

ANTIPLATELET THERAPY FOR ACUTE CORONARY SYNDROMES

Preventing Recurrent Ischemic Events in Patients With STEMI



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 ST-segment elevation myocardial infarction (STEMI).

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 STEMI 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 STEMI managed initially with medical therapy, percutaneous coronary intervention, or surgery.

Accreditation Information

The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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 November 22, 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.

This activity was supported by an educational grant from Daiichi Sankyo, Inc. and Lilly USA, LLC.

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- Read the newsletter.
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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: November 22, 2010

Expiration date: November 22, 2011

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ST-segment elevation myocardial infarction (STEMI) is 1 of 3 clinical manifestations of acute coronary syndrome (ACS), the other 2 being unstable angina (UA) and non-ST-segment elevation MI (NSTEMI). The presenting symptoms of STEMI—chest pain, diaphoresis, nausea, vomiting, numbness, dyspnea, and syncope—are similar to those of UA/NSTEMI¹ but are unremitting until reperfusion occurs. STEMI, however, is differentiated from NSTEMI by persistent ST-segment elevation on the electrocardiogram (ECG). STEMI and UA/NSTEMI also share a common underlying pathophysiology, which is initiated by endothelial plaque rupture. The ensuing platelet activation, adhesion, and aggregation and thrombin generation culminate in thrombus formation in the epicardial artery.² In patients with NSTEMI, the thrombus is usually nonocclusive, with the infarcted artery remaining patent. Occlusive thrombus formation is characteristic of STEMI; more than 90% of STEMI patients have angiographic evidence of thrombus formation compared with 35% to 75% of patients with UA/NSTEMI. Most STEMI patients ultimately develop Q-waves, although a few may not. In contrast, most NSTEMI patients do not ultimately develop Q-waves.

STEMI is diagnosed in an estimated 30% to 45% of patients with ACS.^{3,4} According to a population-based study, the incidence of STEMI has decreased from 1999–2008.⁵ In 1999, 47% of incident acute MI cases recorded in an integrated healthcare delivery system (Kaiser Permanente Northern California) were STEMI; by 2008, the proportion of STEMI cases had decreased to 22.9%. The decrease in the incidence of STEMI, at least partly, was most likely due to substantial improvements in primary prevention efforts.⁵

STEMI is associated with significant mortality. Following occlusion of the coronary artery and in the absence of sufficient collateral supply, a wave front of ischemia and myocardial necrosis begins within 15 minutes and spreads from the endocardium toward

the epicardium.² For every 30-minute delay in prompt treatment, there is an ~10% increase in the relative risk of inhospital mortality.⁶ In the population-based study mentioned above, despite the decrease in the incidence of STEMI from 1999–2008, the 30-day mortality rate after STEMI remained unchanged.⁵ This underscores the utmost importance of timely diagnosis as well as pharmacologic (fibrinolytic) and nonpharmacologic (percutaneous coronary intervention [PCI]) measures to restore perfusion in patients with STEMI.⁷ Irrespective of the reperfusion strategy adopted, adjunctive use of antiplatelet and antithrombotic therapies is important to maximize the effectiveness of reperfusion.

This issue of *Updates in Cardiology: Antiplatelet Therapy for Acute Coronary Syndromes* reviews

recommendations by the American Heart Association/American College of Cardiology (AHA/ACC) for the administration of oral antiplatelet agents in patients with STEMI and examines relevant published data supporting the use of these agents in this patient population. Case-based expert commentary on practical clinical considerations is provided by Mori J. Krantz, MD, FACC, FACP, and Julie A. Davey, MSN, RN, APRN, BC.

Benefit of Oral Antiplatelet Agents With Fibrinolysis in STEMI Aspirin

The effectiveness of aspirin either as monotherapy or in conjunction with fibrinolytic therapy in STEMI was established in the Second International Study of Infarct Survival (ISIS-2).⁸ In this study, ~17,000 patients who entered 417 hospitals up to 24 hours (median 5 hours) after the onset of suspected acute MI were randomized to fibrinolytic therapy (1-hour intravenous [IV] infusion of streptokinase 1.5 MU), 1 month of enteric-coated aspirin 160 mg/d, both active treatments, or placebo. Aspirin monotherapy produced an absolute risk difference in 35-day mortality of 2.4% compared with placebo and a relative risk reduction (RRR) of 23%. When aspirin was combined with streptokinase, the absolute risk difference in mortality was 5.2% compared with placebo; the RRR was 42%. Aspirin also significantly reduced nonfatal reinfarction and nonfatal stroke, and was not associated with any significant increase in cerebral hemorrhage or in bleeds requiring transfusion compared with placebo. The early survival advantage produced by fibrinolytic therapy plus

1 month of aspirin therapy started during acute MI was maintained for at least 10 years.⁹ Further evidence for the effectiveness of aspirin in STEMI was demonstrated in a meta-analysis of 32 studies; it showed that the addition of aspirin after fibrinolytic therapy significantly reduced coronary reocclusion and recurrent ischemic events.¹⁰

