Practical Implementation of the Guidelines for Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction in the Emergency Department

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In the United States each year, >5.3 million patients present to emergency departments with chest discomfort and related symptoms. Ultimately, >1.4 million individuals are hospitalized for unstable angina and non–ST-segment elevation myocardial infarction. For emergency physicians and cardiologists alike, these patients represent an enormous challenge to accurately diagnose and appropriately treat. This update of 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 (UA/NSTEMI) provides an evidence-based approach to the diagnosis and treatment of these patients in the emergency department, in-hospital, and after hospital discharge. Despite publication of the guidelines several years ago, many patients with UA/NSTEMI still do not receive guidelines-indicated therapy. [Ann Emerg Med. 2005;46:185-197.]

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Through this statement, the authors hope to provide a practical approach to implementing the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction (UA/NSTEMI) by succinctly summarizing the diagnostic elements such as electrocardiography and cardiac biomarker testing, as well as treatment regimens including nitrates, morphine, β-blockers, calcium channel blockers, angiotensin-converting enzyme

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ACC/AHA Classification of Recommendations and Levels of Evidence

Class I:	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
Class II:	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
	IIa. Weight of evidence/opinion is in favor of usefulness/efficacy
	IIb. Usefulness/efficacy is less well established by evidence/opinion.
Class III:	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial, or non-randomized studies
Level of Evidence C	Consensus opinion of experts

Adapted from: Braunwald E, Antman EM, Beasley JW et al ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: Summary Article: A Report of the American College of Cardiology/American Heart Associate Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). **Circulation** 2002; 106:1893-1900.

Figure 1. ACC/AHA classification of recommendations and levels of evidence. Adapted from *Circulation*. 2002;106: 1893-1900.

inhibitors, antiplatelet agents, and anti-thrombin drugs for acute coronary syndrome (ACS). Risk stratification of patients with ACS is emphasized so that the patients at highest risk are identified for guideline-directed pharmacological therapy and early invasive therapy for revascularization. Two quality improvement tools, a template for an emergency department (ED) ACS risk assessment record and an initial therapeutic order template, are provided to help emergency physicians and cardiologists at every hospital integrate care in an evidence-based approach for their patients.

Finally, 4 quality improvement initiatives–Guidelines Applied in Practice (GAP), UCLA Cardiovascular Atherosclerosis Management Program (CHAMP), American Heart Association "Get with the Guidelines," and the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines)– are presented. Each of these programs attempts to improve care for patients with ACS by emphasizing guidelines awareness and implementation. Through the implementation of and adherence to the guidelines, improvement in care and outcomes for patients with ACS can be realized.

The 2002 ACC/AHA UA/NSTEMI guidelines represent an evidence-based approach to the care of patients with ACS.[1,2] For patients presenting to the ED, these guidelines represent an opportunity to standardize the diagnosis and treatment of patients with ACS across the United States. Several summaries of the guidelines emphasizing emergency care have been published.[3,4] Now, 3 years after the publication of the 2002 guidelines, adoption into routine practice in the emergency setting remains variable.[5] The purpose of the present effort is to provide the emergency physician and cardiologist at any hospital with a practical approach, along with quality improvement tools, to implement the guidelines.

The 2002 ACC/AHA UA/NSTEMI guidelines provide extensive evidence for diagnostic and treatment regimens that provide substantial benefit in the early period after the patient with ACS presents to the ED. The evaluation of ACS in the emergency setting remains a challenge across the United States. More than 5.3 million patients present to EDs each year, resulting in 1.4 million patients being hospitalized for UA and NSTEMI.[6,7] This undifferentiated population must be evaluated and risk stratified, not only for ACS, but also for a number of other potentially fatal disease processes such as pulmonary embolism and aortic dissection. It is the hope of the present authors that this statement will prove useful to improve care for patients with UA/NSTEMI presenting to EDs across the United States.

Recommendations/Evidence Weighting

The 2002 ACC/AHA UA/NSTEMI guidelines use recommendation classes that rapidly provide the reader with sufficient information to make choices regarding diagnostic and treatment strategies. A Class I recommendation is generally considered to be useful and effective. Aspirin serves as an excellent example of a Class I treatment. Designation of a regimen as Class IIa identifies a treatment as generally considered effective, but some controversy may be present about the usefulness of a treatment. A Class IIb recommendation suggests that a treatment is controversial but leans toward efficacy. A therapy or diagnostic strategy that is Class III is not useful and may actually be harmful in some cases. Weighting of evidence for these Class I, II, and III recommendations is straightforward. If data from multiple large, randomized trials support a recommendation, then the weight of evidence is A. An evidence grade of B for a therapy is provided if fewer, smaller randomized trials, analyses of nonrandomized studies, or observational registries support a recommendation. Expert consensus provides an evidence grade of C.[1] (Figure 1)

Risk Stratification

Emergency physicians must be expert in identifying patients with ACS presenting to the ED. It is critical to perform risk stratification quickly early in the course of a patient's evaluation to promptly provide guidelines-directed therapy. The history, including risk factors for coronary artery disease (CAD) development, as well as the physical examination help the clinician to screen patients for ACS (Table 1). The 12-lead ECG and cardiac biomarkers such as troponin and creatine kinase-MB (CK-MB) serve as the major ancillary testing tools for risk stratification in the emergency setting, a process that involves assessing (1) the likelihood that the patient's symptoms are the result of ACS and (2) among patients with probable/definite ACS, to identify patients who are at higher or lower risk of death and myocardial infarction (MI) as a complication of their ACS event.

The history taken from a patient with ACS typically but not always includes chest discomfort as a central feature. Older

Table 1. Likelihood that Signs and Symptoms Represent an Acute Coronary Syndrome Secondary to Coronary Artery Disease

	High Likelihood	Intermediate Likelihood	Low Likelihood
Feature	Any of the following:	Absence of high-likelihood features and presence of any of the following:	Absence of high- or intermediate- likelihood features but may have:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age>70 Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR, hypotension diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation ($\geq$ 0.05 mV) or T-wave inversion ($\geq$ 0.2 mV) with symptoms	Fixed Q waves Abnormal ST-segments or T waves not documented to be new	T-wave flattening or inversion in leads with dominant R waves Normal ECG
Cardiac Markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

MR indicates mitral regurgitation; all other abbreviations as in text.
Adapted with permission from: Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Théroux P. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). 2002. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf. Accessed May 9, 2005.

adults, patients with diabetes, chronic renal failure, and women may present with less-typical symptoms, yet they are at significant risk for complications with ACS. The older adult patient (>75 years old) in particular requires identification in the emergency setting because typically the benefits afforded this group by therapies recommended in the 2002 ACC/AHA guidelines exceed those of younger patients with ACS. The characterization of this discomfort, location, severity, frequency, and possible radiation all help to identify the patient with ACS. The patient's age, sex, family history of CAD, smoking, dyslipidemia, hypertension, diabetes, previous CAD, and cocaine use help to increase the pretest likelihood of ACS in the individual presenting to the ED. The possibility of non-ACS causes for the patient's symptoms also must be considered, including pulmonary embolism, aortic dissection, parenchymal lung disease, esophageal reflux, biliary disease, psychiatric illnesses including depression and panic disorder, musculoskeletal pain, and trauma. A history of underlying illnesses such as intracranial tumor, gastrointestinal or other major bleeding, aortic dissection, and hemorrhagic stroke, or a major surgery in the previous 2 weeks can make antithrombotic or antiplatelet therapy dangerous.

