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Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

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In 2007, the American College of Cardiology/American Heart Association updated their guidelines for the management of patients with unstable angina/non-ST-segment elevation myocardial infarction, revising important recommendations regarding patient evaluation and treatment. This article reviews the guideline recommendations with a focus on patient presentation with or without classic symptoms, risk stratification as the basis for treatment and disposition decisions, and imaging and stress testing. Specifically, it describes the use of risk scores, electrocardiography, and cardiac isoenzymes and biomarkers to categorize patients with suspected acute coronary syndromes. It also discusses management and treatment modalities for all patients with suspected cardiac ischemia as well as early invasive and conservative strategies that are determined by the patient's global presentation.

A 68-year-old woman presented to the emergency department (ED) with a chief complaint of substernal chest pressure and dyspnea with acute onset. Her symptoms began while she was climbing a flight of stairs, persisted for 30 minutes, resolved with rest, and reoccurred at rest 10 minutes prior to arrival at the ED. She described the pain as a nonradiating dull sensation with 5/10 intensity, and she mimicked the pain by clenching a fist over her mid chest. She denied nausea, vomiting, or diaphoresis. She had 1 similar episode with exertion the previous week, which lasted 2 to 3 minutes and resolved spontaneously. She had a notable past medical history of hypertension, fibromyalgia, and anxiety, and had smoked 1 to 2 packs of cigarettes a day for 20 years. She denied illicit drug use. Her medications included hydrochlorothiazide 25 mg, aspirin 81 mg, hydrocodone/acetaminophen, and lorazepam as needed. Her mother died of a stroke at age 80 years and had a myocardial infarction at age 60 years as well as a history of hypertension. Her father died of Alzheimer's disease at age 82 years. The patient appeared anxious but in no acute distress and had normal vital signs. She had a benign physical exam with notable reproducible pain on palpation, a lack of reproducible discomfort on deep breathing, normal heart sounds with no murmurs, rubs, or gallops, and no jugular venous distension. Electrocardiogram (ECG) demonstrated normal sinus rhythm, no axis deviation, a right bundle branch block, and ST-segment depression of 0.5 mm in leads I, V4, and V5; a prior ECG was not available. Initial laboratory test results were within normal limits, with normal levels of troponin I and creatine kinase (CK)-MB.

Hart disease remains the leading cause of death in the United States, with 451,326 deaths caused by myocardial infarction (MI) in the United States in 2004.¹ In addition, approximately 9.1 million Americans suffer from angina. Heart disease spans a spectrum of pathology, from subclinical atherosclerotic changes to structural dysfunction with symptoms. In 2007 the American College of Cardiology and American Heart Association (ACC/AHA) revised their guidelines for the management of patients with unstable angina (UA) and non-ST-segment elevation MI (NSTEMI), making many important recommendations since their 2002 guidelines.¹ Notably, the guidelines support early risk stratification for choosing therapy. Troponins have become the principle biomarker of necrosis, and novel imaging strategies such as computed tomography (CT) and magnetic resonance imaging (MRI) are also included. There is a greater emphasis on risk reduction through lifestyle modifications, lowering body mass index (BMI) and waist circumference, optimizing lipid and blood pressure management, tobacco cessation, and detection and control of glycemic burden. Mortality associated with ST elevation MI (STEMI) has been well studied,

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TAKE HOME POINTS

- The 2007 American College of Cardiology/American Heart Association guidelines for unstable angina/non-ST-elevation myocardial infarction stress early risk stratification, discuss use of developing imaging modalities and detailed medical management strategies, and emphasize lifestyle modification.
- The primary steps to appropriate triage of chest pain include a focused history and physical examination with an electrocardiogram within 10 minutes of arrival.
- Risk stratification based on likelihood of acute coronary syndrome by symptoms, risk scores, electrocardiography, cardiac enzymes, and imaging is critical to management strategies.
- Disposition is based on risk stratification and may include coronary care intensive care unit, inpatient telemetry units, observation units, or home with physician follow up.
- Risk factor modification is critical in disease prevention and includes optimal medical management at disposition as well as physician follow-up.

but both the incidence and long-term mortality associated with NSTEMI are higher. This article discusses the current guideline recommendations as they pertain to the triage and management of UA and NSTEMI.

DEFINITIONS

Classically, the acute coronary syndromes (ACS) are categorized by the appearance or absence of ST-segment elevation, with elevation present in STEMI and absent in UA/NSTEMI. Within the category of ACS, the new ACC/AHA guidelines define non-ST-segment elevation ACS (NSTEMI-ACS) as ST-segment depression or prominent T-wave inversion with or without positive serum biomarkers in an appropriate clinical setting of angina or anginal equivalent in the absence of ST-segment elevation. Within the first several hours after presentation, the differentiation between UA and NSTEMI may not be entirely clear due to delayed detection of the serum biomarkers CK-MB, troponin I, and troponin T. Until the diagnosis of NSTEMI is made with positive biomarkers, many use the term NSTEMI-ACS to describe patients who present in this manner. There are 3 typical presentations of UA, as described by Braunwald in 1989: (1) angina at rest, (2) new-onset severe angina (less than 60 days), and

Table 1. Subtypes of Myocardial Infarction (MI)

Type 1	Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	MI secondary to ischemia due to either increased oxygen demand or decreased supply (eg, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension)
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	MI associated with percutaneous coronary intervention
Type 4b	MI associated with stent thrombosis as documented by angiography or at autopsy
Type 5	MI associated with coronary artery bypass grafting

Adapted with permission from Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173–95.

