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Evaluation And Management Of Non–ST–Segment Elevation Acute Coronary Syndromes In The Emergency Department

As your shift begins, paramedics bring in a 69-year-old woman with chest pain. You glance in and see that she looks uncomfortable, with diaphoresis and shortness of breath. Your gut tells you that this is "the real deal," a sick cardiac patient. The nurse quickly hands you the ECG, and no ST-segment elevations are evident. The patient was given aspirin and nitroglycerin by EMS personnel, but she is still experiencing pain. Questions run through your mind as you begin talking to the patient: Are there any new tests that can quickly diagnose a myocardial infarction? Which new treatments can be administered in the emergency department? What do you need to tell your cardiology colleague on the phone? Does it matter that the patient is female? After the examination is complete, you think of the best evidence for taking care of patients with non–ST-segment elevation acute coronary syndromes and begin treatment.

Non–ST-segment elevation acute coronary syndromes (NSTE-ACS) refers to a disease process characterized by reduced coronary blood flow resulting in coronary ischemia without ST-segment elevations on an electrocardiogram (ECG).[1,2] NSTE-ACS include both non–ST-segment elevation acute myocardial infarction (MI), as defined by positive biomarkers for MI, and unstable angina (UA), as defined by negative biomarkers.[2]

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Authors

Ankur A. Doshi, MD, FACEP
Assistant Professor of Emergency Medicine, Drexel University College of Medicine; Associate Program Director, Emergency Medicine Residency, Allegheny General Hospital, Pittsburgh, PA

Kara Iskyan, MD
Resident, Emergency Medicine/Internal Medicine, Allegheny General Hospital, Pittsburgh, PA

John M. O'Neill, MD
Assistant Professor of Emergency Medicine, Drexel University College of Medicine; Attending Faculty, Emergency Medicine Residency, Allegheny General Hospital, Pittsburgh, PA

Kelly N. Sawyer, MD
Clinical Instructor of Emergency Medicine, Virginia Commonwealth University Medical Center, Emergent Cardiac Care Fellow, Department of Emergency Medicine, Virginia Commonwealth University Medical Center, Richmond, VA

Peer Reviewers

Francis Fesmire, MD, FACEP
Director, Heart-Stroke Center, Erlanger Medical Center; Assistant Professor, UT College of Medicine, Chattanooga, TN

Scott Silvers, MD, FACEP
Chair, Department of Emergency Medicine, Mayo Clinic, Jacksonville, FL

CME Objectives

Upon completion of this article, you should be able to:

1. Perform risk stratification on patients with NSTE-ACS using a validated risk score.
2. Identify high-risk ECG findings for NSTE-ACS patients.
3. List approved first- and second-line medications for treatment of NSTE-ACS in anti-ischemic, antiplatelet, and anticoagulant classes.
4. Determine in-hospital disposition for NSTE-ACS.

Prior to beginning this activity, see "Physician CME Information" on page 27.

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Cardiovascular disease (CVD) is a common cause of visits to the emergency department (ED). According to the National Center for Health Statistics, CVD was the primary diagnosis in 4,036,000 visits to EDs in 2005. Of these, 1,413,000 visits resulted in a discharge diagnosis of ACS.[3] According to registry data, a minority of patients with ACS (29% to 38%) have ST-segment elevations (STE-ACS). The remainder of these patients have NSTE-ACS.[3-5]

Diagnosing NSTE-ACS in the ED is critical, as the disease has a mortality rate of approximately 5% during patient hospitalization.[1,5] Timely evaluation and treatment as well as appropriate disposition decisions are crucial. This issue of *Emergency Medicine Practice* will focus on the initial evaluation and treatment of patients with NSTE-ACS in the ED and on the most recent literature pertaining to the acute care of these patients.

Abbreviations Used In This Article

Trial Acronyms

ACUITY: Acute Catheterization and Urgent Intervention Triage Strategy
COMMIT: Clopidogrel and Metoprolol in Myocardial Infarction Trial
CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events
CRUSADE: Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
FRISC: Framingham and Fast Revascularization During Instability in Coronary Artery Disease
GRACE: Global Registry of Acute Coronary Events
GUSTO-IV: Global Utilization of Strategies to Open Occluded Coronary Arteries
ISAR: Intracoronary Stenting with Antithrombotic Regimen
JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
NRMI: National Registry of Myocardial Infarction
OASIS-5: Fifth Organization to Assess Strategies in Acute Ischemic Syndromes
PURSUIT: Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
PRISM-PLUS: Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
REACT: Rapid Early Action for Coronary Treatment
SYNERGY: Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors
TIMI: Thrombolysis in Myocardial Infarction

Other Abbreviations

ACS: Acute Coronary Syndromes
CABG: Coronary Artery Bypass Graft
CAD: Coronary Artery Disease
CHF: Congestive Heart Failure
CK-MB: Creatine Kinase Myocardial Band
CMR: Cardiac Magnetic Resonance
CPOU: Chest Pain Observation Units
CT: Computed Tomography
CTA: Computed Tomography Angiography
CVD: Cardiovascular Disease
ECG: Electrocardiogram
ED: Emergency Department
EMS: Emergency Medical Services
GPI: Glycoprotein IIb/IIIa Inhibitors
LBBB: Left Bundle Branch Block
LMWH: Low-Molecular-Weight Heparin
MI: Myocardial Infarction
MONAB: Morphine, Oxygen, Nitroglycerin, Aspirin, β-blocker
MRI: Magnetic Resonance Imaging
NSTE-ACS: Non-ST-Segment Elevation Acute Coronary Syndromes
PDI: Phosphodiesterase Inhibitors
PCI: Percutaneous Coronary Intervention
RBBB: Right Bundle Branch Block
SL: Sublingual
STE-ACS: ST-Segment Elevation Acute Coronary Syndromes
UA: Unstable Angina
UFH: Unfractionated Heparin

Critical Appraisal Of The Literature

The OVID Medline database was searched for articles on ACS, using the key words myocardial infarction, unstable angina, non–ST elevation, acute coronary syndromes, epidemiology, diagnosis, treatment, electrocardiogram, ECG, troponin, CK-MB, myoglobin, aspirin, chest pain, and chest pain observation units. Non–English language articles and articles focusing on STE-ACS were excluded. Identified articles were used as a starting point for further references and manual literature searches, and bibliographies from select articles provided additional references. Other articles known to the authors were reviewed as well. Highest weight was given to randomized clinical trials, prospective cohort studies, and meta-analyses. Less weight was given to retrospective studies, followed by consensus statements and case reports. Overall, more than 300 articles were reviewed, and 189 are included here for reference.

A search of the National Guideline Clearinghouse (www.guideline.gov) using the term *acute coronary syndromes* returned 145 guidelines. Six were found to be useful, including "2007 Guidelines for the Management of Patients with Unstable Angina/

Non–ST-Elevation Myocardial Infarction" from the American College of Cardiology/American Heart Association (ACC/AHA).[2] Similar guidelines have been published by the Scottish Intercollegiate Guidelines Network, the National Heart Foundation of Australia, the Finnish Medical Society, and the European Society of Cardiology.[6-9] Society-specific guidelines include "Antithrombotic Therapy for Non–ST-Segment Elevation Acute Coronary Syndromes" of the American College of Chest Physicians (ACCP)[10] and "Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients with Non–ST-Segment Elevation Acute Coronary Syndromes" from the American College of Emergency Physicians (ACEP).[11] The ACC/AHA and ACCP guidelines recommend some management strategies specific to the ED.[2,10] The ACEP clinical policy contains questions that are pertinent to ED care.[11]

Epidemiology

According to the AHA's 2008 statistics update, 1 in 3 American adults has at least 1 type of CVD including hypertension, coronary artery disease (CAD), and/or stroke.[3] The prevalence of these conditions increases with age and decreases as education level rises. An estimated 770,000 new coronary events and 430,000 recurrent events occurred in 2008.[3] Cardiovascular disease remains the number one killer of American men and women, despite advances in treatments and an emphasis on lifestyle changes.[3] For example, as many as 85% of people with CAD have at least 1 of the 4 traditional risk factors for CAD: hypertension, dyslipidemia, history of smoking, and diabetes mellitus.[12,13]

Data on patients with ACS collected from the National Registry of Myocardial Infarction (NRMI; 1990-2006)[14] and the Global Registry of Acute Coronary Events (GRACE; 1999-2006) further validate these statistics and trends.[15] Although these registries are observational and have inherent limitations, both show an increasing prevalence of NSTE-ACS.[13-15] Explanations for this trend include the use of more sensitive diagnostic tests (biomarkers such as troponin) for detecting acute MI, the increased availability of early invasive therapies such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG), the aging of the population, and the increased use of medical therapy (e.g., aspirin, β-blockers), which may slow or prevent the progression of myocardial ischemia to STE-ACS.[14,16-18]

Although mortality related to STE-ACS has decreased with newer interventions, an examination of both NRMI and GRACE reveals that mortality related to NSTE-ACS has not declined at the same rate. This disparity, which has been observed in other database analyses including the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation (CRUSADE) registry,[17] may be due to slower implementation of the therapies recommended in the guidelines for patients with NSTE-ACS.[13,15] Therefore, more rigid adherence to evidence-based recommendations has been advocated in the Guidelines Applied in Practice (GAP) initiative and the Get With the Guidelines project.[14-20]

Pathophysiology

Acute coronary syndromes result from an imbalance between myocardial oxygen supply and demand and often involve preexisting atherosclerosis with acutely superimposed thrombus formation.[21-23]

Other proposed mechanisms include coronary artery spasm, progressive severe atherosclerotic narrowing without thrombus formation, systemic inflammatory processes, and systemic conditions that alter oxygen supply or demand.[21,23] However, the plaque-based etiology of ACS is at the center of the discussion, and much attention has been given to the definition and identification of vulnerable plaque.[21,22] As a result, current guidelines for the treatment of ACS have targeted plaque stabilization and antithrombotic/anti-inflammatory strategies.[2,24]

The natural history of atherosclerosis is neither linear nor clinically predictable. Atherogenesis is a lifelong process of plaque remodeling, beginning at sites of endothelial injury due to the stress of blood flow.[21,25,26] Some people are particularly predisposed to plaque formation because of CAD risk factors that interfere with normal endothelial hemostasis.[25,27]

When coronary plaques are stable and slow growing, they may obstruct blood flow just enough to cause the clinical symptoms of chronic angina. However, some plaques demonstrate more rapid growth and undergo a large influx of inflammatory cells that can ultimately lead to plaque instability.[26,27] This unstable plaque is thought to be most vulnerable to rupture, erosion, and thrombosis, represented clinically as UA or acute MI.[25,26]

The AHA Committee on Vascular Lesions has offered a classification scheme for atherosclerotic plaque progression that distinguishes stable plaque from more vulnerable versions on the basis of core content, the strength and thickness of the plaque cap, and inflammatory activity.[28,29] Branch points and areas of abrupt curvature in the vessel also play a role in plaque stability and vulnerability.[25,26] When plaque ruptures or erodes, its cap is disrupted, exposing its core to the vessel lumen. This process attracts platelets, fibrin, and clotting factors. If a thrombus forms acutely and completely occludes a vessel supplying a large area of myocardium, the likely outcome is STE-ACS. Conversely, if the thrombus does not fully occlude the vessel, it may

either merely decrease oxygen supply or break into pieces that can embolize distally to smaller vessels. Although beyond the scope of this paper, ongoing research is aimed at identifying the factors that create environments suitable for plaque disruption or rupture.[28-31]

