Therapeutic Goals for Effective Platelet Inhibition: A Consensus Document

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Clopidogrel combined with aspirin is the mainstay of antiplatelet therapy for patients who present with acute coronary syndromes as well as following either bare metal or drug-eluting stent placement. Limitations of clopidogrel therapy include the relatively long time course required to achieve maximal inhibition of platelet aggregation, individual variability in response to its effect, the risk of bleeding during its administration, and the irreversible nature of $P2Y_{12}$ receptor binding, which leads to a prolonged time course for recovery of platelet function following discontinuation of clopidogrel. Several investigational $P2Y_{12}$ receptor antagonists have pharmacological properties that may overcome some or all of these limitations. These novel agents such as prasugrel, AZD6140, and cangrelor are in advanced stages of clinical development for potential use in patients with coronary artery disease.
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Continued advances in antiplatelet therapies have facilitated evolution of percutaneous coronary intervention (PCI) procedures. This article will examine current therapy versus expectations for optimal therapy (ie, strategies to obtain optimal platelet inhibition in the catheterization lab as well as to overcome individual variability in response or resistance to current antiplatelet therapies) and will identify novel antiplatelet agents that may improve on current standards.

Attributes of Current Therapy Versus Expectations for Optimal Therapy

The first PCI, performed in 1979 by Dr. Andreas Gruntzig, involved a discrete, focal lesion in the proximal left anterior descending artery. When comparing the angiographic complexity of that procedure to what is routinely treated today, it is clear that PCI has evolved beyond all expectations of the early pioneers.[1] However, the progress witnessed in the complexity of PCI procedures would not have occurred without concomitant advances in antiplatelet therapies. Early on, pretreatment with aspirin was observed in randomized trials to reduce periprocedural thrombotic events associated with PCI (Table 1). Aspirin specifically and irreversibly inhibits platelet cyclooxygenase-1 (COX-1), preventing arachidonic acid access to the COX-1 catalytic site. A 100-mg dose of aspirin almost completely suppresses thromboxane A_2 synthesis in normal subjects and in atherosclerotic patients.[2] Nevertheless, despite aspirin pretreatment, abrupt vessel closure during or shortly after balloon angioplasty was still observed in 2% to 5% of patients.[3,4]

With the advent of coronary stent implantation, it became clear that aspirin monotherapy was not adequate to prevent thrombotic events, particularly subacute stent thrombosis. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial was a prospective study designed to compare the early clinical outcomes of patients following coronary stenting. Subjects were randomly assigned to receive either combination antiplatelet therapy with ticlopidine (which inhibits the platelet $P2Y_{12}$ adenosine diphosphate [ADP] receptor) plus aspirin or conventional anticoagulant therapy with intravenous heparin, followed by phenprocoumon in combination with aspirin. Patients in the latter group were treated with intravenous heparin until the prothrombin time was 2 to 3 times that of the control level.[5] Combination antiplatelet therapy was associated with a 75% reduction of major adverse cardiac events during the 30-day follow-up period, an observation that led to the adaptation of antiplatelet therapy as optimal adjunctive pharmacotherapy following coronary stenting (Table 2). Despite its advantages, the widespread use of ticlopidine has been limited by its significant side effect profile, including diarrhea, nausea, vomiting (in up to 20% of patients) and rash. Ticlopidine can also induce neutropenia in 2% to 3% of patients, and, more rarely, bone marrow aplasia and thrombotic thrombocytopenic purpura.

The shortcomings of ticlopidine therapy prompted consideration of clopidogrel, another platelet $P2Y_{12}$ ADP receptor antagonist, as an alternative option. The Clopidogrel/Aspirin Stent International Cooperative Study (CLASSICS) trial randomized 1020 patients following successful stent placement to aspirin plus clopidogrel (75 mg/d orally with or without a 300-mg loading dose) or to aspirin plus ticlopidine (250 mg twice daily without a loading dose) for 4 weeks.[6] The primary endpoint consisted of major peripheral or bleeding complications (including false aneurysms, surgical repair of puncture site complications, blood transfusion [≥ 2 U of blood], intracranial bleeding, retroperitoneal bleeding, overt hemorrhage with a decrease of hemoglobin ≥ 3 g/dL compared with baseline); neutropenia (neutrophil count $< 1.5 \times 10^9$/L); thrombocytopenia (platelet count $< 100 \times 10^9$/L); and early discontinuation of study drug because of a noncardiac adverse event (including death of noncardiac origin). This primary endpoint was reached less often with the use of clopidogrel than with

Table 1
The Effect of Aspirin on Acute Complications After Balloon Angioplasty

Study	N	Drug (mg/d)	Endpoints	Complications (%)
White CW et al[79]	333	650 mg ASA and 225 mg dipyridamole, 750 mg ticlopidine, or placebo	AMI and/or CABG	5* versus 2* versus 14
Schwartz L et al[15]	376	330 mg ASA and 225 mg dipyridamole or placebo	Q-wave AMI	1.6* versus 6.9
Chesebro JH et al[80]	207	975 mg ASA and 225 mg dipyridamole or placebo	Occlusion, AMI, urgent reintervention	11 versus 20

