ACUTE CORONARY SYNDROMES

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Learning Objectives

1. Differentiate ST-segment elevation (STE) acute coronary syndromes (ACS) from non-ST-segment elevation (NSTE) ACS by pathology, prognosis, diagnosis, risk stratification, and treatment strategies.
2. For patients with STE ACS, identify high-risk features of their clinical presentation, which makes selection of percutaneous coronary intervention (PCI) the preferred primary therapy over thrombolysis.
3. Describe quality performance measures of treatment of STE ACS.
4. Compare and contrast the pharmacology, clinical trial data, and administration considerations between low-molecular-weight heparins and unfractionated heparin (UFH) in patients with STE ACS and NSTE ACS.
5. Outline the benefits, risks, and cost-effectiveness of adding clopidogrel to aspirin in patients with NSTE ACS.
6. Given patient-specific information, justify appropriate selection of pharmacotherapy in patients with STE ACS.
7. Given patient-specific information, justify appropriate selection of pharmacotherapy in patients with NSTE ACS.
8. For each drug therapy, formulate a monitoring plan for efficacy, adverse reactions, and patient education.

Introduction

Epidemiology of Acute Myocardial Infarction

Although death due to coronary heart disease (CHD) has declined by 25% throughout the past decade, CHD continues to be the leading cause of death in the United States. More than 1 million Americans experience acute myocardial infarction (AMI) each year. More than 250,000 Americans die suddenly of CHD, most commonly from AMI, before reaching the hospital. Data collected from the National Registry of Myocardial Infarction (NRMI) of more than 60,000 patients admitted to United States hospitals report an in-hospital death rate of 7.2% in patients with ST-segment elevation (STE) AMI treated with thrombolysis and 16.1% in patients receiving no reperfusion therapy. In-hospital and 1-year mortality rates are higher for women and older patients. One-year mortality after AMI is 25% for men and 38% for women. Mortality rates are higher in women than men primarily because women present with infarction at an older age than men, with the average age of first AMI being 65.8 years for men and 70.4 years for women. Six-year reinfarction rates are 18% for men and 35% for women, making secondary prevention extremely important, particularly in women. Only 20% of patients presenting with acute coronary syndromes (ACS) have a history of stable angina. Therefore, public education regarding early warning signs of AMI is a duty of all health care professionals.

Differentiating Acute Coronary Syndromes

Although the government statistics described above are derived from data classified according to CHD and AMI events, a new classification scheme is being used in clinical practice (Figure 1-1). Initial triage of patients with suspected ACS includes a history, physical examination, early electrocardiogram (ECG) with interpretation, and blood tests. Patients presenting with chest discomfort and STE are classified as "STE ACS", whereas patients presenting with what was formerly termed "unstable angina" or "non-Q-wave myocardial infarction" are classified as "non-ST-segment elevation (NSTE) ACS". Treatment of either type of ACS is initiated according to national guidelines recommended by the American Heart Association (AHA) and the American College of Cardiology (ACC). Virtually all patients with STE ACS are

Abbreviations in this Chapter

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
ADMIRAL	Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up
ADVANCE AMI	Addressing the Value of Primary Angioplasty after Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction
AHA	American Heart Association
AMI	Acute myocardial infarction
ASSENT	Assessment of Safety and Efficacy of a New Thrombolytic
ATC	Antithrombotic Trialists' Collaboration
CABG	Coronary artery bypass graft
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CCP	Cooperative Cardiovascular Project
CCS-2	Second Chinese Cardiac Study
CHD	Coronary heart disease
CK	Creatine kinase
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
C-PORT	Atlantic Cardiovascular Patient Outcomes Research Team
CREDO	Clopidogrel for the Reduction of Events During Observation
CRP	C-reactive protein
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
DANAMI	Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction
ECG	Electrocardiogram
ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events
EXTRACT	The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction
FTT	Fibrinolytic Therapy Trialists
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Use of Strategies to Open Occluded Arteries
HART-2	Second Trial of Heparin and Aspirin Reperfusion Therapy
HEDIS	Health Plan Employer and Data Information Set
ICH	Intracranial hemorrhage
ISIS	International Study of Infarct Survival Study
LVEF	Left ventricular ejection fraction
MB	Myocardial band
MITI	Myocardial Infarction Triage and Intervention Registry
NICE	National Investigators Collaboration on Enoxaparin
NRMI	National Registry of Myocardial Infarction
NSTE	Non-ST-segment elevation
OPUS	Orbofiban in Patients with Unstable Coronary Syndromes
PCI	Percutaneous coronary intervention
PRAGUE	Primary Angioplasty in Patients from German Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PROVE IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
RITA	Randomized Intervention Trial in Unstable Angina
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
SK	Streptokinase
SPEED	Strategies for Patency Enhancement in the Emergency Department
STE	ST-segment elevation
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors
TACTICS	Treat Angina with Aggrastat (Tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial
TIMI	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin

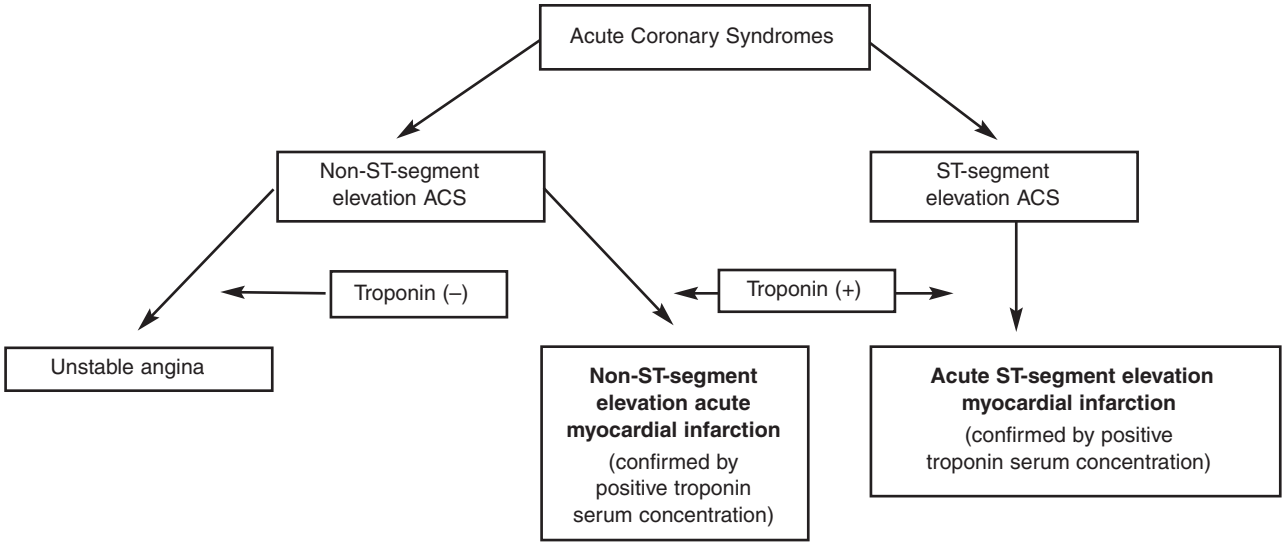

Figure 1-1. Classification of acute coronary syndromes.
ACS = acute coronary syndromes.

diagnosed with AMI, making the ECG an important early tool to stratify patients for appropriate reperfusion therapies. For patients with NSTE ACS, the diagnosis of infarction (i.e., NSTE AMI) is based on the presence of positive biochemical markers in the blood, such as troponin I or troponin T. However, early treatment is initiated before the results of such testing are known, making the classification scheme a functional one, as early treatment of NSTE ACS is identical whether the patient has unstable angina or non-Q-wave AMI. Patients with NSTE ACS are more heterogeneous than those presenting with STE ACS and may have either no changes, ST-segment depression, or T-wave inversion on their ECGs. Patients with NSTE ACS and ST-segment depression are more often diagnosed with AMI and have higher mortality compared to those with T-wave changes or no ECG changes. A more complete discussion of risk-stratification is presented later in this chapter. Recent data from the NRMI of more than 180,000 patients indicate an in-hospital mortality of 11.7% for patients with NSTE AMI. Although most data indicate that patients with STE ACS have higher in-hospital mortality and lower postdischarge reinfarction and mortality rates than patients with NSTE AMI, rates vary widely and both groups should be considered high risk.

Economic Costs of ACS

Chest pain is a leading cause of patient presentation to emergency departments with between 5 and 7 million or 3.3% of all emergency department visits occur annually secondary to chest pain. Costs of CHD are substantial with $10.6 billion being paid to Medicare beneficiaries for CHD hospitalizations in 1999. The average length of stay for patients with AMI was 5.6 days in 1999, the most recent year for which data are available. Nineteen percent of Social Security disability allowances are secondary to CHD, often as a result of angina and heart failure after AMI. This makes CHD the leading cause of premature, permanent chronic disability in the United States labor force.

Pathophysiology

Spectrum From Stable Angina To AMI

Atherosclerosis is a dynamic disease with alternating stages of stability and instability. Coronary heart disease represents a spectrum from asymptomatic atherosclerotic coronary artery disease and symptomatic chronic stable angina to symptomatic ACS.

Pathology

The ACS of unstable angina and evolving AMI share the common pathology of plaque rupture or erosion with superimposed thrombus, causing reduced myocardial perfusion, which leads to ischemia and infarction. Acute coronary syndromes occur as a result of interaction between a vulnerable plaque and triggers. Characteristics associated with plaques that are prone to rupture include the presence of a large lipid core, a thin fibrous cap, low smooth muscle cell density, and high macrophage density. The large number of macrophages present is associated with T lymphocyte activation and inflammation. Inflammatory cytokines also are involved in degradation of the extracellular matrix of the fibrous cap and in increasing the concentration of the procoagulant tissue factor in the endothelium and the lipid core.

Most ACS are caused by ruptured plaques from coronary artery stenoses that are 30–40% in diameter rather than the larger, more stable 70–90% stenoses. Plaque rupture may be either active or passive. Active plaque rupture occurs secondary to proteolytic enzyme secretion by macrophages, which dissolves the fibrous cap. Passive plaque rupture occurs at the "shoulder" regions where the plaque meets the adjacent "normal" arterial wall and is caused by wall stress.

Less common than plaque rupture, plaque erosion also may cause ACS. The exact mechanisms of superficial erosion of the endothelium are not known, but the intima at the site of thrombus formation consists primarily of smooth muscle cells in a proteoglycan-rich matrix with little inflammation. Plaque erosion is believed to cause as many as 40% of all coronary thrombi. In either case, the lipid core and damaged endothelium contain tissue factor, which promotes thrombus formation. Thrombi from patients with NSTE ACS contain more platelets than fibrin, whereas patients with STE have thrombi that contain more fibrin than platelets. Thrombi that predominantly contain platelets appear "white" on angioscopy, whereas those that contain more red blood cells trapped in fibrin appear "red". Microemboli from the ruptured plaque, fibrin clot, and platelet aggregates also may cause ischemia and smaller infarctions. Patients with either STE or NSTE AMI have more persistent occlusion of a coronary artery leading to infarction, whereas patients with unstable angina have ischemia with either transient or incomplete occlusion.

Triggers that promote plaque rupture include an acute arterial pressure surge, vasoconstriction, and increased coagulability. Acute pressure surges may occur in response to heavy physical activity such as shoveling snow. Acute vasoconstriction can occur with cocaine use or during exposure to cigarette smoke. Increased coagulability can occur with acute mental stress; anger; and exposure to cocaine, marijuana, or particulate air pollution. Currently, one of these triggers can be identified in 20% of patients presenting with ACS.

Complications

Complications of ACS include ventricular and atrial arrhythmias, cardiogenic shock, heart failure, heart block, bradycardia, pericarditis, left ventricular free wall rupture, stroke secondary to embolization of left ventricular thrombus, and venous thromboembolism. Most early deaths in patients with ACS are secondary to ventricular fibrillation. Cardiogenic shock develops in 7–12% of patients with AMI with resulting mortality approaching 80%.

Clinical Presentation and Diagnosis

The hallmark symptom in patients presenting with ACS is midline chest discomfort—most often anginal chest pain at rest, new-onset severe anginal chest pain, or increasing angina. Patients with STE ACS and NSTE AMI typically present with prolonged rest angina usually greater than 20 minutes in duration. Other presentations include new-onset angina that severely limits ordinary physical activity (Canadian Cardiovascular Society class III or greater) or more frequent, longer or lower workload threshold for angina in patients with previously diagnosed CHD and angina. The chest discomfort may radiate to the left arm, back, shoulder or jaw and can be associated with diaphoresis, dyspnea, nausea, vomiting, weakness, dizziness, lightheadedness, or unexplained syncope. The discomfort is not reproducible by palpation. Atypical presentations of ACS, such as stabbing chest pain, epigastric pain, or chest pain with pleuritic features, may occur in more than 30% of patients.

The Canadian Cardiovascular Society Classification of Angina is useful for diagnosing NSTE ACS. Patients with ACS have class III or IV angina if there is marked limitation of ordinary activity (class III) or inability to carry on any physical activity without ischemic discomfort (class IV) as opposed to class I or II angina where there is no (class I) or slight (class II) limitation of physical activity.

Electrocardiogram

There are no classic features for ACS found on physical examination. Therefore, evaluation of the resting ECG is key to making the diagnosis of ACS, as well as in risk-stratification. In patients presenting with ischemic chest discomfort, the ECG should be obtained and interpreted within 10 minutes of presentation to the emergency department. Ideally, the ECG should be obtained during symptoms and compared with a prior ECG taken when the patient was asymptomatic. Features suggestive of ACS are ST-segment changes, either elevation or depression, and T-wave changes. When diagnosing STE ACS, ST elevation should be present in two or more contiguous leads and either greater than 0.2 mV (mm) in leads V_1, V_2, or V_3 or greater than or equal to 0.1 mV in other leads. About 50% of patients with ACS who are diagnosed with AMI present with STE. New left bundle branch block is highly indicative of AMI. In NSTE ACS, ST-segment depression should be greater than 0.1 mV in two or more contiguous leads. T-wave inversions of greater than 0.1 mV are less specific than ST-segment depression. However, deep, symmetrically inverted T waves are indicative of anterior infarction. Other changes of the ST-segment or T waves in NSTE ACS that are less than 0.1 mV are less specific. In patients with ischemic chest discomfort but without STE, only 25% are diagnosed with AMI. Therefore, biochemical marker testing, in addition to early ECG interpretation, is important for diagnosis and risk stratification.

Biochemical Markers

The ACC defines acute, evolving or recent AMI as "typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase [CK], myocardial band [MB]) of biochemical markers of myocardial necrosis" with symptoms of ischemia, new Q-waves on ECG, ischemic ECG changes, or percutaneous coronary intervention (PCI) of an infarct-related artery. Therefore, biochemical markers are definitive in making the diagnosis of AMI. Biochemical markers such as troponin and CK MB are released into the blood on myocardial cell death. Troponin and CK MB are sensitive and specific for myocardial necrosis. The preferred biochemical marker is either troponin I or T because it is more specific than the CK-MB (mass assay).

Individual laboratories determine reference values for these biochemical markers. The AMI "decision limit" is a value exceeding the 99th percentile of the reference healthy

Shah PK. Mechanisms of plaque vulnerability rupture and plaque erosion. J Am Coll Cardiol 2003;41:15S–22S.

control value. Troponins and CK-MB typically appear in the blood about 6 hours after the onset of necrosis. In contrast to CK-MB, which returns to normal values within 1–2 days, troponins stay elevated for up to 7–10 days and cannot be used in diagnosing early reinfarction. For diagnosis of early reinfarction, repeated CK-MB measurements are preferred. More rapidly appearing biochemical markers, which are used less commonly to diagnose AMI, include myoglobin and CK-MB isoforms (Figure 1-2).

Blood is obtained for biochemical marker testing from the patient on presentation in the emergency department. If the results of the initial markers are negative and clinical suspicion remains high, blood is obtained two additional times, once between 6 and 9 hours and again between 12 and 24 hours after hospital admission. Biochemical marker evidence for infarction is at least one value of troponin T or I greater than the AMI decision limit within the first 24 hours or a maximal value of CK MB greater than the AMI decision limit on at least two occasions within the first 24 hours.

As previously discussed, the early treatment of STE ACS is not influenced by the results of biochemical marker testing. However, for patients with NSTE ACS, biochemical marker results are an important tool for risk stratification.

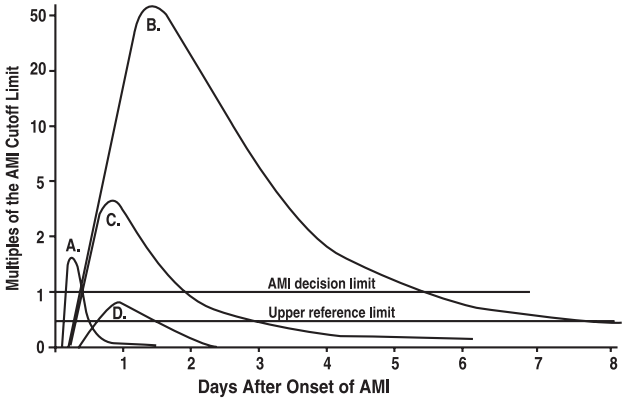

Figure 1-2. Graph of the appearance of cardiac biomarkers in the blood following onsent of ischemic symptoms in acute coronary syndromes.
Peak A, early release of myoglobin or creatinine (CK) MB isoforms. Peaks B and D, cardiac troponin I or T. Peak C, CK-MB. In Peak D, the troponin rise did not meet the decision limit and therefore this patient did not meet the criteria for the diagnosis of acute myocardial infarction (AMI). In Peaks A, B and C, the biomarker rise is well above the decision limit and the patient would be diagnosed with an AMI.
Reprinted with permission from the American Association of Clinical Chemistry. Wu AH, Apple FS, Gibler WB, et al. National Academy of Clinical Biochemistry Standard of Laboratory Practice: recommendations for use of cardiac markers in coronary artery disease. Clin Chem 1999;45:1104.

Risk Stratification

The management strategy for ACS is based on the patient's risk of death and AMI. Risk assessment should be performed as soon as possible after initial diagnosis and repeated or modified as necessary based on response to initial treatment and results of additional testing. Much of the data needed for risk stratification comes from the patient interview. Information used to stratify the patient's risk for death and AMI include clinical history, physical examination, ECG, results of biochemical marker tests, and left ventricular function testing. Although some traditional risk factors for CHD such as advanced age and diabetes mellitus are highly predictive of mortality in patients with ACS, other traditional risk factors do not carry as strong an association; therefore, the presence or absence of such risk factors should not be used as the sole criterion for risk stratification. For example, the prognosis for women is worse than for men with STE ACS, even after adjustment for other comorbidities, but prognosis is better than in men with NSTE ACS.

Table 1-1. Thrombolysis in Myocardial Infarction Risk Score for ST-segment Elevation Acute Coronary Syndromes

Risk Factor	No. of Points
1. Age 65–74	2
2. Age ≥ 75 years	3
3. Systolic blood pressure < 100 mm Hg	3
4. Heart rate > 100 beats/minute	2
5. Heart failure Killip class II–IV	2
6. Anterior ST-segment elevation or left bundle branch block	1
7. Diabetes mellitus or history of hypertension or history of angina	1
8. Weight < 67 kg	1
9. Time to treatment > 4 hours	1

Risk Score 0 to 14 possible points

A risk score from 0 to 14 is calculated by adding up the total number of risk factors above.

Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial substudy. Circulation 2000 Oct 24;102(17):2031–7.

Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999;45:1104–21.

ST-segment Elevation ACS

The presence of STE on the ECG is more than 90% specific for diagnosis of AMI; therefore, reperfusion therapy with thrombolysis or primary PCI is initiated in eligible patients before the results of biochemical marker tests become available. The risk of death is higher in patients presenting with STE ACS compared to patients with NSTE ACS.

