



Antiplatelet Therapy for Acute Coronary Syndromes

MECHANISMS & STRATEGY FOR USE

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Updates in Cardiology for Nurse Practitioners and Physician Assistants



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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) specializing in cardiology.

Activity Goal

To familiarize NPs and PAs in cardiology practices with current concepts concerning the role of platelets in the pathophysiology of acute coronary syndromes (ACS), the mechanisms of action of current and emerging antiplatelet agents, and strategies for incorporating antiplatelet therapy into treatment plans that balance benefits with risks.

Learning Objectives

After completing this activity, participants should be better able to:

- Explain the role of platelets in the pathophysiology of ACS.
- Differentiate among antiplatelet agents based on the mechanisms by which they antagonize platelet activation or aggregation and on their risk profile.
- Formulate antiplatelet treatment plans for ACS based on each patient's risk profile for recurrent ischemic events and bleeding.

Accreditation Information

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Medical Center
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This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board of Registered Nursing, Provider #13699 for 1.2 contact hours.



This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel.

Approval is valid for one year from the issue date of May 14, 2010. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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- Read the newsletter.
- Relate the content material to the learning objectives.
- Complete the self-assessment questions and the evaluation form online at:
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After login, please enter the code: DPCE69310-1.

Successful completion of the self-assessment is required to earn CME/CE credit. Successful completion is defined as a cumulative score of at least 70%.

The estimated time to complete this activity is 1 hour.

Release date: May 18, 2010

Expiration date: May 18, 2011

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The Planning Committee for this activity included Catherine A. Bevil, RN, EdD, of the University of Nebraska Medical Center College of Nursing Continuing Nursing Education, and Ruth Cohen and Christine Olsen, PhD, of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

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INTRODUCTION

Atherosclerosis of the coronary arteries manifests in a spectrum of myocardial ischemic disorders collectively termed *acute coronary syndromes* (ACS).¹ Comprising unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation MI (STEMI), ACS remains a leading cause of morbidity and mortality despite improvements in treatment.² Patients who survive their first MI are at 1.5 to 15 times higher risk for illness and death than the general population.² Within 1 year of the event, 18% of men and 23% of women aged 40 years or older die, and within 5 years, the mortality rates increase to 33% in men and 43% in women (Figure 1).²

Practice guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) recommend long-term antiplatelet therapy to prevent recurrent ischemic events in patients with ACS.^{1,3} Evidence suggests, however, that antiplatelet agents are substantially underused. The Reduction of Atherothrombosis for Continued Health (REACH) Registry includes patients with either established arterial disease (coronary artery disease [CAD], cerebrovascular disease, or peripheral arterial disease [PAD]) or 3 or more risk factors for atherothrombosis.⁴ Among the REACH Registry patients, the usage rates for dual antiplatelet therapy as recommended by the current guidelines^{1,3} are low—13.2% overall and only 16.6% in patients with CAD.⁴ Among high-risk patients with ACS in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Registry, 46% of eligible patients were not prescribed the recommended antiplatelet therapy at hospital discharge.⁵

This issue of *Antiplatelet Therapy for Acute Coronary Syndromes: Mechanisms and Strategy for Use* reviews the role of platelets in ACS; the mechanisms by which antiplatelet agents antagonize platelet activation and aggregation and thereby decrease the risk of ischemic events; and the characteristics of several currently available antiplatelet agents and emerging options. Expert commentary on practical clinical considerations is provided by Randall M. Zusman, MD, and John G. McGinnity, MS, PA-C, DFAAPA. Future issues of *Updates in Cardiology* will examine key clinical issues in antiplatelet therapy, including drug resistance, drug-drug interactions, bleeding risk prediction, and optimal dosing, as well as a review of current practice guidelines and case-based approaches to treatment.

Platelet Activation and Aggregation in ACS

Although platelets are essential for hemostasis and repair of the endothelium, they are also now known to be key mediators in the processes of inflammation, thrombosis, and atherosclerosis that lead to ACS.⁶ Platelets play key roles in the pathophysiology of atherothrombosis by releasing inflammatory mediators that alter endothelial cell function and contribute to the chronic inflammatory process underlying the disorder; adhering to vessel walls at sites of endothelial-cell activation; and triggering the onset of arterial thrombosis when atherosclerotic lesions rupture.⁶

In normal hemostasis, platelets exist in a nonactivated state and are drawn passively into areas of vascular injury. Intact vascular endothelial cells inhibit platelet activation by producing nitric oxide (NO) and prostacyclin (PGI₂), which help keep platelets in an inactive state. Enzymes on the endothelial surface also help prevent platelet activation by converting the potent platelet activator, adenosine diphosphate (ADP) into adenosine monophosphate (AMP). When the endothelium is disrupted, its ability to produce these substances is impaired and the milieu for platelet aggregation is enhanced.^{6,7}