*$P < .05$ versus placebo.
ASA, acetylsalicyclic acid; AMI, acute myocardial infarction; CABG, coronary artery bypass surgery. Adapted with permission from ten Berg JM et al.[14]

Table 2
Relative Risk of Endpoints and Events*

Event	No. (%) Antiplatelet Therapy (N = 257)	No. (%) Anticoagulant Therapy (N = 260)	*P* Value	Relative Risk (95% CI)
Primary cardiac endpoint	4 (1.6)	16 (6.2)	0.01	0.25 (0.06-0.77)
Death	1 (0.4)	2 (0.8)	1.0	0.50 (0.01-9.66)
Myocardial infarction	2 (0.8)	11 (4.2)	0.02	0.18 (0.02-0.83)
Fatal	0	2 (0.8)	0.50	0.00 (0.00-3.51)
Nonfatal	2 (0.8)	9 (3.5)	0.06	0.22 (0.02-1.07)
Reintervention	3 (1.2)	14 (5.4)	0.01	2.22 (0.04-0.77)
CABG	0	1 (0.4)	1.0	
Repeated PTCA	3 (1.2)	13 (5.0)	0.02	0.23 (0.04-0.84)
Primary noncardiac endpoint	3 (1.2)	32 (12.3)	< 0.001	0.09 (0.02-0.31)
Death	0	0		
Cerebrovascular accident	1 (0.4)	0	1.0	
Hemorrhagic event	0	17 (6.5)	< 0.001	0.00 (0.00-0.19)
Surgical correction	0	1 (0.4)	1.0	
Transfusion	0	12 (4.6)	0.001	0.00 (0.00-0.29)
Organ dysfunction	0	7 (2.7)	0.02	0.00 (0.00-0.53)
Peripheral vascular event	2 (0.8)	16 (6.2)	0.001	0.13 (0.01-0.53)
Surgical correction	0	1 (0.4)	1.0	
Ultrasound-guided compression	2 (0.8)	15 (5.8)	0.002	0.14 (0.02-0.57)
Combined clinical endpoint	7 (2.7)	43 (16.5)	< 0.001	0.16 (0.06-0.36)
Occlusion of stented vessel	2 (0.8)	14 (5.4)	0.004	0.14 (0.02-0.62)
Thrombosis	0	13 (5.0)	< 0.001	0.00 (0.00-0.26)
Dissection	2 (0.8)	1 (0.4)	1.0	2.03 (0.11-120)

*Relative risks are for the patients in the antiplatelet therapy group as compared with those in the anticoagulant therapy group. Patients with more than 1 event are counted only once for each type of endpoint, although the events are listed separately in the relevant categories.
CI, confidence interval; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty. Reprinted with permission from Schömig A et al.[5]

ticlopidine (4.6% vs 9.1%, $P = .005$). The secondary endpoint, which included cardiovascular death, any myocardial infarction (MI), and target vessel revascularization, was observed with similar frequency. Thus, the basis for therapeutic conversion to clopidogrel was mainly a reduction in safety endpoints such as those assessed in the CLASSICS trial, not because of a reduction in major adverse cardiac events.[6]

Clopidogrel combined with aspirin continue to be the mainstay of antiplatelet therapy for patients who present with acute coronary syndromes and following placement of both bare metal and drug-eluting stents. Limitations of clopidogrel therapy include the relatively long time course required to achieve maximal inhibition of platelet aggregation, individual variability in response to its effect, the risk of bleeding events during long-term therapy, and the irreversible nature of $P2Y_{12}$ receptor binding, which leads to a prolonged time course for recovery of platelet function following discontinuation of clopidogrel. This last issue is relevant for patients who receive clopidogrel prior to referral for cardiac surgery. Although higher loading doses (600 mg) of clopidogrel accelerate the time-course and enhance the magnitude of platelet inhibition, the minimum of 2 to 4 hours required for maximum effect, as well as the persistent marked variability in response, may be inadequate for patients with acute coronary syndromes who are taken

urgently to the catheterization laboratory.[7] Furthermore, clopidogrel treatment prior to coronary angiography and definition of coronary anatomy may be problematic because of the increase in risk of bleeding in those patients who require coronary artery bypass surgery within 5 days of the last dose.[8] This increased risk of major bleeding and transfusion is attributable to the persistent clopidogrel antiplatelet effect caused by irreversible binding of $P2Y_{12}$ receptors. Chronic clopidogrel therapy may be associated with bleeding events in the absence of intercurrent surgery as well. For example, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial, although no significant increase in severe bleeding was observed, there was an increase in moderate bleeding (defined as the need for transfusion without hemodynamic compromise) following clopidogrel administered in combination with aspirin in both patients with established vascular disease and patients with risk factors for coronary atherosclerosis.[9] Overall, bleeding requiring transfusion was observed in 2.1% of patients who were receiving chronic dual antiplatelet therapy, a relative increase of 0.8% over 28 months compared with patients receiving aspirin and placebo. A similar increased bleeding risk was observed in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which major bleeding occurred more frequently in the clopidogrel group than in the placebo group (3.7% vs 2.7%; relative risk, 1.38; 95% CI, 1.13-1.67; $P = .001$).[10]