After patients are treated in the emergency department and admitted to the coronary intensive care unit, patients with STE may be risk-stratified according to the Thrombolysis in Myocardial Infarction (TIMI) risk score for STE AM (Table 1-1). The higher the risk score, the higher the 30-day mortality rate. For example, the 30-day mortality rates for different patients with TIMI STE risk scores of 0, 7, and higher than 8 are about 2%, 7%, and 36%, respectively. This risk score system was developed from a large clinical trial of more than 14,000 patients with STE treated with thrombolysis, and also has been validated for patients undergoing primary PCI as well as in a community-based cohort of patients. The risk score is less accurate for patients who are not eligible for either thrombolysis or primary PCI. At a minimum, patients should be informed of their general risk of death early in their care, but the TIMI STE risk score can be used to give more precise risk percentages should patients ask for additional information.

Non-ST-segment Elevation ACS

For patients presenting with NSTE ACS, risk stratification is important for selecting their site of care (e.g., a general medical floor or step-down unit versus a coronary intensive care unit) and for identifying their need for early PCI or treatment with a glycoprotein (GP) IIb/IIIa receptor blocker. Low-risk patients may not even need hospital admission, whereas high-risk patients should be treated with a GP IIb/IIIa receptor blocker and should undergo early angiography and PCI.

The first step of risk stratification is to determine the likelihood that the patient's symptoms are due to coronary artery disease (Table 1-2). The next step is to classify the patient's risk. Two risk stratification schemes currently are recommended for use in the ACC/AHA clinical practice guidelines. The first is commonly referred to as the "Braunwald" criteria, which have been part of the unstable angina ACC/AHA clinical practice guidelines since 1995 (Table 1-3). Patients are classified as "high risk", "intermediate risk", and "low risk" based on age, past medical history, physical examination findings, ECG, and biochemical marker results. High-risk patients have at least one high-risk feature such as ST-segment depression, signs of heart failure on physical examination, or an elevated troponin level. For example, an intermediate-risk patient may have known coronary artery disease but only T-wave

Table 1-2. Likelihood that Ischemic Chest Discomfort Symptoms Represent an Acute Coronary Syndrome due to Coronary Artery Disease

Feature	High Likelihood (Any of the following)	Intermediate Likelihood (No high-risk features and any of the following)	Low Likelihood (No high- or intermediate-risk features and any of the following)
History	Known prior CAD, including MI	Chest or left arm discomfort as chief symptom	Probable ischemic symptoms
	Chest or left arm pain discomfort as chief symptom reproducing prior documented angina	Age > 70 years	Recent cocaine use
		Male sex	
		Diabetes mellitus	
Physical examination	Transient MR, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New or presumably new transient ST-segment depression or elevation	Fixed Q-waves	Normal
		Abnormal ST segments or T waves not known to be new	T wave flattening or inversion
	T-wave inversion with symptoms		
Laboratory studies	Elevated troponin I or T	Normal	Normal
	Elevated CK-MB		

CAD = coronary artery disease; CK = creatine kinase; ECG = electrocardiogram; MB = myocardial band; MI = myocardial infarction; MR = mitral regurgitation.

Adapted from Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology; American Heart Association 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40(7):1366–74.

inversions on ECG. A low-risk patient has no prior CHD history, a troponin level that is lower than the AMI decision limit, and no ECG changes. This risk-stratification tool has been validated with the 30-day risk of death or AMI being 0%, 1.2%, and 1.7% in patients at low risk, intermediate risk, and high risk, respectively.

The second risk stratification tool available is the TIMI risk score for NSTE ACS, which was developed from the data in the TIMI 11B trial and validated retrospectively in several other trials and prospectively in one community cohort (Table 1-4). The risk score consists of 0–7 points for past medical history, clinical features, ECG and biochemical marker results. Low-risk patients are those with a TIMI risk score of 0–2; intermediate-risk patients are those with a TIMI risk score of 3–4, and high-risk patients have a risk score of 5–7. In the recent Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, low-, intermediate-, and high-risk patients enrolled in the study had risks for AMI of 3.1%, 5.9%, and 10.7%, respectively, at 9 months. Their risk of cardiovascular death at 9 months was 1.7%, 5.6%, and 9.9%, respectively. The TIMI risk score is available as a personal digital assistant program, which can be downloaded from *www.timi.org*.

Other, more long-term risk prediction tools, which may be used for both STE and NSTE ACS are being developed. The PREDICT score, ranging from 0 to 24 points, was

Table 1-3. Short-term Risk of Death or Nonfatal Acute Myocardial Infarction in Patients with Non-ST-segment Elevation Acute Coronary Syndromes

Feature (Any of the following)	**High Risk**	**Intermediate Risk** (No high-risk features and any of the following)	**Low Risk** (No high- or intermediate-risk features and any of the following)
History	Accelerating tempo of ischemic symptoms in the preceding 48 hours	Prior MI Peripheral or cerebrovascular disease Prior coronary artery bypass surgery	
Character of the pain	Prolonged, ongoing (> 20 minutes) rest pain	Prolonged (> 20 minutes) rest pain, now resolved, with moderate or high likelihood of CAD (see Table 1-2) Rest pain (< 20 minutes) now relieved by either rest or sublingual nitroglycerin	New-onset or progressive angina during the past 2 weeks without prolonged rest pain, but with moderate or high likelihood or CAD
Clinical findings	Pulmonary edema New or worsening MR murmur S_3 or rales Hypotension Bradycardia or tachycardia Age > 75 years	Age > 70 years	
ECG	Angina at rest with ST-segment changes (either ST-segment depression or transient ST-segment elevation) New or presumed new bundle branch block Sustained ventricular tachycardia	Pathological Q waves T-wave inversions	Normal or unchanged
Laboratory studies	Elevated troponin I or T > 0.1 ng/ml	Elevated troponin I or T but < 0.1 ng/ml	Normal

CAD = coronary artery disease; CK = creatine kinase; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation.
Adapted from Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology; American Heart Association 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40(7):1366–74.

Table 1-4. Thrombolysis in Myocardial Infarction Risk Score for Non-ST-segment Elevation Acute Coronary Syndromes

Risk Factor	No. of Points
1. Age ≥ 65 years	1
2. Presence of ≥ 3 other risk factors for coronary heart disease[a]	1
3. Prior history of coronary artery disease (> 50% stenosis on coronary angiography)	1
4. Aspirin use within the past 7 days	1
5. ≥ 2 anginal events within the past 24 hours	1
6. ST-segment deviation (either depression or transient elevation)	1
7. Elevation of cardiac biochemical markers (either troponin I or T or creatine kinase myocardial band)	1
Risk score 0 to 7 possible points	

A risk score from 0 to 7 is calculated by adding up the total number of risk factors above.

[a] Cigarette smoking, diabetes mellitus, hypertension, family history of coronary heart disease, hypercholesterolemia.

Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000;284(7):835–42.

developed from epidemiological surveillance data on AMI in Minnesota. Scores are calculated based on the presence and severity of shock, clinical history features, such as prior AMI, ECG severity score, congestive heart failure, kidney function, and Charlson comorbidity index. Thirty-day, 2-year, and 6-year mortality rates increase with increasing PREDICT score. Mortality as calculated using the PREDICT scores mortality rates observed for STE AMI and NSTE AMI patients were similar in a large cohort of community-based patients. The PREDICT score has been compared with the TIMI risk scores and found to have similar discriminant accuracy for STE ACS and higher discriminant accuracy for NSTE ACS.

Other prognostic factors currently being investigated as risk stratification tools for NSTE ACS include elevated C-reactive protein (CRP), a marker of inflammation, and elevated N-terminal pro brain natriuretic peptide, also called plasma B-type natriuretic peptide, a hormone released from ventricles in response to ventricular wall stretch or tension.

The ACC/AHA unstable angina and NSTE AMI guidelines recommend low-risk patients should be managed as outpatients, whereas intermediate-risk patients should be admitted and monitored in a step-down unit or other telemetry unit in the hospital. High-risk patients should be admitted to a coronary care unit or step-down unit.

Of the more than 5 million patients with chest discomfort presenting to emergency departments, more than 75% will be deemed not to have an ACS after evaluation.

Treatment Goals

The initial goal of ACS treatment is urgent restoration of coronary artery blood flow to the ischemic area of the myocardium to prevent infarction, arrhythmias, and death. Therapies that maintain the patency of the coronary artery by preventing reocclusion and reinfarction should be initiated concurrently. An additional goal is relief of ischemic chest discomfort. Clinical markers of coronary artery blood flow restoration include relief of chest discomfort, a return to baseline of the ST-segments (ST-segment resolution) or T-wave changes on the ECG, and in some cases, the occurrence of "reperfusion" arrhythmias such as idioventricular rhythm. These changes should occur within 90 minutes after the onset of medical therapies. Seventy percent resolution of ST-segment elevation on the ECG is a sign of successful reperfusion but is not yet considered a surrogate marker of mortality in STE ACS. An additional treatment goal is to meet or exceed the quality indicators for drug treatments that have been established by professional associations, governmental, hospital, and managed care regulatory agencies.

If medical therapies alone are unsuccessful in restoring coronary artery blood flow, such additional measures as PCI should be attempted. In some clinical trials, the success of new drug therapies is evaluated through early angiography, which documents the success or failure of the drug in reestablishing flow. Because 24-hour access to interventional cardiology services is limited to less than 15% of all United States hospitals, early angiography and PCI are available to only a few patients.

Quality Patient Care

Patient Case: STE ACS

J.R. is a 49-year-old, 80-kg man with no previous past medical history who is not taking prescription or nonprescription drugs who presents to the emergency department by ambulance complaining of 4 hours of midline chest pressure occurring at rest while watching a football game on television. At his home, paramedics established an intravenous line, administered three sublingual nitroglycerin tablets and one 325-mg aspirin tablet orally before transporting J.R. to the emergency department. A rhythm strip of lead II performed in the field indicated a heart rate of 50 beats/minute and STE. Over the past 2 months, J.R. has noticed brief episodes of similar chest discomfort while walking his dog. The chest discomfort was relieved by rest. J.R. was told 5 years ago that his blood pressure was "high" during a screening at work, but he did not follow-up with his primary care physician. He has had no regular

Anderson HRE, Nielsen TT, Rasmussen K, et al. A comparison of angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 2003;349:733-42.

medical care for the past 15 years. On arrival in the emergency department, a 12-lead ECG was performed within 5 minutes and interpreted as sinus bradycardia, heart rate 50 beats/minute, PR interval 0.2 seconds, normal QRS and QT intervals, and 2 mm STE in leads II, III, and avF. These changes are indicative of an STE ACS, evolving inferior wall AMI. The patient's vital signs were stable with a heart rate of 50 beats/minute, lying blood pressure of 150/96 mm Hg, and temperature of 37°C. His physical examination was within normal limits with no signs of acute heart failure. A rectal guiac test for blood is negative.

Pharmacological Therapy for STE ACS

General Treatment Approach (Algorithm/Guidelines)

The treatment of STE ACS was highlighted in the 1999 ACC/AHA clinical practice guideline. Additional information on primary PCI was included in the 2001 ACC/AHA practice guideline for PCI. Several newer clinical trials published after the guidelines also have influenced ACS STE care and are discussed in the following sections. The ACC/AHA STE ACS treatment guideline is in the process of revision and will be published in spring 2004.

On arrival in the emergency department, the patient with possible ACS should be evaluated immediately and an ECG obtained and interpreted within 10 minutes of arrival. A treatment algorithm for STE ACS is described in Figure 1-3. The general treatment approach to STE ACS includes establishing a minimum of one intravenous line (and potentially additional lines if thrombolysis is administered), bedrest, administration of oxygen if the patient's oxygen saturation is less than 90%, telemetry monitoring of two or three ECG leads for ischemic changes and arrhythmias, sublingual nitroglycerin for relief of ischemic chest discomfort, aspirin, intravenous β-blocker if no contraindications are present, intravenous nitroglycerin, thrombolysis in eligible patients, or primary PCI if facilities for acute intervention are available. Data from more than 1.5 million patients in the NRMI from 1990 to 1999 indicate that the rates of thrombolysis have declined from 34.3% to 20.8% and the rate of primary PCI has increased from 2.4% to 7.3%. Contraindications and dosing for ACS pharmacotherapy are listed in Table 1-5. After initial therapies, the patient should be admitted to the coronary care unit for arrhythmia and frequent vital sign monitoring for complications of AMI. Serial troponin and CK-MB biochemical markers should be measured during the first 16–24 hours. Within the first 24 hours after presentation, a fasting lipid panel should be obtained. Within 1–2 days, an angiotensin-converting enzyme (ACE) inhibitor should be administered to patients without contraindications. Most patients should be started on a statin (hydroxymethyl glutaryl-coenzyme A reductase inhibitor) before hospital discharge. Left ventricular function should be measured in all patients with AMI before hospital discharge. If a patient did not undergo early angiography and primary PCI, and who has refractory or recurrent ischemia, left ventricular dysfunction, or a positive stress test for ischemia, the patient should undergo angiography with possible PCI.

Aspirin, Intravenous Nitroglycerin, and β-Blockers

Administering 325 mg of aspirin acutely reduced the risk of 35-day mortality by 20% compared to placebo and reduced mortality by 40% when combined with streptokinase (SK) in the International Study of Infarct Survival Study (ISIS)-2. The 2001 Antithrombotic Trialists' Collaboration (ATC) recommends initial administration of about 150–300 mg of aspirin for all patients with AMI, followed indefinitely with a maintenance dose of 75–325 mg/day. The ACC/AHA AMI guidelines recommend a dose of 160–324 mg of aspirin initially. Clopidogrel, in a loading dose of 300 mg followed by a maintenance dose of 75 mg, may be administered as an alternative antiplatelet agent if a true aspirin allergy is present. A loading dose of clopidogrel is administered to shorten the onset of antiplatelet effect to less than 2 hours compared to several days if no loading dose is administered. Although the results of studies evaluating clopidogrel in STE ACS are not available, the results of a large secondary prevention trial, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), indicate that clopidogrel has efficacy and safety similar to aspirin for chronic treatment in patients with a history of AMI. The ATC meta-analysis of more than 19,000 patients in 15 trials of antiplatelet therapy (primarily aspirin trials) reported that patients treated with 1 month of antiplatelet therapy experienced 13 fewer vascular deaths, five fewer nonfatal reinfarctions, and two fewer strokes at the expense of 1–2 major extracranial bleeding events per 1000 patients treated compared to placebo.

Although administration of intravenous nitrates has not reduced mortality in AMI, the ACC/AHA practice guideline recommends administration of intravenous nitroglycerin for 24–48 hours in STE ACS for patients with heart failure, large anterior infarction, persistent ischemia, and hypertension. If intravenous nitroglycerin is administered to patients with hypertension, the mean arterial pressure should be reduced by about 30%. The major adverse effects of nitrates are hypotension, flushing, and headache.

Landmark clinical trials performed in the 1980s documented the benefit of early β-blocker administration in decreasing mortality, sudden cardiac death, and reinfarction in patients with AMI. A meta-analysis of more than 18,000 patients and 65 trials indicates a 25% reduction in 1-year mortality after early β-blocker administration. A recent analysis of national data from Medicare for 1994 and 1995 of patients discharged after AMI, indicates that prescription of a β-blocker on hospital discharge was associated with a 14% reduction in mortality after adjustment for potential confounders. Conservative estimates indicate that recurrent infarction and revascularization are both reduced by 27%

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.

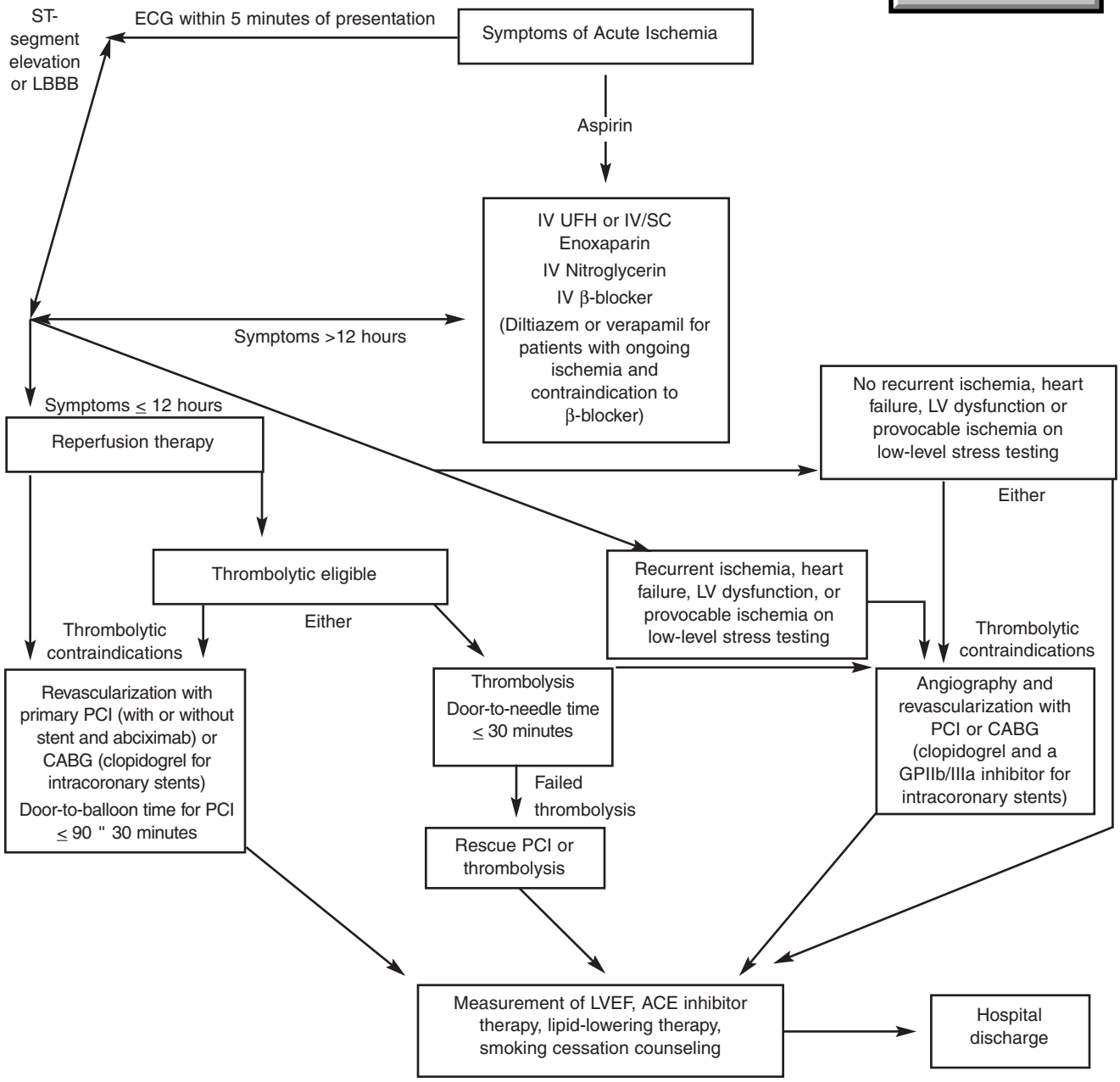

Figure 1-3. Suggested algorithm for treating ST-segment elevation acute coronary syndromes.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; GP = glycoprotein; IV = intravenous; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; SC = subcutaneous; UFH = unfractionated heparin.

and sudden cardiac death by 32% at 1 year in recipients of β-blockers. The ACC/AHA guideline recommends withholding initial therapy with β-blockers in patients presenting with acute decompensated heart failure, heart rates of less than 50 beats/minute in the absence of a pacemaker, heart block or systolic blood pressures of less than 90 mm Hg until those conditions have resolved. Asthma also is considered an absolute contraindication. All other patients should receive early intravenous followed by oral β-blocker therapy within the first 24 hours of infarction. Patients with chronic obstructive airway disease treated with β-agonists should receive β-blockers with extreme caution, starting with low doses of a β_1-selective agent.