(3) accelerating angina which is increasing in intensity, duration, and/or frequency.²

Myocardial necrosis is defined by the ACC/AHA guidelines as an elevated troponin level above the 99th percentile of normal. MI is myocardial necrosis subsequent to ischemia and is defined by evidence of necrosis with the addition of 1 of the following: ischemic ST-segment and T-wave changes, new Q waves, new left bundle branch block, percutaneous coronary intervention (PCI)-related biomarker elevation, or imaging demonstrating new loss of myocardial tissue.³ MI has been described by the 2007 joint task force of the European Society of Cardiology, ACC, AHA, and World Health Organization as cardiac myocyte death as a consequence of perfusion imbalance in supply and demand.¹ It has been further broken down into 5 subtypes based on its etiology, and treatment modalities differ based on the subtype (**Table 1**). For example, a patient with type 1 ischemia secondary to thrombosis will undergo advanced imaging and catheterization, while a patient with a type 2 “supply-demand mismatch” ischemia may have therapy directed at the cause of the mismatch only.

PATHOGENESIS

The principle mechanism of myocardial ischemia is an imbalance in perfusion supply and tissue demand.

Of the 5 leading causes of this imbalance, the predominant cause of ischemic heart disease remains coronary atherosclerosis (Table 2). The lesions of UA/NSTEMI typically are partially obstructive or nonobstructive in nature, while those of STEMI are more likely to be occlusive. It has long been known that the deposition of lipids within the wall of the coronary arteries precedes luminal narrowing. In response to risk factors such as hyperlipidemia, the smooth muscle cells within the wall exhibit proinflammatory cytokines leading to recruitment of monocytes and macrophages. This coupled with the increasing deposition of extracellular lipids leads to lipid-laden macrophages called foam cells. At this fibrofatty stage, smooth muscle cell migration and proliferation occurs and the lesion begins to express the procoagulant tissue factor as well as matrix metalloproteinases that can degrade the fibrous cap. If cap rupture occurs, exposed tissue factor quickly becomes thrombogenic and can occlude a previously nonobstructive lesion. Correspondingly, if the endothelial cells overlying the cap erode, occlusive thrombus can arise. This alternate mechanism can occur in as many as 25% of disrupted lesions.⁴ If endogenous fibrinolytic mechanisms prevail, then resorption can lead to plaque progression with advanced fibrosis or calcified plaque and can produce symptoms of stable angina.

Inflammation is at the center of the evolution and stabilization of the atherosclerotic plaque, and inflammatory mediators alter the balance between extracellular matrix synthesis and degradation as described by Libby.⁵ The fibrous cap itself exhibits metabolic activity and can undergo remodeling.⁶ Inflammation can lead to endothelial cell death as well as breakdown of collagenous support within the structure of the plaque. The loss of the endothelial cells, which maintain and repair the integrity of the cap, has been seen in sites of plaque erosion and rupture, potentially culminating in fatal thrombosis.⁷ These sites also have a higher prevalence of macrophages as compared to smooth muscle cells.⁸ The lymphokine interferon- γ inhibits the production of collagen by the smooth muscle cell, and matrix metalloproteinases can degrade the collagen framework of the cap.⁹ Both of these are increased secondary to a local inflammatory response. Libby further describes local decreases in nitric oxide production within the lesion.⁵ Nitric oxide not only has a local anti-inflammatory effect,¹⁰ but it acts as a vasodilator and serves as an antiplatelet factor. Consequently, a decrease in nitric oxide can lead to local vasospasm around a potentially already narrowed lumen.

Evidence of neovascularization within the atherosclerotic plaque has also been reported.¹¹ This microvascu-

Table 2. Conditions That Lead to Imbalance Between Myocardial Perfusion and Tissue Demand

Coronary artery narrowing: nonocclusive thrombosis on an atherosclerotic plaque
Dynamic obstruction: coronary artery vasospasm, vasospasm around a preexisting plaque, microvascular dysfunction
Isolated severe narrowing: restenosis after percutaneous coronary intervention
Coronary artery dissection: acute coronary syndrome in periparturient women, post-percutaneous coronary intervention, extension of aortic dissection
Secondary unstable angina: increased demand secondary to fever, thyroid storm, anemia, hypotension, hypoxemia, tachycardia with or without underlying atherosclerosis

Adapted from Thygesen K, Alpert JS, White HD: Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525–38.

lar network initially supplies oxygen and promotes endothelial and plaque growth as a compensatory response to inflammation, but it can produce a large number of friable vessels as it grows. These vessels are more prone to hemorrhage with resulting rupture, leading to rapid destabilization and an occlusive plaque.

