Chapter 51: Low-Probability Acute Coronary Syndrome

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INTRODUCTION AND EPIDEMIOLOGY

This chapter discusses the features of *low-probability or possible acute coronary syndrome (ACS)*, which includes patients who have chest pain or another equivalent ischemic symptom but no objective evidence of acute coronary ischemia or infarction—that is, no characteristic ECG ST-segment elevation or depression and normal levels of cardiac markers. Patients with diagnostic ECG or cardiac marker levels or with other high-risk features are discussed in chapter 49, "Acute Coronary Syndromes."

Of ED patients with undifferentiated chest pain, 7% will have ECG findings consistent with acute ischemia or infarction, and 6% to 10% of those in whom cardiac markers are ordered will have initially positive results.[1] The remaining patients who do not have diagnostic ECG changes or initially positive cardiac marker results have *low-probability* or *possible ACS*. The evaluation of those with possible or actual ACS costs approximately $10 billion to $12 billion each year in the United States.[2]

Of all patients with *possible ACS*, 5% to 15% ultimately prove to have ACS.[3] The rate of discharge from the ED for patients with ACS remains approximately 4%. Patients with ACS who are discharged home from the ED have worse clinical outcomes and higher mortality compared with patients who are initially hospitalized. The clinical data readily available to the emergency physician, such as historical features, examination findings, and ECG results, cannot exclude ACS among most patients, because 3% to 6% of patients thought to have noncardiac chest pain or a clear-cut alternative diagnosis will have a short-term adverse cardiac event.[4,5] Therefore, most patients with *possible ACS* undergo further observation and testing.

PATHOPHYSIOLOGY

ACS is a constellation of signs and symptoms resulting from an imbalance of myocardial oxygen supply and demand. There are three general ACS classifications: unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Unstable angina is a type of ACS with no elevation of biomarkers and no pathologic ST-segment elevation, resulting in ischemia but not infarction. Acute myocardial infarction (AMI) occurs when myocardial tissue is devoid of oxygen and substrate for a sufficient period of time to cause myocyte death. NSTEMI is characterized by biomarker elevation and no pathologic ST-segment elevation. STEMI is characterized by ST-segment elevation and biomarker elevation (STEMI), although biomarker elevation is not required at onset to make this diagnosis. Detailed discussion is in chapter 49.

The distinction between NSTEMI and unstable angina is based on elevated cardiac markers of necrosis in the case of NSTEMI. Troponin I and troponin T are the most specific cardiac markers of cell injury or death available. These biomarkers may not reach detectable thresholds for up to 6 hours after infarction. Patients presenting soon after infarction may have normal biomarker results and initially be categorized as having *possible ACS*. Patients with evolving

myocardial infarctions represent approximately 4% of patients undergoing serial cardiac markers and generally have other high-risk features of ACS such as ST-segment depression.[6,7]

CLINICAL FEATURES

HISTORY AND COMORBIDITIES

The history is one tool to help assess patients with suspected or possible ACS but cannot be used to exclude ACS. Obtain detailed information, including symptom quality, location, duration, severity, associated symptoms, precipitating and relieving factors, and similarity to prior episodes. Consider other noncardiac but life-threatening causes of chest pain (see Tables 48–3 and 48–4 in chapter "Chest Pain").

Among patients with possible ACS, historical features can be categorized as low risk, probable low risk, probable high risk, and high risk. **However, even patients with low-risk features or in a low-risk category have a residual risk of ACS.**[8] Lowest risk features include pleuritic, positional, reproducible, or sharp/stabbing pain. Another low-risk feature is pain that is not exertional or located in a small inframammary area. Higher risk features include chest pressure (positive likelihood ratio [LR+] 1.3), pain similar to or worse than prior cardiac pain (LR+ 1.8), and associated nausea/vomiting or diaphoresis (LR+ 1.9 and 2.0, respectively). The highest risk features include radiation to the right arm or shoulder (LR+ 4.7), left arm (LR+ 2.3), or both arms or shoulders (LR+ 4.1), and exertional chest pain (LR+ 2.4).

Traditional cardiac risk factors, such as hypertension, diabetes mellitus, tobacco use, family history of coronary artery disease (CAD) at an early age, and hypercholesterolemia, are modestly predictive of the presence of CAD in asymptomatic patients. In acute decision making, **cardiac risk factors are poor predictors of cardiac risk for myocardial infarction or other ACS**.[9] CAD is rare in patients <30 years old, but possible and usually accompanied by other risk(s).

Although a true alternative diagnosis decreases the likelihood of ACS, many patients with ACS are mistakenly diagnosed with gastric reflux or musculoskeletal pain.[5] Clinical response to treatment with antacids (18% to 45% of ACS patients have relief of pain with antacids), viscous lidocaine, or nonsteroidal anti-inflammatory medications cannot exclude ACS. Lack of pain relief with nitroglycerin is similarly unreliable, because 65% of patients with an ACS in one study failed to have relief of pain.

Prior cardiac testing (previous ECG tracings, echocardiograms, cardiac catheterization reports, and stress testing reports) aids the ED evaluation. ECG changes offer strong bedside evidence of new disease. Recent cardiac catheterization reports are especially useful, because a truly negative (defined as no luminal irregularities) result is associated with a very low incidence of subsequent infarction or ACS in the next 2 years. Although a prior positive stress test increases the likelihood of a subsequent acute cardiac event,[10] a prior negative stress test provides little reassurance that a current chest pain event is benign. Patients with a recent negative evaluation for ACS that included objective cardiac testing (mostly stress testing) have a 6-month incidence of ACS as high as 14%. Furthermore, patients with a prior negative stress test have a similar incidence of ACS compared with those with no prior stress testing when presenting with chest pain to the ED.[11] Overall, previous stress test results add evidence but cannot confirm disease presence or absence.