Thrombolysis

Thrombolytic therapy is indicated in patients presenting with STE ACS with at least 30 minutes of ischemic chest discomfort, symptom onset of 12 hours or less before hospital presentation, and STE of at least 1 mm in two or more contiguous leads. Patients with new or presumed new left bundle branch block also are candidates for reperfusion as their mortality rates are also high. Thrombolytic therapy should be initiated within 30 minutes after presentation to the hospital as shorter times to treatment as associated with lower mortality. The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group reported that, compared to placebo, 49 lives are saved for every 1000 patients with left bundle

Table 1-5. Pharmacotherapy for Acute Coronary Syndromes (ST-segment Elevation and non-ST-segment Elevation)

Drug Category	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose
Aspirin	STE ACS, class I recommendation[b] for all patients NSTE ACS, class I recommendation for all patients	Hypersensitivity Active bleeding Severe bleeding risk	160–325 mg on hospital day 1 75–325 mg/day starting hospital day 2 and continued indefinitely
Clopidogrel	STE ACS, class II recommendation in patients allergic to aspirin NSTE ACS, class I recommendation for all hospitalized patients in whom a noninterventional approach is planned In PCI in STE and NSTE ACS, class I recommendation	Hypersensitivity Active bleeding Severe bleeding risk	300-mg loading dose on hospital day 1 followed by a maintenance dose of 75 mg orally every day starting on hospital day 2 Administer indefinitely in patients with an aspirin allergy (class I recommendation) Administer for at least 9 months in medically managed patients with NSTE ACS (class I recommendation) Administer for at least 30 days to 1 year in patients with STE or NSTE ACS (class I recommendation) undergoing PCI If possible, withhold for at least 5 days in patients whom CABG is planned to decrease bleeding risk (class I recommendation)
Unfractionated heparin	STE ACS, class I recommendation in patients undergoing PCI; class IIa recommendation for patients treated with alteplase, reteplase or tenecteplase; class IIa recommendation for patients not treated with thrombolytic therapy	Active bleeding History of heparin-induced thrombocytopenia Severe bleeding risk Recent stroke	60 units/kg intravenous bolus Constant intravenous infusion at 12 units/kg/hour (maximum 1000 units/hour) Titrate to maintain aPTT between 1.5 and 2.5 times control for NSTE ACS and 50–70 seconds in STE ACS The first aPTT should be measured at 4–6 hours for NSTE ACS and STE ACS in patients not treated with thrombolytics The first aPTT should be measured at 3 hours in patients with STE ACS who are treated with thrombolytics
Low-molecular-weight heparin	NSTE ACS, class I recommendation as an alternative to aspirin; class IIa recommendation over UFH in patients without renal failure who are not anticipated to undergo coronary artery bypass graft surgery within 24 hours	Active bleeding History of heparin-induced thrombocytopenia Severe bleeding risk Recent stroke Creatinine clearance < 15 ml/minute	Enoxaparin 1 mg/kg SC every 12 hours *Adjustment for renal insufficiency* 1 mg/kg SC every 24 hours for patients with creatinine clearance < 30 ml/minute
Thrombolytic therapy	STE ACS, class I recommendation in patients age < 75 years presenting within 12 hours after the onset of symptoms; class IIa recommendation in patients age 75 years and older; class IIb in patients presenting between 12 and 24 hours after the onset of symptoms with continuing signs of ischemia.	Absolute and relative contraindications per Table 1-7	Streptokinase: 1.5 MU IV over 60 minutes Alteplase: 15 mg IV bolus followed by 0.75 mg/kg IV over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg (maximum 35 mg) over 60 minutes (maximum dose = 100 mg) Reteplase: Two doses of 10 units IV, 30 minutes apart Tenecteplase < 60 kg = 30 mg IV bolus 60–69.9 kg = 35 mg IV bolus 70–79.9 kg = 40 mg IV bolus 80–89.9 kg = 45 mg IV bolus ≥ 90 kg = 50 mg IV bolus

Table 1-5. Pharmacotherapy for Acute Coronary Syndromes (ST-segment Elevation and non-ST-segment Elevation) (continued)

Drug Category	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose	
Glycoprotein IIb/IIIa receptor blockers	NSTE ACS, class IIa recommendation for either tirofiban or eptifibatide for patients with either continuing ischemia, elevated troponin or other high-risk features; class I recommendation for patients undergoing PCI; class IIb recommendation for patients without high-risk features who are not undergoing PCI Optional therapy with abciximab for primary PCI in patients with STE ACS (no specific recommendations)	Active bleeding Prior stroke Thrombocytopenia	*Drug Dose for PCI*	Abciximab 0.25 mg/kg IV bolus Followed by 0. 125 mcg/kg/minute (maximum 10 mcg/minute) for 12 hours
			Dose for NSTE ACS with/without PCI	Not recommended
			Adjustment for renal insufficiency	None
			Drug Dose for PCI	Eptifibatide 180 mcg/kg IV bolus, two doses 10 minutes apart with an infusion of 2 mcg/kg/minute started after the first bolus
			Dose for NSTE ACS with/without PCI	180 mcg/kg IV bolus followed by an infusion of 2 mcg/kg/minute
			Adjustment for renal insufficiency	Reduce maintenance infusion to 1 mcg/kg/minute for patients with serum creatinine 2.0–4.0 mg/dl; not recommended for patients with serum creatinine > 4.0 mg/day
			Adjustment for Obesity	Patients weighing more than 121 kg should receive a maximum of 22.5 mg per bolus and a maximum infusion rate of 15 mg/hour
			Drug Dose for PCI	Tirofiban Not recommended
			Dose for NSTE ACS with/without PCI	0.4 mcg/kg IV infusion for 30 minutes followed by an infusion of 0.1 mcg/kg/minute
			Adjustment for renal insufficiency	Reduce bolus dose to 0.2 mcg/kg/minute and the maintenance infusion to 0.05 mcg/kg/minute for patients with creatinine clearance < 30 ml/minute

Table 1-5. Pharmacotherapy for Acute Coronary Syndromes (ST-segment Elevation and non-ST-segment Elevation) (continued)

Drug Category	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose
Nitroglycerin	STE and NSTE ACS, class I indication in patients whose symptoms are not fully relieved with three sublingual nitroglycerin tablets and initiation of β-blocker therapy, in patients with large infarctions, those presenting with heart failure or those who are hypertensive on presentation	Hypotension	5–10 mcg/minute by continuous infusion Titrated up to 75–100 mcg/minute until relief of symptoms or limiting side effects (headache or hypotension with a systolic blood pressure < 90 mm Hg or more than 30% below starting mean arterial pressure levels if significant hypertension is present) Topical patches or oral nitrates and acceptable alternatives for patients without ongoing or refractory symptoms
β-Blockers[b]	STE and NSTE ACS, class I recommendation in all patients without contraindications, class IIb recommendation for patients with moderate left ventricular failure with signs of heart failure provided they can be closely monitored	PR ECG segment > 0.24 seconds 2º or 3º atrioventricular block Heart rate < 60 beats/minute Systolic blood pressure < 90 mm Hg Shock Left ventricular failure with congestive heart failure Severe reactive airway disease	Target resting heart rate 50–60 beats/minute **Metoprolol** 5 mg increments by slow (over 1–2 minutes) IV administration Repeat every 5 minutes for a total initial dose of 15 mg Follow in 1–2 hours with 25–50 mg orally every 6 hours If a very conservative regimen is desired, initial doses can be reduced to 1–2 mg **Propranolol** 0.5–1.0 mg IV dose Follow in 1–2 hours with 40–80 mg orally every 6–8 hours **Esmolol** Starting maintenance dose of 0.1 mg/kg/minute IV Titrate in increments of 0.05 mg/kg/minute every 10–15 minutes as tolerated by blood pressure until the desired therapeutic response has been obtained, limiting symptoms develop, or a dose of 0.20 mg/kg/minute is reached Optional loading dose of 0.5 mg/kg may be given by slow IV administration (2–5 minutes) for more rapid onset of action **Atenolol** 5 mg IV dose Follow 5 minutes later by a second 5 mg IV dose and then 50–100 mg orally every day initiated 1–2 hours after the IV dose
Calcium channel blockers	STE ACS class IIa recommendation and NSTE ACS class I recommendation for patients with ongoing ischemia who are already taking adequate doses of nitrates and β-blockers or in patients with contraindications to or intolerance to β-blockers (diltiazem or verapamil for STE ACS and diltiazem, verapamil or amlodipine for NSTE ACS) NSTE ACS, class IIb recommendation for diltiazem for patients with AMI	PR ECG segment > 0.24 seconds 2º or 3º atrioventricular block Heart rate < 60 beats/minute Systolic blood pressure < 90 mm Hg Shock Left ventricular failure with congestive heart failure Severe reactive airway disease	Diltiazem 30–240 mg sustained-release once daily Verapamil 80–240 mg sustained-release once daily Nifedipine 30–120 mg sustained-release once daily

Table 1-5. Pharmacotherapy for Acute Coronary Syndromes (ST-segment Elevation and non-ST-segment Elevation) (continued)

Drug Category	Clinical Condition and ACC/AHA Guideline Recommendation	Contraindications[a]	Dose
ACE inhibitors	STE ACS, class I recommendation within the first 24 hours after hospital presentation for patients with anterior wall infarction, clinical signs of heart failure and those with ejection fraction less than 40% in the absence of contraindications; class IIa recommendation for all other patients in the absence of contraindications NSTE ACS, class I recommendation for patients with heart failure, left ventricular dysfunction, and ejection fraction < 40%, hypertension or type 2 diabetes mellitus; indicated indefinitely for all patients post-AMI	Systolic blood pressure < 100 mm Hg History of intolerance to an ACE inhibitor Bilateral renal artery stenosis	*Drug* — *Initial Dose (mg)* — *Target Dose (mg)* Captopril — 6.25–12.5 — 50 2 times/day to 50 3 times/day Enalapril — 2.5–5.0 — 10 2 times/day Lisinopril — 2.5–5.0 — 10-20 once daily Ramipril — 1.25–2.5 — 5 2 times/day or 10 once daily Trandolapril — 1.0 4 once daily
Morphine sulfate	STE and NSTE ACS, no class recommendation for patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort

[a]Allergy or prior intolerance contraindication for all categories of drugs listed in this chart.
[b]Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II recommendations are those conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa recommendations, the weight of the evidence/opinion is in favor of usefulness/efficacy. Class IIb recommendations are those for which usefulness/efficacy is less well established by evidence/opinion.
[c]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially selection, and should favor a short-acting agent, such as propranolol or metoprolol or the ultra short-acting agent, esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 mcg/kg/minute esmolol as initial doses) rather than complete avoidance of β-blocker therapy.
ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; AHA = American Heart Association; AMI = acute myocardial infarction; aPTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; ECG = electrocardiogram; IV = intravenous; NSTE = non-ST-segment elevation; PCI = percutaneous coronary intervention; SC = subcutaneous; STE = ST-segment elevation; UFH = unfractionated heparin.
Adapted with permission from the American College of Clinical Pharmacy. Spinler SA. Acute coronary syndromes. In: Mueller BM, Bertch KE, Dunsworth TS, et al, eds. Pharmacotherapy Self-Assessment Program, 4th ed. Cardiovascular II. Kansas City, MO: ACCP, 2001:157–90.
Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology; American Heart Association guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction-2002: summary article. A report of the Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). J Am Coll Cardiol 2002;40:1366–74.
Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.
Smith SC Jr, Blair SN, Bonow RO, et al; American College of Cardiology; American Heart Association Scientific Statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;104:1577–9.

branch block ACS treated, 37 lives are saved for every 1000 patients with anterior wall STE ACS treated and eight lives are saved for every 1000 patients with inferior wall STE ACS treated. Mortality reductions with thrombolysis compared to placebo have been documented for up to 10 years after the initial treatment. Thrombolysis is equally effective in women as in men.

Pharmacological characteristics and dosing of currently available thrombolytic agents are listed in Tables 1-5 and 1-6. Alteplase, reteplase, and tenecteplase are more specific for fibrin than SK. Alteplase and SK are administered by infusions. Alteplase requires a bolus and two different infusion doses to be administered sequentially. Reteplase and tenecteplase are administered by bolus doses. Tenecteplase is given in a single bolus and reteplase as two bolus doses separated by 30 minutes. Alteplase and tenecteplase doses are based on the patient's weight, whereas reteplase and SK are administered in the same dose to all patients.

A large clinical trial found that alteplase decreased total mortality by 1% (absolute reduction) compared to SK. More fibrin-specific thrombolytics such as alteplase, reteplase, and tenecteplase have higher rates of complete patency (TIMI-3 flow) of the infarct artery at 60–90 minutes after treatment initiation. Another large clinical trial, the third Global Use of Strategies to Open Occluded Arteries (GUSTO-III), found that reteplase was not superior to alteplase. Because this was not an equivalency trial, no claim of equivalence could be made. However, the 30-day mortality results of 7.24% for alteplase and 7.47% for reteplase were so clinically similar that practitioners have concluded that the results of the 15,000-patient trial are consistent with clinically equivalency in efficacy and safety between the agents. Tenecteplase and alteplase were equivalent in efficacy and rates of intracranial hemorrhage (ICH) but tenecteplase demonstrated a small (1.28% absolute) lower rate of major bleeding and no difference in minor bleeding in the Assessment of Safety

Table 1-6. Comparison Between Thrombolytic Agents

Agent	Fibrin Specificity	TIMI-3 blood flow Complete perfusion at 90 minutes	Systemic bleeding risk/ ICH risk	Cost per Patient
Streptokinase	+	35%	+++/+	$400
Alteplase	+++	50–60%	++/++	$2400
Reteplase	++	50–60%	++/++	$2400
Tenecteplase	++++	50–60%	+/++	$2400

ICH = intracranial hemorrhage; TIMI = Thrombolysis in Myocardial Blood Flow (TIMI-3 blood flow indicates complete perfusion of the infarct artery).

and Efficacy of a New Thrombolytic (ASSENT)-2 trial. Despite this fact, many institutions have not adopted tenecteplase for their formularies. Most institutions maintain two thrombolytics on their formulary. One agent remains the oldest fibrin-specific agent, alteplase, because it carries the additional Food and Drug Administration-approved labeled indications for ischemic stroke and pulmonary embolism. The other agent is either one of the two bolus thrombolytics, reteplase or tenecteplase, as they are easier to administer than alteplase.

Absolute contraindications to thrombolysis are listed in Table 1-7. The most serious complication of thrombolysis, ICH, occurs in about 1% of patients and is lower in patients treated with SK compared to those treated with more fibrin-specific agents, such as alteplase. Older age, female gender, and low body weight are predictors of bleeding risk, including ICH, in patients treated with thrombolysis. In patients receiving thrombolytics, the use of a lower, weight-based dose of concomitant unfractionated heparin (UFH), as currently recommended in the ACC/AHA guidelines, is associated with a lower frequency of ICH and major bleeding than higher UFH doses recommended for initial treatment of venous thromboembolism. Patients with renal insufficiency have higher rates of bleeding with antithrombotic therapy compared to patients without renal insufficiency. One meta-analysis of clinical trials suggested that bolus thrombolytic therapy was associated with a higher rate of ICH than infusion therapy. The results of this study were questioned because of the heterogeneity of the trials selected and the fact that many of the thrombolytics studied were not commercially available and some were not developed further for clinical use.

Combination therapy with GP IIb/IIIa receptor blockers and thrombolytics has demonstrated an increased risk of bleeding. Two large clinical trials, GUSTO-V and ASSENT-3, demonstrated an increased risk of major bleeding and no mortality benefit with coadministration of abciximab with half-doses of either reteplase or alteplase compared to standard reteplase or alteplase doses without concomitant GP IIb/IIIa receptor blocker therapy. In addition, there was an increased risk of ICH in the subgroup of patients older than 75 years of age treated with combined GP IIb/IIIa receptor blocker and thrombolytic therapy. The risk of ICH was increased by 1% (absolute; p=0.06) in GUSTO-V and major bleeding was increased 3-fold (4.1% vs. 13.3%) in ASSENT-3 with combination therapy compared to standard therapy. Thrombocytopenia also was greater in patients treated with abciximab in both trials. However, these trials demonstrated a significant reduction in reinfarction. The majority of patients admitted with STE ACS in the United States will undergo angiography and PCI during hospitalization. More than 60% of patients receive a GP IIb/IIIa receptor blocker without thrombolytic therapy at that time rather than at initial presentation to the hospital in conjunction with thrombolytics. Reduction in reinfarction has been demonstrated with this approach. (See the Primary PCI Versus Thrombolysis section for further discussion of GP IIb/IIIa receptor administration in STE ACS.) Therefore, the practice of administering one-half dose thrombolytic concomitantly with a GP IIb/IIIa receptor blocker on hospital presentation has not become the standard of care.

There is controversy regarding the use of thrombolysis in patients older than 75 years of age. Although these elderly patients make up only 6% of the population, more than 36% of all AMIs occur in this patient group. In addition, their mortality is extremely high. Sixty percent of all AMI deaths occur in this age group. The ACC/AHA AMI guidelines support the use of thrombolysis in patients older than 75 years old who present within 12 hours after the onset of symptoms, provided they have no contraindications. (See Table 1-5 for a description of the class recommendations.) Clinical trials specifically in this age group have not been completed because of poor patient enrollment. Therefore, data from clinical trials with no specific upper age exclusion have been pooled to examine the risks and benefits of thrombolysis in the elderly. The FTT collaborative group reported that in patients older than 75 years of age, there

Topol EJ; The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet 2001;357:1905–14.

Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605–13.

Table 1-7. Absolute and Relative Contraindications to Thrombolytic Therapy ACC/AHA Guidelines for Management of Patients with Acute Myocardial Infarction

Absolute

- Previous hemorrhagic stroke at any time; other strokes or cerebrovascular events within 1 year
- Known intracranial neoplasm
- Active internal bleeding (not including menses)
- Suspected aortic dissection

Relative

- Severe, uncontrolled hypertension on presentation (blood pressure > 180/110 mm Hg)
- History of prior cerebrovascular accident or known intracerebral pathology not covered in absolute contraindications
- Current use of anticoagulants in therapeutic doses (INR ≥ 3)
- Known bleeding diathesis
- Recent trauma (within 2–4 weeks), including head trauma or traumatic or prolonged (> 10 minutes) CPR or major surgery (< 3 weeks)
- Noncompressible vascular puncture
- Recent (within 2–4 weeks) internal bleeding
- For streptokinase, prior exposure (5 days to 2 years) or prior allergic reactions
- Pregnancy
- Active peptic ulcer
- History of severe, chronic hypertension

CPR = cardiopulmonary resuscitation; INR = international normalized ratio.

Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: American College of Cardiology; American Heart Association guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.

were 10 fewer deaths for every 1000 patients treated compared to placebo. If those data were limited to the elderly who presented with STE or left bundle branch block 12 hours or less after symptom onset, the number of lives saved increases to 34 per 1000 patients treated. In the ISIS-2 trial, the number of lives saved per 1000 patients older than 75 years of age treated with SK and aspirin was 80, the greatest of any age group. However, this benefit is at a cost of increased stroke, which is about 2% in this patient group compared to 1.2% in younger patients. The FTT collaborative group reported no excess of strokes in patients younger than 55 years treated with thrombolysis compared to placebo; however, excess in stroke increased with increasing age. Patients 55–74 years of age experienced an excess of five strokes per 1000 patients treated, whereas those 75 years and older experienced an excess of eight strokes per 1000 patients treated compared to placebo. The absolute mortality benefit in patients 65–75 years ranged from 2.6% to 6.4%, whereas the risk of ICH and stroke ranged from 0.4% to 2.0%. For patients 75 years or older, the mortality benefit ranges from 1% to 9.1%, whereas the ICH and stroke risk ranges from 0.8% to 3.1%. In a large series of patients 65 years of age or older with AMI treated at Minnesota hospitals between 1992 and 1996, there was an approximate 50% increase in mortality in thrombolysis recipients versus nonrecipients on multivariate analysis if one or more contraindications to thrombolysis were present. The lack of benefit of thrombolysis observed in some observational databases, such as the Cooperative Cardiovascular Project (CCP), could be secondary to "overuse" of thrombolysis in elderly patients with contraindications and exclusion of high-risk patients most likely to benefit from thrombolysis, such as those with left bundle branch block or shock. Although information on primary PCI in patients 75 years of age and older is limited, subgroup analysis of pooled data from small trials comparing thrombolysis versus primary PCI suggests a mortality benefit of primary PCI over thrombolysis. Another pooled analysis of data from individual trials determined the number needed to treat to prevent one death or reinfarction was eight patients older than 70 years compared to 15 patients 60–70 years and 23 patients younger than 60 years.

