CHAPTER 53 Approach to the Patient with Chest Pain

Marc S. Sabatine and Christopher P. Cannon

Acute chest pain is one of the most common reasons for presentation to the emergency department (ED), accounting for approximately 7 million ED visits annually in the United States. This presentation suggests acute coronary syndrome (ACS), but after diagnostic evaluation, only 15% to 25% of patients with acute chest pain actually have ACS.[1,2] The difficulty lies in discriminating patients with ACS or other life-threatening conditions from patients with noncardiovascular, non–life-threatening chest pain. The diagnosis of ACS is missed in approximately 2% of patients, leading to substantial consequences—for example, the short-term mortality for patients with acute myocardial infarction (MI) who are mistakenly discharged from the ED increases twofold over that expected for patients who are admitted to the hospital. For patients with a low risk of complications, however, these concerns must be balanced against the costs and inconvenience of admission and against the risk of complications from tests and procedures with a low probability of improving patient outcomes.

Several recent advances have enhanced the accuracy and efficiency of the evaluation of patients with acute chest pain, including better blood markers for myocardial injury,[3] decision aids to stratify patients according to their risk of complications, early and even immediate exercise testing[4] and radionuclide scanning for lower risk patient subsets (see Chap. 17),[5] multislice computed tomography for the anatomic evaluation of coronary artery disease, pulmonary embolism, and aortic dissection (see Chap. 19),[6] and the use of chest pain units[7] and critical pathways for efficient and rapid evaluation of lower-risk patients.[8]

Causes of Acute Chest Pain

In a typical population of patients presenting for the evaluation of acute chest pain in EDs, about 15% to 25% have acute MI or unstable angina.[2] A small percentage have other life-threatening problems, such as pulmonary embolism or acute aortic dissection, but most are discharged without a diagnosis or with a diagnosis of a noncardiac condition. These noncardiac conditions include musculoskeletal syndromes, disorders of the abdominal viscera (including gastroesophageal reflux disease), and psychological conditions (**Table 53-1**).

Myocardial Ischemia or Infarction

The most common serious cause of acute chest discomfort is myocardial ischemia or infarction (see Chaps. 54 to 56), which occurs when the supply of myocardial oxygen is inadequate compared with the demand. Myocardial ischemia usually occurs in the setting of coronary atherosclerosis, but it may also reflect dynamic components of coronary vascular resistance. Coronary spasm can occur in normal coronary arteries or, in patients with coronary disease, near atherosclerotic plaques and in smaller coronary arteries (see Chap. 52). Other less common causes of impaired coronary blood flow include syndromes that compromise the orifices or lumina of the coronary arteries, such as coronary arteritis, proximal aortitis, spontaneous coronary dissection, proximal aortic dissection, coronary emboli from infectious or noninfectious endocarditis or thrombus in the left atrium or left ventricle, myocardial bridge, or a congenital abnormality of the coronary arteries (see Chap. 21).

The classic manifestation of ischemia is angina, which is usually described as a heavy chest pressure or squeezing, a burning feeling, or difficulty breathing (see Chap. 12). The discomfort often radiates to the left shoulder, neck, or arm. It typically builds in intensity over a period of a few minutes. The pain may begin with exercise or psychological stress, but ACS most commonly occurs without obvious precipitating factors.

Atypical descriptions of chest pain reduce the likelihood that the symptoms represent myocardial ischemia or injury. The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines list the following as pain descriptions that are not characteristic of myocardial ischemia[8]:

- Pleuritic pain (i.e., sharp or knifelike pain brought on by respiratory movements or cough)
- Primary or sole location of discomfort in the middle or lower abdominal region
- Pain that may be localized at the tip of one finger, particularly over the left ventricular apex
- Pain reproduced with movement or palpation of the chest wall or arms
- Constant pain that persists for many hours
- Very brief episodes of pain that last a few seconds or less
- Pain that radiates into the lower extremities

Data from large populations of patients with acute chest pain indicate that ACS occurs in patients with atypical symptoms with sufficient frequency that no single factor should be used to exclude the diagnosis of acute ischemic heart disease. In particular, women, older persons, and individuals with diabetes may be more likely to report atypical symptoms of myocardial ischemia or infarction (see Chap. 81).

Pericardial Disease

The visceral surface of the pericardium is insensitive to pain, as is most of the parietal surface. Therefore, noninfectious causes of pericarditis (e.g., uremia; see Chap. 75) usually cause little or no pain. In contrast, infectious pericarditis almost always involves surrounding pleura, so that patients typically experience pleuritic pain with breathing, coughing, and changes in position. Swallowing may induce the pain because of the proximity of the esophagus to the posterior heart. Because the central diaphragm receives its sensory supply from the phrenic nerve, and the phrenic nerve arises from the third to fifth cervical segments of the spinal cord, pain from infectious pericarditis is frequently felt in the shoulders and neck. Involvement of the more lateral diaphragm can lead to symptoms in the upper abdomen and

TABLE 53-1 Common Causes of Acute Chest Pain

SYSTEM	SYNDROME	CLINICAL DESCRIPTION	KEY DISTINGUISHING FEATURES
Cardiac	Angina	Retrosternal chest pressure, burning, or heaviness; radiating occasionally to neck, jaw, epigastrium, shoulders, left arm	Precipitated by exercise, cold weather, or emotional stress; duration 2-10 min
	Rest or unstable angina	Same as angina, but may be more severe	Typically <20 min; lower tolerance for exertion; crescendo pattern
	Acute myocardial infarction	Same as angina, but may be more severe	Sudden onset, usually lasting ≥30 min; often associated with shortness of breath, weakness, nausea, vomiting
	Pericarditis	Sharp, pleuritic pain aggravated by changes in position; highly variable duration	Pericardial friction rub
Vascular	Aortic dissection	Excruciating, ripping pain of sudden onset in anterior of chest, often radiating to back	Marked severity of unrelenting pain; usually occurs in setting of hypertension or underlying connective tissue disorder such as Marfan syndrome
	Pulmonary embolism	Sudden onset of dyspnea and pain, usually pleuritic with pulmonary infarction	Dyspnea, tachypnea, tachycardia, signs of right heart failure
	Pulmonary hypertension	Substernal chest pressure, exacerbated by exertion	Pain associated with dyspnea and signs of pulmonary hypertension
Pulmonary	Pleuritis and/or pneumonia	Pleuritic pain, usually brief, over involved area	Pain pleuritic and lateral to midline, associated with dyspnea
	Tracheobronchitis	Burning discomfort in midline	Midline location, associated with coughing
	Spontaneous pneumothorax	Sudden onset of unilateral pleuritic pain, with dyspnea	Abrupt onset of dyspnea and pain
Gastrointestinal	Esophageal reflux	Burning substernal and epigastric discomfort, 10-60 min in duration	Aggravated by large meal and postprandial recumbency; relieved by antacid
	Peptic ulcer	Prolonged epigastric or substernal burning	Relieved by antacid or food
	Gallbladder disease	Prolonged epigastric or right upper quadrant pain	Unprovoked or following meal
	Pancreatitis	Prolonged, intense epigastric and substernal pain	Risk factors including alcohol, hypertriglyceridemia, medications
Musculoskeletal	Costochondritis	Sudden onset of intense fleeting pain	May be reproduced by pressure over affected joint; occasionally, swelling and inflammation over costochondral joint
	Cervical disc disease	Sudden onset of fleeting pain	May be reproduced with movement of neck
	Trauma or strain	Constant pain	Reproduced by palpation or movement of chest wall or arms
Infectious	Herpes zoster	Prolonged burning pain in dermatomal distribution	Vesicular rash, dermatomal distribution
Psychological	Panic disorder	Chest tightness or aching, often accompanied by dyspnea and lasting 30 minutes or more, unrelated to exertion or movement	Patient may have other evidence of emotional disorder

back, creating confusion with pancreatitis or cholecystitis. Pericarditis occasionally causes a steady, crushing substernal pain that resembles that of acute myocardial infarction.[9]

Vascular Disease

Acute aortic dissection (see Chap. 60) usually causes the sudden onset of excruciating ripping pain, the location of which reflects the site and progression of the dissection. Ascending aortic dissections tend to manifest with pain in the midline of the anterior chest, and posterior descending aortic dissections tend to manifest with pain in the back of the chest. Aortic dissections are rare, with an estimated annual incidence of 3/100,000, and usually occur in the presence of risk factors including Marfan and Ehlers-Danlos syndromes, bicuspid aortic valve, pregnancy (for proximal dissections), and hypertension (for distal dissections).