PRESENTATION

Many patients and medical staff are taught to recognize the typical presentation of crushing substernal chest pain as a cardinal symptom of heart disease. Unfortunately, less common symptoms of diaphoresis, jaw pain, arm pain, and dyspnea are often minimized by patients, especially when they occur in isolation. Failure to associate less common symptoms with possible ischemia has led to delay in diagnosis and treatment in many cases. In the 3783 patients evaluated by the REACT trial, there was on average a 2-hour delay in presentation, with 25% delaying evaluation by over 5 hours.³ Delayed evaluation is highest in those with multiple other chronic illnesses and elderly patients. Many patients found to have infarction present without symptoms and are clinically silent. As demonstrated by the Framingham study, as many as half of documented MIs are unrecognized by patients and are clinically silent upon evaluation.¹² Patients who present without chest pain are more likely to be women, have diabetes and/or congestive heart failure, and be of advanced age.¹³ Providers should maintain a higher level of suspicion in these populations. Unrecognized infarction, due to minimal or absent symptoms, leads to delays in appropriate medical therapy with aspirin, β blockers, heparin, and fibrinolysis and results in higher risk of mortality.

Table 3. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD Feature

	High Likelihood Any of the following:	Intermediate Likelihood Absence of high-likelihood features and presence of any of the following:	Low Likelihood Absence of high- or intermediate-likelihood features but may have:
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including myocardial infarction	Chest or left arm pain or discomfort as chief symptom Age greater than 70 yr Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate-likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5–1 mm or T-wave inversion greater than 1 mm	T-wave flattening or inversion less than 1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac troponin I, troponin T, or creatine kinase-MB	Normal	Normal

ACS = acute coronary syndrome; CAD = coronary artery disease; ECG = electrocardiogram.

Adapted with permission from Anderson J, Adams C, Antman E, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:e1–e157.

Patients with chest pain present to multiple settings, including primary care practitioners as well as the ED. The differential diagnosis for chest pain is substantial and ranges from cutaneous or musculoskeletal origins to gastrointestinal origins to life-threatening cardiac involvement. If the chest pain is thought to arise from ischemic cardiac tissue, the term *angina* can appropriately be used. Classically, stable angina manifests as a deep, poorly localized chest or arm discomfort, reproducibly precipitated by physical or emotional stress, and relieved within 5 to 15 minutes by rest and/or sublingual nitroglycerin.^{14,15} This is in contrast to UA, which is defined as angina pectoris or equivalent with the following features: (1) occurring at rest or with minimal exertion and usually lasting more than 20 minutes if not interrupted by nitroglycerin administration; (2) described as severe frank pain and of new onset; and (3) occurring with a crescendo pattern either in severity, duration, or frequency.¹⁶ Pathways for effective triage and management algorithms have been devised and implemented successfully.¹⁷

The term *anginal equivalent* may be used if a less typical symptom (eg, neck, jaw, back, arm, or shoulder discomfort, or dyspnea) has a clear relationship to physical or emotional stress or is relieved promptly with nitroglycerin.¹⁸ Anginal equivalents may be symptoms in isolation and the only symptoms present in populations such as women or the elderly.¹⁵ The most common anginal equivalent is isolated unexplained dyspnea with less common symptoms of nausea and

vomiting, diaphoresis, or fatigue, all of which present a challenge for diagnosis. Symptoms less frequently associated with ischemic chest discomfort decrease the probability of MI and are pleuritic quality chest pain, location of discomfort in lower or middle abdominal region, pain localizable with one finger, reproducible pain with palpation or position, sharp or stabbing chest pain, pain with a duration of a few seconds or less, and pain that radiates to the lower extremities (**Table 3**).^{18,19} Use of cocaine or methamphetamines should be determined early in the evaluation of the patient. While the presumed but not definitive etiology of cocaine-induced chest pain is vasospasm, there still may coexist underlying atherosclerotic disease warranting evaluation. Management involves use of benzodiazepines and, in patients with ACS, use of vasodilating agents and avoidance of selective β blockers.

RISK STRATIFICATION

In the evaluation of chest pain or angina, patients are often classified as “possible ACS” by prehospital personnel or triage nursing. This designation has been described by a guideline of the National Heart Attack Program,²⁰ which provides an algorithmic approach for the assessment of chest pain. The evaluation of patients with symptoms suggestive of ACS includes categorization of the patients into either a noncardiac diagnosis, chronic stable angina, possible ACS, or definite ACS based on symptomatology (**Figure**). The primary steps to appropriate triage of chest pain include a

