Platelet Response in Acute Coronary Syndromes

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CONTINUING MEDICAL EDUCATION INFORMATION

Description

Atherothrombosis is the major cause of acute coronary syndromes (ACS) and cardiovascular death. Platelets play a substantial role in atherothrombosis, and therapy targeting platelets has the potential to improve outcomes from ACS. This supplement presents a practical and up-to-date overview of research on the management of patients with ACS. It is intended to increase knowledge of biologic platelet responses, cardiac assessment and diagnosis, and current therapeutic strategies, with the ultimate goal of improving the care of cardiac patients.

Objectives

Upon completing this activity, participants will be able to:
- Describe the role of platelets in thrombosis and the development of ACS
- Explain the association between platelet response and clinical outcomes in patients with ACS
- Discuss the properties and potential benefits and risks of novel antiplatelet therapies
- Apply the current American College of Cardiology/ American Heart Association practice guideline recommendations for antiplatelet therapy in patients with ACS.

Target Audience

Cardiologists, internists, primary care physicians, emergency medicine physicians, and other health professionals with an interest in acute coronary artery disease

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Importance of platelets and platelet response in acute coronary syndromes

ABSTRACT

Platelet activation is one of the essential steps in the genesis and propagation of atherothrombosis. Accumulating clinical evidence suggests that an elevated platelet count, platelet activation, and platelet hyperreactivity (defined as residual platelet activity despite antiplatelet drug therapy) may be associated with adverse cardiovascular events in patients with acute coronary syndromes. Platelet function can be analyzed using various assays and measures of platelet activation. The best assays for measuring residual platelet activity in the setting of antiplatelet therapy are still being defined, as are their predictive values. Platelet aggregation remains the gold standard, but other testing methods offer advantages for specific applications, such as detecting overall platelet hyperreactivity in the presence of antiplatelet therapy or detecting inhibition of the adenosine diphosphate receptor $P2Y_{12}$. Standard testing protocols for platelet aggregation are needed to achieve consistency among studies.

KEY POINTS

Platelet function assays are inherently variable because they measure cell function rather than a single analyte.

Screening tests, or global tests for platelet function, do not identify specific causes of platelet dysfunction but combine measurement of different aspects of platelet function.

There appears to be a subgroup of patients with stable cardiovascular disease who have an increased risk of major cardiac events associated with platelet hyperreactivity.

For predicting cardiac events, receiver operating characteristic (ROC) curve analysis should be used to objectively define cutoff values for platelet hyperreactivity as opposed to reliance on arbitrary cutoff values.

Platelets play a substantial role in atherothrombosis, and platelet activation is implicated in the genesis of acute coronary syndromes (ACS) (**Figure 1**). This review describes platelet function and the mechanisms behind platelet activation, the utility of laboratory tests of platelet function for assessing cardiovascular risk, and the role of platelets in various phases of atherosclerosis. Against this backdrop, the article concludes by reviewing current evidence on the association between platelet hyperreactivity—defined as residual platelet activity despite antiplatelet drug therapy—and ACS. Here and throughout this supplement, ACS is understood to comprise unstable angina and myocardial infarction (MI) with or without ST-segment elevation.

PLATELET FUNCTION

Platelets are non-nucleated cells produced by megakaryocytes, which are very large cells (50 to 100 μm in diameter) found in bone marrow. The megakaryocyte surface membrane forms protoplatelet extensions from which platelets "bud off" and are emitted into the circulation, where they number approximately 200,000 to 400,000 per microliter of blood.

Platelet activation

Platelets play a crucial role in the vascular response to injury, and activation of platelets has long been recognized as an important step. Platelets release dense granules that contain the nucleotide adenosine diphosphate (ADP), which activates other platelets. They also possess alpha granules, which contain proteins and protein mediators (eg, platelet-derived growth factor, platelet factor 4) that are involved in inflammatory processes. The platelet surface is coated with hundreds of thousands of receptors for other cells, including activated vascular wall cells and extracellular matrix proteins. Platelets possess an affinity for adherence, especially to injured vessel walls, where they release their granule contents and then aggregate. These properties promote platelets' involvement in many vascular processes, including ACS, as will be explored below.

Platelets exist in a nonactivated state and are

drawn passively into areas of vascular injury. Initially, they adhere to proteins such as von Willebrand factor, which is a large extracellular matrix protein produced by endothelial cells. The platelet glycoprotein Ib/IX/V binds to von Willebrand factor, forming a loose association that results in platelets rolling on the surface of the vessel wall. As a multimer, von Willebrand factor exists in one subunit that is dimerized and then polymerized, making it an ideal substrate for platelets because of the multiple substrates to which platelets can adhere.

Platelets are then engaged through receptors for collagen (ie, glycoprotein Ia/IIa or integrin $\alpha_2\beta_1$) and glycoprotein VI, leading to intracellular signaling and activation of the platelets. Platelet activation is followed by firm adhesion through engagement of another integrin, the $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) receptor, on platelet surfaces for fibrinogen. The glycoprotein IIb/IIIa receptor is involved in a homotypic platelet–platelet interaction with an $\alpha_{IIb}\beta_3$ receptor on another platelet, which attracts further platelets and results in platelet–platelet adhesion, called platelet aggregation. This platelet cascade is depicted in **Figure 2**.

Platelet fibrinogen receptor

The platelet fibrinogen receptor (glycoprotein IIb/IIIa receptor) is an $\alpha_{IIb}\beta_3$ integrin that binds to arginine-glycine-aspartic acid (RGD) epitopes of proteins, such as fibrinogen. Fibrinogen has a two-dimensional symmetry, with RGD groups on both ends of the molecule, which makes it an ideal molecule for linking platelet to platelet.

von Willebrand factor has RGD groups, as do both fibronectin and glycoprotein IIb/IIIa vitronectin, and can therefore bind to many plasma and extracellular matrix proteins. The glycoprotein IIb/IIIa receptor is inactive in resting platelets. It becomes activated during the platelet activation process and binds to fibrinogen, which bridges to other platelets, causing aggregation.

ADP receptors

Various receptors on platelet surfaces are responsible for platelet activation. One is a family of receptors for ADP. As ADP is released from platelets, it can then activate other platelets by binding to the receptors. The ADP receptor $P2Y_{12}$ signals through G protein pathways and is coupled to adenylate cyclase, an enzyme that catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate (cAMP). High levels of cAMP inhibit platelet function; ADP binding to $P2Y_{12}$ shuts down adenylate cyclase, which leads to phosphoinositide 3-kinase activation and accelerated aggregation and platelet release.

A final notable factor in the mediation of platelet activation and aggregation is phospholipase A_2, which liberates arachidonic acid from the platelet membrane,

Platelet activation and hyperreactivity
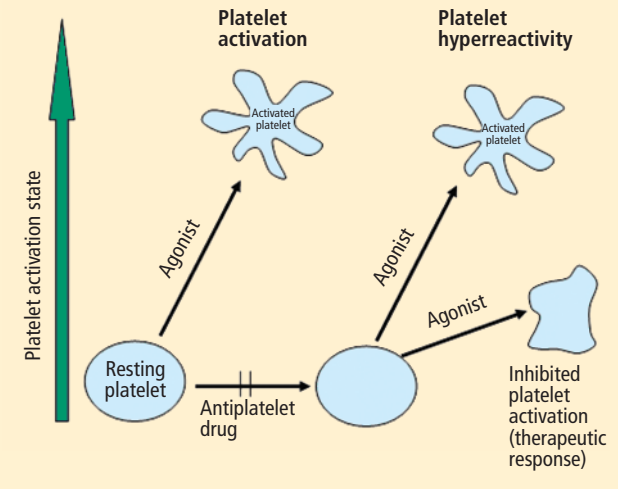
FIGURE 1. Resting platelets stimulated by an agonist become activated; the activated platelets can trigger intravascular thrombosis and inflammatory processes and have been implicated in atherogenesis and development of acute coronary syndromes. Antiplatelet drug therapy is designed to result in a therapeutic response due to inhibited or diminished platelet activation in response to agonists. There is increasing evidence, however, that preserved platelet activity despite the presence of antiplatelet drugs, or platelet hyperreactivity, may be associated with adverse cardiovascular events.

metabolizing it through cyclooxygenase and thromboxane synthase to generate thromboxane A_2, which leads to release of platelet granule contents and aggregation of other platelets.

■ PLATELET FUNCTION TESTS

Platelet function assays are inherently variable because they measure cell function rather than a single analyte. Several new platelet testing devices have come to market with the goal of ease of use; many can now be used at the bedside to measure platelet function.

Platelet count

In my view, the platelet count remains one of the best tests for assessing bleeding risk, as a low platelet count is one of the most common causes of bleeding. However, the platelet count is not a functional assay because it does not evaluate other platelet functions.

Screening tests

Screening tests, or global tests for platelet function, do not identify specific causes of platelet dysfunction but combine measurement of many different aspects of platelet function, such as adhesion, aggregation and granule release.

Bleeding time. The bleeding time is an archaic test because of the poor correlation between bleeding time and

Sequence of platelet activation and aggregation
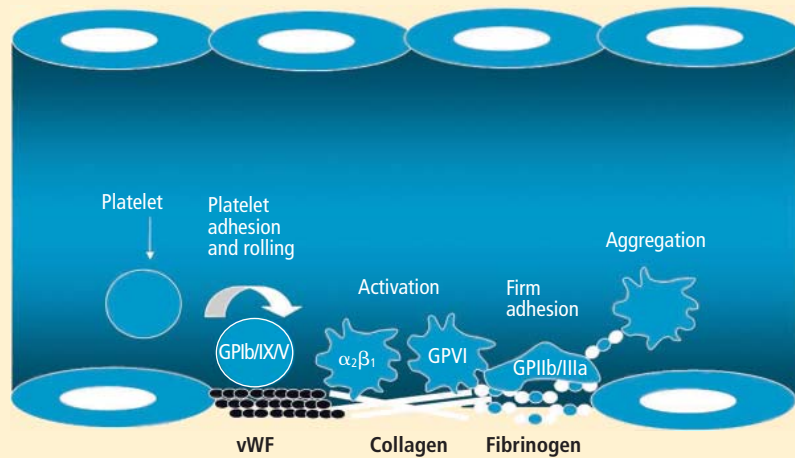
FIGURE 2. In the process of platelet activation, unactivated circulating platelets initially encounter an area of vascular injury and adhere rapidly to exposed von Willebrand factor (vWF) through the glycoprotein (GP) Ib/IX/V membrane receptor. Collagen in the extracellular matrix is also engaged through receptors $\alpha_2\beta_1$ (GPIa/IIa) and GPVI, leading to platelet shape change and activation. Cell signaling results in conformational change in the fibrinogen receptor GPIIb/IIIa ($\alpha_{IIb}\beta_3$), with binding to fibrinogen and fibrin leading to platelet aggregation and thrombus formation.

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bleeding disorders or thrombotic disorders. Its utility in measuring platelet function is therefore highly limited.

PFA-100. The PFA-100 Platelet Function Analyzer system (PFA-100) is one example of a global platelet function assay that measures multiple platelet functions, including platelet adhesion and aggregation. The instrument, which is about the size of a bread box, uses a citrate-anticoagulated whole blood specimen to measure platelet reaction in a high-shear environment. Blood travels at high shear rates through membranes coated with either collagen and ADP or collagen and epinephrine (epinephrine receptors exist on platelet surfaces). Platelets adhere to the membranes and then activate, aggregate, and occlude a small aperture in the center of each membrane, yielding a measurable closure time.

Since the PFA-100 was developed before the availability of the thienopyridine antiplatelet drugs, its utility lies not in monitoring the effects of those agents but in its ability to detect aspirin-induced platelet dysfunction or intrinsic platelet function disorders. An abnormal epinephrine cartridge closure time in the presence of a normal ADP cartridge closure time indicates aspirin-induced platelet dysfunction. An abnormal closure time on both measures is indicative of von Willebrand disease or a platelet defect such as Glanzmann thrombasthenia or Bernard-Soulier syndrome.

Specific functional tests

Platelet aggregation. One of the most common methods of measuring platelet aggregation is called optical platelet aggregation. This technique, which is a high-complexity laboratory test, involves adding an aggregating agent (eg, ADP, epinephrine, thrombin, arachidonic acid) to platelet-rich plasma, a turbid platelet-rich suspension derived from whole blood. The effect of the aggregating agent on the suspension's light transmittance is then measured to assess platelet aggregation progress **(Figure 3)**.

Whole blood platelet aggregation is typically a high-complexity laboratory test. Recently, self-contained assay platforms that can measure whole blood aggregation have been developed. These are applicable for smaller hospitals and near-patient settings. One such rapid platelet function analyzer, known commercially as VerifyNow, offers point-of-care assessment of platelet function. The instrument, which is the size of a telephone answering machine, operates by a principle similar to that of optical platelet aggregation: platelet function is measured by the rate and extent of change in light transmittance in response to the introduction of agonists specific to various antiplatelet medications. Low light transmittance indicates a blood sample with inhibited platelet function; high light transmittance indicates normal platelet function.

Measurement of VASP phosphorylation. Vasodilator-stimulated phosphoprotein (VASP) is an intracellular platelet protein that is nonphosphorylated in basal state. The phosphorylation of VASP depends on the level of activation of the $P2Y_{12}$ receptor, a target of thienopyridine drugs. Thus, measuring VASP phosphorylation by flow cytometry using citrated whole blood can be a highly specific indicator of the action and efficacy of clopidogrel and other thienopyridine drugs.

A flow cytometry assay that measures VASP phosphorylation requires a whole blood sample that is incubated with ADP to measure what is called the platelet reactivity index. Adding ADP to whole blood stimulates adenylate cyclase, lowering cAMP and shutting off protein kinase, which results in low levels of VASP phosphorylation. Thus, if VASP is phosphorylated, the platelets are inhibited; if VASP is not phosphorylated, the platelets are acti-

vated. A satisfactory therapeutic response to clopidogrel or another thienopyridine drug produces a low platelet reactivity index, reflecting platelet inhibition.

■ ROLE OF PLATELETS IN ATHEROSCLEROSIS

Platelets serve major functions in three key aspects of atherosclerosis: atherogenesis, inflammation, and atherothrombosis.

Atherogenesis

Platelets play a pivotal role in atherogenesis.[1] They release matrix metalloproteinases that are involved in degrading the matrix in atherosclerotic plaques. Moreover, they contain and release chemokines and growth factors, including:

- RANTES, a chemokine that stimulates monocytes and T cells to increase the production of monocyte inflammatory mediators
- Platelet-derived growth factor, which stimulates the migration and proliferation of smooth muscle cells
- Transforming growth factor–β, which also stimulates proliferation of smooth muscle cells.

Inflammation

Activated platelets release inflammatory mediators and thereby change the adhesive and chemotactic properties of endothelial cells. Likewise, mediators derived from inflammatory cells (neutrophils) can affect platelet function.

Platelet-derived mediators include the following:
- Pro-interleukin (IL)-β, which triggers the synthesis of E-selectin that enables endothelial cells to interact with leukocytes
- Thromboxane A_2, which increases neutrophil adhesion to facilitate platelet aggregation
- Platelet-derived growth factor and platelet factor 4, which increase neutrophil chemotaxis (the ability of neutrophils to infiltrate atherosclerotic plaque)
- CD40 ligand, a protein expressed on platelets that induces inflammatory responses in the endothelium
- P-selectin, a cell adhesion molecule expressed on activated platelets that enhances the adhesion of monocytes on activated endothelial cells.

