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Part 8: Stabilization of the Patient With Acute Coronary Syndromes

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Part 8: Stabilization of the Patient With Acute Coronary Syndromes

Acute myocardial infarction (AMI) and unstable angina (UA) are part of a spectrum of clinical disease collectively identified as *acute coronary syndromes* (ACS). The pathophysiology common to this spectrum of disease is a ruptured or eroded atheromatous plaque.[1–5] The electrocardiographic (ECG) presentation of these syndromes encompasses ST-segment elevation myocardial infarction (STEMI), ST-segment depression, and nondiagnostic ST-segment and T-wave abnormalities. A non–ST-elevation myocardial infarction (NSTEMI) is diagnosed if cardiac markers are positive with ST-segment depression or with nonspecific or normal ECGs. Sudden cardiac death may occur with any of these conditions. ACS is the most common proximate cause of sudden cardiac death.[6–10]

Effective interventions for patients with ACS, particularly STEMI, are extremely time-sensitive. The first healthcare providers to encounter the ACS patient can have a big impact on patient outcome if they provide efficient risk stratification, initial stabilization, and referral for cardiology care. It is critical that basic life support (BLS) and advanced cardiovascular life support (ACLS) healthcare providers who care for ACS patients in the out-of-hospital, emergency department (ED), and hospital environments be aware of the principles and priorities of assessment and stabilization of these patients.

These guidelines target BLS and ACLS healthcare providers who treat patients with ACS within the first hours after onset of symptoms, summarizing key out-of-hospital, ED, and some initial critical-care topics that are relevant to stabilization. They also continue to build on recommendations from the ACC/AHA Guidelines,[11,12] which are used throughout the United States and Canada.[13] As with any medical guidelines, these general recommendations must be considered within the context of local resources and application to individual patients by knowledgeable healthcare providers.

The primary goals of therapy for patients with ACS are to

- Reduce the amount of myocardial necrosis that occurs in patients with MI, preserving left ventricular (LV) function and preventing heart failure
- Prevent major adverse cardiac events (MACE): death, nonfatal MI, and need for urgent revascularization
- Treat acute, life-threatening complications of ACS, such as ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT), symptomatic bradycardias, and unstable tachycardias (see Part 7.2: "Management of Cardiac Arrest" and Part 7.3: "Management of Symptomatic Bradycardia and Tachycardia")

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An overview of recommended care for the ACS patient is illustrated in Figure 1, the Acute Coronary Syndromes Algorithm. Part 8 provides details of the care highlighted in the numbered algorithm boxes. Box numbers in the text correspond to the numbered boxes in the algorithm.

In this part the abbreviation AMI refers to acute myocardial infarction, whether associated with STEMI or NSTEMI. The diagnosis and treatment of AMI, however, will often differ for patients with STEMI versus NSTEMI. Note carefully which is being discussed.

Out-of-Hospital Management

Recognition (Figure 1, Box 1)

Treatment offers the greatest potential benefit for myocardial salvage in the first hours of STEMI. Thus, it is imperative that healthcare providers evaluate, triage, and treat patients with ACS as quickly as possible. Delays to therapy occur during 3 intervals: from onset of symptoms to patient recognition, during out-of-hospital transport, and during in-hospital evaluation. Patient delay to symptom recognition often constitutes the longest period of delay to treatment.[14]

The classic symptom associated with ACS is chest discomfort, but symptoms may also include discomfort in other areas of the upper body, shortness of breath, sweating, nausea, and lightheadedness. The symptoms of AMI are characteristically more intense than angina and last >15 minutes. Atypical symptoms or unusual presentations of ACS are more common in elderly, female, and diabetic patients.[15–19]

Public education campaigns increase public awareness and knowledge of the symptoms of heart attack but have only transient effects.[20] For patients at risk for ACS (and for their families), physicians should discuss the appropriate use of nitroglycerin and aspirin, activation of the emergency medical services (EMS) system, and location of the nearest hospital that offers 24-hour emergency cardiovascular care. Recent ACC/AHA guidelines recommend that the patient or family members activate the EMS system rather than call their physician or drive to the hospital if chest discomfort is unimproved or worsening 5 minutes after taking 1 nitroglycerin tablet or using nitroglycerin spray.[12]

Initial EMS Care (Figure 1, Box 2)

Half of the patients who die of AMI do so before reaching the hospital. VF or pulseless VT is the precipitating rhythm in most of these deaths,[21–23] and it is most likely to develop during the first 4 hours after onset of symptoms.[24–27] Communities should develop programs to respond to out-of-hospital cardiac arrest that include prompt recognition of symptoms of ACS, early activation of the EMS system, and

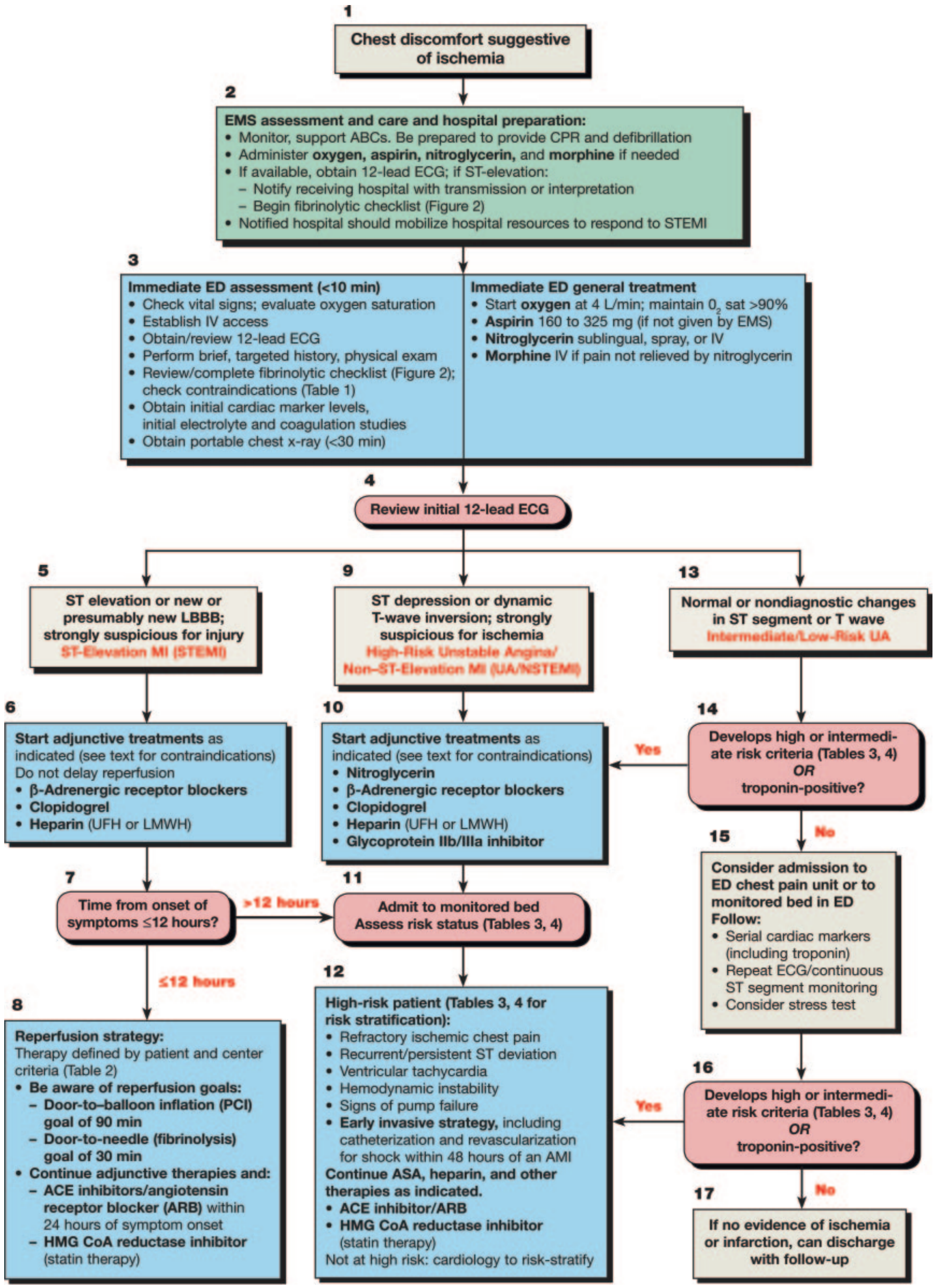

Figure 1. Acute Coronary Syndromes Algorithm.

if needed, early CPR (see Part 4: "Adult Basic Life Support") and early access to an automated external defibrillator (AED) through community AED programs (see Part 5: "Electrical Therapies").[28] EMS and dispatch system personnel should be trained to respond to cardiovascular emergencies.

Dispatchers and EMS providers must be trained to recognize symptoms of ACS. Dispatchers should advise patients with no history of aspirin allergy or signs of active or recent gastrointestinal bleeding to chew an aspirin (160 to 325 mg) while awaiting the arrival of EMS providers (Class IIa).[29]

EMS providers should be trained to determine the time of onset of symptoms and to stabilize, triage, and transport the patient to an appropriate facility and to provide prearrival notification. EMS providers should monitor vital signs and cardiac rhythm and be prepared to provide CPR and defibrillation if needed.

EMS providers may administer oxygen to all patients. If the patient is hypoxemic, providers should titrate therapy based on monitoring of oxyhemoglobin saturation (Class I).[30–44] If the patient has not taken aspirin and has no history of aspirin allergy and no evidence of recent gastrointestinal bleeding, EMS providers should give the patient nonenteric aspirin (160 to 325 mg) to chew (Class I).[45–48]

EMS providers should administer up to 3 nitroglycerin tablets (or spray) for ongoing symptoms at intervals of 3 to 5 minutes if permitted by medical control and if the patient remains hemodynamically stable (systolic blood pressure [SBP] >90 mm Hg [or no more than 30 mm Hg below baseline], heart rate between 50 and 100 beats per minute [bpm]).[49,50] EMS providers can administer morphine for chest pain unresponsive to nitroglycerin if authorized by protocol or medical control. Additional information about out-of-hospital stabilization and care is included in the following sections.