Physical examination of the patient with possible ACS should focus on identifying features that cause the patient to be at high risk for death and nonfatal MI. Evidence of cardiogenic failure, including jugular venous distension, rales, cardiac murmurs, S_3 or S_4 gallops, and peripheral edema, increase the likelihood that ACS is the cause of the patient's symptoms and portends a patient at high risk for ischemic complication. A new mitral regurgitation murmur, hypotension (systolic blood pressure <100 mm Hg), tachycardia (pulse >100 bpm) and bradycardia (pulse <60 bpm) also should alert the clinician to a patient at high risk. The physical examination also should be used to identify contraindications to antithrombotic or antiplatelet therapy such as gross rectal bleeding.[1,2] (Figure 2)

Twelve-Lead ECG

The 12-lead ECG is one of the most useful ancillary tools for detecting ACS. ST-segment depression has been shown to be a significant risk indicator for mortality and MI.[8] Bundle-branch blocks which are new or presumed to be new can indicate a high-risk presentation in the emergency setting. A new bundle-branch block serves as a criterion for STEMI in the appropriate clinical setting, such as prolonged ischemic chest pain. It then indicates a need for rapid reperfusion therapy with immediate intervention in the cardiac catheterization laboratory. Old bundle-branch blocks may suggest underlying coronary disease; however, they also may indicate primary conduction system disease. A paced rhythm can mask underlying electrocardiographic high-risk features, making other cardiac testing such as radionuclide imaging or echocardiography extremely important. Approximately half of the patients with ST-segment depression will develop MI within hours after presentation to the ED. T-wave inversion on the initial 12-lead ECG portends a less-adverse prognosis in patients with ACS; ≈5% of these patients will have an MI or die within 30 days. Deep symmetrical T-wave inversion across the precordial leads may indicate a critical stenosis of the left anterior descending coronary artery (Wellen's phenomena). Patients with suggestive histories and ST changes in the anterior precordial leads and/or

Template for Emergency Department Record which includes Acute Coronary Syndrome Risk Assessment

Demographics: Patient Name, Age, Sex, Race, Date/Time Seen

History of Present Illness:
1) Time of chest pain onset/symptom onset; duration of longest episode of pain prompting visit
2) Other locations of pain: Neck, Left shoulder/arm, Right shoulder/arm, Left hand, Right hand, Abdomen, Back, Other ___________
3) Quality of Pain: Pressing/Crushing/Tightness, Sharp/Stabbing, Burning, Ache, Indigestion/Gas, Numbness, Indescribable, Other ___________
4) Pain is reproduced by: Deep breathing, Palpation, Change in position, Other _________
5) Associated Symptoms: Diaphoresis, Nausea, Vomiting, Dyspnea, Dizziness, Other _________
6) Diagnosis of most similar chest pain: MI, Angina, Other _________
7) Recent pain compared with previously diagnosed angina: Worse, Similar, Better, No previous diagnosis of angina, Different

Cardiac Risk Factors: Family history of premature coronary artery disease in first degree relatives <60 years old, Elevated Cholesterol (>200 or taking medication), hypertension (systolic blood pressure >140, diastolic blood pressure >90 or taking medication), diabetes mellitus, smoking (current, past, never)

Past Medical History: MI, Angina, Cardiac Catheterization, Percutaneous Coronary Intervention, Coronary Artery Bypass Grafting

Medications

Allergies

Physical Examination: Vital signs including O_2 saturation

General: Distress - None; Mild; Moderate; Severe; Diaphoresis

HEENT: JVD; Carotid Bruits

Pulmonary: Clear; Rales (bibasilar or less); Rales (>bibasilar), Other _________

Heart: Mitral regurgitation murmur S_3; S_4

Abdomen: Abdominal Aortic Aneurysm; Renal/Femoral Artery Bruits; Rectal Examination/Guaiac results: positive/negative

Extremities: Decreased Peripheral Pulses/ Decreased Perfusion

Laboratory

Electrocardiogram: Normal; Probable new ST-segment elevation MI (≥ 1.0 mm ST-segment elevation in ≥ 2 leads) or new bundle branch block (left or right); New ischemia (> 1.0 mm ST-segment depression in ≥ 2 leads); Transient ST-segment elevation or ST-segment elevation not reaching 1.0 mm (0.5 mm < ST-segment elevation < 1.0 mm); Other new ST-segment or T-wave changes of ischemia; Old infarction, old ischemia; non-specific ST-segment or T-wave abnormality

Cardiac Biomarkers: Troponin T or I Level
CK/CK-MB Level

Adapted from: Emergency Department Chest Pain/ACS Evaluation template, Brigham & Women's Hospital, Boston, Massachusetts and the University Hospital, Cincinnati, Ohio.

Figure 2. Template for emergency department record which includes ACS risk assessment. Adapted from Brigham & Women's Hospital, Boston, Mass, and the University Hospital, Cincinnati, Ohio.

I and L should have posterior leads recorded to detect possible posterior ST-elevation events. A normal 12-lead ECG on presentation to the ED represents the lowest risk for a given patient; however, up to a 6% rate of NSTEMI still exists for these patients. The initial ECG results therefore provide the clinician with substantial risk stratification information. The ACC/AHA guidelines support obtaining serial 12-lead ECGs in the ED to improve sensitivity for detecting ACS if the initial ECG is nondiagnostic.[1]

Cardiac Biomarkers

The cardiac biomarkers troponin (I and T) and CK-MB represent the second principal method for identifying patients with ACS at risk for significant complications, including death and MI in the ED. Although CK-MB has been the predominant marker of myocardial necrosis used, the troponins I and T have in many centers replaced this traditional marker in accordance with the recent criteria for the redefinition of acute MI promulgated by the European Society of Cardiology and the ACC.[9-13]

Point-of-care testing can accelerate decision making in the ED by providing CK-MB and troponin levels within 15 to 20 minutes after presentation,[14] however, many point-of-care devices are less sensitive than central laboratory analyzers.[15] Thus, some patients with minor and/or modest elevations in troponin may be missed. This factor must be considered by clinicians relying on these results. Some assays lack adequate sensitivity and/or sufficient precision to allow for accurate low-level measurements. Insufficient precision means that too much variability is present in an assay when multiple testing is performed on a uniform set of samples. When central laboratory testing is used, the turnaround time for laboratory results should not exceed 1 hour.

During the last decade, numerous studies have demonstrated that any detectable elevation of troponin identifies patients at high risk for ischemic complications, including patients with renal failure.[16] Elevated troponin in the setting of ischemic symptoms indicates that the patient has experienced an MI. Elevation of troponin is associated with increased risk of death, and the risk of this complication increases proportionately with the absolute level.[17] Like the 12-lead ECG, troponin serves as an independent predictor of substantial patient risk. Studies have also confirmed that patients with ACS and elevated troponins derive greater benefit from treatment with platelet glycoprotein (GP) IIb/IIIa inhibitors, low-molecular-weight heparin, and early percutaneous coronary intervention (PCI) than those not having elevated troponin levels. It should be emphasized that a normal level of troponin (or CK-MB) on ED presentation, particularly within 6 hours of chest pain onset, does not exclude MI. Serial testing in the ED, at 3 and 6 hours, and at an interval of 6 to 10 hours in-hospital, is necessary to exclude myocardial injury.