In general, there are difficulties implementing any reperfusion strategy in very elderly patients. Patient cognitive impairment makes history taking for bleeding risks difficult. Renal failure makes PCI less attractive secondary to contrast media-associated acute renal failure. Serious comorbid illness, which already limits life expectancy, makes treatment decisions more difficult. Later presentation to the hospital is a contraindication to thrombolysis. These data imply that careful assessment of benefit versus bleeding risk for elderly patients presenting with ACS should be performed by an experienced clinician, and particular attention should be paid to ensuring that eligibility criteria, both ECG and time since onset of symptoms, are met before thrombolytic administration. Additional clinical trials specifically performed in elderly patients are warranted.

All patients receiving thrombolytics should be monitored for external and internal bleeding. All stools should be tested for blood. Neurological status should be carefully monitored for any change during administration of the thrombolytic and for 24 hours after completion of the dosing regimen. Unessential needle sticks should be avoided. Intravenous lines, at least two large bore lines, should be

inserted peripherally before thrombolytic drug administration and used for blood draws during the first 24 hours. Insertion of central venous lines should be avoided during this time as well. Blood should be typed and screened so that the information is readily available for transfusion should bleeding occur. If major bleeding occurs, all thrombolytic, antiplatelet, and anticoagulant therapies should be discontinued and blood transfusion or administration of cryoprecipitate should be considered depending on the severity of the bleeding. Chest discomfort should be relieved and STE should be resolving within 60 minutes of therapy initiation. If the patient still has signs of infarction, rescue PCI or rescue thrombolysis should be considered for failed primary thrombolysis.

Unfractionated Heparin Versus Enoxaparin

Although not recommended in the 1999 ACC/AHA AMI guideline, enoxaparin is emerging as an acceptable alternative to UFH for STE ACS based on data from recent clinical trials. The strongest data supporting the use of UFH for STE ACS come from a meta-analysis of 20 small randomized trials published only as an abstract in 1988 documenting a 17% reduction in mortality ($p=0.005$), 22% reduction in reinfarction ($p<0.05$) and 50% reduction in stroke ($p<0.005$). Trials in the 1990s established a role for UFH infusion administered with fibrin-specific thrombolytics, whereas UFH infusion does not seem to be necessary with less fibrin-specific, longer acting agents such as SK. The current ACC/AHA recommendations for UFH infusion in STE ACS come from two clinical trials. The first, GUSTO-I, used a higher dose of UFH than currently recommended by the ACC/AHA guidelines, which was not weight-based. In GUSTO-I, an activated partial thromboplastin time of 50–70 seconds was associated with the best clinical outcomes; therefore, this is the target currently recommended for UFH. The second clinical trial, ASSENT-3, confirmed that the currently recommended UFH dose, an intravenous bolus of 60 units/kg (maximum bolus of 4000 units) followed by an infusion of 12 units/kg/hour (maximum infusion rate of 1000 units/hour), was relatively safe and effective in combination with tenecteplase. The current UFH dose recommended by the ACC/AHA has not been tested specifically with alteplase or reteplase. The ASSENT-3 trial was a 6000-patient, three-arm trial that compared full-dose tenecteplase with UFH (the dose recommended in the Food and Drug Administration-approved labeled indication regimen), to full-dose tenecteplase with enoxaparin, and half-dose tenecteplase and low-dose UFH and full-dose abciximab. Enoxaparin was administered as a 30-mg intravenous bolus followed by a subcutaneous injection every 12 hours. The results of the abciximab arm were discussed in the Thrombolytics section. Patients treated with 30-mg intravenous enoxaparin followed by 1 mg/kg subcutaneously every 12 hours experienced a lower rate of the combined primary end point of 30-day death, in-hospital reinfarction, or in-hospital refractory ischemia compared to full-dose tenecteplase with UFH (11.4% vs. 15.4%, respectively; $p=0.0009$). In comparing the individual components of the primary end point, there was less reinfarction and refractory ischemia in enoxaparin-treated patients compared to UFH-treated patients. Although there was no difference in mortality, the 30-day death rate of 5.4% in enoxaparin-treated patients is the lowest observed in any thrombolytic trial to date. The rates of major bleeding and ICH were not statistically different between the two groups. One criticism of this trial is that enoxaparin was allowed to be administered for up to 7 days, whereas UFH was limited to 48 hours, which is the duration of UFH recommended by the 1999 ACC/AHA AMI guideline. Therefore, the benefit observed could have been secondary to extended anticoagulation in the enoxaparin-treated patients. However, subgroup benefit was already evident at 48 hours with lower event rates in the enoxaparin and abciximab arms ($p<0.0001$). Given the results of this trial, enoxaparin can be considered the preferred anticoagulant in combination with tenecteplase for treating STE ACS. Whether enoxaparin can be administered with alteplase or reteplase is controversial. Two additional small Phase II angiographic trials of intravenous followed by subcutaneous enoxaparin were designed to study restoration of coronary blood flow after treatment with enoxaparin in combination with alteplase and SK compared to UFH. In the Second Trial of Heparin and Aspirin Reperfusion Therapy (HART)-2, alteplase (standard dose) and enoxaparin, administered as a 30-mg intravenous bolus followed by a subcutaneous maintenance dose of 1 mg/kg every 12 hours was compared to UFH and showed similar 90-minute infarct artery patency (combined TIMI-2 and -3 flow, 80.1% vs. 75.1%, respectively; p value not specified) and reocclusion (3.1% vs. 9.1%, respectively; $p=0.12$). In the SK-AMI trial, enoxaparin improved TIMI-3 coronary blood flow at 8 days compared to UFH (70% vs. 50%; $p=0.001$) and had a lower 30-day composite end point of death, reinfarction, or recurrent angina (13% vs. 21%; $p=0.03$). Currently, there are no angiographic or clinical data combining enoxaparin with reteplase. However, there are no data with alteplase or reteplase using the currently recommended ACC/AHA UFH dosing regimen either. One trial, ASSENT-3 Plus, noted a higher rate of ICH with enoxaparin compared to UFH in elderly patients (older than 75 years) treated with tenecteplase. A large clinical trial of enoxaparin versus UFH in patients with STE ACS treated with all currently available thrombolytics is ongoing. The results will determine enoxaparin's expansion into the STE ACS arena. Enoxaparin has not been studied in the setting of primary PCI for AMI and cannot be recommended at this time.

Angiotensin-converting Enzyme Inhibitors

The 1999 ACC/AHA AMI treatment guidelines recommend early low-dose oral ACE inhibitor therapy within the first 24 hours of presentation for patients with STE ACS presenting with either anterior STE on ECG, clinical signs of heart failure, or left ventricular ejection fraction (LVEF) of less than 40% in the absence of hypotension (systolic blood pressure less than 100 mm Hg) as a class I indication. Early administration of ACE inhibitors to other patients with AMI, including those with NSTE AMI and those without impaired left ventricular function, is a class II indication. This recommendation was strengthened by the 2001 AHA/ACC Guidelines for Preventing Heart Attack and Death in Patients with

Atherosclerotic Cardiovascular Disease, which recommended ACE inhibitor therapy for all patients who are post-AMI.

Numerous large randomized, clinical trials have documented the benefit of ACE inhibitors in decreasing mortality, development of heart failure, and reinfarction. The ACE Inhibitor Myocardial Infarction Collaborative Group, a systematic review of more than 100,000 patients who were started on ACE inhibitor therapy within 36 hours of hospital admission, reported a 7% reduction in 30-day mortality or five lives saved per 1000 patients treated. In the 19,000-patient Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto-3 study (7), administration of lisinopril decreased mortality by 12% at 6 weeks compared to placebo. In ISIS-4 (8), captopril, administered within 24 hours of hospital admission, reduced 5-week mortality by 6.5%. This represents a mortality benefit of five lives saved per every 1000 treated. In patients with anterior wall AMI, 10 lives were saved per every 1000 treated. In the Acute Infarction Ramipril study of patients with AMI with clinical heart failure, mortality benefit was demonstrated early as well as at 5-year follow-up. Angiotensin-converting enzyme inhibitor doses and contraindications are described in Table 1-5. Lower doses should be administered initially and patients must be carefully monitored to avoid hypotension, which could decrease coronary artery blood flow. Patients also should be monitored for the development of acute renal failure, especially those receiving concomitant diuretics or nonsteroidal anti-inflammatory drugs.

Proposed mechanisms for benefit by ACE inhibitors include reduction in left ventricular remodeling and ventricular dilitation, which results in less heart failure and sudden death and fewer hospital admissions. Reinfarction and stroke also are reduced. Proposed mechanisms for these benefits include enhancement of nitric oxide release, leading to improvement in endothelial function, promotion of angiogenesis to ischemic myocardium, and a reduction in atrial fibrillation.

Early Initiation of Statin Therapy

As discussed in the Dyslipidemias chapter of this book, the Third National Cholesterol Education Program Adult Treatment Panel recommends treatment with either a statin, bile acid-binding resin, or niacin in patients with coronary artery disease who have a low-density lipoprotein cholesterol value of 130 mg/dl or higher. The low-density lipoprotein target for treatment in these patients is less than 100 mg/dl. Evidence is emerging that statins may be the drug therapy of choice in patients after ACS. Statins have a clear role in preventing atherosclerotic progression and promoting regression in patients with arterial vascular disease. Statins improve endothelial vasodilation by increasing nitric oxide within 24 hours to 3 days after starting treatment. Statins also decrease macrophage and monocyte activity in patients with coronary artery disease, thereby decreasing inflammation and CRP values. As previously discussed, elevated CRP values in patients presenting with ACS have been correlated with increased mortality and reinfarction after ACS. Statins also have antithrombotic effects, such as decreasing fibrinogen, factor Va activation, and thromboxane-A_2 concentrations. Animal models suggest that statins may reduce infarct size when administered in high doses.

Early initiation of statin therapy during hospital admission for AMI has been associated with reduced mortality in registries, a case-control study, and a retrospective analysis of randomized, clinical trials. In the Maximal Individual Therapy in Acute Myocardial Infarction Registry, an increased use of statin therapy was associated with a reduction in in-hospital mortality (from 15.2% to 13.2%; $p<0.001$). Patients in a large Swedish registry who were discharged receiving a statin had a lower adjusted 1-year mortality compared to patients discharged without statin therapy (3.7% vs. 5%; $p<0.0001$). Retrospective analysis of the GUSTO-IIb, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial and the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS)- TIMI 16 trial indicates a reduction in mortality in patients who were discharged on a statin (or in the case of OPUS-TIMI 16 any lipid-lowering therapy) compared to those who were not. In the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial, patients who had received a statin before admission, but discontinued statin therapy during admission, had an increased risk of 30-day death or AMI compared to patients who continued their prior statin therapy.

One prospective, randomized, placebo-controlled, clinical trial evaluated early initiation of statin therapy within 96 hours of hospital admission in 3086 patients presenting with either STE or NSTE AMI. Atorvastatin 80 mg was associated with a reduction in the primary combined end point of death, nonfatal AMI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia at 16 weeks compared to placebo. These results were of borderline statistical significance (95% confidence interval = 0.70–1.00; $p=0.048$). A secondary end point, stroke, was reduced significantly by 51% ($p=0.04$). The mean low-density lipoprotein concentration was 72 mg/dl in treated patients compared to 124 mg/dl in patients receiving placebo. The prevalence of liver function test elevation was 2.5% in atorvastatin-treated patients. Additional randomized, clinical trials should be performed to evaluate the need for high-dose statin therapy and the maintenance of low-density lipoproteins well below 100 mg/dl with their use. Other studies have reported higher drug adherence in

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GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction: Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet 1994;343:1115–22.

ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345:669–85.

individual patients as well as a higher percentage of patients meeting low-density lipoprotein targets when lipid-lowering therapy was initiated during hospitalization. Although these data are not conclusive, based on the results of a lipid panel performed within 24 hours of hospital admission, most patients should be discharged with lipid-lowering therapy with doses targeted to achieve a low-density lipoprotein value of less than 100 mg/dl. The safety, efficacy, and cost-effectiveness of statins for secondary prevention of CHD events have been demonstrated. Statins should be initiated early in patients hospitalized for ACS, excluding those with contraindications, such as pre-existing liver disease.

Important Ongoing Clinical Trials that may Shape Clinical Practice

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 is a 2 x 2 factorial design study of 4000 patients comparing pravastatin 40 mg/day versus atorvastatin 80 mg/day in patients randomized within 10 days of ACS. The second part of the trial randomizes the patients to gatifloxacin 400 mg/day for 10 days of every month versus placebo. The primary end point is a combination of death, AMI, stroke, rehospitalization for unstable angina, and revascularization, occurring more than 30 days after enrollment. The minimum expected follow-up is 18 months. This study is ongoing and completion is anticipated in 2004.

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction (EXTRACT)-TIMI-25 is randomizing about 20,000 patients with STE ACS who are eligible to receive thrombolytics to either UFH or enoxaparin in combination with either SK, alteplase, tenecteplase, or reteplase. The primary end point is the combination of death/AMI and the primary safety end point is major bleeding as defined by the TIMI criteria (TIMI major bleeding). The dose of enoxaparin is reduced in patients older than 75 years to eliminate the 30-mg intravenous bolus and decrease the subcutaneous dose from 1 mg/kg to 0.75 mg/kg every 12 hours.

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-TIMI-28 trial will randomize 3000 patients with STE ACS treated with thrombolysis and either low-molecular-weight heparin or UFH to either a 300-mg loading dose of clopidogrel followed by 75 mg/day or placebo. The primary end point is patency of the infarct artery measured at hospital discharge between days 3 and 8. This trial is expected to be completed in late 2004.

The Second Chinese Cardiac Study (CCS-2) is a 2 x 2 factorial design trial evaluating 30,000 patients with ACS who present with STE, left bundle branch block or ST-segment depression, and suspected AMI who are treated with intravenous thrombolytics. The study has four treatment arms with two different comparisons. The first comparison is aspirin alone versus aspirin plus 75 mg of clopidogrel. The second comparison is intravenous followed by oral metoprolol versus placebo. The two primary end points of the antiplatelet comparison are 1) death, reinfarction, or stroke, and 2) total mortality at 28 days. The two primary end points of the metoprolol comparison are death, reinfarction or cardiac arrest, and mortality at 28 days. The results of this study are expected in early 2004. It is hoped that this study will help determine the need for concomitant β-blocker treatment in the era of reperfusion therapy and widespread ACE inhibitor use. In addition, if clopidogrel plus aspirin reduces mortality, reinfarction, or stroke, clopidogrel use could by justified in STE ACS.

Patient Case: NSTE ACS

L.S. is a 65-year-old Caucasian woman with a past medical history of type 2 diabetes mellitus, hypercholesterolemia, and two-vessel coronary artery disease who presents with midline chest pain for 3 hours unrelieved by rest and sublingual nitroglycerin. She states that the pain is similar in nature to the pain she experienced during her previous hospital admission 8 months ago for NSTE AMI. During that hospital admission, she underwent coronary angiography and left anterior descending artery stent placement. She also had a 60% stenosis of the right coronary artery. Her ejection fraction measured previously by echocardiogram was 45%. She takes oral aspirin 325 mg, extended-release metoprolol 100 mg, and oral simvastatin 40 mg once daily. On arrival in the emergency department, a 12-lead ECG was performed within 5 minutes and interpreted as normal sinus rhythm, heart rate of 70 beats/minute, normal intervals, and 2 mm ST-segment depression in leads V_2–V_4. These changes are indicative of NSTE ACS, anterior ischemia. L.S.'s vital signs were stable with a heart rate of 70 beats/minute, blood pressure of 110/85 mm Hg, and temperature of 37°C. Her physical examination also was notable for an S_3 on heart auscultation and rales on lung auscultation. She did not have peripheral edema and her rectal examination was guiac negative. Her chest radiograph showed mild heart failure. Her troponin I was elevated at 5 ng/ml (AMI decision limit of 0.2 ng/ml). Aspirin 325 mg was administered orally, an intravenous line was inserted, and intravenous nitroglycerin was started at a dose of 5 mcg/minute.

Pharmacological Therapy For NSTE ACS

General Treatment Approach (Algorithm/Guidelines)

Treatment of NSTE ACS was highlighted in the 2002 ACC/AHA practice guideline for unstable angina and NSTE AMI. An NSTE ACS treatment algorithm is described in Figure 1-4. All patients with NSTE ACS should receive aspirin, intravenous followed by oral β-blocker therapy, and

Schwartz GG, Olsson AG, Ezekowitz MD, et al; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA 2001;285:1711–8.

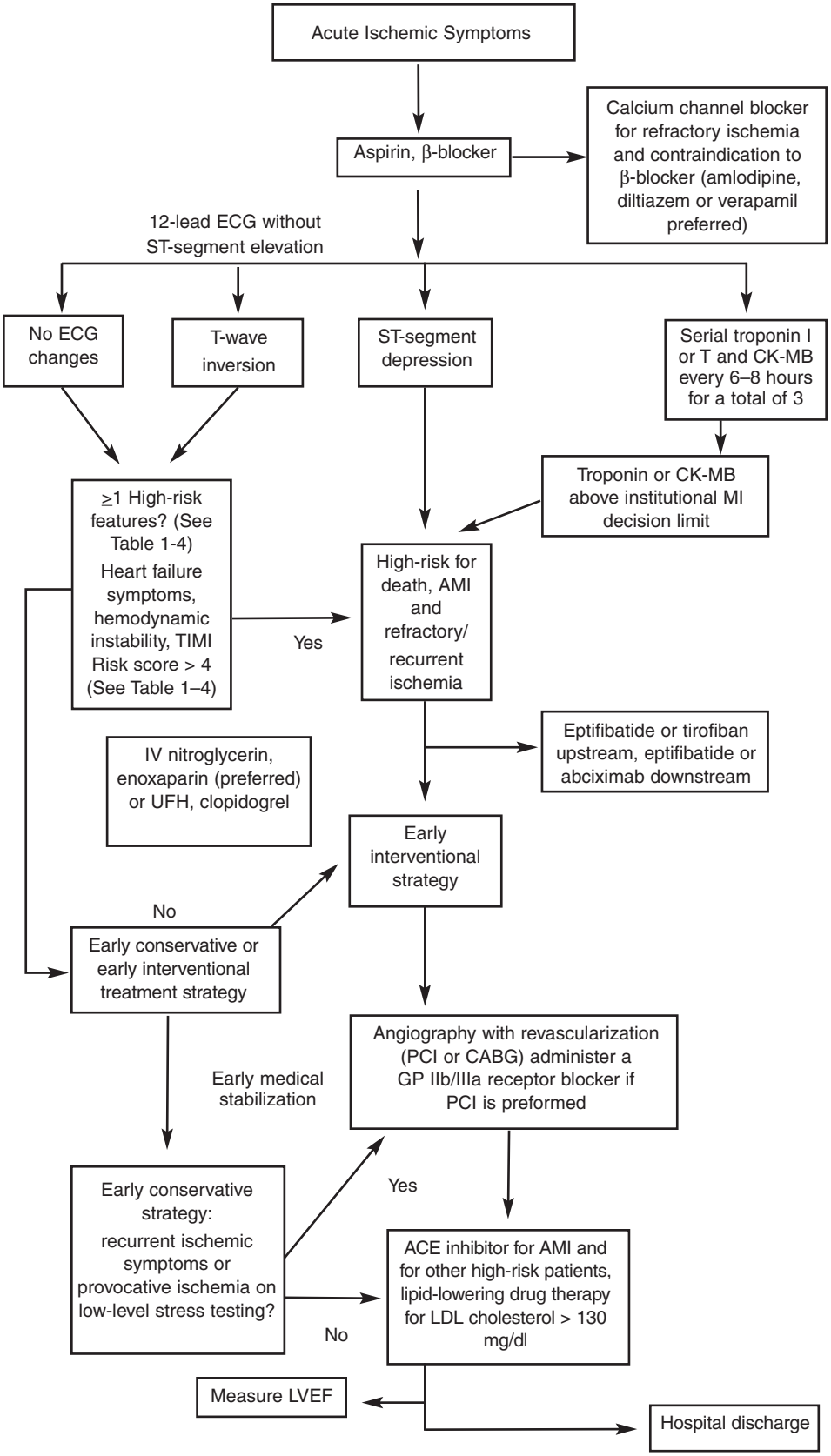

Figure 1-4. Suggested Treatment Algorithm for Non-ST-Segment Elevation Acute Coronary Syndromes
ACE = angiotensin-converting enzyme; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CK = creatine kinase; ECG = electrocardiogram; GP = glycoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction.

intravenous nitroglycerin for the first 24 hours. Indications, contraindications, and dosing of pharmacotherapy for NSTE ACS are summarized in Table 1-5. Patients in whom a medical stabilization strategy is anticipated should receive a 300-mg loading dose of clopidogrel followed by a maintenance dose of 75 mg/day. If angiography is planned, clopidogrel may be delayed until the time of PCI. In general, patients with NSTE ACS should be risk-stratified.

