

Program Title:
Clinical Trial Results Educational Lecture Series
Transcatheter Cardiovascular Therapeutics (TCT) Annual Meeting

CME Program Audience

A variety of current topics in cardiology and disease management were captured during the October 2007 TCT Annual Meeting held in Washington, DC. The purpose of this activity is to assist cardiologists in improving patient outcomes by providing insights from national quality improvement initiatives, 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:

- Identify the results of CRUSADE a national quality improvement initiative designed to improve adherence of healthcare providers to ACC/AHA Acute Coronary Syndromes (ACS) Guidelines.

“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.”¹

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.”¹

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.”²

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.”²

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

- Describe the data found in the ACTION Registry/CRUSADE trial regarding the types of discharge and acute meds and in-hospital outcomes for STEMI and NSTEMI patients.

“Practice guidelines for acute ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) recommend similar therapies and interventions, but differences in patterns of care between MI categories have not been well described in contemporary practice.”³

Source: Roe MT et al. “Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction.” *Arch Intern Med*. 2005 Jul 25;165(14):1630-6.

“The contemporary management of patients with AMI is limited by treatment deficiencies for both categories of patients with MI and by lower use of beneficial medications and interventions in patients with NSTEMI. The inpatient hospitalization is the optimal time to initiate evidence-based medications and secondary prevention interventions regardless of MI classification, so treatment disparities in the enlarging population of patients with NSTEMI represent a further obstacle toward reducing long-term mortality rates and recurrent ischemic events for both categories of patients with MI. As clinical practice guidelines continue to evolve for STEMI and NSTEMI, differentiation of quality indicators by MI classification may clarify treatment decisions and improve overall AMI care. However, rigorous study of quality improvement techniques is needed to ascertain whether common or separate quality improvement strategies will be most successful for improving adherence to guidelines in patients with STEMI vs those with NSTEMI.”³

Source: Roe MT et al. “Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction.” *Arch Intern Med*. 2005 Jul 25;165(14):1630-6.

“Medical personnel generally believe that non-ST elevation (NSTEMI) acute coronary syndromes (ACS) are less damaging than ST elevation myocardial infarction (STEMI), in keeping with the

lower morbidity and mortality attributed to these subgroups in randomized clinical trials.”⁴

Source: Yuval R et al. “Perceived disability and lifestyle modification following hospitalization for non-ST elevation versus ST elevation acute coronary syndromes: the patients’ point of view.” *Eur J Cardiovasc Nurs.* 2007 Dec;6(4):287-92.

“Clinical trials suggested feasibility and safety of early discharge after ST-segment elevation acute myocardial infarction (STEMI) for selected patients. Current United States and European guidelines recommend early discharge for uncomplicated AMI.”⁵

Source: Barchielli A et al. “Early discharge after acute myocardial infarction in the current clinical practice. Community data from the AMI-Florence Registry, Italy.” *Int J Cardiol.* 2007 Jan 2;114(1):57-63.

- Specify the benefit of statin therapy before and after coronary revascularization.

“Previous randomized studies have shown that pretreatment with statins improves clinical outcome in subjects with stable angina undergoing elective percutaneous coronary intervention.... However, data on the effects of statins in subjects with acute coronary syndrome (ACS) treated with PCI are more limited.”⁶

Source: Patti G and G Di Sciascio. *Cardiology Review:* Oct 2007.
http://www.cardiologyreviewonline.com/issues/articles/2007-10_02.asp.

“Previous randomized studies have shown that long-term therapy with statins improves prognosis in subjects with hypercholesterolemia and in patients with stable coronary artery disease; data on the effects of statins in the setting of acute coronary syndromes are more limited.”⁷

Source: Patti G et al. “Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial.” *J Am Coll Cardiol.* 2007 Mar 27;49(12):1272-8.

“Nonrandomized studies on early use of statins in patients with a variety of acute coronary syndromes have shown conflicting results; a number of them have shown a lower occurrence of cardiovascular events, but a recent post-hoc analysis on 12,365 patients has indicated no benefit in terms of death, myocardial infarction, or recurrent ischemia at 90 days. Indeed, a recent meta-analysis evaluating the outcomes for up to 4 months of patients from 12 randomized trials that compared early (<14 days) statin therapy with placebo or usual care after an acute coronary syndrome showed that statins do not decrease the incidence of death, myocardial infarction, or stroke, with a trend toward a reduction of unstable angina.”⁷

Source: Patti G et al. “Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial.” *J Am Coll Cardiol.* 2007 Mar 27;49(12):1272-8.