PHYSICAL EXAMINATION

Usually, the exam in the low-risk or possible ACS patient seeks complications or alternative causes of the symptoms. When an alternate diagnosis is not clear, the physical examination alone cannot distinguish between those with and without ACS. However, pay special attention to examination findings that make ACS more or less likely. High-risk features on physical examination are uncommon and include signs of cardiac failure such as hypotension, diaphoresis,

pulmonary rales, jugular venous distention, new mitral regurgitation, bradycardia, tachycardia, and an S_3 cardiac gallop.[12] Cardiac rate abnormalities are also a high-risk feature, including either bradycardia (seen with ischemia, especially in the inferior myocardium, or infarction that has led to disturbance of the conduction system) or tachycardia (may signify pump failure, pain, or stress, or could be a clue to an alternative diagnosis such as pulmonary embolism). Positional changes in the pain severity can be easily assessed at the bedside and may suggest pericarditis or another pleural-based syndrome as a cause of pain.

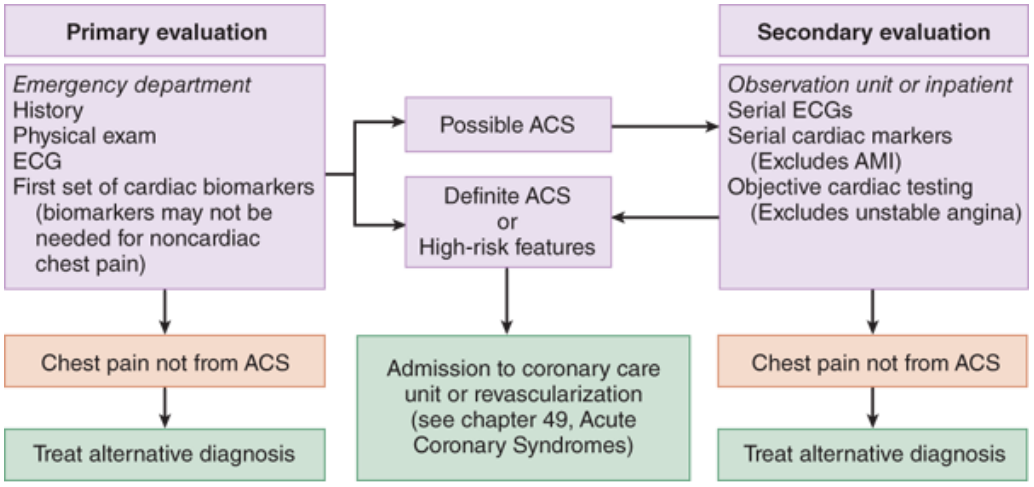
CARDINAL FEATURES

The classic patient with possible ACS has chest pain or another symptom (weakness, dyspnea, other upper body pain), no clear alternative cause, and no clear evidence of cardiac injury or stress on ECG and biomarker tests. **In this group, the likelihood of ACS is >2% but still low, making the diagnosis of *possible ACS***.

DIAGNOSIS

The diagnostic process is conceptually split into a primary and secondary evaluation (**Figure 51–1**).

FIGURE 51–1.
Evaluation process for patients with possible acute coronary syndrome (ACS). AMI = acute myocardial infarction



PRIMARY EVALUATION

The goal during the primary evaluation is to distinguish patients with definite ACS from those with possible ACS and those with symptoms that are definitely not from ACS. This process involves gathering information from the history, physical examination, ECG, chest radiography, and medical record. This information is used to produce an initial risk assessment that guides the subsequent laboratory testing and initial treatment.

ECG

For adult patients with chest pain in whom cardiac causes are possible, obtain a 12-lead ECG rapidly[12,13] and compare to any previous tracings. Patients with ST-segment elevation, a new left bundle-branch block, or ST-segment depression have an ACS and are treated as outlined in chapter 49. Between 1% and 6% of patients with a normal ECG will ultimately prove to have NSTEMI, and at least another 4% will prove to have unstable angina.[12] Obtaining follow-up ECG(s) in patients with ongoing or worsening symptoms helps detect changes diagnostic of ACS, or it can show

reversal of previous ST-segment or T-wave changes thought to be old—both define *dynamic changes* and the high likelihood of ACS. In the setting of dynamic ECG changes, incidence of CAD is 84% with classic anginal symptoms and 8% with nonclassic anginal symptoms as assessed by coronary angiography.[14]

CHEST RADIOGRAPH

Chest radiography provides additional cardiovascular information, including cardiac silhouette size, pulmonary edema, and aortic contour. Additional causes of chest pain, such as pneumothorax, bony metastasis, rib fracture, and pneumonia, may also be detected on chest radiography. Patients presenting with anterior chest pain have findings on chest radiography that influence management 14% of the time.

RISK ASSESSMENT

The goal of early decision making is to determine if the patient actually belongs in the *possible ACS* cohort and is at high enough risk to warrant cardiac testing. All available data are used to create a composite picture for decision making. **Some posit that when the pretest probability of ACS is ≤2%, further testing is not indicated[15]; others have suggested a threshold of <1% to stop testing.[16] Detecting patients with a zero chance of any ACS in the presence of ACS-like symptoms is virtually impossible**.

Most computer algorithms, risk scores, and clinical decision rules have been unsuccessful at identifying a very-low-risk (<2%) cohort that does not require further testing. The HEART score is one tool that identifies low-risk patients who are eligible for evaluation and possible early discharge home from the ED (**Table 51–1**). Large-scale validation data are lacking, although current evidence suggests that patients with a HEART score of 0 to 3 have a 1% to 2% risk for major adverse cardiac events within 6 weeks of presentation.[17,18]

Table 51–1

The HEART Score

	Points
History	
Highly suspicious	2
Moderately suspicious	1
Slightly suspicious	0
ECG	
Significant ST-segment depression	2
Nonspecific repolarization abnormality	1
Normal	0
Age	
≥65	2
45–65	1
≤45	0
Risk factors*	
3 or more risk factors	2
1–2 risk factors	1
No risk factors	0
Troponin	
≥3 × normal limit	2
1–3 × normal limit	1
≤ normal limit	0
Total	

Low risk = 0–3, high risk ≥4.