Unfortunately, the clinical trial experience with oral platelet glycoprotein (GP) IIb/IIIa (integrin αIIbβ3) receptor inhibitors, including xemilofiban, orbofiban, and sibrafiban, failed to show efficacy for the prevention of major adverse cardiovascular events and, in fact, was associated with an increased incidence of major bleeding events as well as total mortality.[11-13] These agents were developed for chronic use in patients who presented with acute coronary syndromes with the hope of extending the clinical benefit observed following intravenous GP IIb/IIIa inhibitor therapy.[14]

Novel inhibitors of the $P2Y_{12}$ receptor, including prasugrel, AZD6140, and cangrelor, may address some of the limitations of the current thienopyridines and will be discussed later.[15]

The goal in the development of newer antiplatelet agents will be to provide a more rapid and uniform antiplatelet effect, reduce major adverse clinical cardiac events, and be well tolerated without a concomitant increase in risk for hemorrhagic events.

Obtaining Optimal Platelet Inhibition in the Catheterization Lab: An Overview of Contemporary Oral Antiplatelet Therapy

Aspirin

Aspirin in a dose of 325 mg was compared with placebo in 2 randomized trials and was found to reduce periprocedural MI and death during coronary balloon angioplasty.[16,17] A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated. These studies have suggested that aspirin absorption and the onset of antiplatelet activity are significantly accelerated by chewing aspirin or drinking solubilized aspirin.[18,19] In a study that evaluated subjects who chewed aspirin in doses of 81 mg, 162 mg, and 324 mg, all of these doses led to an equivalent reduction in thromboxane B_2 production, but maximal inhibition at 15 minutes after ingestion was achieved only following the 162-mg and 324-mg doses.[19] These studies suggest that in order to achieve maximal effects of aspirin rapidly, at least 162 mg should be chewed and swallowed. Based on these studies, and other randomized controlled trials that revealed clinical benefit from aspirin in more than 130,000 patients with vascular disease not undergoing PCI,[20] it is recommended that a dose of 162 mg to 325 mg of aspirin should be administered to patients undergoing any kind of coronary (or peripheral) intervention, including stent placement. Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated aspirin formulations.

Thienopyridines

Ticlopidine. Thienopyridines also prevent thrombotic complications and improve clinical outcome during PCI through greater inhibition of one or more platelet functions than can be achieved by aspirin alone. Randomized trials comparing ticlopidine, the first available thienopyridine, to placebo or to coumadin among patients on aspirin who were treated with bare metal stents revealed that ticlopidine reduces adverse cardiovascular events as well as procedural complications, including stent thrombosis.[21-23]

Clopidogrel. Because ticlopidine is associated with nausea, vomiting, and diarrhea in up to 20% of patients, neutropenia in 2% to 3% of patients, and thrombotic thrombocytopenic purpura in a smaller number of patients, clopidogrel was developed as an alternative therapy with a lower incidence of adverse gastrointestinal and hematologic side effects. Unlike ticlopidine, clopidogrel has never been compared with placebo or warfarin in patients receiving stents. However, 3 randomized trials and

multiple registries indicate that clopidogrel appears to be at least as effective as ticlopidine and has a better tolerance profile.[24-28] Additionally, large loading doses of ticlopidine are not tolerated because of associated nausea and vomiting. In contrast, large loading doses of clopidogrel are well tolerated. Furthermore, larger loading doses of clopidogrel are more rapidly acting and more potent at inhibiting platelet aggregability than smaller loading doses. For example, as compared with the 300-mg oral loading dose, the 600-mg dose demonstrates an accelerated time course and enhanced magnitude of platelet inhibition, as well as a reduction in the prevalence of clopidogrel hyporesponsiveness.[7,29-34] Of currently available studies evaluating a 900-mg (vs 600-mg) oral loading dose of clopidogrel most do not support greater inhibition of aggregation or greater clinical effectiveness with the higher dose.[7,34] Finally, only one small randomized, controlled clinical trial has examined the efficacy of a 600-mg oral loading dose versus a 300-mg oral loading dose.[33] Ironically, widespread utilization of the 600-mg loading dose has already occurred based on its apparent safety and ability to more rapidly inhibit platelet aggregation. A large randomized trial comparing 300 mg and 600 mg of clopidogrel is currently underway.

Resistance to Antiplatelet Therapies

Not all patients respond to oral antiplatelet agents with the same degree of inhibition of aggregation. Possible mechanisms for "hyporesponsiveness" or "resistance" to antiplatelet drugs include poor bioavailability (non-compliance, underdosing, poor absorption, interference by other drugs), accelerated platelet turnover, single nucleotide polymorphisms, and/or pre-existent platelet hyperreactivity.[35-37] Numerous methods are available for the detection of aspirin or clopidogrel "resistance," but there is no consensus as to the optimal method of detection, the clinical relevance, or how it should influence individual patient management.[35-37] A clinically meaningful definition of aspirin and clopidogrel "hyporesponsiveness" can only be based on data linking aspirin- and clopidogrel-dependent laboratory tests to major adverse cardiac events.[35-37] Such studies are underway.