Endothelial cells also produce the cell adhesion ligand von Willebrand factor (vWF), which is secreted and stored in granules within endothelial cells and platelets. When the endothelial layer is injured, collagen is exposed to the bloodstream; platelets can then adhere to the exposed subepithelium via interactions among collagen, vWF, and fibronectin and specific platelet receptors.⁶⁻⁹

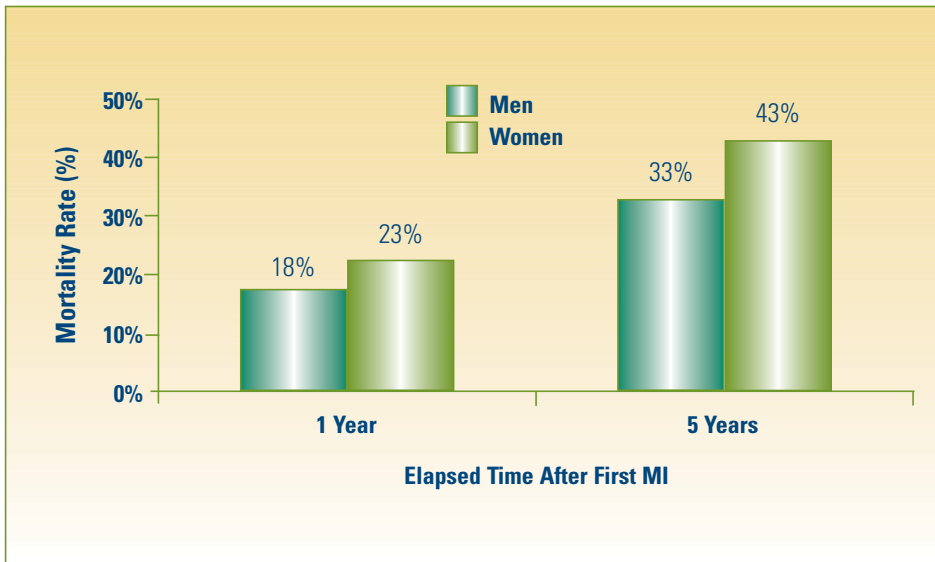


Figure 1. Mortality rates among survivors of a first MI are high. One third of men and nearly one half of women aged ≥ 40 years who survive the initial event die within 5 years. Lloyd-Jones D et al.²

Platelet adherence to the injured epithelial wall triggers their activation, which includes shape change and the secretion of various procoagulant, proinflammatory, and vasoconstrictive secondary messengers, including ADP, platelet-derived growth factor, serotonin, fibrinogen, thromboxane A₂ (TXA₂), and thrombin. These messengers further activate platelets, resulting in a feedback loop and explosive amplification of activation. In particular, ADP interacts with puranergic receptors P2Y₁ and P2Y₁₂ to amplify and sustain this activation.¹⁰

With platelet activation, glycoprotein IIb/IIIa integrin (GPIIb/IIIa) receptors on the surface of activated platelets are exposed and bind fibrinogen, resulting in the formation of fibrinogen bridges between the platelets, platelet cross-linking, and platelet aggregation. This and the simultaneous formation of a fibrin mesh lead to the formation of a platelet thrombus (Figure 2).⁶⁻⁹

Role of Antiplatelet Agents in Modulating Platelet Adhesion/Aggregation

Antiplatelet drugs are widely used for prevention and treatment of arterial thrombosis. These drugs interfere at some point in the process of platelet activation and aggregation.¹¹ Although antiplatelet therapy decreases the risk

of thrombosis, it increases the risk of bleeding, and the balance between coronary thrombosis and hemorrhage is a delicate one.¹² Because the impairment of primary hemostasis by antiplatelet drugs cannot be dissociated from their protection against thrombosis, it appears that similar molecular mechanisms contribute to both processes.^{6,13}

Several drugs that target various pathways in the cascade of events leading to thrombus formation have been or are being developed. Currently available antiplatelet therapies for ACS include aspirin, a TXA₂ inhibitor; and the ADP-receptor antagonists ticlopidine, clopidogrel, and prasugrel (Table).^{7,12} Among the investigational agents are cangrelor and ticagrelor, both ADP-receptor antagonists.

Aspirin

Aspirin, the original antiplatelet agent, has been the foundation of antiplatelet therapy for more than 50 years.¹² Aspirin inhibits platelet cyclooxygenase-1 (COX-1) by