Out-of-Hospital ECGs

Out-of-hospital 12-lead ECGs and advance notification to the receiving facility speed the diagnosis, shorten the time to fibrinolysis, and may be associated with decreased mortality rates.[51–64] The reduction in door-to–reperfusion therapy interval in most studies ranges from 10 to 60 minutes. EMS providers can efficiently acquire and transmit diagnostic-quality ECGs to the ED[53,58,65,66] with a minimal increase (0.2 to 5.6 minutes) in the on-scene time interval.[52,56,65–68]

Qualified and specially trained paramedics and prehospital nurses can accurately identify typical ST-segment elevation (>1 mm in 2 or more contiguous leads) in the 12-lead ECG with specificity ranging from 91% to 100% and sensitivity ranging from 71% to 97% when compared with emergency medicine physicians or cardiologists.[69,70] Using radio or cell phone, they can also provide advance notification to the receiving hospital of the arrival of a patient with ACS.[56,61–64]

We recommend implementation of out-of-hospital 12-lead ECG diagnostic programs in urban and suburban EMS systems (Class I). Routine use of 12-lead out-of-hospital ECG and advance notification is recommended for patients with signs and symptoms of ACS (Class IIa). A 12-lead out-of-hospital ECG with advance notification to the ED may be beneficial for STEMI patients by reducing time to reperfusion therapy. We recommend that out-of-hospital paramedics acquire and transmit either diagnostic-quality ECGs or their interpretation of them to the receiving hospital with advance notification of the arrival of a patient with ACS (Class IIa). If EMS providers identify STEMI on the ECG, it is reasonable for them to begin to complete a fibrinolytic checklist (Figure 2).

Out-of-Hospital Fibrinolysis

Clinical trials have shown the benefit of initiating fibrinolysis as soon as possible after onset of ischemic-type chest pain in patients with STEMI or new or presumably new left bundle branch block (LBBB).[67,71] Several prospective studies (LOE 1)[72–74] have documented reduced time to administration of fibrinolytics and decreased mortality rates when out-of-hospital fibrinolytics were administered to patients with STEMI and no contraindications to fibrinolytics.

Physicians in the Grampian Region Early Anistreplase Trial (GREAT)[73] administered fibrinolytic therapy to patients at home 130 minutes earlier than to patients at the hospital and noted a 50% reduction in hospital mortality rates and greater 1-year and 5-year survival rates in those treated earlier.[75,76] Delaying fibrinolytic treatment by 1 hour increased the hazard ratio of death by 20%, which is equivalent to the loss of 43 lives per 1000 patients over 5 years.

A meta-analysis of out-of-hospital fibrinolytic trials found a relative improvement of 17% in outcome associated with out-of-hospital fibrinolytic therapy, particularly when therapy was initiated 60 to 90 minutes earlier than in the hospital.[71] A meta-analysis of 6 trials involving 6434 patients (LOE 1)[72] documented decreased all-cause hospital mortality rates among patients treated with out-of-hospital fibrinolysis compared with in-hospital fibrinolysis (odds ratio [OR]: 0.83; 95% confidence interval [CI]: 0.70 to 0.98) with a number needed to treat of 62 to save 1 extra life with out-of-hospital fibrinolysis. Results were similar regardless of the training and experience of the provider.

The *ECC Guidelines 2000*[77] recommended consideration of out-of-hospital fibrinolysis for patients with a transport time >1 hour. But in a recent Swiss study (LOE 1),[74] prehospital administration of fibrinolytics significantly decreased the time to drug administration even in an urban setting with relatively short transport intervals (<15 minutes).[74]

In summary, out-of-hospital administration of fibrinolytics to patients with STEMI with no contraindications is safe, feasible, and reasonable (Class IIa). This intervention may be performed by trained paramedics, nurses, and physicians for patients with symptom duration of 30 minutes to 6 hours. System requirements include protocols with fibrinolytic checklists, ECG acquisition and interpretation, experience in ACLS, the ability to communicate with the receiving institution, and a medical director with training/experience in management of STEMI. A process of continuous quality improvement is required. Given the operational challenges required to provide out-of-hospital fibrinolytics, most EMS systems should focus on early diagnosis with 12-lead ECG, rapid transport, and advance notification of the ED (verbal

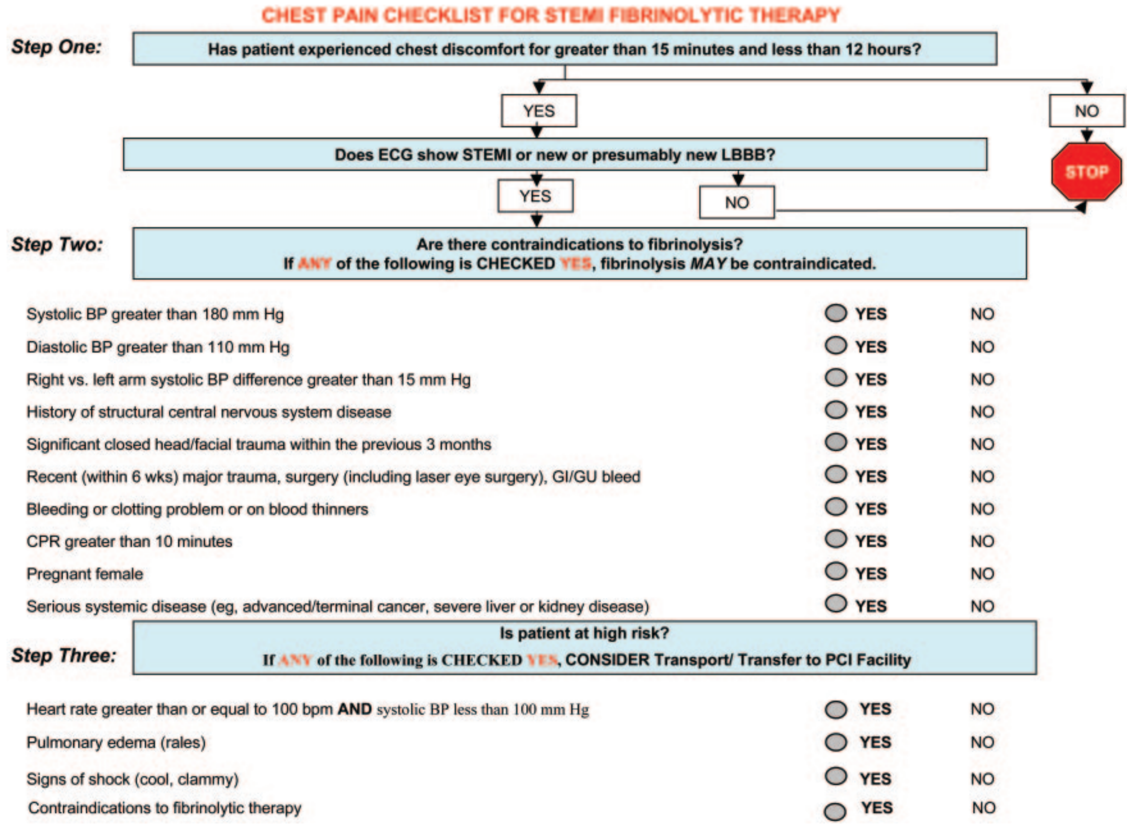

Figure 2. Fibrinolytic Checklist.

interpretation or direct transmission of ECG) instead of out-of-hospital delivery of fibrinolysis.

Triage and Transfer

Out-of-Hospital Triage

Hospital and EMS protocols should clearly identify criteria for transfer of patients to specialty centers and conditions under which fibrinolytics should be initiated before transfer. When transfer is indicated, the ACC/AHA guidelines recommend a door-to-departure time ≤30 minutes.[12] It may be appropriate for the EMS medical director to institute a policy of out-of-hospital bypass of hospitals that provide medical therapy only, particularly for patients who require interventional therapy. Patients who require interventional therapy may include those with cardiogenic shock, pulmonary edema, large infarctions, and contraindications to fibrinolytic therapy.

At present no randomized studies have directly compared triage with an experienced percutaneous coronary intervention (PCI) center with medical management at the local hospital. Extrapolation from several randomized trials on interfacility transfer[78–80] suggests that STEMI patients triaged directly to a primary PCI facility may have better outcomes related to the potential for earlier treatment. A cost-efficacy substudy of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial[81] suggests that direct transport to a primary PCI facility may be more cost-effective than out-of-hospital fibrinolysis when transport can be completed in ≤60 minutes with a physician in a mobile intensive care unit. There is no direct evidence, however, to suggest that these strategies are safe or effective. Patients judged to be at highest risk for a complicated transfer were excluded from some of these studies.

In summary, at this time there is inadequate evidence to recommend out-of-hospital triage to bypass non–PCI-capable hospitals to bring patients to a PCI center (Class Indeterminate). Local protocols for EMS providers are appropriate to guide the destination of patients with suspected or confirmed STEMI.

Interfacility Transfer

All patients with STEMI and symptom duration of ≤12 hours are candidates for reperfusion therapy with either fibrinolysis or PCI (Class I). When patients present directly to a facility capable of providing only fibrinolysis, 3 treatment options are available: administering fibrinolytics with admission to that hospital, transferring the patient for primary PCI, or giving fibrinolytics and then transferring the patient to a specialized center. The decision is guided by a risk-benefit assessment that includes evaluation of duration of symptoms, complications, contraindications, and the time delay from patient contact to fibrinolysis versus potential delay to PCI balloon inflation.

In 2 prospective studies (LOE 2)[78–80] and a meta-analysis,[82] patients with STEMI who presented 3 to 12 hours after onset of symptoms to a hospital without capability for primary PCI had better outcome (improved 30-day combined incidence of death, reinfarction, or stroke) when they were transferred to a skilled PCI center (interventionalist performing >75 procedures per year) rather than receiving fibrinolytics at the presenting hospital. In these studies balloon inflation occurred ≤93 minutes after decision to treat.[80,83–85] Thus, interfacility transfer is indicated for patients with STEMI presenting >3 hours from onset of symptoms from hospitals that lack primary PCI capability to centers capable of providing primary PCI when the transfer can be accomplished as soon as possible. The ACC/AHA guidelines recommend a treatment delay of no more than 90 minutes.[12] In patients with STEMI presenting <3 hours from onset of symptoms, the superiority of immediate administration of fibrinolytics in the hospital or transfer for primary PCI is not established (Class Indeterminate).