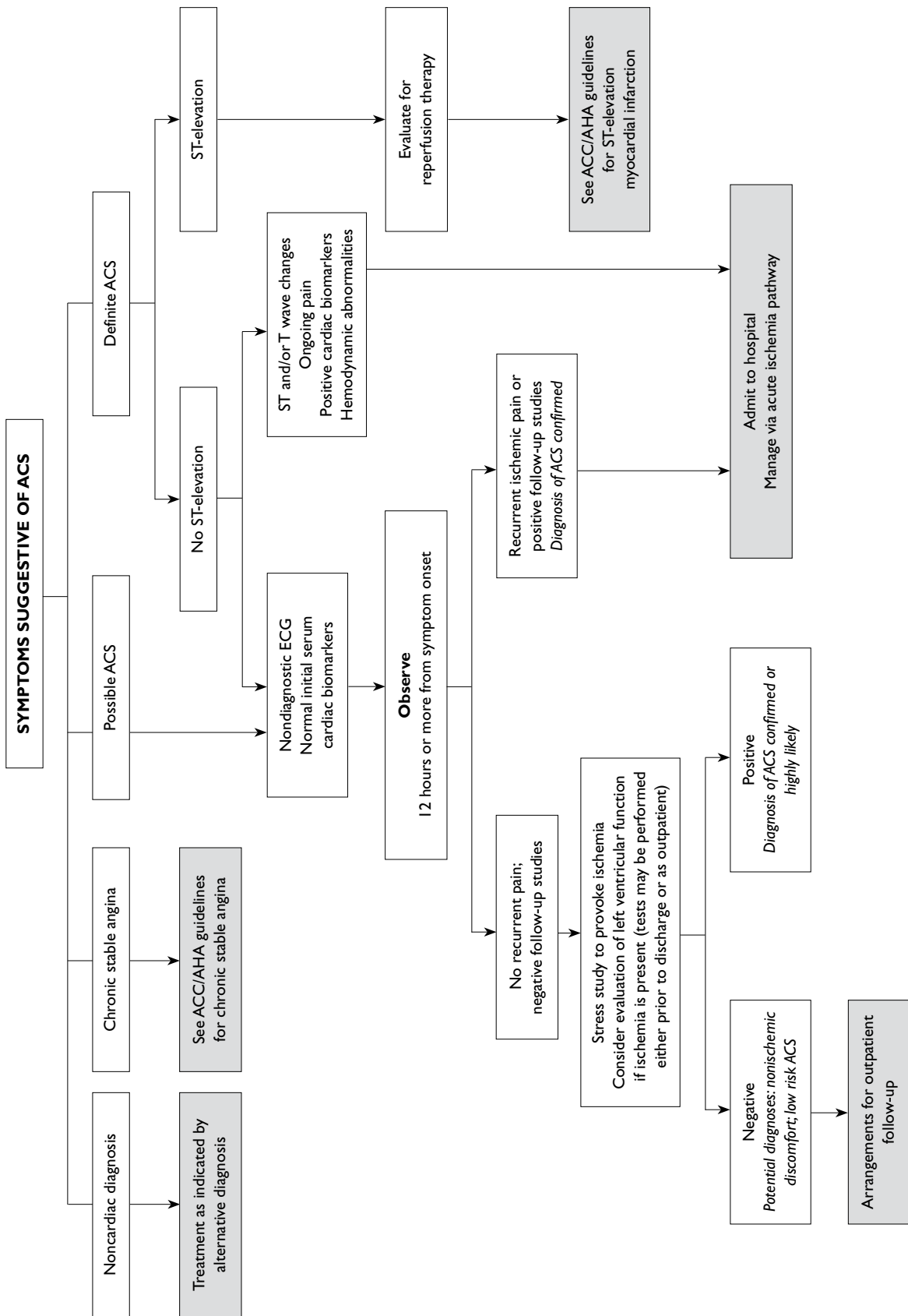


Figure. American College of Cardiology/American Heart Association (ACC/AHA) algorithm for the evaluation and management of patients with suspected acute coronary syndrome (ACS). (Adapted from Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville [MD]: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994. AHCPR publication no. 94-0602).

focused history and physical examination with an ECG evaluation within 10 minutes of arrival. Deviations of ST segment or T-wave inversion upon arrival can increase suspicion of active ischemia. STEMI requires emergent intervention and will not be discussed here. Suspected NSTEMI-ACS, which can reflect as much as two thirds of all ACS events, should be classified as possible ACS or definite ACS based on history, exam, ECG, and cardiac biomarker findings.

Risk Scores

TIMI risk score. The TIMI risk score for NSTEMI was developed after analysis of the TIMI 11B and ESSENCE trials to provide a simple method to categorize a patient's risk of death and ischemic events and provide a basis for therapeutic decision making.²¹ It comprises 7 risk indicators that can be assessed on presentation. These variables include age 65 years or older, the presence of 3 or more risk factors for coronary artery disease (early family history, as defined by infarction or sudden cardiac death in primary male relatives age less than 55 years or in primary female relatives age less than 65 years; diabetes mellitus; hypertension; hyperlipidemia; or current smoking status), prior coronary stenosis of 50% or more, 0.5-mm or greater ST-segment deviation on ECG at presentation, 2 or more angina episodes in the previous 24 hours, elevated serum cardiac markers, and the use of aspirin in the previous 7 days. A value of 1 is assigned for each variable present, and the sum score categorizes patients into a risk group. A higher TIMI risk score correlated significantly with higher rates of death and ischemic events at 2 weeks, ranging from a 4.7% risk with a score of 0 or 1 to a risk of 40.9% with a score of 6 (scores from 2 to 5 are associated with risks of 8.3%, 13.2%, 19.9%, and 26.2%, respectively).

