

ANTIPLATELET THERAPY FOR ACUTE CORONARY SYNDROMES

Preventing Recurrent Ischemic Events in Patients With UA/NSTEMI



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 recommendations in current practice guidelines and the supporting clinical data regarding the use of oral antiplatelet agents for preventing recurrent ischemic events in patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI).

Learning Objectives

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

- Compare the efficacies of aspirin, clopidogrel, and prasugrel for preventing recurrent ischemic events in patients who have experienced an initial UA or NSTEMI event.
- Differentiate the bleeding risks associated with aspirin, clopidogrel, and prasugrel, based on patients' individual risk factor profiles.
- Use current practice guidelines to formulate treatment plans for secondary prevention of ischemic events in patients with UA/NSTEMI managed initially with medical therapy, percutaneous coronary intervention, or surgery.

Accreditation Information

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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 November 1, 2010. Participants may submit the self-assessment at any time during that period.

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Release date: November 1, 2010

Expiration date: November 1, 2011

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Unstable angina/non-ST-segment elevation myocardial infarction

(UA/NSTEMI) constitutes a subset of acute coronary syndrome (ACS).¹ UA/NSTEMI is defined by ST-segment depression or prominent T-wave inversion on an electrocardiogram (ECG) and/or positivity for biomarkers of necrosis (eg, troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent). It is usually, but not always, caused by atherosclerotic coronary artery disease. In this setting, the most common underlying pathophysiologic cause of UA/NSTEMI is reduced myocardial perfusion, subsequent to coronary artery narrowing due to the presence of a thrombus (usually nonocclusive) that develops on a disrupted atherosclerotic plaque. A less common cause of UA/NSTEMI is dynamic obstruction resulting from intense focal epicardial coronary artery spasm, spasm on top of a plaque, or dynamic microvascular dysfunction/spasm.¹

Most cases of ACS are due to UA/NSTEMI. Of 2.43 million hospital discharges annually for ACS, 1.97 million are for UA/NSTEMI and 0.46 million are for ST-segment elevation MI (STEMI).²⁻⁴ UA/NSTEMI is associated with an increased risk of cardiac death and subsequent MI.¹ Patients with non-ST-segment elevation (NSTE) ACS have a moderate-to-high risk of early adverse outcomes—a 5.5% to 10.5% risk of death or MI within 30 days—underscoring the importance of rapid assessment, triage, and treatment in this subset of ACS patients.⁵

Oral antiplatelet agents are central to the management of ACS, including UA/NSTEMI. 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 these patients.¹ This issue of *Antiplatelet Therapy for Acute Coronary Syndromes* reviews recent recommendations in practice guidelines for the administration of oral antiplatelet agents in patients with UA/NSTEMI and examines relevant published data supporting

the use of oral antiplatelet agents in this patient population. Case-based expert commentary on practical clinical considerations is provided by Randall M. Zusman, MD, and John G. McGinnity, MS, PA-C, DFAAPA.

Antiplatelet Agents in the Management of Patients With UA/NSTEMI Aspirin

Aspirin is an integral component of most antiplatelet regimens. Placebo-controlled trials of aspirin in UA/NSTEMI consistently have shown

a benefit with aspirin.⁶⁻⁹ A systematic review of aspirin trials, which included 5031 patients with UA in 12 trials, comparing aspirin with placebo or no treatment reported a 46% relative odds reduction in serious vascular events (nonfatal MI, nonfatal stroke, or vascular death) with aspirin treatment.¹⁰ This systematic review also found the proportional reduction in risk appears to be similar with aspirin doses of 75 to 150 mg, 160 to 325 mg, and 500 to 1500 mg (Table 1). Daily doses of aspirin <75 mg seemed to be less effective with a proportional reduction of 13% in the risk of vascular events.¹⁰