With increasing recognition of the role of inflammation in atherogenesis and plaque vulnerability, a discussion about the vulnerable patient and the risk for ACS has emerged.[28,29] As previously mentioned, patients at risk for atherosclerosis and endothelial dysfunction, and therefore ACS, typically have traditional CAD risk factors. The vulnerable patient, however, may in fact have "vulnerable blood," characterized by systemic inflammatory disorders or coagulation dysfunctions (eg, von Willebrand, factor V Leiden).[28,29] Serum markers of inflammation such as high-sensitivity C-reactive protein (hs-CRP) and homocysteine may be indicators of patients at risk for ACS, meaning that antiplatelet and antilipid therapies should be initiated despite normal low-density lipoprotein (LDL) levels, normal blood pressure readings, and normal insulin sensitivity values.[28,29,32] The vulnerable patient may also have a "vulnerable myocardium," including increased autonomic tone, propensity for coronary vasospasm, and chronic myocardial damage due to chronic healing plaque.[28,29] Much like recent studies in pharmacology and biochemistry, future genetic studies will likely lead to changes in prevention strategies and management practices for ACS.[16,33]

Summary

In contrast to STE-ACS, in which large areas of ischemic or infarcted noncollateralized myocardium result from the complete obstruction of a coronary artery with thrombus, in NSTE-ACS the thrombus does not fully occlude the lumen and allows some antegrade blood flow to continue. This disruption of oxygen supply is more often chronic, gradual, and intermittent, typically allowing time for distal collateral blood vessel formation. In this setting, atherosclerotic progression and moderate thrombus formation or remodeling may be clinically silent. A partially occluding thrombus, however, is subject to blood flow that is turbulent, often at branch points or sharp angles of curvature, which may allow for the shearing of microemboli (platelet clumps/inflammatory components) that flow downstream and fully occlude smaller, more distal vascular beds. If enough blood flow is compromised, an MI occurs, as evidenced by positive biomarkers. If blood flow is sufficient, biomarkers will be negative for MI. Therefore, UA and NSTE-MI are both part of the same clinical spectrum. However, the presence of positive biomarkers ultimately has little bearing on the danger that the culprit plaque represents.[21,23]

Prehospital Care

The first triage decision must be made when the patient with chest pain decides to seek care. Despite public campaigns (such as Act in Time by the National Heart, Lung, and Blood Institute) which seek to educate the public about the signs and symptoms of heart attacks and the importance of calling 9-1-1 within 5 minutes of identifying these worrisome symptoms, the use of emergency medical services (EMS) for chest pain has not improved.[34-37]

In the past, patients with known cardiac disease were instructed to call EMS if their chest pain did not resolve with 3 doses of nitroglycerin. In contrast, the 2007 ACC/AHA guidelines suggest that patients call 9-1-1 if chest pain is not relieved after 1 dose of nitroglycerin. The patient can take additional doses of nitroglycerin as EMS is mobilized, or EMS personnel can administer further doses during transport to the hospital.[2] Although no evidence details a positive outcome from this change, the Writing Committee agreed that patients should not wait at home with active coronary ischemia. The importance of EMS transport for patients with chest pain cannot be overstated. Many patients with chest pain are driven to the hospital in private vehicles, and more than 10% of patients drive themselves. A study of managed care patients in 1998 showed that those patients who spoke with their primary care physicians prior to seeking care for chest pain were more likely to take private transportation to the ED instead of using 9-1-1 compared with those who did not contact their physician.[38] An estimated 1 in 300 patients with chest pain who are transported by private vehicles go into cardiac arrest en route to the hospital.[39]

Although NSTE-ACS is not always diagnosed by a prehospital ECG, the revised 2007 ACC/AHA guidelines increased the emphasis on out-of-hospital 12-lead ECG use in patients with chest pain. Prehospital ECGs are useful in distinguishing STE-ACS from NSTE-ACS. Additionally, in more remote areas, prehospital ECGs help with triaging patients with chest pain to appropriate cardiac care facilities.[2,40,41]

Lastly, standard EMS treatment for chest pain is similar to treatment that occurs in the ED and includes cardiac monitoring, anti-ischemic therapy with oxygen, sublingual (SL) nitroglycerin, narcotics, and antiplatelet therapy with aspirin. Critically ill patients may also require inotropic, vasopressor, or mechanical ventilation prior to ED arrival.

Emergency Department Evaluation

History

A rapid and accurate history is the first step in the ED management of NTSE-ACS. The history

obtained is often influenced by the patient's own reluctance to seek care for chest pain. In fact, the average patient waits 2 hours before seeking care for chest pain.[42,43] According to the Rapid Early Action for Coronary Treatment (REACT) study, patients with chest pain do not seek timely care for the following reasons:

- A lack of knowledge about symptoms, especially atypical or minor symptoms
- A wait-and-see attitude that assumes the pain is self-limiting and will go away
- A false assessment of personal risk factors
- A lack of knowledge about the importance of rapid and timely interventions
- The fear of causing a false alarm[42,44-46]

Using a brief patient history, demographics, mode of transportation, general appearance, and vital signs, triage nurses are able to accurately determine the acuity of most patients with chest pain.[47] Unfortunately, stereotypes and biases do exist, as triage nurses are more likely to associate an MI with a man's symptoms than with a woman's symptoms.[48] Once triaged, 25% of patients with chest pain wait less than 10 minutes before seeing a physician, and more than 50% of patients with chest pain wait less than 20 minutes. The mean wait time for chest pain evaluations is 10 minutes shorter than the mean wait time for other evaluations in the ED.[49]

The emergency clinician's evaluation of a patient with chest pain is multifaceted. Often, diagnostic testing and treatment are concurrent with the history, physical examination, and risk stratification. The history for the present illness should thoroughly evaluate the nature of the patient's symptoms. Angina is defined as deep, poorly localized chest or arm discomfort that is associated with physical exertion or emotional stress and is promptly relieved with rest or the use of nitroglycerin.[2] Some patients with myocardial ischemia may describe chest discomfort or pressure, not chest pain.[50] Other patients may experience anginal equivalents rather than any chest symptoms. Anginal equivalents are exertional pain in the jaw, neck, ear, arm, shoulder, back, or epigastric area; exertional dyspnea; nausea and vomiting; diaphoresis; and fatigue.[2,51]

Characteristics of chest pain that are not usually of cardiac origin include pleuritic pain, discomfort centered in the middle or lower abdominal region, reproducible pain with movement or palpation of the chest wall or arms, pain that lasts a few seconds or less, and pain that radiates to the lower extremities.[2,51]

Description of chest pain alone cannot be used to rule out a cardiac event, however. In a landmark study, Lee et al evaluated the symptoms and ECG results of 596 patients presenting with chest pain to the ED at Brigham and Women's Hospital. They found that patients with characteristics of chest pain usually thought to indicate a noncardiac cause may indeed be suffering from cardiac ischemia. For instance, approximately 7% of patients with an MI or UA had pleuritic chest pain, while up to 20% of patients with an MI or UA had pain reproduced by chest wall palpation; 13% had positional chest pain. Additionally, they determined that no single clinical factor could be used to eliminate cardiac ischemia from the differential diagnosis.[51]

The history should also include the evaluation of a range of risk factors.[52-54] The most predictive risk factor for cardiac ischemia is a past medical history of CAD.[2] Traditional risk factors for CAD, such as family history of the disease, hypertension, hyperlipidemia, diabetes mellitus, and tobacco use, are based on population studies and are predictive for the lifetime development of the disease.[55] However, these factors are only weakly predictive of the likelihood of acute ischemia.[55] Nevertheless, once cardiac ischemia such as NSTE-ACS is established as the diagnosis, traditional CAD risk factors can help predict poor outcomes.[56,57]

Gender is significant in the presentation of cardiac ischemia, as women are more likely than men to present with anginal equivalents. Nausea, vomiting, indigestion, fatigue, and dyspnea are common complaints of women with cardiac ischemia.[58] Similarly, patients with diabetes mellitus often have silent ischemia and present later in the course of an event with exertional dyspnea, severe fatigue, and lightheadedness instead of typical chest pain.[59,60] The delay in identification of ischemia in patients with diabetes mellitus may be a major cause of increased morbidity and mortality in this population.[59-63]

The age of the patient with chest pain can help to focus the clinician's questions during the evaluation. Younger ACS patients are more likely to have traditional risk factors for CAD, especially hyperlipidemia, tobacco use, and a family history of CAD.[2] In contrast, older patients are more likely to have a personal history of CAD or congestive heart failure (CHF). The chance of an acute ischemic event is highest in patients older than 70 years because of the severity of underlying CAD and comorbidities.[2,64,65] The most common symptom of cardiac ischemia in those greater than 85 years is dyspnea.[2] Other common presentations are fatigue, lightheadedness, worsening CHF, syncope, and altered mental status.[2,64]

A recent history of cocaine or methamphetamine use may be revealed in cardiac ischemia patients younger than 40 years.[2] These stimulants cause coronary vasospasm, thrombosis, and increased heart rate and arterial pressure.[2,66] Patients with cocaine-associated chest pain have a 15% risk of ACS.[67,68] Although the risk of ACS increases 24-fold in the hours after cocaine use, symptoms may be delayed for hours or days.[69] Additionally, although cocaine users have the same frequency of CAD as nonusers, long-term use of the drug alters the coronary vasculature, increasing the chances of developing cardiac ischemia.[2,68]

Physical Examination

The physical examination of a patient with chest pain should focus on hemodynamic stability, signs of heart failure/left ventricular dysfunction, and the exclusion of noncardiac and nonischemic cardiac causes. A NSTE-ACS that causes hypotension or hypoxia is indicative of a poor prognosis.[2] Similar to a patient with hemodynamic instability, a patient with jugular venous distention, pulmonary edema, and hypoxia (ie, CHF) with a NSTE-ACS has a poor prognosis.[2] Evaluation of both noncardiac (eg, costochondritis) and nonischemic cardiac causes (eg, pericarditis, aortic dissection) of chest pain requires a thorough examination of the patient's chest wall ~~in~~cluding inspection and palpation ~~as~~ well as careful examination of cardiac and pulmonary functions.