In-Hospital Fibrinolytics and Interfacility Transfer for PCI

Data from the 1980s to 1990s did not support a strategy of fibrinolytic therapy combined with transfer for facilitated PCI (LOE 1[86–88] and meta-analyses[89–91]). But all of the studies involved in-hospital administration of fibrinolytics, and most were completed before the era of coronary stenting and without use of contemporary pharmacologic therapies or PCI techniques. Three small randomized trials (LOE 1)[92–94] supported the strategy of fibrinolytics plus transfer for PCI; however, the timing of PCI after administration of fibrinolytics, the inclusion of patients who required transfer for PCI, the use of coronary stents, and the control group interventions differ considerably among these trials. The most recent study[79] was fairly small and showed a benefit of early PCI with 1-year follow-up.[94]

At present there is inadequate evidence to recommend the routine transfer of patients for early PCI (ie, within 24 hours) after successful administration of fibrinolytics in a community hospital. The use of out-of-hospital administration of fibrinolytics followed by early PCI has not been specifically studied.

Special Transfer Considerations

Special transfer considerations are appropriate for patients with signs of shock (pulmonary congestion, heart rate >100 bpm, *and* SBP <100 mm Hg). The Second National Registry of Myocardial Infarction found that the mortality rate in patients with AMI and shock was lower in those treated with PCI as a primary strategy than in those treated with fibrinolysis.[95] In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, 152 patients with cardiogenic shock were randomly assigned to an early revascularization (ERV) strategy, 150 patients were assigned to a strategy of initial medical stabilization that included fibrinolytics, and 25% had delayed revascularization.[96] Although there was no difference in the 30-day mortality rate, the mortality rate at 6 months was significantly lower in the ERV group (50.3% versus 63.1%). In a prespecified subgroup analysis for patients <75 years of age, early revascularization was associated with a 15.4% reduction in 30-day mortality and improvement in 1-year survival rates.[97] A direct comparison of the outcome of primary or early PCI patients with patients who received fibrinolytic therapy only was not reported.

There is inadequate evidence to recommend routine transfer of stable patients for early PCI after successful administration of fibrinolytics in community hospitals or the out-of-hospital setting. Patients <75 years of age and selected patients >75 years of age who develop cardiogenic shock or persistent ischemic symptoms within 36 hours of STEMI should be transferred to experienced facilities capable of ERV if ERV can be performed within 18 hours of onset of shock.[12]

ED Evaluation and Risk Stratification (Figure 1, Boxes 3 and 4)

Focused Assessment and ECG Risk Stratification

ED providers should quickly assess patients with possible ACS. Ideally within 10 minutes of ED arrival, providers should obtain a targeted history while a monitor is attached to the patient and a 12-lead ECG is obtained (if not done in the prehospital setting).[98] The evaluation should focus on chest discomfort, associated signs and symptoms, prior cardiac history, risk factors for ACS, and historical features that may preclude the use of fibrinolytics or other therapies. This initial evaluation must be efficient because if the patient has STEMI, the goals of reperfusion are to administer fibrinolytics within 30 minutes of arrival (30-minute interval "door-to-drug") or to provide PCI within 90 minutes of arrival (90-minute interval "door-to–balloon inflation" in the catheterization suite).

Potential delay during the in-hospital evaluation period may occur from **d**oor to **d**ata, from data (ECG) to **d**ecision, and from decision to **d**rug (or PCI). These 4 major points of in-hospital therapy are commonly referred to as the "4 D's."[99] All providers must focus on minimizing delays at each of these points. Out-of-hospital transport time constitutes only 5% of delay to treatment time; in-hospital evaluation constitutes 25% to 33% of this delay.[100,101]

The physical examination is performed to aid diagnosis, rule out other causes of the patient's symptoms, and evaluate the patient for complications related to ACS. Although the use of clinical signs and symptoms may increase suspicion of ACS, evidence does not support the use of any single sign or combination of clinical signs and symptoms alone to confirm the diagnosis.[102–105]

When the patient presents with signs of ACS, the clinician uses ECG findings (Figure 1, Box 4) to classify the patient into 1 of 3 groups:

1. ST-segment elevation or presumed new LBBB (Box 5) is characterized by ST-segment elevation >1 mm (0.1 mV) in 2 or more contiguous precordial leads or 2 or more adjacent limb leads and is classified as *ST-elevation MI (STEMI)*.
2. Ischemic ST-segment depression ≥0.5 mm (0.05 mV) or dynamic T-wave inversion with pain or discomfort (Box 9) is classified as *high-risk UA/non–ST-elevation MI (NSTEMI)*. Nonpersistent or transient ST-segment elevation ≥0.5 mm for <20 minutes is also included in this category.

3. Normal or nondiagnostic changes in ST segment or T waves (Box 13) are inconclusive and require further risk stratification. This classification includes patients with normal ECGs and those with ST-segment deviation of <0.5 mm (0.05 mV) or T-wave inversion of ≤0.2 mV. Serial cardiac studies (and functional testing) are appropriate.

Cardiac Biomarkers

New cardiac biomarkers, which are more sensitive than the myocardial muscle creatine kinase isoenzyme (CK-MB), are useful in diagnosis, risk stratification, and determination of prognosis. An elevated level of *troponin* correlates with an increased risk of death, and greater elevations predict greater risk of adverse outcome.[106] Patients with increased troponin levels have increased thrombus burden and microvascular embolization.

Cardiac biomarkers should be obtained during the initial evaluation of the patient, but therapeutic decisions and reperfusion therapy for patients with STEMI should not be delayed pending the results of these tests. Important limitations to these tests exist because they are insensitive during the first 4 to 6 hours of presentation unless continuous persistent pain has been present for 6 to 8 hours. For this reason cardiac biomarkers are not useful in the prehospital setting.[107–112]

Serial marker testing (CK-MB and cardiac troponin) over time improves sensitivity for detection of myocardial infarction but remains insensitive in the first 4 to 6 hours.[113,114]

ST-Segment Elevation MI (Figure 1, Boxes 5 Through 8)

Patients with STEMI usually have complete occlusion of an epicardial coronary vessel. The mainstay of treatment is reperfusion therapy through administration of fibrinolytics (pharmacologic reperfusion) or primary PCI (mechanical reperfusion). Providers should rapidly identify patients with STEMI and quickly screen them for indications and contraindications to fibrinolytic therapy and PCI.

The first physician who encounters a patient with AMI should be able to determine the need for reperfusion therapy and direct its administration (see Tables 1 and 2). If the patient meets the criteria for fibrinolytic therapy, a door-to-needle time (needle time is the beginning of infusion of a fibrinolytic agent) ≤30 minutes is desired. Results of cardiac biomarkers do not delay the administration of fibrinolytic therapy or referral for PCI. They are normal in a significant percentage of patients who present early with STEMI. Consultation with a cardiologist or the patient's personal physician delays therapy, is associated with increased hospital mortality rates, and is recommended only in equivocal or uncertain cases.[115] Hospitals with capabilities for angiography and PCI should have a clear protocol directing ED triage and initial management. Confusion about the method of reperfusion, eg, fibrinolysis or PCI, delays definitive therapy.

UA and NSTEMI (Figure 1, Boxes 9 Through 17)

In the absence of ST-segment elevation, patients with ischemic-type chest pain can present with ST-segment depression or nondiagnostic or normal ECGs. ST-segment depression identifies a population at increased risk for MACE. Patients with ischemic-type pain and ECGs consistent with NSTEMI or normal or nondiagnostic ECGs do not benefit from fibrinolytic therapy, and fibrinolysis may be harmful.[116]

Although many patients will not have ACS (ie, the ECG change is due to an alternative diagnosis, such as LV hypertrophy), initial triage and therapy appropriately includes antiplatelet, antithrombin, and antianginal therapy. These patients usually have a partially or intermittently occluding thrombus. Clinical features can correlate with the dynamic nature of clot formation and degradation, eg, waxing and waning clinical symptoms.

Serial cardiac markers are often obtained during evaluation, including CK-MB and cardiac troponins. At any point during evaluation, elevation of cardiac troponin places a patient at increased risk for MACE. Studies have shown that patients with increased troponin are best managed with a strategy of small-molecule glycoprotein (GP) IIb/IIIa inhibitor therapy and an early invasive strategy (cardiac catheterization with possible revascularization). Troponin serves as an additional and incremental adjunct to the ECG. Physicians

TABLE 1. Fibrinolytic Therapy: Contraindications and Cautions for Fibrinolytic Use in STEMI From ACC/AHA 2004 Guideline Update*

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (eg, AVM)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head trauma or facial trauma within 3 months

Relative Contraindications

- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)†
- History of prior ischemic stroke >3 months, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks)
- Recent (within 2 to 4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: prior exposure (>5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

AVM indicates arteriovenous malformation; SBP, systolic blood pressure; DBP, diastolic blood pressure; and INR, International Normalized Ratio.

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.

†Could be an absolute contraindication in low-risk patients with myocardial infarction.

TABLE 2. ST-Segment Elevation or New or Presumably New LBBB: Evaluation for Reperfusion

Step 1: Assess time and risk	
Time since onset of symptoms	
Risk of STEMI	
Risk of fibrinolysis	
Time required to transport to skilled PCI catheterization suite	
Step 2: Select reperfusion (fibrinolysis or invasive) strategy	
Note: If presentation <3 hours and no delay for PCI, then no preference for either strategy.	
Fibrinolysis is generally preferred if:	**An invasive strategy is generally preferred if:**
• Early presentation (≤3 hours from symptom onset)	• Late presentation (symptom onset >3 hours ago)
• Invasive strategy is not an option (eg, lack of access to skilled PCI facility or difficult vascular access) or would be delayed	• Skilled PCI facility available with surgical backup
—Medical contact-to-balloon or door-balloon >90 min	• Medical contact-to-balloon or door-balloon <90 min
—(Door-to-balloon) minus (door-to-needle) is >1 hour	• (Door-to-balloon) minus (door-to-needle) is <1 hour
• No contraindications to fibrinolysis	• Contraindications to fibrinolysis, including increased risk of bleeding and ICH
	• High risk from STEMI (CHF, Killip class is ≥3)
	• Diagnosis of STEMI is in doubt

Modified from ACC/AHA 2004 Update Recommendations.[112]

need to appreciate that other disorders can increase cardiac troponin, eg, myocarditis, congestive heart failure, and pulmonary embolism.

Risk Stratification

Braunwald Stratification

There are many ways to risk-stratify patients with chest pain. A well-recognized approach is the one initially proposed and later refined by Braunwald and colleagues on the ACC/AHA Task Force on the Management of Patients With Unstable Angina.[11,117–120] This approach is based on a combination of historical, clinical, laboratory, and ECG variables.