*

Risk factors include currently treated diabetes mellitus, current or recent (<90 days) smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of coronary artery disease, obesity (body mass index >30), or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease).

The Heart Pathway involves using the HEART score with the addition of a 4- to 6-hour repeat troponin to increase the sensitivity for major adverse cardiac events.[19] Preliminary data note 100% sensitivity for major adverse cardiac events while decreasing the amount of index visit cardiac testing (CT or stress imaging).

The Accelerated Diagnostic Protocol uses Thrombolysis in Acute Myocardial Infarction (TIMI) study[20] risk scores and ED testing to stratify risk (**Table 51–2**). Patients with ACS-consistent pain, a Thrombolysis in Acute Myocardial Infarction score of 0, no new ischemic changes on ECG, and negative troponins at 0 and 2 hours have a very low risk of subsequent cardiac events and may be discharged. In a prospective observational study, the Accelerated Diagnostic Protocol was 99.7% sensitive (95% confidence interval [CI] 98.1% to 99.9%) for major adverse cardiac events at 30 days.[21] A subsequent randomized trial demonstrated that 19.3% of patients were discharged within 6 hours using the Accelerated Diagnostic Protocol compared to 11.0% of control group patients (P = 0.008), and 1.9% (95% CI 0% to 10%) of patients had a major adverse cardiac event in 30 days.[22] This method also needs wider impact testing to determine safety and utility before mainstream implementation.

Table 51–2

Thrombolysis in Acute Myocardial Infarction Score

Age ≥65 years?
≥3 Risk factors for coronary artery disease (CAD)?*
Known CAD (stenosis ≥50%)?
Aspirin use in last 7 d?
Severe angina (≥2 episodes in last 24 h)?
ST changes ≥0.5 mm?
Positive cardiac marker?

*

Calculate total score giving 1 point for each positive answer.

Risk factors for CAD include diabetes, cigarette smoking, hypertension (≥140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein cholesterol (<40 mg/dL), family history of premature CAD (CAD in male first-degree relative age <55, or female first-degree relative <65).

When risk-stratifying patients with possible ACS, be wary of overconfidence in an alternative diagnosis, because the rate of ACS is as high as 4% among patients with chest pain and a "clear-cut" noncardiac alternative diagnosis.[5] Reserve determinations of noncardiac chest pain to patients with a very low likelihood of coronary disease (<1%) and clear evidence of an alternative diagnosis or with atypical historical features. The rest of patients with ACS-consistent symptoms should have further testing.

After determination that the patient is appropriately categorized as possible ACS, further stratification occurs (**Table 51–3**).[12,13,23] Patients in category I (AMI) and category II (probable acute ischemia) are discussed in chapter 49. Patients in category III (possible ischemia) and IV (probably not ischemia or stable angina pectoris) undergo primary and secondary assessments as detailed below.

Table 51–3

Prognosis-Based Classification System for ED Chest Pain Patients*

I. Acute myocardial infarction: immediate revascularization candidate
II. Probable acute ischemia: high risk for adverse events (any of the following): Evidence of clinical instability (i.e., pulmonary edema, hypotension, arrhythmia, transient mitral regurgitation murmur, diaphoresis) Ongoing pain thought to be ischemic (consider chest pain or discomfort as chief symptom, reproducing documented angina, or pain in setting of known coronary artery disease, including myocardial infarction) Pain at rest associated with ischemic ECG changes (consider new, or presumably new, transient, ST-segment deviation, 1 mm or greater, or T-wave inversion in multiple precordial leads) One or more positive myocardial marker measurements Positive perfusion imaging study
III. Possible acute ischemia: intermediate risk for adverse events. History suggestive of ischemia with absence of high-risk features, and any of the following: Rest pain, now resolved New onset of pain Crescendo pattern of pain Ischemic pattern on ECG not associated with pain (may include ST-segment depression <1 mm or T-wave inversion >1 mm)
IV. Possible acute ischemia: low risk for adverse events. Requires all of the following: History not strongly suggestive of ischemia ECG normal, unchanged from previous, or nonspecific changes Negative myocardial marker measurement *or (requires all of the following)* >2 wk of unchanged symptom pattern or long-standing symptoms with only mild change in exertional pain threshold ECG normal, unchanged from previous, or nonspecific changes Negative initial myocardial marker measurement
V. Definitely not ischemia: very low risk for adverse events. Requires all of the following: Clear objective evidence of nonischemic symptom etiology ECG normal, unchanged from previous, or nonspecific changes Negative initial myocardial marker measurement† *or* Unstructured clinician estimate of acute coronary syndrome ≤2%

*

Authors' analyses from multiple sources.[12,13,23]

†

Literature not conclusive.

CARDIAC MARKERS

Laboratory testing during the primary evaluation focuses on two goals: detecting myocardial cellular necrosis and excluding alternative causes of chest pain. Usual testing includes a CBC, serum electrolytes with renal function, and serum cardiac markers. Other testing is guided by the history and physical examination.

Serum markers of necrosis are used to diagnose AMI. AMI is one component of ACS, which also includes unstable angina. The difference between these two clinical syndromes is the presence of myocardial necrosis. **Thus, although serum markers performed over a period of time can exclude AMI, they cannot exclude unstable angina**.

See chapter 48, "Chest Pain" for an introduction to the use of cardiac markers for the diagnosis of myocardial infarction. In that chapter, Figure 48-1 shows the typical pattern of serum marker elevation after AMI, and Table 48-5 lists conditions associated with elevation of troponin. The unique release kinetics of each marker should be evaluated in the context of the patient's time of symptom onset, compared with the time of presentation. **Patients with positive troponin results *have* ACS**.

Other markers such as C-reactive protein, ischemia-modified albumin, myeloperoxidase, and B-type natriuretic peptide are not robust enough for incorporation into standard ED decision making.

Single-Marker Measurement

Although single-sample normal myocardial marker measurements cannot exclude the diagnosis of AMI in the ED, very-low-risk (Table 51–3) patients may benefit from at least one myocardial marker measurement before discharge, especially if pain is present and unremitting for >6 hours. This area is evolving with the introduction of higher sensitivity troponin assays.