Among the neutrophil-derived mediators, some—such as superoxide and leukotrienes—enhance platelet activation, whereas elastases inhibit platelet activation.

Overall, once inflammation begins in an atherosclerotic plaque, much reciprocal platelet activation can occur, so that the inflammatory process can become a feed-forward loop to eventually promote atherothrombosis.

Atherothrombosis

In the last stage of the atherosclerotic process, platelet enzymes that degrade the matrix may make plaques vulnerable to rupture by creating fissures in the fibrous
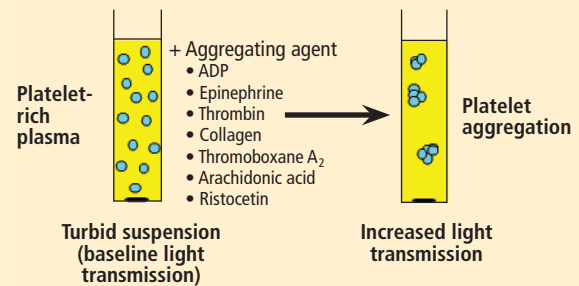
FIGURE 3. Optical platelet aggregation involves introduction of an aggregating agent to platelet-rich plasma to assess its effect on light transmission. The greater the increase in light transmission, the greater the platelet aggregation.

plaque cap. This exposes the lipid-rich core, which contains a significant amount of thromboplastin. Exposure to the extracellular matrix can lead to further platelet adhesion, activation, and aggregation. The development of a platelet thrombus is usually one of the ultimate steps in atherothrombosis leading to ACS, including MI.

■ ROLE OF PLATELETS IN ACUTE CORONARY SYNDROMES: WHAT IS THE EVIDENCE?

How predictive is an elevated platelet count?

Evidence suggests that a simple elevated platelet count may predict adverse outcomes following ACS. Among 10,793 patients with ST-segment-elevation MI in the Thrombolysis in Myocardial Infarction (TIMI) trials database, higher platelet counts on presentation were associated with higher rates of death, reinfarction, and development of congestive heart failure at 30 days **(Figure 4)**.[2] In subsequent follow-up, a greater decrease in platelet counts after MI was associated with an increased risk of reinfarction.[2]

However, another study conducted in a slightly different population—1,616 patients with non-ST-segment-elevation MI/unstable angina—found no correlation between platelet count (by quintiles) and death at 60 months.[3] The lowest mortality was observed in patients with a platelet count in the second-lowest quintile, although the highest mortality was indeed observed in the quintile of patients with the lowest platelet counts.[3]

The differing results in the above two studies suggest that additional platelet factors, beyond platelet count, contribute to the risk of adverse outcomes following ACS.

Platelet hyperreactivity and outcomes in ACS

Platelet hyperreactivity—ie, residual platelet activity despite antiplatelet therapy—appears to be involved

Higher platelet count associated with adverse outcomes in ST-elevation MI

FIGURE 4. Higher platelet counts were associated with adverse outcomes at 30 days among 10,793 patients with ST-segment-elevation myocardial infarction (MI) in the Thrombolysis In Myocardial Infarction (TIMI) trials database.[2]

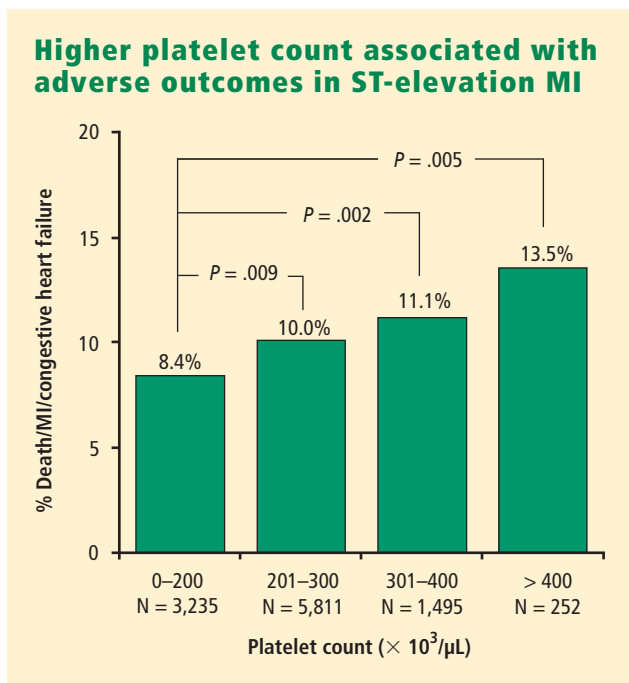Reprinted from *American Journal of Cardiology* (Ly HQ, et al. Association of platelet counts on presentation and clinical outcomes in ST-elevation myocardial infarction. Am J Cardiol 2006; 98:1–5), Copyright © 2006, with permission from Elsevier. www.sciencedirect.com/science/journal/00029149

in the spectrum of ACS. A recent study evaluated the association between hyperreactivity of platelets to ADP and outcomes in 600 patients with stable cardiovascular disease who were on aspirin therapy.[4] Hyperreactivity was defined as a collagen/ADP closure time of less than 90 seconds on the PFA-100 system (short collagen/ADP closure time). On receiver operating characteristic (ROC) curve analysis, a short collagen/ADP closure time served as a significant predictor of recurrent events (relative risk [RR] = 3.65; 95% CI, 1.76–7.57) and death (RR = 6.56; 95% CI, 1.93–22.35) compared with a closure time of 90 seconds or greater. The authors concluded that there appears to be a subgroup of patients with stable cardiovascular disease who have an increased risk of major adverse events associated with platelet hyperreactivity.[4]

An earlier study by Harrison et al assessed platelet function using the PFA-100 in 78 patients presenting with acute chest pain classified as MI, unstable angina, or nonspecific chest pain.[5] Using the PFA-100, they found shorter collagen/ADP closure times and higher levels of von Willebrand factor in subjects with MI compared with those who had unstable angina or nonspecific chest pain.[5] Fuchs et al reported a similar association between

von Willebrand factor and outcomes in 208 patients with ACS,[6] raising the possibility that von Willebrand factor, through its association with increased platelet adhesion and activation, may be a major contributor to risk in ACS.

Similarly, an association between platelet hyperreactivity and cardiovascular events has been suggested in patients with type 2 diabetes. In a 2007 study of 173 patients with type 2 diabetes and coronary artery disease receiving dual antiplatelet therapy (aspirin plus clopidogrel), the 2-year risk of major cardiovascular events was significantly higher in those in the highest quartile of platelet aggregation compared with those in the lower three quartiles (hazard ratio = 3.35; 95% CI, 1.68–6.66).[7] In a separate study, Serebruany et al measured platelet activity by five different testing methods in 822 patients with coronary artery disease and found significantly higher platelet hyperreactivity by all methods in those patients who had diabetes (n = 257) than in those who did not (n = 565).[8]

Marcucci et al recently examined the relationship between clinical characteristics and residual platelet activity in 386 patients with ACS on dual antiplatelet therapy (aspirin plus clopidogrel).[9] The presence of residual platelet activity (determined by platelet aggregation in response to the agonists arachidonic acid and ADP, as well as by the PFA-100) was associated with significantly higher inflammatory status, as determined by leukocyte count and erythrocyte sedimentation rate. The same association was observed among a subset of patients in this study undergoing percutaneous coronary intervention (PCI) who were receiving dual antiplatelet therapy; additionally, residual platelet activity was associated with a significantly higher incidence of diabetes and a significantly lower ejection fraction in this subset.[9]

Platelet hyperreactivity while on dual antiplatelet therapy (aspirin plus clopidogrel) was also found to be predictive of clinical outcome in a study of 195 patients with non-ST-elevation MI undergoing PCI.[10] Hyporesponse to antiplatelet therapy, as measured by a high VASP platelet reactivity index (PRI), predicted an increased risk of recurrent ischemic events within 30 days of PCI. Using ROC curve analysis, the investigators found that a VASP PRI cutoff value of 53% (ie, a high PRI [> 53%] indicates residual platelet activity despite clopidogrel) had a sensitivity of 93%, a specificity of 50%, a positive predictive value of 12%, and a negative predictive value of 99% for ischemic events.[10] Similarly, among 144 patients undergoing PCI assessed for decreased platelet reactivity to a loading dose of clopidogrel, Bonello et al also found that a VASP PRI greater than 50% was optimal for predicting major adverse cardiovascular events: all 21 events in the study

occurred among patients whose VASP PRI was in the highest four quintiles.[11]

■ CONCLUSIONS AND GENERAL ASSESSMENT OF PLATELET FUNCTION TESTS

Platelets clearly are involved in the pathogenesis of atherothrombosis. Accumulating evidence suggests that both an elevated platelet count and platelet hyperreactivity (residual platelet activity despite dual antiplatelet therapy) may be associated with adverse cardiovascular events in patients with ACS.

Platelet function can be measured using several different assays and measures of platelet activation. The best assays for measuring residual platelet activity in the setting of antiplatelet therapy are still being defined, as are their predictive values. Platelet aggregation remains the gold standard. The PFA-100 may detect overall platelet hyperreactivity despite the use of antiplatelet therapy, and is attracting increasing use for this purpose. VASP phosphorylation may be a good assay for detecting $P2Y_{12}$ inhibition but is limited to thienopyridines in terms of detecting platelet hyperreactivity. For predicting adverse cardiac events, ROC curve analysis should be used to objectively define cutoff values for platelet hyperreactivity as opposed to reliance on arbitrarily defined cutoff values.

Moving forward, standard testing protocols for platelet aggregation clearly are needed to achieve consistency among studies.

■ DISCLOSURES

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Novel antiplatelet strategies in acute coronary syndromes

◼ ABSTRACT

Antiplatelet therapies for the treatment of acute coronary syndromes (ACS) act to interrupt various pathways of platelet activation. Clopidogrel, an established thienopyridine antiplatelet medication, inhibits adenosine diphosphate (ADP)–induced platelet aggregation to a modest degree and with wide variability in platelet response. Accumulating data suggest that a 600-mg loading dose of clopidogrel may help overcome the suboptimal response to the standard 300-mg dose seen in some patients. Prasugrel is a third-generation investigational thienopyridine that demonstrates more potent inhibition of platelet aggregation and more consistent platelet response compared with standard- and high-dose clopidogrel. A large clinical trial showed prasugrel to be superior to standard-dose clopidogrel in reducing ischemic events in patients with ACS scheduled for percutaneous coronary intervention, although prasugrel was associated with a significantly higher risk of major bleeding events. Other investigational antiplatelet agents also display more potent and consistent inhibition of platelet aggregation than is seen with clopidogrel. These include AZD6140, a reversible ADP receptor blocker; cangrelor, a rapidly acting intravenous ADP receptor blocker; and the thrombin receptor antagonist SCH 530348.

◼ KEY POINTS

There is substantial interpatient variability in the response to clopidogrel.

In the large TRITON-TIMI 38 trial, the composite rate of death, myocardial infarction, or stroke was reduced by 19% and the rate of stent thrombosis was halved in patients receiving prasugrel compared with standard-dose clopidogrel.

The risk of major bleeding with prasugrel is highest in patients aged 75 or older, those weighing less than 60 kg, and those with a history of stroke or transient ischemic attack.

Thrombin receptor antagonists are being studied to see if their use can reduce ischemic events without increasing bleeding.

An enhanced understanding of platelet biology, as reviewed in the previous article in this supplement, has made it possible to identify a wide variety of platelet agonists. This knowledge has fostered the development of a host of pharmacologic strategies to block agonists such as cyclooxygenase, thromboxane, adenosine diphosphate (ADP), and thrombin, among others. This article will discuss the pharmacologic properties of novel antiplatelet agents, as well as alternative dosing of the established antiplatelet agent clopidogrel, and will review data from available comparative and placebo-controlled trials of these agents. The article concludes with comparative perspectives on the potential roles and relative advantages of these agents in the evolving management of patients with acute coronary syndromes (ACS).

◼ CLOPIDOGREL AND THE CHALLENGE OF VARIABLE RESPONSE

Clopidogrel, a member of the thienopyridine class of ADP receptor inhibitors, is well established for use in patients with ACS at a loading dose of 300 mg followed by a maintenance dose of 75 mg/day. At this loading dose, inhibition of platelet aggregation to ADP is approximately 30%, and the time to peak effect is approximately 4 to 6 hours.[1]

As with most other drugs, the response to clopidogrel is variable. However, in contrast to the accepted measures of response to antihypertensive or lipid-lowering drugs, there are no routinely used tests for measuring response to antiplatelet therapies. As a result, a "one size fits all" strategy in the dosing of clopidogrel has prevailed.

The variability in platelet responsiveness to clopidogrel was assessed in 544 individuals in whom platelet aggregation to 5 μmol of ADP was measured.[2] The pattern of response to ADP produced a bell-shaped distribution with wide variability (**Figure 1**).

This variability in response is clinically relevant. In a study assessing clopidogrel responsiveness by ADP-induced platelet aggregation in 60 patients who experienced ST-segment-elevation myocardial infarction (MI), Matetzky et al found that the lowest levels of clopidogrel responsiveness were associated with a sig-

nificantly elevated rate (P = .007) of recurrent cardiovascular events 6 months after the MI.[3] Gurbel et al found a similar association between clopidogrel responsiveness and subacute stent thrombosis in a study of 120 patients using two different methods—light transmission aggregotomy to 5 μmol/L of ADP, and the ratio of vasodilator-stimulated phosphoprotein reactivity—to assess clopidogrel responsiveness.[4]

Increasing the loading dose raises response rates

One proposed method for boosting responsiveness to clopidogrel in suboptimal responders is the use of a higher dose. In a study of 190 patients undergoing coronary stenting, increasing the loading dose from 300 mg to 600 mg reduced the rate of clopidogrel resistance (defined as a < 10% absolute change in aggregation to 5 μM of ADP at 24 hours) from 28% to 8% (P < .001),[5] a finding that supports the notion of enhanced response at doses up to 600 mg. Single loading doses in excess of 600 mg yield diminishing returns in terms of platelet inhibition, most likely as a result of clopidogrel pharmacokinetics.[6]

Compared with 300 mg of clopidogrel, the more potent platelet inhibitory effect of a 600-mg dose translated to a two-thirds reduction (P = .041) in the composite end point of death, MI, or target vessel revascularization at 30 days in a study of 255 patients with stable coronary artery disease undergoing percutaneous coronary intervention (PCI).[7] The reduction in this composite end point with high-dose clopidogrel was driven by a reduction in the incidence of periprocedural MI.

