Cardiology II

ACUTE CORONARY SYNDROMES: EVOLVING PRACTICES

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Learning Objectives

1. Distinguish ST-segment elevation (STE) and non-STE acute coronary syndrome (ACS) by prognosis and treatment strategy.
2. Evaluate the evidence for and against using C-reactive protein (CRP), lipoprotein phospholipase A_2 (Lp-PLA_2), and cystatin C as risk stratification tools in a patient with ACS.
3. Devise a pharmacotherapy treatment plan for a patient undergoing primary percutaneous coronary intervention (PCI) for STE myocardial infarction (MI).
4. Devise a pharmacotherapy treatment plan for a patient receiving fibrinolytic therapy for STE MI.
5. Devise a pharmacotherapy treatment plan for a patient with non-STE ACS.
6. Evaluate the efficacy and safety of low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) with aspirin and fibrinolytic drugs in patients presenting with STE ACS.
7. Assess the benefits and risks of using immediate oral versus intravenous β-blockade in patients presenting with STE ACS.
8. Justify adding clopidogrel to aspirin in a patient presenting with STE ACS.
9. Measure the quality of patient care using quality performance measures for STE ACS and non-STE ACS.
10. Discover resources to assist clinicians with implementation of practice guidelines.

Introduction

The 2006 Update of Heart and Stroke Statistics from the American Heart Association (AHA) reported that 37% of all deaths in 2003, and 58% of all deaths in 2002 were caused by cardiovascular disease. Coronary heart disease (CHD) is the most frequent cause of death in the United States, with an estimated 221,000 persons dying from myocardial infarction (MI) annually. The estimated annual incidence of MI in the United States is 865,000 per year, with 500,000 Americans experiencing first infarction and 365,000 patients experiencing recurrent infarctions. The rate of MI is expected to rise when statistics become available from recent years, where the diagnosis of MI is based on the more sensitive serum troponin concentration, rather than creatine kinase.

The frequency of percutaneous coronary intervention (PCI) increased by more than 300% between 1987 and 2003 to more than 1.2 million procedure annually. There were more than 467,000 coronary artery bypass graft surgeries performed on 268,000 patients in 2003. Currently, about 85% of patients undergoing PCI receive an intracoronary stent and less than 15% have balloon angioplasty. The estimated cost of CHD in the United States in 2006 is estimated to be $142.5 billion. Drug costs represent only 6.9% of all costs.

Pathophysiology

Plaque Rupture, Thrombosis, and Risk Stratification

The most common cause of acute coronary syndrome (ACS) is rupture of an atherosclerotic plaque followed by vasoconstriction, activation, and aggregation of platelets, and activation of the coagulation system leading to the formation of fibrin. As a result, clot forms at the injury site, leading to partial or complete occlusion of the coronary artery lumen, which may result in myocardial ischemia and/or infarction. Patients presenting with ST-segment elevation (STE) on a 12-lead electrocardiogram (ECG) and ischemic chest discomfort have complete occlusion of a coronary artery leading to MI. Patients presenting with ischemic chest discomfort without STE on a 12-lead ECG are classified as non-STE ACS and may have complete or partial occlusion of a coronary artery, or noncardiac-associated chest discomfort. Additional risk stratification tools, such as serum troponin concentration, the presence of ST-segment depression on the 12-lead ECG,

Abbreviations in this Chapter

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen
CHD	Coronary heart disease
CLARITY	Clopidogrel as Adjunctive Reperfusion Therapy
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
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
ECG	Electrocardiogram
EF	Ejection fraction
ExTRACT	Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
hs-CRP	High-sensitivity C-reactive protein
LMWH	Low-molecular-weight heparin
Lp-PLA_2	Lipoprotein phospholipase A_2
MI	Myocardial infarction
NRMI	National Registry of Myocardial Infarction
NSTE	Non-ST-segment elevation
NTG	Nitroglycerin
OASIS	Organization to Assess Strategies in Acute Ischemic Syndromes
PCI	Percutaneous coronary intervention
REPLACE	Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events
STE	ST-segment elevation
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors
TIMI	Thrombolysis in Myocardial Infarction
UFH	Unfractionated heparin
VALIANT	Valsartan in Acute Myocardial Infarction Trial

or an elevated Thrombolysis in Myocardial Infarction (TIMI) non-ST-segment elevation (NSTE) risk score assist in identifying patients at high risk of MI and recurrent ischemia who require more intensive ECG and hemodynamic monitoring, additional pharmacotherapy, and early diagnostic coronary angiography (Table 1-1). The TIMI risk scores are calculated based on the patient's medical history, clinical signs, and symptoms of ischemia or heart failure, laboratory results, and ECG findings. There are separate scores for STE MI and NSTE ACS. For patients with STE MI, higher scores predict higher likelihood of mortality. For patients with NSTE ACS, higher TIMI risk scores predict a higher likelihood of death, MI, or recurrent ischemia. Initial evaluation of a patient with ACS is presented in Figure 1-1.

Mortality

In-hospital mortality was 9.5% in 6500 patients with STE MI enrolled in the Global Registry of Acute Coronary Events (GRACE) in 2001 and 6.7% in the National Registry of Myocardial Infarction (NRMI) 5 in 2006. Reperfusion therapy was administered to more than 70% of the patients with STE MI in GRACE; 47% (of the total) received fibrinolytic therapy, and 26.7% (of the total) received primary PCI within 12 hours of hospital presentation. The percentage of patients receiving fibrinolytic therapy is declining over time while the percentage receiving primary PCI is rising. Over the 10-year period of 1994–2004, the rate of reperfusion increased from 64% to 72% in the NRMI. In patients with STE MI presenting to the hospital within 12 hours after symptom onset, those who received primary PCI within 2 hours after hospital presentation had a mortality rate of 2.6% compared with 4.6% in those who received primary PCI 2 hours or longer after hospital presentation, based on data for 7100 patients enrolled in NRMI between 1994 and 2002. In NRMI 5, only 50% of patients with STE MI receiving fibrinolysis were administered it within 30 minutes of hospital presentation and 55% received primary PCI within 90 minutes.

In-hospital mortality was 4.8% in 150,000 patients with NSTE ACS and high-risk features on hospital admission enrolled in the United States Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry from 2001 through 2004 and 4.7% in 6000 patients with NSTE MI enrolled in GRACE in 2001. Mortality rates at 6 months are similar in patients with STE MI and high-risk NSTE ACS. Six-month mortality rates for STE MI and high-risk NSTE ACS declined from 7% in patients enrolled in GRACE between 1999 and 2001 to 4.8% in 15,000 patients enrolled in GRACE between 2002 and 2003.

Novel Markers of Risk

Identification of patients at high risk for dying or developing MI plays a pivotal role in the early management of ACS. In addition to TIMI risk scores for STE MI and NSTE ACS, novel markers of risk have been investigated.

Table 1-1. Risk Stratification for Non-ST-Segment Elevation Acute Coronary Syndrome

Using the TIMI Risk Score

Past Medical History	Clinical Presentation
✓ Age = 65 years	✓ ST-segment depression (≥ = 0.5 mm)
✓ ≥ = 3 Risk Factors for CAD	✓ ≥ = 2 episodes of chest discomfort within the past 24 hours
Hypercholesterolemia	✓ Positive biochemical marker for infarction[b]
HTN	
DM	
Smoking	
Family history of premature CHD[a]	
✓ Known CAD (= 50% stenosis of coronary artery)	
✓ Use of aspirin within the past 7 days	

One point is assigned for each of the seven medical history and clinical presentation findings. The score (point) total is calculated and the patient is assigned a risk for experiencing the composite end point of death, myocardial infarction or urgent need for revascularization as follows:

High-Risk	Medium-Risk	Low-Risk
TIMI Risk Score 5–7 points	TIMI Risk Score 3–4 points	TIMI Risk Score 0–2 points

Other Ways to Identify High-Risk Patients:
Other findings which alone, or in combination, may identify a patient at high risk of death or MI:
ST-segment depression
Positive biochemical marker for infarction[b]
Deep symmetric T-wave inversions (≥ 2 mm)
Acute heart failure
Diabetes mellitus
Chronic kidney disease
Recent myocardial infarction (within the past 2 weeks)

[a]As defined by the National Cholesterol Education Program Adult Treatment Panel III Report (2001): the presence of coronary heart disease in a first-degree male relative younger than age 55 or a first-degree female relative younger than age 65.
[b]A positive biochemical marker for infarction is a value of troponin I, troponin T or creatinine kinase MB of greater than the myocardial infarction detection limit.
CAD = coronary artery disease; CHD = coronary heart disease; HTN = hypertension; TIMI = Thrombolysis in Myocardial Infarction.
Adapted with permission from McGraw-Hill. Spinler SA, de Denus S. Acute coronary syndromes. In: DiPiro JT, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: The Pathophysiologic Approach, 6th ed. New York, NY: McGraw-Hill, 2005:291–320.

Because inflammation plays a central role in the development of atherosclerosis, the association of elevated markers of inflammation with ACS outcomes, and their ability to predict risk over and above traditional CHD risk factors, have been investigated.

High-Sensitivity C-Reactive Protein

High-sensitivity C-reactive protein (hs-CRP) is an acute phase reactant that is elevated in tissue injury, inflammation and infection. Plasma hs-CRP concentrations greater than 3 mg/L appear to be an independent predictor of risk for developing ACS in patients without known CHD. Elevated hs-CRP predicts recurrent infarction independent of troponin and the TIMI risk score in patients with either STE MI or NSTE ACS. A study of more than 1800 consecutive patients admitted to the hospital with STE MI or NSTE ACS evaluated the independent association of plasma hs-CRP (measured at the time of hospital admission) and secondary risk. In this study, a plasma hs-CRP value of greater than or equal to 5 mg/L, defined by receiver-operating characteristics, was associated with greater risk of 30-day mortality in patients with STE with a TIMI STE risk score greater than 1. A plasma hs-CRP value of greater than or equal to 3 mg/L, defined by receiver-operating characteristics, was associated with greater risk of death, MI, or recurrent ischemic in patients with NSTE ACS with a TIMI NSTE risk score greater than 2 receiver-operating characteristic curves summarize the sensitivity and specificity of a diagnostic test. A receiver-operating characteristic curve is a plot of the sensitivity versus [1-specificity]. The best predictor would be a graph that is a point in the upper left hand corner that indicates 100% sensitivity with 100% sensitivity. A straight line plotted at a 45-degree angle from the horizontal would indicate equal numbers of true and false positives. However, in other studies, the value of measuring hs-CRP in patients with suspected ACS presenting to the emergency department has not been conclusively demonstrated, as this group of patients, as a whole, present with non-specific chest discomfort and are generally at low risk for mortality and infarction. In addition, the benefit of measuring serial hs-CRP concentrations to monitor change in risk has not been studied. In a 2003 Scientific Statement on the use of hs-CRP testing, the AHA stated that although there may be some role for hs-CRP as an independent predictor of risk in patients admitted with ACS, it should not be used to guide therapy.

Lipoprotein Phospholipase A_2

Lipoprotein phospholipase A_2 (Lp-PLA_2), a secretory phospholipase A_2 of group VIIa, formerly known as platelet-activating factor acetylhydrolase, is produced by inflammatory cells and hydrolyzes phospholipids, generating lysophospholipid and fatty acids. About 80% of human Lp-PLA_2 is carried by low-density lipoprotein

cholesterol bound to apolipoprotein B. Lipoprotein phospholipase A_2 is believed to be a link between lipid accumulation and atherosclerosis. It is expressed in the media of normal and atherosclerotic arteries as well as by myocytes in the acute phase of infarction. Elevations of plasma Lp-PLA_2 are associated with traditional CHD risk factors, such as elevated low-density lipoprotein cholesterol as well as elevations in hs-CRP. One recent study of 446 patients with ACS enrolled in GRACE showed elevated Lp-PLA_2 activity (greater than or equal to 2.9 nmol/minute/mL) on hospital admission to be an independent risk factor for the development of death or MI over a median follow-up of 6 months and was not influenced by other risk factors, such as elevated hs-CRP or low-density lipoprotein cholesterol. Several other case-control and case-cohort studies corroborate these findings. One study suggested that measurement of Lp-PLA_2 soon after ACS was not useful to predict adverse outcomes but when measured 30 days after hospitalization for ACS, Lp-PLA_2 was predictive of the occurrence of either death, MI, unstable angina, revascularization, or stroke independently of measured low-density lipoprotein cholesterol or hs-CRP. Additional studies are under way to determine whether adding Lp-PLA_2 measurement to traditional risk scores improves prediction of adverse cardiac events. Statins, fibrates, and β-blockers have been shown to lower elevated Lp-PLA_2 concentrations.

