

LONG-TERM MANAGEMENT OF ACUTE CORONARY SYNDROME: A Focus on Antiplatelet Therapy

Learning Objectives

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

- Explain the importance of platelets in the pathophysiology of acute coronary syndrome (ACS)
- Apply evidence-based treatment guidelines to long-term antithrombotic therapy for patients who survived an initial ACS event
- Educate patients on ACS and the need for long-term therapy to prevent recurrent thrombotic events

Acute Coronary Syndrome: Clinical Spectrum

Acute coronary syndrome (ACS) encompasses a spectrum of myocardial ischemia, including unstable angina (UA), ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation MI (NSTEMI) (Figure 1).¹ In 2006, the total number of hospital discharge diagnoses for ACS in the United States was estimated at 1,365,000, including 810,000 for MI, 537,000 for UA, and 18,000 for UA that progressed to MI.² The clinical burden of ACS is emphasized by the long-term event rates after a first acute MI. Among patients ages 40 through 69 years, 16% of men and 22% of women will experience a recurrent MI or a fatal event due to coronary heart disease (CHD) within 5 years; within this timeframe they are also at increased risk for heart failure and stroke.² Among patients age 70 years or older who survived an initial acute MI, the 5-year event rates for heart failure and stroke rise dramatically: to 22% and 6%, respectively, in men and to 25% and 11%, respectively, in women.² Given these alarming statistics, long-term management of patients who had a primary ACS event is critical to reducing the risk of recurrent ischemic events.³

Current guidelines from the American College of

Patients with ACS often have multiple plaque ruptures, and an integrated approach to management is essential.

Does dual antiplatelet therapy provide an added benefit?
See page 64

Cardiology (ACC) and the American Heart Association (AHA) for the long-term management of ACS recommend a combination of anti-ischemic, antiplatelet, and antithrombotic therapy; ongoing risk stratification; and risk factor and lifestyle modifications.^{1,3,4} The impact of these treatment options—with a focus on antiplatelet therapy—in the context of clinical care is discussed in a case study of a patient presenting with chest pain (see page 71).

ACS Pathophysiology: Role of Platelets

The underlying pathophysiology of ACS is atherothrombosis, and platelets are intimately involved in this process.⁵ Disruption of vulnerable atherosclerotic plaque leads to activation, adhesion, and aggregation of platelets at the site of rupture and activation of the clotting cascade, resulting in intraluminal thrombus formation. Thrombosis is the body's normal hemostatic repair mechanism. However, if the thrombus completely occludes the coronary artery, STEMI occurs; alternatively, if the thrombus is partially occlusive or transiently totally occlusive and the artery remains patent, UA or NSTEMI occurs.⁶

In addition, platelets are believed to play an important role in inflammation. Atherosclerosis is a chronic inflammatory process, and platelets contribute to this process by producing inflammatory mediators.⁵ Although direct evidence for the role of platelets in atherosclerosis in humans is lacking, the detection of platelet-derived chemokines and growth factors in atherosclerotic plaques⁷ as well as the association between platelet activation and increased carotid artery wall thickness provide indirect evidence.⁸

ACS Management: An Integrated Approach

The approach to ACS management is 2-fold. First, immediate focal intervention is necessary to stabilize the ruptured plaque. The nature of this intervention depends on disease severity, such as extent of luminal narrowing, presence of intraluminal thrombosis, number of vessels affected, and the area of myocardial damage.⁹ Second, as platelets play a critical role in

thrombus formation, systemic antiplatelet therapy is essential to inhibit or modify the atherothrombotic process and reduce the risk of secondary thrombotic events. Patients with ACS usually have more than 1 ruptured plaque. In a study of 24 ACS patients who underwent a percutaneous coronary intervention (PCI) for an index coronary event, 79% had at least 1 plaque rupture some-