Diagnostic Studies

Diagnostic tools may be employed in the ED to assist in the evaluation and risk stratification of patients with suspected NSTE-ACS. These tools include the ECG, cardiac biomarkers, and rest or stress perfusion imaging. However, not every ED has timely access to these modalities.[70]

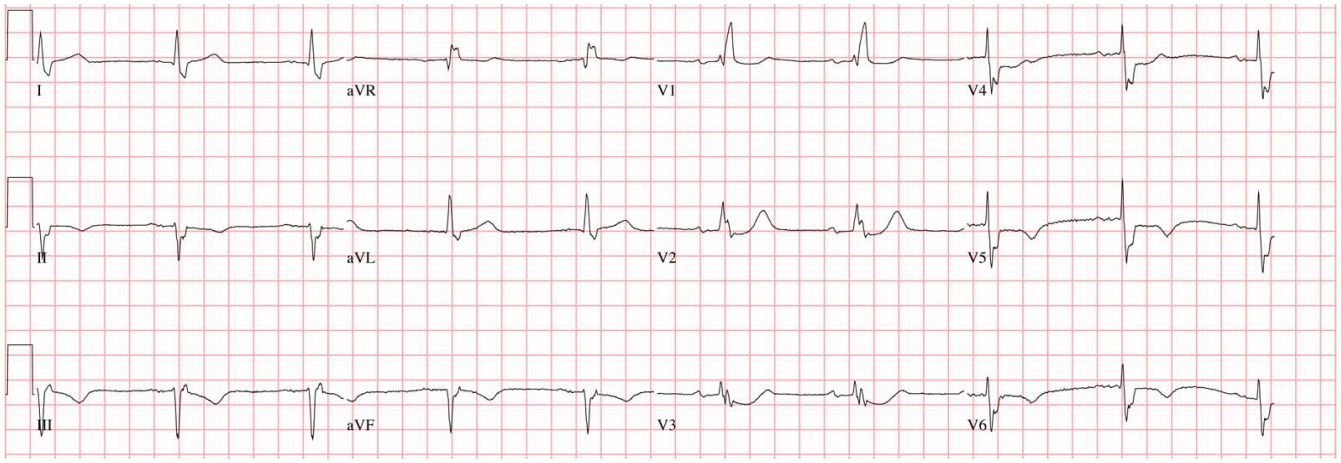
Electrocardiogram

The ECG is the first diagnostic test that a patient with chest pain or other symptoms suggestive of ACS should receive when arriving at an ED.[24] The ECG must be completed and interpreted in a timely fashion so that reperfusion therapy can be initiated as soon as possible if there is evidence of an STE-ACS. Once STE-ACS is ruled out, the ECG is used to help establish the risk for NSTE-ACS.

According to the ACC/AHA guidelines, transient ST-segment changes (≥ 0.05 mV) that occur with chest pain and resolve when pain resolves are the ECG finding most predictive of ACS. Static ST-segment depression is the next most concerning finding with regard to ACS, followed by T-wave inversions greater than or equal to 0.2 mV, and finally, ST-segment depressions or T-wave inversions less than 0.05 mV and 0.2 mV, respectively.[2] The ACC/AHA guideline is supported by a retrospective analysis of data from the GUSTO-IIb trial, which examined 30-day mortality for 12,142 patients with different ECG findings on ED presentation. The most concerning findings associated with a poor outcome in NSTE-ACS were ST-segment depressions greater than 0.05 mV with or without T-wave inversion, followed by T-wave inversions greater than 0.1 mV (**see Figure 1**) or normalization of a prior negative T wave (**see Figure 2**).[71] The 30-day mortality rate of patients with isolated ST-segment depressions was equivalent to the 30-day mortality rate of patients with ST-segment elevations. The magnitude of ST-segment depression on ECG can also be used to predict the failure of medical therapy as well as which patients may benefit from eventual cardiac catheterization.[72]

Electrocardiograms with bundle blocks are particularly difficult to interpret.[73] Current guidelines recommend treating patients with new or presumably new left bundle branch block (LBBB) in the presence of symptoms consistent with myocardial ischemia as STE-ACS patients.[24] This recommendation is based on the improved outcome of patients with LBBB receiving reperfusion therapy in the GUSTO-I study.[74] In terms of an LBBB that is not new, the ACC/AHA clinical guidelines for NSTE-ACS simply state that this finding is a risk factor for

Figure 1. Electrocardiogram Results Suggestive Of Poor Outcome In Patients With Non–ST-Segment Elevation Acute Coronary Syndromes



Note the multiple abnormalities that imply high risk—ST depressions in V3 and V4 and T-wave inversions in V5 and V6 and in the inferior leads. Reprinted with permission from Ankur Doshi, MD.

poor outcome but do not provide strategies for risk stratifying these patients.[2]

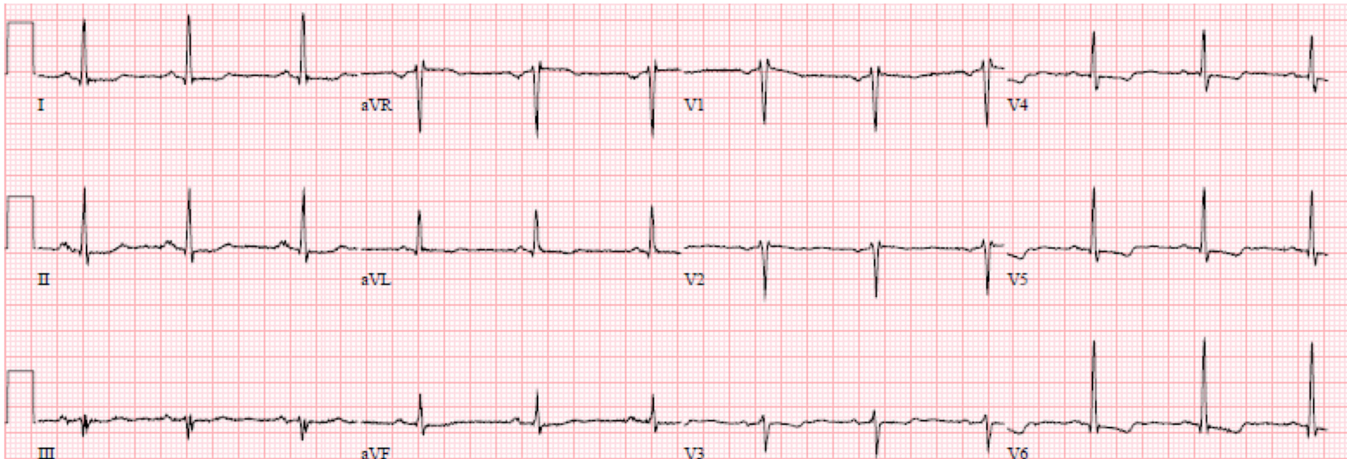
Right bundle branch block (RBBB) is not used to differentiate STE-ACS from NSTE-ACS. It is, however, a marker for older patients who are more likely to have a complicated medical history and atypical presentation.[75] Although these patients have more comorbidities, once they are adjusted for, the outcomes with RBBB are similar to those of patients without RBBB who present with NSTE-ACS.[76]

Isolated ST elevation in aVR is a strong predictor of poor outcome in NSTE-ACS in the absence of ST elevations in other leads. Patients with this finding are more likely to require PCI and CABG.[77] Two studies have shown that these patients have 30-day mortality rates that correspond with the degree of ST elevation in aVR.[77,78] Although these studies provide compelling evidence, a larger subgroup analysis of the GRACE registry found only modest increases in long-term mortality with larger ST elevations in aVR after confounding variables were adjusted for.[79] ST elevations in aVR seem to have a prognostic role, but the extent of that role and its impact on clinical practice needs to be defined. Consequently, the emergency clinician should be able to recognize this pattern and risk stratify the patient accordingly.

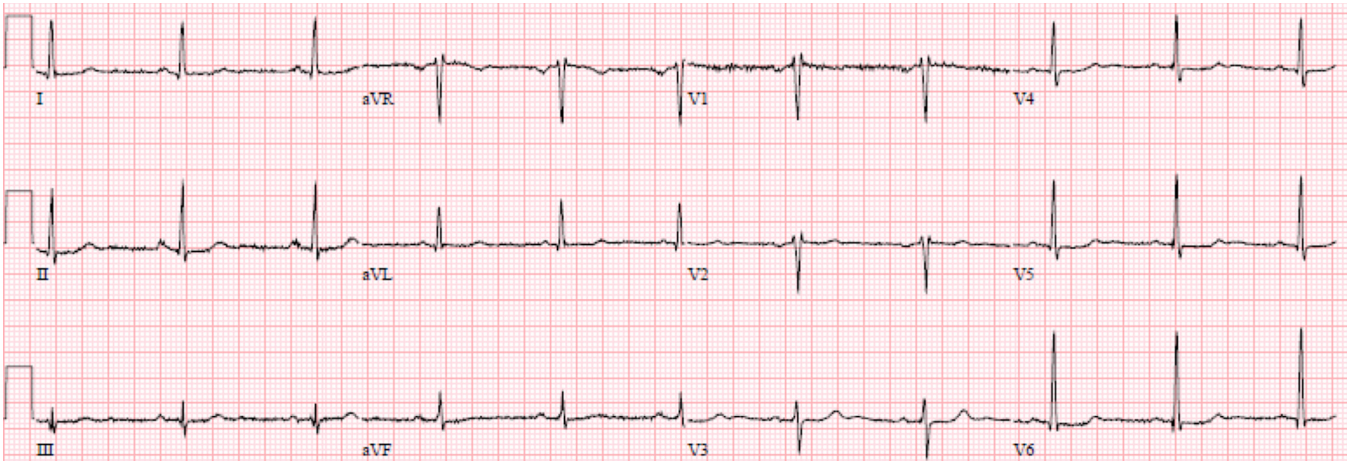
Results from a single ECG, however, will not universally demonstrate the presence of significant myocardial ischemia to the ED clinician. One recent study showed that a single ECG demonstrating "classic criteria" for ACS (ST-segment elevation in 2 or more contiguous leads [> 0.2 mV in leads V1, V2, and V3 or > 0.1 mV in other leads]; ST-segment depression in 2 or more contiguous leads [> 0.1 mV]; or inverted T waves [> 0.1 mV] in leads with predominant R waves) is only 75% sensitive and 69% specific for ACS.[80] Of note, this study did not specifically evaluate the sensitivity and specificity of single ECG criteria for NSTE-ACS.

Serial ECGs have been found to be more sensi-

Figure 2. Electrocardiograms Demonstrating Normalization Of Prior Negative T-Wave In Patient With NSTE-ACS



Patient's baseline electrocardiogram with inverted T-waves in V4-V6.



Electrocardiogram taken during active ischemia from NSTE-ACS. Note upright T-waves in V4-V6. Reprinted with permission from John O'Neill, MD.

tive than the presenting ECG alone for cardiac ischemia.[11,81] One study demonstrated that in patients with acute MI, the results of the first ECG were normal or nondiagnostic in up to 55% of cases.[82] Serial ECGs were found to change patient care decisions in more than 14% of high-risk patients.

In contrast, ECGs taken continuously over time or with change in position are being evaluated as possible tools to more rapidly diagnose NSTE-ACS in the ED. For instance, Schindler et al used a Holter monitor to analyze sequential ST segments and found slight differences between patients with positive biomarkers and those without positive markers.[83] Another small study analyzed ECGs by both time and patient position to differentiate patients with NSTE-ACS from those with chest pain due to other causes.[84] However, considerable work needs to be done before this technology can be applied in the clinical setting.

Proper identification of high-risk patterns on ECG is important for improving patient outcomes. A retrospective study of 1684 patients with acute MI found that 12% of those presenting to the ED had ECG findings indicative of ischemia that were missed by emergency clinicians. The study went on to track the outcomes of these patients for in-hospital mortality. There was a trend toward increased mortality when myocardial ischemia was not initially diagnosed on ECG; however, the result was not statistically significant.[73]

Summary

ST-segment depression is the most concerning ECG finding in NSTE-ACS. T-wave inversions and bundle branch blocks are also of concern. Isolated ST-segment elevation in aVR is likely a predictor of poor outcome; however, more evidence is needed to support this finding.