Pulmonary emboli (see Chap. 77) often cause the sudden onset of dyspnea and pleuritic chest pain, although they may be asymptomatic. The annual incidence is approximately 1 per 1000, though this number is likely an underestimate. Massive pulmonary emboli tend to cause severe and persistent substernal pain, attributed to distention of the pulmonary artery. Smaller emboli that lead to pulmonary infarction can cause lateral pleuritic chest pain. Hemodynamically significant pulmonary emboli may cause hypotension, syncope, and signs of right heart failure. Pulmonary hypertension (see Chap. 78) can cause chest pain similar to that of angina pectoris, presumably because of right heart hypertrophy and ischemia.

Pulmonary Conditions

Pulmonary conditions that cause chest pain usually produce dyspnea and pleuritic symptoms, the location of which reflects the site of pulmonary disease. Tracheobronchitis tends to be associated with a burning midline pain, whereas pneumonia can produce pain over the involved lung. The pain of a pneumothorax is sudden in onset and is usually accompanied by dyspnea. Primary pneumothorax typically occurs in tall, thin young men; secondary pneumothorax occurs in the setting of pulmonary disease such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis. Asthma exacerbations can present with chest discomfort, typically characterized as tightness.

Gastrointestinal Conditions

Irritation of the esophagus by acid reflux can produce a burning discomfort that is exacerbated by alcohol, aspirin, and some foods. Symptoms often are worsened by a recumbent position and relieved by sitting upright and by acid-reducing therapies. Esophageal spasm can produce a squeezing chest discomfort similar to that of angina.[10] Mallory-Weiss tears of the esophagus can occur in patients who have had prolonged vomiting episodes. Severe vomiting can also cause esophageal rupture (Boerhaave syndrome) with mediastinitis. Chest pain caused by peptic ulcer disease usually occurs 60 to 90 minutes after meals and is typically relieved rapidly by acid-reducing therapies. This pain is usually epigastric in location but can radiate into the chest

and shoulders. Cholecystitis produces a wide range of pain syndromes and usually causes right upper quadrant abdominal pain, but chest and back pain caused by this disorder is not unusual. The pain is often described as aching or colicky. Pancreatitis typically causes an intense, aching epigastric pain that may radiate to the back. Relief through acid-reducing therapies is limited.

Musculoskeletal and Other Causes

Chest pain can arise from musculoskeletal disorders involving the chest wall, such as costochondritis, by conditions affecting the nerves of the chest wall, such as cervical disc disease, by herpes zoster, or following heavy exercise. Musculoskeletal syndromes causing chest pain are often elicited by direct pressure over the affected area or by movement of the patient's neck. The pain itself can be fleeting, or can be a dull ache that lasts for hours. Panic syndrome is a major cause of chest discomfort in ED patients. The symptoms typically include chest tightness, often accompanied by shortness of breath and a sense of anxiety, and generally last 30 minutes or longer.

Diagnostic Considerations

Clinical Evaluation

When evaluating patients with acute chest pain, the clinician must address a series of issues related to prognosis and immediate management. Even before trying to arrive at a definite diagnosis, high-priority questions include the following:

- *Clinical stability:* Does the patient need immediate treatment for actual or impending circulatory collapse or respiratory insufficiency?
- *Immediate prognosis:* If the patient is currently clinically stable, what is the risk that he or she has a life-threatening condition such as an ACS, pulmonary embolism, or aortic dissection?
- *Safety of triage options:* If the risk of a life-threatening condition is low, is it safe to discharge the patient for outpatient management, or should he or she undergo further testing or observation to guide management?

Initial Assessment

Evaluation of the patient with acute chest pain can begin before the physician sees the patient, and thus effectiveness may depend on the actions of the office staff and other nonphysician personnel. Guidelines from the ACC and AHA[8] (see Chaps. 55 and 56, Guidelines sections) emphasize that patients with symptoms consistent with ACS should not be evaluated solely over the telephone but should be referred to facilities that allow evaluation by a physician and the recording of a 12-lead electrocardiogram (ECG).[11] These guidelines also recommend strong consideration of immediate referral to an ED or a specialized chest pain unit for patients with suspected ACS who experience chest discomfort at rest for longer than 20 minutes, hemodynamic instability, or recent syncope or near-syncope. Transport as a passenger in a private vehicle is considered an acceptable alternative to an emergency vehicle only if the wait would lead to a delay longer than 20 to 30 minutes.

The National Heart Attack Alert Program guidelines[12] recommend that patients with the following chief complaints should undergo immediate assessment by triage nurses and be referred for further evaluation:

- Chest pain, pressure, tightness, or heaviness; pain that radiates to neck, jaw, shoulders, back, or one or both arms
- Indigestion or heartburn; nausea and/or vomiting associated with chest discomfort
- Persistent shortness of breath
- Weakness, dizziness, lightheadedness, loss of consciousness

For such patients, the initial assessment involves taking a history, performing a physical examination, obtaining an ECG and chest radiograph, and measuring biomarkers of myocardial injury.

HISTORY. If the patient does not need immediate intervention because of impending or actual circulatory collapse or respiratory insufficiency, the physician's assessment should begin with a clinical history that captures the characteristics of the patient's pain, including its quality, location, and radiation, the time and tempo (abrupt or gradual) of onset, the duration of symptoms, provoking or palliating activities, and any associated symptoms, particularly those that are pulmonary or gastrointestinal. ACS is typically described as a diffuse substernal chest pressure that starts gradually, radiates to the jaw or arms, and is worsened by exertion and relieved by rest or nitroglycerin. Studies have suggested that response to nitroglycerin may not reliably discriminate cardiac chest pain from noncardiac chest pain.[13] In contrast to the tempo of the chest pain in ACS, pulmonary embolism, aortic dissection, and pneumothorax all present with chest pain that is sudden and severe in onset. Moreover, pain that is pleuritic or positional in nature suggests pulmonary embolism, pericarditis, pneumonia, or a musculoskeletal condition.

In addition to the characteristics of the acute episode, the presence of risk factors for atherosclerosis (e.g., advanced age, male sex, diabetes) increases the likelihood that the chest pain is caused by myocardial ischemia. A history of MI is associated not only with a high risk of obstructive coronary disease but also with an increased likelihood of multivessel disease. Younger patients have a lower risk of ACS but should be screened with greater care for histories of recent cocaine use (see Chap. 73).[14]

PHYSICAL EXAMINATION (see Chap. 12). The initial examination of patients with acute chest pain should aim to identify potential precipitating causes of myocardial ischemia (e.g., uncontrolled hypertension), important comorbid conditions (e.g., chronic obstructive pulmonary disease), and evidence of hemodynamic complications (e.g., congestive heart failure, new mitral regurgitation, hypotension).[8] In addition to vital signs, examination of the peripheral vessels should include assessment of the presence of bruits or absent pulses that suggest extracardiac vascular disease.

