

Program Title:
Clinical Trial Results Educational Lecture Series
American Heart Association (AHA) Annual Meeting

CME Program Audience

A variety of current topics in cardiology and disease management were captured during the November 2007 American Heart Association (AHA) Annual Meeting held in Orlando, FL. The purpose of this activity is to assist cardiologists in improving patient outcomes by providing insights from national quality improvement initiative, as well as reviewing results from recent and late-breaking clinical trials of treatments in patients with acute coronary syndromes.

Needs summary

Advances in the treatment of acute coronary syndromes are continually being developed and improved through clinical trials. Proven treatments are then included into guidelines and practice recommendations based on these evidence-based trials. However, adaptation of these recommendations into clinical practice can be a slow and inefficient process. Informing cardiologists of the most recent changes in treatment guidelines and educating them on late-breaking clinical trials of up-and-coming treatments may promote adherence to the current guidelines and stimulate interest in future therapies thereby improving patient outcomes.

Program learning objectives

With the needs summary clearly identified, the following learning objectives have been developed and supported by practice gaps.

At the end of the program, participants should be able to:

- Analyze the efficacy of antiplatelet therapies used in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel.

“The mainstay of antiplatelet therapy for patients with acute coronary syndromes (ACS), including those undergoing early percutaneous coronary intervention (PCI), is the combination of aspirin and clopidogrel.... Clopidogrel has several potential limitations, however. First, the onset of action is delayed, with a “therapeutic” level of 50% inhibition of ADP-induced platelet aggregation, as measured by light transmission aggregometry (LTA), not being reached until 4–6 hours after a 300 mg loading dose, and 2 hours after a 600 mg dose. Second, there is a “ceiling” effect — even a 900 mg dose achieves only around 60% inhibition of ADP-induced platelet aggregation. Third, laboratory testing suggests that “therapeutic” platelet inhibition is not achieved in a substantial proportion of patients because of individual variability in platelet inhibition by clopidogrel. Finally, there is uncertainty about the clinical benefit with higher loading doses of clopidogrel of 600 mg or 900 mg compared with 300 mg.”¹

Source: Hankey GJ et al. “Will prasugrel supersede clopidogrel for acute coronary syndromes?” *Med J Aust.* 2008 Apr 7;188(7):381-2.

“The increasing use of higher-than-approved doses of clopidogrel in clinical practice is based in part on the desire for greater levels of inhibition of platelet aggregation (IPA). Prasugrel is a new thienopyridine that is more potent than standard-dose clopidogrel in healthy subjects and patients with stable coronary artery disease. The relative antiplatelet effects of prasugrel versus high-dose clopidogrel in percutaneous coronary intervention patients are unknown.”²

Source: Wiviott SD et al. “Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial.” *Circulation.* 2007 Dec 18;116(25):2923-32.

*"The P2Y12 antagonist clopidogrel has a well-established role as an antithrombotic agent in the settings of percutaneous coronary intervention and acute coronary syndromes. However, several challenges remain, including the relatively slow onset of action of clopidogrel and the phenomenon of clopidogrel response variability or "resistance". Novel P2Y12 antagonists, including prasugrel, AZD6140, and cangrelor, have a faster onset of action, as well as more potent, and less variable, inhibition of platelet function ex vivo. Whether this promise will be translated into clinical benefit for patients will be determined by the results of ongoing phase 3 clinical trials."*³

Source: Michelson AD. "P2Y12 antagonism: promises and challenges." *Arterioscler Thromb Vasc Biol.* 2008 Mar;28(3):s33-8.

- Define the role of the eptifibatide in treating patients undergoing percutaneous coronary intervention (PCI).

*"Antiplatelet and anticoagulation therapies are essential for the prevention of thromboembolic-induced myocardial ischaemia in non-ST-elevation acute coronary syndromes and the ischaemic complications of percutaneous coronary intervention. Although heparin, direct thrombin inhibitors and oral platelet activation inhibitors provide substantial benefit, only glycoprotein (GP) IIb/IIIa inhibitors block the final common pathway leading to platelet aggregation, and the American College of Cardiology/American Heart Association guidelines recommend GP IIb/IIIa inhibitors as an integral component of care in these patients. Abciximab, eptifibatide and tirofiban all act through the GP IIb/IIIa receptor; however, variations in clinical outcomes among patients receiving these agents may be related to their structural and pharmacological differences, as well as to patient demographics."*⁴

Source: Jennings LK. "Current strategies with eptifibatide and other antiplatelet agents in percutaneous coronary intervention and acute coronary syndromes." *Expert Opin Drug Metab Toxicol.* 2005 Dec;1(4):727-37.

*"Although glycoprotein (GP) IIb/IIIa inhibitors (like eptifibatide) are recommended for patients with unstable angina and non-ST-segment elevation myocardial infarction who undergo percutaneous coronary intervention (PCI), the American College of Cardiology/American Heart Association guidelines do not specify optimal timing for their initiation."*⁵

Source: Tricoci P et al. "Timing of glycoprotein IIb/IIIa inhibitor use and outcomes among patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (results from CRUSADE)." *Am J Cardiol.* 2007 May 15;99(10):1389-93.