Based on these data, aspirin is now considered to be integral to the early management of all patients with suspected STEMI. Treatment guidelines recommend that aspirin 162 to 325 mg should be given promptly, within the first 24 hours, and continued indefinitely thereafter at a daily dose of 75 to 162 mg.²

Clopidogrel

The benefit of adding clopidogrel to aspirin in STEMI patients was established in the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28)¹¹ and COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) trials.¹²

CLARITY-TIMI 28 evaluated the effectiveness of adding clopidogrel (a 300-mg loading dose followed by 75 mg/d) to aspirin (150-325 mg on the first day, then 75-162 mg/d thereafter) in conjunction with fibrinolytic therapy.¹¹ The addition of clopidogrel resulted in an absolute reduction of 6.7% in the rate of an occluded infarct-related artery (defined by a TIMI flow grade of 0 or 1) on angiography or death or recurrent MI before angiography compared with placebo, representing a 36% relative reduction. Clopidogrel also reduced the 30-day rate of

cardiovascular (CV) death, recurrent MI, or urgent revascularization by 20% (Figure 1). There was no significant difference in the rates of major or minor bleeding as well as intracranial hemorrhage between the 2 groups.¹¹

The COMMIT/CCS-2 study randomized ~46,000 patients within 24 hours of suspected MI to clopidogrel 75 mg/d (without a loading dose) or placebo in addition to aspirin 162 mg/d.¹² Treatment was continued until discharge or up to 4 weeks in hospital. Of the study population, 93% had STEMI or bundle-branch block, but only 54% were treated with fibrinolytic therapy. The mean age of patients was 61 years, with 26% aged ≥70 years. At 15 days, there was a significant 9% relative reduction in death, reinfarction, or stroke in patients receiving clopidogrel compared with placebo. In addition, there was a significant 7% relative

reduction in all-cause mortality in the clopidogrel group. There was no significant excess risk of bleeding (fatal, transfused, or cerebral) with clopidogrel.¹²

Based on data from CLARITY and COMMIT, the 2008 ACC/AHA guidelines included the following adenosine diphosphate (ADP) receptor antagonist recommendations for STEMI patients, regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy¹³:

- Clopidogrel 75 mg/d should be added to aspirin, and treatment should be continued for at least 14 days.
- It is reasonable to administer an oral loading dose of clopidogrel 300 mg if patients are <75 years of age.
- There are no data to guide decision making regarding an oral loading

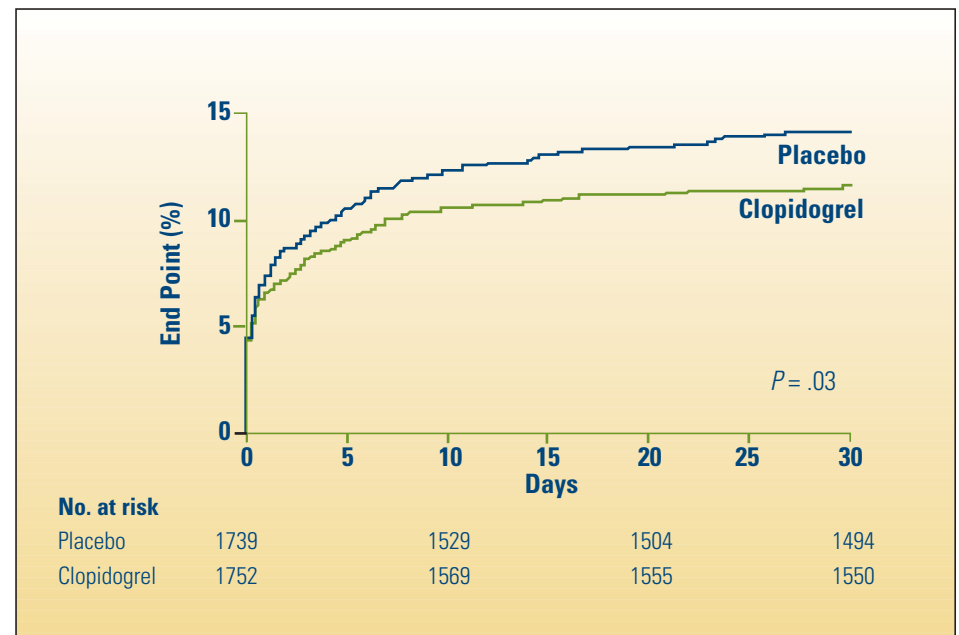


Figure 1. The clinical benefit of adding clopidogrel to aspirin in conjunction with fibrinolytic therapy in STEMI patients. The odds ratio for the end point of death from CV causes, recurrent MI, or recurrent ischemia leading to the need for urgent revascularization was significantly lower in the clopidogrel group than in the placebo group at 30 days (11.6% vs 14.1%; OR, 0.80; 95% CI, 0.65-0.97; $P = .03$). Reprinted with permission from Sabatine MC, et al.¹¹ Copyright © 2005 Massachusetts Medical Society. All rights reserved.

dose of clopidogrel for patients who are ≥ 75 years of age, and clopidogrel should be started at 75 mg/d.