For patients whose clinical presentations do not suggest myocardial ischemia, the search for noncoronary causes of chest pain should focus first on potentially life-threatening issues (e.g., aortic dissection, pulmonary embolism), and then turn to the possibility of other cardiac diagnoses (e.g., pericarditis) and noncardiac diagnoses (e.g., esophageal discomfort). Aortic dissection is suggested by blood pressure or pulse disparities or by a new murmur of aortic regurgitation accompanied by back or midline anterior chest pain. Differences in breath sounds in the presence of acute dyspnea and pleuritic chest pain raise the possibility of pneumothorax. Tachycardia, tachypnea, and an accentuated pulmonic component of the second heart sound (P_2) may be the major manifestations of pulmonary embolism on physical examination.

ELECTROCARDIOGRAPHY (see Chap. 13). A critical source of data, the ECG, should be obtained within 10 minutes after presentation in patients with ongoing chest discomfort and as rapidly as possible in patients who have a history of chest discomfort consistent with ACS but whose discomfort has resolved by the time of evaluation, to identify patients who might benefit from immediate reperfusion therapy (mechanical or pharmacologic).[11]

The ECG provides critical information for both diagnosis and prognosis. New persistent or transient ST-segment abnormalities (≥0.05 mV) that develop during a symptomatic episode at rest and resolve when the symptoms resolve strongly suggest acute ischemia and severe coronary disease. Nonspecific ST-segment and T wave abnormalities are usually defined as lesser amounts of ST-segment deviation or T wave inversion of 0.2 mV or less, and are less helpful for risk stratification. A completely normal ECG does not exclude the possibility of ACS; the risk of acute MI is about 4% among patients with a history of coronary artery disease and 2% among patients with no such history.[15] However, patients with a normal or near-normal ECG have a better prognosis than patients with clearly abnormal ECGs at presentation. Moreover, a normal ECG has a negative predictive value of 80% to 90%, regardless of whether the patient was experiencing chest pain at

the time the ECG was obtained.[16] Diffuse ST-segment elevation and PR-segment depression suggest pericarditis. Right axis deviation, right bundle branch block, T wave inversions in leads V_1 to V_4, and an S wave in lead I and Q wave and T wave inversion in lead III suggest pulmonary embolism.

The availability of a prior ECG improves diagnostic accuracy and reduces the rate of admission for patients with abnormal baseline tracings. Serial electrocardiographic tracings improve the clinician's ability to diagnose acute MI, particularly if combined with serial measurement of cardiac biomarkers. Continuous electrocardiographic monitoring to detect ST-segment shifts is technically feasible but makes an uncertain contribution to patient management. Posterior leads can be useful for identifying ischemia in the territory supplied by the left circumflex coronary artery, which is otherwise relatively silent electrocardiographically.

CHEST RADIOGRAPHY. A chest radiograph is typically obtained in all patients presenting with chest pain. It is usually nondiagnostic in patients with ACS, but can show pulmonary edema caused by ischemia-induced diastolic or systolic dysfunction. It is more useful for diagnosing or suggesting other disorders; for example, it may show a widened mediastinum or aortic knob in aortic dissection. The chest radiograph is usually normal in pulmonary embolism, but can show atelectasis, an elevated hemidiaphragm, a pleural effusion or, more rarely, Hampton's hump or Westermark's sign. The chest radiograph can reveal pneumonia or pneumothorax.

BIOMARKERS. Patients presenting with chest discomfort possibly consistent with ACS should have biomarkers of myocardial injury measured (see Chaps. 55 and 56). The preferred biomarker is a cardiac troponin (T or I; cTnT or cTnI); creatine kinase MB isoenzyme (CK-MB) is less sensitive.[8]

Diagnostic Performance

Studies of the diagnostic performance of cTnI, cTnT, or CK-MB indicate that when any of these test findings are abnormal, the patient has a high likelihood of having an ACS. It should be acknowledged, however, that it is inherently challenging to define the diagnostic performance of biomarkers for MI because part of the definition of MI includes the rise and fall of a cardiac biomarker of necrosis. Nevertheless, these assays are indispensible in the diagnosis of MI, and using the totality of clinical evidence as the reference standard for diagnosis, they have excellent sensitivity and specificity.

TROPONINS. Different genes encode troponins I and T in cardiac muscle, slow skeletal muscle, and fast skeletal muscle; hence, the assays for cardiac troponins are more specific than the assay for CK-MB for myocardial injury, and cardiac troponin is the preferred diagnostic biomarker.[17] The high specificity of cardiac troponins for myocardium make false-positive elevations (i.e., an elevated cardiac troponin in the absence of myocardial injury) exceedingly rare. Rather, elevations in the absence of other clinical data consistent with an ACS usually represent true myocardial damage from causes other than atherosclerotic coronary artery disease. Such damage may occur with other forms of myocardial injury, such as in the setting of myocarditis, myocardial contusion, or cardioversion or defibrillation, left ventricular strain from congestive heart failure,[18] hypertensive crisis, or extreme exercise, right ventricular strain from pulmonary embolus,[19] or other causes of acute pulmonary hypertension. Elevated levels of cardiac troponins have been reported in patients with renal disease.[20] The exact mechanism remains unclear, but in patients with a clinical history suggestive of ACS, an elevated cardiac troponin level conveys a similarly increased risk of ischemic complications in patients across a broad range of renal function.[21] Elevated cardiac troponin levels can also occur in patients with severe sepsis[22]; again, the mechanism remains unclear.

With serial sampling up to 12 hours after presentation, cardiac troponins offer a sensitivity higher than 95% and a specificity of 90%. When using only a single sample at presentation, performance has been substantially worse, with a sensitivity of only 70% to 75%. Recently, however, sensitive assays have been developed that offer a lower limit of detection, (approximately 0.001 to 0.01 ng/mL, depending on the specific assay) and acceptable imprecision at low levels that, importantly, are now below the 99th percentile in a normal reference population (typically 0.01 to 0.07 ng/mL), thereby improving the ability to detect myocardial injury. Using such assays, the sensitivity for detecting myocardial infarction using a single sample at presentation is approximately 90%, the specificity approximately 90%, and the negative predictive value approximately 97% to 99%.[3,23,24] Moreover, among patients presenting within 3 hours of the onset of chest pain, the superior performance of high-sensitivity assays is even more striking, a sensitivity of 80% to 85%, compared with approximately 55% for older assays. The area under the receiver operator characteristic curve is as high as 0.98 using serial samples for high-sensitivity assays.

Ultrasensitive assays with even lower limits of detection (e.g., <0.001 ng/mL or <1 pg/mL) are also being developed, allowing almost all individuals (including healthy persons) to have a quantifiable troponin result. Using such assays, in patients with non–ST-elevation MI, 72% had circulating troponin levels at baseline above the 99th percentile and another 28% had levels above the limit of detection. Moreover, in patients with unstable angina (defined as lack of elevation of troponin level using a current-generation commercial assay), 44% had circulating troponin levels above the 99th percentile and another 52% had levels above the limit of detection at baseline; 6 to 8 hours later, these values were 82% and 18%, respectively.[25] Similarly, ultrasensitive assays can detect increases in circulating troponin in proportion to the amount of ischemia experienced during exercise stress testing.[26] Thus, in the future, troponin may move from a semiquantitative assay (negative in most individuals, quantified in a subset) to quantifiable in all. The clinical implications of very low level values reported from ultrasensitive assays will need to be defined.

CREATINE KINASE MB ISOENZYME. Until the advent of cardiac troponin assays, CK-MB was the biomarker of choice for the diagnosis of MI. The major limitation to CK-MB as a diagnostic biomarker is its relative lack of specificity, because it can be found in skeletal muscle, tongue, diaphragm, small intestine, uterus, and prostate. Use of the CK-MB relative index (the ratio of CK-MB to total CK) partially addresses this limitation for skeletal muscle as a source. However, the amount of CK-MB is increased in skeletal muscle in patients with conditions that cause chronic muscle destruction and regeneration, such as muscular dystrophy, high-performance athletics (e.g., marathon running), or rhabdomyolysis.[27] CK-MB elevations are particularly common in ED patients because they have higher rates of histories of alcohol abuse or trauma. One advantage of CK-MB is a shorter half-life in the circulation, which makes it useful for gauging the timing of an MI (a normal CK-MB with an elevated troponin level could represent a small MI or an MI that occurred several days ago) and for diagnosing reinfarction in a patient who has had an MI in the past week.