Aspirin: Efficacy and Resistance

The mechanism of aspirin's antiplatelet effect is acetylation of serine 239 of COX-1 in the biochemical pathway of thromboxane A_2 generation from arachidonic acid.[38] Aspirin "resistance" is therefore most specifically identified by either: 1) using the endpoint of stable metabolites of thromboxane A_2, ie, serum thromboxane B_2 or urinary 11-dehydrothromboxane B_2, or 2) using arachidonic acid as the stimulus, with the endpoint of platelet activation measured in one of the following assays: platelet aggregation (turbidometric); platelet aggregation (impedance); VerifyNow™ Aspirin Assay (Accumetrics, San Diego, CA); platelet surface P-selectin, platelet surface–activated GP IIb/IIIa, or leukocyte-platelet aggregates (flow cytometry); Plateletworks® (Helena Laboratories, Beaumont, TX); thromboelastograph Platelet Mapping System™ (Haemoscope, Niles, IL); or Impact Cone and Plate(let) Analyzer (DiaMed AG, Cressier sur Morat, Switzerland).[35-37] In addition, the platelet function analyzer (PFA-100®, Dade Behring, Newark, DE) has been widely used to monitor aspirin resistance, although its instructions for use describe it as being effective only for 325 mg doses of aspirin.[35-37]

Small studies suggest that future adverse cardiovascular events for patients who present with acute coronary syndromes, stroke/transient ischemic attacks, and peripheral arterial disease can be predicted by the following tests of aspirin resistance: urinary 11-dehydro thromboxane B_2, arachidonic acid- and ADP-induced platelet aggregation (turbidometric), ADP- and collagen-induced platelet aggregation (impedance), the VerifyNow™ Aspirin Assay, and the PFA-100®.[39-44]

Many clinicians increase the dose of aspirin based on laboratory evidence of aspirin resistance.[45] However, there are mixed data about whether or not higher doses of aspirin are effective in reducing hyporesponsiveness or "resistance" to aspirin. Much of the discrepancy is related to which definition of aspirin "resistance" is considered: clinical or pharmacodynamic. The most powerful data that suggest that higher aspirin doses do not provide incremental benefit come from the meta-analysis performed by the Antiplatelet Trialists coalition, which employs clinical (not laboratory) events as a measure of efficacy. This analysis of more than 70,000 patients with vascular disease indicates that lower doses of aspirin (below a dose of about 100 mg) are associated with a greater reduction in the risk of vascular death, MI, or stroke than are higher doses of aspirin.[46] Since many patients who were enrolled in the studies included in this meta-analysis were undoubtedly aspirin hyporesponders, these data imply indirectly that higher doses (above 100 mg/d) do not provide greater clinical benefit than lower doses, as there were undoubtedly many aspirin hyporesponders included in the studies analyzed. Indeed, analysis of clinical trials across a dose range of 75 mg to 325 mg has shown

similar efficacy, with increased rates of bleeding resulting from the higher doses.[20,47-49] An analysis from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study not only demonstrated an increased risk of bleeding but also a trend towards lesser efficacy with higher aspirin doses.[49] Furthermore, no published studies address the clinical effectiveness of altering therapy based on a laboratory finding of aspirin resistance. The most appropriate treatment for hyporesponsiveness to aspirin therefore remains unknown. The International Society on Thrombosis and Haemostasis Working Group on Aspirin Resistance recently concluded that "other than in research trials, it is not currently appropriate to test for aspirin resistance in patients or to change therapy based on such tests."[37] Similar conclusions have recently been published by both the American College of Chest Physicians 7th Consensus Conference on Antithrombotic and Thrombolytic Therapy[38] and the Consensus Task Force on the Use of Antiplatelet Agents in Patients with Atherosclerotic Cardiovascular Disease of the European Society of Cardiology.[50] Although 325 mg of aspirin is recommended on the day of a PCI procedure, the optimal dose of aspirin among patients undergoing PCI and, particularly, among aspirin hyporesponders, remains unknown.

It has been hypothesized that the greatest benefit of thienopyridines (and of GP IIb/IIIa inhibitors) may exist in patients who are hyporesponsive to aspirin.[36,51] This hypothesis is attractive but unproven. In fact, 2 recent studies suggest that those patients who are hyporesponsive to the platelet inhibitory effects of aspirin are also more frequently hyporesponsive to clopidogrel.[52,53] If true, this observation might suggest the possible existence of a "hyporesponsive phenotype" of patients who exhibit a diminished response to both medications. Other studies have not found that hyporesponsiveness to aspirin and clopidogrel overlap substantially. Regardless, considering the proven benefits of thienopyridine therapy coadministered with aspirin in patients who are undergoing not only stent placement but also balloon angioplasty, it is unlikely that placebo-controlled trials of thienopyridines will be performed in subgroups of patients with varying degrees of responsiveness to aspirin.