- Long-term maintenance therapy (eg, 1 year) with clopidogrel (75 mg/d) is reasonable.

Benefit of Oral Antiplatelet Agents With PCI in STEMI Aspirin

Placebo-controlled trials have unequivocally established the benefits of aspirin therapy during and following PCI. For example, aspirin administered at the time of PCI has been shown to be associated with an $\sim 75\%$ RRR of acute thrombotic events compared with placebo.^{14,15} When administered after PCI, aspirin produced an $\sim 80\%$ relative reduction in MI and other thrombotic events in the following 6 months compared with placebo.¹⁶ Despite the efficacy of aspirin in PCI, the minimal effective dose of aspirin is not known; until recently (CURRENT-OASIS 7 [Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes] trial), there have been no prospective trials comparing different doses of aspirin.

CURRENT-OASIS 7 evaluated the efficacy and safety of a 600-mg versus a 300-mg loading dose of clopidogrel as well as high-dose (300–325 mg/d) versus low-dose (75–100 mg/d) aspirin in patients with ACS intended for an early invasive strategy (N = 25,086).¹⁷ Approximately 29% of the study population had STEMI and 69% underwent PCI. CURRENT-OASIS 7 did not find any significant difference in the rate of CV outcomes (including death from CV causes, MI, or stroke) (Figure 2) or major bleeding (including coronary

artery bypass graft [CABG]-related, severe, symptomatic intracranial, fatal, or TIMI major) between the 2 aspirin-dose groups, with the exception of recurrent ischemia and TIMI minor bleeding, in the overall study population. Patients receiving high-dose aspirin had a lower rate of recurrent ischemia than those receiving the low dose (0.3% vs 0.5%; $P = .02$). The rate of TIMI minor bleeding was higher in the high-dose than in the low-dose group (5.0% vs 4.4%; $P = .04$).¹⁷

Similar to CURRENT-OASIS 7, a subanalysis of the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study also found that increasing doses of aspirin (≤ 100 mg, 101–199 mg, and ≥ 200 mg) were associated with increased bleeding risks (major bleeding: 1.9%, 2.8%, 3.7%; $P < .0001$; life-threatening bleeding: 1.3%, 1.9%, 2.4%; $P = .004$) without increased efficacy.¹⁸

Because of the higher bleeding risks associated with higher doses of aspirin, the 2007 STEMI Focused Update recommends an initial high dose of aspirin after stent placement followed by a lower dose for long-term secondary prevention. The specific recommendations are aspirin 162 mg to 325 mg/d for at least 1 month after bare metal stent (BMS) implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, followed by indefinite long-term aspirin use at a dose of 75 to 162 mg/d.¹³

Clopidogrel

About 53% of the patients in the CLARITY trial ultimately underwent PCI after fibrinolytic therapy (CLARITY-PCI substudy).¹⁹ These patients were randomized to pretreatment with either clopidogrel (300-mg loading dose, then 75 mg/d) or placebo before

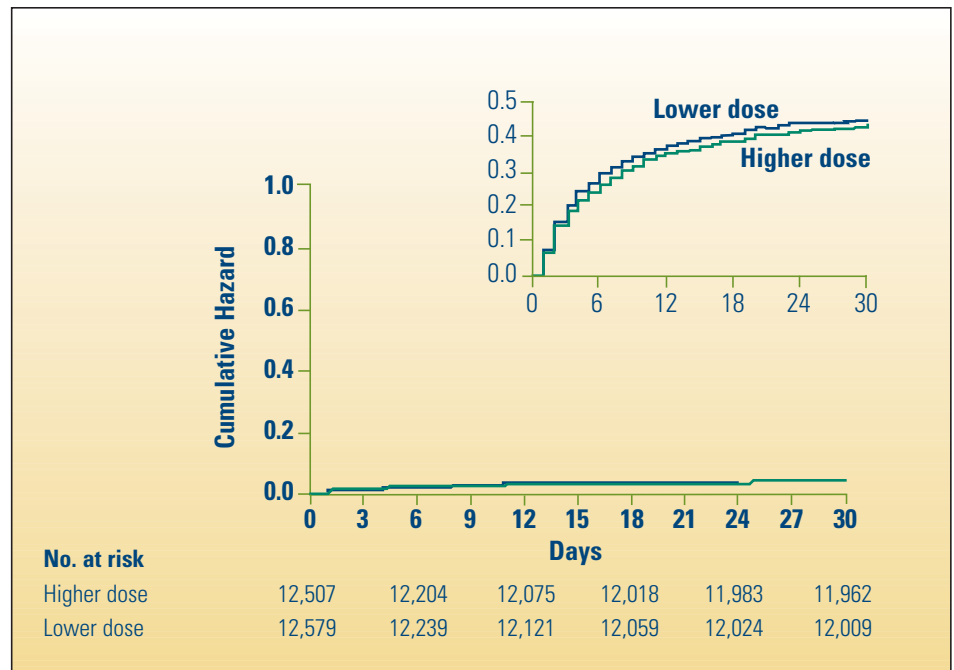


Figure 2. CURRENT-OASIS 7: cumulative hazard ratio for the primary outcome at 30 days in aspirin-treated patients. Higher-dose, aspirin 300–325 mg/d; lower-dose, aspirin 75–100 mg/d. Reprinted with permission from Mehta SR, et al.¹⁷ Copyright © 2010 Massachusetts Medical Society. All rights reserved.