Change in Marker Measurements

In AMI, the initial CK-MB measurement obtained is elevated in about 30% to 50% of patients. Seeking a change in values, referred to as the *delta CK-MB* (ΔCK-MB), helps detect ACS even if threshold positive values are not reached.[24] ΔCK-MB also outperforms Δ myoglobin for early AMI diagnosis. The same principle can be applied with serial measurements of troponin.

SECONDARY EVALUATION

RISK REASSESSMENT

Patient risk is reevaluated as results from diagnostic tests become available. At the beginning of the secondary evaluation, review the results of the initial and any subsequent ECGs and cardiac markers, chest radiography, and previous cardiac evaluations. After data collection, stratify patients into one of five classifications (Table 51–3).

THE DIAGNOSTIC PLAN

Base the diagnostic plan for patients with possible ACS after the primary evaluation on the clinical data and the available resources at each facility. This may include inpatient secondary testing, hospital-based observation testing, or ED-based observation testing. Once ACS is determined to be present or likely, admission and care by an internist or cardiologist are started.

Serial Marker Approach

Patients with possible ACS require serial serum markers to detect necrosis. The purpose of serial markers is twofold. First, evidence of myocardial necrosis confirms the diagnosis of ACS and should change treatment. Second, the presence of necrosis places the patient at higher risk for an adverse event during provocative cardiac testing. Most facilities use a traditional protocol for serial marker timing, whereas some use an accelerated testing protocol in concert with early myocardial imaging. Traditional testing protocols for patients with possible ACS involve obtaining serial troponin and/or serial creatine kinase and CK-MB at presentation and after 6 hours of observation. Accelerated protocols may have similar efficacy. ΔCK-MB measurements over a 2-hour period have 93% sensitivity for AMI.[24] Similarly, changes in myoglobin over 90 minutes when used with troponin results may also have high sensitivity.[25] However, given the imperfect sensitivity and inability to exclude unstable angina, accelerated cardiac marker protocols are not the sole determination to exclude ACS but are used in combination with cardiac imaging.

INDICATIONS FOR ADVANCED CARDIAC TESTING

Normal serial ECGs and myocardial marker measurements reduce the likelihood of AMI but do not exclude unstable angina, which still puts the patient at high risk for a subsequent adverse cardiac event. Therefore, patients with possible ACS should undergo some form of direct cardiac testing to evaluate coronary anatomy, cardiac function, or both. Common modalities used include stress electrocardiography, stress echocardiography, resting and/or stress nuclear medicine testing, stress cardiac MRI, and CT coronary angiography (CTCA).

Advanced cardiac testing is performed after normal biomarkers are present and no clear ischemic ECG changes exist; this happens either as an inpatient or during an observation unit stay, with the latter being less expensive. Another option proffered by the American College of Cardiology/American Heart Association guidelines is to do the advanced testing as an outpatient and within 72 hours of ED discharge if patients are at low risk for ACS, are pain free without recurrent symptoms, have no evidence of ischemia on their ECG, and have normal serial cardiac markers over 6 to 8 hours.[12] This latter approach simply uses the ED stay as the observational interval.

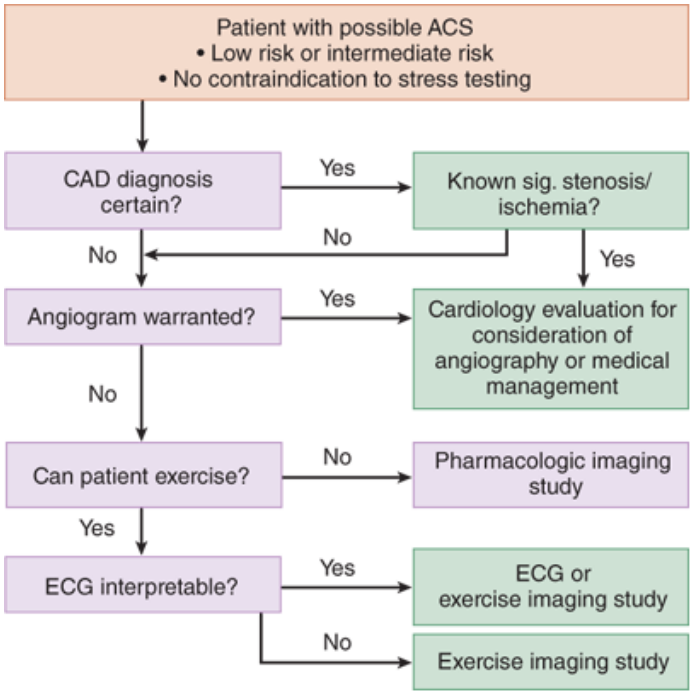
Available data suggest that low-risk patients may safely undergo immediate stress testing. One center performed over 3000 immediate exercise stress tests in low-risk patients who had at least one negative serum cardiac marker, noting no adverse events.[26]

CARDIAC TESTING MODALITIES

ECG-Based Exercise Treadmill Testing

The accuracy of ED stress testing is particularly difficult to quantify, because test sensitivity and specificity are greatly influenced by characteristics of the population being tested. As the pretest probability of CAD increases, the likelihood of a false-negative test also increases. Conversely, when a population with a very low pretest probability of disease is tested, the likelihood of a false-positive result increases. **Based on current data, diagnostic stress testing is recommended for patients with a low to moderate pretest probability of CAD but is unlikely to be helpful in those at very low risk or at high risk**. Guidelines to assist with stress test selection are summarized in **Figure 51–2**.[27]

FIGURE 51–2.
Stress testing decision making for patients with possible acute coronary syndrome (ACS). CAD = coronary artery disease; sig = significant.



ECG-based exercise treadmill testing is commonly used for patients without known coronary disease who are placed in an observation unit. Subjects exercise, most commonly on a treadmill, until a predetermined percentage of predicted maximum heart rate or other end points are reached. The most commonly used definition of a positive exercise test result from an ECG standpoint is ≥1 mm of horizontal or downsloping ST-segment depression or elevation for at least 60 to 80 milliseconds after the end of the QRS complex; ST-segment elevation is not sought because it defines acute ischemia.