Cystatin C

Cystatin C is a cysteine protease inhibitor that is freely filtered at the glomerulus and is metabolized at the proximal tubule and, therefore, neither secreted nor reabsorbed. It has been shown to be a better predictor of glomerular filtration rate than serum creatinine. Elevations in cystatin C are associated with other risk factors for CHD, including age, male gender, diabetes mellitus, elevated low-density lipoprotein cholesterol, and low high-density lipoprotein cholesterol. In a recent report from the Cardiovascular Health Study of more than 4500 community-dwelling persons age 65 and older, elevated cystatin C concentrations (greater than or equal to 1.29 mg/L) were found to be an independent predictor of all-cause mortality, cardiovascular mortality, MI, and stroke during a median follow-up of 7.4 years. In a study of more than 700 patients admitted to the hospital with NSTE ACS, elevated cystatin C levels (greater than 1.06 mg/L, cystatin C-derived glomerular filtration rate of less than 72 mL/minute) were associated with increased mortality over a 35-month follow-up period after adjustment for other known risk factors. Results from additional trials evaluating the predictive value of adding

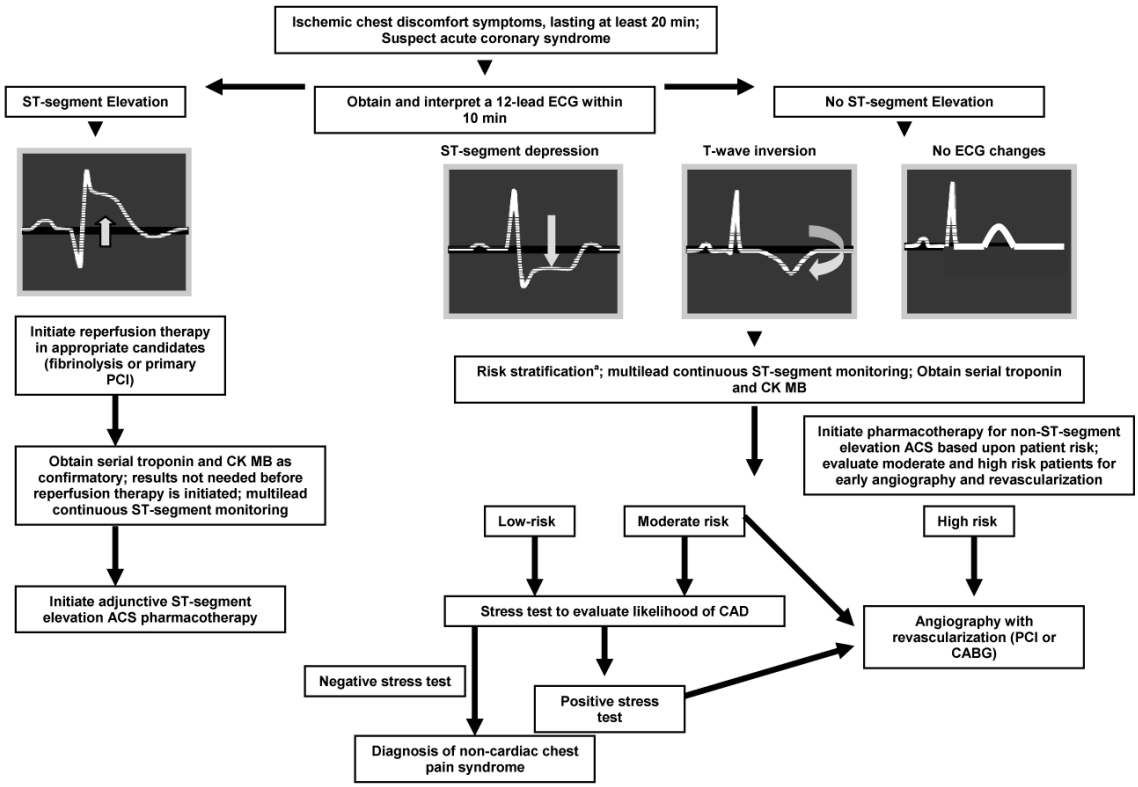

Figure 1-1. Evaluation of the acute coronary syndrome patient.
[a]As described in Table 1-1.
ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CK = creatine kinase; ECG = electrocardiogram; PCI = percutaneous coronary intervention.
Adapted with permission from McGraw-Hill. Spinler SA, de Denus S. Acute coronary syndromes. In: DiPiro JT, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy, 6th ed. New York, NY: McGraw-Hill, 2005:291–320.

cystatin C to traditional risk scores for ACS are eagerly awaited.

Goals of Therapy

The primary goal of therapy for a patient with ACS is rapid and complete coronary artery reperfusion. Secondary goals that accompany reperfusion are: 1) relief of ischemic chest discomfort; 2) prevention of infarction (for patients with NSTE ACS); 3) prevention of reinfarction; 4) prevention of ventricular remodeling leading to systolic dysfunction and low left ventricular ejection fraction (EF); and 5) identification and treatment of hemodynamically significant dysrhythmias. Hemodynamic changes, increased sympathetic tone, and release of neurohormones contribute to ventricular remodeling following MI. Ventricular remodeling is a response to injury whereby the ventricle dilates to maintain stroke volume, leading to increased workload for the non-infarcted myocardium, which results in hypertrophy. This vicious cycle continues and ultimately results in progressive left ventricular dysfunction and heart failure signs and symptoms. The most common dysrhythmias observed in patients with ACS are ventricular fibrillation, ventricular tachycardia, and bradycardia. If the above goals are achieved, the chance of a patient surviving to hospital discharge is increased and long-term mortality is reduced.

Quality Patient Care

Pharmacotherapy for ACS is described in Table 1-2. Effectiveness is assessed by monitoring the patient for resolution of symptoms of chest discomfort and signs of heart failure (if present), resolution of ECG changes (if present), and decreasing the resting heart rate to between 50 beats/minute and 60 beats/minute (normal sinus rhythm). Therapeutic drug monitoring for adverse effects of pharmacotherapy in a patient with ACS is described in Table 1-3.

Treatment Plan

ST-Segment Elevation ACS Algorithm

The AHA and American College of Cardiology (ACC) published updated practice guidelines for treatment of STE MI in 2004. Figure 1-2 is an algorithm for patient management based on the 2004 ACC/AHA guidelines and the findings of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), which evaluated the role of clopidogrel and metoprolol and was published in 2005. The ACC and AHA are expected to publish an update to the 2004 STE MI guidelines in 2007 based on the results of COMMIT as discussed in Pharmacotherapy section below in more detail.

Early pharmacotherapy of STE MI (initiated within the first 24 hours of hospital presentation and preferably in the emergency department) should include intranasal oxygen (if the patient's oxygen saturation is less than 90%), sublingual nitroglycerin (NTG) followed by intravenous NTG, aspirin, clopidogrel, and unfractionated heparin (UFH). Although listed as a class IIb recommendation in the 2004 STE MI ACC/AHA guidelines, no data from randomized, controlled trials support the role of low-molecular-weight heparins (LMWHs) in treating primary PCI. They have been studied in STE MI as an alternative to UFH in patients receiving fibrinolytic drugs and are discussed in more detail under the Pharmacotherapy section. Morphine sulfate is administered for refractory angina or signs of pulmonary congestion. The patient's eligibility for early reperfusion therapy with primary PCI or fibrinolytic drugs should be assessed, preferably before arrival to the hospital. Therapy with a β-blocker should be withheld until the patient is hemodynamically stable without hypotension, shock, or bradycardia. Initial therapy with an oral β-blocker, rather than an intravenous β-blocker, is acceptable. Other therapies that are initiated within the first day or two after hospital admission include lipid-lowering therapy with a statin and an angiotensin-converting enzyme (ACE) inhibitor, or alternatively, an angiotensin receptor blocker (ARB), which also reduces mortality following MI.

Rapid reperfusion therapy with either primary PCI or fibrinolysis is the preferred management strategy for treating STE MI within 12 hours of symptom onset. Selection between primary PCI and fibrinolysis is dependent on access to a cardiac catheterization laboratory and the presence of skilled interventional cardiologists, presence or absence of cardiogenic shock, time from onset of symptoms, and presence of contraindications to fibrinolysis. In general, primary PCI, when available, is the preferred management strategy as it is associated with greater coronary artery reperfusion and a lower risk of stroke. Several meta-analyses of randomized trials of patients eligible for either primary PCI or fibrinolysis suggest a lower mortality rate with primary PCI. Fibrinolysis is generally preferred over primary PCI if the time from onset of symptoms to presentation is less than 3 hours and the time from presentation to primary PCI is greater than 90 minutes. Primary PCI is preferred if a cardiac catheterization laboratory is available with skilled personnel, the patient presents with signs and symptoms of cardiogenic shock, the time from onset of symptoms to presentation is between 3 and 12 hours, a contraindication to fibrinolysis is present, or the diagnosis of MI is in doubt. In a recent meta-analysis, adjunctive therapy with abciximab in primary PCI demonstrated a 32% reduction in 30-day mortality (2.4% vs. 3.4%), preventing 1 death for every 100 patients treated. The effect of timing of administration of abciximab, whether started in the emergency department or at the time of primary PCI, as well as the role of using half-dose fibrinolytic drugs before patient arrival to the cardiac catheterization laboratory to facilitate reperfusion (facilitated PCI), is currently being studied in randomized trials. The combination of half dose fibrinolytic drugs and a glycoprotein (GP) IIb/IIIa inhibitor should be avoided at this time as previous trials demonstrate increased bleeding risk, including increased risk of intracranial hemorrhage in the elderly.

Non-ST-Segment Elevation ACS Algorithm

Treatment of NSTE ACS remains relatively unchanged from 2002 guidelines. Figure 1-3 is an algorithm for patient management based on the 2004 guidelines and the results of newer clinical trials described in Pharmacotherapy. The

Table 1-2. Pharmacotherapy for ST-Segment Elevation and Non-ST-Segment Elevation Acute Coronary Syndromes

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy
Aspirin	STE MI, class I recommendation for all patients NSTE ACS, class I recommendation for all patients	Hypersensitivity Active bleeding Severe bleeding risk	160–325 mg orally once on hospital day 1 75–162 mg once daily orally starting on hospital day 2 and continued indefinitely in patients not receiving an intracoronary stent 325 mg once daily orally for a minimum of 30 days in patients undergoing PCI receiving a bare metal stent, 3 months with a sirolimus-eluting stent and 6 months with a paclitaxel-eluting stent, followed by 75–162 mg once daily orally thereafter Continue indefinitely
Clopidogrel	STE MI, class I recommendation in patients allergic to aspirin NSTE ACS, class I recommendation for all hospitalized patients in whom a non-interventional approach is planned In PCI in STE and NSTE ACS, class I recommendation In STE ACS with fibrinolytics, large randomized trial data published after 2004 guidelines	Hypersensitivity Active bleeding Severe bleeding risk	300–600 mg (class I and IIa recommendations, respectively) loading dose on hospital day 1 followed by a maintenance dose of 75 mg once daily orally starting on hospital day 2. Avoid bolus in patients > 75 years when given with thrombolytics Administer indefinitely in patients with aspirin allergy (class I recommendation) Administer at least 9 months in patients with NSTE ACS who are managed medically (class I recommendation) For post-PCI-stented patients, administer at least 30 days in patients receiving a bare metal stent, 3 months after a sirolimus-eluting stent, and 6 months after a paclitaxel-eluting stent (class I recommendation)
Unfractionated heparin	STE MI, class I recommendation in patients undergoing PCI, and for those patients treated with alteplase, reteplase, or tenecteplase; class IIa recommendation for patients not treated with fibrinolytic therapy NSTE ACS, class I recommendation in combination with aspirin	Active bleeding History of heparin-induced thrombocytopenia Severe bleeding risk Recent stroke	For STE MI, administer 60 units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour) For NSTE ACS, administer 60–70 units/kg IV bolus (maximum 5000 units) followed by a constant IV infusion at 12–15 units/kg/hour (maximum 1000 units/hour) Titrated to maintain an aPTT of 1.5–2.5 times control for NSTE ACS and 50–70 seconds for STE MI The first aPTT should be measured at 4–6 hours for NSTE ACS and STE MI in patients not treated with fibrinolytics The first aPTT should be measured at 3 hours in patients with STE MI who are treated with fibrinolytics Continue for 24–48 hours or until the end of PCI
Low-molecular-weight heparin	STE MI, class IIb recommendation for patients younger than age 75 treated with fibrinolytics, class III for patients older than age 75 treated with fibrinolytics and class IIa for patients not undergoing reperfusion therapy. NSTE ACS, class I recommendation in combination with an 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 For PCI, class IIa recommendation as an alternative to UFH in patients with NSTE ACS For primary PCI in STE MI, class IIb recommendation as an alternative to UFH	Active bleeding History of heparin-induced thrombocytopenia Severe bleeding risk Recent stroke Avoid enoxaparin if CrCl < 10 mL/minute Avoid dalteparin if CrCl < 30 mL/minute	Enoxaparin 1 mg/kg SC every 12 hours for patients with NSTE ACS (CrCl ≥ 30 mL/minute) Enoxaparin 1 mg/kg SC every 24 hours (CrCl 10–29 mL/minute) Dalteparin 120 IU/kg SC every 12 hours for patients with NSTE ACS (maximum single dose of 10,000 units) For patients undergoing PCI following initiation of SC enoxaparin for NSTE ACS, a supplemental 0.3 mg/kg IV dose of enoxaparin should be administered at the time of PCI if the last dose of SC enoxaparin was given 8–12 hours before PCI For patients with STE MI receiving fibrinolytics, administer enoxaparin 30 mg IV bolus followed immediately by 1 mg/kg SC every 12 hours (first two doses administer maximum dose of 100 mg for patients weighing more than 100 kg) Continue throughout hospitalization or up to 8 days for STE MI Continue for 24-48 hours for NSTE ACS or until end of PCI

Table 1-2. Pharmacotherapy for ST-Segment Elevation and Non-ST-Segment Elevation Acute Coronary Syndromes (Continued)