the procedure for a median of 3 days. Both groups received clopidogrel after the procedure. Pretreatment with clopidogrel significantly reduced the odds of CV death, recurrent MI, or stroke following PCI by 46%. Pretreatment with clopidogrel also significantly reduced the odds of MI or stroke prior to PCI by 38%. There was no significant excess in the rates of TIMI major or minor bleeding.

Given the benefits of clopidogrel pretreatment, the ACC/AHA 2009 Joint STEMI/PCI Focused Update recommends that a 300-mg to 600-mg loading dose of clopidogrel should be given as early as possible before or at the time of primary or nonprimary PCI.⁷ The recommendation for the 600-mg dose is based on results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) trial, which evaluated the safety and efficacy of pretreatment

with a 600-mg versus a 300-mg loading dose of clopidogrel in improving ischemic complications during PCI in 255 patients with stable angina or NSTEMI ACS.²⁰ The loading dose was administered 4 to 8 hours prior to PCI. Patients receiving the 600-mg loading dose experienced a significantly reduced 30-day occurrence of death, MI, or target vessel revascularization compared with those receiving the 300-mg loading dose (4% vs 12%; $P = .041$). In addition, multivariable analysis indicated that the high loading regimen was associated with a 50% risk reduction of periprocedural MI. There was no post-procedural major bleedings or the need for transfusion in either group. The incidence of minor bleeding was similar between the groups.

Data from the CURRENT-OASIS 7 trial further support the findings from the ARMYDA-2 trial. A total of 17,263 patients with ACS underwent

PCI in CURRENT-OASIS 7.¹⁷

Among patients who underwent PCI, there was a 15% RRR in the primary outcome of death from CV causes, MI, or stroke in the 600-mg versus 300-mg clopidogrel group (3.9% vs 4.5%; hazard ratio [HR], 0.85; $P = .04$). In addition, there was a 32% RRR in stent thrombosis in the high-dose versus low-dose clopidogrel group (1.6% vs 2.3%; HR, 0.68; 95% confidence interval [CI], 0.55-0.85; $P < .001$).

The efficacy of high-dose clopidogrel, however, was not maintained in the entire CURRENT-OASIS 7 study population. There was no significant difference between the high-dose clopidogrel regimen and the standard-dose regimen with respect to the primary outcome of CV death, MI, or stroke (Figure 3). The higher clopidogrel loading dose, however, was associated with a significantly greater risk of major (2.5% vs 2.0%; $P = .01$) and minor (5.1% vs 4.3%; $P = .01$) bleeding (overall CURRENT-OASIS population).¹⁷

Prasugrel

In patients undergoing primary PCI, the 2009 Joint STEMI/PCI Focused Update considers the prasugrel 60-mg loading dose as an alternative to the clopidogrel 300-mg to 600-mg loading dose.⁷ This recommendation is based on the results of the STEMI population of the TRITON-TIMI 38 trial that showed prasugrel to be more effective than clopidogrel for prevention of ischemic events, without an excess in bleeding.²¹

TRITON-TIMI 38 compared prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) with clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) in patients with ACS scheduled to