One of the TIMI risk score variables, the use of aspirin in the previous 7 days, has been a topic of debate. It is likely that aspirin use is a marker for a larger extent of underlying vascular disease. One study found that while previous aspirin use was associated with a lower incidence of MI on presentation, it was also associated with poorer long-term outcomes compared to patients not taking aspirin.²² Patients who have ACS despite taking aspirin may not only have clinical failure but be aspirin resistant as well.

Killip class. Killip classification categorizes patients into 4 classes based on the presence or absence of physical examination findings that suggest heart failure.²³ Specifically, Killip class I patients have no evidence of heart failure. Class II patients have physical

examination findings consistent with mild to moderate heart failure with rales in the posterior lung fields, a S₃, or jugular venous distention. Class III patients have overt pulmonary edema, and class IV patients have cardiogenic shock with rales. Killip classification is well documented to predict mortality risk in patients with STEMI, and was recently found to also predict mortality rates in patients with NSTEMI at 30 days and 6 months.²⁴ Patients with left ventricular dysfunction, manifested by Killip class greater than 1, are candidates for an early invasive strategy.

GRACE registry score. GRACE is a global registry that was designed to reflect an unbiased and generalized sample of patients with ACS. This registry was used to develop a multivariable prognostic model for hospital mortality in patients with and without ST elevation ACS.²⁵ Eight independent risk factors were identified that accounted for approximately 90% of the prognostic information. The risk factors included age, Killip class, systolic blood pressure, ST-segment deviation, cardiac arrest at presentation, serum creatinine level, positive initial cardiac enzyme findings, and heart rate. A prognostic score is calculated based on points assigned to the above factors and estimates the risk of in-hospital mortality in individual patients.

ACC/AHA classification. The 2007 ACC/AHA guidelines outlined criteria that can be obtained at initial presentation to classify patients with NSTEMI as being at low, intermediate, or high short-term risk for death or nonfatal MI (Table 4).⁸ The criteria include history, character of pain, clinical features, ECG findings, and cardiac markers. A patient needs only one high-risk feature to be considered in the high-risk group, whereas a low-risk patient would not have any of the features listed in the high or intermediate groups. An intermediate risk patient would not have any of the high risk features, but would have at least 1 of the intermediate risk features present. Some criteria included are subjective; therefore, this table's purpose is to offer general guidance rather than a rigid algorithm.

TIMI risk index. The TIMI risk index (TRI) is a simple model used to predict early mortality and is based on 3 variables that have consistently been among the strongest independent prognostic factors: age, heart rate, and systolic blood pressure.²⁶

$$\text{TRI} = (\text{heart rate} \times [\text{age}/10]^2) / \text{systolic blood pressure}$$

The TRI was originally derived from and validated in clinical trials of patients with STEMI, but was also found to be strongly associated with in-hospital mortality among patients with NSTEMI.²⁷

Table 4. American College of Cardiology/American Heart Association Classification of Non-ST-Elevation Myocardial Infarction

	High Risk At least 1 of the following features must be present:	Intermediate Risk No high-risk feature, but must have 1 of the following:	Low Risk No high- or intermediate-risk feature but may have any of the following features:
History	Accelerating tempo of ischemia symptoms in preceding 48 hr	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (> 20 min) rest pain	Prolonged (> 20 min) rest angina, now resolved, with moderate to high likelihood of CAD Rest angina (> 20 min) or relieved with rest or sublingual NG Nocturnal angina New or progressive class III or IV angina in past 2 wk without prolonged (> 20 min) rest pain but with intermediate or high likelihood of CAD	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New-onset angina with onset 2 wk to 2 mo prior to presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S ₃ or new/worsening rales Hypotension, bradycardia, tachycardia, Age > 75 yr	Age > 70 yr	
Electrocardiogram	Angina at rest with transient ST-segment changes > 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression < 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged electrocardiogram
Cardiac markers	Elevated cardiac TnT or TnI or creatine kinase-MB (TnT or TnI > 0.1 ng/mL)	Slightly elevated cardiac TnT, TnI, or CK-MB (eg, TnT > 0.01 but < 0.1 ng/mL)	Normal

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CK = creatine kinase; MI = myocardial infarction; NG = nitroglycerin; TnI = troponin I; TnT = troponin T.

Adapted with permission from Anderson J, Adams C, Antman E, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:e1–e157.

Electrocardiography

The ECG is an important risk-stratification tool in patients with chest pain. In 90% of patients with ST-segment elevation of 1 mm in 2 continuous leads, myocyte necrosis is confirmed with serial cardiac biomarkers.⁸ These patients are stratified as having STEMI and to receive acute reperfusion therapy. NSTEMI/UA presents additional challenges, as ischemic changes of ST-segment depression or T-wave inversion may be transient. The ideal ECG would be one that is taken during an episode of angina or anginal equivalent and can be compared to a baseline ECG. Thrombolytic therapy is principally reserved for STEMI presentations with the exception of true posterior infarction, manifested by ST depression in 2 contiguous anterior precordial leads with or without ST elevation in posterior leads. T-wave inversion greater than 2 mm also strongly suggests acute ischemia, especially in anterior leads. The presence of ST-segment depression or inverted T waves

in 5 or more leads has been shown to be an independent predictor of mortality or infarction at 30 days.²⁸ Nonspecific ST changes (< 0.5 mm) and T-wave changes (< 2 mm) are diagnostically more challenging and should be interpreted in the context of the clinical picture. The presence of Q waves, outside of benign presence in lead III, can indicate prior infarction and may suggest significant coronary atherosclerosis.