The AHA/ACC and the American College of Chest Physicians (ACCP) guidelines for the management of UA/NSTEMI recommend that aspirin be administered as soon as the diagnosis of ACS is made or suspected, unless contraindicated, and continued indefinitely.^{1,11} The initial recommended dose of aspirin is 162 to 325 mg. Although aspirin doses ranging from 75 to 1500 mg per day result in similar reductions in the odds of vascular events, higher aspirin doses are associated with an increased risk of bleeding.¹² Therefore, the ACC/AHA guidelines recommend doses of 75 to 162 mg per day of aspirin

Table 1. Efficacy of Aspirin in Reducing Vascular Events^a in High-Risk Patients

Dose (mg/d)	No. of Trials	Rate of Vascular Events (%) Aspirin	Rate of Vascular Events (%) Control	Odds Reduction (%)
500-1500	34	14.5	17.2	19
160-325	19	11.5	14.8	26
75-150	12	10.9	15.2	32
<75	3	17.3	19.4	13
Any aspirin	65	12.9	16.0	23

^aVascular events included nonfatal MI, nonfatal stroke, and death from vascular causes. Adapted from Antithrombotic Trialists' Collaboration.¹⁰

for long-term therapy,¹ while the ACCP recommends doses of 75 to 100 mg per day, regardless of type of treatment.¹¹ However, the current recommendation is to use high-dose aspirin (162-325 mg) for 1 month after a patient receives a bare metal stent (BMS) and 3 to 6 months after a drug-eluting stent (DES) to prevent stent thrombosis.¹

Clopidogrel

The efficacy of clopidogrel as an antiplatelet agent has been established in a wide spectrum of patients with ACS.

In Aspirin-Contraindicated Patients

Based on the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, clopidogrel is recommended as an alternative antiplatelet agent in patients with UA/NSTEMI who are unable to tolerate aspirin.^{1,13} CAPRIE was a blinded, multicenter, investigation of >19,000 secondary prevention patients observed for 1 to 3 years, randomized to clopidogrel 75 mg/d or aspirin 325 mg/d. At a mean follow-up of 1.91 years, clopidogrel was shown to be more effective than aspirin in reducing vascular events with an overall safety profile that was at least as good as that of medium-dose aspirin. Patients treated with clopidogrel had an annual 5.3% risk of ischemic stroke, MI, or vascular death, compared with 5.8% in patients treated with aspirin, reflecting a statistically significant relative risk reduction of 8.7% with clopidogrel ($P = .043$). The incidences of intracranial hemorrhage (0.33% with clopidogrel and 0.47% with aspirin) and gastrointestinal hemorrhage (0.52% with clopidogrel and 0.72% with aspirin) were similar in the 2 groups.¹³

In Combination With Aspirin

The Clopidogrel in Unstable Angina to

Prevent Recurrent Events (CURE) trial established the efficacy of dual antiplatelet therapy (aspirin plus clopidogrel) in patients with UA/NSTEMI ACS.¹⁴ CURE randomized 12,562 patients with UA/NSTEMI presenting within 24 hours to clopidogrel (300 mg loading dose followed by 75 mg/d) or placebo and followed them for 3 to 12 months. All patients also received aspirin (75-325 mg/d). Patients receiving clopidogrel plus aspirin for 1 year were found to have a 20% relative risk reduction and a 2% absolute risk reduction in incidence of MI, stroke, or cardiovascular (CV) death versus aspirin alone (placebo group) ($P < .001$) (Table 2). Further analysis indicated the benefit of adding clopidogrel to aspirin was apparent within a few hours after randomization. The rate of death from CV causes, nonfatal MI, stroke, or refractory or

severe ischemia was significantly lower in the clopidogrel plus aspirin group by 24 hours after randomization (1.4% vs 2.1%), representing a relative risk reduction of 44% compared with aspirin alone. Clopidogrel plus aspirin also reduced in-hospital severe ischemia and revascularization.