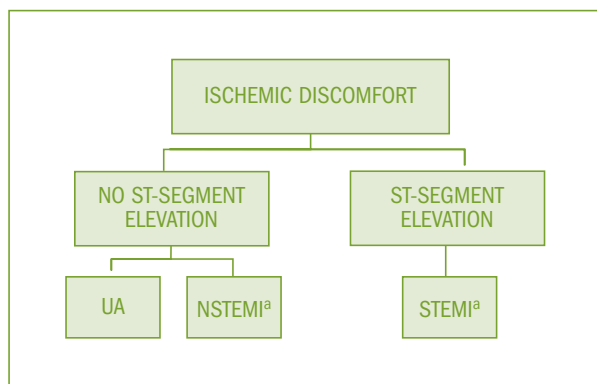


Figure 1. Clinical spectrum of ACS. ^aSerum levels of cardiac biomarkers indicative of myocardial necrosis. Adapted from Antman EM, et al.¹

where other than on the culprit lesion.¹⁰ Systemic antiplatelet therapy helps stabilize diffuse atherosclerosis in patients with cardiovascular (CV) disease, reducing the risk of secondary thrombotic events.⁹

Antiplatelet Therapy: Efficacy in Prevention of Ischemic Events in High-Risk Patients

The efficacy of antiplatelet agents in preventing vascular events (nonfatal MI, nonfatal stroke, or vascular death) was established in the Antiplatelet Trialists' Collaboration study.¹¹ This study evaluated the benefit of antiplatelet therapy in 145 randomized controlled trials of antiplatelet agents versus control and 29 randomized comparisons between antiplatelet regimens in about 70,000 high-risk patients (Figure 2). In each of the 4 main categories of high-risk patients reviewed (prior MI, acute MI, prior stroke or transient ischemic attack, and other high-risk patients [UA or stable angina, peripheral artery disease, diabetes, or postvascular procedures]), antiplatelet therapy was associated with about a 25% reduction in vascular events compared with controls. Overall, among all high-risk patients, antiplatelet therapy reduced nonfatal MI by about one third, nonfatal stroke by about one third, and vascular

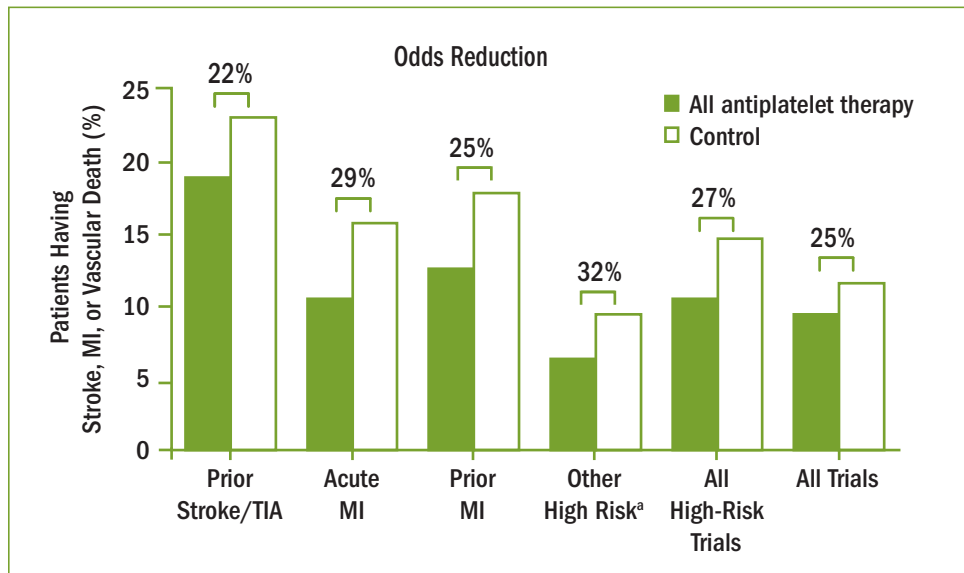


Figure 2. Efficacy of antiplatelet therapy in preventing ischemic events. Agents in the trials analyzed included those whose primary mode of action was inhibition of platelet aggregation or adhesion or both (cyclooxygenase inhibitors; phosphodiesterase inhibitors; platelet calcium ion channel inhibitors; phospholipase inhibitors; thromboxane synthetase inhibitors, receptor blockers, or both; and agents with direct effects on platelet membranes). The most widely tested antiplatelet regimen was aspirin, 75-325 mg/d. ^aOther high-risk patients included those with UA or stable AP, peripheral artery disease, diabetes, or post-CABG status. TIA = transient ischemic attack. Reproduced from Antiplatelet Trialists' Collaboration¹¹ with permission from BMJ Publishing Group Ltd.

death by about one sixth. Aspirin (75-325 mg/d) was the most widely tested antiplatelet regimen in these trials.