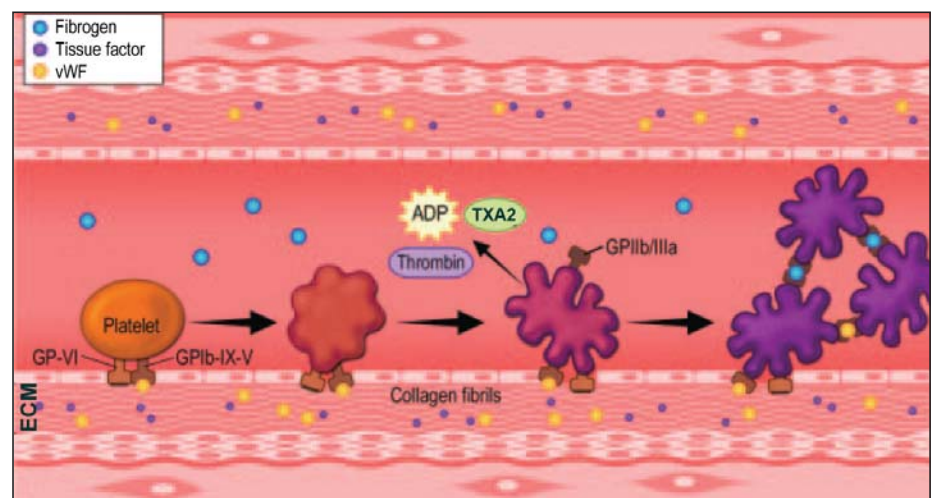


Figure 2. Rupture of an atherosclerotic plaque exposes activating factors that initiate platelet adhesion, activation, and aggregation, which eventually leads to thrombus formation. ADP = adenosine diphosphate; ECM = extracellular matrix; vWF = von Willebrand factor. Reprinted with permission from Meadows TA et al.⁷

irreversible acetylation of Ser529. This renders the catalytic site of COX-1 inaccessible and inhibits the synthesis of prostaglandin H₂ and, subsequently, TXA₂.^{14,15}

Under normal circumstances, TXA₂ is synthesized and released by platelets in response to a variety of stimuli (eg, collagen, thrombin, and ADP) and, in turn, induces irreversible platelet aggregation through its interaction with the TXA₂ receptor. Thus, TXA₂ provides a mechanism for amplifying the responses of platelets to diverse agonists

while inhibition of its release irreversibly blocks platelet activation.¹⁶

Although aspirin also can inhibit COX-2, such inhibition requires a substantially higher dose.¹³ This may account for the need to use higher doses of aspirin to achieve analgesic and anti-inflammatory effects, whereas its antiplatelet effects can be achieved with doses as low as 30 mg daily.¹³

After ingestion, non-enteric-coated aspirin is rapidly absorbed from the stomach and small intestine, reaching peak plasma levels within 30 to 40

minutes (enteric-coated aspirin requires 3 to 4 hours) and inhibiting platelet function within 1 hour.¹¹ Aspirin has a half-life of 15 to 20 minutes, and clearance from the circulation is rapid.

However, because it irreversibly inhibits platelet COX-1, aspirin inhibits platelet function for the life of the platelet, approximately 8 to 10 days.¹¹ Thus, a once-a-day aspirin regimen can be used for antiplatelet therapy despite the short half-life of the drug.¹⁶

Aspirin has been shown to reduce vascular death by approximately 15%

Table. Antiplatelet Therapies for ACS: Overview of Available Agents

Drug	Mechanism of Action	Route of Administration	Dosing Frequency	Side Effects	Limitations
Aspirin	Thromboxane inhibitor; irreversible acetylation of Ser529 of COX-1	Oral	Daily	<ul style="list-style-type: none"> Bleeding GI toxicity: heartburn, indigestion, nausea, vomiting, gastric ulceration 	<ul style="list-style-type: none"> Weak antiplatelet agent
Ticlopidine (<i>first-generation thienopyridine</i>)	ADP-receptor antagonist; active metabolite irreversibly inhibits P2Y ₁₂ receptors	Oral	Twice a day	<ul style="list-style-type: none"> Bleeding GI toxicity: heartburn, indigestion, nausea, vomiting Rash Neutropenia TTP (rare) 	<ul style="list-style-type: none"> More side effects than clopidogrel
Clopidogrel (<i>second-generation thienopyridine</i>)	ADP-receptor antagonist; active metabolite irreversibly inhibits P2Y ₁₂ receptors	Oral	Daily	<ul style="list-style-type: none"> Bleeding Rash Neutropenia TTP (rare) 	<ul style="list-style-type: none"> Patient-to-patient variability in response Variants of the <i>CYP2C19</i> gene are associated with poor metabolism of the drug, which leads to reduced efficacy
Prasugrel (<i>third-generation thienopyridine</i>)	ADP-receptor antagonist; active metabolite irreversibly inhibits P2Y ₁₂ receptors	Oral	Daily	<ul style="list-style-type: none"> Bleeding 	<ul style="list-style-type: none"> More hemorrhagic side effects than clopidogrel Contraindicated in patients with a history of stroke or TIA Not recommended for patients ≥75 years of age unless they are at high risk for CV events

ADP = adenosine diphosphate; COX-1 = cyclooxygenase-1; CV = cardiovascular; GI = gastrointestinal; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura. Adapted from Michelson AD.¹²

