Acute Coronary Syndromes: Morbidity, Mortality, and Pharmacoeconomic Burden

Daniel M. Kolansky, MD

Abstract

Acute coronary syndromes (ACS), which include unstable angina and myocardial infarction (MI) with or without ST-segment elevation, are life-threatening disorders that remain a source of high morbidity and mortality despite advances in treatment. Nearly 1.5 million hospital discharges involve patients with ACS. According to statistics from the American Heart Association (AHA), approximately 18% of men and 23% of women over the age of 40 will die within 1 year of having an initial recognized MI. The economic burden of ACS is also very high, costing Americans more than $150 billion, according to AHA estimates. Approximately 20% of the ACS patients are rehospitalized within 1 year, and nearly 60% of the costs related to ACS result from rehospitalization. However, the evidence-based therapeutic management of ACS remains suboptimal. An understanding of the drivers of morbidity, mortality, and costs associated with ACS will help in developing strategies to reduce the burden of the disease. The evidence regarding the effects of early revascularization and stenting on survival rates in ACS patients is discussed. Currently available evidence-based and new practice guidelines determine the pros and cons of invasive versus conservative strategies for treating ACS. By evaluating the predictors of optimal medical therapy and mortality post-discharge, healthcare providers involved in the managed care play a key role in providing efficient, safe, and cost-effective ACS treatment.

(Am J Manag Care. 2009;15:S36-S41)

Acute coronary syndromes (ACS), including unstable angina (UA) and myocardial infarction (MI) with or without ST-segment elevation, are life-threatening disorders that remain a source of high morbidity and mortality despite advances in treatment.[1] According to the Heart Disease and Stroke Statistics 2008 Update from the American Heart Association (AHA), 1,413,000 hospital discharges in the United States were due to ACS in 2005.[2] Approximately 80% of these cases comprised either UA or non–ST-segment elevation myocardial infarction (NSTEMI), and about 20% were cases of ST-segment elevation myocardial infarction (STEMI). This disease burden along with progress in cardiovascular technology has led to substantial growth in the number of cardiovascular procedures performed in the United States from 1980 to 2005. The rates of percutaneous coronary intervention (PCI) have increased severalfold, with 645,000 patients undergoing PCI annually and 620,000 receiving a stent.[2] In contrast, the rates of coronary artery bypass graft (CABG) have remained relatively stable over the years.

The economic impact of ACS is also very high, costing Americans more than $150 billion annually. A recent analysis of findings from a multiemployer claims database calculated a mean length of stay at 4.6 days, with the cost of initial hospitalization for ACS of approximately $23,000 per patient.[3] Nearly 20% of the patients are rehospitalized within 1 year and approximately 60% of the costs related to ACS are due to rehospitalization.[3] Approaches to reduce ACS-related morbidity, mortality, and costs include both early revascularization with PCI and stenting as well as improving thrombolytic and anticoagulant therapies.[4] The direct medical cost for ACS is estimated at $75 billion, with a significant portion associated with drug therapy.

Drivers of Morbidity and Mortality

ACS results in significant morbidity and mortality, accounting for half of all deaths due to cardiovascular disease. Approximately one third of STEMI patients die within 24 hours of onset of ischemia, thus emphasizing the need for prompt and effective treatment.[5] The morbidity and mortality is lower in UA/NSTEMI patients, but is still substantial, and about 15% of patients die or experience a reinfarction within 30 days of diagnosis.[4] In addition, the survivors have significant morbidity; up to 30% of discharged patients are rehospitalized within 6 months, further adding to the economic burden. As

many as 18% of men and 23% of women over age 40 may die within 1 year following MI.[2] The higher mortality observed in older women may be because they frequently present with atypical chest pain symptoms and may not receive appropriate care.