Cardiac Biomarkers

Several generations of cardiac biomarkers have been used to assist in the diagnosis of MI. Positive biomarkers define MI (ie, necrosis); NSTE-ACS patients with positive biomarkers have a higher risk of complications and death.[85,86] By definition, patients with UA undergo myocardial ischemia, but not infarction; therefore, biomarkers for these NSTE-ACS patients will be negative. However, even in the absence of positive biomarkers, high-risk patients still require aggressive management. To put it another way, negative biomarkers cannot be used to exclude NSTE-ACS in patients with UA, as these patients may progress to MI. Therefore, patients with suspected NSTE-ACS should still receive intensive evaluation and treatment even in the absence of positive biomarkers.

Cardiac troponins and creatine kinase, myocardial band (CK-MB) are the biomarkers most often used in the ED evaluation of patients with chest pain. Both of these enzymes become elevated in the serum 3 to 4 hours after a coronary ischemic event and peak 18 to 24 hours after the event. Although CK-MB levels drop to normal range within 48 hours, troponin levels remain elevated for up to 10 days.[87] Troponins are unique in that the molecules reside in both the cytoplasm and cellular structures. For this reason, troponin levels rapidly rise after injury and remained elevated for a prolonged period after infarction.

Troponin I, cardiac form (cTnI), and troponin T, cardiac form (cTnT), are both specific for cardiac injury.[88] Whereas other biomarkers may be elevated due to injury to various organs, only the timing and type of injury pattern to the myocardium is uncertain when cardiac troponin levels are elevated. The increased specificity of troponin is coupled with increased sensitivity. In 2000, a joint European Society of Cardiology and ACC committee redefined acute MI on the basis of very small troponin elevations (ie, any elevation above the 99th percentile).[89] This change led to a 74% increase in the number of diagnosed MIs in a prospective study at a community hospital.[90] Beyond troponin's value in defining an event as an NSTE-MI rather than a UA, the enzyme also has prognostic and treatment implications. As discussed previously, a positive troponin result has been shown to predict worsened outcome in patients with NSTE-ACS.[85,86] Even a small elevation in troponin levels has been shown to differentiate patients who will benefit from more aggressive treatments such as PCI and glycoprotein IIb/IIIa inhibitors (GPIs).[91]

Although specific for cardiac injury, an elevated troponin level is not always indicative of an acute event. Troponin levels may be elevated as a result of many factors, as listed in **Table 1**.[92] A prospective study of 991 Finnish patients found that a positive troponin value alone had an 83% sensitivity for acute MI. Of note, troponin elevations attributed to noncardiac causes should not lead the clinician to discount the results, as the mortality rate for these patients is twice as high as the rate for patients with elevations attributed to acute MI.[93] Interpretation of troponin values in patients with renal failure is particularly difficult. Levels of cTnI are considered to be

Table 1. Non-MI-Related Causes Of Elevated Troponin

- Renal failure
- Trauma
- Congestive heart failure
- Aortic valve disease
- Pulmonary embolism
- Renal insufficiency
- Pneumonia
- Septic shock

less influenced by renal insufficiency than are cTnT levels.[94] A study of the CRUSADE initiative followed 31,586 patients with ACS and found a modest increase in mortality in patients with chronic kidney disease and elevated troponin levels. Furthermore, no differences were found between cTnI and cTnT values.[95] A prospective study of 817 patients found that a point-of-care cTnI test was superior to myoglobin or CK-MB levels in detecting acute MI.[96] Therefore, cardiac troponin is the best available cardiac marker, even in patients with renal failure.[2]

The biomarker CK-MB is found in the heart as well as the skeletal muscle. In this age of troponin, one may ask why CK-MB still being used. Evidence for the continued use of CK-MB in diagnosing NSTE-ACS is conflicting. A study of 8769 registry subjects followed those patients with discordant CK-MB and troponin levels. An elevated CK-MB fraction in the absence of a positive troponin level doubled the odds of having a diagnosis of ACS and tripled the odds of a positive stress test.[97] In another meta-analysis, an elevated CK-MB level alone was found to increase the odds of a poor outcome.[98] In this study of 19,558 patients, researchers found that CK-MB elevations alone, in the absence of elevations of total CK, still increased the risk of death or MI at 180 days.

The CK-MB value may also be used dynamically in the ED. The change in CK-MB fraction after 2 hours has been used to detect early MIs. A prospective study of 975 patients found that a change greater than 0.7 ng/mL had 93% sensitivity and 94% specificity for acute MI in patients with an initially negative troponin result.[99] This early accuracy in detecting MI is the basis for Erlanger Medical Center's chest pain evaluation protocol, which uses 2-hour serial biomarkers, 2-hour ECGs, clinician judgment, and stress test results to rule out not only acute MI, but also UA.[100]

Nevertheless, some evidence challenges the usefulness of CK-MB in diagnosing NSTE-ACS. A study of frequent measurements of cTnI, CK-MB, and myoglobin levels found cTnI to be the most sensitive and specific biomarker for MI at all times sampled. The study was limited in size, but the authors did note that the sensitivity of elevated CK-MB and myoglobin levels increased in the setting of large infarcts.[101] This study challenges the very high sensitivity of CK-MB and myoglobin in combination found in earlier studies.[102,103] In a small meta-analysis of 3 studies, the outcomes of patients with positive CK-MB and negative troponin values were equivalent to those of patients with negative CK-MB and troponin values.[85] These results led to the most recent ACC/AHA guideline classifying CK-MB as a second-choice biomarker for MI, with use limited to certain clinical situations (ie, MI extension and periprocedural MI).[2]

Myoglobin is a protein found in both skeletal and cardiac muscle. Elevations in myoglobin occur rapidly before peaking and returning to baseline level. Time to elevation of myoglobin in the serum is 1 hour after an ischemic event, with peak levels reached in 6 to 7 hours. Levels fall back to normal in approximately 24 hours.[87] Myoglobin alone is sensitive early in the course of an infarction, but is never specific. Myoglobin has been used in various strategies to rule out acute MI. A study of the Triple Cardiac Marker test, which uses myoglobin, CK-MB and cTnI values, showed that a second testing of these biomarkers 2 hours later allowed for the safe discharge of low- to intermediate-risk patients with a very low 6-month readmission rate and no deaths.[104] As a standalone marker, myoglobin was found to predict increased risk of 6-month mortality (relative risk, 3.3) but not nonfatal MI.[105] Therefore, because of the availability of other, more useful biomarkers (ie, cardiac troponins and CK-MB), the ACC/AHA guidelines do not recommend the use of myoglobin in the evaluation for NSTE-ACS.[2]

Other biomarkers are in use, but none are currently recommended by the ACC/AHA guidelines. Beta natriuretic peptide and CRP levels have been studied along with troponin as part of a multimarker approach. Results showed that as the number of positive biomarkers increased, the 30-day and 6-month mortality rates increased.[106] One cannot deduce from this study that beta natriuretic peptide and CRP are cardiac biomarkers in and of themselves, but they might select for patients with preexisting vulnerability to complications from ACS. Ischemia-modified albumin is a detectable variation of albumin that occurs after ischemic damage to tissues. It has been studied recently in a variety of conditions from cerebrovascular accident to endometriosis. A meta-analysis of 1800 patients showed that a positive ischemia-modified albumin value can be useful in addition to ECG and troponin in ruling out ACS. However, the results are severely limited by the quality of the studies, which were small and included institutional quality control trials.[107] Cardiac biomarkers of further interest include markers for coagulation cascade activation, platelet activation, ischemia, and inflammation.

Summary

The use of cardiac biomarkers to stratify NSTE-ACS patients by risk has not been fully realized. The CRUSADE initiative found that inpatients with an initial positive troponin result received treatment similar to that of patients with negative initial troponin and delayed positive troponin values. Unfortunately, those patients who presented with an initial positive troponin value had increased in-hospital mortality.[108] Biomarkers are tools the emergency clinician can use to risk stratify NSTE-ACS patients early in their medical course. Appropriate use of biomarkers can ensure that these patients receive appropriate therapies.[2]

Risk Stratification

With data gathered from the patient history, physical examination, and preliminary diagnostic testing (eg, ECG and cardiac biomarkers), patients with chest pain can be stratified according to their risk for further cardiovascular events and death. Risk stratification answers the following questions:

- What is the likelihood that the presenting symptoms represent ACS as opposed to another differential diagnosis?
- What is the likelihood of an adverse cardiovascular outcome (eg, death, MI, stroke, CHF, recurrent ischemia, significant arrhythmia)?

Risk stratification also helps to select the appropriate site of care (eg, intensive care unit vs routine telemetry monitoring in the ED) and the appropriate therapy (eg, PCI vs medical management). The recent ACC/AHA guidelines place increased emphasis on specific risk prediction rules early in the patient's assessment.[2] The most common tools for ACS risk stratification are thrombolysis in myocardial infarction (TIMI), PURSUIT, and GRACE, all of which have demonstrated good predictive accuracy for death and MI at 1 year.[109-111]

The TIMI is a simple tool using 7 risk indicators on presentation. (**See Table 2.**) Each positive indicator increases the TIMI score. The TIMI score has been internally validated within the TIMI 11B trial and can be applied in the ED to all patients with chest pain.[112-114] Each TIMI score is associated with a specific risk of poor outcome as defined by death, MI, and acute revascularization within 30 days.[114] (**See Table 3.**) Patients with a TIMI score of 3 or higher are often considered at highest risk. (In one observational study of 3,929 patients, those with a TIMI score of 3 or higher had a 5% chance of death in 14 days and an additional 8% chance of needing urgent revascularization.).[113]

The PURSUIT prediction rule is based on 7 variables as well. (**See Table 4.**) First, the patient's PURSUIT score is calculated according to these variables. The score is then identified on a graph that supplies the probabilities of 30-day mortality and reinfarction.[110]

The GRACE model can be used to evaluate a patient's risk of in-hospital mortality during an acute coronary event. Similar to the PURSUIT prediction rule, a score is calculated according to a patient's clinical variables (**see Table 5**). The score is translated into a probability of in-hospital mortality based on a chart.[111,115]

Patients with NSTE-ACS should be risk stratified in order to help determine the most appropriate diagnostic strategies, treatment, and disposition. The routine incorporation of risk scores into the evaluation of patients with suspected ACS may help minimize both undertreatment and overtreatment of these patients.[2,113]

Treatment

In the ED, treatment of NSTE-ACS begins in parallel with diagnostic testing. Once a diagnosis of NSTE-ACS is suspected or confirmed, aggressive medical therapy should be provided to all patients.[1] The mnemonic MONAB (morphine, oxygen, nitroglycerin, aspirin, and β-blocker) is known to most medical students for the treatment of patients with chest pain. However, this "one size fits all" approach may lead to undertreatment or overtreatment of these patients.[2] Therefore, more detailed, targeted strategies have become commonplace in the ED treatment of NSTE-ACS patients. In addition, many variations in therapy are recommended by the ACC/AHA on the basis of patient risk stratification and in-hospital treatment strategy.[2] These guidelines can be cumbersome to use in a busy, rapidly moving ED.