Efficacy of Aspirin: Is There a Dose Effect?

Aspirin doses <75 mg/d have been suggested to be more effective than higher doses in reducing vascular events in high-risk patients. However, according to a meta-analysis of antiplatelet therapies by the Antithrombotic Trialists' Collaboration, doses of <75 mg/d are less effective than doses \geq 75 mg/d.¹² The greatest proportional reduction (versus controls) in vascular events was in patients taking 75 to 150 mg/d (32% reduction), followed by reductions in those patients taking 160 to 325 mg/d (26%), 500 to 1500 mg/d (19%), and <75 mg/d (13%). Based on these results, it appears that low-dose aspirin (75-150 mg/d) is an effective antiplatelet regimen for long-term use.¹² It is common practice to administer low-dose aspirin of 81 mg/d (baby aspirin) for cardioprotection.

Aspirin Therapy: Concerns

Despite the proven efficacy of aspirin in reducing vascular events, about 28% of patients receiving aspirin therapy do not benefit from therapy and are classified as aspirin-resistant.¹³ These patients are at greater risk of clinically important long-term CV morbidity than patients who respond to aspirin (aspirin-sensitive patients). A meta-analysis of 20 studies comprising approximately 3000 patients with CV disease reported increased risks for any CV-related event (odds ratio [OR], 3.85; 95% confidence interval [CI], 3.08-4.80); death (OR, 5.99; 95% CI, 2.28-15.72), and ACS events (OR, 4.06; 95% CI, 2.96-5.56) in aspirin-resistant patients.¹³

Another concern with aspirin therapy is the attenuation of the effects of aspirin administered concomitantly with ibuprofen. This is particularly important when dosing 81-mg/d aspirin and 400-mg ibuprofen concomitantly because of the known pharmacodynamic interaction between these 2 regimens.¹⁴ Healthcare professionals should be aware of this interaction between aspirin and ibuprofen.

Dual Antiplatelet Therapy: Are 2 Better Than 1?

The Antiplatelet Trialists' Collaboration study showed that a substantial risk of vascular events remains in patients receiving aspirin therapy.¹¹ To reduce this risk further, the idea of combining aspirin with a second antiplatelet agent that has a different mechanism of action than aspirin evolved. The assumption is that dual antiplatelet therapy would provide an additive effect.

CURE Trial: Clopidogrel + Aspirin in Patients With ACS

The benefit of adding clopidogrel, an antiplatelet agent that inhibits platelet aggregation, to an aspirin regimen was demonstrated in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.¹⁵ Patients who presented within 24 hours after onset of ACS symptoms and who did not have ST-segment elevation were randomized to clopidogrel plus

aspirin (n = 6259) or placebo plus aspirin (n = 6303) for 3 to 12 months. Patients in the clopidogrel plus aspirin group received a loading dose of clopidogrel 300 mg immediately at presentation, followed by clopidogrel 75 mg daily, plus aspirin 75 to 325 mg daily; patients in the aspirin group received placebo in addition to aspirin (75-325 mg daily).

The addition of clopidogrel to aspirin reduced the cumulative risk of MI, stroke, or CV death by about 20% compared with aspirin alone (Figure 3). The benefits of clopidogrel were apparent as early as the first 24 hours after randomization, indicating that the oral loading dose was rapidly effective. Thereafter, the differences between the 2 groups were maintained until the end of the study.

Compared with aspirin, clopidogrel increased the risk of minor (5.1% vs 2.4%; $P < .001$) and major bleeding (3.2% vs 2.7%; $P = .001$). The percentage of patients receiving blood transfusions also was higher in the clopidogrel group than in the aspirin group—2.8% versus 2.2% ($P = .02$). However, no excess in bleeding that caused strokes, required surgical intervention or inotropic agents, or caused permanent disability was found with clopidogrel.¹⁵

Because different doses of aspirin (75-325 mg) were used in the CURE trial, the data were reanalyzed by aspirin dose groups.¹⁶ Major bleeding, but not efficacy, increased with increasing aspirin dose (Table 1). The excess risk with clopidogrel was 1.1% for aspirin doses <100 mg, 0.6% for doses 101 to 199 mg, and 1.2% for doses ≥ 200 mg. The combined incidence of MI, stroke, or CV death was reduced by addition of clopidogrel to aspirin in all aspirin-dose groups. These results suggest that clopidogrel is beneficial regardless of aspirin dose and 75 to 100 mg may be the optimal daily dose of aspirin. The bleeding rate with clopidogrel plus 75 mg of aspirin was lower than with high-dose aspirin alone.¹⁶