The best predictive accuracy for elevated troponin occurs with the use of the 99th percentile of the normal value for troponin. To improve specificity, however, some have suggested using the value where the assay precision is <10%.[18] This approach to improving troponin sensitivity and specificity has been proposed recently and should improve diagnostic accuracy in patients with ACS. When troponin is used at these cutoff values, CK-MB may be useful for timing of the infarction. Neither CK-MB nor other markers, however, have been shown to add substantially to predictive accuracy when serial samples are analyzed with sensitive assays for troponin.

An elevated troponin is indicative of cardiac injury but not necessarily ischemic cardiac injury.[19] If the clinical presentation is not one of acute ischemic heart disease, then a careful search for alternative causes of cardiac injury is essential, such as congestive heart failure or pulmonary embolus. It is important in patients with borderline elevated troponin levels to obtain a careful clinical history so that potent antithrombin and antiplatelet agents, which can cause bleeding, are given to appropriate patients with myocardial necrosis resulting from ACS.

Other Diagnostic Testing

In the emergency setting, other modalities such as radionuclide imaging can provide additional evidence for ACS in patients who present with symptoms that are consistent with ischemia but nondiagnostic 12-lead ECGs and normal levels of cardiac biomarkers.[1] Multiple other tests such as echocardiography for wall motion abnormality, contrast echo perfusion, and radionuclide perfusion such as sestamibi can be performed at rest, providing compelling risk stratification information for patients presenting to the ED. When performed while the patient is complaining of chest pain, these studies can provide excellent negative predictive value for acute myocardial ischemia. Patients with chronic electrocardiographic changes such as bundle-branch block or ST-segment/T-wave abnormalities can also be evaluated more extensively with these modalities. The availability of these techniques at a hospital depends upon the particular expertise of the cardiologists or nuclear radiologists at the institution. Standard graded exercise testing and stress echocardiography can be performed in patients with nondiagnostic ECGs, negative cardiac biomarkers, and no recent (< 6 hours) pain at rest; however, exercise testing is contraindicated in patients with acute ischemia. New blood tests such as myeloperoxidase and ischemia-modified albumin, are being evaluated to better diagnose ACS.[20,21] For patients without high-risk features presenting to the ED, negative serial cardiac biomarkers, no evidence of ST-segment of T-wave changes, and negative perfusion imaging at rest, discharge from the ED after a chest pain center evaluation may be appropriate. An Algorithm for the Evaluation and Management of Patients Suspected of Having an Acute Coronary Syndrome is available in the 2002 ACC/AHA UA/NSTEMI guidelines for the clinician in such circumstances.

2002 ACC/AHA Treatment Guidelines – Management Strategies

Basic Therapy for ACS. For all patients with probable ACS, the following therapies are recommended by the 2002 ACC/AHA guidelines. These therapies should be provided in addition to routine therapy such as bed rest, oxygen if needed, and continuous cardiac rhythm monitoring:

1. Nitrates (IC). Nitrates should be given via sublingual administration followed by intravenous administration for the relief of ischemia and associated symptoms. There are no randomized, placebo-controlled clinical trials of nitrate use in unstable angina; however, small studies from the prethrombolytic era suggested a reduction in mortality rate of ≈35%. More contemporary studies (fourth International Study of Infarct Survival[ISIS-4], Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico II [Iisinopril and transdermal glyceryl trinitrate] [GISSI-3]) are confounded by their being STEMI trials and to a lesser extent by the prehospital use of nitrates. As a result, the recommendations are largely extrapolated from pathophysiological principles and uncontrolled observations.[22]
2. Morphine (IC). Morphine is indicated in the initial management of acute coronary syndromes. Although no randomized, controlled trials have been performed with morphine, it remains recommended because of its venodilation properties and modest reductions in heart rate. Morphine sulfate is recommended when symptoms are not immediately relieved with nitroglycerin and a β-blocker or when acute pulmonary congestion or agitation is present.
3. β-blockers (IB). Intravenous administration is recommended in the emergency setting when there is ongoing chest pain without contraindications to β-blockade and the patient is not already taking β-blockers before presentation. An overview of double-blind, randomized, controlled trials in patients with threatening or evolving MI suggests an ≈13% reduction in risk of progression to MI for patients. There are no trials with enough power to evaluate β-blockade in patients with unstable angina; however, the proven efficacy of β-blockers in patients with acute MI, recent acute MI, congestive heart failure, and angina led to their use being recommendated in unstable angina.[23]
4. Nondihydropyridine calcium-channel blockers (verapamil or diltiazem) (IB). Nondihydrophyridine calcium-channel blockers are recommended in patients with continuing or frequently recurring ischemia when β-blockers are contraindicated and there is no left ventricular (LV) dysfunction or other contraindication to their use. When administered to patients with LV dysfunction, there is strong evidence that they are detrimental (Class III).[24-26]
5. Angiotension-converting enzyme inhibitors (ACEIs) (IB). ACEIs are recommended when hypertension persists despite treatment with nitroglycerin and β-blockers in patients with LV systolic dysfunction or congestive heart failure. They are also recommended for patients with ACS patients and diabetes. ACEI initiation in the ED is appropriate; however, it is not necessary to be started in this setting. Angiotensin renin blockers can be substituted if the patient is ACEI intolerant.[27-29]
6. Antiplatelet agents. Agents that inhibit the aggregation of platelets serve as a principal approach to preventing thrombosis in the 2002 ACC/AHA UA/NSTEMI guidelines. There are 3 different classes of agents which have distinct and separate mechanisms of action: aspirin, clopidogrel, and the GPIIb/IIIa receptor inhibitors.
   - Aspirin serves as the prototypical platelet inhibitor by blocking the thromboxane A_2 pathway. It is inexpensive and has been proved effective in a wide variety of thrombotic diseases. The use of aspirin is a Class IA recommendation, and it should be started as soon as possible. Many prehospital emergency medical services programs routinely provide aspirin to patients with possible ACS in the field. If not given there, then it should be given in the ED shortly after presentation. Four randomized trials of aspirin versus placebo in patients with UA have confirmed the salutary effect of this simple treatment. In these studies, there was an ≈50% reduction in death and MI with aspirin.[1,30,31]
   - Another antiplatelet agent, a thienopyridine clopidogrel, has been shown to be effective in blocking adenosine