- Describe the results of the ARMYDA-4 and ARMYDA-5 trials that evaluated the safety and efficacy of clopidogrel to prevent myocardial infarction in patients undergoing angioplasty or percutaneous coronary intervention (PCI).

“There are thus three key questions to consider when evaluating the adequacy of anticoagulation therapy and clopidogrel as foundation pharmacotherapy in PCI. First, is clopidogrel (and aspirin) a sufficiently potent antiplatelet regimen to manage all patients undergoing PCI? Second, in the patient awaiting PCI (typically those with an acute coronary syndrome), do events continue to accrue even while a patient is being treated with clopidogrel and anticoagulation? Third, since bleeding is itself an adverse clinical outcome and is correlated with clinical events, what

approaches are available to further reduce bleeding risk?"⁸

Source: Tcheng JE. "Debate of Adjunctive Pharmacology for Percutaneous Coronary Intervention: Anticoagulation and Clopidogrel Are Not (Always) Enough." *J Int Cardiol.* 2006;19(5): 456-463.

*"Clopidogrel, in combination with acetylsalicylic acid, has become a mainstay of the pharmacological therapy for patients with acute coronary syndromes, especially in those undergoing percutaneous coronary interventions (PCI). While a series of studies has shown that pre-treatment with a loading dose of clopidogrel 300 or 600 mg prior to PCI is effective in reducing cardiovascular complications, the optimal dose and timing in various patient groups is still unclear."*⁹

Source: Zeymer U et al. "Efficacy and safety of clopidogrel 600 mg administered pre-hospitally to improve primary percutaneous coronary intervention in patients with acute myocardial infarction (CIPAMI): study rationale and design." *Cardiology.* 2007;108(4):265-72.

*"Despite clopidogrel therapy, patients undergoing percutaneous coronary intervention (PCI) with stenting are at risk of recurrent coronary events. This could be partly explained by a reduced efficacy of clopidogrel to inhibit platelet aggregation, an ex vivo defined phenomenon called clopidogrel nonresponsiveness or resistance. However, both prevalence and associated cardiovascular risks remain unclear."*¹⁰

Source: Snoep JD et al. "Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis." *Am Heart J.* 2007 Aug;154(2):221-31.

- Explain trial results on the selective thrombin receptor antagonist used in PCI.

*"Despite aggressive antiplatelet and antithrombotic therapies, peri-procedural and post-procedural adverse clinical events continue to occur in patients undergoing percutaneous coronary intervention (PCI)."*¹¹

Source: Moliterno DJ et al. Abstract presented at the American College of Cardiology 2007 annual meeting
<http://www.spectrumscience.com/assets/files/acc07/i2%20LBCT%20Sat%2012%20pm/Moliterno%20Abstract.pdf>

*"Thrombin receptor antagonists are a potential new class of drug with a unique mechanism of action that blocks the impact of thrombin (the most potent platelet agonist) on the platelet."*¹¹

Source: Moliterno DJ et al. Abstract presented at the American College of Cardiology 2007 annual meeting
<http://www.spectrumscience.com/assets/files/acc07/i2%20LBCT%20Sat%2012%20pm/Moliterno%20Abstract.pdf>

*"Inhibition of the cellular activation by thrombin is a potentially promising therapeutic approach for the treatment of thrombotic and vascular proliferative disorders such as atherosclerosis and restenosis."*¹²

Source: Chackalamannil S et al. "Potent non-peptide thrombin receptor antagonists." *Curr Med Chem Cardiovasc Hematol Agents.* 2003 Mar;1(1):37-45.