While the ECG is a key factor in the risk stratification of patients, a normal ECG has been seen in as many as 6% of those with documented MI;²⁹ thus, a normal ECG does not rule out ischemia but does make it less likely. Serial ECG has the capability of identifying transient changes, especially when performed upon recurrence of angina or equivalent. Selected patients may benefit from evaluation of ECG leads V7 to V9, with elevation in these leads demonstrating circumflex artery occlusion, which would qualify them for immediate reperfusion therapy according to ACC/AHA guidelines.³⁰

Cardiac Isoenzymes and Biomarkers

The cardiac biomarkers are macromolecules that leak into the peripheral vasculature in response to cardiac ischemia. Measurement of these markers is widely utilized and is at the center of the diagnosis of MI. A five-fold increase is usually specified to diagnose infarction post-PCI, and a ten-fold increase is usually specified following coronary artery bypass grafting (CABG).⁸ Infarction may be suggested in the absence of positive biomarkers in patients with ST elevation, new left bundle branch block, and sudden cardiac death within 1 hour, and may be diagnosed with loss of myocardium on imaging or by postmortem pathological diagnosis. Positive cardiac biomarkers delineate the difference between UA and NSTEMI, cause changes in risk-stratification scores, and can change recommended treatment modalities.

CK-MB has a low sensitivity and specificity for MI but is utilized in the diagnosis of reinfarction and periprocedural PCI due to its relatively short half-life as compared to the cardiac troponins. The cardiac troponins, specifically troponin I and T, have a high sensitivity and specificity and are not found in healthy individuals. Several troponin I assays are commercially available, and results should be interpreted according to the reference range of the individual assay used; there is only 1 troponin T assay, and it utilizes monoclonal antibodies.³¹ Troponins can be detected in the blood between 2 and 4 hours following MI, but their appearance may be delayed as long as 8 to 12 hours. They persist for 5 to 14 days, while CK-MB often returns to normal within 2 to 3 days. The magnitude of troponin elevation has been directly correlated with mortality.³²

Myoglobin has been used as part of an early multimarker evaluation, although it is nonspecific. It is the earliest biomarker to be elevated in necrosis at less than 2 hours and has the shortest half life. Multimarker approaches are currently under investigation, including CK-MB as well as C-reactive protein (CRP) and brain natriuretic peptide (BNP). Elevated CRP, a marker of inflammation, in the absence of positive cardiac biomarkers that remains elevated after 1 month has been associated with adverse outcomes.³³ Similarly, elevation of the natriuretic peptides BNP or NT-proBNP at admission have been shown to be a marker of higher short- and long-term mortality.³⁴ The previously used biomarkers alanine transaminase, aspartate transaminase, and lactate dehydrogenase have been replaced by new markers.

MANAGEMENT AND TREATMENT MODALITIES

According to the ACC/AHA, all patients with con-

cern for cardiac ischemia should receive prompt observation, ECG, and telemetry monitoring (class I recommendations). Supplemental oxygen may be delivered and is specifically indicated if the saturations by pulse oximetry are less than 90%. Patients should also receive antiplatelet therapy with chewable aspirin³⁵ and sublingual nitroglycerin if they are still experiencing anginal discomfort, with intravenous nitroglycerin reserved for refractory discomfort. Nitroglycerin should be avoided in patients who have taken sildenafil within 24 hours or tadalafil within 48 hours due to risk of profound hypotension. Nonsteroidal anti-inflammatory drugs should be discontinued.³⁶ Morphine sulfate may also be used to relieve symptoms, unless contraindicated.

Oral β blockers should be given within 24 hours unless patients have signs of congestive heart failure, evidence of low-output states, increased risk of cardiogenic shock, or other relative contraindications. Oral β blockers are preferred over intravenous β blockade unless indicated as concomitant treatment for hypertension.³⁷ These β blocker recommendations are a notable change from prior recommendations. Nondihydropyridine calcium channel blockers (CCB) should be used if there are contraindications to β blockade in the absence of hypotension or severe left ventricular dysfunction, although short-acting nifedipine in single therapy should be avoided.³⁸ Calcium antagonists are also indicated in cocaine- and methamphetamine-associated chest pain if accompanied by ST-segment alterations or T-wave changes. Angiotensin-converting enzyme inhibitors (ACEi) should be given in those with documented ejection fractions less than 40% or those with pulmonary congestion who are not hypotensive.³⁹ Angiotensin-receptor blockers (ARB) may be used in those with ACEi intolerance.⁸ Clopidogrel load with maintenance dose should be considered in those with contraindication to aspirin as well as those proceeding to angiography. The subsequent individual treatment modalities are determined by the global presentation, which determine whether the patient is appropriate for early invasive or conservative strategy. Patients with low likelihood features should be investigated for noncardiac etiology, and patients with chronic stable angina should be treated according to the ACC/AHA 2007 guideline update.⁴⁰