Medium- to high-risk patients, such as those with a TIMI risk score of greater than 3 or patients with ST-segment depression or positive troponin, should receive additional antiplatelet therapy with either eptifibatide or tirofiban, especially if PCI is planned. These patients also should undergo early angiography and revascularization. Abciximab may be initiated at the time of PCI in patients with NSTE ACS. Although dalteparin, enoxaparin, or UFH is a class I treatment option for patients with NSTE ACS, the ACC/AHA guideline gives a class IIa recommendation to enoxaparin over UFH in patients not anticipated for coronary artery bypass graft (CABG), making enoxaparin the preferred anticoagulant for NSTE ACS. Other therapies, such as initiating ACE inhibitors and lipid-lowering agents, are identical to treating patients with STE ACS. Patients at low risk and those treated with medical stabilization strategy should undergo noninvasive stress testing for provocable ischemia. Patients with ischemic symptoms on stress testing should then undergo angiography and possible revascularization.

Aspirin remains an integral part of NSTE ACS therapy. Four large clinical trials totaling 2400 patients demonstrated that aspirin reduces the risk of death or AMI by 50%. Data on the use of β-blockers in NSTE ACS have been extrapolated primarily from STE ACS trials. In contrast to STE ACS, no mortality benefit was found after initiating β-blockers in patients with NSTE ACS. However, one meta-analysis of 4700 patients found a 13% reduction in the frequency of AMI. Data on the benefit of intravenous nitroglycerin in NSTE ACS are limited to small uncontrolled trials; therefore, data that support using intravenous nitroglycerin also have been extrapolated from AMI trials. Calcium channel blockers are not recommended for initial therapy in either STE or NSTE ACS because of the lack of consistent benefit on mortality, AMI, and recurrent ischemia. Use of calcium channel blockers is recommended as a class I therapy only for patients with ongoing ischemia who are already being treated with other medical therapies with no benefit or who have contraindications to β-blockers. In that case, amlodipine, diltiazem, or verapamil is preferred. Thrombolysis is not recommended, even for patients with positive biochemical markers of infarction, as several large randomized trials indicated no benefit and possible harm when used in patients with NSTE ACS.

Aspirin Alone Versus Aspirin plus Clopidogrel

A 300-mg loading dose of clopidogrel followed by a maintenance dose of 75 mg/day is indicated as an alternative to aspirin in patients with a true aspirin allergy. Two large randomized, clinical trials have evaluated the addition of clopidogrel to aspirin therapy in patients with NSTE ACS. In the CURE trial (n=12,562), the addition of clopidogrel to aspirin reduced the composite primary end point of cardiovascular death, nonfatal AMI, or stroke at 9 months by 20% compared to aspirin plus placebo (9.3% vs. 11.4%; $p<0.0001$). This benefit was consistent across all levels of patient risk as stratified by the TIMI risk score as well as numerous subgroups of patients. There was no difference between the groups in rehospitalization rates for unstable angina between discharge and 30 days and between 31 days and 1 year. Major bleeding and transfusion rates were slightly increased. Bleeding rates were higher in patients receiving aspirin doses of more than 160 mg compared to lower doses of 75–81 mg in combination with clopidogrel. There was a trend toward increased life-threatening bleeding rates in patients undergoing CABG (n=2072) who received clopidogrel plus aspirin within the 5 days preceding CABG (7.8% vs. 5.0%; 95% confidence interval = 0.93–2.57) compared to aspirin alone. Limitations of this trial are the fact that PCI was used in only 21% of patients and concomitant GP IIb/IIIa receptor blockers were used in less than 10% of patients, which is not consistent with the standard of care in the United States today.

The PCI-CURE study evaluated 2658 patients from the CURE trial who underwent PCI during hospitalization. Open-label thienopyridine therapy, primarily with clopidogrel, was administered for 30 days after PCI. In contrast to current practice whereby PCI occurs within the first few days of hospitalization, patients in PCI-CURE were treated with medical therapy for a median of 10 days before PCI. Clopidogrel plus aspirin reduced the primary end point of cardiovascular death, nonfatal AMI, and stroke at 30 days and 1 year. A statistically significant reduction in the composite end point could not be demonstrated for the time period between 30 days and 1 year. Eighty percent of the patients received intracoronary stents. Because clopidogrel therapy after intracoronary stenting for 30 days was already the standard of care, the results of this study did not change practice. Questions remained about the need to continue clopidogrel for longer than 30 days in patients receiving stents.

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial attempted to answer some of these questions. The CREDO trial was a double-blind, randomized, placebo-controlled trial comparing aspirin plus clopidogrel initiated 3–24 hours before PCI as a loading dose of 300 mg (pretreatment) followed by a maintenance dose of 75 mg/day versus aspirin alone with clopidogrel administered as 75 mg/day starting at the end of PCI and continued for 28 days only. All patients received 325 mg/day of aspirin. About two-thirds of patients in CREDO had recent AMI or unstable angina. Because CREDO started enrollment before the results of earlier trials which established the role of a 300-mg loading dose of

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

clopidogrel at the time of PCI, the comparator arm, which used only 75 mg initiated at the time of PCI, has been criticized for not corresponding to current standard of care. In addition, administration of GP IIb/IIIa inhibitors was limited to 20% of the population or as an emergency bail-out drugs for unsuccessful PCI. As a result, only 45% of the patients received concomitant GP IIb/IIIa receptor blocker therapy during PCI. In addition, only 60% of patients in both groups completed the full 1-year planned treatment. The most common reasons given for early discontinuation were patient choice and adverse events in both study arms. Given these limitations, the results of CREDO showed no benefit of pretreatment on the composite end point of death, AMI, or urgent target vessel revascularization at 28 days, which was 6.8% in the pretreatment group and 8.3% in the no-pretreatment group (p=0.23). At 1 year, the composite end point of death, AMI, or stroke was significantly reduced by 26.9% in the clopidogrel pretreatment group with long-term clopidogrel compared to the 4-week post-PCI clopidogrel treatment group (p=0.02). Benefit of clopidogrel pretreatment was found in a post hoc analysis if pretreatment with clopidogrel was initiated more than 6 hours before PCI. Data from the specific ACS subgroup have not been published or presented at this time. The most encouraging finding from this trial was that clopidogrel did not increase the risk of major bleeding (8.8% with clopidogrel plus aspirin vs. 6.7% with aspirin alone; p=0.07).

A variety of economic models of CURE evaluating the combination of aspirin and clopidogrel compared with aspirin alone and a wide range of results ranging from cost-saving to financially unattractive with costs as high as $130,000 per quality-adjusted life-year gained have been presented or published. Perhaps the disparity is the result of actual or modeled rehospitalization costs being included in some models of CURE but not in others. The formal CURE economic analysis has not been published at this time. Therefore, there is uncertainty currently regarding the cost-benefit of adding clopidogrel to aspirin therapy for patients with NSTE ACS for chronic therapy.

The 2002 ACC/AHA unstable angina and NSTE AMI guideline recommends the combination of aspirin and clopidogrel as a class I recommendation in patients for whom a noninterventional approach is planned. Clopidogrel is recommended to be started as soon as possible and continued for at least 1 month and up to 9 months based on the results of the CURE study. Clopidogrel may be started at the time of intervention for patients in whom an early interventional approach is planned. Although patients appear to have improved outcomes when clopidogrel is started at least 6 hours before PCI, the guidelines recommend that clopidogrel may be started immediately after angiography, especially at centers with high CABG rates. If, after angiography, the patient requires CABG, no clopidogrel is administered and the patient can proceed directly to the operating room for a CABG. If clopidogrel routinely is given to all patients before angiography, some patients who require CABG within 5 days may experience higher bleeding rates. The decision of when to initiate clopidogrel for patients with NSTE ACS undergoing planned PCI is left to the discretion of the individual cardiologist or institution. However, based on subgroup analysis of the CURE data, about 25% of the first 24-hour benefit and 50% of the first 7-day benefit of clopidogrel is lost if clopidogrel initiation is delayed by 1 day. Clopidogrel therapy duration, when combined with aspirin, in NSTE ACS remains controversial with longer follow-up of patients in CURE anticipated to shape practice. Increased bleeding that occurred in CURE was reported with equal frequency during hospitalization as during follow-up, so all bleeding events were not necessarily related to procedures. Most commonly, clinicians reserve long-term clopidogrel therapy for patients with repeated hospitalizations for ACS, those who have undergone CABG or multiple PCIs, and those who have undergone brachytherapy (clopidogrel recommended for at least 6–12 months) or drug-coated stent implantation (clopidogrel recommended for at least 3 months with sirolimus-eluting stent).

Unfractionated Heparin Versus Low-molecular-weight Heparin

Low-molecular-weight heparins offer the advantages of better bioavailability when administered subcutaneously; higher anti-factor Xa to anti-factor IIa activity, resulting in less thrombin generation; higher release of tissue factor pathway inhibitor, a naturally occurring anticoagulant; less ex vivo platelet activation; greater suppression of von Willebrand factor release; and no routine coagulation monitoring (activated partial thromboplastin time) compared to UFH when administered to treat ACS. The 2002 ACC/AHA unstable angina and NSTE AMI guideline recommends that either a low-molecular-weight heparin or UFH be administered to patients with NSTE ACS as a class I indication. Dalteparin reduced the incidence of death or AMI by 63% at 6 days compared to placebo in the Fragmin During Instability in Coronary Artery Disease I trial and had similar outcomes to UFH in the Fragmin in Unstable Coronary Artery Disease trial. However, dalteparin has never been adequately tested for superiority over UFH as the Fragmin in Unstable Coronary Artery Disease trial was underpowered. No additional dalteparin comparisons to UFH are planned. Enoxaparin was superior to UFH in two trials of NSTE ACS—the Efficacy and Safety of

Mehta SR, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.

Steinhubl SR, Berger PB, Mann JT 3rd, et al; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.

Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. N Engl J Med 2002;346:1800–6.

Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial and the TIMI-11B trial. A meta-analysis of the two trials demonstrated a significant reduction of about 20% in the 43-day composite end point of death, AMI, or urgent revascularization. Recent data from one small head-to-head clinical trial comparing tinzaparin to enoxaparin suggest that low-molecular-weight heparins are not interchangeable for NSTE ACS because patients treated with tinzaparin experienced statistically higher rates of revascularization and the triple composite end point of death, AMI, and recurrent angina at 7 and 30 days. Minor bleeding, in particular subcutaneous hematoma, is increased with low-molecular-weight heparins compared to intravenous infusions of UFH as low-molecular-weight heparins are administered subcutaneously. Major bleeding is similar between UFH and low-molecular-weight heparins.

Patients with renal dysfunction were excluded from clinical trials with enoxaparin and dalteparin, and no specific dosing adjustments are recommended at this time. Some centers monitor anti-factor Xa values in patients with renal dysfunction but there are no specific recommendations for target anti-factor Xa values or dosing adjustments in patients with NSTE ACS. Bleeding rates are increased with either UFH or low-molecular-weight heparins in patients with renal dysfunction. Obese patients (at least up to a total body weight of 160 kg) should be dosed on a mg per kg of actual body weight for enoxaparin. Pharmacodynamic data of several different low-molecular-weight heparins in otherwise healthy obese patients suggest no change in volume of distribution or clearance of anti-factor Xa are based on weight; therefore, some centers do not set a maximum dose of enoxaparin.

Glycoprotein IIb/IIIa Receptor Blockers

The 2002 ACC/AHA unstable angina and NSTE AMI guideline recommends administering either eptifibatide or tirofiban to patients with high-risk features, such as a TIMI risk score of greater than 3 or 4, ST-segment depression, elevated troponin, or continued ischemic symptoms despite other therapies as a class IIa indication. Eptifibatide or tirofiban may be administered to other patients with NSTE ACS as a class IIb indication. For patients undergoing PCI, the guidelines recommend that a GP IIb/IIIa receptor blocker be administered either early or just before PCI. For upstream (before PCI) therapy, the GP IIb/IIIa receptor blocker is initiated several hour to days before PCI, using either eptifibatide or tirofiban. For down stream (at the time of PCI) therapy, either abciximab or eptifibatide may be administered.

Clinical trials supporting these recommendations are discussed in more detail in the Chronic Management of Angina chapter. Eptifibatide added to UFH and aspirin therapy reduced the rate of death or AMI by 10% in the PURSUIT trial of 10,948 patients presenting with NSTE ACS (p=0.04). In the subgroup of patients who did not undergo PCI, no benefit of eptifibatide was seen. In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, tirofiban added to aspirin and UFH decreased the composite rate of death, AMI, or refractory ischemia at 7 days, 30 days, and 6 months. Patients enrolled in PRISM-PLUS were pretreated with tirofiban for 48–72 hours before PCI. The rate of death or AMI also was reduced at 30 days. In PRISM-PLUS, early PCI was encouraged. The benefit of tirofiban was limited to patients who underwent PCI during study drug administration. In contrast, 24- and 48-hour administration of abciximab in the GUSTO-IV ACS trial did not reduce the 30-day rate of death or AMI in patients with NSTE ACS, even in the high-risk subgroups.

There are several proposed reasons for beneficial outcomes in PURSUIT and PRISM-PLUS and negative outcomes in GUSTO-IV ACS. Preliminary data from small pharmacodynamic trials indicate that platelet receptor occupancy and platelet inhibition are highest after bolus administration but not consistent when abciximab is administered over longer time periods. Another potential reason for the negative outcome in the GUSTO-IV trial is that patients enrolled in this trial were of lower risk than those enrolled in either PURSUIT or PRISM-PLUS. Patients with elevated troponin in the absence of ST-segment changes were allowed into the study, a smaller extent of ST-segment depression was used as one of the entry criteria, few patients underwent revascularization, and only 2% underwent early revascularization while still receiving study drug. Therefore, abciximab cannot be recommended for medical stabilization therapy for patients with NSTE ACS at this time.

Only one head-to-head comparison between GP IIb/IIIa receptor blockers has been reported to date. The Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial (TARGET) compared abciximab and tirofiban in patients undergoing elective or urgent PCI stent. In the ACS subgroup, abciximab showed a reduction in the 30-day and 6-month composite end point of death or AMI compared to tirofiban (6.3% vs. 9.3%, respectively; p=0.002 at 320 days, 8.2% vs. 10.4%, respectively; p=0.02 at 6 months). Subsequent to TARGET, the dosing strategy of tirofiban used in PCI, 10 mcg/kg followed by 0.15 mcg/kg/minute, which is different than that used in PRISM-PLUS, has been questioned. Specifically, inadequate platelet inhibition was observed at these doses in several small studies, which suggests that a larger or longer bolus dose is necessary. Whether another trial with a revised dose of tirofiban will be conducted is not clear at this time. Because tirofiban administered downstream has not been beneficial in PCI, adjunctive tirofiban cannot be recommended for PCI unless the PRISM-PLUS dose is used upstream (see Table 1-5). The fact that individual trials as well as meta-analyses of all GP IIb/IIIa inhibitor trials of NSTE ACS indicate that

Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. Circulation 1999;100:1602–8.

Michalis LK, Katsouras CS, Papamichael N, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET. trial. Am Heart J 2003;146:304–10.

benefit is seen only in the subgroup of patients undergoing PCI is reflected in the differing class recommendations in the ACC/AHA guidelines. A higher class recommendation for GP IIb/IIIa receptor blockers (IIa) is given to its use for treating patients who receive PCI compared to use in patients with NSTE ACS (IIb) who are medically treated in one section of the guideline. In another section, the recommendation for a GP IIb/IIIa receptor blocker for PCI in NSTE ACS is a class I recommendation. Patients receiving GP IIb/IIIa receptor blockers (with aspirin and UFH) should be monitored closely as bleeding rates are increased compared to use of UFH and aspirin. Major bleeding rates ranged from 0.7% to 4% in major clinical trials of GP IIb/IIIa receptor blocker therapy. These rates are about 1–2% higher (absolute rates) than those observed in placebo-treated patients. Thrombocytopenia, with platelet counts falling within a few hours of starting therapy, also may occur in up to 3% of patients treated with GP IIb/IIIa receptor blockers, especially abciximab. Both tirofiban and eptifibatide are renally eliminated and require dosing adjustments in patients with renal dysfunction (Table 1-5). Experience with these agents is limited in patients with severe renal dysfunction (dialysis patients) and therefore abciximab may be preferred for those patients.

Important Ongoing Clinical Trials that may Shape Clinical Practice

At the time of publication, there are no significant ongoing or planned clinical trials that are expected to alter clinical practice.

Percutaneous Coronary Intervention of STE ACS

Primary PCI Versus Thrombolysis

Early restoration of flow in the infarct artery to preserve the myocardium and improve survival is the primary goal of therapy in STE ACS. Emergent PCI in the absence of thrombolysis for STE ACS, also called "primary" PCI, results in higher TIMI-3 flow rates of 95% compared to thrombolysis with a fibrin-specific agent (50–60%). Primary PCI also is the reperfusion strategy of choice in patients with contraindications to thrombolysis. A recent meta-analysis of 23 trials comparing primary PCI to primary thrombolysis, including 12 trials using primary intracoronary stenting, demonstrated a reduction in short-term mortality (7% vs. 9%; p=0.02), nonfatal reinfarction (3% vs. 7%; p<0.0001), total stroke (1% vs. 2%; p=0.0004) and ICH (p<0.0001). Major bleeding was increased with primary PCI compared to thrombolysis (7% vs. 5%; p=0.032). Mortality (p=0.0019) and reinfarction (p=0.0053) between 6 and 18 months also were significantly reduced with primary PCI compared to primary thrombolysis. These data agree with the most recent registry data available from the Maximal Individual Therapy in Acute Myocardial Infarction and Myocardial Infarction Registries collected between 1994 and 1998 which report a 46% reduction in mortality for primary balloon angioplasty compared to thrombolysis (6.4% vs. 11.3% with a multivariate odds ratio = 0.58; 95% confidence interval = 0.44–0.77). Therefore, the ACC/AHA 2001 PCI guidelines recommend primary PCI as an alternative to thrombolysis as a class I indication in patients with STE or left bundle branch block ACS who present within 12 hours of symptom onset.

In about 6% of patients, AMI is complicated by cardiogenic shock with high mortality. Recent data (1999–2001) from the international Global Registry of Acute Coronary Events (GRACE) indicate an in-hospital mortality rate of 59% even with contemporary treatment. Primary PCI also is preferred over thrombolysis treatment of patients who present with or who develop cardiogenic shock secondary to AMI. The 2001 ACC/AHA PCI guidelines recommend primary PCI as an alternative to thrombolysis as a class I indication in patients younger than 75 years of age who are within 36 hours of symptom onset and 18 hours of development of cardiogenic shock. Patients enrolled in the largest clinical trial evaluating the outcomes of patients with cardiogenic shock, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, and the SHOCK registry of patients screened but not enrolled, had a lower 30-day, 6-month, and 1-year mortality if they underwent early revascularization with PCI or CABG compared to conservative treatment. In the SHOCK trial, patients were randomly assigned to an initial medical stabilization strategy of treatment that included thrombolysis in 63% of patients, intra-aortic balloon counterpulsation in 86% of patients, and subsequent revascularization in 25% of patients, or to an early revascularization strategy in which patients were treated within 6 hours of randomization with either angioplasty (55%) or CABG (38%). Follow-up of patients enrolled in the SHOCK trial showed that early benefit was not maintained in elderly patients with no statistically significant difference in 30-day and 1-year mortality in patients 75 years of age or older who were treated with early revascularization compared to early medical stabilization (20.8% vs. 30.4% at 1 year; no p value provided). The data from this trial make up the basis for the ACC/AHA PCI recommendation. The SHOCK authors concluded that PCI and early revascularization may be performed in carefully selected elderly patients.