Several strategies are available to reduce ACS-related morbidity and mortality, including the interventional approach (eg, early revascularization with PCI and stenting) and the pharmacologic approach (eg, thrombolytic and anticoagulant therapies). Early revascularization improves 1-year mortality rates in ACS.[6] Although it is widely accepted that stenting reduces mortality and the need for repeat revascularizations, research is ongoing regarding the appropriate use for bare-metal stents (BMSs) versus drug-eluting stents (DESs) with the goal of achieving better outcomes. A recent meta-analysis of 7 clinical trials of DESs versus BMSs in a total of 2357 acute MI patients concluded that the use of DESs versus BMSs significantly reduced the rates of subsequent revascularization without any difference in the rates of death or MI.[7]

Following successful coronary intervention in patients with ACS, appropriate pharmacologic therapy is also important and has been shown to significantly reduce 1-year mortality.[8] In addition, there is evidence that in patients with stable coronary artery disease, medical therapy alone plays an important role. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial concluded that in patients with stable coronary artery disease, PCI coupled with optimal medical therapy did not reduce the risk of death and nonfatal MI compared with optimal medical therapy alone.[9]

Available Treatment Approaches for ACS

The appropriate management of ACS requires intensive medical therapy often with associated invasive cardiovascular procedures. The American College of Cardiology (ACC)/AHA guidelines recommend treatments for ACS, including antiplatelet therapy, beta-blockers, nitrates, anticoagulants, angiotensin-converting enzyme inhibitors, and statins for UA/NSTEMI as well as STEMI patients.[10,11] In addition, for patients with STEMI, reperfusion therapy with primary PCI within 90 minutes of initial medical contact or fibrinolytic therapy within 30 minutes of hospital presentation is recommended unless contraindicated. A risk stratification approach should be used for the overall management of UA/NSTEMI ACS because of the heterogeneous nature of the level of risk of death and nonfatal ischemic events in patients with chest discomfort. High-risk patients present with persistent at-rest or recurring angina and elevated cardiac biomarkers or ST-segment depression; intermediate-risk patients present with angina and ST-segment depression; and low-risk patients are typically pain-free with normal cardiac biomarkers and absence of ST-segment changes.[1,12] Risk stratification is useful in the selection of site of care, type of therapy, and management strategy (**Figure**).[13]