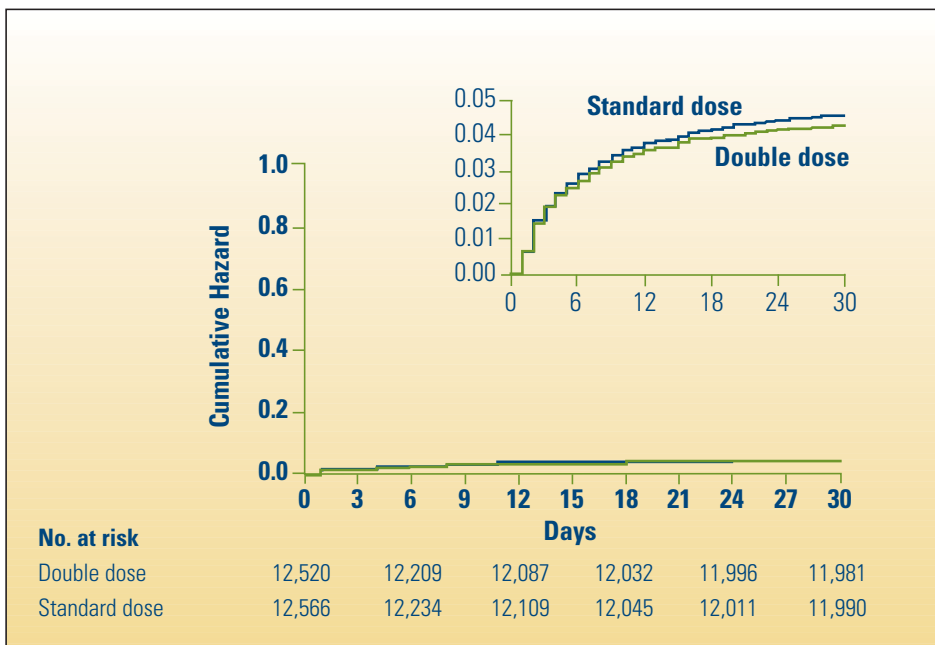


Figure 3. CURRENT-OASIS 7: cumulative hazard ratio for the primary outcome at 30 days in clopidogrel-treated patients. Standard dose, clopidogrel at a 300-mg loading dose and 75 mg daily thereafter; double dose, clopidogrel at a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter. Reprinted with permission from Mehta SR, et al.¹⁷ Copyright © 2010 Massachusetts Medical Society. All rights reserved.

undergo PCI.²² Of the study population, 26% had STEMI. In STEMI patients undergoing PCI, prasugrel significantly reduced the primary efficacy end point of CV death, nonfatal MI, or nonfatal stroke at 30 days (9.5% vs 6.5%; HR, 0.68; 95% CI, 0.54-0.87; $P = .0017$) compared with clopidogrel; this effect was maintained at 15 months (12.4% vs 10.0%; HR, 0.79; 95% CI, 0.65-0.97; $P = .0221$).²¹ Prasugrel also significantly reduced the key secondary end point of CV death, MI, or urgent target vessel revascularization at 30 days (8.8% vs 6.7%; HR, 0.75; 95% CI, 0.59-0.96; $P = .0205$) and 15 months (12.0% vs 9.6%; HR, 0.79; 95% CI, 0.65-0.97; $P = .0250$). Furthermore, at 30 days and 15 months, the individual end points of CV death or MI, as well as stent thrombosis, were significantly reduced with prasugrel. Treatments did not differ with respect to TIMI major bleeding unrelated to CABG surgery, TIMI life-threatening bleeding, and TIMI major or minor bleeding unrelated to CABG surgery, at 30 days and 15 months. Only TIMI major bleeding (18.8% vs 2.7%; $P = .0033$) and TIMI major or minor bleeding (21.9% vs 4.1%; $P = .0032$) at 15 months after CABG surgery was significantly increased with prasugrel compared with clopidogrel.²¹

Although the optimal duration of antiplatelet therapy after stent placement has not yet been established, TRITON-TIMI 38 demonstrated that continuation of prasugrel up to 15 months reduced late stent thrombosis. Consequently, the guidelines recommend that clopidogrel 75 mg/d or prasugrel 10 mg/d should be continued for at least 12 months, unless bleeding risks outweigh the benefit of therapy.⁷ As

stent thrombosis after 1 year of drug-eluting stent (DES) placement has been reported in patients who discontinue antiplatelet therapy,^{23,24} the guidelines also suggest that clopidogrel or prasugrel may be continued beyond 15 months in these patients. Recent registry data from Japan, however, indicate that discontinuation of both aspirin and thienopyridine (ticlopidine or clopidogrel), but not discontinuation of thienopyridine only, is associated with an increased risk of stent thrombosis, and that there is no apparent clinical benefit from thienopyridine use beyond 6 months after DES implantation.²⁵

Ticagrelor

Ticagrelor, a novel antiplatelet agent, is currently under regulatory review at the US Food and Drug Administration. In contrast to clopidogrel and prasugrel, which are irreversible, indirect-acting

oral antagonists of the ADP receptor P2Y₁₂, ticagrelor is a reversible, direct-acting oral antagonist of P2Y₁₂.²⁶ The efficacy of ticagrelor was demonstrated in PLATO (Study of Platelet Inhibition and Patient Outcomes),²⁷ though benefits were not clearly observed among the North American subpopulation.

PLATO compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-mg to 600-mg loading dose, 75 mg daily thereafter) for the prevention of CV events in admitted ACS patients during a 12-month period. Approximately 38% of PLATO patients had STEMI and 59% had UA/NSTEMI. An invasive treatment was planned prior to randomization in ~72% of patients. Treatment with ticagrelor resulted in a significant 16% relative reduction in the rate of