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy
Bivalirudin	No recommendation at this time Consider for high-risk NSTE ACS patients likely to undergo PCI	Active bleeding Severe bleeding risk	For NSTE ACS, administer 0.1 mg/kg IV bolus followed by 0.25 mg/kg/hour infusion Dosing information based on dose administered in ACUITY trial For PCI, administer a second bolus, 0.5 mg/kg IV and increase infusion rate to 1.75 mg/kg/hour Discontinue at end of PCI
Fondaparinux	No recommendation at this time Dosing information based upon dose administered in the OASIS-5 and OASIS-6 trials	Active bleeding Severe bleeding risk SCr ≥ 3.0 mg/dL	For STE MI, 2.5 mg IV bolus followed by 2.5 mg SC once daily starting on hospital day 2 For NSTEACS, 2.5 mg SC once daily For PCI, 2.5 mg once daily SC with an additional IV dose of either 2.5 mg (if administered with a for either GP IIb/IIIa receptor inhibitor) or 5 mg (if no GP IIb/IIIa receptor inhibitor administered) if PCI performed > 6 hours since the last fondaparinux SC dose Continued until hospital discharge or up to 8 days
Fibrinolytic therapy	STE MI, class I recommendation in patients age < 75 years presenting within 12 hours following the onset of symptoms, class IIa recommendation in patients age 75 years and older, class IIb in patients presenting between 12 and 24 hours following the onset of symptoms with continuing signs of ischemia. NSTE ACS, class III recommendation	Any prior intracranial hemorrhage Known structural cerebrovascular lesions such as an arterial venous malformation Known intracranial malignant neoplasm Ischemic stroke within 3 months Active bleeding (excluding menses) Significant closed head or facial trauma within 3 months	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: 10 units IV x 2, 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 80.0–89.9 kg = 45 mg IV bolus ≥ 90.0 kg = 50 mg IV bolus
Glycoprotein IIb/IIIa receptor inhibitor	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 STE MI, class IIa for abciximab for primary PCI and class IIb for either tirofiban or eptifibatide for primary PCI Class III recommendation in combination with a fibrinolytic drug	Active bleeding Thrombocytopenia Prior stroke	Drug / Dose for PCI / Dose for NSTE ACS with/without PCI / Dose adjustment for renal insufficiency Abciximab: 0.25 mg/kg IV bolus followed by 0.125 mcg/kg/minute (maximum 10 mcg/minute) for 12 hours / Not recommended / None Eptifibatide: 180 mcg/kg IV bolus x 2, 10 minutes apart with an infusion of 2 mcg/kg/minute for 12–72 hours / 180 mcg/kg IV bolus followed by an infusion of 2 mcg/kg/minute for for 12–72 hours / Reduce maintenance infusion to 1 mcg/kg/minute for patients with CrCl < 50 mL/minute; not studied in patients with serum creatinine > 4.0 mg/dL;

Table 1-2. Pharmacotherapy for ST-Segment Elevation and Non-ST-Segment Elevation Acute Coronary Syndromes (Continued)

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy			
						Patients weighing ≥ 121 kg or more should receive a maximum infusion rate of 22.6 mg per bolus and a maximum infusion rate of 15 mg/hour
			Tirofiban	Not FDA approved	0.4 mg/kg IV bolus administered over 30 minutes followed by an infusion of 0.01 mcg/kg/minute for 18–72 hours	Reduce maintenance infusion to 0.05 mcg/kg/minute for patients with < 30 mL/minute
Nitrogycerin	STE MI and NSTE ACS, class I indication in patients with ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion	Hypotension Sildenafil or vardenafil within 24 hours or tadalafil within 48 hours hypotension	0.4 mg SL, repeated every 5 minutes for three doses 5–10 mcg/minute IV infusion titrated up to 75–100 mcg/minute until relief of symptoms or limiting side effects (headache 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 are acceptable alternatives for patients without ongoing or refractory symptoms Continue IV infusion for 24–48 hours			
β-blockers[c]	STE MI 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 sec 2nd degree or 3rd degree atrioventricular heart 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 of 50–60 beats/minute Metoprolol 5 mg slow IV push (over 1–2 minutes, repeated every 5 minutes for a total of 15 mg Followed in 1–2 hours by 25–50 mg by mouth every 6 hours If a very conservative regimen is desired, doses can be reduced to 1–2 mg; Propranolol 0.5–1.0 mg IV dose Followed in 1–2 hours by 40–80 mg orally every 6–8 hours Atenolol 5 mg IV dose followed in 1–2 hours Followed 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; Alternatively, initial intravenous therapy can be omitted Continue oral β-blocker indefinitely			
Calcium channel blockers	STE MI 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 MI	Pulmonary edema Evidence of left ventricular dysfunction Systolic blood pressure < 100 mm Hg PR ECG segment > 0.24 sec for verapamil and diltiazem 2nd or 3rd degree atrioventricular heart block for verapamil or diltiazem Heart rate < 60 beats /minute for diltiazem or verapamil	Diltiazem 120–360 mg sustained release orally once daily Verapamil 180–480 mg sustained release orally once daily Nifedipine 30–120 mg sustained release orally once daily Amlodipine 10 mg orally once daily Continue indefinitely if contraindication to oral β-blocker persists			

Table 1-2. Pharmacotherapy for ST-Segment Elevation and Non-ST-Segment Elevation Acute Coronary Syndromes (Continued)

Drug	Clinical Condition and ACC/AHA Guideline Recommendation[a]	Contraindications[b]	Dose and Duration of Therapy		
ACE Inhibitors	STE MI, 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 EF < 40%, hypertension, or type 2 diabetes mellitus Consider in all patients with CAD Class I recommendation	Systolic blood pressure < 100 mm Hg History of intolerance to an ACE inhibitor Bilateral renal artery stenosis Serum potassium > 5.5 mEq/L Acute renal failure	Drug Captopril Enalapril Lisinopril Ramipril Trandolapril Continue indefinitely	Initial Dose 6.25–12.5 mg 2.5–5.0 mg 2.5–5.0 mg 1.25–2.5 mg 1.0 mg	Target Dose 50 mg twice daily orally to 50 mg 3 times/day 10 mg twice daily orally 10–20 mg once daily orally 5 mg twice daily or 10 mg once daily orally 4 mg once daily orally
Angiotensin Receptor Blockers	STE MI, class I recommendation in patients with clinical signs of heart failure or ejection fraction < 40% and intolerant of an ACE inhibitor, class IIa in patients with clinical signs of heart failure or ejection fraction < 40% and no documentation of ACE inhibitor intolerance	Systolic blood pressure < 100 mm Hg Bilateral renal artery stenosis Serum potassium > 5.5 mg/dL Acute renal failure	Drug Candesartan Valsartan Continue indefinitely	Initial Dose 4–8 mg 40 mg	Target Dose 32 mg once daily orally 160 mg twice daily orally
Aldosterone Antagonists	STE ACS, class I recommendation for patients with MI and ejection fraction ≤ 40% and either diabetes mellitus or heart failure symptoms who are already receiving an ACE inhibitor	Hypotension Hyperkalemia, serum potassium > 5.0 mEq/L Serum creatinine > 2.5 mg/dL	Drug Eplerenone Spirono-lactone	Initial Dose 25 mg 12.5 mg	Maximum Dose 50 mg once daily orally 25–50 mg once daily orally
Morphine Sulfate	STE and NSTE ACS, class I recommendation, for patients whose symptoms are not relieved after three serial SL nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV bolus dose May be repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort		

[a]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 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. Class III recommendations are those where the procedure or treatment is not useful and may be harmful.

[b]Allergy or prior intolerance is contraindication for all categories of drugs listed in this chart.

[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 asthma, selection 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 intravenous 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 inhibitor; AHA = American Heart Association; ACS = acute coronary syndrome; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; aPTT = activated partial thromboplastin time; CAD = coronary artery disease; CrCl = creatinine clearance; ECG = electrocardiogram; FDA = Food and Drug Administration; IV = intravenous; MI = myocardial infarction; NSTE = non-ST-segment elevation; OASIS = Organization to Assess Strategies in Acute Ischemic Syndromes; PCI = percutaneous coronary intervention; SC = subcutaneous; SCr = serum creatinine; SL = sublingual; STE = ST-segment elevation.

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Adapted with permission from McGraw-Hill. Spinler SA. Acute coronary syndromes. In: Chisholm MA, Schwinghammer TL, Wells BG, DiPiro JT, Kolesar JM, Malone PM, eds. Pharmacotherapy Principles & Practice. Philadelphia: McGraw-Hill, 2006. In press.

Table 1-3. Therapeutic Drug Monitoring for Adverse Effects of Pharmacotherapy for Acute Coronary Syndromes

Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding[a]; gastrointestinal upset; baseline CBC and platelet count; CBC and platelet count every 6 months
Clopidogrel	Bleeding, TTP (rare), diarrhea, rash	Clinical signs of bleeding[a]; baseline CBC and platelet count; CBC and platelet count every 6 months following hospital discharge
Unfractionated heparin	Bleeding, thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC count, platelet count, aPTT, and INR; aPTT every 6 hours until target then every 24 hours; daily CBC count; platelet count every 2 days (minimum, preferably every day)
Low-molecular-weight heparins	Bleeding, thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC count, platelet count aPTT, and INR; daily CBC count, platelet count every 2–3 days (maximum preferably every day); SCr daily
Fondaparinux	Bleeding	Clinical signs of bleeding[a] ; baseline CBC count, platelet count, INR, SCr and aPTT; daily CBC and SCr
Bivalirudin	Bleeding	Clinical signs of bleeding[a] ; baseline CBC count, platelet count, INR, SCr and aPTT; daily CBC and SCr
Fibrinolytics	Bleeding, especially intracranial hemorrhage	Clinical signs of bleeding[a]; baseline CBC count, platelet count, INR and aPTT; mental status every 2 hours for signs of intracranial hemorrhage; daily CBC count
Glycoprotein IIb/IIIa inhibitors	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding[a]; baseline CBC and platelet count; daily CBC count; platelet count at 4 hours after initiation then daily
Intravenous nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
β-Blockers	Hypotension, bradycardia, heart block, bronchospasm, heart failure, fatigue, depression, sexual dysfunction, nightmares, masking hypoglycemia symptoms in patients with diabetes	BP, RR, HR, 12-lead ECG, and clinical signs of heart failure every 5 minutes during bolus intravenous dosing; BP, RR, HR and clinical signs of heart failure every shift during oral administration during hospitalization, BP and HR every 6 months following hospital discharge
Diltiazem or	Hypotension, bradycardia, heart block, heart failure, gingival hyperplasia, constipation	BP and HR and signs of clinical heart failure every shift verapamil during oral administration during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
Amlodipine	Hypotension, dependent peripheral edema, gingival hyperplasia	BP every shift during hospitalization, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
ACE inhibitors and ARBs	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, angioedema (ACE inhibitors > ARBs); teratogenic throughout pregnancy	BP every 2 hours x 3 for first dose, every shift during oral administration during hospitalization, then every 6 months following hospital discharge; baseline SCr and serum potassium concentrations; daily SCr and potassium while hospitalized, then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in selected patients (e.g., those taking spironolactone or eplerenone or having renal insufficiency); counsel patient on throat, tongue and facial swelling;
Aldosterone antagonists[b]	Hypotension, hyperkalemia, prerenal azotemia	BP and HR every shift during oral administration during hospitalization, then once every 6 months; baseline SCr and serum potassium concentrations; SCr and potassium at 48 hours, monthly for 3 months then every 3 months thereafter
Statins	Myalgia, myopathy, elevated LFTs, rhabdomyolysis, teratogenic in first trimester	Baseline LFTs then repeat LFTs at 6 weeks and when patient titrated to target maintenance dose; if LFTs > 3 times the upper limit of normal, decrease dose or discontinue; if myalgia and/or brown urine, monitor creatine kinase for rhabdomyolysis
Morphine sulfate	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose

[a]Clinical signs of bleeding include: bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.
[b]Spironolactone and eplerenone.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; aPTT = activated partial thromboplastin time; BP = blood pressure; CBC = complete blood cell; ECG = electrocardiogram; HR = heart rate; INR = international normalized ratio; LFT = liver function test; RR = respiratory rate; SCr = serum creatinine, TTP = thrombotic thrombocytopenic purpura.
Adapted with permission from McGraw-Hill. Spinler SA. Acute coronary syndromes. In: Chisholm MA, Schwinghammer TL, Wells BG, DiPiro JT, Kolesar JM, Malone PM, eds. Pharmacotherapy Principles & Practice. Philadelphia: McGraw-Hill, 2006. In press.

major change is that there are new anticoagulant options for management of patients with NSTE ACS.

Beyond Primary Percutaneous Coronary Intervention: Role of Hospital Transfer

Unfortunately, fewer than 1 in 5 hospitals in the United States have cardiac catheterization laboratories and even fewer can perform primary PCI 24 hours/day. There is a clear role for inter-hospital transport for patients with STE MI in two scenarios. The first scenario is when patients present with cardiogenic shock to a hospital that is not capable of performing primary PCI. The second scenario is when a patient with a contraindication to fibrinolytic therapy presents to a hospital that is not capable of performing primary PCI. The role for patient transport for primary PCI is less clear for patients presenting within 12 hours of onset of symptoms who have no contraindication to fibrinolysis. Recent data from registries and clinical trials report reveal a reduction in mortality benefit as "door-to-balloon" time increases but that this benefit reduction is less steep than that observed when "door-to-needle" time increases for fibrinolysis. Therefore, the trade-off of increased time to primary PCI is outweighed by the more complete reperfusion with PCI when compared with fibrinolytic therapy. Conclusions drawn from clinical trials regarding the benefit of transferring patients with STE MI to another hospital for primary PCI, rather than administering fibrinolysis, are confounded by the differing times from symptom onset, low mortality risk at baseline of the population enrolled, and shorter transfer times than those reported in registries. Additional treatment times (door-to-balloon minus door-to-needle) in transfer studies were incredibly short, ranging from 85 minutes to 95 minutes, which are similar to door-to-balloon treatment delays observed for primary PCI within the same hospital in the United States. The most recent data evaluating treatment delay for primary PCI in 2322 patients at a single center suggest that delays do not affect 7-year mortality in patients presenting greater than 3 hours from symptom onset, thus supporting the role for early fibrinolysis in this group and transfer for primary PCI in those presenting between 3 hours and 12 hours since symptom onset. This strategy is supported by the ACC/AHA 2004 STE MI guidelines.