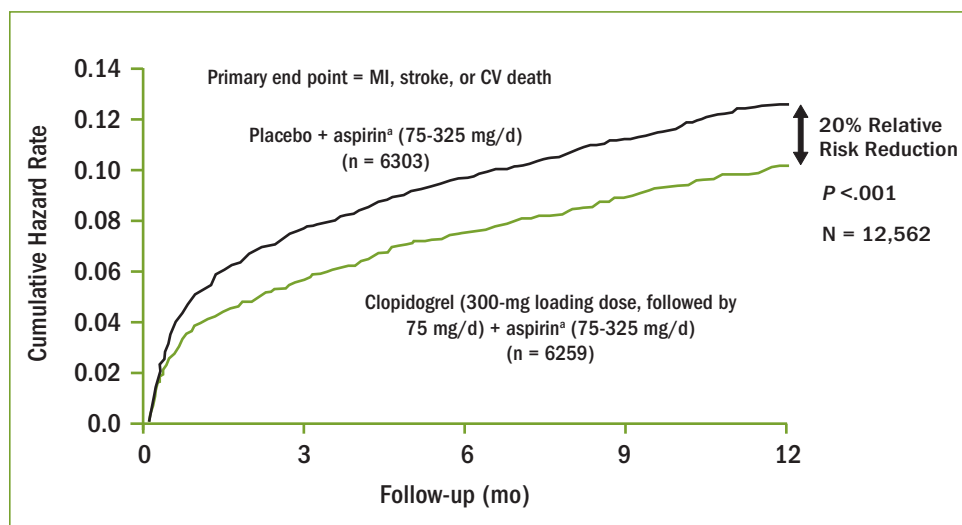


Figure 3. Effects of clopidogrel + aspirin in patients with ACS without ST-segment elevation. ^aIn addition to other standard therapies. Reproduced from Yusuf S, et al.¹⁵ Copyright © 2001 Massachusetts Medical Society. All rights reserved.

CLARITY: Clopidogrel + Aspirin and Fibrinolytic Therapy in ACS Patients With STEMI

The benefit of adding clopidogrel to a standard fibrinolytic regimen, including aspirin, in patients with STEMI was evaluated in the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial.¹⁷ Patients who presented within 12 hours after onset of STEMI were randomly assigned to clopidogrel (300-mg loading dose, followed by 75 mg once daily) or placebo. Patients also received aspirin, a fibrinolytic agent, and when appropriate, heparin (dispensed according to body weight) and underwent angiography 48 to 192 hours after the start of study medication. The primary efficacy end point was a composite of an occluded infarct-related artery (defined by a thrombolysis in myocardial infarction [TIMI] flow grade of 0 or 1) on angiography or death or recurrent MI before angiography.

Clopidogrel therapy reduced the odds of the composite primary end point by 36% (95% CI, 24%-47%; $P < .001$) over placebo (+ aspirin) (Table 2). Unlike the findings in the CURE trial, the addition of clopidogrel did not result in a significant increase in bleeding complications over placebo. The rates of major bleeding, minor bleeding, and intracranial hemorrhage

Table 1. Efficacy and Bleeding Results by Aspirin Dose in CURE Trial

Aspirin Dose (mg)	Aspirin Alone (%)	Aspirin + Clopidogrel (%)	All Patients (%)
Incidence of first coprimary outcome (MI, stroke, or CV death)			
≤100	10.5	8.6	9.6
101-199	9.8	9.5	9.7
≥200	13.6	9.8	11.7
<i>P</i> value for trend	.0016	.17	.0011
Major bleeding			
≤100	1.86	2.97	2.41
101-199	2.82	3.41	3.12
≥200	3.67	4.86	4.26
<i>P</i> value for trend	<.0001	<.001	<.0001
Life-threatening bleeding			
≤100	1.26	1.75	1.50
101-199	1.90	1.39	1.64
≥200	2.37	3.29	2.82
<i>P</i> value for trend	.004	.0006	<.0001