In a separate study of 292 patients with non-ST-segment-elevation ACS who were scheduled for PCI, the superior platelet response to 600 mg versus 300 mg of clopidogrel translated to a 60% reduction in adverse thrombotic events (P = .02), and this benefit extended beyond rates of periprocedural MI.[8]

Similar results with increased maintenance dose

Similarly, emerging data suggest that raising the maintenance dose of clopidogrel can also raise response rates. In a study of 60 patients, doubling the maintenance dose of clopidogrel after PCI from 75 mg/day to 150 mg/day resulted in improved platelet inhibition as assessed by rapid platelet function analysis.[9] Likewise, a 150-mg/day maintenance dose of clopidogrel was associated with a superior antiplatelet effect compared with 75 mg/day in a study of 40 patients with type 2 diabetes.[10]

Large definitive trial is under way

In the wake of these smaller trials, a large randomized trial known as CURRENT is comparing a strategy of high-dose clopidogrel with standard-dose clopidogrel in patients with ACS for whom an early invasive management strategy is planned.[11] The high-dose regimen

Wide variability in platelet response to clopidogrel
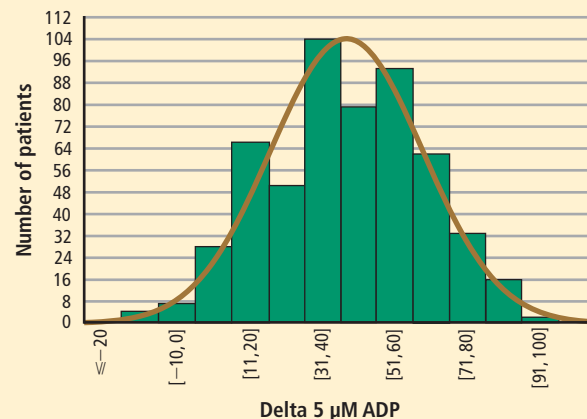
FIGURE 1. Platelet response to clopidogrel, as measured by platelet aggregation in response to 5 μmol of adenosine diphosphate (ADP), follows a bell-shaped distribution with wide variability. Results are among 544 individuals.[2]

Reprinted from *Journal of the American College of Cardiology* (Serebruany VL, et al. Variability in platelet responsiveness to clopidogrel among 544 individuals. J Am Coll Cardiol 2005; 45:246–251), Copyright © 2005, with permission from Elsevier. www.sciencedirect.com/science/journal/07351097

involves a 600-mg loading dose followed by 150 mg/day for 1 week and then 75 mg/day for 3 weeks, whereas the standard-dose regimen involves a 300-mg loading dose followed by 75 mg/day for 4 weeks. Both groups are being further randomized to low-dose aspirin (75 to 100 mg/day) or high-dose aspirin (300 to 325 mg/day) for 30 days after PCI. With a target enrollment well beyond 10,000 patients, CURRENT should definitively clarify the relative efficacy and safety of high-dose clopidogrel in this setting.

Tailoring clopidogrel therapy

Investigators have explored tailoring the dosing of clopidogrel around the time of PCI based on the degree of platelet inhibition. In one study, administering additional loading doses of clopidogrel, up to a total of 2,400 mg, before PCI in patients with a suboptimal degree of platelet inhibition resulted in a lower rate of ischemic complications following PCI.[12]

■ PRASUGREL, A NOVEL THIENOPYRIDINE

Prasugrel is an investigational third-generation thienopyridine currently under US Food and Drug Administration (FDA) review for use in patients with ACS being managed with PCI. Like clopidogrel, prasugrel is a prodrug that requires conversion to an active metabolite prior to binding to the platelet $P2Y_{12}$ receptor for ADP to confer antiplatelet activity. Prasugrel is metabolized more efficiently than clopidogrel, allowing for faster activation

and superior bioavailability to produce a greater and more consistent antiplatelet effect.[1,13]

The active metabolites of clopidogrel and prasugrel are no different in their ability to inhibit platelet aggregation, but approximately 85% of clopidogrel is inactivated by esterases, with the remaining 15% being converted to the active metabolite using the cytochrome P450 pathway via two successive oxidative steps in the liver.[14] In contrast, esterases facilitate the transformation of prasugrel to its active metabolite.[14] This activation requires only one oxidative step that can occur in either the liver or the gut through cytochrome P450.

Both prasugrel and clopidogrel are irreversible $P2Y_{12}$ receptor blockers. For this reason, one must wait approximately 5 days after the last dose of either medication for generation of a sufficient number of new platelets to allow restoration of normal platelet-mediated hemostasis.

Inhibition of platelet aggregation relative to clopidogrel

In a study among healthy volunteers, inhibition of platelet aggregation was significantly higher after a 60-mg loading dose of prasugrel compared with a 300-mg loading dose of clopidogrel.[13] Further, suboptimal responders to clopidogrel who crossed over to prasugrel had levels of platelet inhibition as high as 80% following prasugrel administration. The time to peak effect of prasugrel was about 1 hour. Inhibition of platelet aggregation was more consistent following dosing of prasugrel compared with clopidogrel.[13]

In a study of 201 patients undergoing cardiac catheterization with planned PCI, Wiviott et al demonstrated better levels of inhibition of platelet aggregation at 6 hours after a 60-mg loading dose of prasugrel than after a 600-mg loading dose of clopidogrel ($P < .0001$).[1]

Clinical effects relative to clopidogrel: TRITON-TIMI 38

A large phase 3 clinical trial—the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38—was conducted to compare the effects of prasugrel and standard-dose clopidogrel on death and ischemic end points in 13,608 patients with ACS scheduled to undergo PCI.[15] Patients randomized to clopidogrel were given the standard regimen of a 300-mg loading dose followed by a 75-mg daily maintenance dose; those randomized to prasugrel were given a 60-mg loading dose followed by a 10-mg daily maintenance dose. The study drug was typically given immediately before PCI, a time frame that may mimic real-life use but that favored the faster-onset prasugrel over the slower-onset clopidogrel. Both groups also received low-dose aspirin. Approximately half of the patients in each group were treated with a glycoprotein IIb/IIIa inhibitor. The median duration of therapy was approximately 15 months.

Efficacy. The primary end point—a composite of cardiovascular death, MI, or stroke—occurred in 9.9% of patients randomized to prasugrel compared with 12.1% of those randomized to clopidogrel, corresponding to a 19% relative risk reduction ($P = .0004$) with prasugrel. Based on these results, 46 patients would need to be treated with prasugrel rather than with clopidogrel to prevent 1 additional cardiovascular death, MI, or stroke.[15]

Prasugrel was associated with significant reductions in the occurrence of the primary end point during both the loading-dose phase ($P = .01$) and the maintenance-dose phase ($P = .003$). The event curves for prasugrel and clopidogrel continued to diverge with time **(Figure 2)**, suggesting that prasugrel's relative advantage in preventing ischemic events extends at least through 15 months.[15]

The reduction in the primary end point with prasugrel was driven primarily by a reduction in nonfatal MI; nonsignificant trends favored prasugrel over clopidogrel on rates of cardiovascular death and all-cause mortality, but there was no difference in stroke rates. Prasugrel's effect was consistent across subgroups based on MI type, sex, age, the type of stent used, adjunctive antithrombotic therapy, and renal function.[15]

In the subgroup of patients with diabetes, the relative reduction in the primary end point with prasugrel compared with clopidogrel was 30% ($P < .001$), and the respective relative reduction among patients with diabetes who required insulin was 37%.[16]

Safety. Higher antiplatelet potency carries the trade-off of increased bleeding, and this trade-off was apparent with prasugrel in TRITON-TIMI 38.[15] TIMI major bleeding (not counting bleeding related to coronary artery bypass graft surgery [CABG]) occurred significantly more often in prasugrel-treated subjects than in those receiving clopidogrel (2.4% vs 1.8%; $P = .03$), as did life-threatening bleeds (1.4% vs 0.9%; $P = .01$). Because absolute rates of major bleeding were low in each treatment group, based on these results, 167 patients would need to be treated with prasugrel rather than clopidogrel to result in 1 excess non-CABG-related major bleeding episode. Rates of intracranial hemorrhage were identical in the two treatment groups.[15]

Net clinical outcome and therapeutic considerations. Overall analysis of the balance of efficacy and safety in TRITON-TIMI 38 revealed that 138 events were prevented with randomization to prasugrel instead of clopidogrel, at a cost of 35 additional TIMI major bleeds **(Figure 2)**.[15]

In a post hoc analysis of net clinical outcome, in which major bleeding events were added to the primary composite efficacy end point, prasugrel was associated with a 13% relative risk reduction ($P = .004$).[15] Twenty-three MIs were prevented per 1,000 treated patients

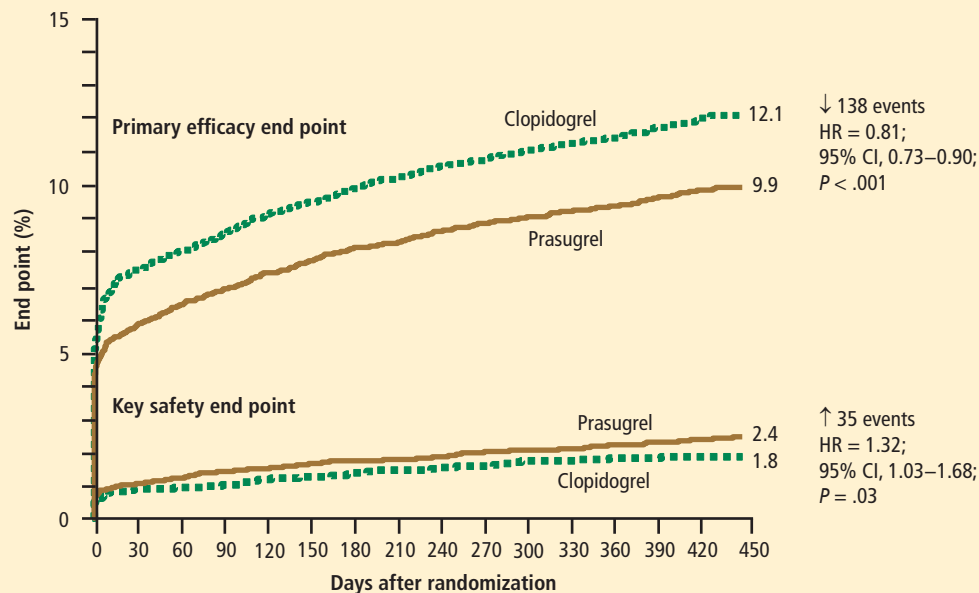## Balance of efficacy and safety in TRITON-TIMI 38 trial

FIGURE 2. Cumulative Kaplan-Meier estimates of the rates of the primary efficacy end point (composite of cardio-vascular death, myocardial infarction, or stroke) and the key safety end point (major bleeding not related to coronary artery bypass grafting) with clopidogrel and prasugrel in the 13,608-patient TRITON-TIMI 38 trial.[15]

with the use of prasugrel instead of clopidogrel, at a cost of 6 excess non-CABG-related major bleeds.[15]

Another post hoc assessment identified three subgroups who had a significantly increased risk of TIMI major bleeds with randomization to prasugrel[15]:

- Patients aged 75 years or older
- Patients with a body weight less than 60 kg
- Patients with a history of stroke or transient ischemic attack (TIA).

In these three subgroups, the net clinical effect either was neutral (for those aged ≥ 75 years and for those weighing < 60 kg) or favored clopidogrel (for those with a history of stroke or TIA). The group with a history of stroke or TIA represented 4% of the entire cohort, and the TRITON-TIMI 38 investigators recommended avoiding prasugrel in patients with a history of these events. The other two subgroups with a significantly increased bleeding risk with prasugrel represented 16% of the entire cohort, and in these two groups the investigators suggested a pharmacokinetics-guided reduction in the maintenance dose of prasugrel, although a recommendation for such dosing is based on modeling and not actual outcomes data.[15]

Stent thrombosis. A subanalysis of TRITON-TIMI 38 examined the risk of stent thrombosis in the 12,844 patients enrolled in the trial who had stents implanted.[17] Stent thrombosis was assessed using the Academic Research Consortium definitions of definite, probable, and possible stent thrombosis.[18] The risk of definite or probable stent thrombosis was halved (hazard ratio

= 0.48; $P < .0001$) with the use of prasugrel compared with clopidogrel, and the reduction was highly significant regardless of the type of stent implanted or the way stent thrombosis was defined. Significant reductions in both early (within the first 30 days) stent thrombosis ($P < .0001$) and late (beyond 30 days) stent thrombosis ($P = .03$) were observed in the prasugrel arm compared with the clopidogrel arm.[17]

■ AZD6140, A REVERSIBLE P2Y$_{12}$ RECEPTOR ANTAGONIST

AZD6140, another investigational antiplatelet agent, is an orally active reversible P2Y$_{12}$ receptor antagonist, in contrast to the thienopyridines, which are irreversible inhibitors. A member of the cyclo-pentyl-triazolo-pyrimidine (CPTP) class, AZD6140 has a rapid onset of action (≤ 2 hours) and does not require metabolic activation. Its plasma half-life is approximately 12 hours, which translates to twice-daily dosing.

Inhibition of platelet aggregation relative to clopidogrel

In a study of clopidogrel-naïve patients with ACS, inhibition of platelet aggregation 12 hours after administration of AZD6140 was approximately 75% with 90-mg, 180-mg, and 270-mg doses, significantly greater than the 30% inhibition achieved after administration of 300 mg of clopidogrel ($P < .0002$ for all doses of AZD6140 vs clopidogrel).[19] Whereas steady state was achieved in approximately 4 to 6 hours with clopidogrel, it was achieved in approximately 2 hours or less with AZD6140.

Clinical safety and efficacy relative to clopidogrel

In a dose-ranging study of AZD6140, adjudicated bleeding rates were similar among two different doses of AZD6140 (90 mg twice daily and 180 mg twice daily) and clopidogrel 75 mg once daily, with no evidence of a dose effect for major bleeding with AZD6140.[20] Although this study, conducted in 990 patients with ACS, was underpowered for efficacy end points, rates of adjudicated MI were numerically lower in each of the AZD6140 groups than in the clopidogrel group.

A more definitive evaluation of the relative effcicacy and safety of AZD6140 is expected from the ongoing PLATO trial, which is comparing 90 mg of AZD6140 twice daily with clopidogrel 75 mg/day among 18,000 patients randomized to one of the two treatments within 24 hours of an index ACS event.[21]

■ CANGRELOR, A RAPID PARENTERAL P2Y$_{12}$ RECEPTOR ANTAGONIST

Cangrelor (formerly known as AR-C69931MX) is an intravenously (IV) administered P2Y$_{12}$ receptor antagonist under investigation for treatment of ACS and use during PCI and other coronary procedures. The compound is an adenosine triphosphate analogue with a plasma half-life of 5 to 9 minutes. Cangrelor is highly reversible, as platelet function returns to normal within 20 minutes of dosing. Within 15 minutes of initiation, cangrelor produces profound platelet inhibition and rapidly achieves steady state; peak effect occurs within minutes.[22] The response to cangrelor is highly consistent, with virtually all recipients achieving the same degree of platelet inhibition. Platelet response approaches baseline 15 minutes after termination.[22]

If approved by the FDA, cangrelor would be administered similar to the way that glycoprotein IIb/IIIa inhibitors are, as it would be used primarily in the catheterization laboratory and then discontinued after the procedure, at which point transition to a long-term oral therapy would be necessary.