These benefits of dual antiplatelet therapy, however, came with a price. Clopidogrel plus aspirin therapy increased the risk of minor and major bleeding episodes, compared with aspirin therapy alone (Table 2).¹⁴ The number of patients receiving blood transfusions (≥ 2 U of blood) also was higher in the clopidogrel plus aspirin group. However, the rates of fatal bleeding (0.2%), bleeding requiring surgical intervention (0.7%), and bleeding causing hemorrhagic stroke (0.1%) did not differ between the 2 groups.¹⁴

Table 2. Efficacy and Safety of Clopidogrel + Aspirin vs Aspirin Alone: CURE Trial

Variable	Clopidogrel + Aspirin (n = 6259)	Placebo + Aspirin (n = 6303)	Relative Risk (95% CI)	P Value
Incidence of outcomes, no. (%)				
Primary: nonfatal MI, stroke, or death from CV causes	582 (9.3)	719 (11.4)	0.80 (0.72-0.90)	<.001
Secondary: first primary outcome or refractory ischemia	1035 (16.5)	1187 (18.8)	0.86 (0.79-0.94)	<.001
Bleeding complications, no. (%)				
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13-1.67)	.001
Necessitating transfusion of ≥ 2 U of blood	177 (2.8)	137 (2.2)	1.30 (1.04-1.62)	.02
Life-threatening	135 (2.2)	112 (1.8)	1.21 (0.95-1.56)	.13
Non-life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22-2.35)	.002
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75-2.56)	<.001

CI = confidence interval; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV = cardiovascular; MI = myocardial infarction.

Adapted from Yusuf S, et al.¹⁴

Based on the CURE trial results, the guidelines recommend adding clopidogrel to aspirin and continuing treatment for ≥ 1 month and preferably for 1 year in patients receiving initial conservative management.¹

In Patients Undergoing Percutaneous Coronary Intervention (PCI)

PCI-CURE was a substudy of the CURE trial in patients who underwent PCI.¹⁵ Patients were randomized to clopidogrel (300-mg loading dose) or placebo for a mean of 6 days before PCI. After PCI, patients received an open-label thienopyridine (clopidogrel or ticlopidine) for 2 to 4 weeks followed by the randomized treatment for a mean of 8 months. At each phase of the study, aspirin also was administered (75-325 mg). Overall, including events before and after PCI, clopidogrel plus aspirin treatment resulted in a 31% reduction in CV death or MI ($P = .002$). After PCI, long-term administration of clopidogrel was associated with a 17% lower rate of CV death, MI, or any revascularization ($P = .03$); and a 25% lower rate of CV death or MI ($P = .047$) compared with aspirin alone (placebo).¹⁵ No significant difference in the rate of major bleeding was observed between the 2 groups, although minor bleeding was significantly higher in the combination group (3.5% vs 2.1%; $P = .03$).

The PCI-CURE study established that in patients with ACS who are receiving aspirin, clopidogrel pretreatment followed by long-term therapy is beneficial in reducing major CV events, compared with placebo. The guidelines recommend that in UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with clopidogrel (loading dose followed

by daily maintenance dose) or an intravenous glycoprotein IIb/IIIa inhibitor. If the invasive procedure entails stent implantation, in patients implanted with a BMS, dual antiplatelet therapy is recommended for at least 1 month and in those implanted with DES, at least 3 to 6 months. The guidelines also recommend that ideally dual therapy be maintained for 1 year.¹

In Patients Undergoing Coronary-Artery Bypass Grafting (CABG)

In the CURE trial, an increase in bleeding risk was noted in patients undergoing CABG within the first 5 days of stopping clopidogrel (5 days being the duration of clopidogrel effect).¹⁴ The rate of major bleeding was 9.6% in the clopidogrel plus aspirin group and 6.3% in the aspirin alone group (relative risk, 1.53; $P = .06$). In patients who discontinued the study medication >5 days before the procedure, no excess major bleeding occurred in the combination group within 7 days after surgery: 4.4% versus 5.3% in the aspirin alone group.