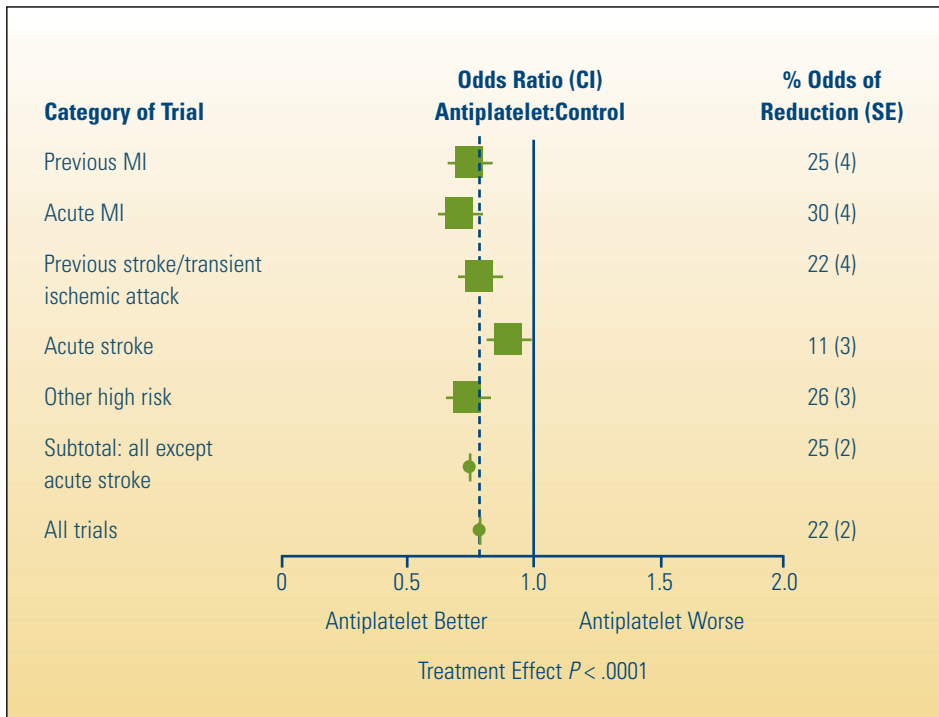


Figure 3. Antiplatelet therapy produces a 25% proportional reduction in serious vascular events (ie, MI, stroke, or vascular death) among high-risk patients. MI = myocardial infarction. Adapted from Antithrombotic Trialists' Collaboration with permission from BMJ Publishing Group Ltd.¹⁷

and nonfatal vascular events by approximately 30% in high-risk patients (Figure 3).¹⁷ Aspirin also may be beneficial in the primary prevention of cardiovascular (CV) events, but this effect is more modest.^{11,17} Guidelines for the long-term management of ACS from ACC and AHA recommend that, unless contraindicated, aspirin therapy be initiated as soon as the diagnosis of ACS is made or suspected and continued indefinitely.^{1,3}

Despite aspirin therapy, 10% to 20% of patients have recurrent vascular events within 5 years of their initial event.¹⁸ As aspirin inhibits the synthesis of only 1 platelet agonist (ie, TXA₂), while other mediators of platelet activation—including ADP, thrombin, and collagen—remain unaltered and continue to activate platelets, aspirin's limited efficacy as

an antithrombotic agent is not surprising. Thus, the current standard of care for the treatment of ACS involves dual antiplatelet therapy with the concomitant use of aspirin plus an ADP antagonist.^{1,3}

Advantages of aspirin include a longstanding record of efficacy and low cost. The most common adverse effect of aspirin is increased risk of bleeding (primarily gastrointestinal [GI]).^{11,16} The potential benefit versus harm of aspirin therapy should be assessed on an individual basis, taking the absolute thrombotic versus hemorrhagic risk of the patient into account. For patients at high risk of CV events, the substantial benefit of aspirin prophylaxis outweighs the risk of excess bleeding.¹⁶

Unresolved issues concerning the clinical efficacy of aspirin include the (1) optimal dose to maximize efficacy

while minimizing toxicity; (2) possibility that some of the antithrombotic effect of aspirin may be unrelated to its inhibition of TXA₂; (3) possibility that some patients may be aspirin-resistant.¹¹ Several lines of evidence support the use of a low-dose aspirin regimen (50–100 mg/d) for long-term management.^{11,17} The term *aspirin resistance* has been used to describe a number of different phenomena, including the inability of aspirin to protect individuals from thrombotic complications (which should be labeled *treatment failure*), the inability of aspirin to reduce TXA₂ production, or its inability to produce a typical effect on 1 or more in vitro tests of platelet function.¹⁹ Thus, reported incidences of aspirin resistance vary, ranging from 5% to 65%.^{12,20} These and other important clinical considerations, including the possibility of increased bleeding with concomitant medications, will be discussed in greater detail in future issues of *Updates in Cardiology*.