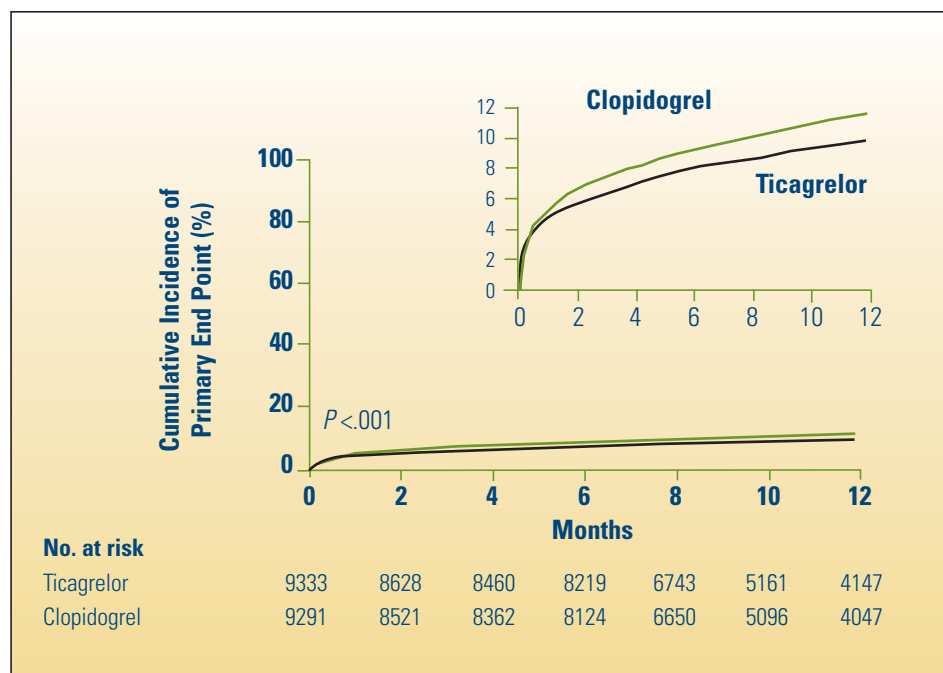


Figure 4. PLATO: Cumulative incidence of death from vascular causes, MI, or stroke. The primary end point occurred significantly less often in the ticagrelor than in the clopidogrel group (9.8% vs 11.7% at 12 months; HR, 0.84; 95% CI, 0.77-0.92; $P < .001$). Reprinted with permission from Wallentin L, et al.²⁷ Copyright © 2009 Massachusetts Medical Society. All rights reserved.

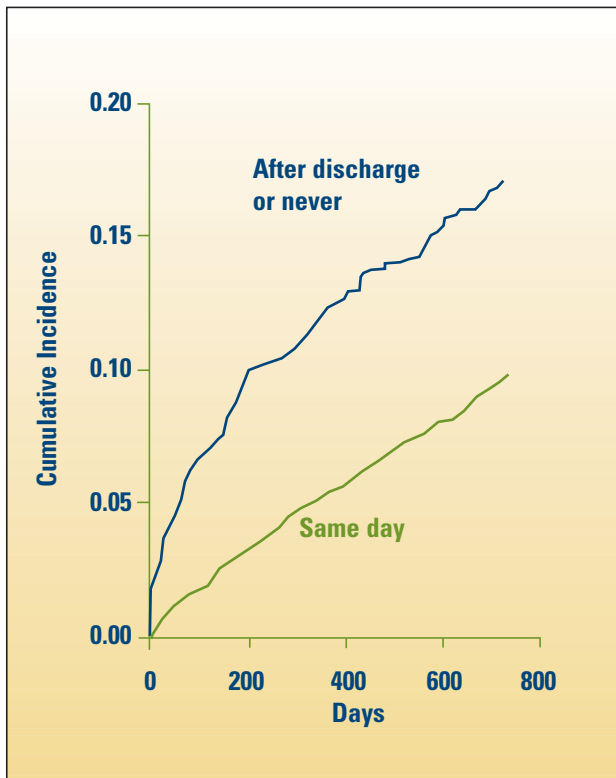


Figure 5. Cumulative incidence of death or MI in patients with delay and without delay in filling clopidogrel after hospital discharge. After discharge or never = patients with delay in filling their prescriptions after discharge; same day = patients who fill their prescriptions without delay on the same day as hospital discharge. Reprinted with permission from Ho PM, et al.²⁹

death from vascular causes, MI, or stroke compared with clopidogrel (Figure 4). A similar benefit was seen for the individual components of death from vascular causes (21% relative reduction) and MI (16% relative reduction), but not for stroke. In addition, there was a 22% relative reduction in death from any cause in ticagrelor-treated patients (4.5% vs 5.9% with clopidogrel; $P < .001$), though this was driven principally by a reduction in CV death.²⁷

In patients who underwent invasive treatment, ticagrelor again proved to be significantly more effective than clopidogrel in reducing death from vascular causes, MI, or stroke (8.9% vs 10.6%; $P = .003$). Among patients who received a stent during the study, the rate of definite stent

thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs 1.9%; $P = .009$).²⁷

There was no significant difference in the rate of major (study criteria or TIMI), fatal, or life-threatening bleeding between ticagrelor- and clopidogrel-treated patients.