Adapted from Peters RJ, et al.¹⁶

were similar in the 2 groups. Thus, in STEMI patients receiving aspirin and a standard fibrinolytic regimen, clopidogrel improved the patency rate of the infarct-related artery and reduced ischemic complications.¹⁷

CHARISMA: Clopidogrel + Aspirin in High-Risk Patients

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial investigated whether the addition of clopidogrel to aspirin would provide greater protection against atherothrombotic events than aspirin alone in a broad population of high-risk patients (ie, patients with established CV disease or asymptomatic patients with multiple risk factors).¹⁸ Patients received a daily dose of 75-mg clopidogrel plus 75- to 162-mg low-dose aspirin or placebo plus low-dose aspirin for 28 months. The primary efficacy end point was a composite of MI, stroke, or death from CV causes.

The combination of clopidogrel plus aspirin was not found to be more effective than aspirin alone in reducing the rate of MI, stroke, or death from CV causes (6.8% vs 7.3%; $P = .22$). Although there was no significant difference in the rates of severe bleeding between the 2 groups, clopidogrel was associated with a significant increase in the rate of moderate bleeding (2.1% vs 1.3%; $P < .001$). A subgroup analysis suggested that clopidogrel was beneficial in symptomatic patients (with established disease) but not in asymptomatic patients (with CV risk factors) (Table 3). Additionally, dual antiplatelet therapy appeared to be more harmful in asymptomatic patients, resulting in an increased risk of bleeding complications.

Clopidogrel Therapy: Concerns

A major concern with clopidogrel is the potential for a rebound effect after stopping treatment.

Table 2. Efficacy of Clopidogrel + Aspirin and Fibrinolysis in Patients With STEMI

Outcome	Clopidogrel (n = 1752)	Placebo (n = 1739)	Odds Ratio (95% CI)	P Value
Primary efficacy end point, n (%)	262 (15.0)	377 (21.7)	0.64 (0.53-0.76)	<.001
TIMI flow grade 0 or 1	192 (11.7)	301 (18.4)	0.59 (0.48-0.72)	<.001
Death	45 (2.6)	38 (2.2)	1.17 (0.75-1.82)	.49
Recurrent MI	44 (2.5)	62 (3.6)	0.70 (0.47-1.04)	.08

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A retrospective cohort study of patients with ACS (N = 3137) discharged with posthospital treatment with clopidogrel reported a significantly higher rate of all-cause mortality or acute MI in the first 90 days versus 91 to 180 days after stopping clopidogrel.¹⁹ This effect was seen in all subpopulations studied—those who took shorter vs longer durations of clopidogrel therapy, among patients with and without diabetes, among medically treated patients, and among PCI-treated patients.¹⁹

Another concern with clopidogrel therapy is clopidogrel resistance. Clopidogrel is a pro-drug and needs to be metabolized to its active form in the liver. Metabolism occurs via *CYP2C19* pathway.²⁰ Loss of clopidogrel activity has been associated with genetic variants of *CYP2C19* (ie, loss-of-function alleles or reduced-function alleles). Patients carrying the *CYP2C19* loss-of-function or reduced-function alleles who received clopidogrel after acute MI had a higher rate of subsequent CV events (death from any cause, nonfatal stroke, or MI) than those who did not carry the defective alleles.^{20,21}

In a recent study, 2485 patients undergoing coronary stent placement after pretreatment with clopidogrel 600 mg were genetically evaluated and monitored for stent thrombosis for 30 days. While 1805 patients (73%) had “normal” *CYP2C19*, 680 patients (27%) carried 1 or 2 “mutant alleles” of the gene. The cumulative 30-day incidence of stent thrombosis was significantly higher in the “mutant allele” carriers than in the “normal” *CYP2C19* carriers: 1.5% versus 0.4% (*P* = .006).²²

In addition, recent evidence indicates that loss of response to clopidogrel occurs when it is coadministered with proton pump inhibitors (PPIs).^{23,24} Most PPIs inhibit the bioactivation

Table 3. Clopidogrel vs Aspirin in Preventing Atherothrombotic Events: Efficacy and Safety Outcomes

Primary Efficacy and Safety Outcome Event Rates	Clopidogrel + Aspirin	Aspirin + Placebo	Relative Risk (95% CI)	P Value
Asymptomatic subgroup^a (n = 3284)				
MI, stroke (of any cause), or death from CV causes (%)	6.6	5.5	1.2 (0.91-1.59)	.20
Severe bleeding (%)	2.0	1.2	NR	.07
Symptomatic subgroup^b (n = 12,153)				
MI, stroke (of any cause), or death from CV causes (%)	6.9	7.9	0.88 (0.77-0.998)	.046
Severe bleeding (%)	1.6	1.4	NR	.39

^aMembers of this subgroup had multiple atherothrombotic risk factors, without documented CV disease.