*"Although randomized trials have clearly demonstrated the clinical efficacy with regimens of platelet glycoprotein IIb/IIIa antagonists (such as eptifibatide) that result in >80% inhibition of baseline platelet aggregation in percutaneous coronary intervention (PCI), there are no data available concerning the optimal duration of infusion of these agents."*⁶

Source: Rebeiz AG et al. "Optimal duration of eptifibatide infusion in percutaneous coronary intervention (an ESPRIT substudy)." *Am J Cardiol.* 2004 Oct 1;94(7):926-9.

*"Adjunctive therapy with glycoprotein IIb/IIIa inhibitors has been shown to reduce ischaemic complications and improve clinical outcome in patients with primary percutaneous coronary intervention (PCI) for acute ST elevation myocardial infarction. Little is known about the use of eptifibatide in this setting."*⁷

Source: Zeymer U et al. "Early eptifibatide improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in

- Discuss how the adverse side effects of warfarin for patients with atrial fibrillation (AF) have driven recent studies.

*“Atrial fibrillation is increasingly prevalent among older adults. It causes approximately 24% of strokes in patients aged 80 to 89 years. The management of atrial fibrillation is directed at preventing thromboembolism and controlling the heart rate and rhythm. Stroke prevention is most effectively accomplished through administering anticoagulants such as warfarin, although older patients have higher hemorrhagic risk. Cognitive dysfunction, functional impairments, and increased fall risk further complicate warfarin management in elderly patients.”*⁸

Source: Fang MC et al. “Atrial fibrillation in the elderly.” *Am J Med.* 2007 Jun;120(6):481-7.

*“Warfarin prevents stroke in atrial fibrillation (AF); however, concerns regarding international normalized ratio control and hemorrhage limit its use in the elderly.”*⁹

Source: Ford GA et al. “Direct thrombin inhibition and stroke prevention in elderly patients with atrial fibrillation: experience from the SPORTIF III and V Trials.” *Stroke.* 2007 Nov;38(11):2965-71.

*“Warfarin and heparin have formed the mainstay in the prophylaxis of deep vein thrombosis (DVT), stroke prevention in atrial fibrillation, and treatment of thromboembolic disease (TED). However, these choices are hampered by difficult administration, interactions with other medications, side effect profile, and limited indications for treatment.”*¹⁰

Source: Desai SS et al. “Recent developments in antithrombotic therapy: will sodium warfarin be a drug of the past?” *Recent Patents Cardiovasc Drug Discov.* 2006 Nov;1(3):307-16.

*“The use of warfarin in the elderly, particularly for stroke prevention in chronic atrial fibrillation, is steadily increasing. Although the benefits of warfarin are greatest in the elderly, so are the risk of adverse outcomes and the difficulties of anticoagulant management.”*¹¹

Source: Bereznicki LR et al. “The risks of warfarin use in the elderly.” *Expert Opin Drug Saf.* 2006 May;5(3):417-31.

- Identify the level of awareness and adherence to ACC/AHA Acute Coronary Syndromes (ACS) guidelines found in the CRUSADE study.

*“The practice of translating the best available research evidence into clinical practice often meets significant obstacles. The publication of treatment guidelines does not guarantee their dissemination, acceptance, or routine use for patient care. Hence, the translation of knowledge regarding the best approaches to providing patient care through evidence-based guideline implementation remains complex. Careful study of the process of successful guideline adherence and reporting of the results of these investigations is critical to decreasing the time required from establishing best practices to routine following of evidence-based guidelines in hospitals across the United States.”*¹²

Source: Blomkalns AL et al. “Guideline Implementation Research: Exploring the Gap between Evidence and Practice in the CRUSADE Quality Improvement Initiative” *Acad Emerg Med* 2007;14(11):949-54.

“Translating research results into routine clinical practice remains difficult. Guidelines, such as the 2002 American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Unstable Angina and non-ST-segment elevation myocardial infarction, have been developed to provide a streamlined, evidence-based approach to patient care that is of high quality and is reproducible. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) Quality Improvement Initiative was developed as a registry for non–ST-segment elevation acute coronary syndromes to track the use of guideline-based acute and discharge treatments for hospitalized patients, as well as outcomes associated with the use of these treatments.”¹³

Source: Blomkalns AL et al. “Guideline Implementation Research: Exploring the Gap between Evidence and Practice in the CRUSADE Quality Improvement Initiative” *Acad Emerg Med* 2007;14(11):949-54.

“Non–ST-segment elevation (NSTEMI) myocardial infarction (MI) acute coronary syndrome (ACS) accounts for more than 1.6 million annual admissions, representing up to 75% of all cases of MI in US hospitals. Appropriate care for patients with NSTEMI ACS is informed by a wealth of recent randomized controlled trials whose findings have been summarized into national clinical practice guidelines by the American College of Cardiology/American Heart Association (ACC/AHA). Despite this evidence, prior studies have demonstrated gaps in the use of evidence-based care of NSTEMI ACS that are wider than those observed in patients with ST-segment elevation MI.”¹⁴

Source: Peterson ED et al. “Association Between Hospital Process Performance and Outcomes Among Patients With Acute Coronary Syndromes.” *JAMA*. 2006;295:1912-1920.