Clinical effects relative to abciximab

Cangrelor has been compared with the glycoprotein IIb/IIIa inhibitor abciximab and placebo in 249 patients undergoing elective or urgent PCI.[22] Rates of the combined end point of death, MI, or need for repeat revascularization at 30 days were similar with cangrelor and abciximab (5.7% vs 5.4%, respectively; P = NS), both of which were lower than the rate with placebo (10.0%). Major or minor bleeding through 7 days occurred in numerically fewer cangrelor recipients compared with abciximab recipients (7.0% vs 9.0%), although the small sample size precluded evaluation for statistical significance.

Clinical effects relative to clopidogrel— the CHAMPION trials

A phase 3 trial program consisting of two multinational studies of cangrelor—the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) program—is currently under way.

CHAMPION-PCI is enrolling 9,000 patients presenting with ACS who are being randomized in a double-blind fashion at the start of PCI to a 600-mg loading dose of clopidogrel or to cangrelor given as an IV bolus of 30 μg/kg followed by an IV infusion of 4 μg/kg/min. The primary end point is a composite of all-cause mortality, MI, or ischemia-driven revascularization in the 48 hours following randomization. Secondary end points include rates of all-cause mortality and MI at 48 hours.[23]

CHAMPION-PLATFORM is enrolling 4,400 patients scheduled for PCI as a result of ACS who are being randomized in a double-blind, double-dummy manner to (1) cangrelor bolus and infusion plus oral placebo or (2) oral clopidogrel plus placebo bolus and infusion before their index procedures. Dosages of the two agents are the same as in CHAMPION-PCI. The primary end point is a composite of death, MI, or urgent target vessel revascularization at 48 hours. Secondary end points include 30-day and 1-year clinical outcomes.[23]

The rationale for the CHAMPION investigations stems from the need to initiate clopidogrel before a patient is taken to the catheterization laboratory, owing to the inability to achieve a high degree of platelet inhibition until 4 to 6 hours after clopidogrel administration. Although this strategy can be undertaken without complication for most patients, a subset of patients with three-vessel disease or left-main disease will require CABG, which then must be delayed several days until clopidogrel's platelet-inhibiting effect diminishes. A rapid-acting IV inhibitor of the P2Y$_{12}$ receptor such as cangrelor would obviate this concern.

■ THROMBIN INHIBITORS

Thrombin plays an important role in platelet activation, and thrombin receptor antagonists may represent a safer means of inhibiting platelet activation relative to traditional antiplatelet agents. This theoretical safety advantage stems from the notion that blocking the action of platelets at the thrombin receptor would preserve platelets' function as mediators of primary hemostasis. Because thrombin's activation of platelets should occur only during clot formation, blocking platelet activation at the thrombin receptor would interrupt thrombin's ability to propagate platelet activation during formation of coronary artery clots.

One agent in this class that is being studied extensively is SCH 530348, an oral thrombin receptor antagonist with potent antiplatelet activity. Its peak antiplatelet potency is

TABLE 1

Pharmacologic properties of current and emerging antiplatelet agents

Drug	Inhibition of platelet aggregation to ADP*	Route	Time to peak effect	Consistency	Offset of action
Clopidogrel 300 mg	~ 30%	Oral	~ 4 hours	+	~ 5 days
Clopidogrel 600 mg	~ 40%	Oral	~ 4 hours	++	~ 5 days
Prasugrel 60 mg	75%–80%	Oral	1 hour	+++	~ 5 days
AZD6140 90 mg twice daily	75%–80%	Oral	1–2 hours	+++	1–2 days
Cangrelor	> 90%	Intravenous	Minutes	+++	20 minutes
SCH 530348 2.5 mg daily	(> 90% to TRAP)	Oral	With load: hours Without load: days	+++	Weeks

* Data from multiple studies; no head-to-head comparisons of novel agents.

ADP = adenosine diphosphate; TRAP = thrombin receptor antagonist peptide

achieved within hours when a loading dose is given, and within days without a loading dose. Wearing-off of the action of SCH 530348 takes weeks.[24]

Inhibition of platelet aggregation with thrombin receptor antagonists is measured in response to the thrombin receptor antagonist peptide (TRAP), not ADP. The proportion of subjects treated with SCH 530348 who achieve greater than 80% inhibition of platelet aggregation to 15 µM of TRAP ranges from 91% (with 0.5 mg of SCH 530348) to 100% (with 1.0 mg and 2.5 mg) at both 30 days and 60 days.[25]

Clinical effects in placebo-controlled trials

SCH 530348 was studied in the Thrombin Receptor Antagonist (TRA)–PCI trial, a dose-ranging study in which patients were randomized to one of three oral loading doses of the study drug (10 mg, 20 mg, or 40 mg) on top of a clopidogrel loading dose before undergoing cardiac catheterization for planned PCI; patients were then randomized to one of three maintenance doses of SCH 530348 (0.5 mg, 1.0 mg, or 2.5 mg) or placebo (depending on loading therapy) for 60 days.[25]

Among the 573 patients undergoing PCI , the rate of TIMI major or minor bleeding was not significantly higher with any dose of SCH 530348 compared with placebo,[25] supporting the hypothesis that thrombin receptor antagonism inhibits platelet aggregation without a significant increase in bleeding.

Although the TRA-PCI study was not powered to detect differences in clinical event rates, a reduction in the rate of major adverse cardiovascular events was observed in a dose-dependent manner with SCH 530348 compared with placebo in the PCI cohort.[25]

On the basis of the TRA-PCI trial, a pair of phase 3 trials of SCH 530348 have been launched—the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P-TIMI 50) study and the Thrombin Receptor Antagonist for Clinical Event Reduction in ACS (TRA-CER) study.

TRA 2°P-TIMI 50 is a multinational double-blind study enrolling 19,500 patients with prior MI or stroke or with existing peripheral arterial disease. Patients are being randomized to placebo plus standard medical care (including aspirin and clopidogrel) or to 2.5 mg of SCH 530348 once daily plus standard medical care. The primary end point is the composite of cardiovascular death, MI, urgent coronary revascularization, or stroke.[26]

TRA-CER is a multinational double-blind study with planned enrollment of 10,000 patients with non-ST-segment-elevation MI. Patients are being randomized to placebo plus standard medical care (including aspirin or clopidogrel) or to SCH 530348 (using the oral 40-mg loading dose and a maintenance dose of 2.5 mg once daily) plus standard medical care. The primary end point is the composite of cardiovascular death, MI, rehospitalization for ACS, urgent coronary revascularization, or stroke. The key secondary end point is the composite of cardiovascular death, MI, or stroke.[27]

■ COMPARATIVE CONSIDERATIONS

Table 1 provides an overview of the pharmacologic properties of the antiplatelet therapies reviewed here. While I would caution against making direct comparisons among agents across this table, in light of the wide variability in how platelet aggregation studies are conducted and the lack of head-to-head comparisons of novel agents, this table provides useful benchmarks for general comparison.

Inhibition of platelet aggregation

Clopidogrel achieves about 30% inhibition of platelet aggregation to ADP at its current FDA-approved loading dose of 300 mg and about 40% inhibition when its dose is doubled to 600 mg. These levels of inhibition are increased to 75% to 80% by clopidogrel's fellow thienopyridine prasugrel, and this increase is attributable to prasugrel's more efficient metabolism from prodrug to active metabolite. The reversible $P2Y_{12}$ receptor antagonist AZD6140 achieves a comparable 75% to 80% inhibition of platelet aggregation. The parenterally administered $P2Y_{12}$ receptor antagonist cangrelor achieves greater than 90% inhibition, as does the oral thrombin receptor antagonist SCH 530348, although the latter agent's inhibition is to the agonist TRAP rather than ADP.

Time to peak effect

The time to peak effect with clopidogrel is approximately 4 hours regardless of the loading dose used (300 mg or 600 mg); this is substantially reduced with all of the investigational agents except SCH 530348. The novel agents' reduced time to peak effect can offer advantages in speeding patients' readiness to undergo catheterization procedures. This is particularly true for the IV agent cangrelor, which achieves its peak effect within minutes, although the 1-hour to 2-hour time frame with oral agents prasugrel and AZD6140 also would usually obviate any need to delay catheterization.

Consistency of platelet response

Standard-dose clopidogrel has the least consistency of platelet response among the therapies reviewed. Although increasing the clopidogrel dose yields somewhat greater consistency in response, it is still lower than the very high degrees of consistency observed with all of the novel compounds, each of which appears to achieve the same degree of inhibition of aggregation in virtually all patients.

Offset of effect

Both of the thienopyridines—clopidogrel and prasugrel—have an offset of effect of about 5 days, which requires delay of surgery, if possible, for several days in patients taking these agents. This is not an issue for the reversible oral agent AZD6140, whose offset of action takes just 1 to 2 days. While this rapid wearing-off of effect translates to a potential advantage for AZD6140, it also poses the potential drawback that a missed dose or two may leave the patient exposed to the risk of a thrombotic event. Cangrelor's rapid offset of 20 minutes promotes its envisioned use as a catheterization lab–based medication like the glycoprotein IIb/IIIa inhibitors that can be started right before a PCI procedure and stopped immediately afterward. Because SCH 530348 has a very long half-life and thus a weeks-long washout

period, the practicality of its use may depend on the hypothesis that thrombin receptor antagonists do not interfere with primary hemostasis, which is supported by data to date but remains to be definitively confirmed.

■ CONCLUSIONS

Clopidogrel achieves modest platelet inhibition with wide variability in response. Higher doses of clopidogrel achieve modestly greater degrees of inhibition than standard doses, and appear to result in a decreased rate of ischemic events. Although higher doses of clopidogrel have been embraced by some clinicians, we await definitive phase 3 trial evidence of net benefit before making high-dose clopidogrel the new standard of care.

Compared with clopidogrel, the investigational thienopyridine prasugrel is a more potent and consistent blocker of the ADP receptor. It results in a decreased rate of ischemic events relative to clopidogrel, including a 50% reduction in the rate of stent thrombosis, but is associated with an increased rate of bleeding. If prasugrel is approved for marketing, its use should be avoided in patients with a history of stroke or TIA, and avoidance or dose adjustment may be necessary in patients aged 75 years or older and in patients weighing less than 60 kg.

Other novel antiplatelet agents being evaluated for use in patients with ACS—the reversible oral ADP receptor blocker AZD6140, the rapid-acting IV ADP receptor blocker cangrelor, and oral thrombin receptor antagonists—offer potential advantages that need to be examined in the context of large-scale clinical trials.

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The current state of antiplatelet therapy in acute coronary syndromes: The data and the real world

■ ABSTRACT

Managing antiplatelet therapy for patients with acute coronary syndromes (ACS) is complex, and current therapy options and approaches for these patients are suboptimal. Despite the use of available antiplatelet therapies—aspirin, clopidogrel, and the parenteral glycoprotein IIb/IIIa inhibitors—recurrence of ischemic events in patients with ACS continues to rise over time. Moreover, bleeding remains an important—and often underappreciated—risk with these therapies, and national registries demonstrate that dosing of antiplatelet therapies frequently strays from evidence-based guidelines. Recent quality-improvement initiatives developed in conjunction with national registries of patients with ACS promise to improve adherence to guidelines through hospital-specific performance reports. More evidence-based use of existing and emerging antiplatelet agents has the potential to improve both ischemic and bleeding outcomes in patients with ACS.

■ KEY POINTS

Recurrent ischemic events have been observed in all antiplatelet trials to date, in spite of the addition of more potent antiplatelet regimens.

There appears to be a gradient of benefit from dual antiplatelet therapy depending on patients' risk of thrombotic events (the greater the risk, the greater the benefit).

Local practice patterns in interventional therapy for ACS should be taken into consideration when applying results from clinical trials to clinical practice.

ACS patients who stand to benefit most from antiplatelet therapies also are at the greatest risk of bleeding from those therapies.

The importance of a tailored approach to antiplatelet therapy and dosing is becoming more widely recognized.

The final event leading to acute coronary syndromes (ACS) is spontaneous atherosclerotic plaque rupture. This event is analogous to the plaque rupture caused by percutaneous coronary intervention (PCI). Both events initiate a platelet response that starts with the adhesion of platelets to the vessel wall, followed by the activation and then aggregation of platelets.

The clinical consequences of intravascular platelet activation and aggregation are well known: death, myocardial infarction (MI), myocardial ischemia, and arrhythmias. In terms of health care burden, ACS is the primary or secondary diagnosis in 1.57 million hospitalizations annually in the United States—specifically, unstable angina or MI without ST-segment elevation in 1.24 million hospitalizations, and MI with ST-segment elevation in 330,000 hospitalizations.[1]

This real-world impact of ACS is tempered by the real-world use and effectiveness of our antiplatelet drug therapies, which is the focus of this article. I begin with a brief review of the evidence surrounding three major antiplatelet therapies used in ACS management—aspirin, clopidogrel, and the glycoprotein IIb/IIIa inhibitors. I then review the updated evidence-based guidelines for the use of antiplatelet therapies in ACS. I conclude with an overview of how US hospitals are actually using these therapies, with a focus on two particularly important challenges—bleeding risk and appropriate dosing—and on initiatives under way to bridge the gap between recommended antiplatelet therapy for ACS and actual clinical practice.

■ ANTIPLATELET THERAPY IN ACUTE CORONARY SYNDROMES

Aspirin
Although aspirin has long been the bedrock of antiplatelet therapy in patients with ACS, its effects on the heart are still being elucidated. Several placebo-controlled trials of aspirin, each with relatively few subjects, have been conducted in the setting of ACS without ST-segment elevation.[2–5] Although confidence intervals were wide, these studies showed a favorable effect of aspirin relative to placebo on the risk of death and nonfatal MI.

TABLE 1

Effect of antiplatelet therapy on vascular events in the Antithrombotic Trialists' Collaboration[6]

Patient population	Adjusted % of vascular events		P for difference	Mean follow-up (months)	Benefit per 1,000 pts (SE)
	Antiplatelet therapy	Control			
Prior myocardial infarction	13.5	17.0	< .0001	27	36 (5)
Acute myocardial infarction	10.4	14.2	< .0001	1	38 (5)
Prior transient ischemic attack/ cerebrovascular accident	17.8	21.4	< .0001	29	36 (6)
Acute cerebrovascular accident	8.2	9.1	.0009	0.7	9 (3)
Other high-risk patients	8.1	10.2	< .0001	22	22 (3)

The Antithrombotic Trialists' Collaboration systematically reviewed randomized trials designed to measure the effect of antiplatelet regimens (most commonly aspirin) on clinical outcomes compared with controls in subjects with acute or previous vascular disease or risk factors predisposing to vascular disease.[6] Relative to controls, antiplatelet therapy was associated with a reduction in the risk of vascular events in all populations studied, including patients with prior or acute events and those considered at high risk of vascular events (**Table 1**).[6] When the aspirin trials were analyzed separately in this meta-analysis, aspirin at dosages of 75 mg/day or greater was found to have a consistently favorable effect on vascular events. No dose response was observed at dosages greater than 75 mg/day, which supports the concept that aspirin achieves complete inhibition of the arachidonic acid pathway of platelet activation at low dosages.