Similar to the results of the CURE trial, analysis of data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) initiative indicated that NSTEMI ACS patients who underwent CABG within ≤ 5 days of last clopidogrel treatment had a significant increase in blood transfusions (65.0% vs 56.9%; adjusted odds ratio [OR] 1.36; 95% confidence interval [CI], 1.10-1.68) as well as the need for transfusion of ≥ 4 U of blood (27.7% vs 18.4%, OR 1.70; 95% CI, 1.32-2.19) compared with those who underwent CABG within >5 days of the last clopidogrel treatment. Acute clopidogrel therapy was not associated with higher bleeding risks if CABG was delayed

>5 days (adjusted OR 1.18; 95% CI, 0.54-2.58).¹⁶

Because of the increased bleeding risk with clopidogrel in NSTEMI ACS patients undergoing CABG, guidelines recommend that clopidogrel be discontinued for at least 5 days prior to CABG.^{1,11}

Optimal Clopidogrel Loading Dose

Clopidogrel currently is administered at a loading dose of 300 mg followed by a daily dose of 75 mg. In patients with UA or acute MI who are undergoing PCI, recent data indicate that a loading dose of 600 mg may provide greater benefit than the standard loading dose of 300 mg. In a subgroup analysis of the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial, treatment with clopidogrel 600-mg loading dose produced a statistically significant reduction in the primary composite end point of death from CV causes, MI, or stroke (4.2% in double-dose group vs 4.4% in standard-dose group; $P = .30$) as well as in stent thrombosis (1.6% vs 2.3%; $P = .001$) compared with the standard 300 mg loading dose in patients undergoing PCI.¹⁷ The increased efficacy, however, was associated with increased rates of major (2.5% vs 2.0%; $P = .01$; double vs standard dose) and severe bleeding (1.9% vs 1.6%; $P = .04$; double vs standard dose) but not intracerebral hemorrhage or fatal bleeds.

Clopidogrel and Genetic Variability

Despite the established efficacy of clopidogrel in preventing ischemic events, approximately 15% to 25% of patients treated with clopidogrel do not derive benefit from treatment.¹⁸ This may be attributed to genetic variability in *CYP2C19*, the enzyme involved in the metabolism of clopidogrel. Several known

loss-of-function alleles of *CYP2C19*—*2, *3, *4, *5, *6, *7, and *8 are known; the *CYP2C19**2 and *3 alleles exhibit no functional metabolism of clopidogrel. *CYP2C19**2 is the most prevalent of the loss-of-function alleles. A higher rate of CV events has been shown to occur in patients with ACS carrying the *CYP2C19* loss-of-function alleles taking clopidogrel after an index event compared with those carrying the wild-type alleles.¹⁹ Consequently, the US Food and Drug Administration (FDA) issued a Drug Safety Communication warning about the reduced effectiveness of clopidogrel in patients who are poor metabolizers of clopidogrel (ie, patients who carry 2 loss-of-

function alleles).²⁰ To guide clinicians on how to manage patients with reduced clopidogrel effectiveness, the ACC Foundation Task Force on Clinical Expert Consensus Documents and AHA recently released a consensus document on *Approaches to the FDA “Boxed Warning.”*¹⁹ The ACC/AHA recommend the following options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance:

- Clopidogrel may be switched to prasugrel, which has been found to result in decreased rates of stent thrombosis.
- Higher loading doses (600 mg vs

300 mg), double-dose loading (600 mg twice over 2 hours) and higher maintenance doses of clopidogrel (150 mg daily) have been found to improve platelet inhibition and might be alternatives for high-risk patients who respond poorly to standard loading and maintenance doses of clopidogrel. There is uncertainty of the long-term safety and efficacy of this approach.

- Functional testing may be performed and considered to help determine if patients are clopidogrel nonresponders. The evidence base is insufficient at present to recommend routine genetic or platelet function testing.

Table 3. Prasugrel vs Clopidogrel Efficacy in Reducing CV Death, Nonfatal MI, or Nonfatal Stroke: TRITON-TIMI 38

Patient Group	N	Rate of CV Death, Nonfatal MI or Nonfatal Stroke (%)		HR for Prasugrel Efficacy (95% CI)	P Value
		Prasugrel	Clopidogrel		
Overall	13,608	9.9	12.1	0.81 (0.73-0.90)	<.001
UA or NSTEMI	10,074	9.9	12.1	0.82 (0.73-0.93)	.002
STEMI	3534	10.0	12.4	0.79 (0.65-0.97)	.02