OTHER MARKERS. Serum myoglobin and heart-type fatty acid binding protein (H-FABP) are smaller molecules and diffuse through interstitial fluids more rapidly after cell death than the larger CK and troponin molecules; they become abnormal as early as 30 minutes after myocardial injury.[28] Because neither is specific to myocardial tissue, however, false-positive rates in ED populations are high.[29]

Many patients presenting with ACS, including those without evidence of myocyte necrosis, have elevated concentrations of inflammatory biomarkers such as C-reactive protein,[30] serum amyloid A, myeloperoxidase,[31] or interleukin-6 (IL-6). To date, no study has identified exact decision cut points or shown an incremental benefit on an admission or treatment strategy based on these new markers, so the clinical usefulness of these observations remains uncertain.

Ischemia-modified albumin (IMA) has been approved by the U.S. Food and Drug Administration for clinical use. The albumin cobalt binding test for the detection of IMA is based on the observation that the affinity of the N-terminus of human albumin for cobalt is reduced in patients with myocardial ischemia.[32] As with the other markers, however, the clinical specificity of IMA in the broad population of patients with chest pain and suspected ACS remains an area for further investigation.[33]

D-dimer testing is useful for patients with chest pain to help rule out pulmonary embolism, because a negative enzyme-linked immunosorbent assay (ELISA) test has a negative predictive value of more than 99% in patients with a low clinical probability (patients with a higher clinical probability should undergo an imaging study).[34]

B-type natriuretic peptides (BNP and N-terminal pro-BNP [NT-proBNP]) arise in the setting of increased ventricular wall stress. Natriuretic peptides are most commonly used to aid in the diagnosis of heart failure.[35] BNP levels can be elevated in the setting of transient myocardial ischemia,[36] and the magnitude of elevation in ACS is correlated with prognosis.[37] However, the lack of specificity of natriuretic peptide elevation for ACS limits its use as a diagnostic marker.

PROGNOSTIC IMPLICATIONS OF TEST RESULTS. Abnormal levels of CK-MB, cTnI, and cTnT predict an increased risk of complications.[8] Even if patients do not have CK-MB elevations, cTnI and cTnT are helpful for early risk stratification in patients with acute chest pain. The notion that a patient who has a slight elevation in troponin has an "infarctlet" of questionable prognostic significance should be abandoned.[38] The prognostic value of cTnI seems to be comparable to that of cTnT.

Testing Strategy

The 2007 National Academy of Clinical Biochemistry (NACB) practice guidelines recommend the measurement of biomarkers of cardiac injury in patients with symptoms that suggest ACS (**Table 53-2**). Furthermore, patients with a very low probability of ACS should not undergo measurement of biomarkers because false-positive results could lead to unnecessary hospitalizations, tests, procedures, and complications.

The ACC, AHA, and NACB guidelines recommend cTnI or cTnT as the preferred first-line markers, but CK-MB (by mass assay) is an acceptable alternative. The preference for cardiac troponins reflects the greater specificity of these markers compared with CK-MB and the prognostic value of troponin elevations in the presence of normal CK-MB levels. If the initial set of markers is negative in patients who have presented within the first 6 hours of the onset of pain, the guidelines recommend that another sample be drawn in the time frame of 8 to 12 hours after symptom onset.

Decision Aids

An algorithm for the diagnostic evaluation of chest pain is shown in **Figure 53-1**. The history, physical examination, ECG, and biomarkers of myocardial injury can be integrated to allow the clinician to assess the likelihood of ACS and the risk of complications (**Tables 53-3 and 53-4**). Furthermore, in terms of prognosis, multivariable algorithms have been developed and prospectively validated, with the goal of improving risk stratification in patients with acute chest pain. These algorithms can be used to estimate the probability of acute myocardial infarction, acute ischemic heart disease, or the risk of major cardiac complications in individual patients.[15] They serve mainly to identify patients who are at low risk for complications and who therefore do not require admission to the hospital or coronary care unit.

A prospectively validated algorithm for the prediction of the risk of complications requiring intensive care is presented as a flow chart in **Figure 53-2**.[39] In this algorithm, patients with suspected myocardial infarction on their ECGs are immediately classified as having a high risk (approximately 16%) of major complications within the next 72 hours. Patients whose ECGs are consistent with ischemia but not infarction are then classified as having an intermediate (approximately 8%) or high risk for complications, depending on the presence or absence of clinical risk factors, including systolic blood pressure below 110 mm Hg, bilateral rales heard above the bases, and known unstable ischemic heart disease (defined as worsening of previously stable angina, a new onset of angina after infarction or after a coronary revascularization procedure, or pain that was the same as that associated with a prior MI). These same risk factors help stratify patients without ischemic changes on their ECGs.

TABLE 53-2 National Academy of Clinical Biochemistry Recommendations for Use of Biochemical Markers for Risk Stratification in Acute Coronary Syndrome

Class I

1. Patients with suspected ACS should undergo early risk stratification based on an integrated assessment of symptoms, physical examination findings, electrocardiographic findings, and biomarkers (level of evidence: C).
2. A cardiac troponin is the preferred marker for risk stratification and, if available, should be measured in all patients with suspected ACS. In patients with a clinical syndrome consistent with ACS, a maximal (peak) concentration exceeding the 99th percentile of values for a reference control group should be considered indicative of increased risk of death and recurrent ischemic events (level of evidence: A).
3. Blood should be obtained for testing on hospital presentation followed by serial sampling, with timing of sampling based on the clinical circumstances. For most patients, blood should be obtained for testing at hospital presentation, and at 6 to 9 hours (level of evidence: B).

Class IIa

4. Measurement of hs-CRP may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (level of evidence: A).
5. Measurement of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (level of evidence: A).

Class IIb

6. Measurement of markers of myocardial ischemia, in addition to cardiac troponin and ECG, may aid in excluding ACS in patients with a low clinical probability of myocardial ischemia (level of evidence: C).
7. A multimarker strategy that includes measurement of two or more pathobiologically diverse biomarkers, in addition to a cardiac troponin, may aid in enhancing risk stratification in patients with a clinical syndrome consistent with ACS. BNP and high-sensitivity C-reactive protein (hsCRP) are the biomarkers best studied using this approach. The benefits of therapy based on this strategy remain uncertain (level of evidence: C).
8. Early repeat sampling of cardiac troponin (e.g., 2-4 hours after presentation) may be appropriate if tied to therapeutic strategies (level of evidence: C).

Class III

Biomarkers of necrosis should not be used for routine screening of patients with low clinical probability of ACS (level of evidence: C).

From Morrow DA, Cannon CP, Jesse RL, et al: National Academy of Clinical Biochemistry Laboratory medicine practice guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation 115:e356, 2007.

Immediate Management

The ACC and AHA guidelines suggest an approach to the immediate management of patients with possible ACS that integrates information from the history, physical examination, 12-lead ECG, and initial cardiac marker tests to assign patients to four categories—noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS (**Fig. 53-3**).[8] In this algorithm, patients with ST-segment elevations are triaged immediately for reperfusion therapy, in accordance with the ACC and AHA guidelines for acute MI. Patients with ACS who have ST wave or T wave changes, ongoing pain, positive cardiac markers, or hemodynamic abnormalities should be admitted to the hospital for the management of acute ischemia. Cost-effectiveness analyses support triage of such patients to the coronary care unit for their initial care. For patients with possible or definite ACS who do not have diagnostic ECGs and whose initial serum cardiac markers are within normal limits, observation in a chest pain unit or other nonintensive care facility is appropriate, with subsequent additional testing (see later).