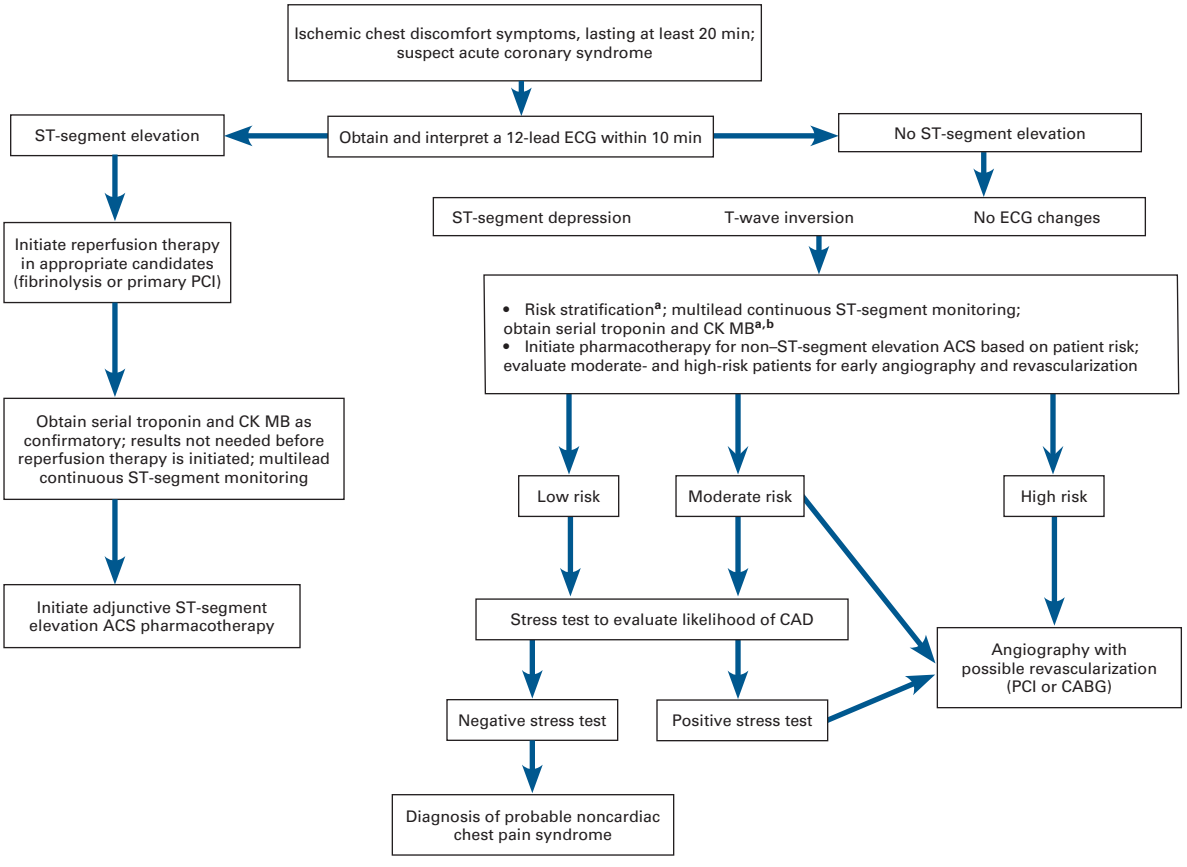
Although ongoing discussion about an ideal approach to UA/NSTEMI ACS management regarding an early invasive versus conservative treatment strategy continues, the ACC/AHA 2007 guidelines recommend an early invasive strategy in patients with the high-risk features mentioned earlier or other factors, such as symptoms of heart failure, hemodynamic instability, PCI within 6 months, prior CABG, high Thrombolysis in Myocardial Infarction or Global Registry of Acute Coronary Events risk score, or a left ventricular ejection fraction of less than 40%.[10] For low-risk patients, a conservative strategy is recommended. A recent meta-analysis of 8 clinical trials of invasive versus conservative strategy for NSTEMI ACS found that both men and high-risk women have a comparable benefit from an invasive strategy for reducing death, MI, or rehospitalization.[14] However, an invasive strategy did not significantly benefit low-risk women, supporting the guideline recommendation of a conservative strategy in this subgroup. For the initial invasive strategy, the anticoagulant regimens with established efficacy include US Food and Drug Administration (FDA)-approved therapies, enoxaparin and unfractionated heparin, as well as others not yet approved by the FDA for this indication, including fondaparinux (generally used in combination with unfractionated heparin) and bivalirudin. Anticoagulants for an initial conservative approach include enoxaparin, unfractionated heparin, or fondaparinux.[10] Among antiplatelet agents, aspirin and clopidogrel are recommended for invasive as well as conservative

approaches; glycoprotein IIb/IIIa agents are added prior to angiography in the setting of recurrent symptoms or electrocardiogram changes in high-risk patients, and are often added for PCI in high-risk patients. In patients undergoing PCI, aspirin, clopidogrel, and unfractionated heparin receive a level 1 recommendation, whereas bivalirudin may be used in low-risk patients undergoing elective PCI, and low-molecular-weight heparin may be considered in PCI patients with STEMI.[15] However, because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI.[16]

Managed Care Perspective on ACS Management

The goal of managed care is to provide efficient, safe, and cost-effective treatment for ACS patients. Drug utilization data obtained from a claims database before and after index hospitalization for ischemic heart disease in patients with ACS showed that hospitalization cost is mostly upfront but goes down over a period of 12 months, whereas the pharmacy costs are proportionately small and remain stable over a 1-year period.[3] Treatment options that reduce resource utilization, in the form of reduced rates of rehospitalization and subsequent outpatient care, can potentially lower the costs of care. To this end, it is important to identify independent predictors of 1-year mortality in ACS patients postdischarge. Age, previous MI, heart failure, ST-segment deviation, and abnormal cardiac biomarkers are predictors of increased mortality, whereas optimal medical therapy postdischarge is a predictor of decreased mortality.[8] It has been suggested that