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non–ST-segment elevation MI; STEMI = ST-segment elevation MI; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in MI 38; UA = unstable angina. Adapted from Wiviott SD, et al.²¹

Table 4. In-Hospital Outcomes in Patients With NSTEMI by Hospital Adherence to ACC/AHA Guidelines

Population	No. of Events (%) by Hospital Adherence Quartile				P Value
	1 (Lowest)	2	3	4	
NSTEMI (N = 57,260)	(n = 9892)	(n = 12,597)	(n = 18,149)	(n = 16,622)	
Death	760 (7.68)	701 (5.56)	843 (4.64)	718 (4.32)	<.001
Death/MI ^a	1055 (10.67)	1128 (8.95)	1206 (6.64)	1105 (6.65)	<.001
Stroke	96 (0.80)	146 (0.98)	171 (0.94)	134 (0.72)	.25
CHF	862 (8.71)	1368 (10.86)	1851 (10.20)	1424 (8.57)	.13

ACC = American College of Cardiology; AHA = American Heart Association; CHF = congestive heart failure; MI = myocardial infarction; NSTEMI = non–ST-segment elevation MI.

^aIn-hospital death or recurrent MI. Adapted from Peterson ED, et al.²⁴

Prasugrel

Prasugrel recently was approved for use in patients undergoing PCI. The basis for prasugrel approval came from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38).²¹ In this trial, patients with moderate- to high-risk ACS and scheduled for 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. Of the randomized patients, 10,074 had UA/NSTEMI and 3534 had STEMI. At 15 months, the incidence of the primary end point (death from CV causes, nonfatal MI, or nonfatal stroke) was significantly lower with prasugrel therapy than clopidogrel in the entire cohort (9.9% vs 12.1%; $P < .001$). Among patients with UA/NSTEMI, there was an 18% risk reduction in the primary end point in prasugrel- versus clopidogrel-treated patients (9.9% vs 12.1%)

(Table 3). Reductions in ischemic risk were partially counterbalanced by increased bleeding in the prasugrel group. TIMI major bleeding (2.4% vs 1.8%; $P = .03$), including life-threatening (1.4% vs 0.9%; $P = .01$) and fatal bleeding (0.4% vs 0.1%; $P = .002$), significantly increased with prasugrel treatment.²¹

Despite the overall greater efficacy of prasugrel, post hoc subgroup analyses revealed that patients with a history of stroke or transient ischemic attack (TIA) before enrollment, the elderly (age ≥ 75 years), and those with a body weight of < 60 kg had less clinical efficacy and greater absolute levels of bleeding than the overall cohort; in effect, these patients had net clinical harm with treatment. When these patients were excluded from the analyses, the prasugrel regimen was found to be superior to the clopidogrel regimen with a significant net clinical benefit (hazard ratio, 0.80; 95% CI, 0.71-0.89; $P < .001$). (Note: this clinical benefit of prasugrel is similar to that achieved with a 600-mg loading dose of clopidogrel in the CURRENT-OASIS 7

trial.) Due to the net clinical harm of prasugrel in patients with a history of TIA or stroke and patients age ≥ 75 years, prasugrel is contraindicated in these patients.²²

In the ACC/AHA 2009 Joint STEMI/PCI Guidelines Focused Update, clopidogrel (75 mg daily) or prasugrel (10 mg daily) was recommended for at least 12 months in patients with UA/NSTEMI receiving a BMS or DES during PCI for ACS.²³ This recommendation was based on efficacy results from TRITON-TIMI 38.²¹

Underutilization of Antiplatelet Agents in Clinical Practice

Despite guideline recommendations for long-term antiplatelet therapy to prevent recurrent ischemic events in patients with ACS,¹ evidence from clinical practice suggests antiplatelet agents are substantially underutilized. Analysis of the CRUSADE registry found up to 25% of opportunities to provide guideline-recommended care in patients with NSTEMI ACS were missed in current practice. Specifically, recommended antiplatelet therapy (clopidogrel) was not prescribed in 46% of eligible patients at hospital discharge.²⁴ Guideline adherence, however, was shown to be significantly associated with better outcomes, especially in-hospital mortality and recurrent MI (Table 4).²⁴ After adjustment for patient demographics and clinical features, in-hospital mortality rates for patients with NSTEMI ACS decreased from 6.31% for the lowest adherence quartile to 4.15% for the highest adherence quartile ($P < .001$). Every 10% increase in the guideline adherence rate at a hospital was associated with an analogous 10% decrease in patients' likelihood of in-hospital mortality (adjusted OR 0.90; 95% CI 0.84-0.97; $P < .001$) (Figure). These results underscore the importance of guideline adherence in improving patient outcomes.