Sensitivity of exercise treadmill testing depends on the risk and severity of disease of the patient population to which it is applied. Meta-analysis of 24,000 patient encounters notes that the sensitivity and specificity for significant coronary disease are 68% and 77%, respectively.[27] Advantages of exercise treadmill testing are low cost, wide availability, and short test performance time. Exercise stress testing is contraindicated for various reasons (**Table 51–4**).[27] Exercise testing may not be safe for patients at high risk for acute ischemia or those with other uncontrolled cardiovascular or pulmonary pathologies. Furthermore, patients with an abnormal baseline ECG, such as those with left ventricular hypertrophy, bundle-branch block, or digoxin effect, are less likely to benefit from standard exercise testing due to difficulties in interpretation of exercise-induced ECG changes.

Table 51–4

Contraindications to Exercise Testing

Absolute
Acute myocardial infarction (within 2 d)
High-risk unstable angina
Uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise
Symptomatic severe aortic stenosis
Uncontrolled symptomatic heart failure
Acute pulmonary embolus or pulmonary infarction
Acute myocarditis or pericarditis
Acute aortic dissection
Relative*
Left main coronary stenosis
Moderate stenotic valvular heart disease
Electrolyte abnormalities
Severe arterial hypertension (>200 mm Hg systolic, >110 mm Hg diastolic)
Tachydysrhythmias or bradydysrhythmias
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Mental or physical impairment leading to inability to exercise adequately
High-degree atrioventricular block

*
Relative contraindications can be superseded if the benefits of exercise outweigh the risks.

Echocardiography

Echocardiography to evaluate wall motion at rest and while under stress (either exercise or pharmacologically induced) is widely used in patients with possible ACS. Advantages of stress echocardiography over exercise treadmill testing are improved accuracy for coronary disease and nondependence on the ECG. Compared with other cardiac imaging techniques, echocardiography is noninvasive, delivers no ionizing radiation, and provides information on myocardial function.

Detection of wall-thickening abnormalities defines acute ischemia; this is dependent on imaging technique and interpretative skills, with up to 10% of tests being technically inadequate. The echocardiogram cannot distinguish between myocardial ischemia and acute infarction, cannot reliably detect subendocardial ischemia, and may be falsely interpreted as positive in the presence of several conditions (notably conduction disturbances, volume overload, heart surgery, or trauma). Timing of the test relative to the onset of symptoms is critical, because transient wall motion abnormalities may resolve within minutes of an ischemic episode. Resting echocardiography within 12 hours of ED arrival does not provide additional predictive value for myocardial infarction over myocardial markers alone. **Thus, a normal resting echocardiogram in the ED cannot exclude ACS, although it lowers the likelihood**.

Stress echocardiography combines a standard ECG stress test with cardiac imaging at rest and after exercise or pharmacologically induced tachycardia. Overall, stress echocardiography is 80% sensitive and 84% specific for significant coronary disease, superior to ECG-based stress testing. In low-risk ED patients, three studies have reported

negative predictive values for subsequent cardiac events to be 97% to 100%, comparable to that of stress testing using nuclear imaging techniques.

Nuclear Medicine

Nuclear medicine techniques use an IV-injected radioactive tracer. Local myocardial uptake and images depend on regional coronary flow and myocardial cell integrity. Tracer uptake occurs in direct proportion to regional myocardial blood flow.

Thallium-201 has been in use longest and is rapidly redistributed after initial uptake. The image generated after thallium injection represents blood flow at the moment of imaging. Areas of positive uptake reflect adequate coronary flow and viable myocardium, whereas areas without uptake represent infarcted or ischemic myocardium. On repeat imaging several hours later, continued lack of perfusion ("irreversible defect") indicates an area of infarction, and tracer uptake only on delayed images ("reversible defect") represents ischemic but not infarcted myocardium. Combined with conventional ECG-based stress testing, thallium imaging offers improved sensitivity and specificity for detection of significant CAD over ECG-based testing alone, and it is not hampered by baseline ECG abnormalities. Thallium-based imaging must be performed soon after injection, making it impractical for use in patients with ongoing chest pain. Also, the long half-life requires a lower injected dose to avoid excessive radiation exposure. This may impair imaging and create false-negative and false-positive results, especially in women and obese patients. Due to these limitations and the lack of ED-based outcome studies, thallium-201 imaging alone is not an ideal agent for use in the ED.

Myocardial perfusion imaging using technetium-99m (^{99m}Tc)-labeled agents such as **sestamibi** offers advantages over thallium for ED use. Because the half-life of ^{99m}Tc is much shorter than that of thallium (6 vs 73 hours), a larger dose is possible without harm to the patient. This produces superior image quality, decreased tissue attenuation–related artifacts, and higher ACS detection specificity for sestamibi imaging. In contrast to thallium, ^{99m}Tc is stable for several hours, allowing accurate imaging up to 3 hours after injection; the image represents the blood flow at the moment of injection. By using "gated" image acquisition technology, sestamibi scanning also estimates ejection fraction. As with thallium, resting and stress (exercise or pharmacologic) images can be compared to yield additional data.

Perfusion sestamibi imaging of patients *with current or recent* (within 30 minutes of injection) *pain* and no cardiac ischemia on ECG and biomarker analysis is very sensitive in detecting physiologic ischemia; a negative test would allow discharge to home. This latter approach requires broader study but is promising in select patients.

Dual-isotope stress testing using thallium and sestamibi is an increasingly common component of ED ACS evaluation protocols. In this technique, a resting thallium scan is first performed. Patients without resting defects can then immediately undergo stress testing with sestamibi imaging, thereby avoiding the delay usually required for isotope "washout" in single-isotope techniques. Dual-isotope stress testing in one trial reliably identified or excluded ACS.