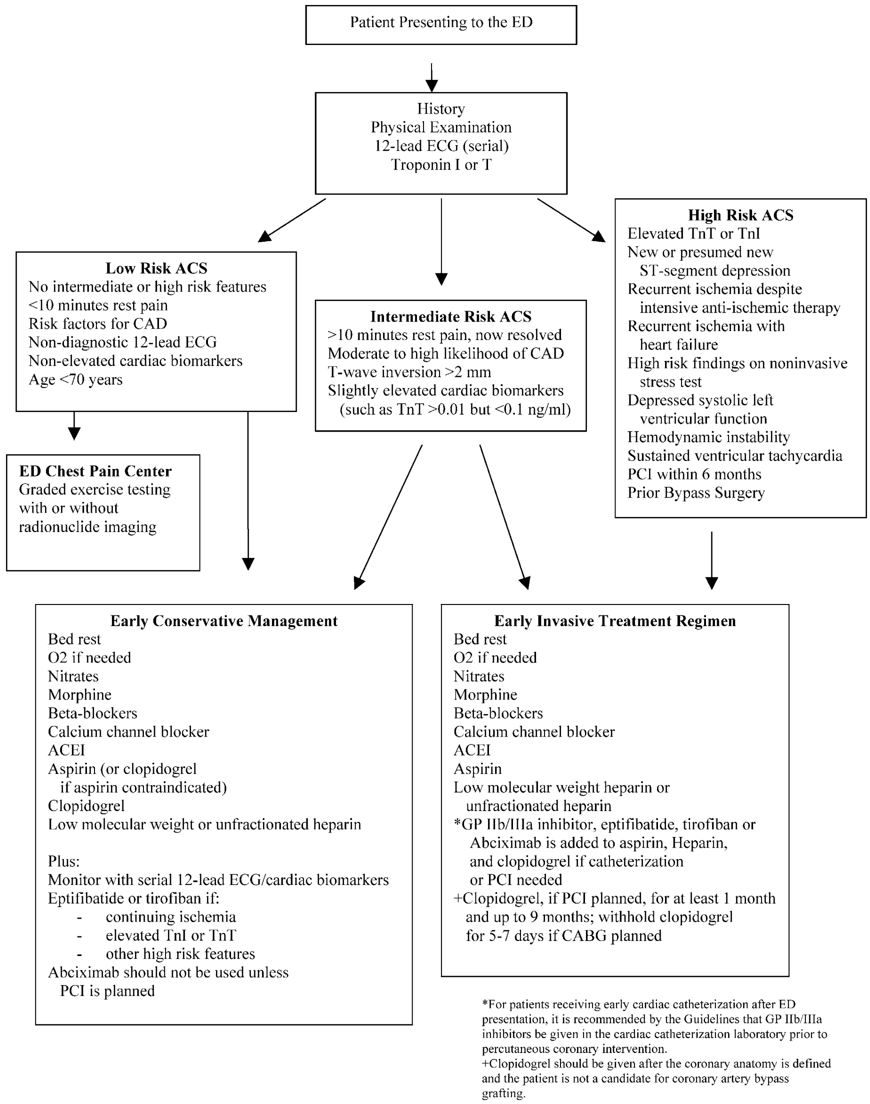

Figure 3. Integration of the 2002 ACC/AHA guidelines for diagnostic and treatment strategies in the emergency department for patients with ACS.

diphosphate–stimulated platelet aggregation. Clopidogrel irreversibly blocks the P_2Y_{12} receptor on platelets, which partially blocks subsequent platelet activation by adenosine diphosphate. The Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) trial confirmed the additional benefit of clopidogrel with aspirin for UA/NSTEMI. There was a 20% reduction in the primary outcome of cardiac death, MI, or stroke in the CURE trial. This agent was incorporated into the 2002 ACC/AHA UA/STEMI guidelines as a Class IA recommendation.[32]

- The GP IIb/IIIa receptor inhibitors are the third class of antiplatelet agents that are important therapies in the 2002 ACC/AHA UA/NSTEMI guidelines. Activated platelets express surface GP IIb/IIIa receptors, which bind fibrinogen to allow aggregation. Eptifibatide and tirofiban (small molecule agents) and abciximab (a monoclonal antibody fragment) are approved for use in patients with ACS and are recommended for patients undergoing early invasive therapy based on the CAPTURE, PURSUIT, PRISM-PLUS, and TACTICS-TIMI 18 trials (c7E3 Antiplatelet Therapy in Unstable Refractory Angina, Platelet glycoprotein IIb/IIIa in Unstable angina; Receptor Suppression Using Integrilin™ Therapy, Platelet Receptor Inhibition for ischemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms, and Treat angina with Aggrastat® and determine Costs of Therapy with Invasive or Conservative Strategies-Thrombolysis In Myocardial Infarction-18, respectively) trials (Class IA). The 2 small-molecule agents eptifibatide and tirofiban provide reversible inhibition of the GP IIb/IIIa receptor and are indicated for patients receiving conservative therapy or early invasive therapy for ACS (Class IIaA).[1,33-37]

Table 2. Short-term risk of Death or Nonfatal MI in Patients with UA/NSTEMI*

	High Risk	**Intermediate Risk**	**Low Risk**
Feature	**At least 1 of the following features must be present:**	**No high-risk feature but must have 1 of the following:**	**No high- or intermediate-risk features but may have any of the following features:**
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG, prior aspirin use	
Character of pain	Prolonged ongoing (>20 minutes) rest pain	Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (>20 min) or relieved with rest or sublingual NTG	New-onset or progressive CCS Class III or IV angina the past 2 weeks without prolonged (>20 min) rest pain but with moderate or high likelihood of CAD (see Table 1)
Clinical Findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age>75 years	Age >70 years	
ECG	Angina at rest with transient ST-segment changes >0.05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave inversions >0.2 mV Pathological Q waves	Normal or unchanged ECG during an episode of chest discomfort
Cardiac Markers	Elevated (e.g., TnT >0.1 ng/mL)	Slightly elevated (e.g., TnT >0.01 but <0.1 ng/mL)	Normal

Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms.
CCS indicates Canadian Cardiovascular Society; *NTG*, nitroglycerin; *MR*, mitral regurgitation; all other abbreviations as in text.
Adapted from: Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA Guideline Update for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction - 2002: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *Circulation* 2002; 106.
*See Table 1.

- Abciximab is not indicated for patients receiving only medical management without cardiac catheterization; this is a Class IIIA recommendation based on the GUSTO-IV (Global Utilization of Streptokinase and tPA for Occluded arteries) ACS trial. It is indicated for use in patients whom early PCI is planned.[38]

7. Antithrombin Agents. The use of heparin is essential to the treatment of patients with ACS. Heparin blocks thrombin formation, when given intravenously, by accelerating the action of antithrombin. Unfractionated heparin binds to a variety of proteins, which reduces heparin available to affect antithrombin, resulting in variable anticoagulant responses in patients. Intravenous heparin, however, is considered a fundamental therapy for treating ACS and is a Class IA therapy when given in conjunction with antiplatelet agents.[1,39-41] In a number of trials, low-molecular-weight heparin has been found to have improved efficacy compared with unfractionated heparin. The low-molecular-weight heparin enoxaparin has been shown to be superior to unfractionated heparin in 2 large clinical trials, ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) and TIMI II-B, but equivalent in the most recent study, SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors).[42,43] The guidelines suggest enoxaparin, but not the other low-molecular-weight heparins, is preferred over unfractionated heparin unless coronary artery bypass grafting (CABG) surgery is planned within 24 hours (Class IIaA).[44] Patients with elevated troponin values are the ones who seem to benefit. The use of low-molecular-weight heparin should be coordinated with the cardiac catheterization team before PCI. Some laboratories prefer not to perform these procedures on patients who have received low-molecular-weight heparin.
   Figure 3 is an algorithm that depicts the integration of the 2002 ACC/AHA UA/NSTEMI guidelines for these diagnostic and treatment strategies in the ED.