Figure. Evaluation of the Acute Coronary Syndrome Patient



ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK, creatine kinase; ECG, electrocardiogram; PCI, percutaneous coronary intervention.
[a]Positive, above the myocardial infarction (MI) decision limit.
[b]Negative, below the MI decision limit.
Adapted with permission from Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program. Book 1. Cardiology*. 6th ed. Kansas City, MO: American College of Clinical Pharmacy; 2007:59-83.

older patients, women, those with previous heart failure, renal dysfunction, and CABG surgery during index hospitalizations are less likely to receive optimal medical therapy; hence, heightened awareness is important in these patients to ensure that optimal medical therapy is provided.

Several STEMI/NSTEMI performance measures have been proposed by ACC/AHA, and endorsed by multiple organizations, to ensure effective, timely, safe, efficient, and patient-centered medical care (**Table**).[17] The new performance and test measures released in December 2008 introduced some of the major changes from the 2006 measures, which include the following:

- *Omitted:* Early beta-blockers at arrival; due to complexity of decision making and inconclusive net benefit
- *Revised:* Statin therapy (rather than low-density lipoprotein [LDL]-lowering therapy) at discharge; recommendations support use of statins regardless of baseline LDL cholesterol levels
- *Revised:* LDL cholesterol testing during inpatient hospitalization for acute MI; changed to a test measure
- *New:* Evaluation of left ventricular systolic function; because this test result affects prognosis and drives treatment decisions
- *New:* Timely reperfusion in STEMI; due to positive impact of timely reperfusion on clinical outcomes and remaining gaps in the delivery of this effective therapy

Adherence to guideline level care is critical in improving patient outcomes. CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation?) data from the National Quality Improvement Initiative of the ACC/AHA guidelines demonstrate that improvement in guideline adherence results in improved survival. An analysis of 64,775 UA/NSTEMI patients from 350 US centers enrolled in CRUSADE showed that every 10% increase in composite guideline adherence was associated with a proportional 10% decrease in in-hospital mortality risk.[18] A significant association was found between the composite adherence rate for ACS and in-hospital mortality, with mortality rates of 6.31% for the lowest adherence quartile decreasing to 4.15% for the highest adherence quartile (P <.001). Further analysis of the CRUSADE results found some surprising gaps (eg, underuse of glycoprotein IIb/IIIa inhibitors in high-risk populations, inadequate use of clopidogrel in medically managed patients, higher real-life mortality risk in patients with UA/NSTEMI than reported in clinical trials, and a lack of familiarity with the guidelines and the safe use of drugs as the likely causes of underprescribing of antiplatelets).[19]

Despite the wide availability of carefully prepared guidelines for ACS care and the demonstrated improvement in patient outcomes achieved with guideline adherence, compliance with the guidelines remains inadequate. Participation in the AHA Get With The Guidelines (GWTG) program for coronary artery disease was found to be independently associated with improvement in guidelines adherence. The GWTG participating hospitals also had greater adherence to the Hospital Compare composite measure compared with non-GWTG hospitals (89.7% vs 85%; P <.001) as well as to performance measures (89.5% vs 83%; P <.001).[20] The use of the GWTG pathway also improved the referral rate for cardiac rehabilitation after acute MI, although most patients did not enroll, signifying the need for improvement in patient enrollment after referral.[21]

Conclusion

More than $150 billion are spent on ACS care annually, with 60% the result of hospitalizations. Treatment of ACS based on risk stratification guides invasive versus conservative strategies and provides optimal medical therapy. Adherence to guideline level care improves survival and quality of life in ACS patients. Healthcare providers involved in managed care play a key role in providing efficient, safe, and cost-effective ACS care.

Acknowledgment: The author would like to thank Nimish Mehta, PhD, MBA, for assistance drafting the manuscript.

Author Affiliation: From the Division of Cardiovascular Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.

Funding Source: Financial support for this work was provided by Daiichi Sankyo, Inc and Eli Lilly and Company.