^bMembers of this subgroup had documented CV disease. NR = not reported. Bhatt DL, et al.¹⁸

of clopidogrel to its active metabolite (pantoprazole is a PPI that does not inhibit bioactivation of clopidogrel).²⁴ Use of PPIs has been associated with an increased risk of adverse outcomes, including all-cause mortality, rehospitalization for ACS, or reinfarction in patients with ACS taking clopidogrel.^{23,24}

Unlike clopidogrel, prasugrel, another antiplatelet agent with a similar mechanism of action to clopidogrel, does not seem to be affected by genetic variations of *CYP2C19*. Prasugrel is metabolized to its active metabolite by any of multiple hepatic enzymes.²⁵ CYP genetic variants do not affect active metabolite levels, inhibition of platelet aggregation, or clinical CV event rates in ACS patients treated with prasugrel.²¹ In addition, prasugrel has been shown to inhibit platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel in healthy volunteers and in ACS patients.²⁶ Prasugrel was recently approved by the FDA for reducing MI risk in patients undergoing angioplasty.

TRITON-TIMI 38: Prasugrel vs Clopidogrel in ACS

Given the greater efficacy of prasugrel in inhibiting platelet aggregation, the Trial to Assess

Table 4. Prasugrel vs Clopidogrel in Patients With Moderate- to High-Risk ACS

Efficacy Outcomes	Prasugrel (n = 6813)	Clopidogrel (n = 6795)	HR for Prasugrel (95% CI)	P Value
Death from CV causes, nonfatal MI, or nonfatal stroke, n (%)	643 (9.9)	781 (12.1)	0.81 (0.73-0.90)	<.001
Death from CV causes, n (%)	133 (2.1)	150 (2.4)	0.89 (0.70-1.12)	.31
Nonfatal MI, n (%)	475 (7.3)	620 (9.5)	0.76 (0.67-0.85)	<.001
Nonfatal stroke, n (%)	61 (1.0)	60 (1.0)	1.02 (0.71-1.45)	.93
Safety Outcomes	Prasugrel (n = 6741)	Clopidogrel (n = 6716)	HR for Prasugrel (95% CI)	P Value
Non-CABG-related TIMI major bleeding, n (%)	146 (2.4)	111 (1.8)	1.32 (1.03-1.68)	.03
Life-threatening bleeding, n (%)	85 (1.4)	56 (0.9)	1.52 (1.08-2.13)	.01
Fatal bleeding, n (%)	21 (0.4)	5 (0.1)	4.19 (1.58-11.11)	.002
Nonfatal bleeding, n (%)	64 (1.1)	51 (0.9)	1.25 (0.87-1.81)	.23

^aPrasugrel is not FDA-approved for treatment of ACS. Wiviott SD, et al.²⁶

Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 assessed whether prasugrel reduced ischemic events to a greater extent in ACS patients than clopidogrel.²⁶ In this trial, patients (N = 13,608) with moderate- to-high-risk ACS (10,074 with UA/NSTEMI and 3534 with STEMI), scheduled to undergo PCI, received prasugrel (60-mg loading dose, 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose, 75-mg daily maintenance dose) for 6 to 15 months. The primary efficacy end point was death from CV causes, nonfatal MI, or nonfatal stroke. The key safety end point was major bleeding. Patients treated with prasugrel had significantly greater reductions in ischemic events and MI compared with clopidogrel-treated patients ($P < .001$) (Table 4). However, prasugrel significantly increased the risk of TIMI major bleeding, including life-threatening and fatal bleeding (Table 4).²⁶