Cardiac MRI

Cardiac MRI assesses wall motion, perfusion, and coronary anatomy, either at rest or after pharmacologic stress. It is noninvasive and does not expose the patients to radiation. However, cardiac MRI cannot be performed on approximately 11% of ED patients with chest pain due to contraindications such as claustrophobia and implanted metallic objects. Another limit is the longer test performance time, although this is improving with newer scanners and software. Cardiac magnetic resonance stress imaging has excellent test performance but currently is not a common tool for early ACS evaluation.

CT Coronary Angiography

CTCA allows gated images of the coronary arteries after rapid, peripheral (not central) IV contrast. Images are improved when the heart rate is <65 beats/min in 16-slice CT scanners, sometimes necessitating β-blocking medications; dual-source scanners (128-slice) can image adequately at higher heart rates but are less available. The advantages of CTCA are ready access to necessary equipment, rapid image acquisition, and the ability to image coronary structure. Notable disadvantages include ionizing radiation exposure, IV contrast exposure (and risk of allergy or kidney injury), need for specially trained technicians, and nondiagnostic scans due to nonvisualization of coronary segments. Additionally, CTCA provides a limited assessment of cardiac function. CTCA-detected lesions of >50% stenosis correlate with lesions on standard left-heart angiography; this means the test offers limited information in those with known coronary disease. Patients with positive scans require confirmation either with a cardiac catheterization or a functional advanced cardiac test.

Two recent clinical trials evaluated the usefulness of CTCA in decreasing ED length of stay and assessing for serious cardiac events within 30 days of discharge.[28,29] Both studies included patients with low to intermediate risk for ACS and considered CTCA results of <50% stenosis as negative. These trials found that patients randomized to CTCA versus traditional care had a higher rate of discharge from the ED and a decreased overall length of stay. No significant coronary disease was missed on CTCA evaluation versus traditional stress testing, although one study found that patients with positive CTCA findings had more overall testing and increased radiation exposure. The cost of care was similar for both groups of patients. Overall, these studies provide evidence that CTCA allows for faster and safe discharge of patients from the ED.[28,29]

CTCA findings also have a strong correlation with 1-year prognosis as demonstrated in a meta-analysis that included 18 studies with 9592 patients. Researchers evaluated for major adverse cardiac events, including death, myocardial infarction, and need for revascularization. The overall event rate for patients with positive CTCA (>50% stenosis of any vessel) versus normal CTCA was 8.8% versus 0.17% per year, thus demonstrating that major adverse events in patients with negative CTCA imaging are rare.[30]

While ED CTCA helps deliver a prompt, safe disposition of patients in the ED, up to 24% of patients will have nondiagnostic CTCA imaging.[2] The ideal approach to these patients is undefined and usually reverts to the previous strategies for evaluating low-risk ACS patients.

DIAGNOSTIC PATHWAYS FOR PATIENTS WITH POSSIBLE ACUTE CORONARY SYNDROME

INPATIENT ADMISSION

In settings without an observation unit, all patients with low or higher risk of ACS are admitted to an inpatient bed. Specific destinations and care level are driven by stratification; those with a prior history of CAD, evidence of congestive heart failure on physical examination, recurrent chest pain, or new or presumed new ischemic ECG changes are at higher short-term risk and may be more appropriately managed in an intermediate-care (step-down) unit.