Clopidogrel and dual antiplatelet therapy

CURE trial: prevention of recurrent events in patients with ACS. Dual antiplatelet therapy with the thienopyridine agent clopidogrel plus aspirin was investigated in patients presenting with ACS without ST-segment elevation in the landmark CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Events).[7] This study randomized 12,562 patients presenting within 24 hours of ACS symptom onset to either clopidogrel or placebo, in addition to aspirin, for 3 to 12 months. Clopidogrel was administered as a loading dose of 300 mg followed by a maintenance dosage of 75 mg/day. Randomization to clopidogrel was associated with a highly significant 20% relative reduction in the primary end point, a composite of cardiovascular death, MI, or stroke at 12 months (9.3% incidence with clopidogrel vs 11.4% with placebo; *P* = .00009). Despite this impressive reduction in ischemic events with clopidogrel, the cumulative event rate continued to increase over the course of

the 12-month trial in both study arms. This persistent recurrence of ischemic and thrombotic events has been observed in all antiplatelet trials to date, in spite of the addition of more potent antiplatelet regimens.

Two subanalyses of the CURE results yielded further insights. One analysis examined the timing of benefit from clopidogrel, finding that benefit emerged within 24 hours of treatment and continued consistently throughout the study's follow-up period (mean of 9 months), supporting the notion of both early and late benefit from more potent antiplatelet therapy in ACS.[8] A separate subgroup analysis found that the efficacy advantage of clopidogrel plus aspirin over aspirin alone was similar regardless of whether patients were managed medically or underwent revascularization (PCI or coronary artery bypass graft surgery [CABG]).[9]

CHARISMA trial: prevention of events in a broad at-risk population. Several years before the CURE trial, clopidogrel was initially evaluated as monotherapy in patients with prior ischemic events in the large randomized trial known as CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events), in which aspirin was the comparator.[10] Rates of the primary end point—a composite of vascular death, MI, or stroke—over a mean follow-up of 1.9 years were 5.3% in patients assigned to clopidogrel versus 5.8% in those assigned to aspirin, a relative reduction of 8.7% in favor of clopidogrel (*P* = .043).

The CAPRIE study set the stage for CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), which set out to determine whether dual antiplatelet therapy with clopidogrel plus aspirin conferred benefit over aspirin alone in a broad population of patients at high risk for atherothrombotic events.[11] No significant additive benefit was observed with dual antiplatelet therapy in the overall CHARISMA population in terms

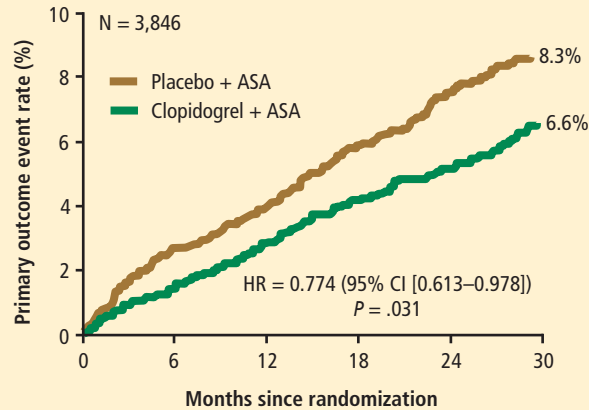## Dual antiplatelet therapy may particularly benefit patients with prior MI

FIGURE 1. A subanalysis of patients from the CHARISMA trial found that those with prior myocardial infarction (MI) experienced a 23% relative reduction in the composite end point of cardiovascular death, MI, or stroke with dual antiplatelet therapy (clopidogrel plus aspirin [ASA]) compared with aspirin alone over a median 27.6 months of follow-up.[12] The continued divergence of the event curves at the end of the follow-up period suggests that the benefits of dual antiplatelet therapy may be particularly enduring in this patient subgroup.

Reprinted from *Journal of the American College of Cardiology* (Bhatt DL, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007; 49:1982–1988), Copyright © 2007, with permission from Elsevier. www.sciencedirect.com/science/journal/07351097

of the composite end point of MI, stroke, or cardiovascular death over the median follow-up of 27.6 months.[11]

The investigators then analyzed outcomes in a large subgroup of the CHARISMA population—the 9,478 patients who had established vascular disease, ie, prior MI, stroke, or symptomatic peripheral arterial disease.[12] Rates of the composite end point (MI, stroke, or cardiovascular death) in this subgroup were 7.3% with clopidogrel plus aspirin versus 8.8% with aspirin alone, representing a 1.5% absolute reduction and a 17% relative reduction with dual antiplatelet therapy (*P* = .01). The CHARISMA investigators concluded that there appears to be a gradient of benefit from dual antiplatelet therapy depending on the patient's risk of thrombotic events.

Notably, this CHARISMA subanalysis showed that dual antiplatelet therapy conferred a 23% relative reduction in the composite end point specifically in the subset of patients with prior MI (n = 3,846) and found that the event curves for the two treatment groups continued to diverge over time in these patients throughout the median 27.6-month follow-up period **(Figure 1)**.[12] This finding suggests that long-term dual antiplatelet therapy may be of particular benefit in patients with prior MI.

Importance of longer-term therapy. Similarly, additional recent data indicate that interrupting clopidogrel therapy leads to an abrupt increase in risk among patients who experienced ACS months beforehand. Analysis of a large registry of medically treated patients and revascularized patients with ACS showed a clustering of adverse cardiovascular events in the first 90 days after clopidogrel discontinuation, an increase that was particularly pronounced in the medically treated patients.[13] Like the findings from the CHARISMA subanalysis above, these data suggest that continuing clopidogrel therapy beyond 1 year may be beneficial, although the ideal duration of therapy and the patient groups most likely to benefit requires further study.

Glycoprotein IIb/IIIa inhibitors

The glycoprotein IIb/IIIa inhibitors—abciximab, eptifibatide, and tirofiban—are parenteral drugs that block the final common pathway of platelet aggregation. With increased focus on the upstream inhibition of platelet activation and the wider availability of more potent oral antiplatelet drugs, the use of glycoprotein IIb/IIIa inhibitors has been declining in recent years.

Efficacy in ACS. A number of placebo-controlled trials of glycoprotein IIb/IIIa inhibitors have been conducted in the setting of ACS without ST-segment elevation. In each trial, the glycoprotein IIb/IIIa inhibitor was associated with a significant reduction in 30-day rates of a composite of death and nonfatal MI. A 2002 pooled analysis of these trials demonstrated an overall 8% relative risk reduction in this end point with active glycoprotein IIb/IIIa inhibitor therapy (*P* = .037).[14] Interpreting the benefit of glycoprotein IIb/IIIa blockade in the setting of clopidogrel therapy, however, is more challenging since upstream use of clopidogrel was rare at the time these studies were performed.

An outlier in the aforementioned pooled analysis was the GUSTO IV-ACS study (Global Utilization of Strategies to open Occluded coronary arteries trial IV in Acute Coronary Syndromes), in which abciximab showed no significant benefit over placebo on the primary end point of death or MI at 30 days.[15] This study included 7,800 patients with ACS without ST-segment elevation who were being treated with aspirin and unfractionated or low-molecular-weight heparin and were then randomized to placebo or abciximab. Abciximab was given as a front-loaded bolus followed by an infusion lasting either 24 or 48 hours.

A trend toward higher all-cause mortality was observed with longer infusions of abciximab in the GUSTO IV-ACS trial.[15] A hypothesis emerged that a front-loaded regimen of abciximab is suitable for patients undergoing PCI, in whom platelet activation and the risk of adverse outcomes is greatest in the catheterization laboratory, but is less well suited for medically managed patients, in whom levels of platelet aggregation and risk are ongoing.

Timing of treatment. The optimal timing of glycoprotein IIb/IIIa inhibitor initiation remains controversial.

Boersma et al pooled data from three randomized placebo-controlled trials and stratified the results into outcomes before PCI and outcomes immediately following PCI.[16] Glycoprotein IIb/IIIa inhibition was associated with a 34% relative reduction in the risk of death or MI during 72 hours of medical management prior to PCI (P = .001) and an enhanced 41% relative reduction in this end point in the 48 hours following PCI when PCI was performed during administration of the study drug (P = .001). The investigators concluded that glycoprotein IIb/IIIa blockade should be initiated early after hospital admission and continued until after PCI in patients who undergo the procedure.

The effect of upstream glycoprotein IIb/IIIa inhibitor use was more ambiguous in the recent Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial of patients with ACS being managed invasively. At 1 year, upstream use—as compared with in-lab use—of glycoprotein IIb/IIIa inhibitors was associated with a reduction in the rate of ischemic events among patients treated with the direct thrombin inhibitor bivalirudin (17.4% vs 21.5%, respectively; P < .01) but not among patients treated with unfractionated heparin or low-molecular-weight heparin (17.2% vs 18.4%; P = .44).[17]

Ongoing clinical trial results may shed further light on the considerable clinical uncertainty that remains regarding the benefits of upstream glycoprotein IIb/IIIa inhibitor use in patients with ACS.

Enrollment has just been completed in a large randomized trial designed to prospectively assess the optimal timing of glycoprotein IIb/IIIa inhibitor initiation in patients with high-risk ACS without ST-segment elevation in whom an invasive strategy is planned no sooner than the next calendar day.[18] The study, known as EARLY-ACS, is randomizing patients to eptifibatide or placebo begun within 8 hours of hospital arrival, with provisional eptifibatide available in the catheterization laboratory. The primary end point is a 96-hour composite of all-cause mortality, nonfatal MI, recurrent ischemia requiring urgent revascularization, or need for thrombotic bailout with a glycoprotein IIb/IIIa inhibitor during PCI. Data should be available in 2009.

■ ANTIPLATELET THERAPY GUIDELINES IN NON-ST-ELEVATION ACUTE CORONARY SYNDROMES

In 2007, the American College of Cardiology (ACC) and American Heart Association (AHA) updated their joint guidelines for the use of antiplatelet therapy in the management of patients with unstable angina or MI without ST-segment elevation.[19] These guidelines incorporate a large degree of flexibility in the choice of antiplatelet therapy, which can make implementation of their recommendations challenging.

The guidelines contain classes of recommendations based on the magnitude of benefit (I, IIa, IIb, III) and

levels of evidence (A, B, C). Following here are key recommendations from the updated guidelines (bulleted and in italics, with the class and level of the recommendation noted in parentheses),[19] supplemented with additional commentary where appropriate.

Antiplatelet therapy: General recommendations

• *Aspirin should be given to all patients as soon as possible after presentation and continued indefinitely in patients not known to be intolerant of aspirin (class I, level A).*

• *Clopidogrel should be given to patients unable to take aspirin because of hypersensitivity or major gastrointestinal (GI) intolerance (class I, level A).*

This recommendation is based on data from the CURE trial[7] and the earlier CAPRIE study.[10] The clopidogrel regimen recommended is a 300-mg loading dose followed by a maintenance dosage of 75 mg/day. The incidence of aspirin intolerance is approximately 5%, depending on how intolerance is defined. A significant proportion of patients will stop aspirin because of GI upset or trivial bleeding, failing to understand the true benefits of aspirin. A much smaller subset—perhaps 1 in 1,000—has a true allergy to aspirin.

• *Patients with a history of GI bleeding with the use of either aspirin or clopidogrel should be prescribed a proton pump inhibitor or another drug that has been shown to minimize the risk of bleeding (class I, level B).*

Initial invasive strategy

• *For patients in whom an early invasive strategy is planned, therapy with either clopidogrel or a glycoprotein IIb/IIIa inhibitor should be started upstream (before diagnostic angiography) in addition to aspirin (class I, level A).*

This recommendation does not give preference to either agent because head-to-head comparisons of antiplatelet and antithrombotic therapies in this setting are not available.

• *Unless PCI is planned very shortly after presentation, either eptifibatide or tirofiban should be the glycoprotein IIb/IIIa inhibitor of choice; if there is no appreciable delay to angiography and PCI is planned, abciximab is indicated (class I, level B).*

This recommendation is based on findings of the GUSTO IV-ACS study.[15]

• *When an initial invasive strategy is selected, initiating therapy with both clopidogrel and a glycoprotein IIb/IIIa inhibitor is reasonable (class IIa, level B).*

Clearly, the guidelines offer some leeway to allow for different practice patterns in the use of an initial invasive strategy. In my practice, if a patient is high risk and has a low likelihood of early CABG, I use both clopidogrel and a glycoprotein IIb/IIIa inhibitor upstream (prior to going to the catheterization laboratory). If a patient has a reasonable likelihood of requiring CABG, I eliminate the thienopyridine and treat with a glycoprotein IIb/IIIa

inhibitor. If a patient is at increased risk of bleeding, I forgo the glycoprotein IIb/IIIa inhibitor in favor of clopidogrel.

• *In patients who are going to the catheterization laboratory, omitting a glycoprotein IIb/IIIa inhibitor upstream is reasonable if a loading dose of clopidogrel was given and the use of bivalirudin is planned (class IIa, level B).*

This recommendation takes into account the duration of clopidogrel's antiplatelet effect and recognizes the likely limited benefit of glycoprotein IIb/IIIa inhibitors in patients who proceed rapidly to the catheterization laboratory.

Initial conservative strategy

• *In patients being managed conservatively (ie, non-invasively), clopidogrel should be given as a loading dose of at least 300 mg followed by a maintenance dosage of at least 75 mg/day, in addition to aspirin and anticoagulant therapy as soon as possible, and continued for at least 1 month (class I, level A) and, ideally, up to 1 year (class I, level B).*

• *If patients who undergo an initial conservative management strategy have recurrent symptoms/ischemia, or if heart failure or serious arrhythmias develop, diagnostic angiography is recommended (class I, level A). Either a glycoprotein IIb/IIIa inhibitor (class I, level A) or clopidogrel (class I, level A) should be added to aspirin and anticoagulant therapy upstream (before angiography) in these patients (class I, level C).*

• *Patients classified as low risk based on stress testing should continue aspirin indefinitely (class I, level A). Clopidogrel should be continued for at least 1 month (class I, level A) and, ideally, up to 1 year (class I, level B). If a glycoprotein IIb/IIIa inhibitor had been started previously, it should be discontinued (class I, level A).*

• *Patients with coronary artery disease confirmed by angiography in whom a medical management strategy (rather than PCI) is selected should be continued on aspirin indefinitely (class I, level A). If clopidogrel has not already been started, a loading dose should be given (class I, level A). If started previously, glycoprotein IIb/IIIa inhibitor therapy should be discontinued (class I, level B).*

• *For patients managed medically without stenting, 75 to 162 mg/day of aspirin should be prescribed indefinitely (class I, level A), along with 75 mg/day of clopidogrel for at least 1 month (class I, level A) and, ideally, for up to 1 year (class I, level B).*

Antiplatelet guidelines for stenting

Antiplatelet therapy is more complicated in the setting of stenting.

• *For patients in whom bare metal stents are implanted, aspirin should be prescribed at a dosage of 162 to 325 mg/day for at least 1 month (class I, level B) and then continued indefinitely at 75 to 162 mg/day (class I, level A). In addition, 75 mg/day of clopidogrel should be continued for at least 1 month and, ideally, up to 1 year unless the patient is at increased risk of bleeding (in which case it should be given for at least 2 weeks) (class I, level B).*

• *For patients receiving drug-eluting stents, aspirin is recommended at a dosage of 162 to 325 mg/day for at least 3 months in those with a sirolimus-eluting stent and at least 6 months in those with a paclitaxel-eluting stent, after which it should be continued indefinitely at 75 to 162 mg/day (class I, level B). In addition, clopidogrel 75 mg/day is recommended for at least 12 months regardless of the type of drug-eluting stent (class I, level B).*

No mention is made of dual antiplatelet therapy beyond 1 year.