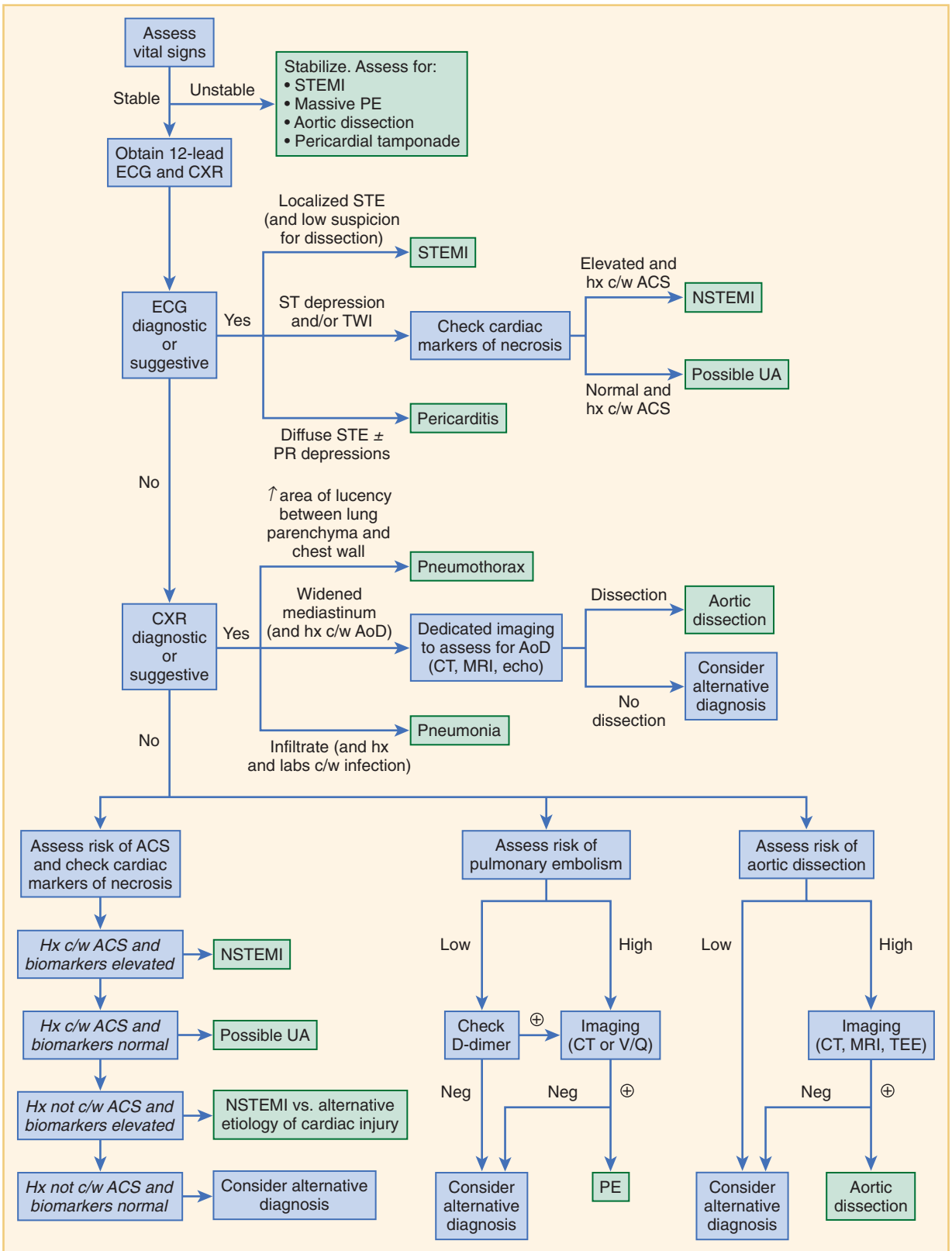

FIGURE 53-1 Algorithm for the initial diagnostic approach to a patient with chest pain. AoD = aortic dissection; c/w = consistent with; CXR = chest x-ray; hx = history; NSTEMI = non–ST-segment myocardial infarction; PE = pulmonary embolism; STE = ST elevation; STEMI = ST-segment myocardial infarction; TEE = transesophageal echocardiography; UA = unstable angina; V/Q = ventilation-perfusion scan.

TABLE 53-3 Likelihood That Signs and Symptoms Represent an Acute Coronary Syndrome

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 ANY OF THE FOLLOWING*
History	• Chest or left arm pain or discomfort as chief symptom reproducing documented angina prior • Known history of coronary artery disease, including MI	• Chest or left arm pain or discomfort as chief symptom • Age > 70 yr • Male sex • Diabetes mellitus	• Probable ischemic symptoms in absence of any of the intermediate-likelihood characteristics • Recent cocaine use
Examination	• Transient mitral regurgitation murmur, hypotension, diaphoresis, pulmonary edema, or rales	• Extracardiac vascular disease	• Chest discomfort reproduced by palpation
Electrocardiogram	• New, or presumably new, transient ST-segment deviation (≥0.1 mV) or T wave inversion (≥0.2 mV) in multiple precordial leads	• Fixed Q waves • ST-segment depression 0.05-0.1 mV or T wave inversion > 0.1 mV	• T wave flattening or inversion < 0.1 mV in leads with dominant R waves • Normal ECG
Cardiac markers	• Elevated cardiac TnI, TnT, or CK-MB	• Normal	• Normal

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): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 116:e148, 2007.

TABLE 53-4 Short-Term Risk of Death or Nonfatal Myocardial Ischemia in Patients with Unstable Angina

FEATURE	HIGH RISK *AT LEAST ONE OF THE FOLLOWING FEATURES MUST BE PRESENT*	INTERMEDIATE RISK *NO HIGH-RISK FEATURES, BUT MUST HAVE ONE OF THE FOLLOWING*	LOW RISK *NO HIGH- OR INTERMEDIATE-RISK FEATURES, BUT MAY HAVE ANY OF THE FOLLOWING*
History	• Accelerating tempo of ischemic symptoms in preceding 48 hours	• Prior MI, peripheral or cerebrovascular disease, or CABG; prior ASA use	
Character of pain	• Prolonged ongoing (>20 min) pain at rest	• Prolonged (>20 min) rest angina, now resolved, with intermediate or high likelihood of CAD • Rest angina (>20 min) or relieved with rest or sublingual nitroglycerin • Nocturnal angina • New-onset or progressive CCS 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-2 mo prior to presentation
Clinical findings	• Pulmonary edema, most likely caused by ischemia • New or worsening MR murmur • S_3 or new or worsening rales • Hypotension, bradycardia, tachycardia • Age >75 yr	• Age > 70 yr	
Electrocardiogram	• Angina at rest with transient ST-segment changes > 0.05 mV • Bundle branch block, new or presumed new • Sustained ventricular tachycardia	• T wave changes • Pathologic Q waves or resting ST-segment depression < 0.1 mV in multiple lead groups (anterior, inferior, lateral)	• Normal or unchanged ECG
Cardiac markers	• Elevated cardiac TnI, TnT, or CK-MB	• Slightly elevated cardiac TnI, TnT, or CK-MB	• Normal

ASA = acetylsalicylic acid; CABG = coronary artery bypass grafting; CCS = *Canadian Cardiovascular Society;* MR = mitral regurgitation; NTG = nitroglycerin.

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): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 116:e148, 2007.