Patients With ACS at Risk for Complications

The 2002 ACC/AHA UA/NSTEMI guidelines define high, intermediate, and low risk for death or nonfatal MI.[1] Initially, in the ED, emergency physicians must risk stratify patients for ACS. Once it is determined that a patient likely has ACS, then

UA/Non-ST-segment Elevation (NSTE) Initial Management Standing Orders

MEDICATION ALLERGIES

☐ **Specify:** ____________

DIAGNOSTIC STUDIES

☐ 12-lead ECG: Now ____ : In AM ____ Date: ________

☐ 12-lead ECG for recurrent chest pain

☐ Cardiac markers → **Specify:** ☐ Troponin I **OR** ☐ Troponin T } 0, 3, 6, 12, 24 hours; ☐ CK **AND** ☐ CK-MB } 0, 3, 6, 12, 24 hours

LABS

☐ Fasting lipid profile in AM ☐ CBC q AM

☐ Chemistry Panels in ED and q AM ☐ Other labs: ________

INITIAL TREATMENT

Oral Antiplatelet Therapies:

☐ Aspirin → **Specify:** 160-325 mg ☐ Enteric-coated ASA **OR** ☐ Non-enteric coated ASA } ________ mg per day

☐ If aspirin intolerant, clopidogrel: 300 mg loading dose followed by 75 mg po QD

Nitrates and Morphine:

☐ SL NTG 0.4 mg as needed for recurrent chest pain

☐ NTG paste: ____ inches q 6 hours, off from midnight-6 AM

☐ IV NTG: Start at 10 mcg/min if pain not relieved by SL or transdermal NTG and titrate (up to 200 mg/min) for relief of chest pain (keep SBP > 90 mmHg)

☐ **Morphine Sulfate** 1-2 mg every ________ hours as needed for recurrent chest pain

Beta Blockers:

☐ Metoprolol → **Specify:** ☐ **IV:** ________ mg q 5 min X ________ doses **OR**; ☐ **po:** ________ mg q ________ hours **OR**

☐ Atenolol → **Specify:** ☐ **IV:** ________ mg q 5 min X ________ doses **OR**; ☐ **po:** ________ mg qd

☐ Other→ **Specify:** ________________

Non-Dihydropyridine Calcium Antagonist (If Beta-blocker contraindicated):

☐ Diltiazem → **Specify:** ☐ **po:** ________ mg q 8 hours **OR**; ☐ **Diltiazem CD/XR:** ________ mg po qd

☐ Verapamil → **Specify:** ☐ **po:** ________ mg q 8 hours **OR**; ☐ **Verapamil SR:** ________ mg po qd

ACE Inhibitor (Angiotensin receptor blocker can be substituted if ACE intolerant):

☐ Enalapril ☐ **po:** ________ mg q 12 hours

☐ Lisinopril ☐ **po:** ________ mg qd

MANAGEMENT STRATEGY

- **NSTE ACS patients with high-risk features should be managed according to the Early Invasive Protocol.**
- **Patients with moderate-risk features can be managed with either Protocol.**
- **Patients with low-risk features should be managed according to the Early Conservative Protocol.**

High-risk: Elevated Cardiac Markers, ST depression, Transient ST elevation, > 20 min rest pain, Hemodynamic instability, signs of CHF

Moderate-risk: No high-risk features, Prior MI, Prior CABG, T-wave inversions, Rest angina (< 20 min) relieved promptly with NTG, Age > 70 years

Low-risk: No high- or moderate-risk features, progressive angina without prolonged rest pain, Normal cardiac markers, Normal ECG with pain

EARLY INVASIVE PROTOCOL

Intravenous Anti-thrombotic Therapies:

☐ **IV unfractionated heparin →** Initial bolus of 60-70 U/kg bolus (not to exceed 5000 U) + 12-15 U/kg/hr infusion (not to exceed 1000 U/hr) to target aPTT range of 50-70 sec, or 1.5-2.5 times control

☐ **Low-molecular-weight heparin → Specify:**
☐ **Enoxaparin:** 1 mg/kg SC q 12 hrs

Intravenous Antiplatelet Therapies:

GP IIb-IIIa Inhibitor → Specify:

☐ **Abciximab:** 0.25 mg/kg IV bolus + 0.125 mcg/kg/min infusion (only for patients planned to undergo PCI within 12-24 hrs) **OR**

☐ **Eptifibatide:** 180 mcg/kg IV bolus + 2.0 mcg/kg/min infusion* **OR**

☐ **Tirofiban:** 0.4 mcg/kg/min IV bolus for 30 min + 0.1 mcg/kg/min infusion*

* For patients with **renal impairment**, administer 1/2 the rate of infusion for eptifibatide and tirofiban

☐ **Schedule for Early Cardiac Catheterization**
Date: __ __/__ __/__ __ __ __ (day month year)

Oral Antiplatelet Therapies:

NOTE: Add clopidogrel after diagnostic catheterization unless CABG is planned.

☐ **Clopidogrel:** 300 mg loading dose • 75 mg po QD

EARLY CONSERVATIVE PROTOCOL

Intravenous Anti-thrombotic Therapies:

☐ **IV unfractionated heparin →** Initial bolus of 60-70 U/kg bolus (not to exceed 5000 U) + 12-15 U/kg/hr infusion (not to exceed 1000 U/hr) to target aPTT range of 50-70 sec, or 1.5-2.5 times control

☐ **Low-molecular-weight heparin → Specify:**
☐ **Enoxaparin:** 1 mg/kg SC q 12 hrs

Oral Antiplatelet Therapies:

☐ **Clopidogrel:** 300 mg loading dose • 75 mg po QD

Intravenous Antiplatelet Therapies:

NOTE: Eptifibatide or tirofiban are indicated for patients with high-risk features who are managed conservatively.

GP IIb-IIIa Inhibitor → Specify:

☐ **Eptifibatide:** 180 mcg/kg IV bolus + 2.0 mcg/kg/min infusion* **OR**

☐ **Tirofiban:** 0.4 mcg/kg/min IV bolus for 30 min + 0.1 mcg/kg/min infusion*

* For patients with **renal impairment**, administer 1/2 the rate of infusion for eptifibatide and tirofiban

☐ **Schedule for assessment of left ventricular function → Type(s):**

☐ Echocardiogram

☐ Nuclear ventriculogram

☐ **Schedule for stress test → Type(s):**
☐ Exercise treadmill test
☐ Exercise nuclear perfusion study
☐ Dobutamine nuclear perfusion study
☐ Persantine nuclear perfusion study
☐ Exercise stress echocardiography
☐ Dobutamine echocardiography

☐ **Lipid-lowering agent:** Name and dose of drug prescribed: ________

Name of Physician: ________ **Date:** ________ **Time:** ________

Signature: ________________

Adapted from: CRUSADE Quality Improvement Initiative tool (http://www.crusadeqi.com)

Figure 4. UA/NSTEMI initial treatment standing orders. Adapted from http://www.crusadeqi.com

it is necessary to identify those patients at high risk for ischemic complications including death and nonfatal MI. Patients with ACS at low risk for ischemic complications, including death and MI, should be admitted and treated with early conservative management, as shown in Figure 3. Early invasive therapy should be considered for all patients with ACS who are deemed to be at high risk for ischemic complications. Patients at intermediate risk for death or nonfatal MI should receive appropriate therapy for ACS and be considered for possible intervention by a cardiologist.

Some low-risk ACS patients are candidates for evaluation in an ED chest pain center. In these individuals with nondiagnostic 12-lead ECGs and nonelevated cardiac biomarkers, graded exercise testing with or without radionuclide imaging can be performed safely. If negative, then the patient can be discharged home from the ED for further follow-up by a cardiologist.