Clopidogrel: Efficacy and Resistance

The mechanism of clopidogrel's antiplatelet effect is the irreversible antagonism of the ADP receptor $P2Y_{12}$.[38] Clopidogrel "resistance" can therefore be identified by either: 1) the $P2Y_{12}$ signaling-dependent phosphorylation of vasodilator-stimulated phosphoprotein, or 2) using ADP as the stimulus, the endpoint of platelet activation measured by one of the following assays: platelet aggregation (turbidometric); platelet aggregation (impedance); VerifyNow™ $P2Y_{12}$ Assay; platelet surface P-selectin, platelet surface activated GP IIb/IIIa, or leukocyte-platelet aggregates (flow cytometry); Plateletworks®; thromboelastograph Platelet Mapping System™; or Impact Cone and Plate(let) Analyzer.[35-37]

Most,[54-57] but not all,[58] small studies suggest that, after the initiation of clopidogrel therapy, patients with higher residual platelet reactivity as determined by ADP-induced platelet aggregation (turbidometric), activated GP IIb/IIIa (flow cytometry), and vasodilator stimulated phosphoprotein phosphorylation, have a greater frequency of subsequent major adverse cardiovascular events. Higher doses of clopidogrel[31,34,59,60] or other antiplatelet therapies may therefore be beneficial in these patients.

Studies evaluating effective doses of clopidogrel have focused on the short-term evaluation of different loading doses. In the CLASSICS trial, a 300-mg oral loading dose of clopidogrel was compared with both 75 mg of clopidogrel (no loading dose) and with ticlopidine 250 mg orally twice daily (without a loading dose).[6] Although the 300-mg loading dose of clopidogrel was not superior to the other 2 regimens, the likelihood that this study would be able to show benefit from a 300-mg loading dose was reduced by the study design, which required that the drug not be administered until 2 to 6 hours following PCI and stent placement.

In the Clopidogrel for Reduction of Events During Observation (CREDO) trial, a 300-mg oral loading dose of clopidogrel prior to PCI was associated with a relative reduction in risk of 19.7% for the composite primary clinical endpoint (death, MI, or urgent revascularization) to 30 days compared with no oral loading dose (75 mg/d) of clopidogrel initiated at the time of the procedure.[61] This relative difference did not reach statistical significance. Nonetheless, given the lack of adverse side effects associated with a 300-mg loading dose in CREDO[61] and other studies, including the CLASSICS[6] and CURE trials,[10] the logical likelihood is that more rapid inhibition of platelet aggregation by the oral loading dose in the periprocedural timeframe (the highest risk period for thrombotic complications) is advantageous. A 300-mg loading dose, administered as early as possible before the PCI procedure, has been the standard of care in most cath labs around the world until recently.

A 600-mg loading dose of clopidogrel. Recent multiple studies evaluating platelet function in both normal volunteers and patients

undergoing PCI have demonstrated that increasing an oral loading dose of clopidogrel from 300 mg to 600 mg accelerates the time course and enhances the magnitude of platelet inhibition.[7,29-34] For example, following a 600-mg oral loading dose of clopidogrel, maximum platelet inhibition is achieved within 2 to 4 hours,[7,44,60] and the prevalence of clopidogrel nonresponsiveness (resistance) (as defined by a change in platelet aggregation of $< 10\%$ compared with baseline) is reduced to less than 10% (compared to about 25% to 28% following the 300-mg oral load). Some studies have shown a further benefit with regard to the time course and magnitude of platelet inhibition in response to higher levels of agonist (20 μM vs 5 μM ADP) used in platelet function testing, raising the possibility of saturation pharmacokinetics and a physiologic "ceiling" in responsiveness to clopidogrel.[22,34] However, the only data comparing these 2 loading doses come from the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)-2 study, a single small randomized trial.[33] A higher level of platelet inhibition and evidence of reduced myocardial necrosis and/or periprocedural events was observed following the 600-mg loading dose versus the 300-mg dose, although this study had fewer than 250 patients.[33] Nonetheless, based largely on tolerability as well as the ability to inhibit platelets more rapidly, European guidelines consider 600 mg to be an acceptable clopidogrel loading dose strategy for PCI, and rapid adoption into US practice has been widely observed.[50]

The rapid assimilation of a 600-mg oral clopidogrel loading dose into clinical PCI practice is somewhat surprising in the context of the limited clinical trial–based evidence in support of safety and greater efficacy. Indeed, in the ARMYDA-2 study,[33] the composite primary endpoint of death, MI, or urgent coronary revascularization to 30 days was less in the 600-mg loading dose group ($P = .041$) versus the 300-mg loading dose group, an observation entirely due to a relative reduction in periprocedural enzymatically defined infarctions that were not clinically evident. However, the rate of infarction observed in the 300-mg loading dose group was higher than that observed in prior studies that employed this dose. The ARMYDA-2 study was not able to determine whether patients who received the 600-mg dose of clopidogrel had a lower event rate because this dose was more rapidly acting or because it achieved a higher level of platelet inhibition and a lesser degree of hyporesponsiveness compared with the 300-mg loading dose. The results of the Intracoronary Stenting and Antithrombotic Regimen: Choose between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE) trial showed increased levels of platelet inhibition with the 300-mg dose over the 600-mg dose of clopidogrel, and higher levels of plasma concentrations of the active metabolite of clopidogrel for the 600-mg dose versus the 300-mg dose.[34] The increased response to clopidogrel in the 600-mg dose is probably related to the ability to achieve higher levels of the active metabolite with that dose.