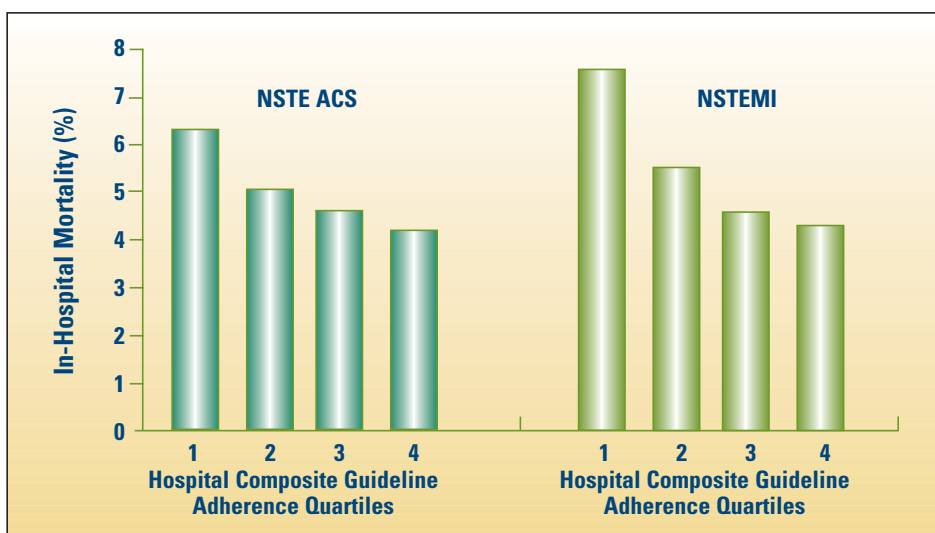
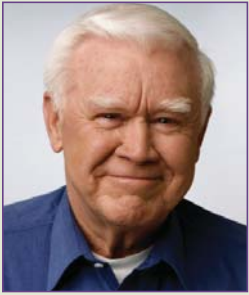


Figure. Hospital adherence to ACC/AHA guidelines for ACS management decreases in-hospital mortality in the NSTEMI ACS and NSTEMI patient population. At total of 350 hospitals were grouped by composite guideline adherence into quartiles, with quartile 1 representing lowest adherence and quartile 4 representing the highest. Every 10% increase in overall guideline adherence was associated with a corresponding 10% decrease in patients' risk of in-hospital mortality. ACC = American College of Cardiology; AHA = American Heart Association; NSTEMI ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction. Reprinted with permission from Peterson ED, et al.²⁴ Copyright © 2006 American Medical Association. All rights reserved.



Case: 72-Year-Old Man With Retrosternal Chest Pressure

Mr Jones is a 72-year-old man with hypertension and dyslipidemia. He is an active smoker who presented in the hospital with a retrosternal chest pressure of 1 hour's duration.

Medical History

- Hypertension, dyslipidemia, hypothyroidism
- Surgeries: tonsillectomy and adenoidectomy (as a child); abdominal hernia repair
- Family history: mother, with hypertension, had a stroke at age 56 years
- Smoking history: tobacco use; 50 pack years
- Alcohol use: none

Medications

Outpatient

- Aspirin: 81 mg daily
- Lisinopril/hydrochlorothiazide: 10/12.5 mg daily
- Simvastatin: 40 mg daily
- Levothyroxine: 75 µg daily