At my institution, Duke University Medical Center, patients are assessed carefully for their ability and willingness to adhere to extended antiplatelet therapy before drug-eluting stents are implanted. This assessment includes an evaluation of their insurance status, their history of adherence to other prescribed drug regimens, their education level, and the dispenser of their medications.

No guidance on concomitant anticoagulation

One omission in the current ACC/AHA guidelines is the lack of guidance for patients who require concomitant antiplatelet therapy and anticoagulation. Such guidance is needed, as many patients with ACS also have indications for long-term anticoagulation, such as atrial fibrillation or valvular heart disease requiring prosthetic valves. The ACC/AHA guidelines recommend simply that anticoagulation be added to patients' antiplatelet regimens.

■ HOW ARE WE DOING? APPLICATION OF GUIDELINES IN PRACTICE

No discussion of guidelines is complete without consideration of their implementation. Those interested in the use of antiplatelet therapy in ACS are fortunate to have the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry, a collaborative voluntary surveillance system launched in January 2007 to assess patient characteristics, treatment, and short-term outcomes in patients with ACS (MI with and without ST-segment elevation). In addition to the registry, ACTION offers guidance on measuring ACS outcomes and establishing programs for implementing evidence-based guideline recommendations in clinical practice, improving the quality and safety of ACS care, and potentially investigating novel quality-improvement methods.[20]

Findings from ACTION's first 12 months

In its first 12 months (January–December 2007), the ACTION Registry captured data from 31,036 ACS cases from several hundred US hospitals, according to the ACTION National Cardiovascular Data Registry Annual Report (personal communication from Matthew T. Roe, MD, September 2008). Data were collected at two time points: acutely (during the first 24 hours after presentation) and at hospital discharge. One caveat to interpreting data from the ACTION Registry is the voluntary and

retrospective reporting system on which it relies.

Intervention rates. Among patients with non-ST-segment MI in whom catheterization was not contraindicated, 85% underwent catheterization and 70% did so within 48 hours of presentation; 53% underwent PCI and 45% did so within 48 hours of presentation; and 13% underwent CABG. The median time to catheterization was 21 hours, and the median time to PCI was 19 hours.

Although many patients who go to the catheterization laboratory are managed invasively, many do not undergo PCI and are managed medically or with CABG following coronary angiography. The message, therefore, is that local practice patterns should be taken into consideration when results from clinical trials are applied to clinical practice.

Acute antiplatelet therapy. The 2007 ACTION Registry data showed that aspirin was used acutely (< 24 hours) in almost all patients in whom it was not contraindicated (97%), clopidogrel was used in 59%, and glycoprotein IIb/IIIa inhibitors were used in 44%. Given the ACC/AHA guidelines' strong endorsement (class I, level A) of clopidogrel in this setting, one would expect wider use of clopidogrel in this context. Moreover, this relatively low rate of clopidogrel use (59%) cannot be explained by use of glycoprotein IIb/IIIa inhibitors instead, since this rate comprises patients who received clopidogrel either with or without a concomitant glycoprotein IIb/IIIa inhibitor; only 12% of patients received a glycoprotein IIb/IIIa inhibitor without clopidogrel. In contrast, a full 28% of patients received neither clopidogrel nor a glycoprotein IIb/IIIa inhibitor, contrary to current ACC/AHA guideline recommendations.

Antiplatelet therapy at discharge. At discharge, 97% of ACTION Registry patients were being treated with aspirin and 73% with clopidogrel. Notably, the use of clopidogrel at discharge was highly correlated with overall management strategy: whereas it was used in 97% of patients undergoing PCI, it was used in only 53% of patients being managed medically and in 31% of those undergoing CABG. These findings are somewhat reassuring since they generally mirror the strength of evidence supporting clopidogrel use in these different settings.

◼ IMPORTANT REAL-WORLD CONSIDERATIONS: BLEEDING AND DOSING

Do not neglect bleeding risk

As antiplatelet therapy becomes more potent in an effort to reduce ischemic events, bleeding risk has become a concern. Major bleeding events occur in more than 10% of patients with ACS receiving antiplatelet therapy,[21] although lower rates have been reported in clinical trials in which carefully selected populations are enrolled.[7,14,22–24]

Major bleeding affects overall outcomes. Major bleeding has clinical significance. The Global Registry of Acute Coronary Events (GRACE), which analyzed
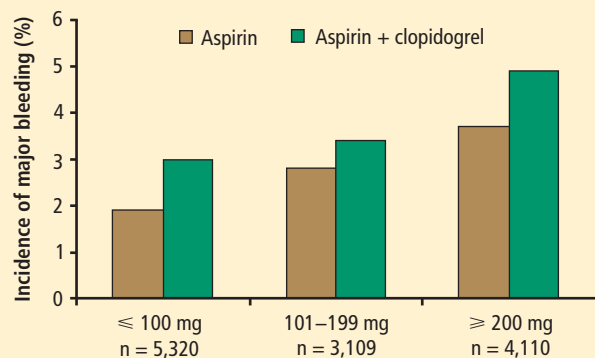

FIGURE 2. In the CURE trial of patients with acute coronary syndromes, the risk of major bleeding increased significantly with aspirin dose (x axis), with or without concomitant use of clopidogrel ($P < .001$ for trend across aspirin doses).[26]

Reprinted, with permission, from *Circulation* (Peters RJG, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes. Circulation 2003; 108:1682–1687), Copyright © 2003 American Heart Association. http://www.lww.com

data from 24,000 patients with ACS, revealed that major bleeding was associated with significantly worse outcomes: rates of in-hospital death were three times as high—15.3% versus 5.3%—in patients who had major bleeding episodes compared with those who did not (odds ratio = 1.64 [95% CI, 1.18–2.28]).[25] The relationship between bleeding and adverse overall outcomes is not fully understood but is nevertheless real and has been observed in multiple databases.

Risk factors for bleeding mirror those for ischemic events. Models are currently being developed to predict bleeding. Unfortunately, the factors that predict bleeding tend to also predict recurrent ischemic events. As a result, patients who stand to benefit most from antithrombotic therapies also are at the greatest risk of bleeding from those therapies.

Additive risk from dual antiplatelet therapy. The additional bleeding risk from adding clopidogrel to aspirin is often not fully appreciated. In the CURE trial, the absolute excess risk of major bleeding by adding clopidogrel to aspirin was 1% (3.7% vs 2.7%), which translates to a 35% relative increase compared with aspirin alone.[7] In that trial, major bleeding was most prevalent in patients undergoing CABG, and the rate of major bleeding was increased by more than 50% in patients receiving dual antiplatelet therapy when clopidogrel was discontinued 5 days or less before CABG (compared with CABG patients randomized to aspirin alone). This prompted the recommendation that clopidogrel be discontinued more than 5 days prior to CABG.

Similarly, the CHARISMA trial, which used the

Data dissemination may be driving improved dosing practices

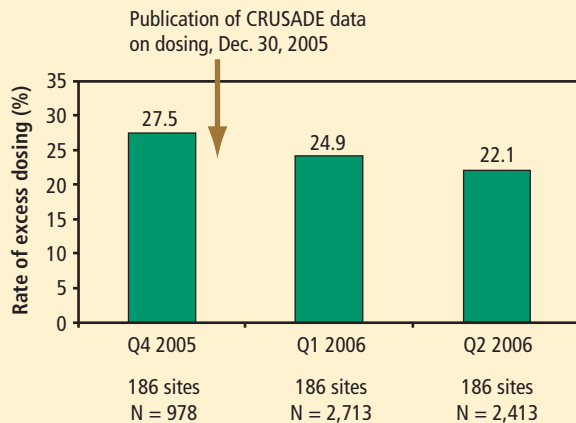Publication of CRUSADE data on dosing, Dec. 30, 2005

FIGURE 3. A decrease in the frequency of excess dosing of glycoprotein IIb/IIIa inhibitors was observed in the CRUSADE national database following publication in late 2005 of CRUSADE data[28] spotlighting the prevalence and adverse outcomes of this inappropriate dosing. This finding suggests that the CRUSADE database and other quality-improvement initiatives in antiplatelet therapy may be having an effect.[29]

GUSTO scale for bleeding classification, revealed a significant excess of moderate bleeding with the combination of clopidogrel and aspirin relative to aspirin alone (2.1% vs 1.3%; $P < .001$) and a nonsignificant trend toward an excess of GUSTO-defined severe bleeding.[11]

Aspirin's risk is not negligible. The bleeding risk with aspirin alone may also be underappreciated in clinical practice. In the CURE trial, higher doses of aspirin with or without clopidogrel were associated with higher rates of major bleeding **(Figure 2)** in a trend that was highly statistically significant.[26]

Dosing: Time to end 'one size fits all' approach
Dosing of antiplatelet therapies has traditionally been a "one size fits all" strategy, but the importance of tailored therapy and dosing is starting to be realized.

Excess dosing of glycoprotein IIb/IIIa inhibitors is common, dangerous. As an example, the CRUSADE initiative, an ongoing national database of patients with high-risk ACS without ST-segment elevation, showed that 27% of patients treated with glycoprotein IIb/IIIa inhibitors at 400 participating US hospitals in 2004 were overdosed, based on dose-adjustment recommendations in the medications' package inserts.[27] Patients who received excessive doses were significantly more likely to suffer major bleeding than were those who were dosed correctly (odds ratio = 1.46 [95% CI, 1.22–1.73]), an increased risk that was particularly pronounced in women.

Quality-improvement initiatives. The above-mentioned

CRUSADE initiative, which was launched in 2001 and involves hundreds of participating US hospitals, has served as a road map for improving dosing practices in antithrombotic therapy. Like the newer ACTION Registry,[20] CRUSADE issued performance report cards to its participating hospitals in which antithrombotic medication use over the prior 12 months was compared with each institution's past performance and with data from similar hospitals across the nation.

In a heartening development, efforts such as these and the publication and dissemination of CRUSADE data[28] have coincided with a decrease in the rate of excess dosing of glycoprotein IIb/IIIa inhibitors, according to the CRUSADE database **(Figure 3)**.[29]

■ **SUMMARY AND CONCLUSIONS**
Managing antiplatelet therapy for patients with ACS is complex, given the array of medications available and the various combinations in which they can be used. Therapy is likely to become even more complicated, as several new medications are under review by the US Food and Drug Administration or in phase 3 clinical trials.

Current antiplatelet therapy for patients with ACS is suboptimal. Ischemic event recurrence rates continue to rise despite the use of current antiplatelet therapies, bleeding remains an underappreciated risk, and dosing often varies from evidence-based recommendations. Developing prospective strategies for antiplatelet therapy will improve utilization in keeping with a more evidence-based approach. Current ACC/AHA guidelines are the beginning of a roadmap to optimal use of antiplatelet drugs, and quality-improvement initiatives linked to national registries like ACTION promise even more guidance toward optimal therapy through institution-specific benchmarking and performance reports.

Thus far, more effective antiplatelet therapy has led to a greater risk of bleeding. Emerging novel antiplatelet agents and smarter use of existing therapies have the potential to improve both ischemic and bleeding outcomes.

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Platelet response in practice: Applying new insights and tools for testing and treatment

■ CASE STUDY: THROMBOSIS AFTER STENTING DESPITE ANTIPLATELET THERAPY

Dr. Deepak Bhatt: We have taken in a wealth of terrific information from the three preceding talks in this symposium. Let's now share some questions from the audience and explore some of the points raised in the preceding talks in a bit more practical detail for clinicians. Our three prior speakers are joined in this panel discussion by Cleveland Clinic's Dr. Frank Peacock, who brings an emergency medicine perspective.

Let's begin with a case-based question supplied from the audience. The patient is a 42-year-old morbidly obese man without diabetes who had a non-ST-elevation myocardial infarction (MI) less than 1 year ago. A drug-eluting stent was placed at the time of his MI, and now restenosis has occurred. He is on aspirin and clopidogrel 75 mg/day. Do you recommend running a vasodilator-stimulated phosphoprotein (VASP) test and possibly increasing the clopidogrel dose to 150 mg/day, or should the patient just be switched to prasugrel (assuming it is commercially available) without running the VASP test?

I'll take a quick initial stab at this question. Studies of antiplatelet therapies to prevent in-stent restenosis have been a mixed bag. Some of the trials with glycoprotein IIb/IIIa inhibitors have shown an effect on restenosis, but most have not. Similarly, some of the analyses of the thienopyridines ticlopodine and clopidogrel have shown an effect on restenosis, but most have not.

For the most part, restenosis does not appear to be heavily mediated by platelets, at least not in a way that we can influence by therapy. On the other hand, stent thrombosis is highly platelet mediated, so I would alter the case to one in which stent thrombosis is the clinical problem. Assuming that the patient has been adherent to his antiplatelet regimen, which tests would you perform, and how would you act on the information from those tests?

Dr. Kandice Kottke-Marchant: The 2007 guidelines on acute coronary syndrome (ACS) management from the American College of Cardiology and American Heart Association (ACC/AHA)[1] do not address platelet function testing, and almost none of the clinical trials of antiplatelet agents had an arm that included testing and dose adjustment based on platelet function studies. Platelet testing is available at some centers; at Cleveland Clinic, we use platelet aggregation testing. One can do platelet aggregation testing on a patient-by-patient basis; if inhibition appears to be suboptimal, a treatment decision should be made, but there is little guidance from the literature to steer that decision. I have seen clinicians increase the dose of clopidogrel or aspirin in response to platelet function tests, which occasionally triggers a confirmatory call from the pharmacy department.

Dr. Bhatt: When I was still at Cleveland Clinic, our chief medical resident did an analysis of platelet function testing, and it was remarkable how much testing was performed and how often it changed management, largely in the absence of any outcomes data, as Dr. Kottke-Marchant pointed out. Dr. Alexander, what are your recommendations with respect to platelet function testing today?

Dr. John Alexander: The case you describe is one in which applying evidence is not easy. There are no trials to supply any evidence to change therapy in this patient, a morbidly obese man receiving 75 mg/day of clopidogrel. There is certainly a rationale, however, to believe that a standard "one size fits all" 75-mg daily dose of clopidogrel may not be enough for him. The trade-off with a higher dosage is a higher risk of bleeding, however, so I would first be sure that he has been adherent to his current regimen of clopidogrel and aspirin.

Dr. Bhatt: Is there a role for point-of-care testing to determine whether he is adherent to the medicines?

Dr. Kottke-Marchant: Several of the point-of-care tests, such as the VerifyNow rapid platelet function ana-

lyzer, have specific cartridges for aspirin and for clopidogrel. If platelets were not being inhibited, it would suggest that the doses were too low, given the patient's weight, but you probably would not be able to determine whether he was resistant to clopidogrel.

Dr. W. Frank Peacock: One way to verify that patients are taking their aspirin is to take a small urine sample and squirt in 2 mL of ferric chloride. If the sample turns purple, it means they are taking their aspirin. Once that is established, you can try to determine whether the drug is working on their platelets.

Dr. Alexander: Another potential explanation for stent thrombosis is faulty stent placement. In this case I would consider asking an interventional colleague to perform intravascular ultrasonography to make sure the stent was implanted properly before I changed the patient's antithrombotic therapy.