Early Invasive Strategy

The early invasive strategy with prompt diagnostic coronary angiography and intent to revascularize was previously prescribed for many patients who presented with UA and is now reserved for and favored in those who fall into the definite ACS category. Patients who were initially within the conservative strategy but had

changes or positive biomarkers may switch to an invasive strategy. According to the ACC/AHA guidelines, an early invasive strategy should be pursued in stabilized patients without contraindication to procedure with elevated risk for event, typically within 48 hours. This elevated risk is seen when there is recurrent angina at rest or with low exertion, elevated cardiac biomarkers, ST depression, high-risk score, new heart failure or ejection fraction below 40%, new or worsening mitral regurgitation, hemodynamic instability, high-risk results from stress evaluation, sustained ventricular tachycardia, prior PCI in 6 months, or history of CABG.⁸

The combination of aspirin therapy, additional antiplatelet therapy, and anticoagulant therapy is indicated in early invasive patients. In this group, anticoagulant therapy should be added with enoxaparin or unfractionated heparin (UFH) with higher level of evidence (1A) over bivalirudin and fondaparinux (1B), though fondaparinux is preferred in patients with risk of bleeding. Ease of use and lower risk of heparin-induced thrombocytopenia favor the use of a low-molecular-weight heparin (LMWH), such as enoxaparin or fondaparinux.⁴¹ It should be noted that the pharmacodynamics of enoxaparin dictate that a 30-mg intravenous loading dose should be coadministered with the first 1 mg/kg subcutaneous dose in those under age 75 years and 0.75 mg/kg without bolus in those older than 75 years. An increased risk of bleeding has been associated with switching from LMWH and UFH and has increased mortality. Prior to angiography, initiation of clopidogrel, glycoprotein IIb/IIIa inhibitor, or both is recommended, with both favored in patients with delay to angiography, high-risk features, or early recurrent ischemic symptoms. Abciximab is indicated if there is no delay in angiography; otherwise eptifibatid or tiroban are preferred as IIb/IIIa inhibitors. There should be dose adjustment of IIb/IIIa inhibitors in the elderly and those with renal impairment as this is a common underdiagnosed cause of increased bleeding and subsequent poor outcomes.⁴² Initiation of clopidogrel is supported with a loading dose of 300 to 600 mg and 75 mg thereafter; however, due to its lasting effects, there is an increased risk of bleeding in patients who subsequently require CABG within 5 days of last dose.⁴³ In many institutions, clopidogrel is not initiated until necessity of immediate CABG is ruled out, and if PCI is needed, the load may be administered within the catheterization laboratory.

Conservative Therapy

The conservative therapy of repeated ECG and serial biomarker with plans to optimize medical therapy and consider noninvasive stress exam is the preferred

route for patients with low probability of ACS. This may also be optimal according to patient preference and in women with low-risk features on presentation. Patients with negative biomarkers who had initial possible ACS presentation should undergo an appropriate exercise or pharmacologic stress evaluation. Measurement of BNP or NT-pro-BNP may be done to further assess global risk. Much of the medical therapy for the conservative therapy arm is the same as above except for the initiation of GP IIb/IIIa inhibitors, where there is a 1B recommendation of its implementation in conservative treatment as compared to the 1A recommendation in the early invasive group, and anticoagulation therapy, where bivalirudin is not included. The primary benefit from the implementation of IIb/IIIa inhibitors is seen in patients who have positive biomarkers. The CURE trial demonstrated that additional antiplatelet therapy with clopidogrel in addition to aspirin should be used on admission if a noninvasive approach is taken.⁴⁴ Final duration has not been completely determined, although beneficial effects have been seen at 9 months and 1 year within the trial. Maintenance of clopidogrel for at least 1 month, and ideally up to 1 year, is recommended once implemented.

Imaging and Stress Testing

Early echocardiography to evaluate for new reduced ejection fraction or ejection fraction below 40% should be done. Medical management should be pursued and optimized while awaiting stress evaluation. The ACC/AHA recommends that patients with normal biomarkers and ECG can undergo noninvasive coronary imaging with coronary CT angiography (CCTA) as a reasonable alternative to stress evaluation.⁸ The high negative predictive value of a CCTA supports its use because if no plaque is found, calcified or noncalcified, then there is a very high likelihood that the patient's symptoms are not related to atherosclerosis.⁴⁵ The notable limitation with the use of this imaging modality is that while it provides highly detailed angiographic anatomy, it provides no functional information nor does it characterize microvascular dysfunction. Cardiac magnetic resonance is able to assess both structure and function and is quickly becoming a more utilized technology in those without contraindications. Both CCTA and MRI have limited use within the chronic kidney disease population. The choice of stress test is based on the technologies available, ECG findings, and ability to exercise. Exercise stress testing is favored in those who are able to exercise and are free from baseline ST-segment abnormalities, bundle branch block, left ventricular hypertrophy, paced rhythm, intraventricular conduction abnormalities, preexcitation, and digoxin

affect.⁸ Pharmacologic stress test should be performed when exercise stress test cannot be performed, although this approach also has limitations: increased arrhythmias are associated with dobutamine use, and caution must be used in patients with left main disease. Cocaine- and methamphetamine-associated chest pain without ST-segment or T-wave changes and negative stress test and biomarkers does not routinely require angiography.

