstrated in ex vivo studies of healthy volunteers and patients treated with the same dose.74 The explanation for the high rate of dual antiplatelet treatment failure remains a critical unresolved and underinvestigated issue. Because the large-scale trials of dual antiplatelet therapy did not implement simultaneous platelet function measurements, it was impossible to determine whether insufficient P2Y\(_{12}\) blockade marked by high on-treatment platelet reactivity to ADP was the major cause of treatment failure and whether excessively low platelet reactivity was the cause of bleeding. If these possibilities were the primary explanations for the 2 major limitations of aspirin plus thienopyridine therapy, then dose modification would be a logical first therapeutic option instead of the implementation of alternative agents that inhibit other signaling pathways. All of the clinical trials described above have been limited by a “one size fits all” dosing approach that ignores the individual patient’s antiplatelet response. Current research is addressing the importance of thrombin-induced platelet activation as a predictive tool for in-hospital and postdischarge ischemic event occurrence and as an explanation for treatment failure.98,99 The administration of specific protease-activated receptor-1 (PAR-1) blocking agents is now being investigated in 2 large phase III clinical trials. Thrombin-induced platelet activation is incompletely checked by currently available antplatelet agents. Only parenteral administration of glycoprotein IIb/IIIa inhibitors has been demonstrated to markedly inhibit thrombin-induced platelet aggregation.99 Oral PAR-1 antagonists may provide several advantages over thrombin inhibitors by not influencing the enzymatic effect of thrombin in the coagulation cascade, the generation of the fibrin network, or stimulation of anticoagulant pathways (activation of protein C). These attributes make PAR-1 antagonism a unique antithrombotic treatment associated with potential limited bleeding side effects.100

SCH-530348 is a himbacine derivative that is a specific, potent, and reversible PAR-1 antagonist with a long half-life and no effect on bleeding time or other receptor signaling pathways in platelets. In a recently completed randomized, double-blind, placebo-controlled, dose-ranging phase II study, patients undergoing nonurgent PCI or coronary angiography with planned PCI were treated with a 10-, 20-, or 40-mg loading dose of SCH530348 or matching placebo in addition to aspirin plus clopidogrel and anticoagulant therapy. Patients in the SCH530348 group who subsequently underwent PCI (primary PCI cohort) were continued on an SCH530348 maintenance dose (0.5, 1.0, or 2.5 mg QD) or placebo for 60 days. SCH530348 was not associated with an increase in the primary end point of clinically significant TIMI major or minor bleeding compared with placebo (2.8% versus 3.3%; \(P=0.77\)). In addition, there was a nonsignificant reduction in the secondary efficacy end point of 60-day death or major cardiovascular events (32% overall) and a 41% overall reduction in MI compared with placebo. Moreover, the 40-mg SCH530348 loading dose was associated with a more pronounced reduction in major cardiovascular events and MI (46% and 52%, respectively).101 SCH530348 is now being studied in a randomized, multicenter, \(\approx 10\ 000\)-patient study of high-risk NSTEMI ACS, the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) phase III trial. The primary end point is 1-year cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization.102 In another phase III multicenter, double-blind, randomized, placebo-controlled trial (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events [TRA2P-TIMI50]), the efficacy of SCH530348 in addition to standard antithrombotic therapy in patients with established stable atherosclerotic disease is being studied. This study will involve \(\approx 20\ 000\) patients with coronary artery disease, ischemic cerebrovascular disease, and symptomatic peripheral vascular disease.103

Another thrombin receptor inhibitor undergoing investigation is E5555. Dose-dependent inhibition of thrombin-induced platelet aggregation by E5555 has been demonstrated in healthy volunteers. More than 80% inhibition of thrombin-induced platelet aggregation was achieved by single doses of \(\approx 50\) mg. Nearly complete inhibition of thrombin-induced platelet aggregation was achieved at drug steady state after repeated administration of 100- and 200-mg doses. There were no significant adverse effects or effects on ADP-induced platelet aggregation, coagulation, or bleeding time associated with E5555 administration.104 Two phase II clinical trials assessing safety, tolerability, and the effect
on intravascular inflammation and thrombosis in patients with coronary artery disease and with ACS are being undertaken.105,106

Dipyridamole Plus Aspirin Versus Aspirin Versus Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative that inhibits the cyclic nucleotide PDE enzymes (PDE5, PDE6, PDE10, and PDE11) in endothelial cells and platelets. In addition, dipyridamole blocks the active transport of adenosine into red blood cells and endothelial cells. The resultant increase in adenosine concentration enhances the binding of adenosine to adenosine receptor on platelets. Subsequently, adenyl cyclase activity is stimulated, resulting in increased intracellular cAMP levels in platelets. Increased cAMP levels are associated with attenuated platelet aggregation in response to various agonists. Dipyridamole also stimulates endothelial cell prostacyclin and nitric oxide synthesis and increases platelet cGMP (an inhibitor of platelet aggregation) and nitric oxide levels.107 It has been reported that aspirin plus extended-release dipyridamole treatment was associated with more rapid and consistent inhibition of platelet aggregation in whole blood compared with either agent alone.108