Ticagrelor, however, was associated with a higher rate of major bleeding not related to CABG (study criteria: 4.5% vs 3.8%; $P = .03$; TIMI criteria: 2.8% vs 2.2%; $P = .03$) and intracranial bleeding (0.3% vs 0.2%; $P = .06$), including fatal intracranial bleeding (0.1% vs 0.01%; $P = .02$) as well

as an increased incidence of dyspnea and bradycardia.²⁷

Clinical Implications of Nonadherence to Prescribed Antiplatelet Therapy After Hospital Discharge

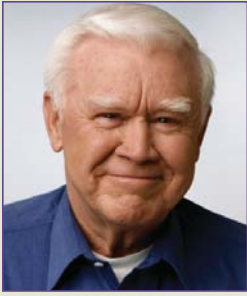
STEMI patients who have undergone PCI with stent placement, especially DES, are at increased risk for stent thrombosis. Stent thrombosis can occur early after the procedure, and lack of adjuvant thienopyridine therapy has been identified as one of the major risk factors for this complication.²⁸ It is, therefore, critical that patients do not delay filling thienopyridine prescriptions after stent implantation.

Delay in filling antiplatelet prescription can occur during the transition

period from hospital discharge to the outpatient setting as was shown in a recent retrospective cohort study of patients discharged after DES implantation from 3 large integrated healthcare systems. This study found that 1 in 6 patients delay filling their initial clopidogrel prescription after DES implantation and that any delay in filling clopidogrel was associated with a 2-fold higher risk of death or MI compared with no delay (14.3% vs 7.9%; $P < .001$) (Figure 5).²⁹ Much of the risk of death or MI occurred within the initial 30 days after hospital discharge, highlighting the importance of adhering to prescribed thienopyridine therapy after hospital discharge.

There are many potential reasons for delays in filling prescribed medication after hospital discharge including cost of the medication, logistics of obtaining the medication at discharge, and lack of understanding of the intended medication regimen.³⁰ Further, a study of patients after DES implantation found that the most common reasons for early discontinuation of clopidogrel therapy were that patients were unaware that they should be taking the medication and for how long.³¹

These data indicate that there are gaps in the care of patients with ACS after hospital discharge and a need to address these gaps to improve patient outcomes after stent placement.



CASE: 72-Year-Old Man With Substernal Chest Pressure and Dyspnea

Mr Jones was introduced in Issue 3 of Updates in Cardiology: Antiplatelet Therapy for Acute Coronary Syndromes. Read how his case progressed after stent placement for NSTEMI.

Mr Jones is a 72-year-old man who presents to the emergency department with crushing substernal chest pressure and dyspnea. His symptoms began 30 minutes earlier while he was mowing his lawn. He is also diaphoretic and tachypneic. His symptoms are similar to but more severe than what he experienced 8 months prior. At that time he sustained an NSTEMI and underwent DES implantation in the left anterior descending artery (LAD).

Medical History

- Coronary artery disease (status: DES to LAD 8 months ago), 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: 325 mg daily
- Clopidogrel: 75 mg daily (discontinued 2 months ago)
- Metoprolol: 25 mg twice daily (discontinued 2 months ago because of fatigue)
- Lisinopril/hydrochlorothiazide: 10/12.5 mg daily
- Simvastatin: 80 mg daily
- Levothyroxine: 75 µg daily

Emergency Department

- Aspirin: 325 mg PO
- Nitroglycerin drip: 20 µg/min
- Heparin drops: loading dose of 60 U/kg, followed by 12 U/kg/h
- Morphine: 2 mg IV
- Clopidogrel: 300-mg PO loading dose

Physical Findings

- Weight: 195 lb; height: 5 ft 10 in
- Blood pressure: 160/90 mm Hg
- Pulse: 99 beats/min, regular; temperature: 97.8°F
- Neck: no jugular venous distension; no carotid bruits, carotid pulsations 2+
- Chest: fine bibasilar crackles, no wheezing
- Heart: regular rate and rhythm; S₁ and S₂; no S₃, S₄, or murmurs
- Abdomen: bowel sounds X4; no tenderness, distension, or masses; normal liver span
- Extremities: trace edema bilateral lower extremities; distal pulses, 2+

ECG, Imaging, and Laboratory Findings

- ECG: ST elevation leads V1-V4 with reciprocal ST depression inferior leads
- Echocardiogram: no apical thrombus
- White blood cell count: 4000/µL
- Red blood cell count: 4.94 X 10⁶/µL
- Hemoglobin: 14.0 g/dL
- Hematocrit: 42.0%
- Platelet count: 290 X 10³/µL
- Glucose: 93 mg/dL
- Aspartate aminotransferase: 29 U/L
- Alanine aminotransferase: 40 U/L
- Total cholesterol: 150 mg/dL
- Triglycerides: 60 mg/dL
- High-density lipoprotein cholesterol: 43 mg/dL
- Low-density lipoprotein cholesterol: 65 mg/dL
- Sodium: 139 mEq/L
- Potassium: 4.0 mEq/L
- Chloride: 103 mEq/L
- Carbon dioxide: 26.0 mEq/L
- Creatinine: 1.2 mg/dL
- Blood urea nitrogen: 15 mg/dL
- Troponin T: 10 ng/mL

Hospital Management

Mr Jones was taken immediately to the cardiac catheterization laboratory. Cardiac catheterization revealed 100% thrombotic occlusion of the proximal LAD within the site of previous stent placement, 40% occlusion of the distal left circumflex coronary artery, and diffuse 30% to 40% lesions in the right coronary artery. Left ventriculogram demonstrated an ejection fraction (EF) of 35% to 40%. Percutaneous transluminal coronary angioplasty with thrombectomy of the LAD was performed without complication.