Dr. Bhatt: That's a great technical point. We always want to make sure that a case of stent thrombosis is not due to a mechanical problem. We should be asking: Is the stent properly sized and well opposed? Is there a distal dissection or any other issue that could predispose to stent thrombosis?

Dr. Alexander: This case illustrates a host of other challenges that underscore how much more work we need to do to define optimal antiplatelet therapy. Suppose we perform platelet function testing and find a low level of platelet inhibition in this patient with stent thrombosis, and we change his antiplatelet regimen. When should we test him again? If we retest in 3 months and find that he has a higher than expected level of platelet inhibition on the new antiplatelet regimen, do we dial down the intensity? Once again, there is no evidence to guide these decisions, and levels of platelet inhibition are driven not just by the medications but also by what is going on in the patient's platelets—it is quite multifactorial.

> **Levels of platelet inhibition are driven not just by the antiplatelet drugs but also by what is going on in the patient's platelets—it is quite multifactorial.**
> —*Dr. John Alexander*

■ **POINT-OF-CARE PLATELET FUNCTION TESTING: CURRENT LIMITS, FUTURE ROLES**

Dr. Bhatt: While we're discussing platelet function testing, I found it interesting, Dr. Kottke-Marchant, that you said the use of bleeding time as a platelet test is finally going away. Testing of bleeding time has been around forever, but I agree that it doesn't have much value in clinical practice. Do you think bleeding time will continue to have any role in drug development? Most phase 2 trials, and certainly phase 1 trials, still capture bleeding time to assess whether or not a drug is working. Should that, too, be jettisoned, or does bleeding time still have some merit in this context?

Dr. Kottke-Marchant: I would jettison it in drug development as well because of the considerable variability in bleeding time. It is not a test that can be standardized, and no quality control can be done. The results depend on skin turgor, age, and many other variables.

We need a global assay that will pick up multiple aspects of platelet function, such as flow-based adhesion, aggregation, and granule release. The bleeding time is a shear-dependent test, whereas the platelet aggregation test that is used in most drug trials is an artificial assay that measures only aggregation, but not under shear. The VerifyNow rapid platelet function analyzer does not measure platelets under shear and is not a global assay.

Dr. Marc Sabatine: I would underscore the need for a reliable point-of-care test of platelet function. When we prescribe a statin or an antihypertensive drug, we don't just send the patient out the door and hope that everything will be okay. We measure the response, knowing that genotype, environmental factors, or medication factors can affect the response. When we prescribe an antiplatelet drug, we need a reliable point-of-care device to make certain that the patient is getting appropriate platelet inhibition.

I am reminded of a recent study of point-of-care measurement of platelet inhibition in patients receiving clopidogrel prior to nonemergent percutaneous coronary intervention (PCI).[2] Rather than just treating patients with PCI and sending them out the door, the investigators kept giving patients clopidogrel and measuring their platelet inhibition until they achieved an appropriate degree of inhibition, after which PCI was performed. Event rates were significantly reduced in the patient group treated this way, which suggests a need to individualize therapy and move away from the "one size fits all" mindset.

Dr. Bhatt: Dr. Peacock, you've led a study of point-of-care assays in the emergency department. What might ultimately be the role of point-of-care testing in emergency medicine, and might it influence drug selection?

Dr. Peacock: My short answer is that I think there will be a role for point-of-care testing, with all the caveats that have been discussed. There may even be a day when we do genetic testing and look for DNA. Honestly, though, I'm somewhat of a skeptic because I'm not looking at the genetics. I see many patients who do crack cocaine who come to the emergency room with chest pain and

have risk factors, but I send these patients home because they are not having an event. The real question is, "Is it an event?" If a patient is having an event and he or she has platelet resistance or hyperreactivity—whatever we term it—then you have to decide the next step.

As you mentioned, we just completed a study that evaluated a couple hundred patients for platelet inhibition resistance to aspirin, and one finding was that the incidence of platelet resistance to aspirin was much lower than we had anticipated. Studies from the literature suggest that the prevalence of resistance is around 30%, but in our study it was 6.5%.[3]

Dr. Kottke-Marchant: It depends on how and in whom you measure resistance. Different tests will give you different numbers. Even among studies using the same measurement techniques, the results depend on the patient population. If it's a fairly stable cardiac population, you may see aspirin resistance rates of 4% or 5%. If it's a population of patients who have had multiple MIs, the rate may be higher.

Dr. Peacock: That's exactly my point. In the emergency department we see a mixed bag. We see many people who have had no prior events and have no acute event occurring. So in that setting you are going to get results that suggest that no intervention is required, whereas in that small percentage of patients in whom something is happening, your drug choice may be different.

Dr. Alexander: We are still talking about resistance to antiplatelet drugs as though it were a patient-level variable, but it's my impression that it changes over time and within a patient.

Dr. Kottke-Marchant: It can change over time. There aren't many good longitudinal studies. Most of the studies of "aspirin resistance" are really snapshot studies with measurements taken at one point in time. A term I prefer is "platelet reactivity." To really assess treatment efficacy, we are going to have to look at the basal level of platelet reactivity.

■ WHAT ROLE FOR GENOTYPING IN GUIDING ANTIPLATELET THERAPY?

Dr. Bhatt: Dr. Peacock alluded to a potential role for genetic testing. Dr. Sabatine, you have done a lot of interesting work with genotyping in the TRITON-TIMI 38 study of prasugrel and clopidogrel. What is the future role of genotyping in determining which antiplatelet therapy is best for which patient?

Dr. Sabatine: As I mentioned, cytochrome P450

enzymes play a critical role in the metabolism of clopidogrel. These enzymes are fairly polymorphic—mutations in their encoding genes are responsible for subtle changes in effect, unlike the traditional mutations that we think about for sickle cell disease, for example. A wealth of data has been published showing that genetic variants are associated with decreased functional activity of cytochrome P450 enzymes, demonstrating the pharmacologic importance of these variants.

Individuals who carry variant alleles appear to respond differently to clopidogrel. A variety of small studies show that those who carry specific variants—particularly in the CYP2C19 enzyme, but in other enzymes as well—appear to have a diminished response to clopidogrel. There are also data showing that individuals with a diminished response to clopidogrel have worse outcomes.[4] Our group is studying the impact of genetic variants that decrease the functional activity of cytochrome P450 enzymes on clinical outcomes. (*Editor's note: This study has since been published by Mega et al.[5]*)

The practical implication may lie in point-of-care genotyping, which appears possible and will be clinically useful if a strong link can be demonstrated between genotype and outcomes. If point-of-care genotyping becomes practical, it will raise the question of whether both genotyping and platelet aggregation testing are needed. I think they might indeed be complementary in risk prediction, as is the case with genetic variants that affect low-density lipoprotein cholesterol (LDL-C) levels. In the lipid arena, we have seen that genetic effects and lipid levels provide independent incremental information about risk. That's because of the high degree of variation in LDL-C levels: an LDL-C measurement is a snapshot in time, yet a variety of factors can influence LDL-C levels. In contrast, genotype is an invariant factor. Similarly, in the platelet arena, platelet aggregation studies and genotyping may be synergistic in predicting an individual's predisposition to events and response to medications.

Dr. Bhatt: While we're discussing pathways of metabolism, the literature, though scant, suggests a potential interaction between proton pump inhibitors and clopidogrel. I was co-chair of a recent American College of Cardiology/American Heart Association/American College of Gastroenterology consensus document that endorsed liberal use of proton pump inhibitors in patients who are at gastrointestinal risk, including those on antiplatelet therapy.[6] The gastroenterologists believed strongly that proton pump inhibitors were safe and in fact underused in these patients. What do you think about the clopidogrel–proton pump inhibitor interaction? Should we be concerned?

> **We need a global assay that will pick up multiple aspects of platelet function, such as flow-based adhesion, aggregation, and granule release.**
> —*Dr. Kandice Kottke-Marchant*

Dr. Sabatine: Proton pump inhibitors are not only substrates for, but also inhibitors of, CYP2C19, a key enzyme that helps transform clopidogrel into an active metabolite. For this reason, there has been interest in whether concomitant use of proton pump inhibitors would blunt the efficacy of clopidogrel. The same concern was raised about giving clopidogrel with certain statin drugs that are also metabolized by the cytochrome P450 system, and several studies have shown an effect of these statins on clopidogrel's platelet inhibition. However, there is no evidence that coadministration of these statins has affected clinical outcomes with clopidogrel in clinical trials. So it may be that while competition for the cytochrome P450 system is one factor, it's not enough of a factor to tip the scale and result in a clinical event. The same may be true of coadministration of proton pump inhibitors; meanwhile, we await definitive data that concomitant use with clopidogrel leads to higher rates of ischemic events.

■ DIAGNOSTIC UNCERTAINTY IN THE EMERGENCY SETTING

Dr. Bhatt: We heard about quite a few new antiplatelet drugs in Dr. Sabatine's presentation, some of which will likely be taken up in clinical practice. Dr. Peacock, from an emergency department perspective, how will you integrate all these new agents with the numerous therapies already available? What should emergency departments do to come to grips with and ultimately take advantage of these different forms of therapy as well as emerging platelet function tests?

Dr. Peacock: The piece that's unique or especially pertinent to the emergency department is diagnostic uncertainty. Diagnosis and management are easy when a patient has an ST-elevation MI because we all know what that looks like and we know what to do in response. To some extent non-ST-elevation MI is fairly simple too. ACS is a lot more difficult because we don't have a good definition for unstable angina, and that's where diagnosis and management become problematic. And with high-sensitivity troponins coming out now, the question of non-ST-elevation MI is going to get more and more confusing because we will have a lot more patients who meet criteria without having an acute coronary artery event.

So it is going to be important that studies be designed correctly. A lot of the studies reviewed today were efficacy studies, showing that a particular drug works well in a carefully defined population, but they were not efficiency studies: they did not take into account the real-world diagnostic uncertainty—and inevitable misdiagnoses—that emergency departments encounter before starting therapy.

Take the CURE trial, for example. It was a great study, showing that clopidogrel reduced the hazard ratio for major coronary events by 20% in patients with unstable angina,[7] and the message was that everybody should be using clopidogrel. A close look at the study, however, reveals that about half the patients did not receive clopidogrel in the emergency department. When patients did receive it early, it was driven by the cardiologist, who was absolutely certain of the diagnosis. But if the study was not designed to test early use, then it is a big leap to extrapolate its findings to this circumstance.

Many of the patients in the CURE trial were enrolled the day after presentation, when their diagnosis was certain—ie, they had a rise in troponin after their symptoms. But when a patient first arrives in the emergency department, we are not certain of the diagnosis. And if we use a drug such as clopidogrel, with a duration of action as long as 5 days, we have committed the entire medical system to a certain course of management for that period of time. If we get the diagnosis wrong, this commitment could restrict management options for up to 5 days.

The question for emergency physicians becomes, "How long is long enough to know whether I can pull the trigger on a therapy and be correct?" With all the new drugs coming along, the way to answer this is to do efficiency studies in a real-world environment in addition to efficacy studies.

Dr. Alexander: Yes, one of the biggest limitations of antiplatelet drug studies to date is that they usually haven't really addressed the timing of drug initiation. We often assume that if a drug is shown to be beneficial, then it should be started as soon as possible. As we just heard, that may have been an unfounded extrapolation from the CURE trial. The same sort of thing happened with the ISIS trial of aspirin in patients with ST-elevation MI.[8] In response to the ISIS results, clinicians rushed to give patients aspirin right away even though many of the patients in the trial may have received their aspirin the day after presentation. For these reasons, the EARLY-ACS study,[9] which is addressing a very simple question—whether early upstream use of glycoprotein IIb/IIIa inhibitors is beneficial—has been a challenging trial to complete.

■ WHAT ROLE FOR THIENOPYRIDINE PRETREATMENT?

Dr. Bhatt: Dr. Sabatine, you presented data from the large TRITON-TIMI 38 trial comparing prasugrel with clopidogrel. I'm interested in how you would use

> We still talk about resistance to antiplatelet drugs as if it were a patient-level variable, but it changes over time and within patients.
> —*Dr. John Alexander*

prasugrel in practice, assuming it receives marketing approval, especially in light of its bleeding risk, particularly in patients in whom coronary artery bypass graft surgery (CABG) is planned. Many hospitals pretreat patients with clopidogrel in the emergency department. How would you manage a patient who shows up in the emergency room with ACS? Would you give clopidogrel, would you wait and give prasugrel, or would you do something else? If you gave clopidogrel, what loading dose would you use—300 mg, 600 mg, or, as some have suggested, 900 or 1,200 mg?

Dr. Sabatine: I am a strong proponent of pretreatment. Data from multiple studies show a benefit to this strategy, and even the original CURE trial showed a roughly 30% reduction in ischemic events within the first 24 hours of clopidogrel initiation.[7]

I think the dosing strategy depends on how the patient is going to be managed. If management is going to be conservative, then I would start the patient on 300 mg of clopidogrel when he or she came in. If the patient is going to the cardiac catheterization laboratory in a few hours, I would pretreat with 600 mg of clopidogrel. For prasugrel, the need for pretreatment is less clear, given the drug's faster onset of action and greater degree of platelet inhibition. In the TRITON-TIMI 38 study,[10] prasugrel was given, by and large, after diagnostic angiography, and thus one could use that approach in practice.

In terms of clopidogrel versus prasugrel, I would embrace prasugrel for the large majority of my patients, being mindful of the risk of bleeding. I would not hesitate to give the medication to diabetics or to younger, more robust patients. The 50% reduction in stent thrombosis with prasugrel versus clopidogrel in TRITON-TIMI 38 is huge,[11] given that the risk of death with stent thrombosis is probably 25% or greater. So I would want to have prasugrel on board to reduce the risk of stent thrombosis, especially if a drug-eluting stent were being implanted.

Dr. Bhatt: Dr. Alexander, let's get your take on a similar scenario. Assuming that prasugrel gains marketing approval, how would you manage patients with non-ST-elevation MI who present to the emergency department? Would you pretreat with clopidogrel? Would you wait until angiography and then, depending on the anatomy, treat with prasugrel? Or would you potentially pretreat with prasugrel, which has not been studied and would not be a labeled indication? How would you reconcile the data?

Dr. Alexander: At Duke, I expect that prasugrel will not be used prior to the catheterization laboratory in patients with non-ST-elevation ACS due to concerns about whether the patients will undergo PCI or be managed medically or with CABG.

Dr. Bhatt: That makes sense, since there was a fair amount of bleeding with prasugrel in those patients in TRITON-TIMI 38.

Dr. Alexander: Correct. Moreover, at Duke we don't use as much upstream clopidogrel as we would, based on the evidence, if I were managing all the patients. There is still a lot of pushback about upstream clopidogrel from our surgeons because patients are going to surgery quickly these days, sometimes just a day after catheterization, and that's when a loading dose of clopidogrel can be problematic. We are also still fairly heavy users of glycoprotein IIb/IIIa inhibitors.

Where I can see prasugrel being used prior to the cath lab at Duke is in ST-elevation MI, where the rate of PCI is very high. In primary angioplasty for ST-elevation MI, it would likely be given upstream. The bigger issue for us will be that we serve as a referral base for a lot of regional hospitals, and thus have some influence on their practices.