Emergency clinicians can more easily navigate appropriate treatment strategies if they categorize therapy based on the intended effect, using the following 4 treatment categories:

Table 2. TIMI Risk Factors For NSTE-ACS[112]

Age greater than 65 years
At least 3 risk factors for coronary artery disease (including family history of the disease, hypertension, hypercholesterolemia, diabetes mellitus, and current tobacco use)
Significant coronary stenosis (prior known coronary stenosis ≥ 50%)
ST-segment deviation
Severe anginal symptoms (≥ 2 anginal events in the previous 24 hours)
Use of aspirin in the previous 7 days
Elevated serum cardiac marker levels (CK-MB fraction and/or cardiac troponin level)

Note: Each of the listed risk factors is worth 1 point (range, 0-7 points).

Table 3. Probability Of Death, Myocardial Infarction, And Revascularization Within 30 Days Of Presentation By TIMI Risk Score[113]

TIMI Risk Score	Probability Of Death, Myocardial Infarction, and Revascularization Within 30 Days, %
0	2.1
1	5
2	10.1
3	19.5
4	22.1
5	39.2
6	45
7	100

- Anti-ischemic therapy
- Reperfusion therapy
- Antiplatelet therapy
- Antithrombin therapy

The emergency clinician should consider all 4 classes of therapy for each NSTE-ACS patient and select the appropriate interventions. (**See the Clinical Pathway, page 12.**) The extent of intervention is dependent on the risk stratification (**eg, the TIMI risk score in Table 2**) performed by the emergency clinician and is thus tailored for each patient. This pathway for treatment is slightly different than other schematics. Reperfusion therapy is considered earlier in the pathway because the decision to treat the patient with either an "invasive" or "conservative" approach significantly affects both antiplatelet and anticoagulant therapies. Unless otherwise specified, the outcome endpoints of the studies described below are a composite of death, MI, and unplanned revascularization.

Anti-Ischemic Therapy

Anti-ischemic therapy for the NSTE-ACS patient in the ED should focus on correcting the oxygen supply/demand mismatch within myocardial cells. Treatments include both increasing supply and decreasing demand. Importantly, anti-ischemic therapy is essential for the NSTE-ACS patient as prognosis, decisions on other types of therapy, and disposition rely on the response to anti-ischemic therapy. For instance, a patient with refractory ischemic symptoms may have a worse outcome when compared to a patient who is responsive to anti-ischemic therapy. The patient with refractory ischemia should be treated more aggressively.[1,2]

Classic anti-ischemic therapy begins with bed rest and supplemental oxygen. In theory, bed rest decreases myocardial oxygen demand, and supplemental oxygen administration increases supply. No data show that these therapies are effective in patients without signs of ongoing ischemia (ie, pain or ECG changes) or respiratory distress or in those with normal oxygen saturation (≥ 90%). The most recent ACC/AHA guidelines acknowledge this lack of data but continue to recommend these therapies based on the consensus of the Writing Committee.[2]

Nitroglycerin is an anti-ischemic medication that functions to both increase oxygen supply and decrease demand. As a coronary vasodilator, nitroglycerin allows increased myocardial blood flow and hence increased oxygen delivery. In addition, nitroglycerin-mediated peripheral vasodilatation may decrease preload and myocardial stretch, thereby decreasing oxygen demand.[2] In patients with symptoms of ischemia such as pain or ECG changes, doses of nitroglycerin 0.4 mg SL should be given 5 minutes apart, up to a total of 3 doses.[2] For patients who continue to display signs of ischemia after SL nitroglycerin therapy, intravenous (IV) nitroglycerin should be initiated and titrated every 3 to 5 minutes to resolution of the ischemia. It is generally recommended that the infusion not exceed 200 μg per minute.[2] Studies showing a mortality benefit to the use of nitrates were done more than 20 years ago and indicated a benefit only when combined in a meta-analysis. The analysis also examined nitroglycerin and nitroprusside in a combined fashion.[116] The GISSI-3 trial randomly assigned more than 19,000 patients in Italy to the use of nitroglycerin IV and then transdermal nitrates vs open control for 6 weeks after MI and showed no benefit to the use of nitroglycerin.[117] A larger study, ISIS-4, compared oral nitrates vs placebo for 4 weeks after MI and showed no survival benefit, although "upstream" nitroglycerin use during the ischemic event was not tested. The ISIS-4 researchers performed a meta-analysis of all known nitroglycerin studies (> 80,000 patients) and showed a 0.38% survival benefit with the use of nitroglycerin.[118]

In the general NSTE-ACS population, nitroglycerin is well-tolerated. However, because nitroglycerin causes a drop in blood pressure, it should generally not be used in patients with systolic blood pressure less than 90 mm Hg (or 30 mm Hg below the patient's known baseline), heart rate greater than 100 bpm, or heart rate less than 50 bpm.[2] In addition, infarction of the right ventricle causes a preload dependent state; therefore, nitroglycerin should be avoided with known right ventricular infarct.[2] Finally, phosphodiesterase inhibitors (PDIs; eg, sildenafil, vardenafil, tadalafil) commonly used for

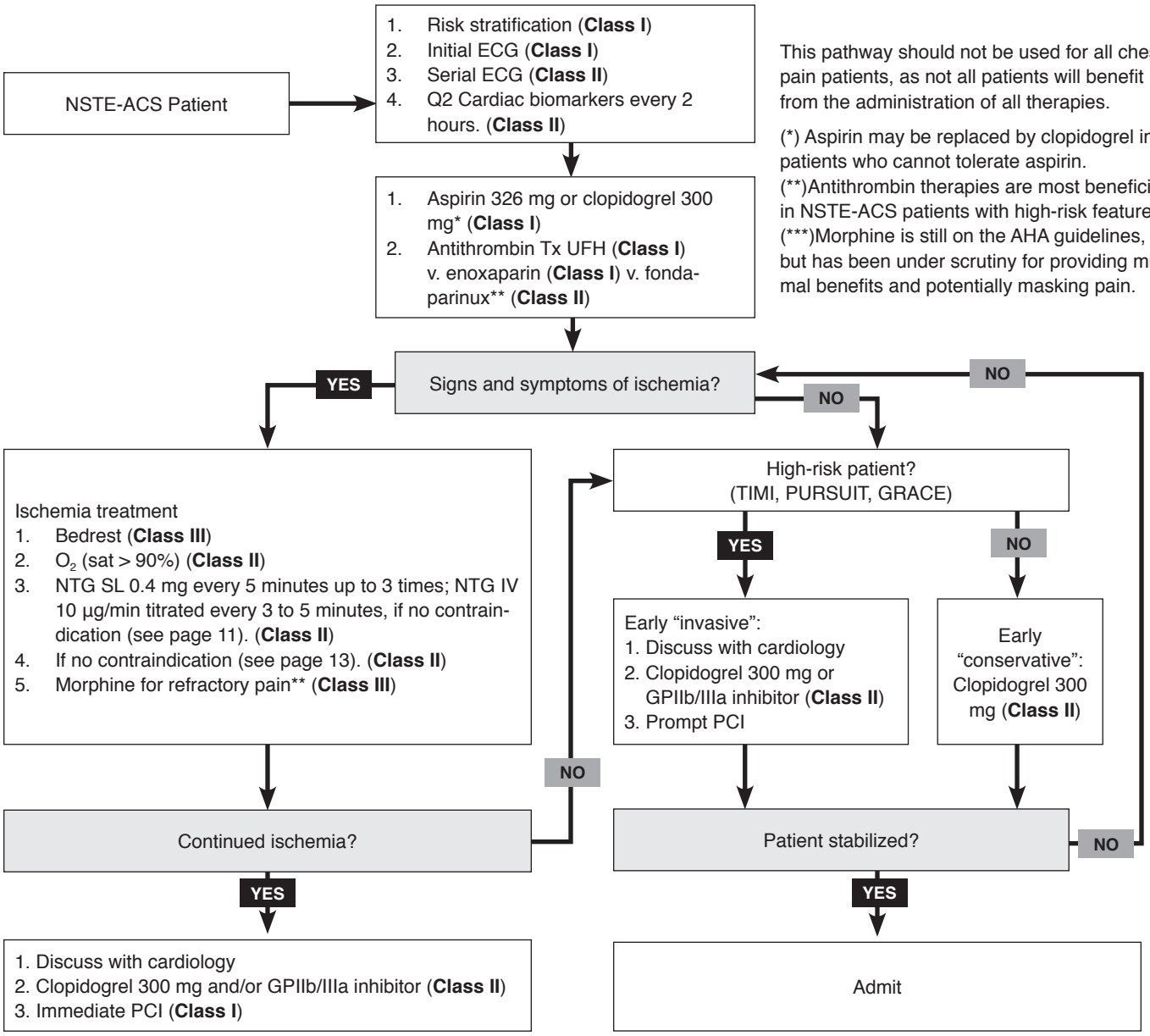
Table 4. PURSUIT Risk Factors For Acute Myocardial Infarction[110]

- Age
- Gender
- Highest Canadian Cardiovascular Society angina classification in previous 6 weeks
- Heart rate
- Systolic blood pressure
- Signs of heart failure (eg, rales)
- ST depression on presenting electrocardiogram

Table 5. GRACE Risk Factors For In-Hospital Mortality

- Killip heart failure class
- Systolic blood pressure
- Heart rate
- Age
- Creatinine level
- Cardiac arrest at admission
- ST-segment deviation
- Elevated cardiac enzyme levels

Clinical Pathway For Evaluation And Management Of NSTE-ACS In The ED



This pathway should not be used for all chest pain patients, as not all patients will benefit from the administration of all therapies.

(*) Aspirin may be replaced by clopidogrel in patients who cannot tolerate aspirin.
(**)Antithrombin therapies are most beneficial in NSTE-ACS patients with high-risk features.
(***)Morphine is still on the AHA guidelines, but has been under scrutiny for providing minimal benefits and potentially masking pain.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA*. 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

erectile dysfunction were found in premarketing and postmarketing studies to interact with nitroglycerin, causing prolonged hypotension.[119-121] No study has specifically tested the use of PDIs with nitroglycerin in order to assess the magnitude of this effect. According to an independent review article, PDIs may provide some cardioprotective effect when used without nitroglycerin.[122] According to an ACC/AHA consensus statement, administration of nitroglycerin and sildenafil within the same 24-hour period has also been associated with MI and death.[123] Therefore, nitroglycerin use should generally be avoided when the patient has used sildenafil or vardenafil within the previous 24 hours or tadalafil within the previous 48 hours.[2,119-121,124]

β-adrenergic blockers lower myocardial oxygen demand directly by decreasing myocardial work. The routine ED use of β-blockers in NSTE-ACS patients has been extrapolated from data demonstrating benefit in patients with ST elevations. Some recent research has tested IV β-blocker therapy during PCI in low-risk, electively catheterized patients, but not in NSTE-ACS patients.[125] In patients with NSTE-ACS, no data favor the use of IV or oral β-blocker therapy in the ED.[126] In addition, a meta-analysis of 18 studies (more than 74,000 patients) found no reduction in 6-week mortality rates when patients were treated with oral β-blockers within the first 72 hours of diagnosis of acute MI. A subgroup analysis of patients with Killip class I heart disease (ie, those without any clinical signs of CHF) did show a statistical benefit.[127] This study did not specifically separate NSTE-ACS patients, however.