Table 3 is a modified version of what has been a work in progress by Braunwald and colleagues over several publications.[118,120,121] Patients are initially risk-stratified according to the likelihood that symptoms are due to unstable coronary artery disease (CAD). Patients at intermediate or high risk for CAD are further classified by their risk of MACE. This second classification is useful for prospectively identifying patients at intermediate or high risk who can benefit from an invasive strategy and more aggressive pharmacology with antiplatelet and antithrombin agents.

TIMI Risk Score

The risk of MACE has been further studied and refined. Researchers who derived the important Thrombolysis in Myocardial Ischemia (TIMI) risk score used data from the TIMI-11B and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events) trials for UA/NSTEMI[122,123] and from the In-TIME trial for STEMI.[124] The TIMI risk score comprises 7 independent prognostic variables (Table 4). These 7 variables were significantly associated with the occurrence within 14 days of at least one of the primary end points: death, new or recurrent MI, or need for urgent revascularization. The score is derived from complex multivariate logistic regression and includes variables that seem counterintuitive. It is useful to note that traditional cardiac risk factors are only weakly associated with MACE. Use of aspirin within the previous 7 days, for example, would not seem to be an indicator of a bad outcome. But aspirin use was in fact found to be one of the most powerful predictors.[122] It is possible that aspirin use identified a subgroup of patients at higher risk or on active but failed therapy for CAD.

The creators of the TIMI risk score validated it with 3 groups of patients, and 4 clinical trials showed a significant interaction between the TIMI risk score and outcome.[124–128] These findings confirm the value of the TIMI risk score as a guide to therapeutic decisions. A PDA download of this risk assessment is available at *www.TIMI.org*.

By classifying patients into 1 of 3 risk strata, the Braunwald (Table 3) and TIMI (Table 4) risk scores serve as the dominant clinical guides for predicting the risk of MACE in patients with ACS. Risk stratification is applicable to patients at intermediate or high risk of symptoms due to CAD and not the larger general population of patients presenting with chest pain or symptoms possibly due to anginal equivalents. Risk stratification enables clinicians to direct therapy to those patients at intermediate or high risk of MACE and avoids unnecessary therapy and the potential for adverse consequences in patients who are at lower risk.

The TIMI risk score has become the primary tool for evaluating therapeutic recommendations. Incrementally greater benefit from some of the newer therapies may be gained for patients with higher risk scores.

One additional product of the TIMI trials is the TIMI grading system of coronary artery blood flow. Investigators from the TIMI study developed and validated a coronary artery perfusion scoring system, characterizing the degree of reperfusion of a coronary artery on a scale of 0 (no flow) to 3 (normal, brisk flow). This TIMI grading system is now used as an outcome measure in many studies of ACS interventions.

Indicators for Early Invasive Strategies

Risk stratification (Figure 1, Box 12) helps the clinician identify patients with NSTEMI and UA who should be

TABLE 3. Likelihood of Ischemic Etiology and Short-Term Risk

Part I. Chest Pain Patients Without ST-Segment Elevation: Likelihood of Ischemic Etiology

	A. High likelihood High likelihood that chest pain is of ischemic etiology if patient has *any* of the findings in the column below:	**B. Intermediate likelihood** Intermediate likelihood that chest pain is of ischemic etiology if patient has NO findings in column A and *any* of the findings in the column below:	**C. Low likelihood** Low likelihood that chest pain is of ischemic etiology if patient has NO findings in column A or B. Patients may have any of the findings in the column below:
History	• Chief symptom is chest or left arm pain or discomfort *plus* Current pain reproduces pain of prior documented angina *and* Known CAD, including MI	• Chief symptom is chest or left arm pain or discomfort • Age >70 years • Male sex • Diabetes mellitus	• Probable ischemic symptoms • Recent cocaine use
Physical exam	• Transient mitral regurgitation • Hypotension • Diaphoresis • Pulmonary edema or rales	• Extracardiac vascular disease	• Chest discomfort reproduced by palpation
ECG	• New (or presumed new) transient ST deviation (≥0.5 mm) *or* T-wave inversion (≥2 mm) with symptoms	• Fixed Q waves • Abnormal ST segments *or* T waves that are not new	• Normal ECG *or* T-wave flattening *or* T-wave inversion in leads with dominant R waves
Cardiac markers	• Elevated troponin I or T • Elevated CK-MB	*Any finding in column B above PLUS* • Normal	• Normal

[High (A) or Intermediate (B) Likelihood of Ischemia]

Part II. Risk of Death or Nonfatal MI Over the Short Term in Patients With Chest Pain With High or Intermediate Likelihood of Ischemia (Columns A and B in Part I)

	High risk: Risk is high if patient has *any* of the following findings:	**Intermediate risk:** Risk is intermediate if patient has *any* of the following findings:	**Low risk:** Risk is low if patient has NO high- or intermediate-risk features; may have any of the following:
History	• Accelerating tempo of ischemic symptoms over prior 48 hours	• Prior MI *or* • Peripheral-artery disease *or* • Cerebrovascular disease *or* • CABG, prior aspirin use	
Character of pain	• Prolonged, continuing (>20 min) rest pain	• Prolonged (>20 min) rest angina is now resolved (moderate to high likelihood of CAD) • Rest angina (<20 min) or relieved by rest or sublingual nitrates	• New-onset functional angina (Class III or IV) in past 2 weeks without prolonged rest pain (but with moderate or high likelihood of CAD)
Physical exam	• Pulmonary edema secondary to ischemia • New or worse mitral regurgitation murmur • Hypotension, bradycardia, tachycardia • S_3 gallop or new or worsening rales • Age >75 years	• Age >70 years	
ECG	• Transient ST-segment deviation (≥0.5 mm) with rest angina • New or presumably new bundle branch block • Sustained VT	• T-wave inversion ≥2 mm • Pathologic Q waves or T waves that are not new	• Normal or unchanged ECG during an episode of chest discomfort
Cardiac markers	• Elevated cardiac troponin I or T • Elevated CK-MB	*Any of the above findings PLUS* • Normal	• Normal

Modified from Braunwald et al. *Circulation*. 2002;106:1893–1900.

TABLE 4. TIMI Risk Score for Patients With Unstable Angina and Non–ST-Segment Elevation MI: Predictor Variables

Predictor Variable	Point Value of Variable	Definition
Age ≥65 years	1	
≥3 risk factors for CAD	1	Risk factors • Family history of CAD • Hypertension • Hypercholesterolemia • Diabetes • Current smoker
Aspirin use in last 7 days	1	
Recent, severe symptoms of angina	1	≥2 anginal events in last 24 hours
Elevated cardiac markers	1	CK-MB or cardiac-specific troponin level
ST deviation ≥0.5 mm	1	ST depression ≥0.5 mm is significant; transient ST elevation >0.5 mm for <20 minutes is treated as ST-segment depression and is high risk; ST elevation ≥1 mm for more than 20 minutes places these patients in the STEMI treatment category
Prior coronary artery stenosis ≥50%	1	Risk predictor remains valid even if this information is unknown
Calculated TIMI Risk Score	**Risk of ≥1 Primary End Point* in ≤14 Days**	**Risk Status**
0 or 1	5%	Low
2	8%	
3	13%	Intermediate
4	20%	
5	26%	High
6 or 7	41%	

*Primary end points: death, new or recurrent MI, or need for urgent revascularization.

managed with an invasive strategy. Coronary angiography then allows the clinician to determine whether patients are appropriate candidates for revascularization with PCI or coronary artery bypass grafting (CABG).

The *2005 AHA Guidelines for CPR and ECC* define high-risk patients with indicators that overlap to a considerable degree with the more rigorously validated TIMI risk score[122]:

- New ST-segment depression and positive troponins
- Persistent or recurrent symptoms
- Hemodynamic instability or VT
- Depressed LV function (ejection fraction <40%)
- ECG or functional study that suggests multivessel CAD

Normal or Nondiagnostic ECG Changes (Boxes 13 to 17)

The majority of patients with normal or nondiagnostic ECGs do not have ACS. Patients in this category with ACS are most often at low or intermediate risk. The physician's goal involves risk stratification (see above) to provide appropriate diagnostic or treatment strategies for an individual patient. These strategies then target patients at increased risk for benefit while avoiding risk (eg, anticoagulation therapy and invasive cardiac catheterization) in patients with low or minimal risk.

Initial General Therapy for ACS

Several initial measures are appropriate for all patients with suspected ACS in both the out-of-hospital and ED setting. These include immediate oxygen therapy, continuous cardiac monitoring, establishment of intravenous (IV) access, and several medications discussed below.

Oxygen

Administer oxygen to all patients with overt pulmonary congestion or arterial oxygen saturation <90% (Class I). It is also reasonable to administer supplementary oxygen to all patients with ACS for the first 6 hours of therapy (Class IIa). Supplementary oxygen limited ischemic myocardial injury in animals,[31] and oxygen therapy in patients with STEMI reduced the amount of ST-segment elevation.[35] Although a human trial of supplementary oxygen versus room air failed to show a long-term benefit of supplementary oxygen therapy for patients with MI,[30] short-term oxygen administration is beneficial for the patient with unrecognized hypoxemia or unstable pulmonary function. In patients with severe chronic obstructive pulmonary disease, as with any other patient, monitor for hypoventilation.

Aspirin

Early administration of aspirin (acetylsalicylic acid [ASA]), including administration in the out-of-hospital setting,[47] has been associated with decreased mortality rates in several clinical trials.[47,129–131] Multiple studies support the safety of aspirin administration. Therefore, unless the patient has a known aspirin allergy, nonenteric aspirin should be given as soon as possible to all patients with suspected ACS.

Aspirin produces a rapid clinical antiplatelet effect with near-total inhibition of thromboxane A_2 production. It reduces coronary reocclusion and recurrent ischemic events after fibrinolytic therapy. Aspirin alone reduced death from AMI in the Second International Study of Infarct Survival (ISIS-2), and its effect was additive to that of streptokinase.[129] In a review of 145 trials, aspirin was found to substantially reduce vascular events in all patients with AMI, and in high-risk patients it reduced nonfatal AMI and vascular death.[132] Aspirin is also effective in patients with UA. The standard dose (160 to 325 mg) is recommended, although higher doses may be used. Chewable or soluble aspirin is absorbed more quickly than swallowed tablets.[133,134]

The early administration of a single chewed dose of aspirin (160 to 325 mg) is recommended in either the out-of-hospital or ED setting for patients with suspected ACS (Class I). Other formulations of ASA (soluble, IV) may be as effective as chewed tablets. Aspirin suppositories (300 mg) are safe and can be considered for patients with severe nausea, vomiting, or disorders of the upper gastrointestinal tract.