Most patients in the SHOCK trial and registry underwent balloon angioplasty. Recently, a few small observational trials as well as GRACE documented the benefit of stenting in patients with AMI with cardiogenic shock treated with adjunctive abciximab compared to balloon angioplasty, including one study showing lower 30-day mortality.

Intracoronary stenting has become the most common PCI procedure. As discussed in the Chronic Management of

Topol EJ, Moliterno DJ, Herrmann HC, et al; TARGET Investigators. Do Tirofiban and ReoPro Give Similar Efficacy Trial. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med 2001;344:1888–94.

Keely EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.

Angina chapter, intracoronary stents improve acute patency by preventing acute closure and reducing restenosis compared to balloon angioplasty. Early trials of intracoronary stents in primary PCI were concerning as some showed stent thrombosis and lower TIMI-3 flow. More recent data from several small randomized trials and the 2081 patient trial (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications [CADILLAC]), do not suggest worse outcomes but rather improved early patency, lower reocclusion and reinfarction, and less late restenosis and target vessel revascularization in patients treated with abciximab and stenting. However, despite these benefits, mortality has not been reduced with primary stenting compared with primary balloon angioplasty PCI. More routine use of adjunctive GP IIb/IIIa inhibitors in the setting of primary PCI may be responsible for improvement in outcomes. Overall 1-year costs for primary stenting are about $1000 higher than primary balloon angioplasty PCI. Current practice trends favor stent implantation versus balloon angioplasty for primary PCI. Careful attention should be given to UFH dosing and monitoring for bleeding complications, especially if abciximab is administered. Currently, the 2001 ACC/AHA PCI guidelines do not make a specific recommendation regarding the use of stents for primary PCI.

The best results in primary PCI are obtained in centers with high-procedure volume with interventional cardiologists and staff experienced in treating patients with STE ACS. The ACC/AHA target "door-to-balloon" time for primary PCI is 90 ± 30 minutes. To meet this goal, a well-trained, experienced staff must be available 24 hours/day. Mortality rates have been correlated directly with "door-to-balloon" times. Data from the NRMI-2 collected from 1994 to 1998 revealed that the median door-to-balloon time for primary PCI was 1 hour and 56 minutes. Mortality increased with door-to-balloon times longer than 2 hours. This reconfirmed ACC/AHA target door-to-balloon time of 90 ± 30 minutes as a quality-of-care indicator.

The current ACC/AHA 2001 PCI guidelines recommend use of primary PCI in centers that perform more than 200 PCI procedures per year by interventionalists who each perform 75 or more PCI procedures per year. In fact, the guidelines give a class III recommendation, meaning that the therapy is not useful or effective and may be harmful to patients, to primary PCI by an inexperienced operator. If cardiac surgical backup is not available at that hospital, ACC/AHA criteria for performance of primary angioplasty recommends that the institution should perform at least 35 primary PCIs per year. The recommendation to use high-volume centers for better outcomes is supported by data from NRMI-2 and NRMI-3 collected from 1994 to 1998 which reported lower mortality in patients treated with primary PCI compared to patients treated with primary thrombolysis in intermediate-volume (17–48 procedures per year) and high-volume (49 or more procedures per year) compared to low-volume (16 or more procedures per year) centers. The recommendation that primary PCI be performed by more experienced interventionalists is supported by data from the 1995 New York State Coronary Angioplasty Reporting System Registry indicating that mortality is reduced if primary PCI is performed by an interventional cardiologist who performs more than 10 primary PCIs per year.

Because there are few interventional facilities, several trials have examined the feasibility and outcomes associated with transferring patients with primary PCI to tertiary care centers. In the recent Danish Multicenter Randomized Trial on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI), 1572 patients with ACS and at least 4 mm STE who presented to the emergency department within 12 hours after symptom onset were randomized to either thrombolysis with alteplase or transfered within hospital or between hospitals if no interventional cardiology facilities were available at the presenting institution. Results indicated that those assigned to transfer for PCI showed a reduction in the primary composite end point of death, reinfarction, or disabling stroke at 30 days compared to those assigned alteplase (8.0% vs. 13.7%; p=0.0003). The benefit was seen in patients presenting to community hospitals who were transferred for primary PCI (8.5% vs. 14.2% alteplase; p=0.002) and in patients at tertiary care centers who were transferred within their own hospital (6.7% vs. 12.3% alteplase; p=0.048). The community hospitals in this study were well prepared to organize patients' transfer to the tertiary care center as times between presentation and primary PCI were only 20 minutes longer compared to transfer within the tertiary care center (110 minutes vs. 90 minutes). Two other smaller studies—Primary Angioplasty in Patients from German Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis (PRAGUE) and Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT)—confirm the benefit of transfer for primary PCI. A recent meta-analysis of five trials that compared emergent hospital transfer for PCI to on-site thrombolysis showed nonsignificant trends toward reduced mortality (p=0.057), reduction in nonfatal AMI (p<0.0001), and reduction in total stroke (p=0.049) with primary PCI despite an increase of 39 minutes in time to treatment in the primary PCI group compared to the on-site thrombolysis group.

Despite the benefit of primary PCI in STE ACS, the small number of 24-hour interventional cardiology services capable of performing primary PCI in the United States is low and transfer of patients from their presenting hospital to a hospital with 24-hour interventional services is not routine at this time. Under current practice, use of this strategy is limited to less than 3% of patients presenting with STE ACS. Formation of collaborative networks of hospitals with regional ACS centers should be considered as a potential solution for this problem.

Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341:625–34.

Adjunctive GP IIb/IIIa Receptor Blockers

Although the role of adjunctive GP IIb/IIIa receptor blockers in elective PCI and PCI associated with NSTE ACS is well established, there are few data from randomized, clinical trials of GP IIb/IIIa receptor blockers in primary PCI. A landmark clinical trial, Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL), compared primary stenting versus primary stenting plus abciximab in patients presenting within 12 hours of onset of symptoms with STE ACS. In the ADMIRAL study, there was a reduction in the 1-month (6.0% vs. 14.6%; p=0.01) and 6-month (7.4% vs. 15.9%; p=0.02) composite end point of death, reinfarction, and urgent target vessel revascularization with abciximab compared to placebo. Although TIMI minor bleeding was increased with abciximab, TIMI major bleeding was not. In another large comparative, observational study of 650 patients presenting within 12 hours of symptom onset, abciximab plus intracoronary stenting improved TIMI-3 flow (flow suggesting complete reperfusion) and reduced target vessel revascularization at 30 days compared to either balloon angioplasty alone or balloon angioplasty plus abciximab. Thirty-day mortality in this trial also was lower in patients treated with the combination of abciximab-stenting compared to balloon angioplasty alone. Because the preponderance of data demonstrating benefit of adjunctive GP IIb/IIIa receptor blocker therapy in primary PCI is limited to trials with abciximab, other GP IIb/IIIa receptor blockers cannot be recommended for this use at this time outside the setting of a clinical trial. Because angiographic outcomes of TIMI-3 flow were improved to as high as 32% with early administration of abciximab with UFH in the angiographic trials TIMI-14 and Strategies for Patency Enhancement in the Emergency Department (SPEED), many physicians initiate abciximab therapy in STE ACS in the emergency department in patients proceeding to primary PCI before hospital transfer or transfer to the cardiac catheterization laboratory PCI.

The SPEED trial also explored the concept of "facilitated" PCI, whereby early administration of a GP IIb/IIIa receptor blocker in combination with reduced-dose thrombolytic, in this case abciximab plus half-dose reteplase, preceding PCI improved procedural success and final TIMI-3 flow rates after primary PCI. Final TIMI-3 flow rates were higher after PCI in patients presenting to the cardiac catheterization laboratory with initially patent infarct arteries compared to patients with occluded arteries (95% vs. 83%; p=0.001). The procedural success rate, defined as TIMI grade 3 flow or residual stenosis of less than 50%, was higher as well (93% vs. 81%; p=0.001). No specific recommendations regarding adjunctive GP IIb/IIIa receptor blockers for primary PCI are noted in the 2001 ACC/AHA PCI practice guideline. Larger clinical trials examining the role of GP IIb/IIIa receptor blockers and reduced-dose thrombolytic agents to facilitate primary PCI are planned.

Rescue PCI and Rescue Thrombolysis

Although the value of primary PCI for STE ACS is well established, the role of rescue PCI and rescue thrombolysis (readministration of thrombolysis for failed initial therapy with thrombolysis) is less clear. With fibrin-specific thrombolytics, TIMI-3 flow is restored to the infarcted artery only 50–60% of the time. Complete resolution of chest discomfort and STE on ECG identifies patients with patent coronary arteries after thrombolysis. However, complete early resolution of STE occurs in few patients. If patients do not have symptom or ECG resolution at 90 minutes after initiation of thrombolysis, about 50% will have an occluded artery. Rescue therapy may be attempted for these patients. Data on rescue PCI are limited to about 2000 patients from several small randomized, controlled, clinical trials; several case series; and nonrandomized studies. Recent data indicate that the technical success rate of establishing TIMI-2 or -3 flow is between 88% and 96%, which is lower than primary PCI. Rates from the recent trials, most with intracoronary stent use, have the highest rate of having an open artery at the end of the procedure. Pooled data from four of the most recent trials suggest that rescue PCI reduces early heart failure (3.8% vs. 11.7%; p=0.04) with a lower but not significant reduction in recurrent AMI (4.3% vs. 11.3%; p=0.08) compared to conservative medical treatment alone. No early mortality reduction was demonstrated (8.5% vs. 12.2%; p=0.26). Mortality rates in the rescue PCI studies and case series were about 30%, which are substantially higher than those observed after primary PCI. However, mortality in these reports and studies varies with the most recent studies reporting lower mortality rates for rescue PCI of less than 10%. Lower mortality in these trials is probably related to shorter delays in initiating rescue therapy with one study reporting an in-hospital mortality rate of 4.7% with a median difference of only 22 minutes between the time of thrombolysis initiation and rescue PCI. Mortality rates are higher after failed rescue PCI compared to successful rescue PCI.

More recently, rescue PCI involves intracoronary stent implantation with or without use of GP IIb/IIIa receptor blockers. Reinfarction is reduced with stent implantation compared to balloon angioplasty. Major bleeding rates for rescue PCI are higher than those for primary PCI. Some, but not all, studies suggest concomitant GP IIb/IIIa receptor blockers during rescue PCI result in a small increase in bleeding risk. The addition of intra-aortic balloon counterpulsation may decrease the rate of reocclusion after rescue PCI but data with this therapy are limited to one small case series. Completion of randomized trials of rescue versus conservative management in the United States has failed because most cardiologists think it is unethical to randomize patients to a conservative strategy if PCI were

Montalescot G, Barragan P, Wittenberg O, et al; ADMIRAL Investigators. Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–903.

available. In general, the data support a possible benefit in reduction of mortality and reinfarction with a slight increase in bleeding risk. Intracoronary stent implantation in this setting reduces reinfarction. Rescue PCI is given a class I recommendation in the 2001 ACC/AHA PCI guideline (over no rescue therapy) but the weight of evidence was less than that recommending primary PCI.

Controversy exists surrounding the use of a GP IIb/IIIa receptor blocker with rescue PCI. Individual clinical decision-making on a case-by-case basis must be done, depending on the timing since thrombolysis, the patient's age, and the results obtained during PCI. In ASSENT-3 and GUSTO-V trials of thrombolytic therapy in patients with STE ACS, abciximab increased major bleeding events overall with a trend toward increased ICH rates in the elderly. No specific recommendations regarding the use of GP IIb/IIIa receptor blockers in rescue PCI were included in the 2001 ACC/AHA PCI guideline.

Rescue readministration of thrombolysis also has been reported in small case series, totaling about 150 patients. Alteplase was administered after either initial alteplase or SK therapy. Patients originally treated with alteplase received a second infusion of 50 mg of alteplase if rescue therapy was within the first 24 hours or 100 mg if rescue therapy was more than 24 hours since initial therapy. Patients originally treated with SK received 100 mg of alteplase. These reports indicate that retreatment with thrombolytics may decrease infarct size and improve LVEF, and possibly decrease mortality (one study) with an increase in minor bleeding but not major bleeding or ICH. Because data are limited at this time, no firm conclusions can be drawn.

The addition of intra-aortic balloon counterpulsation to rescue therapy may decrease reocclusion, but may increase bleeding risk as the patient must be maintained on UFH to prevent clot formation on the balloon and catheter.

Percutaneous Coronary Intervention During Hospitalization of AMI

If early reperfusion therapy is not initiated, the 2001 ACC/AHA PCI guideline recommends angiography and PCI as class I recommendations in patients with provocable ischemia on low-level stress testing and those with persistent hypotension. Patients receiving thrombolysis who do not have recurrent symptoms also should undergo low-level stress testing before hospital discharge. Angiography and PCI also are recommended as class IIa recommendations during AMI hospitalization for patients with heart failure, LVEF of less than 40%, ventricular tachycardia, or ventricular fibrillation. Because patient survival is higher and sudden cardiac death is lower in those with a patent infarct artery, angiography and PCI also are given class IIb recommendations for all patients who are post-AMI, including those with non-Q-wave AMI. Therefore, most patients with AMI in the United States will undergo angiography and revascularization with either PCI or CABG.

Important Ongoing Trials that may Shape Clinical Practice

Because several trials have demonstrated that the presence of TIMI-3 flow before primary PCI was associated with a lower mortality than TIMI 0–2 flow, future clinical trials will examine adjunctive therapies to improve coronary artery blood flow before primary PCI for STE ACS. The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events trial is randomizing patients with anterior STE or left bundle branch block ACS presenting within 6 hours after the onset of ischemic symptoms to either facilitated PCI or to primary PCI. Patients in the facilitated PCI arm receive abciximab and half-dose (5 units) reteplase administered in the emergency department followed by PCI. The patients treated with primary PCI receive abciximab administered at the time of PCI and no thrombolysis. The primary end point is a composite of 30-day death, reinfarction, and new or worsening heart failure. This trial is expected to complete enrollment of more than 2700 patients in late 2004.

Another trial evaluating facilitated PCI is Addressing the Value of Primary Angioplasty after Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction (ADVANCE AMI). In this trial, more than 5000 patients will be randomized to facilitated PCI with eptifibatide and half-dose tenecteplase followed by immediate PCI or eptifibatide and placebo tenecteplase with primary PCI. There will be a subrandomization to either enoxaparin or UFH in both groups. The primary end point of this trial is a 30-day composite of death or heart failure.

Percutaneous Coronary Intervention of NSTE ACS

Medical Stabilization Versus Early PCI

Two general treatment approaches to PCI have evolved for NSTE ACS. The "early conservative" therapy involves administration of drugs to stabilize the patient, eliminating ischemic symptoms and ECG changes. If the patient has no recurrent ischemic symptoms, the patient would undergo low-level stress testing before hospital discharge. With this approach, angiography and revascularization are limited to patients with recurrent ischemic symptoms and those with provocable ischemia, including chest discomfort, ST-segment changes, ventricular arrhythmias, or findings on either echocardiogram or radionuclide scans accompanying the stress test. In the "early invasive" strategy, patients without contraindications to angiography routinely undergo early angiography and revascularization with either PCI or CABG.

The 2002 ACC/AHA unstable angina and NSTE AMI guidelines recommend (class I recommendation) an early invasive strategy for high-risk patients, including those with any of the following: recurrent ischemic symptoms despite medical therapy or with contraindications to medical therapy, elevated troponin, new ST-segment changes on presentation, heart failure symptoms, high-risk findings on stress testing, LVEF less than 40%, hemodynamic instability, sustained ventricular tachycardia, PCI within the past 6 months, or prior CABG.

Data supporting an early invasive strategy in these patient groups come from three randomized trials comparing contemporary PCI versus medical stabilization,

Fragmin and Fast Revascularization during Instability in Coronary Artery Disease II, Treat Angina with Aggrastat (Tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI-18, and Randomized Intervention Trial in Unstable Angina (RITA) 3 (Table 1-8). Early revascularization with the PCI or CABG procedure typically is associated with a small increase in early AMIs, which is offset by later decreases in AMI and need for repeat revascularization. All three trials had significant reductions in their primary end points. The Fragmin and Fast Revascularization during Instability in Coronary Artery Disease II showed a reduction in 1-year mortality. A pooled analysis of eight clinical trials, which compared a strategy of early routine angiography and revascularization with ischemic-provoked angiography and revascularization to a strategy of ischemia-provoked angiography and revascularization, and included Fragmin and Fast Revascularization during Instability in Coronary Artery Disease II, TACTICS-TIMI-18, and RITA 3, reported a combined risk ratio of 0.88 (95% confidence interval = 0.78–0.99). Economic analysis of TACTICS-TIMI-18 indicate that an early invasive strategy is less costly than an early conservative strategy ($6098 vs. $7180 per patient). Estimated cost per year of life gained using models projecting life expectancy indicate that an early invasive strategy is associated with a cost of between $8371 and $25,769, depending on model assumptions. These costs are well within accepted costs for other medical therapies. The results of these clinical trials and economic analyses support the ACC/AHA recommendation for early angiography and revascularization in these medium- to high-risk patients with NSTE ACS.

Enoxaparin

The current ACC/AHA unstable angina and NSTE AMI guidelines offer the option of using low-molecular-weight heparin in conjunction with GP IIb/IIIa receptor blockers and clopidogrel in PCI. They specifically state that, "Although the data are not definitive, it does appear that GP IIb/IIIa receptor blockers can be used with low-molecular-weight heparin." The guidelines also cite data from small trials demonstrating that PCI can be performed safely with the usual dose of enoxaparin, supplemented by a 0.3-mg/kg intravenous dose in the laboratory before PCI if the last subcutaneous dose was administered between 8 and 12 hours before PCI. This recommendation stems primarily from preliminary data from the National Investigators Collaboration on Enoxaparin (NICE)-3 trial where enoxaparin was administered safely to patients undergoing PCI with abciximab, tirofiban, or eptifibatide. The rate of major non-CABG bleeding observed was 1.9%, which was similar to historical data from trials using GP IIb/IIIa inhibitor and UFH. Data from several small trials in elective PCI indicate that no routine monitoring of anti-factor Xa concentrations is necessary in PCI as weight-based dosing of enoxaparin results in anti-factor Xa concentrations of 0.5–1.5 IU/ml in greater than 97% of patients.

Important Ongoing Trials that may Shape Clinical Practice

The Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial with enoxaparin is enrolling more than 10,000 patients with NSTE ACS who are being randomized to UFH or enoxaparin, which is continued through PCI. Patients are treated with clopidogrel and a GP IIb/IIIa receptor blocker. The primary end point is death or AMI at 30 days. This trial, which is expected to be completed in early 2004, will compliment NICE-3 and determine the efficacy of enoxaparin in patients undergoing PCI.

There is an ongoing international trial comparing enoxaparin (with or without a GP IIb/IIIa receptor blocker), bivalirudin, a direct thrombin inhibitor, (with or without a GP IIb/IIIa receptor blocker), and bivalirudin alone with provisional GP IIb/IIIa receptor blocker (should the interventionalist deem the result unsuccessful) in moderate- to high-risk patients with NSTE ACS who are undergoing early PCI within 48 hours of randomization. The primary end point of this study is a 30-day composite end point of death, AMI, target vessel revascularization or major bleeding. This 14,000-patient trial is just starting enrollment and it is unknown at this time when results can be expected.

Patient-Specific Treatment Plan

Patient Case: STE ACS

J.R. (previously discussed in the STE ACS patient case) presents with STE ACS and a probable inferior wall AMI. The decision to offer reperfusion therapy, either primary PCI or thrombolysis, should be made before knowing the results of a troponin concentration. J.R. presented within 4 hours of ischemic chest discomfort with no contraindications for thrombolysis. Because he presented at 4 hours, which is within 12 hours after symptom onset, he is eligible for thrombolytic therapy. He does not have any contraindications or cardiogenic shock, which would make primary PCI preferable to thrombolysis; therefore, either reperfusion strategy is acceptable for his treatment. At this point, this type of patient should probably not be transferred for primary PCI if such facilities are not available at the presenting hospital unless the facilities are experienced and those transfers are part of routine practice. If thrombolysis is chosen, a more fibrin-selective agent, such as alteplase, reteplase, or tenecteplase, should be administered with therapy initiated within 30 minutes of hospital presentation (see Table 1-5 for dosing of thrombolytics). If primary PCI is selected, J.R.