Although technical difficulties persist in the United States to operationalize inter-hospital transfer for primary PCI and to develop networks of "reperfusion" hospitals, many European countries demonstrated improved outcomes with streamlined care for the patient with STE MI. For example, in Vienna, Austria, a network of hospitals that provide primary PCI around-the-clock has been put into place with STE MI on ECG identified early and patients transferred rapidly. This network has resulted in an increase in the rate of primary PCI from 16% to 60% of all patients presenting with STE MI and a mortality reduction from 16%

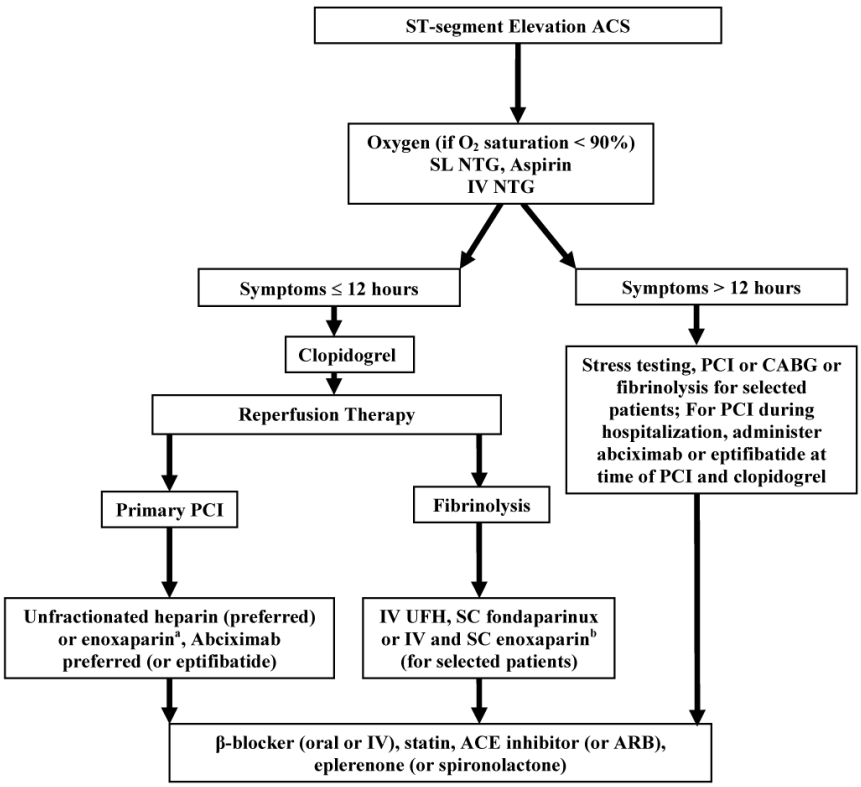

Figure 1-2. Initial pharmacotherapy for ST-segment elevation acute coronary syndromes.
[a]While recommended by the 2004 American College of Cardiology and American Heart Association practice guidelines, no dose recommendation is given.
[b]See Table 1-3 for specific types of patients receiving fibrinolytic drugs who should not receive enoxaparin.
ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; IV = intravenous; NTG = nitroglycerin; O_2 = oxygen; PCI = percutaneous coronary intervention; SC = subcutaneously; SL = sublingual; UFH = unfractionated heparin.

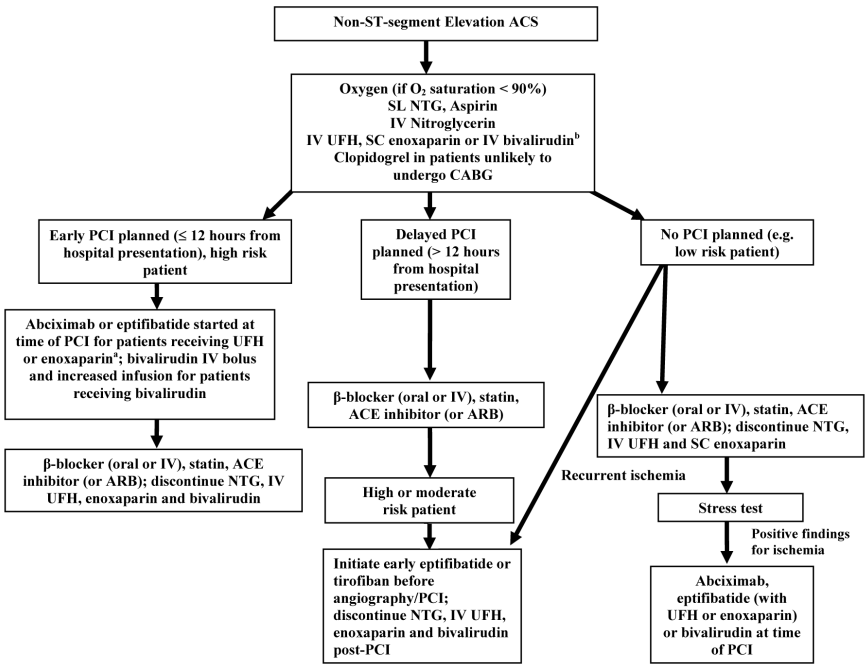

Figure 1-3. Initial pharmacotherapy for non-ST-segment elevation acute coronary syndrome.
[a]May require supplemental IV dose; See Table 1-2 .
[b]Fondaparinux may be used as anticoagulant if no PCI planned.
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; IV = intravenous; NTG = nitroglycerin; O_2 = oxygen; PCI = percutaneous coronary intervention; SC = subcutaneous; SL = sublingual; UFH = unfractionated heparin

[AU: In left-side middle box, not sure what the last line means "bivalirudin IV bolus and increased…]

Figure 1-3. Initial pharmacotherapy for non-ST-segment elevation acute coronary syndrome.
[a]May require supplemental IV dose of enoxaparin; See Table 1-2.
[b]Fondaparinux may be used as anticoagulant if no PCI planned.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; IV = intravenous; NTG = nitroglycerin; O_2 = oxygen; PCI = percutaneous coronary intervention; SC = subcutaneous; SL = sublingual; UFH = unfractionated heparin.

of all patients to 9.5% of all patients and 8.1% in patients receiving primary PCI, respectively, in patients undergoing any form of reperfusion.

Pharmacotherapy

LMWHs Versus UFH in Combination with Aspirin and Fibrinolytic Drugs for ST-Segment Elevation ACS

In the 2004 ACC/AHA STE MI guidelines, LMWHs are recommended as an alternative to UFH in patients receiving fibrinolytic therapy. In a meta-analysis of more than 6000 patients randomized to receive either enoxaparin 30 mg intravenous bolus followed by 1 mg/kg subcutaneously 2 times/day or UFH bolus and infusion, the rate of recurrent MI was significantly reduced by 42% and the rate of recurrent ischemia by 31%. Overall, the rate of major bleeding and intracranial hemorrhage were not increased with enoxaparin. However, in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS trial in patients receiving tenecteplase, the rate of intracranial hemorrhage was increased about 7-fold with combined use with enoxaparin compared with combined use with UFH in patients older than age 75 (6.7% vs. 0.8%). Therefore, the 2004 ACC/AHA STE MI guidelines recommend against using enoxaparin in this elderly age group as well as patients with severe renal insufficiency. Although no specific dosing recommendations for enoxaparin in STE MI are described in the 2004 ACC/AHA guidelines, it would seem prudent to use doses studied in clinical trials, which were a 30 mg intravenous bolus followed by 1 mg/kg subcutaneously 2 times/day. In the recent Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI-25 trial using a reduced dose of enoxaparin for patients older than age 75, enoxaparin reduced death or nonfatal MI compared with UFH but increased major bleeding compared with UFH in the overall study population. At this time, results of safety data in the subgroup of patients age 75 and older has not been reported. Therefore, it seems reasonable to adhere to the 2004 ACC/AHA recommendations for enoxaparin use in patients with STE MI receiving fibrinolytic drugs. Data evaluating the use of enoxaparin in patients undergoing primary PCI or in patients not receiving reperfusion are too sparse to recommend its use in these groups at this time. Data evaluating the safety and efficacy of dalteparin in STE

MI is too limited to recommend its use. Data from the NRMI registry, indicate that a LMWH is administered to between 30% and 50% of patients receiving fibrinolytic drugs.

New Role for Clopidogrel in ST-Segment Elevation ACS

Clopidogrel is administered to patients undergoing PCI with intracoronary stents to prevent stent thrombosis and to patients with NSTE ACS (with or without PCI) to reduce the risk of cardiovascular death, MI, or stroke. As a result of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial in more than 12,000 patients with NSTE ACS, clopidogrel added to aspirin was recommended as a class I therapy in the 2002 ACC/AHA NSTE ACS guidelines. Major bleeding was increased by about 1% (absolute increase) with the addition of clopidogrel to aspirin in the CURE trial, where the majority of patients with NSTE MI were not managed using PCI. However, clopidogrel added to aspirin has not been shown to increase the risk of bleeding in patients with NSTE ACS who undergo PCI. Clopidogrel has demonstrated cost-effectiveness in PCI and in NSTE ACS with estimates ranging from $3500 to $15,700 per life-year gained. However, until recently, the role of clopidogrel in patients with STE MI was not as clear. Although clopidogrel is indicated as part of primary PCI therapy, the question of whether or not there is benefit or risk in adding clopidogrel to aspirin in patients receiving reperfusion with fibrinolytics was investigated in two clinical trials published in 2005. The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-TIMI 28 trial evaluated whether or not clopidogrel, started in the emergency department as an oral loading dose of 300 mg and continued as 75 mg/day for 30 days, improved infarct artery patency in patients with STE MI receiving fibrinolytic drugs and other usual STE MI care. Patients underwent angiography at a median of 84 hours after randomization to clopidogrel or placebo. Open-label clopidogrel was permitted following angiography if the patient underwent PCI. The primary end point, a composite of occluded infarct artery (TIMI flow grade 0 or 1 observed in the infarct artery on angiography), death before angiography, or recurrent MI before angiography was significantly lower in the clopidogrel group by 36% compared with the placebo group, with the primary benefit being a lower rate of occluded arteries (18.4% in the placebo group compared with 11.7% in patients treated with clopidogrel). Despite the fact that more than 50% of all patients underwent PCI and received open-label clopidogrel, the group receiving early clopidogrel therapy (within the first 24 hours of hospital presentation) demonstrated a significantly lower rate of 30-day cardiovascular death, recurrent MI, or recurrent ischemia leading to urgent revascularization, with the primary benefit being a lower rate of recurrent infarction (4.1% compared with 5.9% with placebo). In the subgroup of patients who underwent PCI, the risk of cardiovascular death, MI, or stroke at 30 days was significantly reduced by 46% (3.6% vs. 6.2% with placebo). Unlike results of the CURE trial where the frequency of major bleeding was higher with clopidogrel plus aspirin versus aspirin alone, the rate of major bleeding in the CLARITY trial was surprisingly low, given patients underwent cardiac catheterization and was similar in both groups (1.2% clopidogrel vs. 1.1% placebo). In the subgroup of patients undergoing PCI (PCI-CLARITY sub-study), there was no increased risk of major bleeding (2% vs. 1.9%) or minor bleeding (40% vs. 0.8%) with clopidogrel pretreatment plus aspirin compared with aspirin alone. Two reasons may account for this finding. The first is that patient follow-up was longer in the CURE than the CLARITY trial, with bleeding assessed for an average of 9 months in the CURE and only 30 days in the CLARITY. Second, it is more common today to use percutaneous closure devices, which may have decreased bleeding from the catheterization site in the CLARITY trial.

In COMMIT, one of the largest STE MI trials performed to date, 45,852 Chinese patients presenting within 24 hours of symptom onset and either STE, left bundle branch block, or ST-segment depression on 12-lead ECG, were randomized in a 2 X 2 factorial design to clopidogrel, metoprolol, metoprolol and clopidogrel, or placebo. The results of the metoprolol arms are discussed in the next section. More than 87% of patients presented with STE on ECG, almost 50% received fibrinolytic therapy and 95.8% of patients had MI confirmed by local investigators. The clopidogrel dose was 75 mg once daily started in the emergency department and continued through hospital discharge or up to 28 days in hospital. The primary end points of the study were death and a composite end point of death, reinfarction, or stroke at hospital discharge (or day 28 whichever came first). The mean duration of treatment was 15 days. Clopidogrel significantly reduced mortality compared with the placebo group by 7% and the rate of the composite end point by 9%. As in the CLARITY trial, the rate of fatal and nonfatal bleeding was low and similar in the two groups. This benefit represents one life saved for every 14 patients treated.

The ACC and AHA are reviewing the results of these studies to determine their recommendation on the role of clopidogrel in patients with ACS. Unlike in the United States where most patients receive a fibrin-specific fibrinolytic drug such as alteplase, tenecteplase, or reteplase, most patients in the COMMIT were treated with urokinase. Some unresolved issues are the optimal dosing and duration of clopidogrel in patients with STE MI. The 2005 ACC/AHA PCI guidelines give clear recommendations on the dosing and duration of clopidogrel for patients undergoing primary PCI based on the type of stent. A loading dose of at least 300 mg is recommended, followed by 75 mg/day for at least 4 weeks following a bare metal stent, 3 months for a sirolimus-eluting stent, and 6 months for a paclitaxel-eluting stent. The ACC/AHA practice guidelines do not provide recommendations for the dosing and duration of clopidogrel therapy for patients who receive fibrinolytic drugs. A loading dose of 300 mg was administered to patients enrolled in the CLARITY trial but not COMMIT. Clopidogrel was administered for at least 30 days in the CLARITY trial while in the COMMIT clopidogrel was given for a mean of 15 days but as few as 8 days. The length of hospitalization in the United States, unlike China, is often less than 5 days in uncomplicated MI, so continuing clopidogrel until hospital discharge would be much shorter than the regimen used in the COMMIT.