“Using data from a large quality improvement initiative, the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative, we characterized the degree to which contemporary NSTEMI ACS care is consistent with guideline recommendations as well as the variation in specific care processes among 350 US hospitals. We evaluated the degree to which hospital performance varied among individual process metrics and identified hospital characteristics that were predictive of higher adherence to guidelines. Finally, we assessed whether hospitals’ overall measure of composite adherence to these ACC/AHA guideline metrics was associated with observed and risk-adjusted in-hospital mortality rates.”¹⁵

Source: Peterson ED et al. “Association Between Hospital Process Performance and Outcomes Among Patients With Acute Coronary Syndromes.” *JAMA*. 2006;295:1912-1920.

- Discuss the results of decompensated heart failure (ADHF) clinical trials.

“Addressing the challenge of ADHF has been daunting. Acute decompensated HF accounts for more than 1 million acute hospitalizations per year in the United States at an annual cost of more than \$30 billion and is associated with significant mortality. The risk of inpatient death is approximately 4% (but ranges from 2%-22%), and the risk of death/rehospitalization at 60 to 90 days after an episode of ADHF is 36%. At the core of this challenge, however, is the limited understanding of the pathophysiology of ADHF.... Another challenge of ADHF involves clinical trial design and construct. The studies to date have been small to moderate short-term hemodynamic or symptom-focused designs, constructed primarily to meet regulatory requirements. Important questions, including mechanistic hypotheses and the effect of interventions on rehospitalizations/mortality, have been inadequately studied. Trials in ADHF have also been confounded by considerable heterogeneity of the patient phenotype. Patients with ADHF are older, represent a mix of new-onset HF and decompensated chronic HF, have both reduced and preserved ejection fraction HF, have equal gender representation, and frequently have a number of important comorbidities, especially renal insufficiency.”¹⁶

Source: Yancy, CW et al. "Climbing the Mountain of Acute Decompensated Heart Failure: The EVEREST Trials." *JAMA*. 2007;297:1374-6.

*"Despite this dramatic increase in the public health burden of hospitalization for heart failure, models for the risk stratification of patients during admission for acute decompensated heart failure (ADHF) are not well established. Clinical risk prediction tools may be helpful in guiding medical decision making."*¹⁷

Source: Fonarow GC, et al. "Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure: Classification and Regression Tree Analysis." *JAMA* 2005;293:572-80.

*"Assessment of quality of care in heart failure has focused on the development and use of process-based performance measures, with the presumption that these processes are associated with improved clinical outcomes. However, this link remains largely untested."*¹⁸

Source: Fonarow GC et al. "Association Between Performance Measures and Clinical Outcomes for Patients Hospitalized With Heart Failure." *JAMA*. 2007;297:61-70.

- Identify the effectiveness of anticoagulants that target factor Xa versus anticoagulants that inhibit factor IIa.

*"Heparins and VKAs have been the cornerstones of anticoagulation therapy for several decades and these agents have become most important drugs in the primary and secondary prevention of venous and arterial thromboembolic disease. Although effective, their use has been hampered by numerous limitations. In the search for new agents matching the 'ideal' anticoagulant profile, a number of different steps in the coagulation cascade have been targeted, including direct thrombin inhibition, and direct inhibition of Factor Xa."*¹⁹

Source: Haas S. "New oral Xa and IIa inhibitors: updates on clinical trial results." *J Thromb Thrombolysis*. 2008 Feb;25(1):52-60.

*"Traditional anticoagulant drugs, including unfractionated heparin and warfarin, have several limitations. A new strategy for the design of new antithrombotic drugs is based on selective inhibition of a specific coagulation factor. These include direct thrombin inhibitors and factor Xa inhibitors."*²⁰

Source: Bauer KA. "New anticoagulants: anti IIa vs anti Xa--is one better?" *J Thromb Thrombolysis*. 2006 Feb;21(1):67-72.

*"Anticoagulants are recommended for the prevention and treatment of a wide variety of thromboembolic events. Although existing anticoagulants are effective, their use is limited by parenteral administration or the requirement for frequent monitoring and subsequent dose adjustment. Therefore, there is an urgent need for novel, oral agents with a predictable anticoagulant action. Because of its key position in the coagulation cascade and its limited roles outside of coagulation, Factor Xa has emerged as an attractive target for novel anticoagulants. As a result, the past decade has witnessed an explosion of research into small-molecule, oral, direct Factor Xa inhibitors, and several are now in clinical development. Rivaroxaban, LY517717, YM150, apixaban, PRT054021, and DU-176b, among others, have shown considerable promise; rivaroxaban is currently furthest ahead in its developmental program, having entered phase III in 3 indications. It is hoped that, before long, these anticoagulants will allow us to enter an era of convenient, oral anticoagulation, without the need for regular monitoring or dose adjustment."*²¹

Source: Turpie AG. "Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases." *Arterioscler Thromb Vasc Biol*. 2007 Jun;27(6):1238-47.

References:

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