In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) of patients at high risk for ST-segment elevation, the use of IV β-blockers caused significantly greater cardiogenic shock than the use of placebo ($p < 0.00001$). Although fewer patients had reinfarction or cardiac arrest, the composite endpoint (death, reinfarction, cardiac arrest, and shock) was increased with the use of IV β-blockers in the first day after acute MI.[128] Therefore, the most recent ACC/AHA guidelines recommend the use of oral β-blockers for NSTE-ACS patients without contraindications only within the first 24 hours of arrival in the ED. Contraindications include (1) signs of acute CHF; (2) evidence of low output state; (3) increased risk for cardiogenic shock (> 70 years old, systolic blood pressure < 120 mm Hg, pulse rate > 110 bpm or < 60 bpm, and increased time since onset of symptoms); or (4) other relative contraindications to β-blockade such as heart block or bronchospasm.[2]

Angiotensin-converting enzyme inhibitors may be useful for a patient's long-term survival, but no data have shown a benefit to treatment in the ED. Therefore, these medications do not need to be routinely given during the ED phase of the patient's treatment for NSTE-ACS.[2,126] Other antihypertensives such as calcium channel blockers may be used in addition to or in lieu of β-blockers if the patient continues to have ischemic symptoms. Again, no data demonstrate the effectiveness of these medications when given in the ED.[2] As previously detailed, use of stimulants such as cocaine or methamphetamine play a role in NSTE-ACS, especially in younger patients. According to consensus, β-blockers should be avoided in patients known to have used these stimulants because of the risk of reflexively worsening coronary artery vasospasm.[2]

Morphine sulfate is often used in the ED for NSTE-ACS patients with continued ischemic symptoms despite nitroglycerin therapy. Morphine is a vasodilator and also causes direct decreases in systolic blood pressure and heart rate, thereby decreasing myocardial oxygen demand. No randomized trials have detailed benefits of morphine therapy for NSTE-ACS patients.[2] In addition, in the CRUSADE database, an observational registry of more than 57,000 NSTE-ACS patients, those receiving morphine had an increased likelihood of death compared with those who did not receive the medication.[129] The authors postulate that morphine may provide pain control to the NSTE-ACS patient via its analgesic effect, even when myocardial ischemia is continuing, falsely reassuring the treating physician and leading to a worse outcome. They recognize, however, that this observational study does not clearly prove that morphine use is detrimental. Therefore, it is unknown whether morphine is beneficial or harmful in this population. Morphine should be used sparingly in the ED, and generally only when other anti-ischemic medications have already been used in appropriate doses or when the decision has already been made to take the patient to cardiac catheterization.

Reperfusion Therapy

Reperfusion therapy, as either fibrinolytic therapy or PCI, is the mainstay of treatment for STE-ACS. However, its use in treating NSTE-ACS is less clear. This uncertainty is likely due to the pathophysiologic difference in ACS with and without ST-segment elevation. In NSTE-ACS, complete coronary artery occlusion does not occur, and therefore, reperfusion therapy is not universally beneficial. Three randomized controlled trials have shown no benefit to fibrinolytic (thrombolytic) reperfusion therapy in the NSTE-ACS patient.[130-132] Additionally, a nonsignificant trend toward harm in NSTE-ACS patients who received fibrinolytic therapy was demonstrated in each of these studies, as well as in a 1994 meta-analysis.[130-133]

The use of coronary arteriography and PCI for the NSTE-ACS patient from the ED is similarly unclear. Multiple studies have compared an initial, or early invasive, strategy with an initial conserva-

tive strategy. These studies have focused on the use of cardiac arteriography without prior noninvasive testing in the first 4 to 24 hours after presentation (the early invasive strategy) as opposed to the use of cardiac arteriography in those patients who demonstrate coronary disease via noninvasive testing.[2] Some studies have demonstrated benefits with the invasive approach,[134-138] but others showed benefits with the conservative strategy.[139,140] A meta-analysis of these studies demonstrated a statistical benefit to an invasive approach at 2-year follow-up,[141] as did a review of data in the Cochrane database.[142] Another more recent meta-analysis that included 8 studies found that an invasive strategy benefited both men and women with positive biomarkers at 12-month follow-up when compared with a conservative strategy. In women with negative biomarkers, an invasive strategy was harmful; in men with negative biomarkers, the strategies were equivalent.[143]

For the emergency clinician, the decision regarding invasive vs conservative strategies is less important with stable patients (even those with risk factors or positive biomarkers) because the previously noted studies did not evaluate the use of immediate coronary arteriography with planned PCI from the ED. Instead, the invasive strategy was defined as planned PCI within 48 hours. The conservative strategy did not involve coronary arteriography or PCI during the patient's acute event.

One trial did attempt to study outcomes when the patients were taken immediately to the catheterization laboratory (median time, 2.4 hours) vs patients taken there after a delay (median time, 86 hours). This trial showed a benefit in 30-day mortality for patients taken immediately for planned PCI.[138] More relevant for emergency clinicians, based on these trials, treatment algorithms for both invasive and conservative strategies maximize medical therapies, including anti-ischemic, antiplatelet, and antithrombin therapies. In addition, with either strategy, patients with refractory or recurrent ischemia should be taken to the catheterization laboratory for evaluation and possible intervention, according to the ACC/AHA guidelines.[2]

The emergency clinician may therefore need to assure that a NSTE-ACS patient with continued ischemia is managed at an institution where immediate PCI or CABG can be done.[126] Finally, ACC/AHA guidelines call for use of an invasive strategy in patients with high-risk features, as defined by TIMI, PURSUIT, or GRACE risk scores. (**See Tables 2, 4, and 5, pages 10 and 11.**) The patient may not require immediate coronary arteriography but still should be managed with an expectant invasive strategy. The ACC/AHA Writing Committee recommended by consensus that patients with extensive comorbid conditions and a high risk of revascularization not undergo an early invasive strategy.[2]

Antiplatelet Therapy

Antiplatelet therapy during NSTE-ACS is essential because of the active nature of coronary artery clot and the role of platelet aggregation in these patients. Therefore, all NSTE-ACS patients should be treated with antiplatelet therapy.[2] Treating all patients who experience NSTE-ACS with aspirin, ~~an~~ irreversible COX-1 inhibitor, is emergency medicine dogma. For once, the dogma is correct ~~w~~with some exceptions. The best data for aspirin use come from the ISIS-2 trial published in 1988. This trial of more than 17,000 patients demonstrated an absolute risk reduction of death within 36 days of almost 3% in patients treated with aspirin vs placebo.[144] A meta-analysis of this study along with 14 others revealed similar results, with an absolute risk reduction in outcome of stroke, MI, or death of 3.8% (14.2% in patients treated with placebo vs 10.4% in patients treated with aspirin).[145] Based on the 162-mg dose of aspirin used in the ISIS-2 trial, present ACC/AHA guidelines recommend that a dose of oral aspirin between 162 and 325 mg be given to NSTE-ACS patients as soon as possible.[2] ACC/AHA contraindications to aspirin include intolerance and allergy, active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, and an active peptic ulcer or other serious source of gastrointestinal tract or genitourinary bleeding.

Clopidogrel is a thienopyridine-derivative antiplatelet medication that is an adenosine diphosphate receptor antagonist. Although no studies have assessed treatment of NSTE-ACS patients with clopidogrel vs aspirin in the ED, one study compared event rate (stroke, MI, or death) in high-risk patients (ie, those with a recent MI or stroke or peripheral artery disease) receiving either clopidogrel or aspirin. The medications were equally effective.[147] Therefore, the ACC/AHA guidelines recommend that clopidogrel be used when aspirin is not tolerated in patients with acute NSTE-ACS.[2] Double antiplatelet therapy was tested in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which NSTE-ACS patients were randomly assigned to aspirin plus placebo or aspirin plus clopidogrel. Despite more bleeding complications overall, patients treated with double antiplatelet therapy had an absolute risk reduction of death, MI, or stroke of 2.1% (11.4% for aspirin plus placebo vs 9.3% for aspirin plus clopidogrel).[148] Almost two-thirds of these patients did not undergo PCI; in this subset of patients, dual antiplatelet therapy also had an outcome benefit vs aspirin alone. CRUSADE data demonstrate that patients who received clopidogrel but not PCI within the first 24 hours after admission had an almost 2% absolute risk reduction for in-hospital mortality.[149] Consequently, the current guidelines state that NSTE-ACS patients undergoing a conservative strategy (ie, no planned coronary arteriog-

raphy within 48 hours) should receive clopidogrel 300 mg early in their hospital course ~~in~~ the ED if no contraindications exist.[2]

In the CURE subgroup that received PCI, dual antiplatelet therapy showed some benefit, although these data are complicated by open use of thienopyridine derivatives both before and after PCI.[148] A subgroup analysis paper, the PCI-CURE trial, demonstrated a benefit in outcome at 30 days in patients receiving aspirin plus clopidogrel prior to PCI when compared with patients receiving aspirin alone.[150] However, 32% of patients assigned to

Risk Management Pitfalls for NSTE-ACS

1. **"The ECG didn't show any ST elevations."**
   Non–ST-segment elevation acute coronary syndromes have a similar mortality rate as STE-ACS and should be evaluated and treated with the same urgency. However, NSTE-ACS require more thought on the part of the treating physician in order to ensure that each class of therapy that is needed (antiplatelet, anticoagulant, antiischemic, and reperfusion) has been used.

2. **"She didn't look that sick. Her chest pain resolved with nitro."**
   Anginal chest pain is a TIMI risk factor when it occurs within 24 hours before presentation, even if the patient is pain-free while in the ED.

3. **"I don't think her epigastric pain is due to cardiac disease."**
   Many patients present with atypical symptoms or anginal equivalents. This presentation is more common in women, patients with diabetes mellitus, and older patients.

4. **"He used cocaine yesterday. Those T-wave changes are just due to his left ventricular hypertrophy."**
   Stimulant-induced vasospasm can occur for days after drug use by patients. These patients should be treated similarly to other NSTE-ACS patients, with the exception of holding β-blockers. In addition, routine stimulant abuse increases the lifetime risk of CAD.

5. **"I didn't think to ask this young man about sildenafil use."**
   Phosphodiesterase inhibitors are used by patients of all ages. The patient history conducted by the emergency clinician must include questions about their use. Nitroglycerin therapy is contraindicated within 24 hours of sildenafil or vardenafil use and within 48 hours of tadalafil use to avoid the complication of hypotension.

6. **"I thought those T-wave inversions were old."**
   ST-segment depression, new T-wave inversions, and ST elevation in aVR are 3 acute NSTE-ACS injury patterns the emergency clinician must know. Assuming that these changes are old (especially changes considered nonspecific) may lull the clinician into a false sense of security. Old ECGs should be used for comparison whenever possible to determine if changes are new or dynamic.