Early β-Blockade in ST-Segment Elevation ACS: Intravenous Versus Oral Therapy

Intravenous β-blocker therapy followed by oral β-blocker therapy has been an integral part of early treatment for STE MI since the mid-1980s. Most of the trials were performed before early reperfusion therapy became the standard of care. Therefore, COMMIT evaluated the role of intravenous metoprolol followed by oral metoprolol in patients with STE MI. Three 5-mg intravenous bolus doses of metoprolol or placebo, separated by 2–3 minutes, were administered to patients with a heart rate greater than 50 beats/minute and systolic blood pressure greater than 90 mm Hg. Fifteen minutes later, an oral dose of 50 mg of metoprolol or placebo was given every 6 hours on the first 2 days, followed by 200 mg controlled-release metoprolol or placebo once daily during hospitalization for up to 28 days (as stated above mean duration was about 15 days). Thereafter, study follow-up was discontinued and patients could be treated with routine post-MI therapies, including β-blockers. Early metoprolol therapy did not reduce in-hospital mortality compared with placebo (7.7% vs. 7.8%), but did reduce the rate of reinfarction by 18% (2.0% vs. 2.5%) and ventricular fibrillation by 17%. However, more patients randomized to metoprolol developed cardiogenic shock (5.0% vs. 3.9%). The benefit of five reinfarctions prevented and five fewer episodes of ventricular fibrillation with metoprolol were balanced by an excess of 11 cases of cardiogenic shock per 1000 patients treated. Results of additional analyses indicated that the risk of cardiogenic shock was highest during the first 2 days of hospital admission, whereas the benefits in prevention of reinfarction and ventricular fibrillation emerged from day 2 onward. As mentioned earlier, the ACC and AHA intend to issue a formal statement regarding the role of β-blockers in MI. At issue is whether an early intravenous strategy may be abandoned in favor of an approach whereby oral β-blockers are started at some time during hospitalization when hemodynamic stability has been assured. This strategy was not directly tested but may be more practical. Oral β-blockers are especially useful as chronic therapy in MI survivors with systolic heart failure.

Newer Anticoagulant Drugs for Acute Coronary Syndromes

Two newer anticoagulants, fondaparinux and bivalirudin, have proven to be acceptable alternatives to UFH and enoxaparin for management of patients with ACS. Additional information regarding the use of enoxaparin in patients with NSTE ACS undergoing PCI has been published.

Enoxaparin

Previously, limited information was known regarding the safety and efficacy of enoxaparin in patients with NSTE ACS undergoing PCI. A large randomized, clinical trial of almost 10,000 patients, Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIA Inhibitors (SYNERGY), found than enoxaparin had similar rates of 30-day death or MI and 1-year mortality compared to UFH in the setting of early angiography (within the first 24 hours of hospital presentation) for patients with high-risk NSTE ACS. In the SYNERGY trial, almost 50% of patients underwent PCI. Therefore, enoxaparin is recommended as an option, along with UFH, in patients who are either medically managed or who receive PCI. Careful attention must be paid to dosing adjustments in patients with renal insufficiency and monitoring for bleeding, because the rates of non-coronary artery bypass graft surgery-associated major hemorrhage reported in the SYNERGY trial were higher with enoxaparin compared with UFH (2.4% vs. 1.8%). The higher rate of bleeding has been suggested to be secondary to a "crossover" effect whereby patients treated with UFH were randomized to enoxaparin without sufficient washout time. In addition, protocol violations occurred whereby some patients received intravenous UFH in addition to their prior enoxaparin therapy when undergoing PCI. In the SYNERGY trial, slightly more than 50% of patients were treated with a GP IIb/IIIa inhibitor and 60% with clopidogrel in addition to aspirin.

Fondaparinux

Fondaparinux, an indirect-acting factor Xa inhibitor, has been studied in two large ACS trials, the fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 and OASIS-6. Both trials were performed primarily outside the United States. In OASIS-5, the largest NSTE ACS trial performed to date, fondaparinux, administered as a 2.5-mg subcutaneous dose once daily, was found to be non-inferior to enoxaparin with respect to the clinical end point of 9-day death, MI, or refractory ischemia. The rate of major bleeding was lower with fondaparinux compared with enoxaparin. At 30 days, mortality was lower in the fondaparinux-treated patients. The higher mortality observed in patients treated with enoxaparin was suggested to be related to higher bleeding with enoxaparin, as patients with bleeding events had higher mortality. Because the fondaparinux dose that was studied is not equivalent to the enoxaparin dose, it is not unexpected that the bleeding events were lower.

In the OASIS-6 trial of more than 12,000 patients with STE ACS undergoing either primary PCI, medical therapy with a fibrinolytic drug, or no reperfusion therapy, a lower 30-day death or MI rate of more than 6000 patients randomized to either fondaparinux 2.5 mg subcutaneous dose once daily compared with UFH infusion in a subgroup analysis. There was no benefit of fondaparinux compared with UFH in another subgroup of more than 3700 patients receiving primary PCI. There was no significant difference in major bleeding between patients given fondaparinux and either control or UFH in the study population as a whole. Major limitations of OASIS-6 are that the duration of study drug administration was shorter in patients treated with UFH (median of 47 hours vs. 8 days) and that only 5% of the patients treated with fibrinolysis underwent PCI while in the hospital. Because the primary benefit of anticoagulant drugs is to prevent reocclusion after fibrinolysis, it is not unexpected that higher rates of reinfarction would occur in patients who did not receive a revascular procedure and who were treated with a shorter duration of anticoagulation. During the trial it was noted that an excess of clots forming on the PCI catheter and more PCI complications, such as abrupt closure, in patients randomized to fondaparinux.

Although fondaparinux seems to be an alternative to UFH for patients receiving fibrinolytic drugs, it will not replace UFH for primary PCI and was not included in the STE ACS algorithm in Figure 1-2.

Bivalirudin

Bivalirudin, a direct thrombin inhibitor, has been studied in patients with STE MI and found to have similar 30-day mortality rates, lower reinfarction rates and higher bleeding rates than UFH when combined with fibrinolytic drugs. In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2, in which patients were undergoing primarily non-urgent or elective PCI, bivalirudin demonstrated similar efficacy and lower bleeding rates when given as a bolus and brief infusion during the PCI procedure compared with UFH combined with a GP IIb/IIIa inhibitor administered for 12–18 hours following PCI.

Data from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial demonstrate that bivalirudin is an acceptable anticoagulant choice for patients with NSTE ACS. The ACUITY trial compared multiple antithrombotic strategies in 13,819 patients with NSTE ACS and clinical features suggesting that they were at higher risk of death or MI, such as elevated troponin concentration, ST-segment depression or a TIMI risk score of at least 3, and who were expected to undergo angiography and revascularization within the first 48–72 hours. Patients were randomized to one of three regimens: heparin (UFH or enoxaparin according to investigator preference) plus a GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor (according to investigator preference), or bivalirudin alone. Patients randomized to bivalirudin therapy were initially treated with a regimen of 0.1 mg/kg bolus and a 0.25 mg/kg/hour continuous infusion started either on hospital admission, cessation of previous UFH infusion, or at least 6 hours following administration of an enoxaparin dose. If at the time of angiography it was determined that the patient was to undergo PCI, an additional 0.5 mg/kg intravenous bolus was given, and the infusion dose was increased to 1.75 mg/kg/hour and continued for the duration of the procedure. The same dose was used during the REPLACE-2 study. The primary 30-day end point was a quadruple composite end point consisting of death, MI, unplanned revascularization, plus a broadly defined end point of major bleeding. Results of the trial are that the quadruple end point occurred in 11.7% of the heparin plus GP IIb/IIIa inhibitor group, 11.8% of the bivalirudin plus GP IIb/IIIa inhibitor group, and 10.1% of the bivalirudin alone group. The UFH/enoxaparin plus GP IIb/IIIa inhibitor was non-inferior (25% non-inferiority margin) to bivalirudin plus GP IIb/IIIa inhibitor. However, bivalirudin alone reduced the quadruple end point significantly better than UFH/enoxaparin plus GP IIb/IIIa inhibitor. Major bleeding rates were lower in patients treated with bivalirudin alone compared with patients receiving UFH/enoxaparin plus a GP IIb/IIIa inhibitor or the combination of bivalirudin and a GP IIb/IIIa inhibitor. Although not randomized data, individual results comparing enoxaparin-treated patients with UFH-treated patients suggest similar rates of the 30-day ischemic composite end point as well as major bleeding, including the rate of major bleeding in the subgroup of patients with creatinine clearance less than 60 mL/minute where one may have anticipated more bleeding with enoxaparin. This data are contrary to the findings in SYNERGY where the rate of major bleeding was higher with enoxaparin as compared to UFH.

Another interesting finding was that there appeared to be an interaction between the timing of clopidogrel administration prior to angiography rather than at the time of angiography with the occurrence of 30-day composite ischemic end point. The patients who did not receive pretreatment with clopidogrel and who received bivalirudin alone had a higher ischemic event rate than those not pretreated and who received heparin plus a glycoprotein IIb/IIIa inhibitor. Clopidogrel use was not randomized and was left to investigator usual practice. Such findings reinforce results of the earlier NSTE ACS and PCI trials with clopidogrel demonstrating an early reduction in death, MI, or stroke with the earlier use of clopidogrel, especially in patients undergoing PCI. Limitations of the trial include the long duration of pretreatment with nonstudy anticoagulants and GP IIb/IIIa inhibitors that was permitted before randomization (more than 14 hours) in some patients with the short duration of study drug administration (less than 6 hours) before PCI, the inclusion of both enoxaparin and UFH in the control group, a short 6-hour washout period for prerandomized treatment with enoxaparin before study drug administration, the large 25% noninferiority margin, the large percentage of patients who received tirofiban with no specific guidance on dosing for early PCI, and lack of eptifibatide dose adjustment for patients with creatinine clearance less than 50 mL/minute (change in product label came late in study enrollment) and its open-label design. These results suggest that bivalirudin is at least as safe and effective as either UFH or enoxaparin plus a GP IIb/IIIa inhibitor for patients with NSTE ACS and thus bivalirudin is included in the algorithm in Figure 1-3.

Given the preliminary results of the ACUITY trial, practitioners are using pre-procedure bivalirudin in the doses described in Table 1-2. It is unclear whether or not dosing adjustment is needed for patients with renal insufficiency. Patients with renal insufficiency (creatinine clearance less than 30 mL/minute) were excluded from the ACUITY trial. In patients with creatinine clearance less than 60 mL/minute enrolled in ACUITY, the composite ischemic outcome was similar in patients treated with bivalirudin alone versus heparin plus a GP IIb/IIIa inhibitor (11.1% vs. 9.2%) while the rate of major bleeding was lower in bivalirudin-treated patients (6.2% vs. 9.8%). Given that both fondaparinux and bivalirudin have been shown to have lower rates of major bleeding compared with enoxaparin and heparin, some may consider those drugs preferred in patients with renal insufficiency. Design limitations of OASIS trials and ACUITY may lead others to suggest that this issue is still unresolved. The ACC and AHA have not addressed the role of bivalirudin in any guidelines for treating patients with NSTE ACS since the results of the ACUITY trial were presented in April 2006. An ongoing trial is comparing bivalirudin and UFH in patients undergoing primary PCI for STE MI.

Table 1-4. 2006 American College of Cardiology/American Heart Association ST-Segment Elevation and Non-ST-Segment Elevation Myocardial Infarction Performance Measures

Performance Measure	Description
1. Aspirin at arrival	STE MI and NSTE MI patients without aspirin contraindications who received aspirin within 24 hours before or after hospital arrival
2. Aspirin prescribed at hospital discharge	STE MI and NSTE MI patients without aspirin contraindications who are prescribed aspirin at hospital discharge
3. β-blocker at hospital arrival	STE MI and NSTE MI patients without β-blocker contraindications who received a β-blocker within 24 hours after hospital arrival
4. β-blocker prescribed at hospital discharge	STE MI and NSTE MI patients without β-blocker contraindications who are prescribed a β-blocker at hospital discharge
5. LDL cholesterol assessment	STE MI and NSTE MI patients with documentation of LDL cholesterol level in the hospital record or documentation that LDL cholesterol testing was done during the hospital stay or is planned for after hospital discharge
6. Lipid-lowering therapy at hospital discharge	STE MI and NSTE MI patients with elevated LDL-cholesterol (= 100 mg/dL or narrative equivalent[a]) who are prescribed lipid-lowering medicine at hospital discharge
7. ACE inhibitor or ARB for LVSD at discharge	STE MI and NSTE MI patients with LVSD and without ACE inhibitor and ARB contraindications who are prescribed an ACE inhibitor or ARB at hospital discharge
8. Time to fibrinolytic therapy	Median time from arrival to administration of fibrinolytic therapy in patients with STE or LBBB on the ECG performed closest to hospital arrival time.
	STE MI or LBBB patients receiving fibrinolytic therapy during the hospital stay and having a time from hospital arrival to fibrinolysis of 30 min or less.
9. Time to PCI	Median time from arrival to PCI in patients with STE or LBBB on the ECG performed closest to hospital arrival time.
	STE MI or LBBB patients receiving PCI during the hospital stay with a time from hospital arrival to PCI of 90 minutes or less.
10. Reperfusion therapy	STE MI patients with STE on the ECG performed closest to the arrival time who receive fibrinolytic therapy or primary PCI.
11. Adult smoking cessation advice counseling	STE MI and NSTE MI patients with a history of smoking cigarettes who are given smoking cessation advice or counseling during hospital stay.

[a]Mention in the patient's medical record of elevated LDL cholesterol if not measured.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ECG = electrocardiogram; LDL = low-density lipoprotein; LBBB = left bundle branch block; LVSD = left ventricular systolic dysfunction; cholesterol; MI = myocardial infarction; NSTE = non-ST-segment elevation; PCI = percutaneous coronary intervention; STE = ST-segment elevation.
Reprinted with permission from the American Heart Association. Krumholz HM, Anderson JL, Brooks NH, Fesmire FM, Lambrew CT, Landrum MB, et al. ACC/AHA Clinical Performance Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures on ST-Elevation and Non-ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2006;47(1):236–65.