Nitroglycerin (or Glyceryl Trinitrate)

Nitroglycerin is an effective analgesic for ischemic chest discomfort. It also has beneficial hemodynamic effects, including dilation of the coronary arteries (particularly in the region of plaque disruption), the peripheral arterial bed, and venous capacitance vessels. The treatment benefits of nitroglycerin are limited, however, and no conclusive evidence has been shown to support *routine* use of IV, oral, or topical nitrate therapy in patients with AMI.[135] With this in mind, these agents should be carefully considered, especially when low blood pressure precludes the use of other agents shown to be effective in reducing morbidity and mortality (eg, β-blockers and angiotensin-converting enzyme [ACE] inhibitors).

IV nitroglycerin is indicated in the following clinical situations (Class I):

- Ongoing ischemic chest discomfort
- Management of hypertension
- Management of pulmonary congestion

Patients with ischemic discomfort may receive up to 3 doses of sublingual or aerosol nitroglycerin at 3- to 5-minute intervals until pain is relieved or low blood pressure limits its use (Class I). IV nitroglycerin is indicated for ongoing chest discomfort, control of hypertension, or management of pulmonary congestion in patients with STEMI associated with LV failure (Class I). In patients with recurrent ischemia, nitrates are indicated in the first 24 to 48 hours. IV rather than long-acting preparations should be used acutely to enable titration.

Do not use nitrates (Class III) in patients with hypotension (SBP <90 mm Hg or >30 mm Hg below baseline), extreme bradycardia (<50 bpm), or tachycardia (>100 bpm). Administer nitrates with extreme caution if at all to patients with suspected inferior wall MI with possible right ventricular (RV) involvement because these patients require adequate RV preload. Do not administer nitrates (Class III) to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (longer for some preparations).

Morphine Sulfate

Morphine sulfate is the analgesic of choice for continuing pain unresponsive to nitrates, and it is also effective in patients with pulmonary vascular congestion complicating ACS. Morphine is a venodilator that reduces ventricular preload and oxygen requirements. For this reason it should not be used in patients who may have hypovolemia. If hypotension develops, elevate the patient's legs, administer volume, and monitor for signs of worsening pulmonary vascular congestion. Start with a 2 to 4 mg IV dose, and give additional doses of 2 to 8 mg IV at 5- to 15-minute intervals.

Reperfusion Therapies (Figure 1, Box 8)

Perhaps the most significant advance in the treatment of cardiovascular disease in the last decade is reperfusion therapy for AMI. Many clinical trials have established early fibrinolytic therapy as a standard of care for patients with AMI who present within 12 hours of the onset of symptoms with no contraindications.[136–140] Reperfusion reduces mortality, and the shorter the time to reperfusion, the greater the benefit: a 47% reduction in mortality was noted when fibrinolytic therapy was provided within the first hour after onset of symptoms.[139,140]

The major determinants of myocardial salvage and long-term prognosis are

- Short time to reperfusion[136,140]
- Complete and sustained patency of the infarct-related artery with normal (TIMI grade 3) flow[141,142]
- Normal microvascular perfusion[116,143–145]

Fibrinolytics

In the absence of contraindications and the presence of a favorable risk-benefit stratification, fibrinolytic therapy is one option for reperfusion in those STEMI patients with onset of symptoms of $\leq$12 hours and ECG findings of STEMI (elevation >1 mm in 2 or more contiguous precordial or adjacent limb leads or new or presumably new LBBB) (Class I). In the absence of contraindications, it is also reasonable to administer fibrinolytics to patients with onset of symptoms within the prior 12 hours and ECG findings consistent with true posterior MI (Class IIa).

The ED physician should administer fibrinolytics to eligible patients as early as possible according to a predetermined process of care developed by the ED and cardiology staff. The goal is a door-to-needle time of $\leq$30 minutes. Every effort must be made to minimize the time to therapy. Patients treated within the first 70 minutes of onset of symptoms have >50% reduction in infarct size and 75% reduction in mortality rates.[146] Pooled data from 22 randomized controlled trials of fibrinolytic therapy documents 65 lives saved per 1000 patients treated if fibrinolytics are provided in the first hour and pooled total of 131 lives saved per 1000 patients treated if fibrinolytics are provided within the first 3 hours of onset of symptoms.[147] Fibrinolytics may be beneficial $\leq$12 hours after onset of symptoms.[148,149]

Fibrinolytic therapy is generally not recommended for patients presenting >12 hours after onset of symptoms, although it may be considered if continuing ischemic pain is present with ST elevation >1 mm in 2 or more contiguous precordial or adjacent limb leads (Class IIa).

Fibrinolytic therapy should not be administered (Class III) to patients who present >24 hours after the onset of symptoms or to patients who show ST-segment depression (unless a true posterior MI is suspected).

Risks of Fibrinolytic Therapy

Physicians who administer fibrinolytic agents should be aware of the indications, contraindications, benefits, and major risks of administration so that they may be able to weigh the net clinical benefit for each patient (see Table 1).[150,151] This net clinical benefit requires integration of relative and absolute contraindications versus overall potential clinical gain.

Patients who present with extensive ECG changes (consistent with a large AMI) and a low risk of intracranial bleeding receive the greatest benefit from fibrinolytic therapy.[136] Patients with symptoms highly suggestive of ACS and ECG findings consistent with LBBB are also appropriate candidates for intervention because they have the highest mortality rate when LBBB is due to extensive AMI. Fibrinolytics have been shown to be beneficial across a spectrum of patient subgroups with comorbidities such as previous MI, diabetes, cardiogenic shock, tachycardia, and hypotension.[136] The benefits of fibrinolytic therapy are less impressive in inferior wall infarction except when it is associated with RV infarction (ST-segment elevation in lead V_4R or anterior ST-segment depression).

Although older patients (>75 years) have a higher absolute risk of death, their absolute benefit appears to be similar to that of younger patients. There is only a small trend for benefit of fibrinolytic therapy administered 12 to 24 hours following the onset of symptoms. The incidence of stroke does increase with advancing age,[152,153] reducing the relative benefit of fibrinolytic therapy. Older age is the most important baseline variable predicting nonhemorrhagic stroke.[152] Although 1 large trial reported lower early and 1-year mortality rates with accelerated administration of tissue plasminogen activator (tPA) in patients <85 years of age,[154] a recent retrospective analysis found no specific survival advantage and possible risk for patients >75 years of age.[155] Additional studies are needed to clarify risk-benefit parameters in the elderly.

The presence of high blood pressure (SBP >175 mm Hg) on presentation to the ED increases the risk of stroke after fibrinolytic therapy.[156] Current clinical practice is directed at lowering blood pressure before administration of fibrinolytic agents, although this has not been shown to reduce the risk of stroke.[156] Fibrinolytic treatment of ACS patients who present with an SBP >180 mm Hg or a diastolic blood pressure >110 mm Hg is relatively contraindicated. Note that this SBP limit is slightly lower than the upper limit of 185 mm Hg used in eligibility criteria for fibrinolytic therapy for acute ischemic stroke; the diastolic limit of 110 mm Hg is consistent with the diastolic limit for tPA administration for stroke (see Part 9: "Adult Stroke").

Several fibrinolytics are available for clinical use, including streptokinase,[129,140,157] anistreplase,[158,159] various regimens of alteplase,[147,160,161] reteplase,[162,163] and tenecteplase.[138,164] Choice of agent is typically based on ease of administration, cost, and preferences of each institution.

Intracranial Hemorrhage

Fibrinolytic therapy is associated with a small but definite increase in the risk of hemorrhagic stroke, which contributes to increased mortality.[136] More intensive fibrinolytic regimens using tPA (alteplase) and heparin pose a greater risk than streptokinase and aspirin.[147,165] Clinical factors that may help risk-stratify patients at the time of presentation are age (≥65 years), low body weight (<70 kg), initial hypertension (≥180/110 mm Hg), and use of tPA. The number of risk factors can be used to estimate the frequency of stroke, which ranges from 0.25% with no risk factors to 2.5% with 3 risk factors.[151] Several risk factor estimates are available for use by clinicians, including Simoons,[151] the Co-Operative Cardiovascular Project,[166] and the In-Time 2 trial.[167]

Percutaneous Coronary Intervention

Coronary angioplasty with or without stent placement is the most common form of PCI. PCI has been shown to be superior to fibrinolysis in combined end points of death, stroke, and reinfarction in many studies.[78,80,82,96,168–173] These results, however, have been achieved in experienced medical environments with skilled providers (performing >75 PCIs per year) at a skilled PCI facility (performing >200 PCIs annually for STEMI, with cardiac surgery capabilities).

At this time primary PCI is preferred in patients with STEMI and symptom duration of >3 and ≤12 hours if skilled personnel can ensure that door-to-balloon time is ≤90 minutes or the difference in time between administration of fibrinolysis versus inflation of the PCI balloon is ≤60 minutes (Class I). PCI is also preferred in patients with contraindications to fibrinolysis and is reasonable in patients with cardiogenic shock or heart failure complicating MI.

In patients with STEMI presenting ≤3 hours from onset of symptoms, treatment is more time-sensitive, and there is inadequate research to recommend one treatment over the other (Class Indeterminate). In these "early presenters," any possible benefit from primary PCI will be lost in prolonged transfers.

Complicated AMI

Cardiogenic Shock, LV Failure, and Congestive Heart Failure

Infarction of ≥40% of the LV myocardium usually results in cardiogenic shock and carries a high mortality rate. Of those who developed shock,[174] patients with ST-segment elevation developed shock significantly earlier than patients without ST-segment elevation.