ADP-Receptor Antagonists

ADP has 2 types of receptors in the platelet plasma membrane: P2Y₁ and P2Y₁₂. ADP signaling through the P2Y₁ receptor leads to calcium mobilization, a change in platelet shape, and rapidly reversible platelet aggregation. Signaling through the P2Y₁₂ receptor lowers cyclic AMP levels and leads to amplification of platelet aggregation and secretion.¹² All currently available antiplatelet agents that target the ADP receptor belong to a class of drugs known as thienopyridines. The thienopyridines are ADP-receptor antagonists that irreversibly block the platelet P2Y₁₂ receptor, inhibiting platelet activation and platelet aggregation.^{7,8,11}

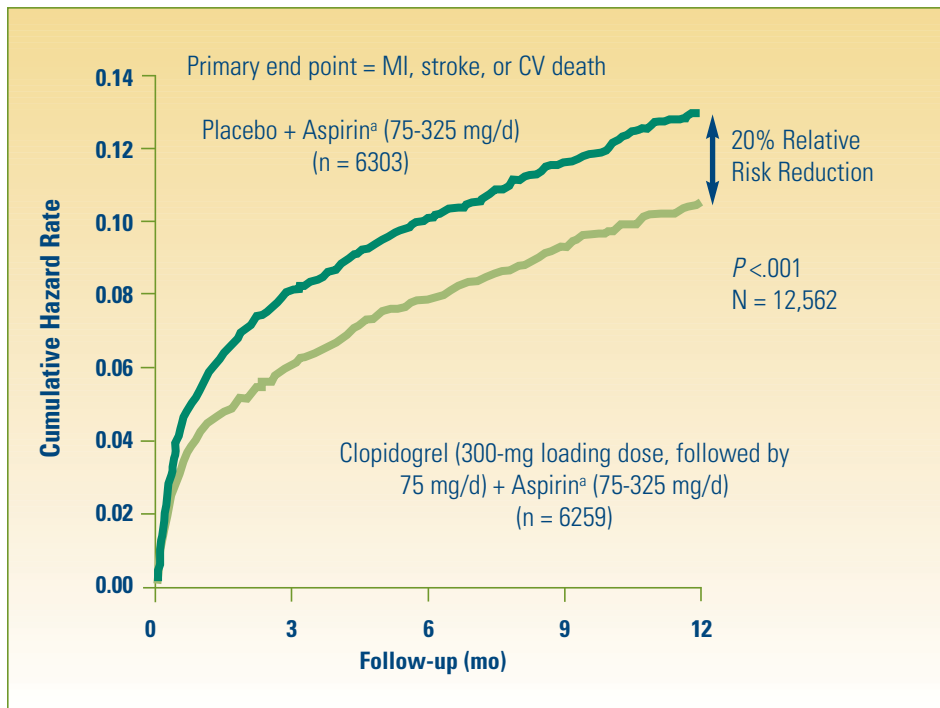


Figure 4. Clopidogrel plus aspirin resulted in a 20% relative reduction in CV death, MI, or stroke in patients with ACS, compared with aspirin alone. ^aIn addition to other standard therapies. Yusuf S et al.²⁸ Copyright ©2001 Massachusetts Medical Society. All rights reserved.

Ticlopidine

Ticlopidine is a first-generation thienopyridine that was developed in the 1970s.^{7,8,11} It is metabolized in the liver, and an active metabolite, rather than the parent molecule, irreversibly antagonizes the P2Y₁₂ receptor.^{7,8,11,12} A delayed antithrombotic effect was observed with ticlopidine (250 mg twice a day) in patients with UA, with no protection during the first 2 weeks of administration.²¹ Thus, ticlopidine is not useful for producing a rapid antiplatelet effect.¹¹ Ticlopidine has been used successfully for the secondary prevention of stroke and MI and for prevention of thrombotic complications after percutaneous coronary intervention (PCI) when administered in combination with aspirin.^{1,22}

The use of ticlopidine is associated with neutropenia, thrombocytopenia,

aplastic anemia, and more rarely, thrombotic thrombocytopenic purpura (TTP), which can be life-threatening.¹¹ Patients taking ticlopidine require serial monitoring of leukocyte counts, which adds a substantial burden to patient management.²³ Ticlopidine is no longer widely used in the United States due to its poor tolerability and difficult management issues. It may be used in combination with aspirin for the long-term management of UA or NSTEMI in patients who are allergic to clopidogrel.¹

Clopidogrel

Clopidogrel is a second-generation thienopyridine with a safer profile than ticlopidine.^{7,8,11} Clopidogrel is an inactive prodrug. Approximately 85% of what is absorbed in the GI tract is rapidly hydrolyzed into an inactive

compound, and the remaining 15% is metabolized in the liver into a short-lived, active metabolite.²⁴ Clopidogrel inhibits ADP-induced platelet aggregation in a dose-dependent fashion, up to a maximum of 40% inhibition after single doses and up to 60% inhibition after 4 to 7 days of repeated dosing.^{11,25} The onset of action for clopidogrel is slower than aspirin, but faster than ticlopidine. Inhibition of platelet aggregation is detectable within 2 hours of administration, peaks 4 to 6 hours after administration, and remains relatively stable for up to 48 hours.^{11,25,26} A loading dose (eg, 300 mg) of clopidogrel results in a much more rapid onset of platelet inhibition than that achieved with a 75-mg dose.^{11,27} The platelet defect induced by clopidogrel is permanent and cannot be restored but only replaced by platelet turnover, with platelet function returning to normal about 7 days after the last dose of drug.¹¹