The rapid assimilation of a 600-mg oral clopidogrel loading dose into clinical percutaneous coronary intervention practice is somewhat surprising in the context of the limited clinical trial–based evidence in support of safety and greater efficacy.

A 900-mg loading dose of clopidogrel. Recently, randomized studies have been performed to evaluate a 900-mg loading dose of clopidogrel.[7,34] These studies suggest that inhibition of platelet aggregation after doses of 600 mg and 900 mg are similar. One study reported similar levels of not only clopidogrel's active metabolite but also of the clopidogrel prodrug itself, which suggests that absorption may be limited after very large loading doses and/or that conversion of clopidogrel prodrug to the active metabolite (via CYP3A4 hepatic enzymes) demonstrates saturation kinetics.[7] Thus there are no adequate clinical or laboratory data at this time to support the use of a 900-mg oral clopidogrel loading dose.

GP IIb/IIIa inhibitors. It is unknown whether patients who are hyporesponsive to clopidogrel, aspirin, or both agents will derive preferential periprocedural benefit from adjunctive platelet GP IIb/IIIa inhibitor therapy. As noted previously, patients who are resistant to aspirin may be more likely to have concomitant hyporesponsiveness to clopidogrel.[52,53] The ability of these patients to respond appropriately to platelet GP IIb/IIIa inhibition and the magnitude of clinical benefit provided by GP IIb/IIIa blockade in this population is under evaluation in the Research Evaluation to Study Individuals who Show Thromboxane Or $P2Y_{12}$ Receptor Resistance (RESISTOR) trial.

Chronic clopidogrel therapy. On a molar basis, clopidogrel has greater platelet inhibitory effects than ticlopidine. The currently recommended daily dose of 75 mg clopidogrel was designed to provide about equivalent platelet inhibition to an oral 250-mg twice-daily dose of ticlopidine.[62] Although higher daily

doses of ticlopidine are limited by its adverse side effect profile, the platelet response to 75 mg clopidogrel is quite variable on an individual basis.[63] For example, in a population of patients administered a clopidogrel 300-oral loading dose and 75 mg/d following PCI (stenting), the average level of platelet inhibition observed at days 5 and 30 of therapy (5 μM ADP) was about 40%, with a range of 20% to 80%.[63] Given the frequent occurrence of hyporesponsiveness and the wide interindividual variability to daily doses of 75 mg of clopidogrel, 3 small randomized trials have recently been performed that compare a daily dose of 75 mg with a dose of 150 mg of clopidogrel. Different patient populations were included in these 3 studies, which have been reported in preliminary fashion. In the study by von Beckerath and colleagues, 60 patients with coronary disease were randomly assigned to receive either 75 mg or 150 mg of clopidogrel daily for 30 days.[64] Although this study demonstrated that 150 mg/d of clopidogrel inhibits platelet aggregation more effectively than 75 mg/d, the study was too small to assess the effect of the larger dose on clinical thrombotic events. The other 2 studies also found a greater degree of platelet inhibition with the higher dose of clopidogrel (Stephen Steinhubl, MD, personal communication, November 21, 2006). Studies are ongoing in clopidogrel hyporesponsive patients to determine whether larger daily doses of clopidogrel (150 mg vs 75 mg) effectively enhance platelet inhibition and, more importantly, whether or not they are able to reduce the occurrence of ischemic events without an undue increase in hemorrhagic events.

Definitive evidence for the benefit of guided antiplatelet therapy based on the degree of platelet reactivity will not be available until the results of prospective clinical outcomes studies are presented.[35] Nevertheless, the 2005 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) PCI guidelines provide a Class IIb recommendation (based on Level C evidence) that, in patients in whom subacute stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the maintenance dose of clopidogrel increased from 75 mg/d to 150 mg/d if less than 50% inhibition of platelet aggregation is demonstrated.[8] How this total daily dose (150 mg) of clopidogrel should best be administered (75 mg twice daily or 150 mg in a single dose) is not specified.

Novel Antiplatelet Agents: Improving on Current Standards

Limitations of currently available antiplatelet agents include delayed onset of action, irreversibility of effect, response variability among individual patients, and modest levels of antiplatelet effect. Several investigational $P2Y_{12}$ receptor antagonists have pharmacological properties that may overcome some or all of these limitations. These include prasugrel (CS-747, LY640315, an oral subsequent-generation thienopyridine), AZD6140 (an oral nonthienopyridine), and cangrelor (AR-C69931MX, an intravenous $P2Y_{12}$ receptor inhibitor).