Emergency Department

- Aspirin: 325 mg
- Nitroglycerin drip: 20 µg/min

Physical Findings

- Weight: 195 lb; height: 5 ft 10 in
- Blood pressure: 146/88 mm Hg
- Pulse: 78 beats/min, regular; temperature: 98.8°F
- Neck: no jugular venous distension; no carotid bruits, carotid pulsations 2+
- Chest: clear to auscultation; no wheezing or rhonchi
- Heart: regular rate and rhythm; S₁ and S₂; no S₃, S₄, or murmurs
- Abdomen: bowel sounds ×4; no tenderness, distension, or masses; normal liver span
- Extremities: no significant edema; distal pulses, 2+

ECG and Laboratory Findings

- ECG: normal sinus rhythm; rate 82 beats/min; T-wave inversion in leads V1-V4
- White blood cell count: 4300/µL
- Red blood cell count: $4.94 \times 10^6/\mu\text{L}$
- Hemoglobin: 15.3 g/dL

- Hematocrit: 43.7%
- Platelet count: $276 \times 10^3/\mu\text{L}$
- Glucose: 85 mg/dL
- Aspartate aminotransferase: 27 U/L
- Alanine aminotransferase: 36 U/L
- Total cholesterol (TC): 179 mg/dL
- Triglycerides (TGs): 62 mg/dL
- High-density lipoprotein cholesterol (HDL-C): 45 mg/dL
- Low-density lipoprotein cholesterol (LDL-C): 80 mg/dL
- Sodium: 139 mEq/L
- Potassium: 4.2 mEq/L
- Chloride: 105 mEq/L
- Carbon dioxide: 27.0 mEq/L
- Creatinine: 1.2 mg/dL
- Blood urea nitrogen: 15 mg/dL
- Troponin T: 7 ng/mL

Hospital Management

The patient was taken immediately to the catheterization laboratory. Cardiac catheterization revealed 95% proximal left anterior descending artery (LAD) that is hazy, 40% distal left circumflex coronary artery (LCX), and diffuse minor 20% to 30% lesions in the right coronary artery (RCA). Left ventriculogram demonstrated an ejection fraction of 45% to 55%. PCI with stenting was performed to LAD without complication. A DES was placed with a 0% residual stenosis.

What is the optimal postdischarge regimen for this patient? For an expert opinion, read the following Case Commentary by Randall M. Zusman, MD, and John G. McGinnity, MS, PA-C, DFAAPA.

Commentary

RZ: This case represents a typical presentation of an ACS event. The patient, a 72-year-old man with multiple cardiac risk factors (hypertension, hypercholesterolemia, and tobacco abuse) presents with chest pain, ECG changes, and

an elevated troponin level characteristic of a diagnosis of NSTEMI. The initial goals of therapy are to relieve the chest pain with nitrates, control the heart rate and blood pressure (with beta-adrenergic receptor blockers if needed), and prevent formation and/or propagation of intraluminal coronary thrombosis.

The most aggressive strategy in this setting is the initiation of heparin anticoagulation, reloading with aspirin, and use of an adenosine diphosphate (ADP) receptor antagonist, either clopidogrel or prasugrel. In CURE, which included a large study population of ACS patients, clopidogrel in combination with aspirin and heparin was shown to reduce morbidity and mortality markedly when given within 24 hours of presentation. Although the CURE study used a loading dose of 300 mg, more recent studies suggest a 600-mg loading dose is more effective, and most interventional cardiologists have adopted the higher loading dose schedule.

An alternative strategy is to delay initiating ADP-receptor blocker therapy and proceed immediately to coronary angiography to assess the coronary anatomy and determine whether PCI or CABG is needed. The TRITON-TIMI 38 trial used such a strategy under these circumstances and demonstrated prasugrel use was associated with a superior outcome compared with clopidogrel (300-mg loading dose). However, older patients (>75 years of age), smaller patients (<132 lb), and patients with a history of a cerebrovascular event had a higher risk of fatal bleeding and are not candidates for prasugrel. Given that up to 20% of the population may be resistant to clopidogrel, in this setting, the more rapid onset of action and the more predictable antiplatelet effect are advantages of prasugrel.