Other Medical Management

In all patients, short-term medical management should be optimized with attention to fasting lipid profile, aspirin prophylaxis, β blockade, and addition of ACEi in those with prior MI prior to disposition. An HMG-CoA reductase inhibitor, or statin, should be given regardless of baseline low-density lipoprotein cholesterol level. As left ventricular function is related to prognosis, evaluation should be performed in all patients with documented ischemia. Diagnostic angiography is indicated in patients with ejection fractions less than 40%. Those who received angioplasty require specific therapy based on the type of stent placed. Bare metal stent recipients should receive lifelong aspirin (162 mg to 325 mg for 1 month and 75 mg to 162 mg thereafter) and at least 1 month of clopidogrel therapy and preferably 1 year. In patients who have received a drug-eluting stent, lifelong aspirin is indicated (162 mg to 325 mg for 3 to 6 months and 75 mg to 162 mg thereafter) along with clopidogrel for at least 1 year.⁴⁶ Current drug-eluting stents are trade named Cypher (a sirolimus-eluting stent), Taxus (a group of paclitaxel-eluting stents), Xience (an everolimus-eluting stent), and Endeavor (the most recent, a zotarolimus-eluting stent). Long-term medical management optimization should be an integral part of any discharge planning, and specific goals of blood pressure reduction less than 130/80 mm/Hg and tobacco cessation should be achieved.⁸

DISPOSITION

Once patients are evaluated within a clinical setting, usually an ED, and ECG and serum biomarkers are evaluated, disposition may be considered. Those appropriate for early invasive therapy may go directly to coronary angiography; otherwise, admission to an inpatient coronary care unit or telemetry step down unit should be pursued. Patients in the conservative strategy group can either be admitted to a telemetry unit or managed within a hospitalized observational status or a chest pain unit based on the discretion of the physician and risk assessment. Often chest pain units are a section of an existing ED, and the American College of Emergency Physicians has

published guidelines for monitoring the outcomes of such units.⁴⁷ Using predetermined algorithms for serial cardiac biomarker evaluation and stress evaluation if indicated, these units offer a substantial cost-saving mechanism to medical settings where there is a high prevalence of admissions for low-risk “rule out MI.”⁴⁸ While in observational status, patients may be admitted to a classical coronary care unit setting for management if they develop recurrent angina, ECG changes, or positive biomarkers. Those with low-risk characteristics without transient ST-segment depressions (≥ 0.5 mm) or T-wave inversions (≥ 2 mm), without positive cardiac biomarkers, and with a negative stress exam or CCTA may be discharged and treated as an outpatient.⁸ At sites where stress testing is not readily available, patients with low-risk profiles may undergo outpatient stress evaluation in a timely fashion after presentation; these patients are discharged with anti-ischemic agents such as nitroglycerin and β blockers and are instructed on their use. The individual’s primary care provider should be notified of the evaluation and all results obtained, and follow-up evaluation should be arranged, if possible. Outpatient follow up with goals of lifestyle modifications including diet, exercise, smoking cessation, and medical compliance should be emphasized to all patients discharged following a chest pain evaluation. Patients with documented infarcts should be referred to outpatient cardiac rehabilitation when available, as this can lead to improved long-term functional capability.

Case Conclusion

Presenting with a classical Levine’s sign,⁴⁹ or clenched fist over mid sternum as a physical descriptor of chest pain, this patient has concerning features for ischemia. She presented with accelerating angina and associated dyspnea with risk factors of hypertension, tobacco use, and advanced age. She also had reproducible chest pain, which is typically not associated with ischemia, but with the preexisting musculoskeletal pain disorder fibromyalgia the possibility of ongoing ischemia cannot be excluded. Documented T-wave inversions greater than 0.5 mm are concerning for ischemia and should be considered new in the absence of prior ECG for comparison. For risk stratification, she would receive a TIMI risk score of 5 (points for age, 3 risk factors, angina, aspirin use prior to presentation, and ECG changes). This score imparts a 26% chance of all-cause mortality, MI, and severe recurrent ischemia prompting urgent revascularization within 2 weeks. This patient should be triaged into the early invasive strategy as she has a high TIMI score and high-risk features by the ACC/AHA classification.

Prompt cardiology consultation should be pursued with administration of at least 162 mg of chewable aspirin, or clopidogrel if allergic, and proper administration of anticoagulation with UFH or LMWH. Therapy to alleviate chest pain should be initiated with nitrates, provided there is no evidence of inferior infarct, and narcotics. Oral β blockers should be administered, with intravenous administration reserved for overlapping acute management of hypertension. Clopidogrel load and GPIIb/IIIa inhibitors should be started if catheterization facilities are not readily available. The patient should be dispositioned to the catheterization laboratory, a coronary care unit, or a telemetry unit based on the discretion of the consulting cardiologist.

HP

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