Whether patients had been managed medically or surgically, clopidogrel has been effective in preventing ischemic events in patients with ACS and is recommended by the AHA and ACC for the long-term management of ACS.^{1,3} In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, clopidogrel plus aspirin treatment was effective in reducing CV death, MI, or stroke in patients with ACS, compared with aspirin alone (Figure 4).²⁸ This benefit came at the cost of increased major and minor bleeding (3.7% vs 2.7%, $P = .001$), but the risk of life-threatening bleeding was not significantly increased.²⁸ In a substudy of the CURE trial, PCI-CURE, the primary end point (CV death, MI, or urgent target vessel

revascularization at 30 days after PCI) was significantly reduced among patients treated with clopidogrel prior to intervention (4.5% vs 6.4% for placebo).²⁹

Unresolved issues regarding clopidogrel use in clinical practice include its irreversible mechanism of action (which is shared by all thienopyridines); its delayed onset of action, which might have negative consequences in unstable patients; the optimal duration of treatment, especially after stent implantation; clopidogrel resistance; and interpatient variability in response.²⁶ Clopidogrel resistance may result from various factors, including the presence of a genetic variant of the liver enzyme *CYP2C19* in some patients, which leads to significantly lower levels of the active metabolite of the drug.³⁰⁻³³ Concomitant use of certain drugs such as proton pump

inhibitors (PPIs) that, like clopidogrel, are metabolized by cytochrome P450 in the liver may reduce clopidogrel's antiplatelet effects.³⁴⁻³⁶

Use of clopidogrel plus a PPI (compared with no concomitant PPI use) has been reported to be associated with increases in death or rehospitalization,³⁴ revascularization procedures,³⁴ and reinfarction.³⁵ In November 2009, the US Food and Drug Administration (FDA) issued a warning stating that patients who take clopidogrel should avoid using the PPI omeprazole because it reduces the antiplatelet activity of clopidogrel by about 50%.³⁷ However, recent study findings suggest that clinical concerns about this association may be premature.

Preliminary results from 1 randomized clinical trial revealed no effect on CV outcomes when omeprazole was given with clopidogrel.³⁸ A recent

analysis of data from the Guthrie PCI Registry also found no increase in CV event rates with concomitant PPI use among patients discharged on clopidogrel plus aspirin after successful PCI.³⁹ An analysis of the subset of patients given omeprazole or esomeprazole with dual antiplatelet therapy was also conducted; the use of either of these PPIs (compared with no PPI use) was independently associated with lower rates of major adverse CV events.³⁹ In a retrospective cohort study, patients with serious coronary heart disease treated with clopidogrel, concurrent PPI use (including pantoprazole or omeprazole) was associated with a reduced incidence of hospitalizations for gastroduodenal bleeding.⁴⁰ Thus, although clinicians should take the FDA warning seriously, the issue of a clopidogrel-PPI interaction remains controversial.⁴¹

Prasugrel

Prasugrel is a third-generation thienopyridine that, like clopidogrel, is a direct ADP-receptor antagonist. Compared with clopidogrel, prasugrel has a more rapid onset of action (t_{max} ~30-60 minutes vs 2-3 hours for clopidogrel),²⁶ achieves a higher degree of platelet inhibition, and has a more uniform response.⁴² Like clopidogrel, prasugrel is a prodrug, and the active metabolites of clopidogrel and prasugrel have equivalent inhibitory effects via inhibition of the platelet P2Y₁₂ receptor.⁴³ However, metabolism of prasugrel to its active metabolite is more efficient than the metabolism of clopidogrel, because it is metabolized by esterases and is less dependent on cytochrome P450 enzymes.^{8,44,45} As a result, prasugrel provides a more rapid, potent, and