Cannon CP, Weintraub WS, Demopoulos LA, et al; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879–87.

should undergo the PCI within 90 minutes of hospital presentation.

Most, but not all patients presenting with STE ACS for primary PCI will receive a stent of the culprit artery and, as such, receive concomitant clopidogrel and a GP IIb/IIIa receptor blocker. Published data recommend abciximab as a bolus and 12-hour infusion in primary PCI. Current practice guidelines do not recommend GP IIb/IIIa receptor blocker therapy or clopidogrel in patients with STE ACS who do not undergo primary PCI as initial therapy. However, GP IIb/IIIa receptor blockers and clopidogrel may be administered to patients when undergoing PCI later in the hospitalization.

Patients should be put on bedrest in a room with telemetry monitoring and receive immediate anticoagulant therapy with either intravenous UFH, or intravenous followed by subcutaneous enoxaparin, simultaneously with thrombolysis. Although enoxaparin is not mentioned in the 1999 ACC/AHA practice guideline, data from the ASSENT-3 trial indicate that it is more effective and safer than UFH. Care should be taken not to administer too large an UFH dose concomitant to thrombolysis. In J.R., a maximum bolus of 4000 units followed by 1000 units/hour is indicated. If enoxaparin is used for STE ACS, a bolus dose of 30 mg intravenously should be followed immediately by a subcutaneous injection of 1 mg/kg every 12 hours. Patients who undergo primary PCI should receive UFH as there are no clinical trial data with low-molecular-weight heparins in primary PCI.

Other adjunctive therapies that should be administered include intravenous β-blocker, such as metoprolol followed by oral β-blocker therapy, and intravenous nitroglycerin for 24 hours. J.R. does not have hypotension or any contraindications to β-blockers (Table 1-5). Because he presented with hypertension and a mean arterial pressure of 114 mm Hg, the dose of nitroglycerin should be titrated to reduce the mean arterial pressure by 30%, or to about 81 mm Hg, maintaining the systolic blood pressure above 100 mm Hg. Aspirin 81–325 mg orally once daily should be continued indefinitely. The β-blocker dose should be increased as tolerable to a resting heart rate of between 50 and 60 beats/minute.

Before hospital discharge, J.R. should have left ventricular function assessed by measurement of LVEF. Typically, LVEF is measured noninvasively by echocardiogram. An ACE inhibitor should be initiated before discharge. Dose titration to the target doses described in Table 1-5 is indicated if the patient has a reduced ejection fraction of less than 40%. If the patient has an ejection fraction of less than 30% consideration should be given to an implantable cardioverter defibrillator to prevent sudden cardiac death.

J.R. should have a fasting lipid panel performed within 24 hours of hospital presentaion. If J.R.'s low-density lipoprotein cholesterol is greater than 130 mg/dl, a statin should be started before hospital discharge with the dose titrated as an outpatient to achieve a target low-density lipoprotein cholesterol of less than 100 mg/dl.

Timing of β-Blocker and ACE Inhibitor Administration in Patients with ACS Presenting with Acute Heart Failure

Although initial therapy with β-blockers is not routinely recommended for patients presenting with acute decompensated heart failure, such patients ultimately benefit greatly if β-blockers are initiated after they become more stable. Data supporting the use of β-blockers in patients with heart failure are reviewed extensively in the Chronic Management of Heart Failure chapter. Therefore, patients should be examined daily for resolution of hypotension or signs of heart failure such as rales, the presence of an S_3, and peripheral edema. After a period of stability, and in the absence of inotropic therapy, β-blockers can be initiated cautiously in the absence of other contraindications. The dose should be titrated to a resting heart rate in the range of 50 beats/minute to 60 beats/minute in conjunction with an ACE inhibitor dose titration. In patients presenting with acute decompensated heart failure, ACE inhibitors probably should be initiated before β-blocker therapy, although there are no data from clinical trials specifically assessing this issue. Earlier administration of ACE inhibitors prevents remodeling and ventricular dilitation. In practice, often patients may not reach a target dose of either a β-blocker or an ACE inhibitor before hospital discharge. Therefore, close follow-up of these high-risk patients with careful attention to slow upward dose titration of β-blocker and ACE inhibitor is important.

Patient Case: NSTE ACS

L.S. (previously discussed in the NSTE ACS patient case) presents with NSTE ACS and probable anterior wall AMI. Her TIMI risk score is 5, indicating a high risk of death, AMI, or recurrent angina. She should be placed on bedrest and receive telemetry monitoring for arrhythmias. She should receive aspirin, intravenous nitroglycerin, and enoxaparin. If she is taken for immediate PCI therapy, UFH may be administered instead of enoxaparin. She has signs of acute heart failure, including an S_3, rales, and mild heart failure on chest radiograph. Therefore, acute β-blocker therapy should be withheld initially. If her blood pressure remains above 100 mm Hg after initiation of nitrates, early low-dose oral ACE inhibitor should be initiated within the first 24 hours. She should be reevaluated daily to assess whether her heart failure symptoms have resolved and β-blocker therapy can be initiated. Because of her high-risk features, including ST-segment depression, prior PCI, and heart failure, she should be treated with an early invasive strategy, which includes administration of a GP IIb/IIIa receptor blocker. Clopidogrel can be administered early in the emergency department or at the time of angiography. L.S. is a good candidate for chronic clopidogrel therapy as she has experienced recurrent ACS while

Table 1-8. Contemporary Clinical Trials Comparing Early Invasive Versus Conservative Medical Stabilization for Patients with Non-ST-segment Elevation Acute Coronary Syndrome

Clinical Trial	N	Patient Risk Features	Timing of Early Invasive Therapy	Revascularization Rates	Stent/GP IIb/IIIa Blocker Use in PCI	Results (Invasive vs. Conservative)
TACTICS-TIMI-18	2220	Symptoms < 24 hours from admission ST-depression or T-wave inversion or positive biochemical markers or history of CAD	PCI 25 hours CABG 89 hours	During index admission: Early invasive: 60% Early conservative: 36% At 6 months: Early invasive: 61% Early conservative: 44%	83%/94% 86%/59%	Death, nonfatal MI, rehospitalization for ACS at 6 months[a]: 15.8% versus 19.4% OR = 0.78 (95% CI = 0.62–0.97) Death, nonfatal MI, rehospitalization for ACS at 30 days: 7.4% versus 10.5%, OR = 0.67 (95% CI = 0.50–0.91) 6-month death or nonfatal MI: 7.3% versus 9.5%, OR = 0.74 (95% CI = 0.54–1.00) 6-month MI: 4.8% versus 6.9%, OR = 0.67 (95% CI = 0.46–0.96) 6-month rehospitalization for ACS: 11.0% versus 13.7% OR = 0.78 (95% CI = 0.60–1.00) There were no significant differences in mortality at 30 days or 6 months
FRISC II	2457	Symptoms < 48 hours from admission ST-depression or T-wave inversion or Positive biochemical markers Age < 76 years	PCI 4 days CABG 8 days	At 10 days: Early invasive: 71% Early conservative: 9% At 1 year: Early invasive: 78% Early conservative: 43% PCI at 1 year: Early invasive: 44% Early conservative: 21% CABG at 1 year: Early invasive: 38% Early conservative: 23%	 62%/10% 69%/10%	1-year mortality: 2.2% versus 3.9%, RR = 0.57 (95% CI = 0.36–0.90) 1-year MI: 8.6% versus 11.6%, RR = 0.74 (95% CI = 0.59–0.94) 1-year death/MI[a]: 10.4% versus 14.1%, RR = 0.74 (95% CI = 0.60–0.92) Hospital readmission at 1 year: 3.2% versus 16.0% RR = 0.20 (95% CI = 0.14–0.28) 2-year mortality: 3.7% versus 5.4%, RR = 0.68 (95% CI = 0.47–0.98)

Table 1-8. Contemporary Clinical Trials Comparing Early Invasive Versus Conservative Medical Stabilization for Patients with Non-ST-segment Elevation Acute Coronary Syndrome (continued)

Clinical Trial	N	Patient Risk Features	Timing of Early Invasive Therapy	Revascularization Rates	Stent/GP IIb/IIIa Blocker Use in PCI	Results (Invasive vs. Conservative)
RITA 3	1810	ST-depression or T-wave inversion or New LBBB or Transient ST-elevation or Chest pain at rest Prior CABG, PCI < 12 months or CK-MB Twice the upper limit of normal were excluded	PCI 3 days CABG 22 days	During index admission: Early invasive: 44% Early conservative: 10% At 1 year: Early invasive: 57% Early conservative: 28% PCI at 1 year: Early invasive: 36% Early conservative: 16% CABG at 1 year: Early invasive: 22% Early conservative: 12%	88%/25%	Death/nonfatal MI/refractory angina at 4 months[a]: 9.6% versus 14.5%, RR = 0.66 (95% CI = 0.51–0.85) 1-year death/MI[a]: 7.6% versus 8.3%, RR = 0.91 (95% CI = 0.67–1.25) Mortality at 4 months, 1 year, and 2 years were not statistically different MI at 4 months, 1 year, and 2 years were not statistically different 1-year refractory angina: RR = 0.56 (95% CI = 0.41–0.76)

[a]Primary end point.
ACS = acute coronary syndromes; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CK = creatine kinase; FRISC = Fragmin and Fast Revascularization during Instability in Coronary Artery Disease; LBBB = left bundle branch block; MB = myocardial band; MI = myocardial infarction; N = number of patients; OR = odds ratio; PCI = percutaneous coronary intervention; RITA = Randomized Intervention Trial in Unstable Angina; RR= relative risk; TACTICS = Treat Angina with Aggrastat (Tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy); TIMI = Thrombolysis in Myocardial Infarction.

receiving aspirin alone. Before hospital discharge, the patient should have her left ventricular function assessed by a LVEF measurement. Her fasting lipid panel should be measured within 24 hours of admission and her simvastatin dose increased, if necessary to achieve a target low-density lipoprotein cholesterol of less than 100 mg/dl. The ACE inhibitor dose should be titrated to the target dose described in Table 1-5 if L.S.'s LVEF is less than 40%. If L.S. has an ejection fraction of less than 30%, consideration should be given to implanting an implantable cardioverter defibrillator to prevent sudden cardiac death.

Patient Education

Before hospital discharge, patients with ACS should be educated about the risk factors for CHD, symptoms of ACS, and the importance of early presentation to the hospital if they experience recurrent ischemic symptoms. Results of all diagnostic and stress tests should be discussed with patients. Patients should receive dietary, counseling using the low-fat diet recommended by the National Cholesterol Education Program Adult Treatment Panel. Patients who smoke should be counseled on the importance of cessation as well as referred to an organized smoking cessation program if desired. Clinical trials have shown that smoking cessation is more likely to be successful after an acute, life-threatening event, such as an ACS, as well as when the treating physician firmly recommends smoking cessation. The importance of drug adherence should be emphasized. Indications for each therapy and expected side effects should be explained carefully to patients.

Quality Improvement

ST-segment Elevation ACS

Quality indicators of excellent patient care for STE ACS include initial ECG within 5 minutes of presentation and early reperfusion therapy with either thrombolysis within 30 minutes of presentation or primary PCI in eligible patients within 120 minutes of presentation. Asprin and β-blocker should be administered within the first 24 hours in patients without contraindications. An ACE inhibitor should be initiated minimally for all patients with LVEF less than 40% and preferably all patients with AMI (Table 1-9). A fasting lipid panel should be obtained and patients should be given a diet and drug therapy plan with follow-up to achieve a target low-density lipoprotein cholesterol of less than 100 mg/dl. Patients who smoke should be counseled and cessation encouraged. Documentation of performance for the quality indicators improves patient care and outcomes.

Table 1-9. Quality Indicators for Acute Myocardial Infarction

Quality Indicator	Criterion Met or Acceptable Alternative
1. Early administration of aspirin	1. Within 24 hours of hospital arrival
2. Early administration of β-blocker	2. Within 24 hours of hospital arrival
3. Timely reperfusion	3. Interval from time of arrival to initiation of thrombolysis ≤ 30 minutes or primary angioplasty ≤ 120 minutes
4. β-Blocker at discharge	4. Evidence of prescription upon hospital discharge
5. Aspirin at discharge	5. Evidence of prescription upon hospital discharge
6. ACE inhibitor at discharge for low left ventricular ejection fraction	6. Evidence of prescription upon hospital discharge
7. Smoking cessation counseling	7. Documentation of counseling in medical record
8. Measurement of left ventricular function	8. Evidence of ejection fraction test results in medical record
9. Mortality	9. Report of institutional acute myocardial infarction mortality

In patients presenting 12 hours or less after the onset of symptoms with STE or left bundle branch block, the use of immediate reperfusion therapy with either thrombolysis or primary PCI remained constant from 1994 through 1999 (NRMI data). However, the use of thrombolysis declined and PCI increased by about 6% each. During that same time period, the median "door-to-needle" time (or time from presentation to thrombolytic administration) decreased from 61.8 minutes to 37.8 minutes, but did not meet the target of 30 minutes or less. Underuse, failure to administer reperfusion therapy to patients without contraindications, and overuse of thrombolysis, administering thrombolytic therapy to patients who do not meet eligibility criteria or who have contraindications, is still common. A Danish study of patients with STE ACS admitted to the hospital between 1990 and 1992 reported a thrombolytic overuse rate of about 14%; in contrast, a conservative estimate from 1994 to 1996 NRMI data (only including eligible patients presenting within 6 hours after symptom onset) indicated that thrombolysis was underused in 24% of eligible patients. Thrombolysis is more often withheld in elderly patients, women, and those presenting with cardiogenic shock, despite the absence of contraindications. The Myocardial Infarction Triage and Intervention Registry (MITI) reported that the rate of thrombolysis in patients with AMI who were older than 75 years was only 5% compared to 39% in younger patients. In addition, the use of emergency medical services has been associated with shorter presentation times to the hospital and lower mortality rates. In a community-based survey, 90% of the respondents indicated that they would use emergency medical services for chest pain, whereas only 23% of patients who had chest pain in that community actually did so. Therefore, additional efforts in patient education are needed. The AHA, the National Heart, Lung, and Blood Institute, the American Red Cross, and the National Council on Aging have all initiated programs aimed at increasing patient awareness of heart attack signs. The general goals of these programs are to increase emergency medical services activation by 15% and awareness of heart attack signs by 20%.

Aspirin use was reported by MITI to be only 57% in patients 75 years and older versus 82% in younger patients. According to recent trial data from the Worcester, Massachusetts, area, patients with AMI and heart failure or cardiogenic shock also are less likely to receive aspirin therapy.

Although the benefits of β-blocker administration in patients with ACS have been known for more than 2 decades, they remained underused. Retrospective analysis of a large cohort of Medicare patients discharged after AMI in 1998 and 1999 indicates that only 57% of all patients and 71% of ideal candidates received prescriptions for β-blockers when they were discharged from the hospital. This represents significant improvement compared with rates of 38% and 50%, respectively, from a similar survey of Medicare patients in 1994 and 1995. Data from the Health Plan Employer and Data Information Set (HEDIS) indicate that β-blocker use in managed care plans ranged from 40% to 100% with an average of 80% in patients who are post-AMI. Limitations to this type of data are that all potential confounders and reasons why patients did not receive prescriptions a β-blocker may not have been documented in the patient medical record. Data from NRMI indicated that use of intravenous β-blockers for STE ACS within the first 24 hours of symptoms increased from about 13% to 23% and oral β-blockers increased from 30% to 47% from 1990 to 1999. Institutional characteristics associated with greater β-blocker use include a high degree of goal sharedness among the clinical staff, a high level of administrative support, strong physician leadership, and high-quality data feedback on improving β-blocker prescription performance. The cost-effectiveness of β-blocker therapy is less than $11,000 per quality-adjusted life-year and in some scenarios, cost-saving. Patients should be educated regarding the expected benefit of each of their drugs. Sadly, data from AMI Medicare patients discharged in 1998 and 1999 indicate the rate of smoking cessation counseling dropped from 41% in 1994 and 1995 to 37%.

Tools to assist institutions in developing treatment algorithms are available from the AHA (e.g., "Get with the Guidelines" available from *www.americanheart.org*) as well as the ACC.

Non-ST-segment Elevation ACS

In recent data from GRACE, more than 7000 registry patients with the diagnoses of NSTE AMI and unstable angina received aspirin in 90% and 91%, β-blockers in 78% and 74%, ACE inhibitors in 50% and 50%, clopidogrel in 29% and 21%, GP IIb/IIIa receptor blockers without PCI in

5% and 8%, and GP IIb/IIIa receptor blockers with PCI in 51% and 51%, respectively. Preliminary second quarter results from Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE), a large United States registry of more than 19,000 patients with NSTE ACS, showed acute use rates of aspirin in 90%, β-blockers in 76%, heparins in 83%, and clopidogrel in 35% of patients. Glycoprotein IIb/IIIa inhibitors were administered to 84% of patients undergoing PCI. Rates of drugs taken at the time of hospital discharge were 88% for aspirin, 80% for β-blockers, 59% for ACE inhibitors, 49% for clopidogrel, and 77% for a lipid-lowering agent. These results indicate improvement in aspirin and β-blocker therapy but additional efforts are needed to improve therapy with ACE inhibitor, clopidogrel, and GP IIb/IIIa receptor blockers.

Data from NRMI-4 indicate that GP IIb/IIIa receptor blockers are underused, with only 25% of the patients at the highest risk for death or AMI receiving a GP IIb/IIIa receptor blocker within the first 24 hours of hospital arrival. Patients with NSTE ACS who received early GP IIb/IIIa receptor blockers (within the first 24 hours) in NRMI-4 had lower mortality compared with those who did not receive a GP IIb/IIIa receptor blocker (adjusted odds ratio 0.88; 95% confidence interval 0.79–0.97).

Because of rapid changes in NSTE ACS data, it is difficult to initiate pathways as treatment strategies are changing rapidly. The publication of the 2002 ACC/AHA guidelines provides a framework for institutions to develop treatment algorithms. Example NSTE ACS pathways are available online at *www.clinicaltrialresults.org* and from *www.theheart.org*. Development of institutional treatment strategies for NSTE ACS may improve patient care.

Conclusions

Both STE and NSTE ACS continue to dominate medical care of hospitalized patients who have high mortality and AMI rates. Antithrombotic therapy plays a central role in pharmacological management. Enoxaparin is becoming the predominant anticoagulant in the patient with ACS. Combination antiplatelet therapy with aspirin, clopidogrel, and GP IIb/IIIa receptor blockers is indicated for high-risk patients, whereas aspirin and clopidogrel are beneficial even in patients at low-risk for death or AMI. Early initiation of statin therapy is becoming more routine, even in the absence of in-hospital lipid panel results. Patient care is evolving rapidly to focus more on interventional therapy for the STE and NSTE patient. Use of new revascularization therapies is expanding into the population with ACS, including the use of drug-coated intracoronary stents. Results of clinical trials may impact patient care even before their publication. Pharmacists are involved in patient care in several ways, such as adaptation of practice guidelines to institutional pathways, staff education, and patient education. Core performance measures for each hospital should be developed and the results disseminated to hospital staff. Pharmacists are encouraged to keep current with care of patients with ACS through information provided by the ACC, AHA, and through important Web sites, such as *www.theheart.org*, *www.clinicaltrialresults.org*, and *www.timi.org*, which provide summaries of the study design and results of new clinical trials shaping practice.

Annotated Bibliography

1. Braunwald E, Antman EM, Beasley JW, et al; American College of Cardiology; American Heart Association Committee on the Management of Patients With Unstable Angina. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002;40:1366–74.

   These guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) outline the treatment strategy for non-ST-segment elevation (NSTE) acute coronary syndromes (ACS) and are the most important source for practitioners developing patient treatment pathways and institutional quality indicators. There are no formal organizational or governmental quality indicators for NSTE ACS, except those for patients with NSTE acute myocardial infarction (AMI), which are reviewed in the 2001 AMI ACC/AHA guidelines. The primary changes to the 1999 treatment guidelines are promotion of risk stratification, especially using the Thrombolysis in Myocardial Infarction (TIMI) risk score; encouragement of early angiography and percutaneous coronary intervention (PCI); the addition of clopidogrel to aspirin for most patients; the addition of amlodipine to diltiazem and verapamil as acceptable calcium channel blockers for refractory patients or those with contraindications to β-blockers; and the recommendations that enoxaparin is preferred to unfractionated heparin (UFH) and that enoxaparin can be used with glycoprotein (GP) IIb/IIIa receptor blockers and in patients undergoing PCI.

2. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–7.

   This study describes the TIMI risk score for ST-segment elevation (STE) ACS. Although not as well known as the TIMI risk score for NSTE ACS, this study highlights the main risk factors used to predict mortality outcomes (Table 1-1). The study is important because this risk score can be used in other trials to either stratify patients before randomization or to look for balance of risk factors after randomization.

3. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision-making. JAMA 2000;284:835–42.

   This is a landmark study, which will significantly impact patient care over the next several years. Early risk stratification is encouraged by the ACC/AHA NSTE ACS treatment guidelines. In previous NSTE ACS guidelines, risk stratification seemed cumbersome. Numerous risk features were listed in a table but seemed too overwhelming for clinicians to use for patients in the emergency department. The TIMI risk score for NSTE ACS provides a simple seven-factor list, available for use on a personal digital assistant (PDA); six items are available quickly from a

history; and one item, the troponin, is a laboratory result, typically available within 45 minutes or less. Many institutions have used the TIMI risk score to assist in assigning the level of patient care, with low-risk patients cared for in emergency department chest pain units and high-risk patients assigned to coronary intensive care units and often early PCI. In addition, some centers have used the risk score to define a medical treatment strategy with patients having risk scores of 3 or above receiving enoxaparin and a GP IIb/IIIa receptor blocker. Additional ways to use the score should emerge as the score is now being incorporated prospectively into clinical trials.

4. Smith SC Jr, Dove JT, Jacobs AK, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines. Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). J Am Coll Cardiol 2001;37:2215–39.

   This recent ACC/AHA PCI guideline describes the role of primary PCI in STE ACS. This guideline has the most comprehensive description of the data supporting the qualifications of the institution and the PCI operators who should be performing primary PCI. In addition, data comparing balloon angioplasty versus stents are well summarized. However, there are no recommendations specifically addressing which strategy is preferred for primary PCI. Data describing the role of GP IIb/IIIa receptor blockers in primary PCI are lacking and there are no conclusive recommendations for their use. With the emergence of drug-coated stents in 2003, it is likely that a substantial revision to these guidelines will be undertaken by ACC/AHA.

5. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.

   These guidelines are now somewhat dated. A new revision is expected in spring 2004. However, this guideline forms the focus of most patient care pathways and governmental and managed care quality indicators. Benchmark time frames for treatment initiation are described. These recommendations lack new data on the use of enoxaparin and the recommendation that all patients receive an angiotensin-converting enzyme inhibitor after discharge. The strengths of the guidelines are the description of thrombolytic clinical trials and data related to UFH and β-blockers.

SELF-ASSESSMENT QUESTIONS

Questions 1–5 pertain to the following case.
J.S. is a 77-year-old Caucasian man who is brought to the emergency department by ambulance complaining of 90 minutes of substernal chest pressure at rest. He states that in the past 2 weeks he had noticed fleeting twinges of chest pressure after exertion but these episodes were relieved by rest. After his walk from his car to the office this morning, he developed chest pressure which he described as his chest "being held in a vice grip". When the chest discomfort did not go away after 1 hour, he called 911. En route to the hospital, the paramedics administered three sublingual nitroglycerin tablets and aspirin 325 mg orally one time without relief. His past medical history is significant for type 2 diabetes mellitus diagnosed 6 months ago. He takes aspirin 81 mg orally once daily and metformin 500 mg orally 2 times/day. The patient denies any recent trauma or bleeding tendencies. On physical examination, he is an obese man in moderate distress. His vital signs are: blood pressure = 142/88 mm Hg, heart rate = 89 beats/minute, and he is afebrile. His physical examination is significant for regular rate and rhythm, normal S_1 and S_2, presence of S_3, bilateral rales one-quarter of the way up the lung fields, and rectal guiac negative. An electrocardiogram (ECG) taken 5 minutes after presentation reveals normal sinus rhythm with ST-segment elevation (STE) in the anterior leads. His troponin, creatine kinase (CK) myocardial band (MB) and chemistry panel are pending. Reteplase and alteplase are hospital formulary thrombolytics for acute myocardial infarction (AMI). Interventional cardiologists are on staff and the cardiac catheterization laboratory is fully staffed at this time.

1. Which one of the following criteria identifies J.S. as high risk of death?
   A. Ischemic chest discomfort for 90 minutes.
   B. Prior use of aspirin.
   C. Rales on physical examination.
   D. Elevated blood pressure.

2. Which one of the following reasons best supports primary percutaneous coronary intervention (PCI) as an initial management strategy in J.S. versus administration of thrombolytic therapy?
   A. History of diabetes mellitus.
   B. Rales on physical examination.
   C. Increased risk of bleeding.
   D. Open cardiac catheterization laboratory.

3. Which one of the following additional adjunctive pharmacotherapies should be administered to J.S. in the emergency department?
   A. Intravenous nitroglycerin, intravenous β-blocker, and intravenous unfractionated heparin (UFH).
   B. Intravenous nitroglycerin, intravenous furosemide, and intravenous UFH.
   C. Intravenous glycoprotein (GP) IIb/IIIa receptor blocker, intravenous furosemide, and intravenous enoxaparin.
   D. Intravenous GP IIb/IIIa receptor blocker, intravenous β-blocker, and intravenous and subcutaneous enoxaparin.

4. Which one of the following describes the quality performance measures for the care of J.S.?
   A. Performance of an ECG within 5 minutes of presentation, performance of PCI within 120 minutes of presentation, administration of aspirin within 24 hours, and administration of β-blocker within 24 hours.
   B. Performance of an ECG within 5 minutes of presentation, administration of thrombolytic therapy within 90 minutes of presentation, administration of aspirin within 24 hours, and administration of β-blocker within 24 hours.

C. Performance of an ECG within 10 minutes of presentation, administration of thrombolytic therapy within 90 minutes of presentation, and administration of aspirin within 24 hours.
D. Performance of an ECG within 10 minutes of presentation, performance of PCI within 90 minutes of presentation, and administration of aspirin within 24 hours.

5. Which one of the following is the most important efficacy outcome parameter of therapy for J.S.?
   A. Resolution of STE.
   B. Elevated troponin concentration returning to baseline.
   C. Absence of atrial tachycardia.
   D. Disappearance of rales.

6. When considering the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for treating patients with non-ST-elevation (NSTE) acute coronary syndromes (ACS), which one of the following is a rationale for selecting UFH over enoxaparin as an anticoagulant?
   A. Patient weighing 100 kg with creatinine clearance less than 10 ml/minute.
   B. Patient weighing 150 kg with creatinine clearance 30–60 ml/minute.
   C. Anticipated treatment duration longer than 2 days.
   D. Lower rate of death, myocardial infarction, or recurrent ischemia.

Questions 7 and 8 pertain to the following case.

T.R. is a 66-year-old man with no significant past medical history who presents to the emergency department of a community hospital complaining of substernal chest pain that awoke him from sleep. T.R. experienced the same pain two additional times during the past 24 hours. The pain went away the first two times but has continued this time. The pain is associated with nausea and diaphoresis. T.R. takes aspirin 81 mg/day orally. His vital signs are within normal limits. His blood chemistries and coagulation tests are within normal limits (including a platelet count of 190,000 cells/m^3 and troponin I concentration is less than 0.3 ng/ml, which is normal). T.R.'s ECG shows ST-segment depression of 1 mm in the inferior leads. The chest discomfort is now 1 out of 10 on a pain scale after administration of three sublingual nitroglycerin tablets and the ECG shows 0.5 mm ST-segment depression in the inferior leads. This hospital does not have interventional cardiology services.

7. According to the AHA/ACC NSTE ACS treatment guidelines, which one of the following antithrombotic combinations should T.R. receive (class I indications) in the emergency department?
   A. Eptifibatide, clopidogrel, and UFH.
   B. Aspirin, clopidogrel, and UFH.
   C. Aspirin, abciximab, and dalteparin.
   D. Aspirin, enoxaparin, and tenecteplase.

After initial medical stabilization, T.R. is transferred to another hospital for angiography and PCI of the right coronary artery. At the time of intervention, T.R. was receiving aspirin and UFH. On angiography, the patient received a loading dose of clopidogrel followed by a daily maintenance dose, UFH dosed to an activated clotting time of 200 seconds, and abciximab bolus and 12-hour infusion. T.R.'s UFH was discontinued immediately after the PCI. The morning of the PCI (hospital day 2), T.R.'s platelet count was 150,000 cells/mm^3. A platelet count measured 4 hours after PCI was 30,000 cells/mm^3.

8. Which one of the following antithrombotic therapy-induced adverse events is most likely?
   A. Heparin-induced thrombocytopenia.
   B. Clopidogrel-associated thrombotic thrombocytopenic purpura.
   C. Abciximab-associated thrombocytopenia.
   D. Aspirin-associated thrombocytopenia.

9. Which one of the following patients with STE ACS has the lowest risk of intracranial hemorrhage (ICH) and bleeding?
   A. An 80-year-old patient with persistent inferior STE after primary thrombolysis who also is receiving aspirin and UFH, and is now undergoing rescue PCI.
   B. A 78-year-old patient with anterior STE who received half-dose thrombolytic, aspirin, UFH, and abciximab who is transferred to your hospital with STE elevation for primary PCI.
   C. A 65-year-old patient with ACS with anterior STE now undergoing primary PCI with aspirin, clopidogrel, weight-based UFH, and abciximab.
   D. A 70-year-old patient with chronic renal failure and inferior STE who is receiving primary thrombolysis and enoxaparin demonstrating ST-segment resolution within 90 minutes after the onset of therapy.

Questions 10–12 pertain to the following case.

L.B. is a 90-kg, 67-year-old man who presents to the emergency department complaining of 4 continuous hours of chest pain and associated diaphoresis, which began after he had an argument with his wife. His ECG shows 3 mm ST-segment depression with T-wave inversion in the inferior leads II, III and aVF. L.B.'s past medical history includes elevated low-density lipoprotein, low high-density lipoprotein cholesterol, and type 2 diabetes mellitus for 10 years. He smokes cigarettes occasionally drinks alcohol. His drugs on admission were aspirin 81 mg/day, atorvastatin 20 mg/day, and rosiglitazone. He admits to not filling his atorvastatin or rosiglitazone prescription, stating that he has no health insurance and does not qualify for medical assistance. On physical examination, his blood pressure is 140/85 mm Hg and his heart rate is regular at 55 beats/minutes. His physical examination is normal and he has no signs of acute decompensated heart failure. His chest radiograph demonstrates no active disease and his troponin I is 2.0 ng/ml (range is 0.01 IU/ml to 0.1 IU/ml).

10. Which one of the following is L.B.'s Thrombolysis in Myocardial Infarction (TIMI) risk score?
    A. 3 points.
    B. 4 points.
    C. 5 points.
    D. 6 points.

11. Which one of the following clinical features of this case indicates that L.B.'s ACS can be considered high risk for death or AMI?
    A. T-wave inversion.
    B. Diaphoresis.
    C. Troponin of 2 ng/ml.
    D. Heart rate of 55 beats/minute.

12. If an early interventional strategy is planned whereby L.B. is taken emergently to coronary angiography for probable intracoronary stenting, which one of the following antiplatelet regimens is recommended to be administered as soon as possible?
    A. Aspirin 81 mg, clopidogrel 75 mg, and tirofiban.
    B. Aspirin 325 mg, clopidogrel 450 mg.
    C. Aspirin 325 mg, clopidogrel 300 mg, and eptifibatide.
    D. Aspirin 81 mg and abciximab.

13. As an annual average, your 750-bed tertiary care hospital sees 60 patients with STE ACS who present within 12 hours after symptom onset (half of whom undergo primary PCI); sees 120 patients who have had ischemic strokes presenting within 3 hours of symptom onset; and treats 25 patients for acute pulmonary embolism and hemodynamic instability with thrombolysis. Which one of the following combinations of thrombolytic agents should you select for your hospital's formulary?
    A. Alteplase and reteplase.
    B. Streptokinase (SK) and tenecteplase.
    C. Tenecteplase and reteplase.
    D. Reteplase and SK.

14. The normal range for activated partial thromboplastin time (aPTT) in your hospital is 24–32 seconds. Which one of the following is a desired aPTT target when using UFH in a patient with STE ACS treated with aspirin and thrombolysis?
    A. 28 seconds.
    B. 48 seconds.
    C. 68 seconds.
    D. 88 seconds.

15. Which one of the following is the rationale for using "facilitated" PCI in patients with STE ACS?
    A. The combination of thrombolysis, a GP IIb/IIIa receptor blocker, and PCI results in lower mortality compared to thrombolysis alone.
    B. The combination of thrombolysis, UFH, a GP IIb/IIIa receptor blocker, and PCI results in lower mortality compared to thrombolysis alone.
    C. Administration of UFH, a GP IIb/IIIa receptor blocker, and half-dose thrombolytic before PCI results in increased TIMI-3 blood flow compared to UFH alone.
    D. Administration of a GP IIb/IIIa receptor blocker and full-dose thrombolytic before PCI results in increased TIMI-3 blood flow compared to GP IIb/IIIa recpetor blocker alone.

16. Which one of the following patients should receive an intravenous β-blocker to treat ACS?
    A. A patient with STE ACS and associated chest pain and diaphoresis with a past medical history of type 2 diabetes mellitus, cigarette smoking, and hypertension with new atrial fibrillation presents with rales, S_3 and absent bowel sounds, blood pressure of 120/70 mm Hg, and heart rate of 110 beats/minute on physical examination.
    B. A patient with NSTE and associated chest pain unrelieved by three sublingual nitroglycerin tablets and a past medical history significant for peripheral vascular disease and hypercholesterolemia. Physical examination findings include diminished peripheral pulses. Vital signs are blood pressure of 88/48 mm Hg and heart rate of 85 beats/minute.
    C. A patient with STE ACS and chest pain for 3 hours who has a past medical history of asthma treated with a chronic inhaled β-agonist inhaler and insulin-dependent diabetes mellitus. Physical examination reveals lung crackles, rectal guiac negative, blood pressure of 120/88 mm Hg, and heart rate of 90 beats/minute.
    D. A patient with NSTE ACS and chest discomfort for 4 hours with a past medical history of chronic obstructive pulmonary disease treated with ipratropium bromide and as needed β-agonist inhaler and hypercholesterolemia; physical examination reveals clear lungs, arterio-venous nicking on ophthalmologic examination, blood pressure of 110/70 mm Hg, and heart rate of 65 beats/minute.

17. For which one of the following patients should early ACE inhibitor therapy be withheld during the first 24 hours after ACS presentation?
    A. A 50-year-old patient with diabetes and NSTE ACS, who is troponin-negative, has a left ventricular ejection fraction (LVEF) of 70%, blood pressure of 120/70 mm Hg, and heart rate of 75 beats/minute; no significant findings on physical examination.
    B. A 65-year-old patient with NSTE ACS who is troponin-positive and has two-vessel coronary artery disease on angiography and a LVEF of 50%.
    C. A 50-year-old patient with STE ACS who has mild renal insufficiency, rales, S_3, blood pressure of 110/70 mm Hg, heart rate of 50 beats/minute, and mild heart failure on chest radiograph.

D. A 65-year-old patient with STE ACS, new-onset atrial fibrillation, mild renal insufficiency, S_3, rales, LVEF of 30%, blood pressure of 88/60 mm Hg, and heart rate of 110 beats/minute.

18. Which one of the following patients is the best candidate for primary PCI compared to primary thrombolysis?
    A. A 50-year-old patient with diabetes and NSTE ACS, who is troponin-negative, has a LVEF of 70%, blood pressure of 120/70 mm Hg, and heart rate of 75 beats/minute; no significant findings on physical examination.
    B. A 65-year-old patient with NSTE ACS who is troponin-positive and has a history of two-vessel coronary artery disease on angiography and a LVEF of 50%.
    C. A 50-year-old patient with STE ACS who has mild renal insufficiency, blood pressure of 110/70 mm Hg, heart rate of 50 beats/minute, and no signs of heart failure on chest radiograph.
    D. A 65-year-old patient with STE ACS, new-onset atrial fibrillation, mild renal insufficiency, S_3, rales, LVEF of 30%, blood pressure of 88/60 mm Hg, and heart rate of 110 beats/minute.

19. A 68-year-old man who smokes and no significant past medical history presents to the emergency department with chest pain for 18 hours. An ECG shows anterior STE; his blood pressure is 170/98 mm Hg and heart rate is 100 beats/minute. An echocardiogram is performed in the emergency department, which indicated a LVEF of 30%. Which one of the following quality indicators applies to this patient?
    A. Administration of aspirin within 24 hours, administration of intravenous nitroglycerin within 24 hours, and smoking cessation counseling at the hospital.
    B. Administration of thrombolysis within 30 minutes, administration of aspirin within 24 hours, and administration of a statin at hospital discharge.
    C. Primary PCI within 90 minutes, prescription for an angiotensin-converting enzyme (ACE) inhibitor at hospital discharge, and administration of a statin at hospital discharge.
    D. Administration of a β-blocker within 24 hours, prescription for an ACE inhibitor at hospital discharge, and smoking cessation counseling at discharge.

20. Clinical data supporting the rationale for monitoring anti-factor Xa concentrations in patients receiving low-molecular-weight heparins are strongest for which one of the following groups of patients?
    A. Patients with renal insufficiency.
    B. Patients weighing more than 150 kg.
    C. Patients receiving enoxaparin doses greater than 100 mg.
    D. Patients undergoing PCI.

21. For which one of the following patients would SK be preferred as a thrombolytic over alteplase if primary PCI were not available and early reperfusion was indicated for STE ACS?
    A. A patient receiving warfarin with an international normalized ratio of 3.0.
    B. A patient with a history of SK treatment for a peripheral arterial occlusion 6 months ago.
    C. A patient with gastrointestinal bleeding 1 week ago.
    D. A patient presenting with a blood pressure of 190/110 mm Hg.

22. Which one of the following is the rationale for recommending either abciximab or eptifibatide and not tirofiban for patients undergoing early (less than 4 hours) interventional procedures in patients with NSTE ACS who are at high risk of death or AMI?
    A. Eptifibatide has demonstrated greater reductions in the frequency of death or AMI compared to tirofiban.
    B. Tirofiban has not been studied in patients with NSTE ACS who are at high risk of death or MI; therefore, the dosing is unclear.
    C. The benefit of tirofiban in PCI has only been demonstrated when pretreatment is at least 24 hours before PCI.
    D. Platelet suppression using doses of tirofiban in PCI trials is inconsistent.

23. A patient with a LVEF of 35%, normal renal function, and NSTE ACS has demonstrated triple vessel disease on angiography and will be proceeding to elective coronary artery bypass graft (CABG). Which one of the following actions regarding antiplatelet therapy should be done now for a patient receiving enoxaparin, eptifibatide, aspirin and clopidogrel to prevent bleeding?
    A. Discontinue enoxaparin, eptifibatide, and clopidogrel for 5 days before CABG; continue aspirin.
    B. Continue enoxaparin and aspirin but discontinue clopidogrel for 5 days and eptifibatide until 4 hours before CABG.
    C. Switch enoxaparin to UFH now and continue eptifibatide, clopidogrel, and aspirin until CABG.
    D. Switch enoxaparin to UFH, discontinue eptifibatide 4 hours before CABG, continue aspirin, and discontinue clopidogrel for 5 days before CABG.

24. When evaluating recurrent chest discomfort and ST-segment changes in a patient who was diagnosed with AMI 3 days ago, which one of the following laboratory tests would indicate that the patient has experienced reinfarction?
    A. A CK MB concentration that is elevated above the AMI decision limit and above the value reported yesterday.

B. A troponin I concentration that is elevated above the AMI decision limit and above the value reported yesterday.
C. A troponin T concentration that is elevated above the AMI decision limit and above the value reported yesterday.
D. A CK concentration that is doubled above the value reported yesterday.