Early Conservative Strategy

Patients presenting to the ED with ACS who are at low risk for ischemic complications should be treated with an early conservative management strategy that includes the following:[1,35]

1) Aspirin (Class IA); clopidogrel if aspirin is contraindicated (Class IA)
2) Clopidogrel for at least 1 month (Class IA) and for up to 9 months (Class IB); clopidogrel should be given in the ED for these patients if cardiac catheterization is not planned.
3) Enoxaparin or unfractionated heparin (Class IA)
4) Eptifibatide or tirofiban in patients with:
   - continuing ischemia (Class IIaA)
   - elevated TnI or TnT (Class IIaA)
   - other high risk-features (Class IIaA)
5) Abciximab should not be used unless PCI is planned (Class IIIA).[39]

Patients can evolve in the emergency setting from low through intermediate to high risk. Serial ECGs and cardiac biomarkers should be performed on any patient suspected of having ACS but with initially negative cardiac biomarkers or a nondiagnostic 12-lead ECG. Should a patient be low risk initially, warranting a conservative strategy, surveillance through serial ECGs and cardiac biomarkers may detect intermittent ischemic events requiring a switch to an invasive treatment strategy.

Early Invasive Treatment Strategy

An early invasive treatment strategy defined as coronary angiography and revascularization within 12 to 48 hours after presentation to the ED is a Class IA level of evidence for all patients considered to be at high risk for UA/NSTEMI.[35,36,45] The following criteria are indicative of the high risk patient as noted in Table 2:[1]

1) New or presumed new ST-segment depression
2) Elevated troponin I or T
3) Recurrent angina/ischemia at rest or with low levels of activity despite intensive anti-ischemic treatment
4) Recurrent ischemia with associated heart failure (S_3 gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation)
5) High-risk findings on noninvasive stress testing
6) Depressed systolic LV function (EF < 0.40 on noninvasive study)
7) Hemodynamic instability
8) Sustained ventricular tachycardia
9) PCI within the last 6 months
10) Previous coronary artery bypass surgery.

In these high-risk patients, in addition to O_2 (if needed), nitrates, morphine, β-blockers, calcium-channel blockers, and ACEI therapies in the early invasive strategy should include the following:

1) Aspirin (Class IA); clopidogrel if aspirin is contraindicated (Class IA).
2) Low-molecular-weight heparin or unfractionated heparin (Class IA); low-molecular-weight heparin is considered preferable to unfractionated heparin unless bypass surgery is planned within 24 hours (Class IIaA).
3) GP IIb/IIIa inhibitor, if catheterization or PCI is planned (Class IA); the 2002 ACC/AHA UA/NSTEMI guidelines recommend that this therapy be given immediately before PCI in patients receiving early invasive therapy for non–ST-segment elevation ACS.
4) GP IIb/IIIa inhibitor is added to aspirin, heparin, and clopidogrel if cardiac catheterization or PCI is planned (Class IIaB).
5) Clopidogrel, if PCI is planned, for at least 1 month (Class IA) and for up to 9 months (Class IB). In most situations in which the patient with ACS is receiving early cardiac catheterization, clopidogrel therapy can wait until coronary anatomy can be defined. It should be noted that some cardiologists prefer the initial use of clopidogrel even if cardiac catheterization/PCI is planned because the likelihood of the patient's needing CABG is low and many cardiac surgeons feel that if CABG is urgently required, then a 5- to 7-day wait is not necessary. If CABG is necessary, then clopidogrel therapy should be withheld until after surgery. It is suggested that CABG be delayed for 5 to 7 days if clopidogrel has already been administered.

Improving Guideline Adherence

The development of expert-prepared strategies such as the 2002 ACC/AHA UA/NSTEMI guidelines presents enormous challenges to general implementation of this best-practice approach. Several quality improvement initiatives have been developed to demonstrate methods for changing physician behavior and improving patient outcomes for patients with ACS.[46-58]

The GAP project, undertaken in Michigan, used educational tools distributed to health care providers and patients describing the newest therapies for acute MI. Indicators such as smoking cessation, biomarker use, and cholesterol levels improved after GAP use. These tools improved the appropriate use of aspirin, β-blockers, and cholesterol-lowering agents.[59]

In a similar fashion, CHAMP stressed the initiation of aspirin, cholesterol-lowering treatment, ACEIs, and β-blockers in the hospital. The researchers used adherence guidelines, standardized treatment orders, and precise tracking of medication use rates. Treatment rates and clinical outcomes were improved in patients with acute myocardial infarction after CHAMP was implemented.[60,61]

Another proactive approach to improving adherence, the AHA's "Get with the Guidelines" program, demonstrated that didactic best-practice presentations, interactive multidisciplinary team workshops, a customized guideline tool kit, and an interactive Web-based management tool significantly improved performance of practitioners. Measurements of aspirin, β-blocker, and ACEI use; cholesterol level management; smoking cessation counseling; blood pressure control; and cardiac rehabilitation referral demonstrated an improved use of these therapies for patients with ACS for early, in-hospital, and discharge therapies.[62]

Finally, the CRUSADE Quality Improvement Initiative is an ongoing effort to track adherence to the 2002 ACC/AHA UA/NSTEMI guidelines and to provide mechanisms to improve performance. This initiative is a partnership of academicians, industry, and emergency physicians and cardiologists at hospitals throughout the United States. The objectives of CRUSADE include the following:

1) Determine the current awareness and adherence to the 2002 ACC/AHA UA/NSTEMI guidelines for ACS.
2) Implement quality improvement initiatives at site hospitals to promote ACC/AHA diagnostic and treatment recommendations for high-risk ACS patients.
3) Improve clinical outcomes through early guideline implementation, for example, in the ED.

Early evidence with more than 100,000 patients enrolled suggests that this effort has been successful in increasing awareness and adherence to the 2002 ACC/AHA UA/NSTEMI guidelines. Since October 2003, data have been collected on ED guideline adherence for UA/NSTEMI that provides information that emergency physicians and cardiologists can use to improve the care of these patients.[63,64] A structured order set provides specific guideline-based therapy for patients with ACS enrolled into the CRUSADE Quality Improvement Initiative (Figure 4).

Barriers to Guideline Implementation

A variety of barriers to guideline implementation are experienced in the emergency setting. Delays in receiving cardiac biomarker data because of slow laboratory turnaround, high patient volume in the ED decreasing throughput, and a lack of standardized diagnostic and treatment approaches are only some of the barriers that can inhibit providing appropriate care to patients. Specialties other than cardiology provide inpatient care to individuals with ACS. Making all physicians who care for these patients aware of the 2002 ACC/AHA UA/NSTEMI guidelines is a significant challenge in any hospital setting. Finally, multiple cardiology groups at an institution can make an agreement on specific diagnostic and treatment regimens for patients with ACS difficult to achieve.

Predictors for Successful Guideline Implementation

A variety of circumstances can predict a high likelihood for improvement in guideline implementation. Strong clinical champions in emergency medicine and cardiology who have effective communication with other emergency physicians, cardiologists, internists, and family physicians at their institution, can develop consensus on clear diagnostic and treatment pathways that incorporate guidelines directives. Physicians must demonstrate a clear willingness to partner with other hospital health care specialists.

Support from the laboratory and hospital administration also is essential. Improving laboratory turnaround time for cardiac biomarkers can ensure that high-risk patients are identified early while in the ED. Hospital administration can provide needed resources and clear support, which encourages involvement in quality improvement efforts by all hospital departments, including pharmacy and nursing. Having the significant involvement of nursing, administration, laboratory, and pharmacy is essential to reaching agreement on a pathway. Aligning the incentives of all parties to provide guideline-directed care is extremely important.