"The incidence of thrombosis as a complication of invasive surgery, in cancer patients, as a cause or complication of stroke, acute myocardial infarction (AMI), thrombolysis, unstable angina (UA) or angioplasty is substantial. To better serve this patient population in the prevention and prophylaxis of thrombosis, new types of anticoagulant drugs are under development by the pharmaceutical industry. The goal of these efforts are orally-active anticoagulants with specificity

and pharmacokinetic properties that could translate into better control of anticoagulation and thrombosis and less bleeding liability compared to the currently used anticoagulants.”¹³

Source: McKean ML and Adelman SJ. “Future therapies for the prevention and treatment of venous and arterial thrombosis.” *Expert Opin Investig Drugs*. 1998 May;7(5):687-90.

- Recall the safety and effectiveness of the next generation of paclitaxel eluting stents.

“The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. Such studies have been inconclusive because of their insufficient size, the use of historical controls, a limited duration of follow-up, and a lack of access to original source data.”¹⁴

Source: Stone GW et al. “Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents.” *N Engl J Med*. 2007 Mar 8;356(10):998-1008.

“Paclitaxel-eluting stents (PES) have been proved effective in randomized trials enrolling highly selected patients, yet there is uncertainty concerning results of PES implantation in very high-risk patients and lesions.”¹⁵

Source: Biondi-Zoccai GG et al. “Testing prospectively the effectiveness and safety of paclitaxel-eluting stents in over 1000 very high-risk patients: design, baseline characteristics, procedural data and in-hospital outcomes of the multicenter Taxus in Real-life Usage Evaluation (TRUE) Study.” *Int J Cardiol*. 2007 May 2;117(3):349-54.

“Intracoronary polymer-based stent delivery of paclitaxel has been shown to be effective in reducing restenosis in simple coronary lesions, but the evidence base for contemporary use in longer, more complex coronary stenoses is lacking.”¹⁶

Source: Dawkins KD et al. “Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice.” *Circulation*. 2005 Nov 22;112(21):3306-13.

“Contemporary use of this new technology in the treatment of the long, complex coronary stenoses commonly seen in clinical practice is lacking an evidence base.”¹⁶

Source: Dawkins KD et al. “Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice.” *Circulation*. 2005 Nov 22;112(21):3306-13.

- Explain which studies have confirmed a marked response variability to clopidogrel therapy.

“Controversy surrounds the optimal platelet aggregation measurement to assess clopidogrel non-responsiveness.”¹⁷

Source: Gurbel et al. Assessment of clopidogrel responsiveness: Measurements of maximum platelet aggregation, final platelet aggregation and their correlation with vasodilator-stimulated phosphoprotein in resistant patients. *Thrombosis Research*, Volume 121, Issue 1, 2007, Pages 107-115.

“Controversy exists in the interventional cardiology community regarding the optimal loading dose of clopidogrel. Currently, 300 mg is the most widely prescribed clopidogrel loading dose in the U.S.”¹⁸

Source: Gurbel et al. “The Relation of Dosing to Clopidogrel Responsiveness and the Incidence of High Post-Treatment Platelet Aggregation in Patients Undergoing Coronary Stenting” *J Am Coll Cardiol.* 2005;45:1392-6.

“Stent thrombosis remains a significant clinical problem. High post-PA and NR are possible risk factors for stent thrombosis and the late ischemic events. Recent studies have strongly supported this relation and suggest that a 300-mg load is not potent enough in some patients to overcome the thrombotic burden during and after percutaneous interventions.”¹⁸

Source: Gurbel et al. “The Relation of Dosing to Clopidogrel Responsiveness and the Incidence of High Post-Treatment Platelet Aggregation in Patients Undergoing Coronary Stenting” *J Am Coll Cardiol.* 2005;45:1392-6.

“We have reported response variability and nonresponsiveness (NR) after a 300-mg clopidogrel loading dose for coronary artery stenting. Since then other studies have confirmed that some patients do not achieve optimal platelet inhibition and exhibit NR after standard clopidogrel therapy. The mechanisms responsible for NR are incompletely defined.”¹⁸

Source: Gurbel et al. “The Relation of Dosing to Clopidogrel Responsiveness and the Incidence of High Post-Treatment Platelet Aggregation in Patients Undergoing Coronary Stenting” *J Am Coll Cardiol.* 2005;45:1392-6.