Prasugrel

Prasugrel, a novel thienopyridine, has more rapid onset and achieves higher levels of inhibition of ADP-induced platelet aggregation than clopidogrel.[65-67] Like clopidogrel, prasugrel is inactive in its parent state and must be metabolized by cytochrome-dependent pathways to an active form that binds the $P2Y_{12}$ receptor.[68,69] In a study of healthy volunteers treated with either clopidogrel 300 mg or prasugrel 60 mg followed by a washout period and then crossed over to the alternate therapy, prasugrel resulted in higher levels of inhibition of ADP-induced platelet aggregation (mean peak induced platelet aggregation to 20 μM ADP was 78.8% for prasugrel compared to 35% for clopidogrel; $P < .001$). These levels were achieved more rapidly and consistently (with less interindividual variability) than with clopidogrel. Furthermore, the 42% of subjects who were considered poor responders (< 20% induced platelet aggregation to 20 μM ADP at 24 hours) following clopidogrel, were all responsive to prasugrel.[66] In a separate study of patients with chronic coronary artery disease, higher levels of inhibition of platelet aggregation and a lower prevalence of antiplatelet resistance were observed following treatment with prasugrel 40 mg to 60 mg followed by 7.5 mg/d to 10 mg/d when compared with standard clopidogrel dosing.[65]

The clinical utility of prasugrel was initially studied in the 900-patient, Phase II, dose-ranging safety study, Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis in Myocardial Infarction (JUMBO-TIMI)-26 study.[70] This study compared clopidogrel therapy with a range of loading and maintenance doses of prasugrel in patients undergoing elective or urgent PCI with stenting. Prasugrel was found to be well tolerated with no significant difference in TIMI major and minor bleeding. Although JUMBO-TIMI 26 was not powered for clinical efficacy, a non-significant trend toward reduction of cardiovascular ischemic events, including periprocedural MI, was observed following prasugrel therapy.[70]

Based on preclinical and clinical data, the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 trial is currently underway (Clinicaltrials.gov identifier NCT00097591).[71] This trial will enroll more than 13,000 patients with acute coronary syndromes who will be randomized to receive either clopidogrel (300-mg loading dose followed by 75 mg/d) or prasugrel (60-mg loading dose followed by 10 mg/d) for the prevention of cardiovascular death, recurrent MI, or stroke. In addition to comparing prasugrel to clopidogrel, TRITON-TIMI 38 will be the first large-scale clinical events trial to determine whether a therapy that achieves a higher level of inhibition of ADP-induced platelet aggregation results in improved clinical outcomes.

Pharmacokinetic and dynamic data suggest that prasugrel has the ability to overcome several of the limitations of clopidogrel, specifically clopidogrel's modest antiplatelet effect, relatively delayed speed of onset, and interindividual response variability. However, because prasugrel, like clopidogrel, binds irreversibly to the $P2Y_{12}$ receptor, several days off therapy are required for full reversal of antiplatelet effects.

AZD6140

AZD6140 is the first drug in a new class of antiplatelet agents, the cyclopentyltriazolopyrimidines. This drug is an orally available competitive inhibitor of the $P2Y_{12}$ receptor. Unique features of this molecule compared with thienopyridines include the lack of need for metabolism for antiplatelet effect (ie, the parent molecule is active) and the fact that binding to the receptor is reversible.[72] AZD6140 has a more rapid onset of action and achieves higher and more consistent levels of inhibition of ADP-induced platelet aggregation than standard doses of clopidogrel.[73] A short half-life (terminal half-life is approximately 12 hours) requires twice-daily dosing, but results in a more rapid offset of action than thienopyridines.[74] However, because of the persistence of AZD6140 in plasma, offset of effect would not be expected to be immediate.

The Dose confirmatIon Study assessing anti-Platelet Effects of AZD6140 vs clopidogRel in NSTEMI (DISPERSE)-2 trial was a randomized, dose-ranging study of AZD6140 compared with clopidogrel in 990 subjects with non–ST-elevation acute coronary syndrome.[75] Subjects treated with AZD6140 had similar rates of bleeding and a trend toward a lower rate of recurrent MI than clopidogrel-treated patients. In this study, those patients treated with higher doses of AZD6140 had more frequent complaints of dyspnea and nausea than patients treated with clopidogrel, although study drug discontinuation for adverse events was similar.[75] The Platelet Inhibition and Platelet Outcomes (PLATO) trial will compare AZD6140 to clopidogrel in patients with acute coronary syndromes.

Pharmacological data suggest that AZD6140 has the ability to overcome many of the limitations of clopidogrel, including modest and delayed antiplatelet effect and interindividual response variability. Because of reversible receptor binding, AZD6140 is more rapid in offset, but it will likely require more than once-daily dosing in clinical practice.