Careful data analyses, which can be used to provide high-quality feedback to ED and coronary care unit personnel (physicians and nurses), can serve as a ready stimulus for quality improvement. These data, compared with national benchmarks, can be shared with multiple physician groups across the hospital (emergency medicine, cardiology, internal medicine, family medicine, and cardiac surgery) and nonphysician members of the healthcare team to identify areas of success and potential improvement. Quality management teams having constituents from all of these physician disciplines, as well as the laboratory, nursing, pharmacy, and hospital administration can use these high-quality data to improve adherence to guidelines.

In addition, the use of quality improvement tools such as standard diagnostic evaluations for the ED that readily identify high-risk criteria in ED patients as well as standardized medication order sets can also increase adherence to guidelines. Early identification of high-risk patients with ACS in the emergency setting can decrease time to cardiac catheterization and revascularization. The combination of improved communication between all members of the care team involved with ACS patients, the collection of high-quality data on these patients, and the use of quality improvement tools can provide improved, more consistent care for these patients.

CONCLUSIONS

The 2002 ACC/AHA UA/NSTEMI guidelines represent an evidence-based approach to the care of patients with ACS. Adherence to the guidelines can be improved by enhanced communication between emergency physicians and cardiologists, as well as by the implementation of quality improvement initiatives. Through this approach, better, more consistent care can be provided for patients with ACS and can lead to improved outcomes.

REFERENCES

1. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-segment Elevation Myocardial Infarction: A Report of the American College of Cardiology/Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol*. 2002;40(7):1366-1374.
2. Braunwald E, Mark DB, Jones RH, et al: Unstable Angina: Diagnosis and Management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart Lung and Blood Institute, US Public Health Service, US Department of Health and Human Services. 1994:1. AHCPR publication No. 94-0602.
3. Pollack CV Jr, Gibler WB. 2000 ACC/AHA Guidelines for the management of Patients with Unstable Angina and Non-ST-segment Elevation Myocardial Infarction: a Practical Summary for Emergency Physicians. *Ann Emerg Med*. 2001;38:229-240.
4. Pollack CV Jr, Roe MT, Peterson ED. 2002 Update to the ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-segment Elevation Myocardial Infarction: Implications for Emergency Department Practice. *Ann Emerg Med*. 2003;41:355-369.
5. McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, Kerr EA. The Quality of Health Care Delivered to Adults in the United States. *N Engl J Med*. 2003;348:2635-2645.
6. Nourjah P. National Hospital Ambulatory Medical Care Survey: 1997 Emergency Department Summary. Hyattsville, MD: National Center for Health Statistics; 1999:304. Advance data from Vital and Health Statistics.
7. National Center for Health Statistics. Detailed Diagnosis and Procedures: National Hospital Discharge Survey, 1996. Hyattsville, MD: National Center for Health Statistics; 1998:13. Data from Vital and Health Statistics.
8. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281:707-713.
9. Apple FS, Wu AHB, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: How to use existing assays clinically and for clinical trials. *Am Heart J*. 2002;144:981-986.
10. Jaffe AS, Ravkilde J, Roberts R, Naslund U, Apple FS, Galvani M, Katus H. It's Time for a Change to a Troponin Standard. *Circulation*. 2000;102:1216-1220.

11. Keidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol*. 2001;38: 478-485.
12. Newby LK, Christenson RH, Ohman EM, et al. Value of serial troponin T measures for early and late risk stratification in patients with acute coronary syndromes. The GUSTO IIa Investigators. *Circulation*. 1998;98:1853-1859.
13. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined - a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *JACC*. 2000;36:959-969.
14. Novis DA, Jones BA, Dale JC, Walsh MK. Biochemical markers of myocardial injury test turnaround time. *Arch Pathol Lab Med*. 2004; 128:158-164.
15. James SK, Lindahl B, Armstrong P, Califf R, Simoons ML, per Venge, Wallentin L. A rapid troponin I assay is not optimal for determination of troponin status and prediction of subsequent events at suspicion of unstable coronary syndromes. *International J Cardiol*. 2003;93:113-120.
16. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, Mahaffey KW, Newby LK, Califf RM, Simoons ML, Topol EJ, Berger P, Lauer MS. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med*. 2002; 346:2047-2052.
17. James S, Armstrong P, Califf R, Simoons ML, Venge P, Wallentin L, Lindahl B. Troponin T levels and risk of 30-day outcomes in patients with the acute coronary syndrome: prospective verification in the GUSTO-IV trial. *Am J Med*. 2003;115:178-184.
18. Panteghini M, Pagani F, Yeo KTJ, Apple FS, Christenson RH, Dati F, Mair J, Ravkilde J, Wu AH. Evaluation of the Imprecision at Low-Range Concentrations of the Assays for Cardiac Troponin Determination. *Clin Chem*. 2004;50:327-330.
19. Jaffe AS. Elevations in cardiac troponin measurements: False false-positives. *Cardiovascular Toxicology*. 2001;1(2):87-92.
20. Brennan ML, Penn MS, Van Lente F, et al. Prognostic Value of Myeloperoxidase in Patients with Chest Pain. *N Engl J Med*. 2003; 249:1595-1604.
21. Wu AHB, Morris DL, Fletcher DR, et al. Analysis of the Albumin Cobalt Binding (ACB™) Test as an Adjunct to Cardiac Troponin I for the Early Detection of Acute Myocardial Infarction. *Cardiovascular Tox*. 2001;1:147-151.
22. Yusuf S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction; an overview of randomized trials. *Lancet*. 1988;1:1088-1092.
23. Armstrong P. Stable Ischemic Syndromes: Section 2: Clinical Cardiology (Califf RM, section ed). In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven;1998: 351-353.
24. White HD. Unstable Angina: Ischemic Syndromes. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven;1998:365-393.
25. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and re-infarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. *N Engl J Med*. 1986; 315:423-429.
26. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol*. 1987;60:18A-25A.
27. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation*. 1998;97: 2202-2212.
28. Flather M, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000; 355:1575-1581.
29. VALIANT Investigators. Valsartan in Acute Myocardial Infarction. *Am Heart J*. 2000;140:727-734. Results presented, American Heart Association Scientific Sessions, November 2003. Orlando, Florida.
30. Yusuf S, Wittes J, Friedman L. Overview of the results of randomized clinical trials in heart disease, II. Unstable angina, heart failure, primary prevention with aspirin and risk factor modification. *JAMA* 1988;260:2259-2263.
31. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308: 81-106.
32. The CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
33. Antman EM. Glycoprotein IIb/IIIa inhibitors in patients with unstable angina/non-ST-segment elevation myocardial infarction: Appropriate interpretation of the guidelines. *Am Heart J*. 2003; 146:S18-S22.
34. Cannon CP, Weintraub WS, Demopoulos LA, et al. TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) – Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-1887.
35. Boersma E, Akkerhuis KM, Theroux P, et al. Platelet glycoprotein IIb-IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation*. 1999;100:2045-2048.
36. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation*. 1998; 98:2829-2835.
37. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb-IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med*. 1998;339:436-443.
38. Simoons ML. GUSTO IV-ACS Investigators: Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularization: the GUSTO IV-ACS randomized trial. Lancet 2001;357: 1915-1924.
39. Lincoff AM. Direct thrombin inhibitors for non-ST-segment elevation acute coronary syndromes: What, when and where? *Am Heart J*. 2003;146:S23-S30.
40. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. *JAMA*. 1996;276:811-815.
41. Antman EM. Hirudin in acute myocardial infarction – thrombolysis and thrombin in myocardial infarction (TIMI) 9B trial. *Circulation*. 1996;94:911-921.
42. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of LMWH for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602-1608.
43. Ferguson J, Califf R, Antman E, et al. Enoxaparin vs Unfractionated Heparin in High-Risk Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Managed With an Intended Early Invasive Strategy. Primary Results of the SYNERGY Randomized Trial. *JAMA*. 2004;292:45-54.