Quality Improvement

Update in Quality Performance Measures

Despite published guidelines for treating ACS, recent data from GRACE suggest that there is still a need for improvement in quality patient care. Among ideal candidates (those without contraindications) with either STE MI or NSTE MI enrolled in the GRACE between April 1999 and March 2002, only 92.4% of patients received aspirin and 66.9% received a β-blocker on the first day of hospital admission while 78.9% of patients received a β–blocker and 73.1% received an ACE inhibitor at hospital discharge. Data from NRMI 5 indicate that the percentage of patients receiving reperfusion therapy remained unchanged between 1999 and 2000, with about 35% undergoing primary PCI within 90 minutes and 46% of patients receiving fibrinolytic therapy within 30 minutes. There is some indication that adherence to quality improvement measures may be increasing as the median frequency of patients receiving aspirin within 24 hours, aspirin at hospital discharge, smoking cessation counseling, β-blocker within 24 hours of hospital arrival, and β-blocker at hospital discharge all exceed 95% in the NRMI 5 in 2006. However, the frequency of patients with left ventricular EF of less than 40% who receive either an ACE inhibitor or an ARB at hospital discharge is only 81% in the NRMI 5 in 2006.

In 2006, the AHA/ACC published Clinical Performance Measures for STE and NSTE MI. These performance measures, presented in Table 1-4, are intended to be used by hospitals for measurement of key performance indicators, which then result in educational efforts to improve the quality of patient care. These quality measures are used by the Joint Commission on Accreditation of Healthcare Organizations and Centers for Medicare and Medicaid Services.

Pharmacotherapy quality care performance measures for patients with either STE MI or NSTE MI (without contraindications) include administration of aspirin within the first 24 hours of hospital admission and at hospital discharge, administration of a β-blocker within the first 24 hours of hospital admission and at hospital discharge, and prescription of either an ACE inhibitor or ARB to patients with left ventricular systolic dysfunction (an EF of less than 40%) at hospital discharge, administration of fibrinolytic within 30 minutes of hospital presentation and

primary PCI within 90 minutes of hospital presentation. In patients with low-density lipoprotein cholesterol of 100 mg/dL or greater, lipid-lowering therapy should be prescribed at hospital discharge. A prescription of intravenous nitrates at hospital admission and long-acting nitrates at hospital discharge are not quality indicators because nitrates have not been shown to reduce mortality in clinical trials.

The quality indicator that was added in 2004 was prescription of an ARB as an alternative to an ACE inhibitor in patients with MI and left ventricular systolic dysfunction. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), all-cause mortality was similar at 2 years in patients with left ventricular systolic dysfunction receiving valsartan compared with captopril following MI.

One quality indicator was revised. In the 1999 ACC/AHA STE MI guidelines, the permitted time to primary PCI was 120 minutes, which was reduced to 90 minutes in the 2004 guidelines. At this time, there are no performance quality indicators in patients with NSTE ACS who do not have MI. Public and health care professionals may access and compare individual hospital performance for eight of these quality indicators in Medicare beneficiaries at *http://www.hospitalcompare.hhs.gov*.

The Role of Registries

Large national and international registries play a role in benchmarking quality care of patients with either STE MI (NRMI), NSTE MI (CRUSADE), or both (GRACE). As described above, GRACE and NRMI report rates and times to reperfusion therapy. Although there are no specific quality indicators for NSTE ACS, the CRUSADE registry tracks administration of 2002 ACC/AHA guideline-recommended therapies for patients with NSTE ACS who are at high risk of death or MI. Data from the CRUSADE registry from October 2003 until September 2004 indicated that 95% of patients received aspirin, 88% a β-blocker, 83% an UFH or LMWH, and 51% clopidogrel within 24 hours of hospital arrival. Forty-four percent receive a GP IIb/IIIa inhibitor at some time during hospitalization. At hospital discharge, 93% of eligible patients without contraindications are prescribed aspirin, 89% a β-blocker, 64% an ACE inhibitor, 86% a lipid-lowering drug, and 69% clopidogrel. Rates of ACE inhibitor prescription appear to be lower in patients with NSTE ACS than similarly eligible patients with STE MI.

Registries also play a role in highlighting disparities in care between patient groups. It is well recognized that elderly, blacks, and women receive guideline-recommended therapies less often than younger, white male patients.

Participation in these registries has been associated with improved outcomes at individual hospitals, and reports are available to compare performance between hospitals with similar characteristics. Both the GRACE and CRUSADE registries developed quality performance scoring in terms of provision of guideline-recommended drugs. In both registries, analyses reveal that hospitals that achieve the highest quality scores (highest quality quartile or adherence to ACC/AHA guideline-recommended therapies) had significantly lower adjusted mortality rates compared with hospitals that had the lowest quality scores (lowest quartile), thereby demonstrating the value of performance measures. In an observational analysis of more than 60,000 patients enrolled in the CRUSADE registry from 350 United States medical centers, a 10% increase in adherence to nine ACC/AHA guideline-recommended treatments produced a 10% lower risk of in-hospital mortality.

Registries also provide valuable information about how guidelines are used in the "real-world" setting outside of a clinical trial. For example, 42% of 30,136 patients enrolled in the CRUSADE registry between January and September 2004 received at least one injectable antithrombotic drug including UFH, LMWH, or a GP IIb/IIIa inhibitor at a dose above the recommended range. Factors associated with receiving an excessive dose included older age, female gender, and renal insufficiency. Patients with renal insufficiency were 4 times more likely to receive an excessive dose of a GP IIb/IIIa inhibitor compared with patients without renal insufficiency. Eptifibatide and tirofiban require dose reductions in patients with creatinine clearance less than 50 mL/minute and 30 mL/minute, respectively. Major bleeding was also higher in patients receiving excessive doses of LMWH or a GP IIb/IIIa inhibitor. An excessive dose of a GP IIb/IIIa inhibitor was associated with a significant 1.5-fold increased risk of mortality. Data from this landmark study have resulted in major new educational efforts impacting pharmacists and cardiologists regarding careful attention to dosing of injectable antithrombotics. The CRUSADE registry will then track the potential success of these educational efforts over time.

Practice Guideline Implementation

Practice guidelines are available from each of the registry Web sites (e.g., CRUSADE at *http://www.crusadeqi.com/*), as well as from the AHA (Get with the Guidelines at *http://www.americanheart.org/presenter.jhtml?identifier=1165*) and the ACC (Guidelines in Applied Practice [GAP] program at *http://www.acc.org/qualityandscience/gap/mi/ami_downloadA.htm*). A group of 33 hospitals in southeastern Michigan reported a significant reduction in 30-day (21.6% vs. 16.7%) and 1 year (38.3% vs. 33.2%) mortality following GAP guideline implementation.

The Role of the Pharmacist

Pharmacists play a vital role in the care of patients hospitalized in the coronary intensive care unit with ACS. In addition to potentially maximizing adherence to guidelines, pharmacists can ensure appropriate drug dosing and identification of drug interactions. Because excessive dosing of heparin, enoxaparin, and GP IIb/IIIa inhibitors is prevalent, pharmacists can play an active role to ensure that the correct dose is administered based on patient body weight and renal function. Because quality of care is typically measured by chart review, accuracy of data can be improved if pharmacists document drug contraindications and adverse effects in the chart. Patients with known contraindications to aspirin, β-blockers, ACE inhibitors, ARBs, or fibrinolytic drugs are excluded from the calculation of compliance with quality measures of

performance. If no contraindication or intolerance is documented, but one existed, the patient would be included in a quality of care report as a patient who did not meet the performance measures. Therefore, chart documentation of contraindications or intolerance to drugs is essential. Pharmacists play a key role in writing critical pathways, implementing practice guidelines, educating other healthcare professionals, and measuring performance of quality indicators and practice guidelines.

Conclusion

Morbidity and mortality from ACS remain substantial. Novel markers such as hs-CRP, Lp-PLA_2, and cystatin C are being evaluated for use as risk stratification tools, which may provide additional benefits when used in conjunction with, or as alternatives to, traditional tools such as the TIMI risk scores for NSTE ACS and STE MI. There is an emerging role for enoxaparin in combination with aspirin and fibrinolytics for patients with STE MI. However, concerns regarding bleeding risk and safety in older patients remain. Clopidogrel should be administered to patients with STE ACS who undergo reperfusion therapy with either primary PCI or fibrinolytic drugs. Lower mortality was reported in patients treated with clopidogrel drugs who received fibrinolytic drugs in the COMMIT. Less emphasis should be placed on administration of intravenous β-blockers early in MI, and more careful attention should be given to hemodynamic monitoring for signs of shock before β-blocker administration. Initiation of therapy with oral β-blocker within 24 hours of hospital admission to patients without significant hypotension and bradycardia is acceptable. Enoxaparin, fondaparinux, and bivalirudin may be used as alternatives to anticoagulation with UFH in NSTE ACS. Practitioners should be alert for updates in quality of care performance measures based on practice guidelines from AHA and ACC. Close adherence to these performance measures has been shown to reduce mortality. Pharmacists play a role in educating hospital staff regarding significant findings of clinical trials and updates in practice guidelines. Pharmacists can serve to improve guideline adherence and documentation of contraindications to guideline-recommended therapy.

Annotated Bibliography

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   This guideline remains the most recent for treating patients with NSTE elevation ACS. New guidelines are expected to be published in 2007. Major changes from the prior guideline include a larger role for clopidogrel in both PCI and medical management of NSTE ACS based on the results of the CURE trial. The current guideline also lists enoxaparin as the preferred anticoagulant over UFH. Changes expected with the next revision include an equivalent role for UFH and enoxaparin in patients at higher risk of death or MI, whereas enoxaparin is likely to remain the preferred anticoagulant for medical management. There will be an option of giving bivalirudin in high-risk patients expected to undergo PCI, but whether or not it is preferred over UFH and enoxaparin rests in the interpretation of the risk of bleeding as defined in the ACUITY trial.

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   This is an update of the 1999 ACC/AHA guidelines. Major changes include the following: a reduction in the desirable time from presentation until primary PCI from 120 minutes to 90 minutes; a reduction in the number of sublingual NTG tablets from three tablets to one that a patient takes before contacting emergency medical services; the inclusion of a fibrinolytic eligibility checklist that may be used by medical personnel to evaluate the patient before reaching the hospital; an intracranial hemorrhage risk calculator for fibrinolytic therapy; emphasis on primary PCI over fibrinolysis when access is rapid; recommendations for treating intracranial hemorrhage-associated with fibrinolytic therapy; recommendation against giving half-dose reteplase or tenecteplase as well as enoxaparin to patients older than age 75 due to increased risk of intracranial hemorrhage; a recommendation to use abciximab in primary PCI with an option to use eptifibatide as an alternative; an option to use an ARB in patients with systolic dysfunction who are intolerant of an ACE inhibitor; and a recommendation to use an aldosterone antagonist in patients already receiving an ACE inhibitor, who present with signs of heart failure and are without renal dysfunction. Updates to this guideline are expected in 2007 with the most significant difference to be a recommendation regarding the use of clopidogrel.

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   This is an update of the 2001 ACC/AHA guidelines. Major changes include a recommendation for 325 mg (rather than 81 mg) of aspirin for a minimum of 30 days in patients receiving a bare metal stent, 3 months for a sirolimus-eluting

stent and 6 months following a paclitaxel-eluting stent, the option of a 600-mg loading dose of clopidogrel before PCI, the recommendation for pretreatment time of at least 6 hours before PCI for clopidogrel where possible, and the recommendation for using bivalirudin in low-risk patients undergoing PCI or in patients with heparin-induced thrombocytopenia. Whether or not bivalirudin is specifically recommended for patients with renal failure is not clear. There is a statement, but not recommendation, supporting bivalirudin in patients with renal failure, a group at risk for high rates of bleeding. However, the numbers of patients with severe renal failure who were treated with bivalirudin in clinical trials are small, as those patients were generally excluded. In the ACUITY trial, bivalirudin had similar efficacy as UFH in the subgroup of patients with moderate renal insufficiency. No information on safety with bivalirudin in this patient group in the ACUITY trial has been reported at this time.

4. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366(9497):1607–21.

   The COMMIT is a landmark clinical trial that established the role for clopidogrel in patients with STE ACS treated with fibrinolytic therapy and aspirin. Although a small benefit in terms of mortality reduction was observed (7%) with clopidogrel compared to placebo, this benefit was in addition to that observed with other life-saving treatments, including an ACE inhibitor and antithrombin drug. Benefit was observed across a wide range of patient subgroups and bleeding rates were not increased, even in elderly patients. The primary benefit of clopidogrel is to prevent reocclusion and reinfarction. How well this clinical trial is applied to patient care may depend on the recommendation of the ACC/AHA guideline for STE MI expected in 2007. Because of the difference in the dosing of clopidogrel (no loading dose versus a 300 mg loading dose) and duration of therapy (2 weeks vs. 30 days) in the COMMIT and CLARITY, respectively, the final recommendation from ACC/AHA will guide how clopidogrel is used in practice.

5. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366(9497):1622–32.

   This analysis of COMMIT is significant in that it is the first to suggest that there is minimal benefit, and potentially harm by the use of early intravenous followed by oral β-blocker therapy. This trial initiated 50 mg of metoprolol orally every 6 hours starting on hospital day 1. In practice, much smaller doses are used, such as 12.5 mg orally every 6 hours and titrated slowly. The impact of this trial on practice patterns may be minimal, as the 2004 guidelines had already given the option to abandon intravenous β-blocker therapy. It is still important that patients with significant left ventricular dysfunction receive a β-blocker before hospital discharge as those patients have high mortality and rates of ventricular arrhythmias.

6. Alexander KP, Chen AY, Roe MT, Newby LK, Gibson CM, Allen-LaPointe NM, et al; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 2005;294(24):3108–16.

   This trial is an example of the impact that registries have on clinical practice. In a sample of 30,136 patients enrolled in the CRUSADE registry from 2003 to 2004, 42% of patients received an excessive dose of either UFH, LMWH, or a GP IIb/IIIa inhibitor. An excessive dose was associated with a higher risk for bleeding in patients receiving a GP IIb/IIIa inhibitor. Mortality was higher (50% increase with an excessive dose of a GP IIb/IIIa inhibitor) and length of hospital stay longer (0.3 days for LMWH, 0.4 days for UFH and 1.2 days for a GP IIb/IIIa inhibitor) in those receiving an excessive dose. Patients with renal dysfunction were at risk for receiving an excessive dose. Efforts are under way to educate cardiologists and pharmacists about the importance of precise dose calculation of enoxaparin and eptifibatide based on patient weight and calculation of creatinine clearance.