Cardiogenic shock and congestive heart failure are not contraindications to fibrinolysis, but PCI is preferred if the patient is at a facility with PCI capabilities. The ACC/AHA guidelines note that primary PCI is reasonable in those who develop shock within 36 hours of MI and are suitable candidates for revascularization that can be performed within 18 hours of the onset of shock.[12] In hospitals without PCI facilities, rapidly administer a fibrinolytic agent and transfer the patient to a tertiary care facility where adjunct PCI can be performed if low-output syndromes or ischemia continues.[175] The ACC/AHA STEMI guidelines recommend a door-to-departure time of ≤30 minutes for transfer.[12]

RV Infarction

RV infarction or ischemia may occur in up to 50% of patients with inferior wall MI. The clinician should suspect RV infarction in patients with inferior wall infarction, hypotension, and clear lung fields. In patients with inferior wall infarction, obtain a right-sided or 15-lead ECG; ST-segment elevation (>1 mm) in lead V_4R is sensitive (sensitivity, 88%; specificity, 78%; diagnostic accuracy, 83%) for RV infarction and a strong predictor of increased in-hospital complications and mortality.[176] The in-hospital mortality rate of patients with RV dysfunction is 25% to 30%, and these patients should be routinely considered for reperfusion therapy. Fibrinolytic therapy reduces the incidence of RV dysfunction.[177] Similarly PCI is an alternative for patients with RV infarction and is preferred for patients in shock. Patients with shock caused by RV failure have a mortality rate similar to that for patients with shock due to LV failure.

Patients with RV dysfunction and acute infarction are dependent on maintenance of RV "filling" pressure (RV end-diastolic pressure) to maintain cardiac output.[178] Thus, nitrates, diuretics, and other vasodilators (ACE inhibitors) should be avoided because severe hypotension may result. This hypotension is often easily treated with an IV fluid bolus.

Adjunctive Therapies for ACS and AMI

Clopidogrel

Clopidogrel irreversibly inhibits the platelet adenosine diphosphate receptor, resulting in a reduction in platelet aggregation through a different mechanism than aspirin. Since the publication of the *ECC Guidelines 2000*, several important clopidogrel studies have been published that document its efficacy for patients with both UA/NSTEMI and STEMI.

Clopidogrel was shown to be effective in 2 in-hospital randomized controlled trials (LOE 1)[179,180] and 4 post-hoc analyses (LOE 7).[181–184] In these studies patients with ACS and a rise in cardiac biomarkers or ECG changes consistent with ischemia had reduced stroke and MACE if clopidogrel was added to aspirin and heparin within 4 hours of hospital presentation. One study confirmed that clopidogrel did not increase risk of bleeding in comparison with aspirin.[185] Clopidogrel given 6 hours or more before elective PCI for patients with ACS without ST elevation reduced adverse ischemic events at 28 days (LOE 1).[186]

In patients up to 75 years of age with STEMI who are treated with fibrinolysis, aspirin, and heparin (low-molecular-weight heparin [LMWH] or unfractionated heparin [UFH]), a 300-mg oral loading dose of clopidogrel given at the time of initial management (followed by a 75-mg daily dose for up to 8 days in hospital) improved coronary artery patency and reduced MACE.[187]

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial documented an increased rate of bleeding (but not intracranial hemorrhage) in the 2072 patients undergoing CABG within 5 to 7 days of administration of this agent.[184] In addition, a post-hoc analysis of this trial reported a trend toward life-threatening bleeding. A subsequent risk-to-benefit ratio analysis concluded that the bleeding risk with clopidogrel in patients undergoing CABG was modest.[184] One recent large prospective trial (LOE 1)[187] failed to show any increase in bleeding in 136 patients undergoing CABG within 5 to 7 days of administration of clopidogrel. In patients with ACS, the risk of bleeding must be weighed against the risk of perioperative ACS events recurring if these agents are withheld. Current ACC/AHA guidelines, published soon after the large CURE trial, recommend withholding clopidogrel for 5 to 7 days in patients for whom CABG is anticipated.[12] Ongoing studies are evaluating the efficacy and risk-benefit issues.

On the basis of these findings, providers should administer a 300-mg loading dose of clopidogrel in addition to standard care (aspirin, UFH, or LMWH and GP IIb/IIIa inhibitors if indicated) to ED patients with ACS with elevated cardiac markers or new ECG changes consistent with ischemia (excluding STEMI)[184] in whom a medical approach or PCI is planned (Class I). It is reasonable to administer a 300-mg oral dose of clopidogrel to ED patients with suspected ACS (without ECG or cardiac marker changes) who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Class IIa). Providers should administer a 300-mg oral dose of clopidogrel to ED patients up to 75 years of age with STEMI who receive aspirin, heparin, and fibrinolysis.

β-Adrenergic Receptor Blockers

In-hospital administration of β-blockers reduces the size of the infarct, incidence of cardiac rupture, and mortality in patients who do not receive fibrinolytic therapy.[188–190] They also reduce the incidence of ventricular ectopy and fibrillation.[191,192] In patients who do receive fibrinolytic agents, IV β-blockers decrease postinfarction ischemia and nonfatal AMI. A small but significant decrease in death and nonfatal infarction has been observed in patients treated with β-blockers soon after infarction.[193] IV β-blockers may also be beneficial for NSTEMI ACS.

Oral β-blockers should be administered in the ED for ACS of all types unless contraindications are present. They should be given irrespective of the need for revascularization therapies (Class I). Use IV β-blockers for the treatment of tachyarrhythmias or hypertension (Class IIa).

Contraindications to β-blockers are moderate to severe LV failure and pulmonary edema, bradycardia (<60 bpm), hypotension (SBP <100 mm Hg), signs of poor peripheral perfusion, second-degree or third-degree heart block, or reactive airway disease. In the presence of moderate or severe heart failure, oral β-blockers are preferred. They may need to be given in low and titrated doses after the patient is stabilized. This permits earlier administration of ACE inhibitors that are documented to be efficacious in reducing 30-day mortality rates (see below).

Heparins

Heparin is an indirect inhibitor of thrombin that has been widely used in ACS as adjunctive therapy for fibrinolysis and in combination with aspirin and other platelet inhibitors for the treatment of UA and NSTEMI. UFH is a heterogeneous mixture of sulfated glycosaminoglycans with varying chain lengths. UFH has several disadvantages, including an unpredictable anticoagulant response in individual patients, the need for IV administration, and the requirement for frequent monitoring of the activated partial thromboplastin time (aPTT). Heparin can also stimulate platelet activation, causing thrombocytopenia.[194]

When UFH is used as adjunctive therapy with fibrin-specific lytics in STEMI, the current recommendations call for a bolus dose of 60 U/kg followed by infusion at a rate of 12 U/kg per hour (a maximum bolus of 4000 U and infusion of 1000 U/h for patients weighing >70 kg).[195] An aPTT of 50 to 70 seconds is considered optimal. Because of the limitations of heparin, newer preparations of LMWH have been developed.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin in UA/NSTEMI

Six in-hospital randomized controlled trials (LOE 1[196,197] and LOE 2[130,198,199] <24 hours; LOE 1[200] <36 hours) and additional studies (including 7 meta-analyses [LOE 1[201–207]]) document similar or improved composite outcomes (death, MI and/or recurrent angina, or recurrent ischemia or revascularization) when LMWH is given instead of UFH to patients with UA/NSTEMI within the first 24 to 36 hours after onset of symptoms.

Although major bleeding events are not significantly different with LMWH compared with UFH, there is a consistent increase in minor and postoperative bleeding with the use of LMWH.[208] Omission of LMWH (enoxaparin) on the morning of angiography resulted in vascular complication rates comparable to that of UFH.[209]

Four trials have compared UFH and LMWH in patients with NSTEMI who were treated with a GP IIb/IIIa inhibitor.[210–213] In terms of efficacy, LMWH compared favorably with UFH, and in terms of safety there were similar or less frequent major bleeding events with LMWH but again an increased frequency of minor bleeding complications.

In summary, ED administration of LMWH (specifically enoxaparin) is beneficial compared with UFH when given in addition to antiplatelet therapy such as aspirin for patients with UA/NSTEMI (Class IIb). UFH should be considered if reperfusion is planned in the first 24 to 36 hours after onset of symptoms. Changing from one form of heparin to another (crossover of antithrombin therapy) during an acute event is not recommended because it may lead to an increase in bleeding complications.[214]

Unfractionated Heparin Versus Low-Molecular-Weight Heparin in STEMI

LMWHs have been found to be superior to UFH in patients with STEMI in terms of overall TIMI flow[215,216] and reducing the frequency of ischemic complications,[217] with a trend to a 14% reduction in mortality rates in a meta-analysis.[218] No superiority was found in studies in which an invasive strategy (PCI) was used.

Two randomized controlled trials compared UFH with LMWH as ancillary treatment with fibrinolysis in the out-of-hospital setting.[219,220] Administration of LMWH for patients with STEMI showed superiority in composite end points compared with UFH. This must be balanced against an increase in intracranial hemorrhage in patients >75 years of age who received LMWH (enoxaparin) documented in one of these randomized controlled trials (LOE 2).[220]

LMWH (enoxaparin) is an acceptable alternative to UFH in the ED as ancillary therapy for patients <75 years of age who are receiving fibrinolytic therapy, provided that significant renal dysfunction (serum creatinine >2.5 mg/dL in men or 2 mg/dL in women) is not present (Class IIb). UFH is recommended for patients ≥75 years of age as ancillary therapy to fibrinolysis (Class IIa) and for any STEMI patient who is undergoing revascularization. In patients with STEMI who are not receiving fibrinolysis or revascularization, LMWH (specifically enoxaparin) may be considered an acceptable alternative to UFH in the ED setting (Class IIb).

Glycoprotein IIb/IIIa Inhibitors

After plaque rupture in the coronary artery, tissue factor in the lipid-rich core is exposed and forms complexes with factor VIIa, setting in motion the coagulation cascade resulting in platelet activation. The integrin GP IIb/IIIa receptor is considered the final common pathway to platelet aggregation. GP IIb/IIIa inhibitors modulate this receptor activity. Three agents are available for use: abciximab, eptifibatide, and tirofiban.

GP IIb/IIIa Inhibitors in UA/NSTEMI

Several large studies of GP IIb/IIIa inhibitors in UA/NSTEMI have shown a clear benefit when combined with standard aspirin and heparin and a strategy of mechanical reperfusion (LOE 1[221]; LOE 2[222]; and 3 meta-analyses[221,223,224]). Severe bleeding complications (and no increase in intracranial hemorrhage) in the GP IIb/IIIa group were offset by the large benefit of these agents. The benefit of GP IIb/IIIa inhibitors extends to high-risk patients with UA/NSTEMI treated with PCI.[223]

In UA/NSTEMI patients not treated with PCI, the effect of GP IIb/IIIa inhibitors has been mixed. In 2 studies (LOE 1)[212,221] and 3 meta-analyses (LOE 1),[223–225] GP IIb/IIIa inhibitors produced no mortality advantage and only a slight reduction in recurrent ischemic events in one large meta-analysis[224] but did show a reduction in 30-day mortality in a later, equally large meta-analysis.[225] Of note, the benefit of GP IIb/IIIa inhibitors was dependent on coadministration of UFH or LMWH. Interestingly abciximab appears to behave differently from the other 2 GP IIb/IIIa inhibitors. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) IV-ACS trial and 1-year follow-up involving 7800 patients,[226,227] abciximab showed a lack of treatment effect compared with placebo in patients treated medically only.