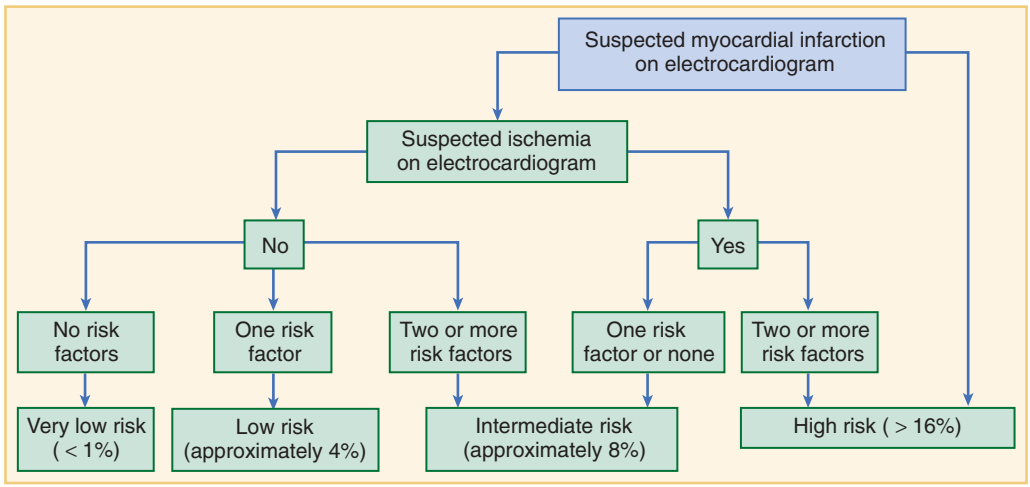

FIGURE 53-2 Derivation and validation of four groups into which patients can be categorized, according to the risk of major cardiac events within 72 hours after admission. Risk factors include: systolic blood pressure below 110 mm Hg, bilateral rales heard above the bases, and known unstable ischemic heart disease (see text for details). *(From Goldman L, Cook EF, Johnson PA, et al: Prediction of the need for intensive care in patients who come to emergency departments with acute chest pain. N Engl J Med 334:1498, 1996.)*

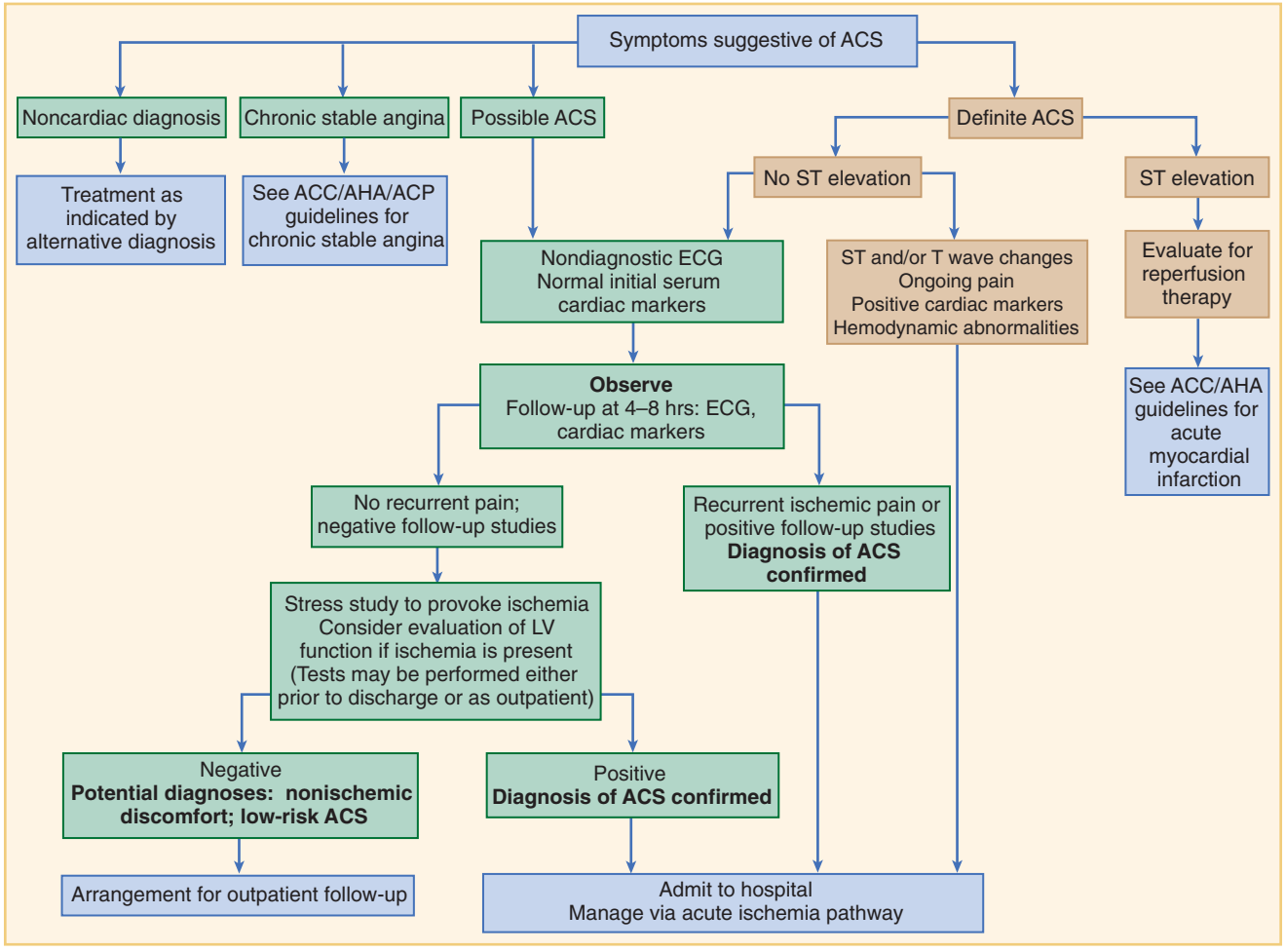

FIGURE 53-3 Algorithm for the evaluation and management of patients suspected of having ACS. ACP = American College of Physicians. *(From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report 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]: Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 116:e148, 2007.)*

Chest Pain Protocols and Units

The main elements of a typical chest pain critical pathway are included in Figure 53-3 (lower section). According to the ACC and AHA recommendations,[8] patients with a low risk of acute coronary syndrome or associated complications can be observed for 6 to 12 hours while undergoing electrocardiographic monitoring and serial measurement of cardiac markers. Patients who develop evidence of ischemia or other indicators of increased risk should be admitted to the coronary care unit for further management. Patients who do not develop recurrent pain or other predictors of increased risk can be triaged for early noninvasive testing (see later) before or after discharge. Outpatient stress testing is a reasonable option if the patient is at low risk for ACS and if the testing can be accomplished within 72 hours; such a strategy has been shown to be safe. In such patients, it is prudent to prescribe aspirin and possibly beta blockers, and to provide them with sublingual nitroglycerin.

To enhance the efficiency and reliability of implementation of such chest pain protocols, many hospitals triage low-risk patients with chest pain to special chest pain units.[40] These units often are located adjacent to or within EDs, but sometimes are located elsewhere in the hospital. In most of these units, the rate of MI has been about 1% to 2%, and they have proven to be safe and cost-saving sites of care for low-risk patients. Chest pain units are also sometimes used for intermediate-risk patients, such as those with a prior history of coronary disease but no other high-risk predictors. In one community-based randomized trial, patients with unstable angina and an overall intermediate risk of complications had similar outcomes and lower costs if they were triaged to a chest pain unit versus conventional hospital management.