In the subgroup of patients with STEMI, prasugrel again significantly reduced ischemic events compared with clopidogrel (HR, 0.68 [95% CI, 0.54-0.87]; $P = .0017$) at 30 days after treatment; this effect was sustained to 15 months (HR, 0.79; 95% CI, 0.65-0.97; $P = .0221$).²⁷ In contrast to the entire ACS population in this study, patients with STEMI treated with prasugrel did not have more bleeding episodes than patients treated with clopidogrel. Rates of major bleeding unrelated to coronary artery bypass graft (CABG) surgery at 30 days and 15 months as well as life-threatening bleeding and TIMI major or minor bleeding were similar in the 2 treatment groups. The only exception was TIMI major bleeding after CABG surgery, which was significantly increased with prasugrel ($P = .0033$).²⁷ Thus, in patients with STEMI undergoing PCI, prasugrel seems to be more effective than clopidogrel in preventing ischemic events without increasing bleeding complications. Nonetheless, the risk of bleeding with prasugrel in high-risk ACS patients, especially those who are >75 years of age, who have had a previous stroke or TIA, or who weigh <132 lb (60 kg), is a concern and needs to be taken into consideration when evaluating the risk/benefit of therapy.

CASE STUDY

A 58-Year-Old White Man With Chest Pain

Presentation

A 58-year-old white male construction worker presents with increasing chest pain. He was recently evaluated in the emergency department. Based on electrocardiographic (ECG) findings and cardiac enzyme levels, a coronary event was ruled out, and he was discharged and referred to his primary care clinician for follow-up. His current complaints include increasing frequency and severity of chest pain, fatigue, and tightness in the upper chest and throat on mild exertion (eg, when taking out the trash). He reports being told in the hospital that his nonfasting plasma glucose (PG) was slightly elevated (145 mg/dL). He is not taking any medications and does not consume alcohol, but has a 30-year smoking history. He smokes 2 packs of cigarettes per day and is trying to cut down.



Physical Findings

- Height: 5 ft 9 in
- Weight: 205 lb
- Waist circumference: 41 in
- Blood pressure (BP): 140/85 mm Hg
- Pulse: 72 beats/min
- Vascular: no bruits; upper-extremity pulses within normal limits
- Heart: regular rhythm and rate, S₁ and S₂ with no murmurs or gallops
- Chest: clear to auscultation/percussion
- Abdomen: rotund, no pulsatile masses or distention

Clinical Decision Point

What is your diagnosis?

- Coronary artery disease (CAD)
- Metabolic syndrome
- Tobacco abuse
- All of the above

Comment

This patient's chest pain symptoms are suggestive of CAD. His waist circumference, elevated nonfasting PG level, and BP fit the criteria for metabolic syndrome.²⁸ His smoking history indicates tobacco abuse. With this risk factor profile and the increasing severity and frequency of his chest pain, ACS should be suspected.

Clinical Decision Point

How would you assess this patient?

- Stress test
- Resting ECG
- Coronary angiogram
- Glucose tolerance test
- All of the above

Comment

The ACC and AHA recommend early risk stratification for patients with symptoms

suggestive of ACS.³ The clinical suspicion of ACS in this patient is high. While a resting ECG is nonspecific, it should be done, as should exercise stress testing. Immediate referral to diagnostic angiography also might be considered and would be warranted if findings on the ECG or exercise stress test suggest CAD. Because this patient has a slightly elevated nonfasting glucose level, a glucose tolerance test should be included in the risk assessment to guide future therapy.

Test Results

- Resting ECG shows nonspecific ST-T wave abnormalities
- Stress test shows ischemia in area of the left anterior descending coronary artery (LAD)
- Coronary angiogram shows a 90% lesion in the LAD, an 80% lesion in the circumflex artery, and 20% to 30% lesion in the right coronary artery (RCA)
- Glucose tolerance test shows impaired glucose tolerance, but not frank diabetes

Clinical Course

The patient underwent PCI and received drug-eluting stents to the lesions in the LAD and the circumflex artery. His ejection fraction was normal, and the post-PCI course was unremarkable.

Clinical Decision Point

How should antiplatelet therapy be managed for this patient?

- Aspirin 325 mg/d indefinitely
- Clopidogrel 75 mg/d indefinitely
- Aspirin and clopidogrel for 1 month
- Aspirin and clopidogrel for 6 months

- Aspirin and clopidogrel for at least 12 months

Comment

ACC/AHA recommendations for antiplatelet therapy after drug-eluting stent placement for UA/NSTEMI include aspirin 162 to 325 mg/d for at least 3 to 6 months, then 75 to 162 mg/d indefinitely, and clopidogrel 75 mg/d for at least 1 year.³ While current treatment guidelines recommend dual antiplatelet therapy for at least 1 year in patients who undergo stent placement, most experts feel this treatment should be continued indefinitely (if patients tolerate the drugs) because of concerns about thrombosis, especially with drug-eluting stents.