> If point-of-care testing becomes practical, it will raise the question of whether both genotyping and platelet aggregation testing are needed. I think they might be complementary.
> —*Dr. Marc Sabatine*

Dr. Bhatt: In that case, what would you advise those regional hospitals to do for non-ST-elevation MI?

Dr. Alexander: For the time being, we would advise continuing with our current practice, which is to load clopidogrel in patients in whom there is a reasonable certainty that CABG will not be performed, and to use glycoprotein IIb/IIIa inhibitors in high-risk patients. As we get more experience with prasugrel or with additional trial results, however, that practice could easily change.

Dr. Bhatt: So you would still use glycoprotein IIb/IIIa inhibitors?

Dr. Alexander: Yes, I advocate upstream clopidogrel use, but not all my colleagues do. Based on the guidelines, I'd use one or the other—either clopidogrel or a glycoprotein IIb/IIIa inhibitor. As I mentioned in my talk, if a patient is at high risk for bleeding, I am more inclined to use clopidogrel, although patients at higher risk of bleeding are often at higher risk for ischemic events as well.

■ **WHAT'S DRIVEN THE DROPOFF IN GLYCOPROTEIN IIb/IIIa INHIBITOR USE?**

Dr. Bhatt: While we're on the topic of glycoprotein IIb/IIIa inhibitors, a question card from the audience asks why there has been a decrease in glycoprotein IIb/

IIIa inhibitor use and whether this decline is appropriate or inappropriate. Have clopidogrel pretreatment, higher loading doses of clopidogrel, and use of the direct thrombin inhibitor bivalirudin contributed to the decrease in glycoprotein IIb/IIIa inhibitor use?

Dr. Alexander: I do think that the decline has been driven by the changing environment, with greater use of other antithrombotic strategies that include clopidogrel and bivalirudin, as you suggest, as well as an increased attention to bleeding. From an evidence-based standpoint, we don't know whether the decrease in glycoprotein IIb/IIIa use is appropriate or not because the studies of these agents were conducted before the widespread upstream use of clopidogrel and bivalirudin. Clopidogrel is attractive because it's a pill given as one dose in the emergency department, the wards, or the catheterization laboratory, rather than a much more complicated infusion with weight-based dosing and dosage adjustments based on creatinine clearance. It is possible that we should perhaps be dosing clopidogrel the same way, but we don't know that yet.

■ PRASUGREL IN PRACTICE: HOW LOW CAN THE DOSE GO, AND IS THERE A GENDER EFFECT?

Dr. Bhatt: Let's stick with this focus on dosing but turn back to discussion of prasugrel. In your presentation of the TRITON-TIMI 38 data, Dr. Sabatine, you proposed a potential prasugrel dosage modification, down to a 5-mg loading dose, in subgroups that were identified as being at high bleeding risk—namely, elderly patients and patients with low body weight. However, no outcomes data with 5 mg of prasugrel came out of TRITON-TIMI 38.[10] Is this proposed modification based on pharmacokinetic extrapolation? Could clinicians be comfortable using 5 mg of prasugrel, assuming the drug receives regulatory approval and a 5-mg tablet would be available?

Dr. Sabatine: Of course, evidence at the grade A level would consist of a trial showing that patients who received a lower dose enjoyed the same benefit as those who got standard dosing in TRITON-TIMI 38—a 60-mg loading dose followed by 10 mg/day—with an acceptable risk profile. However, such a trial would be difficult and costly to conduct, and would take roughly half a decade to pull off. It is only through large trials like TRITON-TIMI 38 that you identify subgroups that respond differently, and then to go back and do a separate trial for those subgroups takes a great deal of time. It may not be practical.

I think the Food and Drug Administration is moving

> **If we use a drug like clopidogrel, with a duration of action as long as 5 days, in the emergency setting, we have committed the entire system to a certain course of management for up to 5 days.**
> —*Dr. Frank Peacock*

toward embracing careful pharmacokinetic/pharmacodynamic substudies within trials, with these substudies having adequate numbers of subjects to provide a sense for the ideal target dose and what an acceptable dose range would be, without limiting approval to a single dose. The analogy would be warfarin dosing, with the aim being to figure out an acceptable dose range, discover which patients fall outside that range, and then model the effect of a lower dose in those patients. Thus, approving a 5-mg dose of prasugrel based on TRITON-TIMI 38 would be a reasonable approach if this dose passed muster under pharmacokinetic/pharmacodynamic modeling. If this approach were taken, there would clearly be a need for postmarketing surveillance to confirm whether the modeling on the effects of the lower dose was borne out by actual outcomes.

Dr. Bhatt: The audience has posed another interesting question raised by TRITON-TIMI 38: Can you comment on the lesser effect of prasugrel in women?

Dr. Sabatine: It is true that there was not a statistically significant effect of prasugrel among women in TRITON-TIMI 38, but statistical tests among subgroups found no significant heterogeneity for the effect between men and women, and that is the relevant measure to determine any gender effect. Keep in mind that not all subgroups represent a univariate slice of the population. For example, women generally have lower body weight than men, and since prasugrel's net clinical benefit was reduced in patients with lower body weight, that may explain some of the differing extent of effect between men and women.

Dr. Bhatt: That's a good point about the lack of heterogeneity between men and women. In fact, a meta-analysis of clopidogrel data conducted by one of the fellows I work with revealed that men and women appear to benefit similarly from clopidogrel.[12] There was a slight signal of excess bleeding in women, but there were more elderly women in the pooled population, which may have been a confounding factor. As best as anyone can tell, antiplatelet therapy works well in both men and women.

■ NAVIGATING MANAGEMENT ACROSS THE SPECTRUM OF CARE

Dr. Bhatt: I would like to explore a bit further how all of these issues translate across the spectrum of care, beginning in the emergency department, which we know is a key component of the entire ACS management strategy for a health care system. What should

emergency medicine doctors do, given all of the potential options—clopidogrel, different loading doses of clopidogrel, prasugrel, glycoprotein IIb/IIIa inhibitors, even bivalirudin?

Dr. Peacock: It depends on the practice setting. Some emergency physicians work at community hospitals with no backup. They must have relationships with the larger centers to which they'll be transferring patients, because ACS patients should not be staying at community hospitals. These emergency physicians must have close relationships with the physicians who will be receiving their patients, and they know the potential head-butting with surgeons surrounding early clopidogrel use better than anybody does. If they treat with clopidogrel in the emergency room, and it turns out that the patient needs to go to the catheterization laboratory, can the receiving hospital use platelet testing to shorten the standard 5-day interval from treatment to catheterization?

Dr. Bhatt: Yes, that's a rather useful, although not completely validated, way of using point-of-care platelet testing—to potentially reduce the time to surgery.

Dr. Peacock: Right. So if the policies for handling these types of transfer-related issues are worked out in advance, all players have a pathway to follow, which can allow quick action when necessary. If you don't have these issues worked out in advance, you either lose many opportunities to act quickly in the emergency room or you risk taking actions that will cause problems later in the course of management.

Dr. Alexander: I totally agree. The key is to sit down with all the players involved—the surgeons, the interventional cardiologists, the intensivists, the emergency room personnel—and come up with strategies for different populations of patients. Write down the collective strategy and hang it on the wall so that everybody can be comfortable with it. The strategy can be reevaluated when prasugrel or other new antithrombotic drugs come on the market.

Dr. Peacock: The other environment is the academic center, which is even more challenging, but for different reasons. At a large academic center like the Cleveland Clinic, any of 25 different cardiologists may be taking call and receiving patients from the emergency department on a particular night. A lot of phone interaction is required to elicit the planned management strategy, including if and when the patient will be going to the cath lab. Individualizing care to a particular cardiologist

then becomes a time-consuming challenge, especially in clinical situations where outcomes are time-dependent.

Dr. Alexander: Agreed. Management needs to be integrated across the entire spectrum of care. The anticoagulants that we plan to use in the cath lab will affect the antithrombotic regimen used upstream.

Dr. Kottke-Marchant: One circumstance where platelet function testing has been helpful is in determining the washout of the clopidogrel effect before surgery. At Cleveland Clinic, we have implemented platelet function testing in this circumstance instead of waiting a blanket 5 days after clopidogrel administration to go to surgery. A return to normal platelet function on platelet aggregation testing, depending on the cutoff value used, is an indicator that the patient can proceed to surgery.

Dr. Bhatt: That's a logical approach. How should we be using antiplatelet therapy in the medically managed patient, Dr. Alexander?

Dr. Alexander: When I think of medical management, I include patients who don't go to the cath lab, but also those who do, with regards to their management prior to and following their time in the cath lab.

In patients who don't go to the cath lab for angiography, the ACC/AHA guidelines recommend aspirin and either clopidogrel, a glycoprotein IIb/IIIa inhibitor, or both.[1] In making this choice, I consider the patient's risk of bleeding and the dosing complexity of the regimen, especially with the use of glycoprotein IIb/IIIa inhibitors in a patient with renal insufficiency. In a patient at relatively low risk for bleeding, I often use both clopidogrel and a glycoprotein IIb/IIIa inhibitor, although this strategy does not have a lot of data to support it.

The more challenging population consists of patients who go to the cath lab but do not undergo PCI; this population is managed medically too. We often drop the ball with clopidogrel in this population. Many patients in whom PCI is not performed do not receive clopidogrel upstream, for all of the reasons we've discussed, and there is pretty good evidence that if clopidogrel is not instituted before hospital discharge, the patient is not likely to be receiving it at 30 days either. We have an obligation to treat these patients.

Treatment following bypass surgery is much murkier, and I don't really know what we should be doing. The ACC/AHA guidelines suggest that clopidogrel be started in a patient with non-ST-elevation ACS after bypass surgery,[1] but I believe the evidence to support that recommendation is pretty weak.

> **Platelet function testing has been helpful in determining clopidogrel washout before surgery, allowing some patients to proceed to surgery sooner than the 5-day blanket waiting period.**
> —*Dr. Kandice Kottke-Marchant*

Dr. Bhatt: Well, the CURE trial did contain a sizeable group that underwent bypass surgery,[7] and although this group was underpowered in some respects, it was still a very large group, so I personally favor treatment in those patients. We should mention that an ongoing trial called TRILOGY ACS is comparing clopidogrel and prasugrel specifically in patients who are being managed medically,[13] so more data on this strategy will be emerging.

■ ARE GUIDELINES DESTINED TO BECOME EVER MORE COMPLEX?

Dr. Bhatt: Here's a comment and question from the audience that pulls together a lot of what we've discussed while also looking forward: The antiplatelet therapy guidelines are already complicated. If the ongoing studies of emerging antiplatelet drugs all have results that are qualitatively similar to those of the TRITON-TIMI 38 study of prasugrel—ie, better efficacy with more potent therapy but more bleeding—how do you foresee these antiplatelet drugs being used in clinical practice?

Dr. Sabatine: The contrast between the US guidelines and the European guidelines for ACS management is stark. The US guidelines—from the ACC and AHA[1]—are essentially an encyclopedia that includes nearly every trial of antiplatelet therapy in ACS along with complicated algorithms; they do a wonderful job of being complete. The European guidelines[14] are probably one tenth the size of their US counterpart document, and they suggest treatments for various patient types; they are very simple.

In a sense, the US guidelines lay out the data and force practitioners to evaluate the trials and consider how our patients fit into the study populations. In this way they are analogous to current guidelines for anticoagulant therapy. Several anticoagulants have been compared with heparin in clinical trials. These newer anticoagulants appear to reduce the risk of ischemic events compared with heparin; some have lower rates of bleeding, while others have higher rates of bleeding. There have been few head-to-head studies of these agents, however, so we wind up with guidelines that are not definitive but rather suggest agents to "consider" in various settings.

It's unlikely that a head-to-head trial will be conducted comparing prasugrel with the reversible $P2Y_{12}$ antagonist AZD6140, assuming that both are approved for marketing. If the drugs appear equally efficacious in placebo-controlled trials, it will take consensus to determine the appropriate choice at your hospital, factoring in your patient profile, the cost of the drugs, and

> An ongoing trial called TRILOGY ACS is comparing clopidogrel and prasugrel specifically in patients who are being managed medically, so more data on this strategy will be emerging.
> —Dr. Deepak Bhatt

other variables. It's more complicated when one agent is slightly more efficacious but causes more bleeding or, conversely, a little less efficacious but less apt to cause bleeding. In such cases, you may need to tailor therapy to the patient, trying to gauge bleeding risk. All of the emerging data appear to point to the importance of bleeding on outcomes: patients who bleed fare poorly, in part due to the bleeding itself and in part perhaps because they have a proclivity for bleeding.

■ THE FUTURE: MONITORING-BASED DOSING AND NICHE ANTIPLATELETS?

Dr. Bhatt: That's a good observation. Let's wrap up by having the other panelists share any final thoughts you may have.

Dr. Alexander: I'd like to return to the issue of measuring antiplatelet response and using it to guide therapy. Earlier we cited the examples of antihypertensive therapy and lipid-lowering therapy to support this model of monitoring-based treatment. Guidelines for dyslipidemia treatment recommend using LDL-C levels to guide therapy, but this practice is difficult to study in a randomized trial. In fact, none of the randomized trials of statins used LDL-C levels to guide therapy. They all studied fixed doses of statins versus placebo or fixed doses of another statin. Higher doses of statins were always beneficial compared with lower doses, and this finding was extrapolated into the guidelines as a justification to treat to target LDL-C levels.

Dr. Bhatt: It's not even necessarily clear that LDL-C level is the best target, if you consider the JUPITER trial, in which patients received statin therapy based on their baseline level of high-sensitivity C-reactive protein, not their LDL-C level.[15] It goes to show how incomplete our knowledge of a class of drugs may be, even decades after the drugs are introduced.

Dr. Kottke-Marchant: To speak to Dr. Alexander's point, dose adjustment guided by platelet monitoring is a bit more problematic for antiplatelet drugs that are irreversible inhibitors, such as clopidogrel and aspirin, than for those that are reversible inhibitors, which are being developed and may eventually make more sense to use. From a drug development standpoint, a drug that requires monitoring and dose adjustment will not gain wide acceptance because it will increase medical costs and morbidity.

Dr. Bhatt: Yes, we know from experience with warfarin

that doctors and patients don't like the ongoing need for monitoring and testing.

Dr. Peacock: The drugs that are going to be adopted by the emergency department are those with the shortest half-lives, for several reasons: (1) using a drug with a short half-life won't commit us to a particular course of action; (2) the potential for drug interactions is lower; and (3) in the event of an erroneous diagnosis, the consequence of misapplication may be mitigated by early recognition and termination of the drug. If we later decide that we've gone down the wrong therapeutic road or reached a wrong diagnosis, or if a complication occurs, we can turn off the therapy quickly. That level of flexibility is needed.

Dr. Kottke-Marchant: I think we are moving into an era of niche antiplatelet drugs. One might be used in a patient going to surgery, for example, and another for long-term therapy.

Dr. Peacock: One thing that I don't have a feel for is how to transition from one drug to another. When you change drugs for a patient, it so often seems like it goes badly. If we're eventually going to use drugs with ultra-short half-lives in the in the emergency department for the first day or two, and then switch patients to a pill for a week, a lot more platelet function testing may be needed.

■ DISCLOSURES

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