7. **"I admitted him to the hospital after the ECG and enzymes were back. His pain was mostly controlled. The primary care physician said to admit him to the floor. I don't know why he had a ST-segment elevation MI upstairs."**
   Risk stratification of NSTE-ACS patients in the ED is essential to ensure that high-risk patients are treated with an appropriate level of care. Patients with continued ischemia may need serial ECGs or biomarker tests to ensure that they do not need more intensive management.

8. **"I dosed her by her body weight. I don't know why she bled."**
   Many studies have demonstrated that overdosing of anticoagulant and antithrombin medications leads to poorer outcomes. Elderly patients, women, and the obese are particularly prone to having their medications dosed incorrectly. Body weight and creatinine clearance levels are useful in determining appropriate doses of medications.

9. **"Why would the β-blocker I gave worsen his heart failure?"**
   Morphine sulfate and IV β-blockers have been shown to increase the rate of mortality in NSTE-ACS patients when used indiscriminately. Both of these medications should be reserved for special situations and not used routinely in the ED.

10. **"Why would I transfer this patient? He didn't have ST-segment elevations."**
    High-risk patients with NSTE-ACS benefit from early invasive strategy. This strategy includes PCI within 24 to 48 hours after admission. Also, patients with refractory or recurrent ischemia should receive immediate PCI. Patients in these categories may require transfer to a center where this therapy is available.

the aspirin only group received clopidogrel prior to PCI as well. No other randomized controlled trial has evaluated the use of clopidogrel plus aspirin vs aspirin alone in patients undergoing emergent PCI for NSTE-ACS. Therefore, the benefit of routine ED use of dual antiplatelet therapy with clopidogrel and aspirin in patients assigned to an invasive strategy is less clear when compared with its use in patients assigned to a conservative strategy. For this reason, it is reasonable to delay dual antiplatelet therapy until after consultation with the treating cardiologist.

The safety of clopidogrel has been debated extensively, most importantly for the emergency clinician in the setting of bleeding after CABG. In the CURE trial, patients receiving aspirin plus clopidogrel had a higher (although not significant: p=0.06) rate of major bleeding (defined as life threatening or requiring transfusion of 2 or more units of blood) than did patients receiving aspirin plus placebo when CABG was done less than 5 days after the last dose of clopidogrel or placebo (9.6% vs 6.3%, respectively).[148] When the study drug was held for 5 or more days prior to CABG, rates of bleeding did not differ. Overall, even in the group receiving early CABG (< 5 days after the study drug), no increase in mortality was evident with the use of clopidogrel vs placebo. In fact, other outcomes (ie, refractory ischemia, nonplanned revascularization) were improved in patients receiving clopidogrel.

The CRUSADE database also retrospectively examined whether clopidogrel use increased bleeding in patients undergoing early CABG. In a data set of 852 patients receiving clopidogrel, more patients who underwent CABG less than 5 days after administration of clopidogrel needed blood transfusions than did patients who underwent CABG later (65.0% vs 56.9%, respectively). This difference continued even when the effect of GPI inhibitors was taken into account. However, outcomes of death, revascularization, cardiogenic shock, and stroke were not affected by the use of clopidogrel.[151] Predicting which NSTE-ACS patients will need CABG during their time in the ED is difficult. It is even more difficult for the emergency clinician to control when the CABG will occur. Therefore, the emergency clinician can reasonably treat the NSTE-ACS patient with clopidogrel if indicated, as noted previously, without taking into account a possible eventual need for CABG. For patients who do need the procedure, CABG can be delayed by the treating team to minimize bleeding complications, or it can be undertaken early without the risk of increased mortality.[2]

Glycoprotein IIb/IIIa inhibitors block fibrinogen-activated platelet aggregates. These medications come in many varieties (abciximab, eptifibatide, and tirofiban are the most well known) and dosing regimens (they may need to be renally dosed) and therefore can be confusing to use in the ED. In addition, some studies show superiority of GPIs and some show no change in outcome with their use.[2] Published studies have used different inclusion/exclusion criteria and different treatment strategies, making a coordinated statement regarding their use in the ED difficult. Some of the more useful trials are detailed in this paper.

The first distinction the emergency clinician must know is the difference between large-molecule GPIs (eg, abciximab) and small-molecule GPIs (eg, eptifibatide and tirofiban). These classes of medications affect NSTE-ACS patients differently, and their use should be tailored to the clinical setting. For example, sufficient data define the specific role of abciximab in patients with NSTE-ACS who will undergo immediate PCI. The most useful data come from the Intracoronary Stenting with Antithrombotic Regimen (ISAR)-REACT-2 trial. This study demonstrated a 3% absolute benefit with the addition of abciximab to previous aspirin, clopidogrel, and unfractionated heparin (UFH) regimens for high-risk patients receiving PCI for NSTE-ACS.[152] Even with the higher risk of bleeding, in high-risk NSTE-ACS patients going directly to PCI from the ED, therapy with either clopidogrel, or GPI, or both should be used in the ED.

For other NSTE-ACS patients, evidence demonstrates that abciximab should not be used. The GUSTO-IV trial evaluated the use of abciximab in addition to aspirin and anticoagulation therapy for NSTE-ACS patients undergoing a conservative strategy. Patients were randomly assigned to receive a 24-hour infusion of abciximab, a 48-hour infusion of abciximab, or placebo. The results showed no significant change in death or MI rates at 30 days based on treatment with abciximab.[153] However, complications were more frequent in the abciximab groups. Therefore, it is essential that the emergency clinician have a conversation with the treating cardiologist prior to beginning abciximab to ensure that immediate PCI is planned

Similar to abciximab, small-molecule GPIs demonstrate benefit to patients with NSTE-ACS who undergo invasive treatment. Studies demonstrating this benefit include the PURSUIT and PRISM-PLUS trials, each of which treated patients with planned PCI between 48 to 72 hours after confirmation of NSTE-ACS.[154,155] Therefore, current guidelines recommend that patients with invasive treatment receive a small-molecule GPI or clopidogrel in addition to aspirin prior to planned PCI.[2] The use of triple antiplatelet therapy (ie, aspirin, clopidogrel, and small-molecule GPI) has not been well studied, but current AHA/ACC guidelines consider the use of triple antiplatelet therapy prior to planned PCI to be "reasonable."[2] A meta-analysis of more than 23,000 NSTE-ACS patients who received small-molecule GPI vs placebo confirmed a reduction in poor outcomes (defined as death or MI) at 5 (6.6% vs 7.7%, respectively) and 40 days (11.7% vs 12.8%, respectively)

after NSTE-ACS.[156] This meta-analysis included both patients treated with PCI and those treated medically. No randomized trials of exclusively medically treated NSTE-ACS patients (ie, no coronary arteriography planned through the patient's acute event) have compared small-molecule GPI to placebo. In addition, the meta-analysis showed no benefit to patients with initially positive CK-MB or troponin values in outcome of death or MI with the use of GPIs.[156]

Summary

Present recommendations for all patients with suspected NSTE-ACS include treatment with aspirin unless contraindications exist. Clopidogrel is an acceptable alternative to aspirin in the setting of allergy. The guidelines recommend that patients with planned invasive treatment, especially those undergoing immediate planned PCI, be treated with a GPI or clopidogrel. Triple antiplatelet therapy may be beneficial in this group as well. For patients with planned conservative treatment, clopidogrel is recommended in the ED.

Anticoagulation Therapy

Anticoagulant medications inhibit the coagulation cascade either directly at thrombin or proximal to it, causing decreased thrombin activation and decreased clot formation. Because clot progression is important to the pathophysiology of NSTE-ACS, inhibition of thrombin seems to be a major aspect of NSTE-ACS treatment. The first studied anticoagulant was UFH. A number of small randomized studies have shown trends toward benefit when UFH is added to standard aspirin therapy.[157-159] However, none of these studies demonstrated statistical significance, likely because of their small sizes. A meta-analysis including 6 trials also failed to show statistical significance for the outcome of death or nonfatal MI, possibly because of the large variety of patients enrolled in these studies.[160] For instance, a number of these studies enrolled very low–risk patients in addition to high-risk patients.

In contrast, the FRISC study demonstrated an absolute outcome benefit with the use of low-molecular-weight heparin (LMWH) (dalteparin in this study) when added to aspirin and compared with placebo and aspirin.[161] The absolute benefit at 6 days was 3% (endpoint was death or new MI), and the absolute benefit at 40 days was 5.7%. When directly compared with UFH, however, dalteparin showed no difference in outcome.[162] Enoxaparin, the LMWH of choice for most institutions, has been compared directly with UFH in 6 trials. Four of these trials showed a benefit from enoxaparin use.[163-166] A number of these studies treated all patients with dual antiplatelet therapy using aspirin and GPIs.[164-166]

The most recent large trial, known as the SYNERGY trial, showed equivalence between UFH and enoxaparin in a high-risk NSTE-ACS population undergoing PCI.[167] All patients were treated with GPIs and either enoxaparin or UFH. No difference in death or nonfatal MI was found at 30 days, but a significant increase in major bleeding was seen with enoxaparin (p=0.008). The researchers suggested in a post hoc analysis that this finding was due to increased bleeding in patients treated initially with enoxaparin and switched to UFH in the catheterization laboratory. At the 6-month follow-up, patients receiving only enoxaparin had a lower rate of death or MI when compared with patients receiving UFH or combination therapy.[168] Therefore, enoxaparin and UFH provide similar protection in medium-risk to high-risk NSTE-ACS patients. Either medication can be used in both invasive and conservative strategies for all patients not deemed to be low-risk; however, mixing the medications seems detrimental, and consultation with the admitting team is essential to ensure that the selected regimen will continue throughout the hospital course.[2]

The ACC/AHA guidelines also recommend the use of fondaparinux (a factor Xa inhibitor) or bivalirudin instead of UFH or LMWH as anticoagulation therapy.[2] The recommendation for fondaparinux comes from results of the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, which demonstrated equivalence of this medication with enoxaparin in medium-risk to high-risk NSTE-ACS patients.[169] In addition, when major bleeding is factored into the standard outcome, fondaparinux outperformed enoxaparin (absolute risk reduction, 1.7%). Fondaparinux can therefore be used instead of UFH or LMWH for medium-risk to high-risk NSTE-ACS patients and may even provide benefits for patients who are at high risk for bleeding.[2] Women in particular may have a higher risk of bleeding and therefore may benefit from fondaparinux use.

The data on bivalirudin is limited to 1 large study, the ACUITY trial. Although bivalirudin was equivalent to enoxaparin in outcome and outperformed enoxaparin when major bleeding was added as an endpoint, the data are limited by the complicated nature of the trial. First, one-third of patients received PCI within 3 hours of randomization and therefore did not receive the standard invasive strategy. Also, the effect of bivalirudin was most apparent when clopidogrel was administered in advance of PCI and GPIs were not used until PCI was begun.[170] These limitations make bivalirudin too complicated to use in the typical ED, unless specifically requested by the cardiologist.