On the basis of these findings, GP IIb/IIIa inhibitors should be used in patients with high-risk stratification UA/NSTEMI as soon as possible in conjunction with aspirin, heparin, and clopidogrel and a strategy of early PCI (Class I). High-risk features include persistent pain, hemodynamic or rhythm instability, diabetes, acute or dynamic ECG changes, and any elevation in cardiac troponins attributed to cardiac injury. Extrapolation from efficacy studies suggests that this therapy may be administered in the ED once a decision has been made to proceed to PCI (Class IIa).

GP IIb/IIIa inhibitors tirofiban and eptifibatide may be used in patients with high-risk stratification UA/NSTEMI in conjunction with standard therapy if PCI is not planned (Class IIb), although studies are not conclusive at this time. As a result of the lack of benefit demonstrated in the GUSTO IV ACS trial, abciximab should not be given unless PCI is planned (Class III).

GP IIa/IIIb Inhibitors in STEMI

There is insufficient evidence to recommend for or against GP IIb/IIIa inhibitor therapy in STEMI; studies are ongoing. These agents have been used to facilitate antiplatelet therapy in patients undergoing direct PCI, but relatively few patients have been evaluated. GP IIb/IIIa inhibitors are now being evaluated early in STEMI to "facilitate" fibrinolytic therapy and serve as "upstream" adjuncts to planned direct PCI for STEMI, for example, achieving some degree of infarct artery patency during preparation or transfer. One study using abciximab (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events [*FINESSE*]) is ongoing. Use of these agents in STEMI requires institutional-individualized protocols developed in conjunction with interventional cardiologists.

Calcium Channel Blockers

Calcium channel blocking agents may be added as an alternative or additional therapy if β-blockers are contraindicated or the maximum dose has been achieved.

The 1996 ACC/AHA guidelines for the management of patients with AMI[228] make the following comment about calcium channel blockers:

> Calcium channel blocking agents have not been shown to reduce mortality after acute MI, and in certain patients with cardiovascular disease there is data to suggest that they are harmful. There is concern that these agents are still used too frequently in patients with acute MI and that β-adrenergic receptor blocking agents are a more appropriate choice across a broad spectrum of patients with MI. In general, give calcium antagonists only when β-blockers are contraindicated or have been given at maximum clinical doses without effect (Class Indeterminate).

ACE Inhibitor Therapy

ACE inhibitor therapy has improved survival rates in patients with AMI, particularly when started early.[229–233] Evidence from 7 large clinical trials,[135,232–237] 2 meta-analyses,[238,239] and 10 minor trials[237,240–249] documents consistent improvement in mortality when oral ACE inhibitors are administered in the hospital setting to patients with AMI with or without early reperfusion therapy. In these studies ACE inhibitors were not administered in the presence of hypotension (SBP <100 mm Hg or more than 30 mm Hg below baseline). The beneficial effects are most pronounced in patients with anterior infarction, pulmonary congestion, or LV ejection fraction <40%.

Administration of an oral ACE inhibitor is recommended within the first 24 hours after onset of symptoms in STEMI patients with pulmonary congestion or LV ejection fraction <40%, in the absence of hypotension (SBP <100 mm Hg or more than 30 mm Hg below baseline) (Class I). Oral ACE inhibitor therapy can also be recommended for all other patients with AMI with or without early reperfusion therapy (Class IIa). IV administration of ACE inhibitors is contraindicated in the first 24 hours because of risk of hypotension (Class III).

HMG Coenzyme A Reductase Inhibitors (Statins)

A variety of studies documented consistent reduction in indicators of inflammation and complications such as reinfarction, recurrent angina, and arrhythmias when statin treatment is administered within a few days after onset of an ACS.[250–253] There is little data to suggest that this therapy should be initiated within the ED; however, early initiation (within 24 hours of presentation) of statin therapy is safe and feasible in patients with an ACS or AMI (Class I). If patients are already on statin therapy, continue the therapy (Class IIb).

Glucose-Insulin-Potassium

Although glucose-insulin-potassium (GIK) therapy was formerly thought to reduce the chance of mortality during AMI by several mechanisms, recent clinical trials found that GIK did not show any benefit in STEMI.[254,255] At this time there is little evidence to suggest that this intervention is helpful.

Management of Arrhythmias

This section discusses management of arrhythmias during acute ischemia and infarction.

Ventricular Rhythm Disturbances

Treatment of ventricular arrhythmias during and after AMI has been a controversial topic for 2 decades. Primary VF accounts for the majority of early deaths during AMI.[21–23] The incidence of primary VF is highest during the first 4 hours after onset of symptoms[24–27] but remains an important contributor to mortality during the first 24 hours. Secondary VF occurring in the setting of CHF or cardiogenic shock can also contribute to death from AMI. VF is a less common cause of death in the hospital setting with the early use of fibrinolytics in conjunction with β-blockers.

Although prophylaxis with lidocaine reduces the incidence of VF, an analysis of data from ISIS-3 and a meta-analysis suggest that lidocaine increased all-cause mortality rates.[256] Thus, the practice of prophylactic administration of lidocaine has been largely abandoned.

Routine IV administration of β-blockers to patients without hemodynamic or electrical contraindications is associated with a reduced incidence of primary VF. Low serum potassium but not magnesium has been associated with ventricular arrhythmias. It is prudent clinical practice to maintain serum potassium >4 mEq/L and magnesium >2 mEq/L.

Routine administration of magnesium to patients with MI has no significant clinical mortality benefit, particularly in patients receiving fibrinolytic therapy. The definitive study on the subject is the ISIS-4 study (LOE 1).[135] ISIS-4 enrolled >58 000 patients and showed a trend toward increased mortality rates when magnesium was given in-hospital for primary prophylaxis to patients within the first 4 hours of known or suspected AMI.

Following an episode of VF, there is no conclusive data to support the use of lidocaine or any particular strategy for preventing VF recurrence. β-Blockers are the preferred treatment if not initiated before the episode of VF. If lidocaine is used, continue it for a short time after MI but no more than 24 hours unless symptomatic VT persists. Exacerbating or modulating factors should be identified and corrected. Further management of ventricular rhythm disturbances is discussed in Part 7.2: "Management of Cardiac Arrest" and Part 7.3: "Management of Symptomatic Bradycardia and Tachycardia."

Summary

There has been tremendous progress in reducing disability and death from ACS. But many patients still die before reaching the hospital because patients and family members fail to recognize the signs of ACS and fail to activate the EMS system. Once the patient with ACS contacts the healthcare system, providers must focus on support of cardiorespiratory function, rapid transport, and early classification of the patient based on ECG characteristics. Patients with STEMI require prompt reperfusion; the shorter the interval from symptom onset to reperfusion, the greater the benefit. Patients with UA/NSTEMI or nonspecific or normal ECGs require risk stratification and appropriate monitoring and therapy. Healthcare providers can improve survival rates and myocardial function of patients with ACS by providing skilled, efficient, and coordinated out-of-hospital and in-hospital care.

References

1. Chesebro JH, Rauch U, Fuster V, Badimon JJ. Pathogenesis of thrombosis in coronary artery disease. *Haemostasis*. 1997;27(suppl 1):12–18.
2. Fuster V. Elucidation of the role of plaque instability and rupture in acute coronary events. *Am J Cardiol.* 1995;76:24C–33C.
3. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med*. 1992;326:242–250.
4. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *N Engl J Med*. 1992;326:310–318.
5. Fuster V, Fallon JT, Badimon JJ, Nemerson Y. The unstable atherosclerotic plaque: clinical significance and therapeutic intervention. *Thromb Haemost*. 1997;78:247–255.
6. Davies MJ. Anatomic features in victims of sudden coronary death: coronary artery pathology. *Circulation*. 1992;85(suppl I):I-19–I-24.
7. Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. *JAMA*. 1999;281:921–926.
8. Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death: frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation*. 1995;92:1701–1709.
9. Virmani R, Burke AP, Farb A. Plaque morphology in sudden coronary death. *Cardiologia*. 1998;43:267–271.
10. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation*. 1985;71:699–708.
11. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366–1374.
12. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation*. 2004;110:588–636.
13. Armstrong PW, Bogaty P, Buller CE, Dorian P, O'Neill BJ. The 2004 ACC/AHA Guidelines: a perspective and adaptation for Canada by the Canadian Cardiovascular Society Working Group. *Can J Cardiol*. 2004; 20:1075–1079.
14. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM; NRMI Investigators. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. *Circulation.* 2005;111:761–767.
15. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med*. 1996;334:1311–1315.
16. Solomon CG, Lee TH, Cook EF, Weisberg MC, Brand DA, Rouan GW, Goldman L. Comparison of clinical presentation of acute myocardial infarction in patients older than 65 years of age to younger patients: the Multicenter Chest Pain Study experience. *Am J Cardiol*. 1989;63: 772–776.
17. Peberdy MA, Ornato JP. Coronary artery disease in women. *Heart Dis Stroke*. 1992;1:315–319.
18. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ*. 1994;308:883–886.
19. Dempsey SJ, Dracup K, Moser DK. Women's decision to seek care for symptoms of acute myocardial infarction. *Heart Lung*. 1995;24: 444–456.
20. Blohm M, Herlitz J, Schroder U, Hartford M, Karlson BW, Risenfors M, Larsson E, Luepker R, Wennerblom B, Holmberg S. Reaction to a media campaign focusing on delay in acute myocardial infarction. *Heart Lung*. 1991;20:661–666.
21. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. *Lancet*. 1967;2:271–273.
22. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death [published correction appears in *Am J Cardiol.* 1998;81:260]. *Am J Cardiol*. 1997;79:1512–1516.
23. Colquhoun MC, Julien DG. Sudden death in the community: the arrhythmia causing cardiac arrest and results of immediate resuscitation. *Resuscitation.* 1992;24:177A.
24. Campbell RW, Murray A, Julian DG. Ventricular arrhythmias in first 12 hours of acute myocardial infarction: natural history study. *Br Heart J*. 1981;46:351–357.
25. O'Doherty M, Tayler DI, Quinn E, Vincent R, Chamberlain DA. Five hundred patients with myocardial infarction monitored within one hour of symptoms. *BMJ*. 1983;286:1405–1408.
26. Lie KI, Wellens HJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation*. 1975;52:755–759.
27. Chiriboga D, Yarzebski J, Goldberg RJ, Gore JM, Alpert JS. Temporal trends (1975 through 1990) in the incidence and case-fatality rates of primary ventricular fibrillation complicating acute myocardial infarction: a communitywide perspective. *Circulation*. 1994;89: 998–1003.