In the European Stroke Prevention Study-2 (ESPS-2), aspirin (25 mg BID), extended-release dipyridamole (200 mg BID), aspirin plus extended-release dipyridamole, and placebo were compared in a randomized, double-blind fashion in 6602 patients who had suffered a stroke or TIA within the preceding 3 months. There was a significant decrease in the incidence of stroke by treatment with aspirin alone versus placebo (RRR, 18.1%; *P* = 0.013) and extended-release dipyridamole alone versus placebo (RRR, 16.3%; *P* = 0.04) but no accompanying reduction in MI or mortality. Moreover, there was a greater decrease in stroke with aspirin plus extended-release dipyridamole combination therapy compared with placebo (RRR, 37%; *P* = < 0.01), aspirin alone (RRR, 23.1%; *P* = 0.006), or extended-release dipyridamole alone (RRR, 24.7; *P* = 0.0002). There were twice the number of bleeding events in both the aspirin and aspirin plus extended-release dipyridamole regimens compared with placebo or extended-release dipyridamole alone.109 A formulation of combined 25 mg aspirin plus 200 mg extended-release dipyridamole was approved by the FDA in 1999 for stroke prevention in patients with a history of TIA or stroke.

In the European Stroke Prevention Reversible Ischemia Trial (ESPRIT), the efficacy and safety of aspirin alone (30 to 325 mg QD; median, 75 mg QD) were compared with aspirin plus extended-release dipyridamole (83% of patients were treated with 200 mg BID) in patients who had experienced a TIA or minor stroke of arterial origin within the past 6 months. After a mean follow-up of 3.5 years, combination therapy was associated with an absolute 1% reduction per year in the primary outcome of the composite of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (HR, 0.80; 95% CI, 0.66 to 0.98). Major bleeding complications occurred more frequently with combination therapy than aspirin alone. In addition, a significant reduction in the risk of the compos-
of major hemorrhage (2.0% versus 1.3%, respectively; \( P<0.001 \))\textsuperscript{116}

Conclusions
Platelets play a critical role in the genesis of ischemic complications in patients with arterial diseases. This role is mediated by multiple receptor signaling pathways that are activated by specific agonists. In patients not on antiplatelet therapy, platelet reactivity is variable. Moreover, patients do not respond uniformly to antiplatelet therapy. These 2 facts greatly influence the clinical outcomes associated with strategies that employ uniform antiplatelet drug regimens and dosing. The “one size fits all” and “one mechanism fits all” approach inherent in current therapies reflects the limitations of available evidence and our incomplete understanding of the mechanisms of action of antiplatelet agents. Patient outcomes may be improved in the future by personalized antiplatelet therapy based on objective measurements of platelet function. The enhanced antithrombotic effect following the addition of \( \text{P2Y}_{12} \) blockers to aspirin in preclinical studies has been reflected in major clinical trials by significant anti-ischemic benefits in patients with acute coronary disease and in patients treated with stents. However, there remains an unacceptable recurrent ischemic event rate despite the use of more potent \( \text{P2Y}_{12} \) blockers with aspirin. The latter may in part be explained by three possibilities: 1) a ceiling effect of \( \text{P2Y}_{12} \) inhibition, 2) selected patients with high on-treatment platelet reactivity despite therapy with an overall more potent \( \text{P2Y}_{12} \) inhibitor than clopidogrel, and 3) platelet activation pathways that are not inhibited by current antiplatelet regimens (e.g. thrombin-PAR-1). The latter hypotheses are being tested in ongoing clinical trials. All of the evidence thus far demonstrates that there is an accompanying increased risk of bleeding with more potent \( \text{P2Y}_{12} \) inhibition on top of aspirin therapy. Whether a therapeutic window exists for \( \text{P2Y}_{12} \) inhibitors to simultaneously limit thrombotic and bleeding events is unknown. Preclinical data suggest that at an equivalent antithrombotic level, a reversible \( \text{P2Y}_{12} \) inhibitor may be associated with less bleeding than an irreversible inhibitor.

Dual antiplatelet therapy with aspirin and clopidogrel has proven inferior to clopidogrel therapy alone in the treatment of patients with established cerebrovascular disease. The data from the trials of patients with cerebrovascular disease suggest a benefit of the addition of a PDE inhibitor to aspirin. However, this strategy has not been adequately examined in the patient with coronary artery disease. The future holds the promise of better defining the differences in the pathophysiology responsible for the cerebrovascular versus the cardiac ischemic event that may lead to improvements in therapy.

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