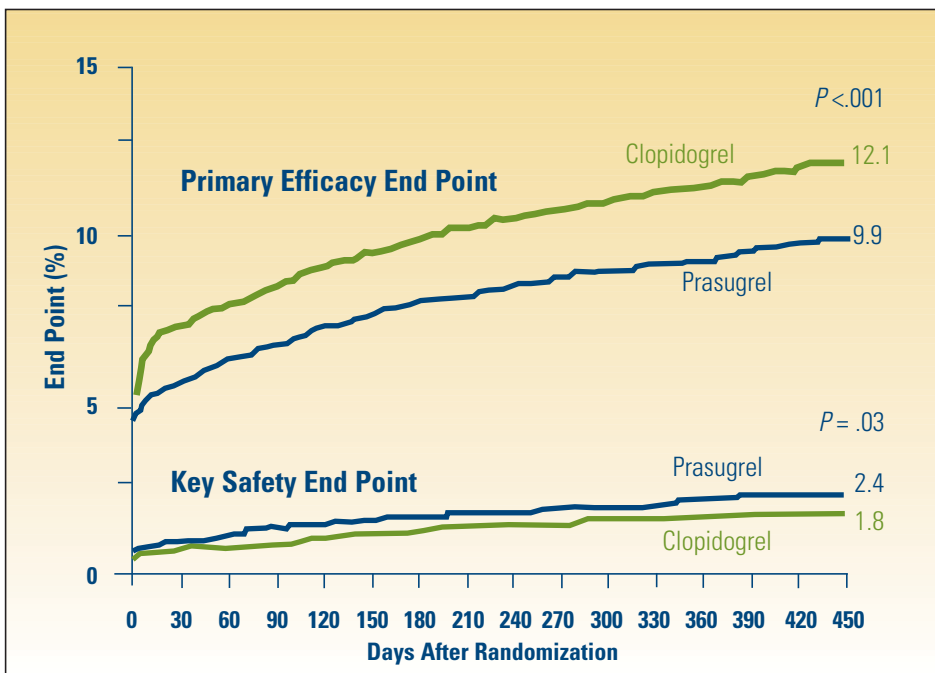


Figure 5. Prasugrel significantly reduces ischemic events, compared with clopidogrel, but causes more major bleeding. The primary efficacy end point was death from CV causes, nonfatal MI, or nonfatal stroke. The key safety end point was major bleeding not related to coronary artery bypass grafting. Adapted from Wiviott SD et al.⁴⁶ Copyright ©2007 Massachusetts Medical Society. All rights reserved.

consistent inhibition of platelet function than clopidogrel.⁴⁶

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study, prasugrel (compared with clopidogrel) was associated with significantly reduced rates of CV death, MI, or stroke (9.9% vs 12.1%; $P < .001$) and a reduced rate of stent thrombosis (1.1% vs 2.4%; $P < .001$) in patients with ACS undergoing PCI (Figure 5). However, the bleeding rates were significantly greater with prasugrel: major bleeding (2.4% vs 1.8%; $P = .03$), life-threatening bleeding (1.4% vs 0.9%; $P = .01$), and fatal bleeding (0.4% vs 0.1%; $P = .002$).⁴⁶ Thus, while prasugrel produces a significantly greater degree of platelet inhibition than clopidogrel,⁴² it also has a greater risk of major bleeding.^{8,45,46} In a subgroup analysis, 3 patient groups were identified as having an increased risk of hemorrhage: patients with a previous stroke or transient ischemic attack (TIA), patients ≥ 75 years of age, and patients weighing < 60 kg.⁴⁶

Prasugrel is FDA-approved for reducing the thrombotic CV event rate in patients with ACS undergoing PCI. It is contraindicated in patients with active pathological bleeding or a history of TIA or stroke and generally should not be used in patients aged ≥ 75 years unless they are at high risk of a recurrent event (eg, because of diabetes or other risk factors).⁴⁷

Emerging Options

Cangrelor

Cangrelor is an investigational, non-thienopyridine adenosine triphosphate (ATP) analogue that blocks the ADP

receptor P2Y₁₂. It has the potential advantages of a rapid onset of action, high potency, and rapid reversibility.⁴⁸ Cangrelor acts directly at the P2Y₁₂ receptor without the need for conversion to an active metabolite, and it completely inhibits platelet aggregation within 2 to 4 minutes.⁴⁹ At studied doses, cangrelor achieves $>95\%$ inhibition of the P2Y₁₂ receptor and nearly complete inhibition of platelet aggregation.⁴⁸ Cangrelor is administered intravenously, and its effects are rapidly reversed after the end of the infusion. Cangrelor has a plasma half-life of 3 to 6 minutes, and platelet function normalizes within 30 to 60 minutes after cangrelor discontinuation.⁵⁰ These properties make cangrelor attractive for patients who require rapid but reversible platelet inhibition (eg, those who are likely to require an invasive procedure or whose coronary anatomy is unknown).⁵⁰

In phase 2 studies, cangrelor showed no significant increase in major bleeding compared with clopidogrel.^{48,51} However, 2 phase 3 trials of cangrelor were stopped early due to lack of efficacy. When administered intravenously 30 minutes prior to PCI and continued for 2 hours afterward, cangrelor was not superior to clopidogrel administered orally 30 minutes before PCI in reducing the composite end point of death, MI, or ischemia-driven revascularization at 48 hours. Minor bleeding was more common with cangrelor than with clopidogrel, and a trend toward increased major bleeding was noted with cangrelor.⁵⁰ Cangrelor is being studied as bridge therapy for patients receiving clopidogrel who need to stop treatment before undergoing surgery.¹²