Management Plan: Risk Reduction

In addition to antiplatelet therapy, the long-term management for this patient should include measures to reduce the modifiable risk factors for CAD. Treatment to reduce BP, a statin to decrease low-density lipoprotein cholesterol (LDL-C) levels, and agents to lower glucose levels; counseling for smoking cessation; an exercise program for cardiac rehabilitation; and measures to reduce weight are recommended.³ After initiation of risk factor modification measures, the patient was scheduled for a follow-up visit 1 month later and then at regular intervals.

9-Month Follow-Up

After 9 months, the patient reports having no chest pain or shortness of breath and feeling better than he has in 20 years. He has stopped smoking. His BP on angiotensin-converting enzyme inhibitor therapy has dropped to

125/80 mm Hg, and he has lost weight (weight, 175 lb; waist circumference, 37 in). His fasting glucose level is 90 mg/dL, and his LDL-C level is 70 mg/dL. He does complain about taking “a lot of medicine.” His current medications include aspirin: 81 mg/d, clopidogrel: 75 mg/d, atorvastatin: 40 mg/d, ramipril: 10 mg/d, and metformin: 2 g/d.

Clinical Decision Point

What should be your next step?

- Stop aspirin (the patient has had no further angina)
- Stop clopidogrel (9 months have elapsed since the stent placement)
- Decrease atorvastatin (his LDL-C level is now 70 mg/dL)
- Decrease ramipril (his BP is now 125/80 mm Hg)
- Decrease metformin (his fasting glucose level is now 90 mg/dL)
- None of the above

Comment

This patient’s current treatment regimen should not be changed. To reduce his risk for recurrent ischemic events, low-dose aspirin should be continued indefinitely, and clopidogrel should be continued for at least 1 year.³ Decreasing the antihypertensive, cholesterol-lowering, and glucose control therapies is also inadvisable. The patient should be congratulated on how well he has done and educated about the need for long-term treatment to control his risk factors to try to prevent any future CV events.

PCEFORUM

It's your turn. Post your comments to this clinical question:



Do you temporarily discontinue clopidogrel in a patient undergoing dental procedures, colonoscopy, or major surgery?

Post your answer to this question and more on the PCE Forum www.practicingclinicians.com/forumhomestudy

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QUESTIONS From Symposium Participants

Q: Should I tell my patients to discontinue clopidogrel before undergoing dental procedures, colonoscopy, or major surgery?

A: Minor bleeding from dental procedures can be managed (eg, with ice packs or pressure) without discontinuing clopidogrel. Any bleeding during a screening colonoscopy would also be minor and probably would not warrant stopping the drug and potentially increasing the patient's risk of a cardiac event. If the patient is likely to have colonic polyps or to require biopsy, stopping the drug would be advisable. Major surgery would require clopidogrel discontinuation because the risk of excessive bleeding would be higher, but discontinuing it would place the patient at risk for a thrombotic event. These decisions need to be based on each patient's risk profile, and the risks and benefits of stopping the drug should be explained to the patient.

Q: Is thrombotic thrombocytopenic purpura (TTP) a concern with clopidogrel?

A: It can occur, but fortunately it is a rare complication.

Q: Is PPI prophylaxis a standard of care for gastric protection in patients receiving antiplatelet therapy?

A: No. PPIs for routine prophylaxis tend to be overused. The main thing for clinicians to remember is that concomitant PPI and clopidogrel therapy may attenuate the benefits of clopidogrel after ACS. PPIs should not be used in the absence of a clear indication. H₂ blockers may be tried for occasional dyspepsia.

Q: Do patients receiving clopidogrel who develop a condition requiring heparin treatment need to discontinue clopidogrel before starting anticoagulant therapy?

A: No. The mechanisms of action of the 2 drugs are different.

Q: Do age or gender impact the effects of aspirin?

A: The gender issue is interesting. For primary prevention, aspirin appears to be more cardioprotective in men than in women. However, it decreases the risk of stroke more in women than in men. Age is not an issue for prescribing aspirin.

Read more Q&A from the live symposia at www.practicingclinicians.com/H2_2009/acsqa.pdf