44. Peterson JL, Mahaffey KW, Hasselblad V. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for Antithrombin therapy in non-ST-segment elevation acute coronary syndromes: A systematic overview. *JAMA*. 2004;292:89-96.
45. Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. *Circulation*. 2000;101:751-757.
46. Allison JJ, Kiefe CI, Weissman NW, Person SD, Rousculp M, Canto JG, Bae S, Williams OD, Farmer R, Centor RM. Relationship of Hospital Teaching Status With Quality of Care and Mortality for Medicare Patients With Acute MI. *JAMA*. 2000;284: 1256-1262.
47. Alexander KP, Peterson ED, Granger CB, et al. Potential impact of evidence-based medicine in acute coronary syndromes: insights from GUSTO IIb. Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes trial. *J Am Coll Cardiol*. 1998;32: 2023-2030.
48. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PC, Rubin HR. Why Don't Physicians Follow Clinical Practice Guidelines? A Framework for Improvement. *JAMA*. 1999;282: 1458-1465.
49. Califf RM, Faxon DP. Need for Centers to Care for Patients with Acute Coronary Syndromes. *Circulation*. 2003;107: 1467-1470.
50. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med*. 1992;326:242-250.
51. Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association Clinical Practice Guidelines: Part I Where Do They Come From? *Circulation*. 2003; 107:2979-2986.
52. Gibbons RJ, Smith SC, Antman E. American College of Cardiology/ American Heart Association Clinical Practice Guidelines: Part II Evolutionary Changes in a Continuous Quality Improvement Project. *Circulation*. 2003;107:3101-3107.
53. Grili R, Magrini N, Penna A, Mura G, Liberati A. Practice guidelines developed by specialty societies: the need for a critical appraisal. *Lancet*. 2000;355:10306.
54. Hamm CW, Bertrand M, Braunwald E. Acute coronary syndrome without ST elevation: Implementation of new guidelines. *Lancet*. 2001;358:1533-1538.
55. Leape LL, Weissman JS, Schneider EC, Piana RN, Gatsonis C, Epstine AM. Adherence to practice guidelines: The role of specialty society guidelines. *Am Heart J*. 2003;145:19-26.
56. Boden WE, Pepine CJ. Introduction to 'Optimizing Management of Non-ST-Segment Elevation Acute Coronary Syndromes'. *J Am Coll Cardiol*. 2003;41:1S-6S.
57. The Lipid Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339: 1349-1357.
58. Biviana AB, Rabbani LE, Paultre F, Hurley E, Sulivan J, Giglio J, Mosca L. Usefulness of an Acute Coronary Syndrome Pathway to Improve Adherence to Secondary Prevention Guidelines. *Am J Cardiol*. 2003;91:1248-1250.
59. Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, Roychoudhury C, Borak S, Fox S, Franklin M, Freundl M, Kline-Rogers E, LaLonde T, Orza M, Parrish R, Satwicz M, Smith MJ, Sobotka P, Winston S, Riba AA, Eagle KA for the GAP Steering Committee of the American College of Cardiology. Improving Quality of Care for Acute Myocardial Infarction: The Guidelines Applied in Practice (GAP) Initiative. *JAMA*. 2002;287:1269-1276.
60. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved Treatment of Coronary Heart Disease by Implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87:819-822.
61. Fonarow GC, Gawlinski A. Rationale and Design of the Cardiac Hospitalization Atherosclerosis Management Program at the University of California Los Angeles. *Am J Cardiol*. 2000;85: 10A-17A.
62. LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get With the Guidelines for Cardiovascular Secondary Prevention. *Arch Intern Med*. 2004;164:203-209.
63. Hoekstra J, Pollack C, Roe M, Peterson E, Brindis R, Harrington R, Christenson R, Smith S, Ohman M, and Gibler B. Improving the Care of Patients with Non-ST-Elevation Acute Coronary Syndromes in the Emergency Department: The CRUSADE Initiative. *Acad Emerg Med* 2002;9:1146–1155.
64. Staman KL, Roe MR, Fraulo ES, Lytle BL, Gibler WB, Ohman EM, Peterson ED. Quality Improvement Tools Designed to Improve Adherence to the ACC/AHA Guidelines for the Care of Patients with Non-ST-Segment Acute Coronary Syndromes: The CRUSADE Quality Improvement Initiative. *Critical Pathways in Cardiology*. 2003;Vol. 2,No 1, 34-40.

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Writing Group Member	Employment	Research Grant and Other Research Support	Speakers Bureau/ Honoraria	Stock Ownership	Consultant/Advisory Board	Other
W. Brian Gibler	University of Cincinnati College of Medicine	Millennium, Schering-Plough, iSTAT, Abbott, Biosite	None	None	Aventis/Sanofi, Inovise Medical, Ischemia Technologies, Scios, ArgiNOx Pharmaceuticals	None
Christopher P. Cannon	Brigham & Women's Hospital	Bristol-Myers Squibb, Merck, Aventis/ Sanofi, AstraZeneca	AstraZeneca, Bristol-Myers Squibb, Guilford Pharmaceuticals, Merck, Millennium, Pfizer, Aventis/ Sanofi, Schering-Plough, BESTmed, i3 Magnifi, New England Continuing Medical Education	None	AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Guilford Pharmaceuticals, Merck, Merck/ Schering-Plough Partnership, Pfizer, Aventis/Sanofi, Schering-Plough, Vertex Pharmaceuticals	None
Andra L. Blomkalns	University of Cincinnati Dept of Emergency Medicine	Millennium, Schering-Plough, iSTAT, Abbott, Biosite	None	None	Aventis/Sanofi, Inovise Medical, Ischemia Technologies, Scios, AgriNOx Pharmaceuticals	None
Douglas M. Char	Washington University School of Medicine	Inovise Medical	Aventis/Sanofi, Scios	None	Scios	None
Barbara J. Drew	University of California-San Francisco	National Heart, Lung, and Blood Institute, Medtronic Physio-Control, Inovise Medical	Philips Medical, General Electric Medical	None	None	None
Judd E. Hollander	University of Pennsylvania	None	Aventis, Sebos	None	Sebos	None
Allan S. Jaffe	Mayo Clinic	Roche, Dade-Behring, Beckman-Coulter	None	None	None	None
Robert L. Jesse	Department of Veterans Affairs	None	Abbott Laboratories	None	Biosite, Ischemia Technologies, Crusade/DCR1	None
L. Kristin Newby	Duke University Medical Center	Roche Diagnostics, Millennium, Novartis, Schering-Plough, Bristol-Meyers Squibb/Sanofi	None	None	None	None
E. Magnus Ohman	University of North Carolina	None	None	Medtronic, Inovise Medical, Response Biomedical	None	None
Eric D. Peterson	Duke University Medical Center, Duke Clinical Research Institute	Millennium, Schering-Plough, Bristol-Myers Squibb, Society of Thoracic Surgeons	None	None	None	None
Charles V. Pollack	University of Pennsylvania	Aventis	Aventis, Millennium, Schering-Plough, BMS, Sanofi, Genentech	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.