Early Noninvasive Testing

TREADMILL ELECTROCARDIOGRAPHY. A major goal of the initial short period of observation of low-risk patients in chest pain units is to determine whether performance of exercise testing or other noninvasive tests is safe. Treadmill exercise electrocardiography is inexpensive and available at many hospitals every day, beyond traditional laboratory hours, and prospective data indicate that early exercise test results provide reliable prognostic information for low-risk patient populations. Most studies have used the Bruce or modified Bruce treadmill protocol. One study found that among low-risk patients who underwent exercise testing within 48 hours of presentation for acute chest pain, the 6-month event rate among 195 patients with a negative test was 2%, in contrast to a rate of 15% among patients with a positive or equivocal test result.[41] Another study documented the safety of this approach in 3000 consecutive patients.[4]

Patients who have a low clinical risk of complications can safely undergo exercise testing within 6 to 12 hours after presentation at the hospital or even immediately.[4] In general, protocols for early or immediate exercise testing exclude patients with electrocardiographic findings consistent with ischemia not recorded on previous tracings, ongoing chest pain, or evidence of congestive heart failure. Analyses of pooled data have suggested that the prevalence of coronary disease in populations undergoing early exercise testing averages approximately 5%, and that the rate of adverse events is negligible. The AHA has issued an advisory statement regarding indications and contraindications for exercise on electrocardiographic stress testing in the ED (**Table 53-5**).[4,42]

IMAGING TESTS. Stress echocardiography and radionuclide scans are the preferred noninvasive testing modalities for patients who cannot undergo treadmill electrocardiographic testing because of physical disability or who have resting ECGs that confound interpretation. Imaging studies are less readily available and more expensive than exercise electrocardiography, but have increased sensitivity for the detection of coronary disease and the ability to quantify the extent of, and localize, jeopardized myocardium. High-risk rest perfusion scans are associated with an increased risk of major cardiac complications, whereas patients with low-risk scans have low 30-day cardiac event rates (<2%).[43-45]

TABLE 53-5 Indications and Contraindications for Exercise Electrocardiographic Testing in the Emergency Department

Requirements before exercise electrocardiographic testing that should be considered in the Emergency Department setting:
- Two sets of cardiac enzymes at 4-hr intervals should be normal.
- ECG at the time of presentation and preexercise 12-lead ECG shows no significant abnormality.
- Absence of rest electrocardiographic abnormalities that would preclude accurate assessment of the exercise ECG
- From admission to time that results are available from the second set of cardiac enzymes: patient asymptomatic, lessening chest pain symptoms, or persistent atypical symptoms
- Absence of ischemic chest pain at the time of exercise testing

Contraindications to exercise electrocardiographic testing in the Emergency Department setting:
- New or evolving electrocardiographic abnormalities on the rest tracing
- Abnormal cardiac enzyme levels
- Inability to perform exercise
- Worsening or persistent ischemic chest pain symptoms from admission to the time of exercise testing
- Clinical risk profiling indicating that imminent coronary angiography is likely

In addition to stress imaging studies to detect provocable ischemia, rest radionuclide scans also can help determine whether a patient's symptoms represent myocardial ischemia.[46] In a multicenter prospective randomized trial of 2475 adult ED patients with ongoing or recently resolved (<3 hours) chest pain or other symptoms suggestive of acute cardiac ischemia, and with normal or nondiagnostic initial electrocardiographic results, patients were randomly assigned to receive the usual evaluation strategy or the usual strategy supplemented with results from acute resting myocardial perfusion imaging.[47] The availability of scan results did not influence the management of patients with acute MI or unstable angina, but it reduced rates of hospitalization for patients without acute cardiac ischemia from 52% to 42%. Rest myocardial perfusion imaging is most sensitive if performed when a patient is experiencing ischemic symptoms, and progressively diminishes thereafter. It is recommended that imaging be performed within 2 hours of the resolution of symptoms, although data support its use for up to 4 hours.[48]

Echocardiography can also be used, with and without stress, to detect wall motion abnormalities consistent with myocardial ischemia. The presence of induced or baseline regional wall motion abnormalities correlates with a worse prognosis. The sensitivity of stress echocardiography appears to be comparable to myocardial perfusion imaging (~85%), and the specificity is somewhat better (95% versus 90%).[49] As is the case for myocardial perfusion imaging, the results are less interpretable in patients with prior MI, in whom it is difficult to exclude that the abnormalities are preexisting unless a prior study is available. Myocardial contrast echocardiography (MCE)[50] using microbubble imaging agents offers reasonable (77%) concordance with radionuclide scanning, and the combination of regional wall motion abnormalities or reduced myocardial perfusion has a sensitivity of 80% to 90% and a specificity of 60% to 90% for ACS.[51,52]

Cardiac magnetic resonance imaging (MRI) is also being explored in the assessment of patients with suspected ACS.[53] In a study that used cardiac MRI to quantify myocardial perfusion, ventricular function, and hyperenhancement in patients with chest pain, the sensitivity for ACS was 84% and the specificity was 85%. The addition of T2-weighted imaging, which can detect myocardial edema and thus help differentiate acute from chronic perfusion defects, improves the specificity to 96% without sacrificing sensitivity.[54] Integration of MRI coronary angiography is being studied.[55] Stress MRI using adenosine, although more labor intensive, has also been studied and shows excellent sensitivity and specificity.[56]

In contrast to the functional imaging data from stress testing, coronary computed tomography angiography (CTA) offers noninvasive anatomic data. Using multidetector computed tomography (MDCT), coronary CTA has a sensitivity of approximately 90% and a specificity of 65% to 90% for coronary stenosis greater than 50%. Coronary CTA has been evaluated in a single-center study of chest pain patients presenting to the ED.[6] Of 368 patients with a nondiagnostic ECG and negative initial biomarker of necrosis, 31 were ultimately diagnosed with ACS. Approximately half of the patients were free of coronary artery disease (CAD) on coronary CTA and 0% had an ACS, yielding a negative predictive value of 100%. The remaining 50% had evidence of atherosclerosis, with 32% having minor plaque and 18% having a stenosis greater than 50%. A final diagnosis of ACS was made in 6% of those with only minor plaque and in 35% with a significant stenosis. The negative predictive value of coronary stenosis by coronary CTA for ACS was 98%. Thus, given the anatomic rather than the functional data provided, coronary CTA may be best suited to rule out rather than rule in ACS. Of the patients who underwent CTA in a randomized comparison of myocardial perfusion imaging versus coronary CTA, 68% had a normal test and were discharged home. Another 24% had an intermediate or nondiagnostic test and underwent myocardial perfusion imaging; most of the results were negative. In total, 89% were discharged from the ED. Among patients who underwent myocardial perfusion imaging, 97% were discharged from the ED. The patients randomized to coronary CTA had a time to diagnosis that was 8 hours shorter, and consequently incurred lower hospital costs. Higher rates of cardiac catheterization and coronary revascularization occurred in the coronary CTA group (11% versus 3% and 5% versus 1%, respectively).[57] The most recent ACC and AHA guidelines acknowledge that coronary CTA is a reasonable alternative to stress testing in patients with low to intermediate probability of CAD.[8]

For both MRI and coronary CTA, additional multicenter studies and considerations related to radiation exposure are needed before such approaches are widely adopted clinically.

REFERENCES

Causes of Acute Chest Pain

1. Pope JH, Aufderheide TP, Ruthazer R, et al: Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342:1163, 2000.
2. Lindsell CJ, Anantharaman V, Diercks D, et al: The Internet Tracking Registry of Acute Coronary Syndromes (i*trACS): A multicenter registry of patients with suspicion of acute coronary syndromes reported using the standardized reporting guidelines for emergency department chest pain studies. Ann Emerg Med 48:666, 2006.
3. Morrow DA: Clinical application of sensitive troponin assays. N Engl J Med 361:913, 2009.
4. Amsterdam EA, Kirk JD, Diercks DB, et al: Exercise testing in chest pain units: Rationale, implementation, and results. Cardiol Clin 23:503, 2005.
5. Ekelund U, Forberg JL: New methods for improved evaluation of patients with suspected acute coronary syndrome in the emergency department. Emerg Med J 24:811, 2007.
6. Hoffmann U, Bamberg F, Chae CU, et al: Coronary computed tomography angiography for early triage of patients with acute chest pain: The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. J Am Coll Cardiol 53:1642, 2009.
7. Blomkalns AL, Gibler WB: Chest pain unit concept: rationale and diagnostic strategies. Cardiol Clin 23:411, 2005.
8. Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 116:e148, 2007.
9. Lange RA, Hillis LD: Clinical practice. Acute pericarditis. N Engl J Med 351:2195, 2004.
10. Eslick GD: Noncardiac chest pain: Epidemiology, natural history, health care seeking, and quality of life. Gastroenterol Clin North Am 33:1, 2004.