What issues should be addressed in this patient given the findings on cardiac catheterization?

What is the optimal postdischarge regimen?

*Commentary by Mori J. Krantz, MD, FACC, FACP
and Julie A. Davey, MSN, RN, APRN, BC*

Commentary



MJK: This case illustrates the perils of nonadherence to ADP-receptor antagonist therapy after stent implantation. Mr Jones experienced classic in-stent thrombosis that can present either as sudden cardiac death or acute STEMI. The patient experienced the latter complication and is now left with significant

myocardial dysfunction. Emergent revascularization for STEMI is essential. When available, PCI is preferable to thrombolysis; door-to-balloon times less than 90 minutes are essential for improving outcomes and are considered a hospital performance measure.



JAD: This patient is 8 months post-DES placement to the LAD. He was treated with clopidogrel for 6 months post-PCI. Two months after discontinuation of clopidogrel he presents with an acute anterior STEMI secondary to in-stent thrombosis. ACC/AHA guidelines recommend dual antiplatelet therapy for 3 to 6 months

in patients receiving a DES. However, the guidelines also state that, ideally, dual therapy should be continued for at least 12 months and possibly for 15 months or longer unless the

bleeding risk outweighs the benefit of therapy. TRITON-TIMI 38 demonstrated a reduction in late stent thrombosis with continuation of prasugrel up to 15 months post-DES placement.

Although we know that patients with STEMI who have undergone PCI with DES placement are at increased risk for stent thrombosis, patients themselves may not understand why they need long-term antiplatelet therapy, particularly after they begin feeling better as they recover from an ACS event. As ADP-receptor antagonists can be costly, patients may be reluctant to continue the treatment. It is imperative that we educate patients about the importance of taking these medications daily without a break in therapy. If cost is an issue, providers should make every attempt to connect patients with an appropriate assistance program.

Postcatheterization/discharge therapy in this patient is of utmost importance to prevent future events and hopefully improve left ventricular (LV) function. On left ventriculogram, the patient's EF was noted to be 35% to 40%, with moderate anteroapical wall hypokinesis. Although this patient's postdischarge regimen for his NSTEMI event included a beta-blocker, he discontinued it because he felt fatigued and also thought he was taking too many medications. He will need the addition of a beta-adrenergic blocking agent to his medical regimen as well as education to reinforce the need to continue the drug. He is already taking an angiotensin-converting enzyme (ACE) inhibitor. Both of these medications should be titrated upward to high doses if tolerable to achieve the maximum benefit. An echocardiogram was obtained while he was in the hospital and did not show the presence of apical thrombus. A repeat echocardiogram can be performed within 3 months to reassess his LV function.

Education regarding overall lifestyle modifications is crucial as well. Education should include the benefits of a diet low in sodium, fat, and cholesterol; exercise; smoking cessation; and the importance of daily weighing to monitor fluid status. In the case of post-MI patients, referral to phase 1 and phase 2 cardiac rehabilitation programs is an important opportunity to improve outcomes. Adherence to appropriate medical regimens, based on current practice guidelines, and adherence to lifestyle modifications are critical components in overall CV risk reduction. Patient adherence to treatment begins with appropriate *EDUCATION*. It is our responsibility to ensure that patients have a clear understanding of their condition and the benefits and risks of treatment.

PCE Takeaways

- Dual antiplatelet therapy (with aspirin plus clopidogrel or prasugrel) is essential for the management of all patients with ACS; postdischarge adherence to long-term antiplatelet therapy is especially important for patients with STEMI who have undergone PCI with stent implantation.
- Aspirin at a dosage of 162 to 325 mg/d is recommended for at least 1 month after BMS implantation or 3 to 6 months after DES implantation; thereafter, a dosage of 75 to 162 mg/d should be continued indefinitely. Patients at high risk for bleeding may be given the lower dose initially.
- Clopidogrel at a dosage of 75 mg/d should be given for at least 12 months; continuation of treatment beyond 15 months may be considered for patients who underwent DES implantation.
- Prasugrel at a dosage of 10 mg/d should be given for at least 12 months; continuation of treatment beyond 15 months may be considered for patients who underwent DES implantation. For patients with a body weight <60 kg, a dosage of 5 mg/d may be considered.
- Long-term management of patients with STEMI should also include treatment with a beta-blocker, ACE inhibitor, and a statin (if appropriate) as well as cardiac rehabilitation to help improve survival and reduce the risk of reinfarction.

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