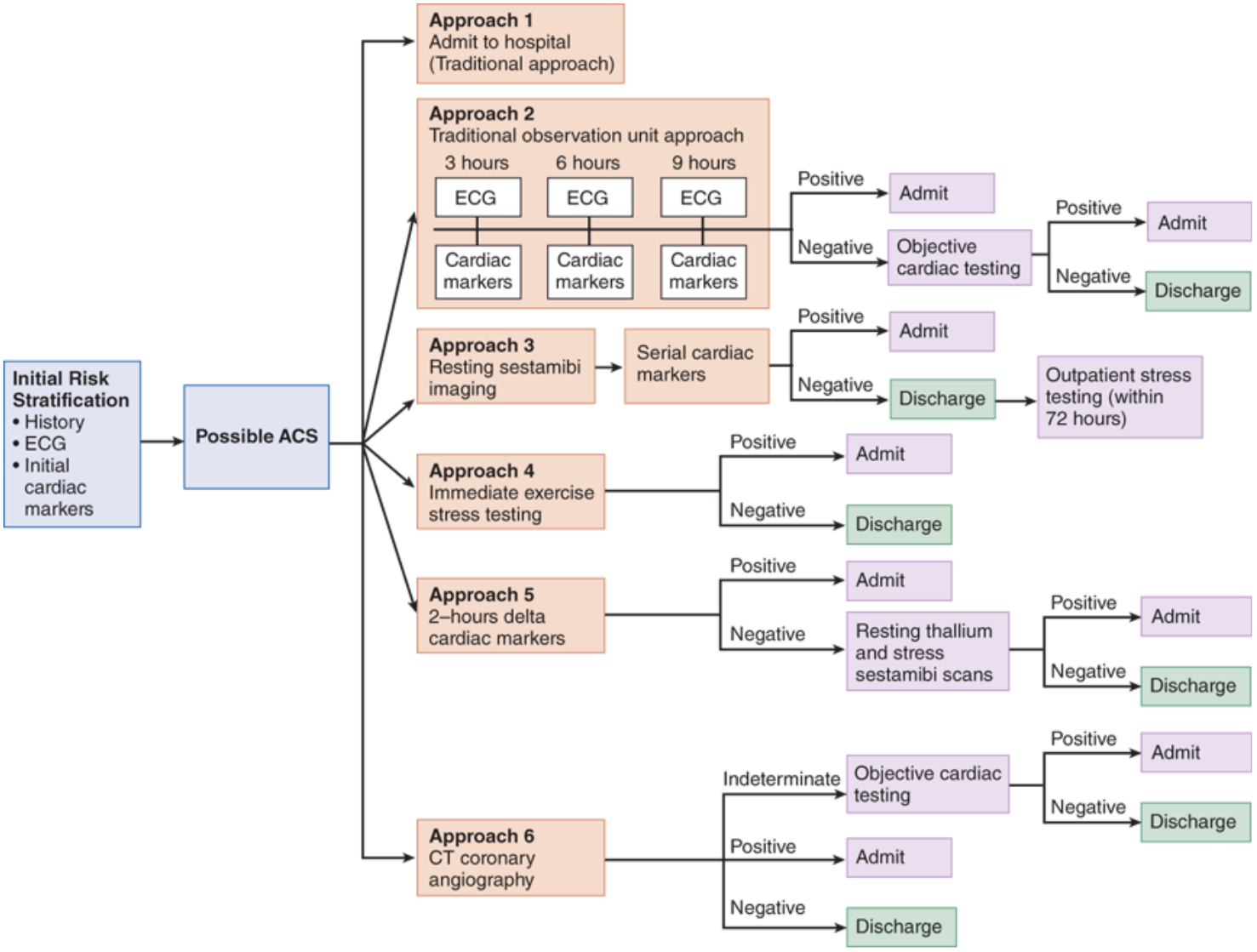
ED OBSERVATION AND TESTING

ED observation unit management decreases hospital admissions, length of stay, and hospital cost while providing a high level of care. The traditional observation unit chest pain protocol was refined by Lateef and colleagues,[32] with patients observed for 9 hours with continuous 12-lead ST-segment ECG monitoring and serial CK-MB testing at 0, 3, 6, and 9 hours after presentation. Those who completed a negative 9-hour evaluation subsequently underwent echocardiography followed by graded exercise stress testing in the ED before discharge. With this approach, 82.1% of patients were released home from the cardiac evaluation unit. The approach of **serial cardiac markers followed by objective**

cardiac testing remains the foundation of ED and other observation unit protocols. Although early observation unit protocols focused on low-risk patients, more recent investigations successfully studied patients with intermediate-risk chest pain.

Figure 51–3 describes alternative approaches to the observation unit management of patients with possible ACS. For approach 3,[33] patients with intermediate and low-risk chest pain underwent immediate resting myocardial perfusion imaging and serial cardiac markers. Patients with negative results were discharged for outpatient evaluation and stress testing. At 30 days, no patients with normal perfusion imaging experienced AMI, and 2% required revascularization. Based on this work, immediate perfusion imaging, serial cardiac markers, and outpatient stress testing are diagnostic options for patients with possible ACS.

FIGURE 51–3.
Pathways for secondary assessment of patients with possible acute coronary syndrome (ACS).



After identification of patients as having possible ACS, immediate exercise stress testing is a safe option (Approach 4, Figure 51–3).[26] This approach had no stress testing–related adverse outcomes and allowed discharge of approximately two thirds of evaluated patients.[26] Immediate exercise stress testing has also been successfully extended to patients with known coronary disease.

The Erlanger chest pain evaluation protocol[34] (Approach 5, Figure 51–3) incorporates baseline and 2-hour marker determinations along with continuous ST-segment monitoring and serial ECGs. Those with positive results or any increase in markers are admitted for further evaluation. Patients thought to be at very low risk for ACS do not undergo stress testing and are discharged home, whereas those with low-risk chest pain undergo cardiac imaging with resting thallium and stress sestamibi scans. This protocol demonstrated a sensitivity of 99% and specificity of 87% for ACS at 30 days.

Some observation units adequately manage patients at intermediate risk for ACS, whereas some facilities manage these patients in the hospital. Any protocol that treats all patients with possible ACS equally should incorporate serial cardiac markers and stress testing. Second, no data exist to support exclusion of ACS based on cardiac markers without cardiac imaging except possibly in very-low-risk patients. Third, early stress testing after a negative ultra-short cardiac marker testing strategy, or exercise stress testing after one negative cardiac marker in patients with possible ACS, appears safe in low- and intermediate-risk patients. Fourth, outpatient stress testing is an option for low-risk patients in whom AMI has been excluded in reliable patients presenting to a facility where a mechanism exists to arrange this testing. Compliance with follow-up testing is better when scheduled before discharge.[35]

TREATMENT

STANDARD TREATMENT

Clinical trials often do not include patients with possible ACS and instead focus on the higher risk patients with positive cardiac markers or ST-segment changes on their ECG. Therefore, treatment recommendations for patients with possible ACS are derived from reviewing the risk-to-benefit profile suggested from clinical trial results in the higher risk patient populations. Additional information on the mechanisms of action and data from clinical trials are discussed in chapter 49.

Therapy for patients with possible ACS is linked to the patient's stratification level (Table 51–3). In general, patients at low risk of adverse events (Level IV) receive aspirin, anti-ischemic therapy with nitroglycerin, and β-blockers. Patients at intermediate risk (Level III) additionally receive antithrombin therapy and dual antiplatelet therapy (**Table 51–5**).[12]

Table 51–5

Recommended Treatment for Patients with Possible Acute Coronary Syndrome (ACS)

Class	Common Dosing	Common Contraindications (all include known hypersensitivity)
Core Therapy for Patients with Possible ACS		
Oxygen	As needed to keep O_2 saturation >95%	Not applicable
Aspirin	160–325 milligrams PO	Active bleeding; see text for further details
Nitroglycerin	0.4 milligram sublingual or spray	Right ventricular infarction, phosphodiesterase use, hypotension
Morphine sulfate	1–5 milligrams IV	—
β-Blockers (metoprolol, esmolol)	Metoprolol: 25–50 milligrams PO in the first 24 h	Bradycardia, heart block, hypotension, chronic obstructive pulmonary disease, severe left ventricular dysfunction, active reactive airway disease, PR interval >0.24 s, at risk for cardiogenic shock (age >70 y old, systolic blood pressure <120 mm Hg systolic, sinus tachycardia >110 beats/min)
Adjunctive Therapy for Patients at Intermediate Risk for Adverse Events*		
Dual antiplatelet therapy		
Clopidogrel (in addition to aspirin)	300–600 milligrams PO (loading dose)	Active bleeding
Antithrombin therapy		
Unfractionated heparin	60 units/kg IV bolus (maximum bolus 4000 units) 12 units/kg/h IV infusion (maximum infusion 1000 units/h)	Active bleeding, history of heparin-induced thrombocytopenia
Low-molecular-weight heparin	Enoxaparin, 1 milligram/kg SC every 12 h	