7. De Luca G, Suryapranata H, Stone GW, Antoniucei D, Tcheng JE, Neumahn FJ, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;293(14):1759–65.

   This meta-analysis of 11 clinical trials evaluated the role of abciximab in patients with STE MI. When combined with fibrinolysis, abciximab did not reduce mortality but did reduce reinfarction (2.3% vs. 3.6% with fibrinolysis alone; $p<0.001$). When used with primary PCI, abciximab reduced both mortality (2.4% vs. 3.4% with PCI alone; $p=0.047$) and reinfarction (1.0% vs. 1.9% with PCI alone; $p=0.03$). One reinfarction was prevented for every 111 patients treated with primary PCI. Abciximab was associated with increased bleeding when administered with fibrinolytic drugs (number needed to harm = 50) but not after primary PCI. Abciximab received a grade IIa recommendation for use in primary PCI, whereas eptifibatide received a grade IIb recommendation due to lack of clinical trial data in the 2004 ACC/AHA guidelines. When full-dose fibrinolytic drugs and a GP IIb/IIIa inhibitor have been administered to elderly patients with STE MI, increased rates of intracranial hemorrhage have been observed. Thus, this combination should be avoided in elderly patients at this time. The preponderance of the evidence supports using abciximab for primary PCI. However, due to cost considerations and lack of head-to-head trials, along with the ACC/AHA recommendation in the 2004 guidelines, many centers use eptifibatide.

8. Kalus JS, Moser LR. Evolving role of low-molecular-weight heparins in ST-elevation myocardial infarction. Ann Pharmacother 2005;39:481–91.

   This article reviews the pharmacological rationale, clinical trials, and meta-analyses supporting the role of LMWHs in STE MI. Enoxaparin has been studied primarily in combination with tenecteplase, where it has been shown to reduce the rate of reinfarction compared with UFH. No data support the recommendation in the 2005 ACC/AHA PCI guidelines for the use of either enoxaparin or dalteparin for primary PCI (class IIb recommendation compared with UFH which carries a grade Ia recommendation).

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suspected or confirmed non-ST-elevation acute coronary syndrome. Circulation. 2004;110(16):2342–8.

This clinical trial is one of the first to suggest a possible role for measuring cystatin C concentrations in patients presenting with ACS. Cystatin C is a better estimate of renal function than is the Cockcroft-Gault equation. The cystatin C-derived glomerular filtration rate is calculated using the following equation: glomerular filtration rate = 77.24 x cystatin $C^{-1.2623}$. Renal dysfunction is increasingly being recognized as an independent predictor of cardiovascular events. In this study, elevated cystatin C concentration on hospital presentation was associated with increased 6-month mortality (but not reinfarction). Cystatin C was a better predictor of risk than was troponin, hs-CRP, or N-terminal pro-brain natriuretic peptide.

10. Granger CB, Steg PG, Peterson E, Lopez-Sendon J, Vandewerf F, Kline-Rogers E, et al; GRACE Investigators. Medication performance measures and mortality following acute coronary syndromes. Am J Med 2005;118(8):858–65.

This report from the GRACE registry reported the percentage of patients receiving aspirin within 24 hours of hospital admission, a β-blocker within 24 hours of hospital admission, aspirin at hospital discharge, a β-blocker at hospital discharge, and an ACE inhibitor at hospital discharge in patients with heart failure or systolic dysfunction (EF less than or equal to 40%). A quality score was designed using these five measures. Hospitals with the highest quartile of quality performance had the lowest adjusted mortality, 4.1%, compared with that of the lowest quartile of performance, 5.6%, reflecting a 27% lower mortality. This is the first published trial that links quality performance indicators with mortality.

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This scientific statement from the ACC/AHA describes performance measures for MI treatment. Precise definitions are given for calculating the percentage of eligible patients receiving a therapy. Because quality is measured using chart review, and patients with known contraindications to a therapy are excluded, it is important for the clinician to document contraindications in the chart clearly. The recommendations are similar to those of the Joint Commission on Accreditation of Healthcare Organizations with the one difference from the Joint Commission on Accreditation of Healthcare Organizations being the reduction in time to primary PCI from 120 minutes to 90 minutes. Unlike the Joint Commission on Accreditation of Healthcare Organizations, however, no pharmacist representatives were members of the Task Force that developed these measures. All pharmacists caring for patients with ACS should read these recommendations.

12. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, et al; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA 2004;292(1):45–54.

In the SYNERGY trial, patients receiving either enoxaparin or UFH, administered for about 22 hours, had similar rates of death or MI at 30 days. There were significant confounders in both treatment groups with open label UFH used in the enoxaparin arm and patients receiving antithrombin therapy before randomization. In a prespecified analysis, patients receiving only enoxaparin, compared to those receiving only UFH, had lower rates of death or MI (13.3% vs. 15.9%; hazard ratio = 0.82, 95% confidence interval [CI] = 0.72–0.94). One concept that emerged from this study was the idea to "start and stay" with whichever antithrombin therapy was begun and that switching between UFH and enoxaparin seemed to be associated with increased bleeding risk. Another important point for clinical practice emerged as this trial described the efficacy and safety of using an intravenous supplemental bolus dose of enoxaparin in PCI (as described in Table 1-2).

13. Eagle KA, Montoye CK, Riba AL, DeFranco AC, Parrish R, Skorcz S, et al; American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan; American College of Cardiology Foundation (Bethesda, Maryland) Guidelines Applied in Practice Steering committee. Guideline-based standardized care is associated with substantially lower mortality in Medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. J Am Coll Cardiol 2005;46(7):1242–8.

This study is the first to report that ACS guideline implementation could result in mortality benefit. Mortality rates in Medicare beneficiaries with STE MI at 30 days, 6 months, and 1 year were compared before (n=1368) and after (n=1489). Mortality rates were significantly lower at 30 days and 1 year after implementation.

14. Peterson ED, Roe MT, Mulgund J, DeLong ER, Lytle BL, Brindis RG, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. JAMA 2006;295:1912–20.

This is the most significant article published from the CRUSADE registry to date. In more than 77,000 patients enrolled in CRUSADE, investigators evaluated the impact of four acute process-of-care measures (aspirin, β-blockers, heparin, and intravenous GP IIb/IIIa inhibitors used within the first 24 hours, as well as five discharge drugs (aspirin, β-blockers, clopidogrel, ACE inhibitors, and lipid-lowering therapies) on in-hospital mortality. When adjusted for patient demographic and clinical features, the mortality rate from NSTE ACS decreased from 6.31% for quartile 1 to 4.15% for quartile 4 ($p<0.001$). For every 10% increase in overall composite guideline adherence, the likelihood of in-hospital death decreased by 10% (adjusted odds ratio = 0.90; 95% CI = 0.84–0.97; $p<0.001$). Few characteristics of participating hospitals identified hospitals with better adherence scores. This article demonstrates the value of registries and illustrates how registries can be used to validate practice guidelines.

15. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, et al; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354(14):1477–88.

In the recent ExTRACT-TIMI-25 trial of more than 20,000 patients with STE MI receiving fibrinolysis and randomized to either enoxaparin or UFH, the enoxaparin dose was adjusted to 1 mg/kg every 24 hours and the intravenous bolus dose omitted for patients age older than 75 years. In addition, the first two enoxaparin subcutaneous doses were capped at 100 mg for patients younger than age 75 weighing more than 100 kg and at 75 mg for patients age 75 or older weighing more than 75 kg. In ExTRACT-TIMI-25, there was a significant 17% reliable reduction in death or nonfatal MI (9.9% vs. 12%; p<0.001) with enoxaparin compared to UFH but an increase in major bleeding (1.4% vs. 2.1%; p<0.001) in the overall study population. In the subgroup of 2532 patients age 75 or older, there was a 6% non-significant reduction in 30-day death or MI. No information on bleeding risk in elderly patients was reported. One criticism of this trial, which was performed outside the United States, is that UFH was only administered for 48 hours while enoxaparin was administered until hospital discharge or a maximum of 8 days (median of 7 days), a duration of therapy considerably longer than routine practice in the United States. In addition, angiography and revascularization were performed in very few patients. It is known that intracoronary stenting with PCI reduces the rate of infarct-artery reocclusion following STE MI. A shorter period of anticoagulation in the UFH arm combined with low rates of revascularization would seem to favor enoxaparin (a strategy of longer anticoagulation). In the United States, angiography and revascularization for STE MI are performed in more than 60% of patients, which obviates the need for prolonged inpatient anticoagulation after fibrinolytic therapy in most cases. Therefore, the application of this trial to clinical practice in the United States is questionable.

16. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Poque J, Granger CB, et al; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA 2006;295:1519–30.

In the OASIS-6 trial of 12,092 patients with STE ACS undergoing primary PCI, medical therapy with a fibrinolytic drug, or no reperfusion therapy, fondaparinux reduced the rate of death or MI at 30 days compared with control, which consisted of either placebo, in patients perceived to need no anticoagulation, or UFH infusion (9.7% vs. 11.2%; hazard ratio = 0.86; 95% CI = 0.77–0.96). Fondaparinux was administered as an intravenous bolus of either 2.5 mg or 5 mg followed by a once daily subcutaneous injection of 2.5 mg. Mortality was also significantly reduced with fondaparinux at 9 days, 30 days and 6 months. However, there was no benefit of fondaparinux compared to control in a subgroup of more than 3700 patients receiving primary PCI (6.1% vs. 5.1%; hazard ratio = 1.20; 95% CI = 0.91–1.57). Administration of UFH was permitted during primary PCI following the initial dose of intravenous fondaparinux. There was no significant difference in major bleeding between fondaparinux and control in the study population as a whole (1.8% vs. 2.1%, hazard ratio = 0.83; 95% CI = 0.64–1.06). The major limitations of OASIS-6 are that the duration of study drug administration was shorter in the patients treated with UFH than in those treated with fondaparinux (median of 47 hours vs. 8 days) and that only 5% of patients treated with fibrinolytic drugs underwent PCI while in the hospital. Also, assignment to each stratum of the control group, either placebo or UFH, was not random. Because the majority of patients in the United States receive primary PCI, application of OASIS-6 to clinical practice may be limited.

17. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators; Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Poque J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464–76.

In OASIS-5, the largest NSTE ACS trial performed to date with over 20,000 patients, fondaparinux, administered as a 2.5-mg subcutaneous dose once daily, was found to be non-inferior to enoxaparin with respect to the clinical end point of 9-day death, MI or refractory ischemia (5.8% vs. 5.7%; hazard ratio = 1.01; 95% CI = 0.90–1.13). The rate of major bleeding was lower with fondaparinux (2.2% vs. 4.1%; p<0.001). At 30 days, mortality was lower in patients treated with fondaparinux (8.0% vs. 8.6%; hazard ratio = 0.83; 95% CI = 0.71–0.97). The higher mortality observed in patients treated with enoxaparin was suggested to be related to the higher bleeding rate in the enoxaparin group as patients with bleeding events had higher mortality. The major limitation of OASIS-5 is that only 30% of patients underwent PCI and the duration of administration of both drugs was several days longer than usual practice in the United States (median of about 5 days). The longer treatment may have increased bleeding events. Because the fondaparinux dose that was studied is not considered to be equivalent to the enoxaparin dose, it is not unexpected that the bleeding events were fewer. In addition, intravenous UFH was administered to more than 50% of patients treated with enoxaparin compared to only 20% of patients treated with fondaparinux and, as suggested by the SYNERGY trial described above, may have led to increased risk of bleeding. More clots were seen on guiding catheters during PCI in the fondaparinux group compared with enoxaparin (0.9% vs. 0.4%; hazard ratio = 3.59; 95% CI = 1.64–7.84). As a result, interventional cardiologists may be reluctant to use low-dose fondaparinux in patients undergoing PCI.

18. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, et al; Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16. Supplementary Appendix available at *http://content.nejm.org/cgi/data/355/21/2203/DC1/1*. Accessed November 30, 2006.

The ACUITY trial randomized 13,819 patients with NSTE ACS and moderate to high risk of death or MI who were expected to undergo coronary angiography within the first 48–72 hours of hospital admission to one of three antithrombotic treatment strategies: heparin (UFH or enoxaparin) plus a GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor or bivalirudin alone. The primary end point was "net clinical benefit" at 30 days, which was a quadruple end point consisting of the composite ischemic end point (death, MI, or unplanned revascularization for ischemia) plus non-CABG major bleeding. The quadruple end point occurred in 11.7% of the heparin plus GP IIb/IIIa group, 11.8% of the bivalirudin plus GP IIb/IIIa group, and 10.1% of the bivalirudin alone group (p value for noninferiority < 0.001, p value for superiority = 0.93 UFH/enoxaparin plus a GP IIb/IIIa inhibitor versus bivalirudin plus a GP IIb/IIIa inhibitor, and p value for noninferiority less than 0.001, p value for superiority = 0.015 for UFH/enoxaparin plus a GP

IIb/IIIa inhibitor versus bivalirudin alone. Differences were observed in the non-CABG major bleeding rates, which were lower in patients treated with bivalirudin (alone) compared with those receiving UFH/enoxaparin plus a GP IIb/IIIa inhibitor or the combination of bivalirudin and a GP IIb/IIIa inhibitor (3.0% vs. 5.7% vs. 5.3%) (p value for noninferiority = 0.001, p value for superiority = 0.38 UFH/enoxaparin plus a GP IIb/IIIa inhibitor vs. bivalirudin plus a GP IIb/IIIa inhibitor, and p value for noninferiority < 0.001, p value for superiority < 0.001 for UFH/enoxaparin plus a GP IIb/IIIa inhibitor versus bivalirudin alone). Additional analyses suggested similar results across a variety of subgroups (including patients age older than 65, women, patients with diabetes mellitus, those with elevated troponin concentrations, ST-segment changes, different strata of TIMI risk score, those undergoing PCI, medical management, or CABG surgery, patients crossed-over at the time of randomization to another therapy that differed from pre-randomized treatment, and patients proceeding early [less than 3 hours] or late [greater than 19.7 hours] to angiography or intervention). With similar efficacy and a lower bleeding rate, bivalirudin alone appears the preferred therapy. However, in the trial, 9.1% of patients randomized to open-label bivalirudin required "bail out" administration of a GP IIb/IIIa inhibitor during the procedure. This may raise drug costs in this group. Full publication of the economic substudy with prospective data collection of costs of the 7851 patients in the United States who participated in ACUITY are eagerly awaited and may help determine bivalirudin's place in therapy. One-year follow-up of these patients for additional ischemic outcomes will also be performed. This is the second trial suggesting similar efficacy with a lower rate of bleeding with bivalirudin compared with using a GP IIb/IIIa inhibitor plus heparin.