The patient's postcatheterization therapy is crucial to long-term CV risk reduction. In my opinion, this patient's post-PCI therapy should include a beta-adrenergic receptor blocker to control blood pressure and heart rate and reduce subsequent mortality risk, an angiotensin-converting enzyme inhibitor to decrease blood pressure and prevent ventricular remodeling during the post-MI period, high-dose statin therapy to reduce his LDL-C to <70 mg/dL, as well as aspirin plus clopidogrel or prasugrel. Although long-term (multiyear) data for the benefits of clopidogrel or prasugrel are not available, because the physiologic processes involved in thrombotic events are not eliminated by short-term antiplatelet therapy and patients' risk of a recurrent vascular event (MI, stroke, or vascular death) is ongoing, I am convinced that indefinite therapy with an ADP-receptor

antagonist is warranted. In addition, lifestyle modification (dietary modification, weight loss, exercise, and sodium restriction) is an important part of the long-term cardiac risk reduction strategy for patients with ACS.

JM: This patient will need aspirin therapy for life. Because he received DES placement, he initially will need full-dose aspirin therapy (162-325 mg/d) for 3 to 6 months. We would typically prescribe aspirin for 6 months at a dose of 325 mg/d unless a patient has bleeding risk factors or GI issues that would preclude it.

What the optimal next step is in antiplatelet therapy is a more difficult question to answer. Until recently, the most common approach would be a loading dose of 300-mg clopidogrel, followed by 75 mg/d for at least 3 to 6 months. In our patients, we would wait to administer the loading dose of clopidogrel until the coronary anatomy and need for CABG were determined by catheterization to avoid bleeding complications during surgery. With the results of TRITON-TIMI 38 and FDA approval of prasugrel, we have another choice for ADP-receptor blocker therapy. Prasugrel showed an 18% risk reduction in CV death and nonfatal MI or stroke in certain patient populations. Risks of bleeding were higher with prasugrel in patients with a history of stroke or TIA who were aged >75 years or had a body weight <60 kg. This patient does not meet any of those criteria, but at 72 years of age, he is approaching the age limit, and this might cause some clinicians to be reluctant to use prasugrel. Whether the 18% risk reduction in events outweighs the risks of bleeding depends on the clinician's judgment. Also, like clopidogrel, prasugrel should not be given when urgent CABG is needed. Regardless of the ADP receptor blocker chosen, typically, we would keep the patient on antiplatelet therapy for at least 1 year unless cost or bleeding issues mandate a shorter treatment period of 3 to 6 months.

For patients with a new ACS event, it is imperative that clinicians review all the risks for future adverse events before hospital discharge. Risk reduction therapy starts with appropriate lifestyle changes, including heart healthy diet, exercise (which may begin with cardiac rehabilitation), and smoking cessation programs. Controlling all other risk factors for coronary artery disease to therapeutic goals is essential. Antiplatelet therapy is a critical component of ACS risk reduction. We cannot discharge a patient without reviewing these essential treatments and considering the risks and benefits. As PAs and NPs we need to lead patient education efforts and ensure all patients are treated according to current guidelines. ■

PCE Takeaways

- Aspirin has been shown to have a consistent benefit in patients with UA/NSTEMI. Practice guidelines recommend aspirin therapy be initiated as soon as the diagnosis is made or suspected (unless contraindications are present) and continued indefinitely.
- Clopidogrel is recommended by practice guidelines for secondary prevention of ACS in patients with UA/NSTEMI who are being managed medically or undergoing PCI or CABG. To reduce bleeding risks, clopidogrel should be discontinued at least 5 days prior to surgery.
- Prasugrel is recommended in practice guidelines as an option for dual antiplatelet therapy to reduce risk of recurrent ischemic events in patients with UA/NSTEMI receiving a stent during PCI.
- For patients who are poor metabolizers of clopidogrel and in whom the effectiveness of clopidogrel may be reduced, practice guidelines suggest switching to prasugrel or adjusting the clopidogrel dose (eg, higher loading doses, double-dose loading, or higher maintenance doses), although the long-term safety and efficacy of this approach are uncertain.

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