Class	Common Dosing	Common Contraindications (all include known hypersensitivity)
Direct thrombin inhibitors	Bivalirudin (only for patients undergoing an initial invasive approach), 0.1 milligram/kg IV bolus, 0.25 milligram/kg/h IV infusion	Active bleeding
Factor Xa inhibitor	Fondaparinux, 2.5 milligrams SC once daily	Active bleeding, creatine clearance <30 mL/min, body weight <50 kg

*

See text for discussion; information is the author's interpretation of clinical trial data and guidelines from Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non ST-Elevation Myocardial Infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non ST-Elevation Myocardial Infarction). *J Am Coll Cardiol* 50: e1, 2007.

Contraindications to aspirin include allergy, active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or other serious causes of GI or GU bleeding.[12] Use clopidogrel in patients who are unable to tolerate aspirin due to allergy or GI intolerance.[12]

Very little data are available to support or refute β-blocker use in patients with possible ACS. No evidence suggests superiority of one β-blocker medication over another; however, cardioselective β_1 antagonism is often preferred over the nonselective effects of other agents, making metoprolol, esmolol, and atenolol common choices. β-Blocker medications also offset reflex tachycardia that can be seen with nitrates, and thus, these medications should be administered simultaneously.[12] The first dose of β-blockers can be administered PO or IV, with oral administration preferred and IV administration reserved for patients with hypertension at the time of treatment.[12] Do not use β-blockers with in those with signs of acute heart failure, low cardiac output, heart blocks, active asthma, or reactive airway disease, or in those at risk for cardiogenic shock (age >70 years old, systolic blood pressure <120 mm Hg systolic, sinus tachycardia >110 beats/min).[12]

DISPOSITION AND FOLLOW-UP

ADMISSION AND DISCHARGE CRITERIA

Disposition after the Primary Evaluation

After the primary evaluation, if the treating physician estimates that the probability of ACS is <2%, further testing for ACS is not warranted. After exclusion of other life-threatening causes of chest pain, these patients may be discharged home. These patients may benefit from primary care follow-up or care from another specialty physician depending on the suspected cause (e.g., GI, pulmonary).

Disposition after the Secondary Evaluation

Most patients with possible ACS undergo further evaluation to diagnose or exclude ACS. Upon completion of these protocols, those with negative cardiac markers, no dynamic ECG changes, and negative objective cardiac testing can be safely discharged home. Patients with positive cardiac markers, diagnostic ECG changes, or diagnostic testing

supporting ACS are admitted to the hospital for cardiac care. Those with nondiagnostic cardiac testing are handled on a case-by-case basis after discussion with a cardiologist.

SUGGESTED FOLLOW-UP INTERVAL

Despite advanced testing, a negative evaluation does not entirely exclude ACS. Patients discharged after exclusion of ACS should be given detailed precautions describing reasons to return to the ED. Ideally, patients should follow up with their primary care physician within the next 2 to 3 days.

SPECIAL POPULATIONS

Age, ethnic, racial, and gender differences are well described in patients presenting with ACSs. Most current knowledge of ACS-related symptoms and risk factors comes from population-based studies. Studies have suggested that women are more likely to present without chest pain and often have a prodrome of fatigue. Similarly, the elderly less often present with a chief complaint of chest pain and, less frequently, have typical chest pain. Other studies have noted delayed presentation for ACS in black women[36] and less frequent chest pain with ACS in those of Asian descent.[37] The Framingham criteria overestimate the risk of coronary disease when applied to Chinese patients,[38] and these patients are less likely to experience classic symptoms of ACS. Be aware of all these confounders as you assess the clinical likelihood of ACS.

COCAINE-ASSOCIATED CHEST PAIN

In a study of 130 patients with cocaine-associated myocardial infarction, the mean age was 38 years. AMI occurs in approximately 6% of patients who present to the ED with chest pain after cocaine use. The initial evaluation of the patient with cocaine-associated chest pain is the same as outlined earlier, using the history, exam, ECG, and cardiac biomarkers as the foundation. The sensitivity, specificity, positive predictive value, and negative predictive value of the ECG to identify cocaine-associated myocardial infarction are 36%, 89.9%, 17.9%, and 95.8%, respectively. Cardiac troponin is the most sensitive biomarker for cocaine-associated myocardial infarction. Aspirin, nitrates, and benzodiazepines are the mainstays of therapy for chest pain; β-blockers are contraindicated. Thrombolysis in Acute Myocardial Infarction scoring has little predictive value in patients with cocaine-associated chest pain,[39] but patients with nondiagnostic initial ECGs can be managed in an observation unit using serial ECGs and biomarkers over 6 to 12 hours. There is no difference in the outcomes of patients managed with or without stress testing. The American Heart Association guideline recommends stress testing as an option for patients with cocaine-associated chest pain absent other higher risk factors or features.[40] In one study, the 1-year rate of myocardial infarction after a negative chest pain observation evaluation for patients with cocaine-associated chest pain was <1%, despite a 66% rate of ongoing cocaine use.[41]

PRACTICE GUIDELINES

The American College of Cardiology and American Heart Association offer guidance for the management of patients with unstable angina and NSTEMI.[12]

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USEFUL WEB RESOURCES

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2a. American College of Cardiology Scientific Clinical Statements (NSTEMI guidelines, ECG guidelines, and others)—http://www.acc.org/qualityandscience/clinical/statements.htm

3a. American Heart Association Scientific Statement for the Management of Cocaine-Associated Chest Pain and Myocardial Infarction—http://circ.ahajournals.org.une.idm.oclc.org/cgi/content/full/117/14/1897

4a. Guidelines from the European Society of Cardiology, Clinical Practice Guidelines—http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/GuidelinesList.aspx