Self-Assessment Questions

Please start new PSAP-VI online test.

1. A 60-kg patient (calculated creatinine clearance of 60 mL/minute) with non-ST-segment elevation (NSTE) acute coronary syndrome (ACS) is scheduled to undergo early angiography and percutaneous coronary intervention (PCI). Which one of the following initial antithrombotic regimens (hospital day 1) is the best choice for this patient?
   A. Aspirin 81 mg, unfractionated heparin (UFH) 4200 units bolus followed by an infusion of 1000 units/hour, and clopidogrel 75 mg.
   B. Aspirin 81 mg, enoxaparin 30 mg intravenous bolus followed by 60 mg subcutaneously 2 times/day, and clopidogrel 600 mg.
   C. Aspirin 325 mg, enoxaparin 90 mg subcutaneously 2 times/day, and clopidogrel 300 mg.
   D. Aspirin 325 mg, UFH 3600 unit bolus followed by an infusion of 750 units/hour, and clopidogrel 300 mg.

2. A 78-year-old, 70-kg patient (calculated creatinine clearance of 25 mL/minute) with ST-segment elevation (STE) myocardial infarction (MI) is undergoing primary PCI. Which one of the following antithrombotic regimens is the best choice for this patient?
   A. Aspirin 325 mg, enoxaparin 30 mg intravenously followed by 70 mg subcutaneous dose, clopidogrel 600 mg, and reteplase 10 units intravenous for two doses, 30 minutes apart.
   B. Aspirin 325 mg, UFH 4000 unit intravenous bolus followed by an 850 units/hour infusion, clopidogrel 300 mg, and abciximab 17.5 mg loading dose followed by an infusion of 8.75 mcg/minute for 12 hours.
   C. Aspirin 81 mg, enoxaparin 30 mg intravenously followed by 70 mg subcutaneous dose, clopidogrel 300 mg, eptifibatide 12.6 mg intravenous bolus for two doses, 10 minutes apart followed by an infusion of 140 mcg/minute for 18 hours.
   D. Aspirin 81 mg, UFH 5000 unit intravenous bolus followed by an 1000 units/hour infusion, clopidogrel 300 mg, eptifibatide 12.6 mg intravenous bolus for two doses, 10 minutes apart followed by an infusion of 140 mcg/minute for 18 hours.

3. A 80-year-old, 70-kg patient (creatinine clearance 28 mL/minute) with STE on electrocardiogram presents 2 hours after the onset of tight squeezing chest pain to a hospital without PCI capability. Which one of the following is the best approach to reperfuse this patient?
   A. Reteplase 5 units intravenously for one dose, UFH, and transfer for primary PCI.
   B. Reteplase 10 units intravenously for two doses, abciximab 17.5 mg loading dose followed by an infusion of 8.75 mcg/minute infusion for 12 hours, and UFH.
   C. Reteplase 10 units intravenously for two doses, 30 minutes apart, and UFH.
   D. Tenecteplase 40 mg intravenous bolus and enoxaparin.

4. Which one of the following markers of risk would provide the best stratification of risk of mortality or recurrent coronary heart disease events in a patient with renal insufficiency and ACS?
   A. High-sensitivity C-reactive protein.
   B. Cystatin C.
   C. Cockcroft-Gault estimate of creatinine clearance.
   D. Lipoprotein phospholipase A_2.

5. Which one of the following presentations indicates the lowest risk of death or reinfarction in patients with ACS (consider a value of troponin of less than 0.2 ng/mL as normal)?
   A. An STE greater than 1 mm and a troponin concentration of 0.0 ng/mL.
   B. An ST-segment depression greater than 0.5 mm, renal insufficiency, and a troponin concentration of 5.0 ng/mL.
   C. T-wave inversion and a troponin concentration of 0.1 ng/mL.
   D. An ST-segment depression greater than 0.5 mm, signs of congestive heart failure, and troponin concentration of 0.0 ng/mL.

6. Which one of the following is the mechanism of clopidogrel's benefit in a patient with STE MI who is also receiving aspirin, intravenous UFH, fibrinolytic therapy, and metoprolol?
   A. Open the infarct-related artery and improve myocardial oxygen supply.
   B. Reduce mortality and prevent reinfarction.
   C. Open the infarct artery and reduce myocardial oxygen demand.
   D. Prevent reinfarction and reduce myocardial oxygen demand.

7. Which one of the following clinical findings in patients with ACS predicts the best response to early (within the first 24 hours of hospital admission) intravenous β-blocker therapy?
   A. Signs of acute heart failure, heart rate of 100 beats/minute, and systolic blood pressure of 88 mm Hg.
   B. An NSTE ACS, no electrocardiographic changes, heart rate of 50 beats/minute, and systolic blood pressure of 100 mm Hg.

C. An STE MI, heart rate of 120 beats/minute, systolic blood pressure of 110 mm Hg, and electrocardiogram showing atrial fibrillation.
D. An NSTE ACS, rales, and S3 on physical examination, and ejection fraction of 35%.

8. What is the optimal timing for adding clopidogrel therapy to a patient presenting with STE MI who receives fibrinolytic therapy and who has no contraindications to clopidogrel?
   A. At the time of PCI.
   B. Within the first 24 hours of hospital admission.
   C. Any time before hospital discharge.
   D. In the emergency department.

9. What is the minimum duration of therapy for clopidogrel therapy (in addition to aspirin) in a patient undergoing primary PCI who receives a sirolimus-eluting stent?
   A. 4 weeks.
   B. 3 months.
   C. 6 months.
   D. 1 year.

10. Which one of the following treatment plans would represent the highest quality of care for patients with STE MI?
   A. Primary PCI at 110 minutes following hospital presentation; atorvastatin 80 mg/day initiated before hospital discharge for a low-density lipoprotein cholesterol of 65 mg/dL.
   B. Tenecteplase 13 hours after the onset of symptoms and 50 minutes following hospital presentation; metoprolol 25 mg orally every 6 hours beginning on hospital day 1.
   C. Reteplase 2 hours after the onset of symptoms and 25 minutes following hospital presentation; aspirin 325 mg before hospital arrival.
   D. Primary PCI 13 hours after the onset of symptoms; three sublingual nitroglycerin tablets before hospital arrival.

11. Patient 1 received intravenous metoprolol 2 hours after hospital admission; Patient 2 did not receive metoprolol secondary to a blood pressure of 80/40 mm Hg; Patient 3 received oral metoprolol 28 hours after hospital admission and had no documented contraindications; Patient 4 received metoprolol 36 hours after hospital admission but had bradycardia on hospital day 1; Patient 5 received oral metoprolol 12 hours after hospital admission. What is the percentage compliance with the quality performance measure for acute β-blocker therapy for the hospital that treated these five patients who presented with STE MI?
   A. 100%.
   B. 66%.
   C. 50%.
   D. 33%.

12. Which one of the following is a risk factor for recurrent coronary heart disease events in a patient with ACS?
   A. Troponin value below the MI decision limit.
   B. High-sensitivity C-reactive protein (CRP) concentration of greater than 5 mg/L.
   C. Lipoprotein phospholipase A_2 plasma concentration of less than 2.9 nmol/minute/mL.
   D. Thrombolysis In Myocardial Infarction (TIMI) risk score of 0.

13. A 57-year-old, 90-kg man with a history of hypertension is brought to the emergency department by ambulance complaining of 8 hours of substernal chest pressure at rest. He states that over the past 2 weeks he noticed fleeting twinges of chest pressure after exertion, but these episodes were relieved by rest. Last evening while walking his dog, he developed heavy chest pressure. He returned home and rested without relief of chest discomfort. This morning he called 911. On route to the hospital, the paramedics administered three sublingual nitroglycerin tablets and aspirin 325 mg orally for one dose without relief. His drugs taken at home are aspirin 81 mg/day and extended-release metoprolol 50 mg/day. The patient denies any recent trauma or bleeding tendencies. On physical examination, his vital signs are blood pressure 180/98 mm Hg and heart rate 70 beats/minute, and he is afebrile. His physical examination is significant for regular rate and rhythm with normal S_1 and S_2, and his rectal examination was negative for occult blood. He has no clinical signs of heart failure. An electrocardiogram taken 5 minutes after presentation reveals normal sinus rhythm with STE in the inferior leads of the II, III and aVF. His troponin concentration is elevated, and other laboratory data are within normal limits. Tenecteplase and alteplase are hospital formulary fibrinolytic drugs for acute MI. The hospital does not have a cardiac catheterization laboratory. Which one of the following additional pharmacotherapy is the best regimen to treat this patient in the emergency department?
   A. Alteplase, intravenous nitroglycerin, UFH, oral metoprolol, and clopidogrel.
   B. Clopidogrel, intravenous nitroglycerin, enoxaparin, and oral metoprolol.
   C. Tirofiban, intravenous nitroglycerin, enoxaparin, clopidogrel, and enalapril.
   D. Tirofiban, oral metoprolol, enoxaparin, and intravenous nitroglycerin.

14. R.L. is a 67-year-old, 80-kg man who presents to the emergency department complaining of 4 hours of continuous chest pain and associated diaphoresis, which began after the patient had an argument with his wife. His electrocardiogram shows no acute changes. The patient's medical history includes dyslipidemia for 10 years. He is a cigarette smoker and drinks occasional alcohol. His drugs taken before hospital admission were aspirin 81 mg/day and atorvastatin 20 mg/day. On physical examination, his blood pressure is 140/85 mm

Hg and his heart rate is 52 beats/minute. 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 concentration is 0.0 ng/mL (range 0.01–0.1 ng/mL) and serum creatinine is 1.0 mg/dL. This hospital does not have interventional cardiology services. Alteplase and reteplase are hospital formulary fibrinolytic drugs. In addition to aspirin and atorvastatin, which one of the following set of drugs is the most appropriate for RL to receive within the next 24 hours?

A. Alteplase, intravenous nitroglycerin, intravenous UFH, and clopidogrel.
B. Clopidogrel, enoxaparin, eptifibatide, intravenous metoprolol, and intravenous nitroglycerin.
C. Clopidogrel, intravenous UFH, and intravenous nitroglycerin.
D. Bivalirudin, oral metoprolol, and intravenous nitroglycerin.

15. Which one of the following antiplatelet regimens would be the best choice for a patient with severe renal dysfunction (estimated creatinine clearance 10 mL/minute) undergoing primary PCI?

A. Eptifibatide, clopidogrel, and aspirin.
B. Tirofiban and clopidogrel.
C. Clopidogrel and aspirin.
D. Abciximab, clopidogrel, and aspirin.

16. For which one of the following patient characteristics is an angiotensin-converting enzyme inhibitor preferred over an angiotensin receptor blocker following MI?

A. Serum potassium of 5.6 mEq/L.
B. Left ventricular ejection fraction of 60%.
C. Left ventricular ejection fraction of 30%.
D. Serum creatinine concentration of 2.0 mg/dL.

17. P.P. is a 59-year-old man with no significant medical history who experienced an STE MI 4 days ago and received fibrinolysis on hospital day 1 and PCI on day 2. He had a paclitaxel-coated intracoronary stent placed in his left anterior descending artery on hospital day 2. He initially presented with signs of acute decompensated heart failure. His ejection fraction is now 35%. His laboratory values are within the normal range and his blood pressure is 120/80 mm Hg, heart rate 65 beats/minute, and his signs of heart failure have resolved with treatment. In addition to aspirin and an aldosterone antagonist, which one of the following regimens is the best for secondary prevention of MI in P.P.?

A. Clopidogrel, metoprolol, and isosorbide mononitrate.
B. Clopidogrel, ramipril, and simvastatin.
C. Candesartan, captopril, atorvastatin, and atenolol.
D. Clopidogrel, metoprolol, valsartan, and simvastatin.

18. Stress testing is indicated for risk stratification in which one of the following presentations of ACS?

A. No ST-segment changes and normal troponin concentration.
B. An STE MI and normal troponin concentration.
C. An ST-segment depression and TIMI risk score of 6.
D. Primary PCI for STE MI.

19. In which one of the following situations is major bleeding increased by adding clopidogrel to aspirin compared with using aspirin alone?

A. Medical management of NSTE ACS with no angiography or PCI.
B. An STE MI treated with fibrinolytic therapy and percutaneous coronary intervention.
C. An STE MI and primary PCI.
D. An NSTE ACS with PCI.

20. The quality performance measures of NSTE MI include which one of the following?

A. Administration of β-blocker within 30 minutes of presentation to hospital admission; administration of an angiotensin-converting enzyme inhibitor to a patient with an ejection fraction of 20% at hospital discharge.
B. Administration of aspirin at hospital discharge, administration of fibrinolytic therapy within 30 minutes of hospital presentation.
C. Administration of an angiotensin-converting enzyme inhibitor to a patient with diastolic dysfunction and an ejection fraction of 60%, and administration of aspirin at hospital discharge.
D. Administration of an angiotensin receptor blocker to a patient with an ejection fraction less than 40% at hospital discharge, and administration of aspirin within 24 hours of hospital admission.