Initial Assessment

11. Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 110:e82, 2004.
12. National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group: Emergency department: rapid identification and treatment of patients with acute myocardial infarction. Ann Emerg Med 23:311, 1994.
13. Diercks DB, Boghos E, Guzman H, et al: Changes in the numeric descriptive scale for pain after sublingual nitroglycerin do not predict cardiac etiology of chest pain. Ann Emerg Med 45:581, 2005.
14. McCord J, Jneid H, Hollander JE, et al: Management of cocaine-associated chest pain and myocardial infarction: A scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 117:1897, 2008.
15. Lee TH, Goldman L: Evaluation of the patient with acute chest pain. N Engl J Med 342:1187, 2000.
16. Turnipseed SD, Trythall WS, Diercks DB, et al: Frequency of acute coronary syndrome in patients with normal electrocardiogram performed during presence or absence of chest pain. Acad Emerg Med 16:495, 2009.

Biomarkers

17. Thygesen K, Alpert JS, White HD: Universal definition of myocardial infarction. J Am Coll Cardiol 50:2173, 2007.
18. Peacock WF 4th, De Marco T, Fonarow GC, et al: Cardiac troponin and outcome in acute heart failure. N Engl J Med 358:2117, 2008.
19. Becattini C, Vedovati MC, Agnelli G: Prognostic value of troponins in acute pulmonary embolism: A meta-analysis. Circulation 116:427, 2007.
20. Khan NA, Hemmelgarn BR, Tonelli M, et al: Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: A meta-analysis. Circulation 112:3088, 2005.
21. Wu AH, Jaffe AS, Apple FS, et al: National Academy of Clinical Biochemistry laboratory medicine practice guidelines: Use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. Clin Chem 53:2086, 2007.
22. Favory R, Neviere R: Significance and interpretation of elevated troponin in septic patients. Crit Care 10:224, 2006.
23. Reichlin T, Hochholzer W, Bassetti S, et al: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 361:858, 2009.
24. Keller T, Zeller T, Peetz D, et al: Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 61:868, 2009.
25. Wilson SR, Sabatine MS, Braunwald E, et al: Detection of myocardial injury in patients with unstable angina using a novel nanoparticle cardiac troponin I assay: Observations from the PROTECT-TIMI 30 Trial. Am Heart J 158:386, 2009.
26. Sabatine MS, Morrow DA, de Lemos JA, et al: Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 30:162, 2009.
27. Leers MP, Schepers R, Baumgarten R: Effects of a long-distance run on cardiac markers in healthy athletes. Clin Chem Lab Med 44:999, 2006.
28. O'Donoghue M, de Lemos JA, Morrow DA, et al: Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. Circulation 2114:550, 2006.
29. Morrow DA, Cannon CP, Jesse RL, et al: National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation 115:e356, 2007.
30. Scirica BM, Morrow DA, Cannon CP, et al: Clinical application of C-reactive protein across the spectrum of acute coronary syndromes. Clin Chem 53:1800, 2007.
31. Schindhelm RK, van der Zwan LP, Teerlink T, Scheffer PG: Myeloperoxidase: A useful biomarker for cardiovascular disease risk stratification? Clin Chem 55:1462, 2009.
32. Peacock F, Morris DL, Anwaruddin S, et al: Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. Am Heart J 152:253, 2006.
33. Sabatine MS: When prognosis precedes diagnosis: Putting the cart before the horse. CMAJ 172:1697, 2005.
34. van Belle A, Buller HR, Huisman MV, et al: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 295:172, 2006.
35. Braunwald E: Biomarkers in heart failure. N Engl J Med 358:2148, 2008.
36. Sabatine MS, Morrow DA, de Lemos JA, et al: Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 44:1988, 2004.
37. Morrow DA, de Lemos JA, Blazing MA, et al: Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. JAMA 294:2866, 2005.
38. Bonaca MP, Morrow DA: Defining a role for novel biomarkers in acute coronary syndromes. Clin Chem 54:1424, 2008.
39. Goldman L, Cook EF, Johnson PA, et al: Prediction of the need for intensive care in patients who come to the emergency departments with acute chest pain. N Engl J Med 334:1498, 1996.

Immediate Management

40. Farkouh ME, Smars PA, Reeder GS, et al: A clinical trial of a chest-pain observation unit for patients with unstable angina. N Engl J Med 339:1882, 1998.
41. Polanczyk CA, Johnson PA, Hartley LH, et al: Clinical correlates and prognostic significance of early negative exercise tolerance test in patients with acute chest pain seen in the hospital emergency department. Am J Cardiol 81:288, 1998.
42. Gibbons RJ, Balady GJ, Bricker JT, et al: ACC/AHA 2002 guideline update for exercise testing: summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 106:1883, 2002.
43. Kontos MC, Tatum JL: Imaging in the evaluation of the patient with suspected acute coronary syndrome. Cardiol Clin 23:517, 2005.
44. Marcassa C, Bax JJ, Bengel F, et al: Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: a position statement. Eur Heart J 29:557, 2008.
45. Wyrick JJ, Kalvaitis S, McConnell KJ, et al: Cost-efficiency of myocardial contrast echocardiography in patients presenting to the emergency department with chest pain of suspected cardiac origin and a nondiagnostic electrocardiogram. Am J Cardiol 102:649, 2008.
46. Klocke FJ, Baird MG, Lorell BH, et al: ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 108:1404, 2003.

47. Udelson JE, Beshansky JR, Ballin DS, et al: Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: A randomized controlled trial. JAMA 288:2693, 2002.
48. Schaeffer MW, Brennan TD, Hughes JA, et al: Resting radionuclide myocardial perfusion imaging in a chest pain center including an overnight delayed image acquisition protocol. J Nucl Med Technol 35:242, 2007.
49. Conti A, Sammicheli L, Gallini C, et al: Assessment of patients with low-risk chest pain in the emergency department: Head-to-head comparison of exercise stress echocardiography and exercise myocardial SPECT. Am Heart J 149:894, 2005.
50. Kaul S: Myocardial contrast echocardiography: A 25-year retrospective. Circulation 118:291, 2008.
51. Kaul S, Senior R, Firschke C, et al: Incremental value of cardiac imaging in patients presenting to the emergency department with chest pain and without ST-segment elevation: A multicenter study. Am Heart J 148:129, 2004.
52. Korosoglou G, Labadze N, Hansen A, et al: Usefulness of real-time myocardial perfusion imaging in the evaluation of patients with first time chest pain. Am J Cardiol 94:1225, 2004.
53. Lockie T, Nagel E, Redwood S, Plein S: Use of cardiovascular magnetic resonance imaging in acute coronary syndromes. Circulation 119:1671, 2009.
54. Cury RC, Shash K, Nagurney JT, et al: Cardiac magnetic resonance with T2-weighted imaging improves detection of patients with acute coronary syndrome in the emergency department. Circulation 2118:837, 2008.
55. Yang Q, Li K, Liu X, et al: Contrast-enhanced whole-heart coronary magnetic resonance angiography at 3.0-T: A comparative study with X-ray angiography in a single center. J Am Coll Cardiol 54:69, 2009.
56. Ingkanisorn WP, Kwong RY, Bohme NS, et al: Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. J Am Coll Cardiol 47:1427, 2006.
57. Goldstein JA, Gallagher MJ, O'Neill WW, et al: A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. J Am Coll Cardiol 49:863, 2007.