“Dual antiplatelet therapy with aspirin and clopidogrel are the gold standard to attenuate platelet function during PCI. However, despite the superior protection documented in clinical trials with dual antiplatelet therapy, it has been demonstrated that nearly 20% of patients undergoing PCI will experience recurrent ischemic or thrombotic events. It has been repeatedly shown that a significant percentage of patients display no demonstrable antiplatelet effect by ex vivo measurements after a 300-mg clopidogrel loading dose.”¹⁹

Source: Bliden et al. “Increased Risk in Patients With High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing Percutaneous Coronary Intervention: Is the Current Antiplatelet Therapy Adequate?” *J Am Coll Cardiol.* 2007;49:657-66.

References:

1. 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.
2. Peterson ED et al. “Association Between Hospital Process Performance and Outcomes Among Patients With Acute Coronary Syndromes.” *JAMA.* 2006;295:1912-1920.
3. Roe MT et al. “Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction.” *Arch Intern Med.* 2005 Jul 25;165(14):1630-6.
4. Yuval R et al. “Perceived disability and lifestyle modification following hospitalization for non-ST elevation versus ST elevation acute coronary syndromes: the patients' point of view.” *Eur J Cardiovasc Nurs.* 2007 Dec;6(4):287-92.
5. Barchielli A et al. “Early discharge after acute myocardial infarction in the current clinical practice. Community data from the AMI-Florence Registry, Italy.” *Int J Cardiol.* 2007 Jan 2;114(1):57-63.
6. Patti G and G Di Sciascio. Cardiology Review: Oct 2007.
http://www.cardiologyreviewonline.com/issues/articles/2007-10_02.asp.
7. Patti G et al. “Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial.” *J Am Coll Cardiol.* 2007 Mar 27;49(12):1272-8.
8. Tchong JE. “Debate of Adjunctive Pharmacology for Percutaneous Coronary Intervention: Anticoagulation and Clopidogrel Are Not (Always) Enough.” *J Int Cardiol.* 2006;19(5): 456–463.
9. Zeymer U et al. “Efficacy and safety of clopidogrel 600 mg administered pre-hospitally to improve primary percutaneous coronary intervention in patients with acute myocardial infarction (CIPAMI): study rationale and design.” *Cardiology.* 2007;108(4):265-72.

10. Snoep JD et al. "Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis." *Am Heart J.* 2007 Aug;154(2):221-31.
11. Source: Moliterno DJ et al. Abstract presented at the American College of Cardiology 2007 annual meeting <http://www.spectrumsience.com/assets/files/acc07/i2%20LBCT%20Sat%2012%20pm/Moliterno%20Abstract.pdf>
12. Chackalamannil S et al. "Potent non-peptide thrombin receptor antagonists." *Curr Med Chem Cardiovasc Hematol Agents.* 2003 Mar;1(1):37-45.
13. McKean ML and Adelman SJ. "Future therapies for the prevention and treatment of venous and arterial thrombosis." *Expert Opin Investig Drugs.* 1998 May;7(5):687-90.
14. Stone GW et al. "Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents." *N Engl J Med.* 2007 Mar 8;356(10):998-1008.
15. Biondi-Zoccai GG et al. "Testing prospectively the effectiveness and safety of paclitaxel-eluting stents in over 1000 very high-risk patients: design, baseline characteristics, procedural data and in-hospital outcomes of the multicenter Taxus in Real-life Usage Evaluation (TRUE) Study." *Int J Cardiol.* 2007 May 2;117(3):349-54.
16. Dawkins KD et al. "Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice." *Circulation.* 2005 Nov 22;112(21):3306-13.
17. Gurbel et al. Assessment of clopidogrel responsiveness: Measurements of maximum platelet aggregation, final platelet aggregation and their correlation with vasodilator-stimulated phosphoprotein in resistant patients. *Thrombosis Research*, Volume 121, Issue 1, 2007, Pages 107-115.
18. Gurbel et al. "The Relation of Dosing to Clopidogrel Responsiveness and the Incidence of High Post-Treatment Platelet Aggregation in Patients Undergoing Coronary Stenting" *J Am Coll Cardiol.* 2005;45:1392-6.
19. Bliden et al. "Increased Risk in Patients With High Platelet Aggregation Receiving Chronic Clopidogrel Therapy Undergoing Percutaneous Coronary Intervention: Is the Current Antiplatelet Therapy Adequate?" *J Am Coll Cardiol.* 2007;49:657-66.