Author Disclosure: Speakers' bureau for Bristol-Myers Squibb Company and Sanofi Pharmaceuticals Partnership.

Authorship Information: Concept and design; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

Table. 2008 American College of Cardiology/American Heart Association STEMI/NSTEMI Performance Measures: Inpatient Measure Descriptions

Measure Name	Measure Description
Performance measures	
1. Aspirin at arrival	AMI patients who received aspirin within 24 h before or after hospital arrival
2. Aspirin prescribed at discharge	AMI patients who are prescribed aspirin at hospital discharge
3. Beta-blocker prescribed at discharge	AMI patients who are prescribed a beta-blocker at hospital discharge
4. Statin at discharge	AMI patients who are prescribed a statin at hospital discharge
5. Evaluation of LVSF[a]	AMI patients with documentation in the hospital record that LVSF was evaluated during hospitalization or is planned after discharge
6. ACEI or ARB for LVSD	AMI patients with LVSD who are prescribed an ACEI or ARB at hospital discharge (for purposes of this measure, LVSD is defined as chart documentation of an LVEF less than 40% or a narrative description of LVSF consistent with moderate or severe systolic dysfunction)
7. Time to fibrinolytic therapy	Median time from hospital arrival to administration of fibrinolytic therapy in AMI patients with ST-segment elevation or LBBB on the ECG performed closest to hospital arrival time; AMI patients with ST-segment elevation or LBBB on the ECG closest to hospital arrival time receiving fibrinolytic therapy during the hospital stay with a time from hospital arrival to fibrinolysis of 30 min or less
8. Time to PCI	Median time from hospital arrival to primary PCI in AMI patients with ST-segment elevation or LBBB on the ECG performed closest to arrival time; AMI patients with ST-segment elevation or LBBB on the ECG closest to hospital arrival time receiving primary PCI during the hospital stay with a time from hospital arrival to PCI of 90 min or less
9. Reperfusion therapy	AMI patients with ST-segment elevation or LBBB on the ECG performed closest to arrival receiving either fibrinolysis or primary PCI or who are transferred to another facility for primary PCI
10. Time from ED arrival at STEMI referral facility to ED discharge from STEMI referral facility in patients transferred for primary PCI[a]	Median time from ED arrival at STEMI referral facility to ED discharge from STEMI referral facility for AMI patients with ST-segment elevation or LBBB on the ECG performed closest to hospital arrival time who are transferred to a STEMI receiving facility for primary PCI
11. Time from ED arrival at STEMI referral facility to primary PCI at STEMI receiving facility among transferred patients[a]	Median time from patient arrival at a STEMI referral facility's ED to time of primary PCI at a STEMI receiving facility for AMI patients presenting with ST-segment elevation or LBBB on the ECG performed closest to first hospital arrival time who are transferred to a STEMI receiving facility for primary PCI
12. Adult smoking cessation advice/counseling	AMI patients with a history of smoking cigarettes who are given smoking cessation advice or counseling during hospital stay
13. Cardiac rehabilitation patient referral from an inpatient setting[17,b]	All patients hospitalized with a primary diagnosis of AMI referred to an early outpatient CR program
Test measures[b]	
T-1. LDL cholesterol assessment	AMI patients with documentation of LDL cholesterol level in the hospital record or documentation that LDL cholesterol testing was done during the hospital stay or is planned after discharge
T-2. Excessive initial heparin dose[a]	AMI patients who receive excess dosing of UFH initially
T-3. Excessive initial enoxaparin dose[a]	AMI patients who receive excess dosing of subcutaneous enoxaparin initially
T-4. Excessive initial abciximab dose[a]	AMI patients who receive excess dosing of abciximab initially
T-5. Excessive initial eptifibatide dose[a]	AMI patients who receive excess dosing of eptifibatide initially
T-6. Excessive initial tirofiban dose[a]	AMI patients who receive excess dosing of tirofiban initially
T-7. Anticoagulant dosing protocol[a]	Presence of a protocol or other clinical aid (eg, nomogram, electronic order entry) in the hospital record of AMI patients that addresses dosing of anticoagulant therapy and parenteral antiplatelet therapy (ie, UFH low-molecular-weight heparin, and glycoprotein IIb/IIIa inhibitors)
T-8. Anticoagulant error tracking system[a]	Evidence of a tracking system for identifying dosing errors in anticoagulation therapy in the hospital record of AMI patients
T-9. Clopidogrel prescribed at discharge for medically treated AMI patients[a]	Medically treated AMI patients who are prescribed clopidogrel or ticlopidine at hospital discharge

ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CR, cardiac rehabilitation/secondary prevention; ECG, electrocardiogram; ED, emergency department; LBBB, left bundle branch block; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; LVSF, left ventricular systolic function; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.
[a]New measures.
[b]Test measures have been designated for use in internal quality improvement programs only and are not appropriate for any other use (eg, pay for performance, physician ranking, or public reporting programs).
Reprinted with permission from Krumholz HM, et al. *Circulation.* 2008;118(24):2596-2648.

Address correspondence to: Daniel M. Kolansky, MD, Director, Cardiac Care Unit, Associate Professor of Medicine, Hospital of The University of Pennsylvania, Department of Medicine, 9 Gates West, 3400 Spruce St, Philadelphia, PA 19104. E-mail: Daniel.kolansky@uphs.upenn.edu.

REFERENCES

1. Boden WE, Shah PK, Gupta V, Ohman EM. Contemporary approach to the diagnosis and management of non-ST-segment elevation acute coronary syndromes. *Prog Cardiovasc Dis*. 2008;50(5):311-351.

2. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117(4):e25-e146.

3. Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. *Curr Med Res Opin*. 2008;24(2):461-468.

4. Turpie AG. Burden of disease: medical and economic impact of acute coronary syndromes. *Am J Manag Care*. 2006;12(suppl 16):S430-S434.

5. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110(9):e82-e292.

6. Yan AT, Yan RT, Tan M, et al. In-hospital revascularization and one-year outcome of acute coronary syndrome patients stratified by the GRACE risk score. *Am J Cardiol*. 2005;96(7):913-916.

7. Pasceri V, Patti G, Speciale G, Pristipino C, Richichi G, Di Sciascio G. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J*. 2007;153(5):749-754.

8. Yan AT, Yan RT, Tan M, et al. Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. *Am Heart J*. 2007;154(16):1108-1115.

9. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356(15):1503-1516.

10. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50(7):e1-e157.

11. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation*. 2008;117(2):296-329.

12. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-842.

13. Spinler SA. Acute coronary syndromes. In: Dunsworth TS, Richardson MM, Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program. Book 1. Cardiology*. 6th ed. Kansas City, MO: American College of Clinical Pharmacy; 2007:59-83.

14. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300(1):71-80.

15. Smith SC, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention-Summary Article: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47(1):216-235.

16. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation*. 2008;117(2):261-295.

17. Krumholz HM, Anderson JL, Bachelder BL, et al. ACC/AHA 2008 Performance Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non-ST-Elevation Myocardial Infarction): developed in collaboration with the American Academy of Family Physicians and the American College of Emergency Physicians: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Society for Cardiovascular Angiography and Interventions, and Society of Hospital Medicine. *Circulation*. 2008;118(24):2596-2648.

18. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA*. 2006;295(16):1912-1920.

19. Bottorff MB, Nutescu EA, Spinler S. Antiplatelet therapy in patients with unstable angina and non-ST-segment-elevation myocardial infarction: findings from the CRUSADE national quality improvement initiative. *Pharmacotherapy*. 2007;27(8):1145-1162.

20. Lewis WR, Peterson ED, Cannon CP, et al. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. *Arch Intern Med*. 2008;168(16):1813-1819.

21. Mazzini MJ, Stevens GR, Whalen D, Ozonoff A, Balady GJ. Effect of an American Heart Association Get With the Guidelines program-based clinical pathway on referral and enrollment into cardiac rehabilitation after acute myocardial infarction. *Am J Cardiol*. 2008;101(8):1084-1087.