Ticagrelor

The investigational nonthienopyridine agent ticagrelor, like cangrelor, is a reversible and direct-acting antagonist of the ADP receptor P2Y₁₂; however, it is administered orally rather than intravenously.⁵² Ticagrelor requires twice-daily dosing due to its relatively short half-life (7–8 hours).⁵³ Compared with clopidogrel, ticagrelor is a more rapid and more potent inhibitor of platelets but does not significantly increase major bleeding.⁵⁴ Like cangrelor, ticagrelor does not require hepatic metabolism for conversion to an active form. Ticagrelor has a rapid onset of action of approximately 2 hours, at which time near-complete inhibition of platelet aggregation is observed. Its plateau level of inhibition is greater than that of clopidogrel (90%–95% vs 60%).⁵⁵

The Study of Platelet Inhibition and Patient Outcomes (PLATO) compared ticagrelor and clopidogrel in patients hospitalized with ACS. Ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) significantly reduced the composite end point (death from vascular causes, MI, or stroke) compared with clopidogrel (300- to 600-mg loading dose, 75 mg daily thereafter) (9.8% vs 11.7%; $P < .001$). No increase in the rate of overall major bleeding was noted with ticagrelor, but there was an increase in non-procedure-related bleeding.⁵² In phase 2 studies, the occurrence of dyspnea and ventricular pauses were greater in a dose-dependent manner in patients receiving ticagrelor versus those receiving clopidogrel.^{54,55}

Clinical Considerations

Randall M. Zusman, MD, and John G. McGinnity, MS, PA-C, DFAAPA, comment on the clinical considerations raised by the various mechanisms of antiplatelet drugs.

RZ: There is no question that the use of antiplatelet therapies reduces the risk of major adverse CV events in patients with established CAD. Together with other measures—lipid-lowering agents, blood pressure control (especially with β -adrenergic blocking drugs and agents that disrupt the renin-angiotensin-aldosterone system), glucose control, weight loss, dietary modifications, and exercise—these drugs provide an additive, if not synergistic, reduction in CV events. Although a limited treatment period (perhaps up to 1 year) has been suggested for clinical benefit, many clinicians believe, as I do, that indefinite therapy is needed to provide sustained protection from future atherothrombotic events (MI, stroke, sudden death).

Only clopidogrel has been demonstrated to reduce the risk of subsequent CV events in populations of patients who have survived a stroke or who have PAD. Prasugrel is contraindicated in patients with a history of cerebrovascular disease. Still to be defined are the benefits of other available or emerging antiplatelet agents for the diverse patient cohorts at risk for recurrent ACS events. Additional unresolved questions include the extent of platelet inhibition needed to maximize clinical benefit and the utility of genetic profiling for guiding drug selection and treatment.

The differences in drug metabolism to active moieties, the rapidity of onset of the antiplatelet response, the reversibility of the drug's actions, as well as toxicities and adverse consequences (fatal or nonfatal bleeding) are factors to consider as new agents are

introduced into the clinical armamentarium. In the meantime, an aggressive risk reduction strategy based on blood pressure, blood glucose, and cholesterol control; lifestyle modifications including weight loss, regular exercise, and dietary improvement; and the judicious use of pharmacologic agents to inhibit platelet aggregation can reduce the risk of major adverse CV events in patients with established vascular disease or multiple cardiac risk factors.

JM: Nurse practitioners (NPs) and physician assistants (PAs) who specialize in cardiology devote much of their clinical practice to the care of patients with ACS. With the 1-year recurrent event rates among ACS survivors at 18% for men and 23% for women aged 40 years or older, NPs and PAs must remain knowledgeable about strategies for improving clinical outcomes. After a STEMI or NSTEMI event, not all patients are discharged with aspirin, let alone other antiplatelet therapy to prevent future events. This issue of *Updates in Cardiology* allows us to be informed about current and emerging

ADP-receptor antagonists.

The good news is that clinicians have a variety of agents from which to choose, depending on patient needs and clinical situations. However, the benefits of new therapeutic strategies always come with a cost. When clopidogrel was added to aspirin, the benefits of dual antiplatelet therapy came with an increased risk of bleeding. Some of the newer ADP-receptor antagonists have been shown to reduce major adverse cardiac event rates above what has been achieved with the combination of aspirin and clopidogrel. The cost, however, is a significant increase in bleeding risk, especially in certain patient populations. All NPs and PAs should be aware of this data and ensure that these newer agents are used appropriately.

NPs and PAs also play a critical role in the care of ACS patients in inpatient settings. We need to be leaders in advocating for all effective strategies to reduce patient risk factors for future cardiac events. That includes ensuring our patients receive all appropriate medical therapies and education prior to discharge.

PCE Takeaways

- Platelets play key roles in the pathways leading to thrombosis and CV events; thus, antiplatelet therapy is essential for preventing ischemic events in patients with ACS.
- Currently available antiplatelet drugs inhibit platelet adhesion and platelet aggregation pathways by inhibiting the synthesis of TXA₂ or irreversibly inhibiting the ADP P₂Y₁₂ receptor.
- Although antiplatelet agents reduce the risk of thrombosis, this benefit cannot be dissociated from the associated risk of bleeding; thus, treatment must be individualized to each patient's risk profile.

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