Cangrelor

Cangrelor (AR-C69931MX) is a nonthienopyridine direct-acting $P2Y_{12}$ antagonist that has several distinct features from clopidogrel and AZD6140. Cangrelor is an intravenous agent with a very short half-life (terminal half-life is 3 to 5 minutes). These properties allow for near-total inhibition of ADP-induced platelet aggregation within minutes of initiation of intravenous infusion as well as restoration of normal platelet aggregation within 1 hour after discontinuation.[76,77] In Phase II studies that compared cangrelor to the platelet GP IIb/IIIa inhibitor abciximab in subjects undergoing PCI, cangrelor provided potent inhibition of platelet aggregation; was well tolerated, with similar rates of bleeding and ischemic events; and was more rapid in offset.

The pharmacological features of rapid onset and offset may be particularly advantageous for use in the cardiac catheterization laboratory, where an inherent conflict for the physician is created by the need for pretreatment with clopidogrel to achieve optimal efficacy balanced by the concerns for bleeding associated with an irreversible drug effect if surgical coronary revascularization is required based on coronary anatomic considerations.

These 3 novel agents, prasugrel, AZD6140, and cangrelor, are in advanced stage testing for use in patients with coronary artery disease. Each of these medications has potential pharmacologic features that could be advantageous to patients with coronary disease when compared with clopidogrel, the current $P2Y_{12}$ standard of care. Whether or not these novel agents, which provide more consistent, rapid, and higher levels of platelet inhibition with differing rates of reversibility, prove to be more clinically efficacious in randomized clinical trials will be the subject of considerable interest over the coming years. In addition, the results of these trials will either validate or refute the hypothesis that inhibition of in vitro platelet aggregation is an important measure for predicting clinical outcomes.

Summary

In reviewing therapeutic goals for effective platelet inhibition, a number of summary statements can be made:

1. Combination (dual) antiplatelet therapy with aspirin and a thienopyridine is the optimal currently available combination following percutaneous coronary revascularization procedures (particularly stenting) and in patients who present with an acute coronary syndrome.
2. The baseline level of platelet reactivity prior to initiation of oral antiplatelet therapy (pretreatment) correlates directly with the level of reactivity measured following (post) treatment. Patients who manifest higher levels of pretreatment platelet aggregability, in general, demonstrate higher levels of post-treatment activity as well.[78]
3. Multiple studies suggest that pre-PCI and post-PCI platelet reactivity correlates directly with periprocedural and post-procedural adverse clinical outcomes. Preliminary data suggest that the level of post-clopidogrel platelet reactivity also correlates directly with the occurrence of adverse clinical outcomes following PCI.[55,57]
4. Individual variability in platelet inhibitory response to both aspirin and clopidogrel exists, but the prevalence of these phenomena is dependent on the definition(s) employed (clinical events vs pharmacodynamic testing) as well as the specific pharmacodynamic test methodologies used (eg, type and dose of agonist, specific threshold definition of nonresponsiveness employed).
5. Although the prevalence of clopidogrel "nonresponsiveness" can be reduced by increasing the dose of this medication (from a 300-mg to a 600-mg oral loading dose), nonresponsiveness cannot be eliminated and interindividual variability in response persists.
6. Patients defined as being resistant to the platelet inhibitory effects of aspirin (by platelet pharmacodynamic testing) may also manifest a diminished level of responsiveness to clopidogrel and a greater prevalence of clopidogrel "resistance."
7. Ongoing large-scale randomized clinical trials will better define the relationship between the level of in vitro (ex vivo) platelet inhibition by a specific therapeutic agent and the magnitude of clinical benefit observed following therapy.
8. Novel platelet inhibition therapies (prasugrel, AZD6140, cangrelor), which provide more rapid onset as well as greater magnitude and consistency of effect, are currently in clinical trials. The relative safety and efficacy of these agents remains to be determined. ■

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Main Points

- Aspirin, ticlopidine, clopidogrel, and glycoprotein (GP) inhibitors have been used for antiplatelet therapy in patients who present with acute coronary syndromes and following drug-eluting stent placement. Drawbacks of these approaches include a potential increase in hemorrhagic events, individual variability in response, and other gastrointestinal, hematologic, or hypersensitivity-related clinical side effects.
- Possible mechanisms for platelet resistance to antiplatelet drugs include poor bioavailability (non-compliance, underdosing, poor absorption, interference by other drugs), accelerated platelet turnover, single nucleotide polymorphisms, and/or pre-existent platelet hyperreactivity.
- Prasugrel, a novel thienopyridine, has more rapid onset and achieves higher levels of inhibition of adenosine diphosphate–induced platelet aggregation than clopidogrel.
- Subjects treated with AZD6140, the first drug in a new class of agents called *cyclopentyltriazolopyrimidines*, had similar rates of bleeding and a trend toward a lower rate of recurrent myocardial infarction than clopidogrel-treated patients. Dyspnea and nausea were more commonly observed following AZD6140 than with clopidogrel.
- In subjects undergoing percutaneous coronary intervention, cangrelor, a non-thienopyridine direct-acting $P2Y_{12}$ antagonist, provided potent inhibition of platelet aggregation; was well tolerated, with similar rates of bleeding and ischemic events; and was more rapid in offset as compared with abciximab, a platelet GP IIb/IIIa inhibitor.

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