Summary

All NSTE-ACS patients should be stratified according to risk. Tailored medical management is essential to maximize outcome. (**See Clinical Pathway, page 12.**) Current guidelines recommend that all patients

receive antiplatelet therapy with aspirin (or clopidogrel if intolerant) on arrival. Evidence suggests that the initial treatment for patients with active ischemia should be nitroglycerin SL and IV. The use of IV β-blockers and morphine sulfate is less beneficial. All NSTE-ACS patients should receive anticoagulation therapy unless a contraindication exists. Unfractionated heparin, enoxaparin, and fondaparinux all demonstrate equivalence in trials, with fondaparinux possibly causing less bleeding in high-risk populations. The ACC/AHA guidelines state that fondaparinux is an "acceptable alternative" to UFH or enoxaparin.[2] The emergency clinician should consider discussing the choice of anticoagulant with the admitting physician because changing anticoagulant therapy during admission is associated with poorer outcome.[167,168] Patients with refractory ischemia may benefit from immediate PCI from the ED. The evidence suggests that these patients may be treated with clopidogrel or GPI, or both, prior to PCI, although benefit from the administration of these agents in the ED is more difficult to assess. Current guidelines suggest that patients without continued ischemia should be risk stratified. Evidence indicates that high-risk patients benefit from an invasive strategy (PCI within 48 hours) and therefore may benefit from treatment with either clopidogrel or GPI in the ED after discussion with the admitting service. Non–high-risk patients may be treated with either invasive or conservative strategies. The emergency clinician should consider a loading dose of clopidogrel (300 mg) for patients receiving conservative therapy. The evidence suggests that patients with new refractory ischemia be treated with PCI and therefore may benefit from treatment at a center capable of immediate coronary arteriography.

Special Circumstances

Much time has been spent debating the role of comorbid conditions such as diabetes mellitus, chronic renal disease, and hypertension, as well as gender and age, in patients with NSTE-ACS. Although comorbid conditions play a significant role in NSTE-ACS, leading to poor results and higher mortality rates, their role seems less understood by most physicians. The use of risk scores takes the effects of these comorbid conditions into account. The more comorbid conditions a patient has, the higher his or her risk scores and the worse his or her outcome will be. These patients should be treated more aggressively, as their risk scores dictate.

Gender and age differences, in particular, deserve further discussion here.[171] The ACC/AHA guidelines recommend that men and women undergo equal evaluation and treatment strategies. In the CRUSADE database, women had higher unadjusted odds of in-hospital mortality due to NSTE-ACS.[172] When presenting variables are adjusted for, women received statistically less treatment with anticoagulants such as UFH or LMWH and less antiplatelet therapy with GPIs within the first 24 hours after diagnosis of NSTE-ACS.[172] Women received PCI less often when presenting for acute MI.[173] Women in this cohort had more comorbidities, which may have made physicians less likely to prescribe aggressive therapy because they feared causing harm. Interestingly, women also were more likely to be treated with excess doses of anticoagulants and antiplatelet agents.[174] In another meta-analysis, women had less benefit from treatment with GPIs, possibly due to dosing difficulties.[156] A third study showed than women also waited longer to have an initial ECG performed, demonstrating that clinicians failed to consider the diagnosis of NSTE-ACS as quickly in women as in men.[172] The emergency clinician should therefore take care to accurately evaluate, risk stratify, and treat women for NSTE-ACS.

Elderly patients, generally defined as those older than 74 years, also bear a significant burden of disease from NSTE-ACS. Data from the Bronx Aging Study, collected over 8 years, revealed that of 115 Q-wave MIs in elderly patients, 50 (43%) went unrecognized at the time of the actual ischemic event. Instead, these events were recognized only on annual screening ECGs (as new Q waves when compared with a prior ECG).[175] This may be because older persons have fewer typical cardiac symptoms during ACS.[176] The NRMI cohort demonstrated that patients older than 75 years had a statistically lower rate of PCI than younger patients.[173] In the GRACE registry, older persons had a greater number of comorbidities on arrival than younger patients, but were treated less frequently with aspirin and GPIs.[177] Although at higher risk from NSTE-ACS, older patients, like women, are less often treated aggressively. The emergency clinician should assure that this group of patients is accurately assessed and treated.

Controversies And Cutting Edge

Given the rapidly aging population, new research is aimed at finding ways to prevent ACS. As alluded to previously, much of the attention in the last 5 years has focused on finding new biomarkers that will identify patients at risk for ACS. Although target LDL cholesterol levels have long been dropping, hs-CRP levels have been receiving more attention, especially since high levels were found to be associated with increased risk of MI, sudden cardiac death, and stroke.[32] In 2008, results from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study were published. Sponsored by AstraZeneca, this trial was stopped early because of promising results: Initiating rosuvastatin in patients with LDL level lower than 130 mg/dL and hs-CRP level greater

than 2 mg/L led to a decreased incidence of major cardiovascular events.[32] This study is likely the first of many investigating inflammatory biomarkers, as numerous enzymes may be targeted for anti-inflammatory therapy.

Although newer preventive therapies may appear in the future, research and technology is also focused on developing better ways to rule out ACS in patients who present to the ED with chest pain. The use of serial cardiac marker levels followed by stress testing and nuclear imaging is the most common method for ruling out ACS. This technique is commonly used in chest pain observation units (CPOUs) throughout the United States, averting hospital admission for patients who are stable and considered to be at low to intermediate risk for ACS. A few studies have shown the CPOU to be both an effective clinical tool and a cost-effective means for managing increasing numbers of patients with chest pain who present to the ED.[178] Those patients with ACS ultimately require full admission to the hospital.

Currently, the criterion standard for imaging atherosclerotic plaques is invasive angiography, with or without therapeutic intervention. New imaging modalities, including computed tomography angiography (CTA) and cardiac magnetic resonance (CMR), are being explored for their usefulness in evaluating patients for ACS; yet, as with any new technology, there are inherent limitations in both their application and accessibility.

Advances in computed tomography include the ability to make smaller image cuts and the use of multiple detectors. Several studies using 64-slice CTA to visualize vulnerable coronary plaque and diagnose ACS when initial biomarkers are negative have been published recently.[179-183] However, most of these studies are biased and had small patient sample sizes. Furthermore, CTA use is somewhat controversial because of the lack of validation, the radiation exposure, and the need to use IV dye.[184-187] On the other hand, the predictive value of a negative CTA result is well documented, and CTA could prove to be useful in identifying patients with chest pain who are considered low to intermediate risk (ie, with negative troponin values and low risk scores) and do not need to be admitted.[186,187] This recommendation was expressed in a statement by the AHA regarding the use of multidetector computed tomography (CT) in the clinical setting.[2,188]

CMR also holds promise as a tool for ruling out ACS in the ED. Although the literature on this technology is even more limited than studies on CT, magnetic resonance imaging (MRI) has several advantages over CT, including no radiation exposure and no need for IV dye. Studies with CMR have shown high positive predictive value and high specificity for MI.[189] Preliminary data suggest that certain image sequences (ie, T2 weighting, left ventricular wall thickness analysis, and delayed hyperenhancement imaging) add enough information not only to discern acute MI from chronic MI, but also to distinguish UA from NTSE-MI.[189] This technology seems promising, and the ACC/AHA has included CMR in its guidelines, but deemed the technology not yet ready for routine clinical use.[2]

Disposition

Early risk stratification helps to determine the disposition of the patient with NSTE-ACS. All unstable patients should be admitted to an intensive care unit or should undergo immediate coronary arteriography to evaluate the need for PCI or CABG. Current guidelines also recommend that stable patients who are high risk for NSTE-ACS may require an early coronary arteriogram, and therefore, consideration should be given for early transfer of these patients to a facility where such intervention is possible. Even low-risk, stable patients will require cardiac monitoring. Decisions on dual antiplatelet therapy may be made in conjunction with the admitting physician or consulting cardiologist to ensure an appropriate level of treatment. Finally, all NSTE-ACS patients should receive anticoagulant therapy if no contraindication exists. This therapy also should be given after discussion with the admitting physician to assure that patients do not receive combination therapy with UFH and enoxaparin.

Summary

NSTE-ACS is a critical and increasingly common diagnosis in the ED. Physicians and hospitals that provide up-to-date, evidence-based care offer the best service to their patients and maximize outcomes. A simple approach to this complex disease is to quickly assess and risk stratify the patient using a validated score and the ECG findings and biomarkers. A 4-step approach to treatment will help the emergency clinician treat ischemia and provide antiplatelet and antithrombin therapies. The emergency clinician's knowledge of specific high-risk patient types and ECG findings can help determine the need for emergent revascularization. By tailoring therapy, the emergency clinician can ensure that patients have the highest rates of survival, both in-hospital and long-term.

Case Conclusion

By the time your point-of-care troponin test is done, your patient feels much better on her nitroglycerin drip. You repeat her ECG and notice T-wave inversions. Her enzyme values are positive. You maximize her therapy, and by the time you talk to her family, the cardiologist is on the way in to perform a catheterization. It has been another successful day in the ED.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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1. The role of emergency medical services in treating patients with chest pain without ST-segment elevations may include all of the following EXCEPT:
a. Aspirin
b. Nitroglycerin
c. Thrombolytics
d. Transport to an appropriate medical center
e. 12-Lead ECG

2. How can prehospital ECGs best help with the emergency treatment of NSTE-ACS?
a. By allowing activation of the catheterization laboratory prior to patient arrival in the ED
b. By allowing patients with normal ECG results to stay home
c. By facilitating triage of patients to appropriate facilities
d. By giving ED staff time to obtain thrombolytic medications from the pharmacy

3. Which of the following statements about traditional cardiac risk factors (eg, hypertension, hyperlipidemia, and tobacco use) is true?
a. They are predictive of an acute cardiac event.
b. They are predictive of an acute cardiac event and lifetime risk of CAD.
c. They are not predictive of an acute cardiac event, but they are predictive of lifetime risk of CAD.
d. They are independent of prognosis if cardiac ischemia is established.

4. Which of the following statements about older patients with NSTE-ACS is true?
a. They are more likely to present early.
b. They are more likely than younger patients to have typical chest pain.
c. They rarely have exertional dyspnea or lightheadedness.
d. They often report experiencing dyspnea and fatigue.

5. **Which of the following statements about risk stratification of patients with chest pain is true?**
   a. Risk stratification should be done only on the basis of history and physical examination.
   b. Risk stratification is cumbersome in the ED.
   c. Risk stratification excludes traditional risk factors such as hypertension.
   d. Risk stratification can be used to help guide treatment and appropriate treatment location.
   e. Risk stratification should be used only for patients with STE-ACS.

6. **Contraindications to nitroglycerin use include all the following EXCEPT:**
   a. Heart rate > 100 bpm
   b. Inferior wall MI
   c. Negative cardiac biomarkers
   d. Phosphodiesterase inhibitor use within 24 hours
   e. Systolic blood pressure < 90 mm Hg

7. **Antiplatelet therapy in NSTE-ACS is focused on treating which pathophysiology?**
   a. Coronary artery vasospasm
   b. Local inflammatory processes
   c. Myocardial oxygen supply
   d. Plaque thrombosis

8. **Which of the following statements about fondaparinux is true?**
   a. It should be used in addition to UFH for high-risk patients.
   b. It should be used exclusively in the catheterization laboratory.
   c. It should be used in patients with a higher risk of bleeding.
   d. It should be used only when the patient has refractory ischemia.
   e. It should be used for all patients with NSTE-ACS.

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