28. The Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med.* 2004;351:637–646.
29. Eisenberg MJ, Topol EJ. Prehospital administration of aspirin in patients with unstable angina and acute myocardial infarction. *Arch Intern Med*. 1996;156:1506–1510.
30. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *BMJ*. 1976;1:1121–1123.
31. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation*. 1975;52:360–368.
32. Kelly RF, Hursey TL, Parrillo JE, Schaer GL. Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion. *Am Heart J*. 1995;130: 957–965.
33. Radvany P, Maroko PR, Braunwald E. Effects of hypoxemia on the extent of myocardial necrosis after experimental coronary occlusion. *Am J Cardiol*. 1975;35:795–800.
34. Shnier CB, Cason BA, Horton AF, Hickey RF. Hyperoxemic reperfusion does not increase myocardial infarct size. *Am J Physiol*. 1991; 260:H1307–H1312.
35. Madias JE, Madias NE, Hood WB Jr. Precordial ST-segment mapping: 2: effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. *Circulation*. 1976;53:411–417.
36. Horvat M, Yoshida S, Prakash R, Marcus HS, Swan HJ, Ganz W. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. *Circulation*. 1972;45:837–844.
37. Kenmure AC, Murdoch WR, Beattie AD, Marshall JC, Cameron AJ. Circulatory and metabolic effects of oxygen in myocardial infarction. *BMJ*. 1968;4:360–364.
38. Fillmore SJ, Shapiro M, Killip T. Arterial oxygen tension in acute myocardial infarction: serial analysis of clinical state and blood gas changes. *Am Heart J*. 1970;79:620–629.
39. Bourassa MG, Campeau L, Bois MA, Rico O. The effects of inhalation of 100 percent oxygen on myocardial lactate metabolism in coronary heart disease. *Am J Cardiol*. 1969;24:172–177.
40. Malm A, Arborelius MJ, Bornmyr S, Lilja B, Gill RL. Effects of oxygen on acute myocardial infarction: a thermographic study in the dog. *Cardiovasc Res*. 1977;11:512–518.
41. Sayen JJ, Sheldon WF, Horwitz O, Kuo PT, Peirce G, Zinsser HF, Mead J Jr. Studies of coronary disease in the experimental animal, II: polarographic determinations of local oxygen availability in the dog's left ventricle during coronary occlusion and pure oxygen breathing. *J Clin Invest*. 1951;30:932–940.
42. Sayen JJ, Sheldon WF, Peirce G, Kuo PT. Polarographic oxygen, the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle. *Circ Res*. 1958;6:779–798.
43. Rivas F, Rembert JC, Bache RJ, Cobb FR, Greenfield JC Jr. Effect of hyperoxia on regional blood flow after coronary occlusion in awake dogs. *Am J Physiol*. 1980;238:H244–H248.
44. Baron JF, Vicaut E, Hou X, Duvelleroy M. Independent role of arterial O2 tension in local control of coronary blood flow. *Am J Physiol*. 1990;258:H1388–H1394.
45. Haynes BE, Pritting J. A rural emergency medical technician with selected advanced skills. *Prehosp Emerg Care*. 1999;3:343–346.
46. Funk D, Groat C, Verdile VP. Education of paramedics regarding aspirin use. *Prehosp Emerg Care*. 2000;4:62–64.
47. Freimark D, Matetzky S, Leor J, Boyko V, Barbash IM, Behar S, Hod H. Timing of aspirin administration as a determinant of survival of patients with acute myocardial infarction treated with thrombolysis. *Am J Cardiol*. 2002;89:381–385.
48. Verheugt FW, van der Laarse A, Funke-Kupper AJ, Sterkman LG, Galema TW, Roos JP. Effects of early intervention with low-dose aspirin (100 mg) on infarct size, reinfarction and mortality in anterior wall acute myocardial infarction. *Am J Cardiol*. 1990;66:267–270.
49. Held P. Effects of nitrates on mortality in acute myocardial infarction and in heart failure. *Br J Clin Pharmacol.* 1992;34(suppl 1):25S–28S.
50. Tan WA, Moliterno DJ. Aspirin, ticlopidine, and clopidogrel in acute coronary syndromes: underused treatments could save thousands of lives. *Cleve Clin J Med.* 1999;66:615–618, 621–624, 627–628.
51. Access to timely and optimal care of patients with acute coronary syndromes: community planning considerations. A report by the National Heart Attack Alert Program. *J Thromb Thrombolysis.* 1998;6: 19–46.
52. Karagounis L, Ipsen SK, Jessop MR, Gilmore KM, Valenti DA, Clawson JJ, Teichman S, Anderson JL. Impact of field-transmitted electrocardiography on time to in-hospital thrombolytic therapy in acute myocardial infarction. *Am J Cardiol*. 1990;66:786–791.
53. Grim P, Feldman T, Martin M, Donovan R, Nevins V, Childers RW. Cellular telephone transmission of 12-lead electrocardiograms from ambulance to hospital. *Am J Cardiol*. 1987;60:715–720.
54. Kudenchuk PJ, Ho MT, Weaver WD, Litwin PE, Martin JS, Eisenberg MS, Hallstrom AP, Cobb LA, Kennedy JW. Accuracy of computer-interpreted electrocardiography in selecting patients for thrombolytic therapy. MITI Project Investigators. *J Am Coll Cardiol*. 1991;17: 1486–1491.
55. Kereiakes DJ, Gibler WB, Martin LH, Pieper KS, Anderson LC. Relative importance of emergency medical system transport and the prehospital electrocardiogram on reducing hospital time delay to therapy for acute myocardial infarction: a preliminary report from the Cincinnati Heart Project. *Am Heart J*. 1992;123(pt 1):835–840.
56. Foster DB, Dufendach JH, Barkdoll CM, Mitchell BK. Prehospital recognition of AMI using independent nurse/paramedic 12-lead ECG evaluation: impact on in-hospital times to thrombolysis in a rural community hospital. *Am J Emerg Med*. 1994;12:25–31.
57. Aufderheide TP, Kereiakes DJ, Weaver WD, Gibler WB, Simoons ML. Planning, implementation, and process monitoring for prehospital 12-lead ECG diagnostic programs. *Prehospital Disaster Med*. 1996;11: 162–171.
58. Aufderheide TP, Hendley GE, Woo J, Lawrence S, Valley V, Teichman SL. A prospective evaluation of prehospital 12-lead ECG application in chest pain patients. *J Electrocardiol*. 1992;24(suppl):8–13.
59. Weaver W, Cerqueira M, Hallstrom A, Litwin P, Martin J, Kudenchuk P, Eisenberg M. Prehospital-initiated vs hospital-initiated thrombolytic therapy: the Myocardial Infarction Triage and Intervention Trial (MITI). *JAMA*. 1993;270:1203–1210.
60. Canto JG, Rogers WJ, Bowlby LJ, French WJ, Pearce DJ, Weaver WD. The prehospital electrocardiogram in acute myocardial infarction: is its full potential being realized? National Registry of Myocardial Infarction 2 Investigators. *J Am Coll Cardiol*. 1997;29:498–505.
61. Banerjee S, Rhoden WE. Fast-tracking of myocardial infarction by paramedics. *J R Coll Physicians Lond*. 1998;32:36–38.
62. Melville MR, Gray D, et al. The potential impact of prehospital electrocardiography and telemetry on time to thrombolysis in a United Kingdom center. *Ann Noninvasive Electrocardiol*. 1998;3:327–333.
63. Millar-Craig MW, Joy AV, Adamowicz M, Furber R, Thomas B. Reduction in treatment delay by paramedic ECG diagnosis of myocardial infarction with direct CCU admission. *Heart*. 1997;78:456–461.
64. Wall T, Albright J, Livingston B, Isley L, Young D, Nanny M, Jacobowitz S, Maynard C, Mayer N, Pierce K, Rathbone C, Stuckey T, Savona M, Leibrandt P, Brodie B, Wagner G. Prehospital ECG transmission speeds reperfusion for patients with acute myocardial infarction. *N C Med J*. 2000;61:104–108.
65. Aufderheide TP, Hendley GE, Thakur RK, Mateer JR, Stueven HA, Olson DW, Hargarten KM, Laitinen F, Robinson N, Preuss KC, et al. The diagnostic impact of prehospital 12-lead electrocardiography. *Ann Emerg Med*. 1990;19:1280–1287.
66. Grim PS, Feldman T, Childers RW. Evaluation of patients for the need of thrombolytic therapy in the prehospital setting. *Ann Emerg Med*. 1989;18:483–488.
67. Weaver WD, Cerqueira M, Hallstrom AP, Litwin PE, Martin JS, Kudenchuk PJ, Eisenberg M. Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA*. 1993;270:1211–1216.
68. Aufderheide TP, Haselow WC, Hendley GE, Robinson NA, Armaganian L, Hargarten KM, Olson DW, Valley VT, Stueven HA. Feasibility of prehospital r-TPA therapy in chest pain patients. *Ann Emerg Med*. 1992;21:379–383.
69. Brinfield K. Identification of ST elevation AMI on prehospital 12 lead ECG: accuracy of unaided paramedic interpretation. *J Emerg Med.* 1998;16:22S.
70. Ioannidis JP, Salem D, Chew PW, Lau J. Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: a meta-analysis. *Ann Emerg Med*. 2001;37:461–470.
71. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. *N Engl J Med.* 1993;329:383–389.

72. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA*. 2000;283:2686–2692.
73. GREAT. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. GREAT Group. *BMJ.* 1992;305:548–553.
74. Dussoix P, Reuille O, Verin V, Gaspoz JM, Unger PF. Time savings with prehospital thrombolysis in an urban area. *Eur J Emerg Med*. 2003;10:2–5.
75. Rawles J. Halving of mortality at 1 year by domiciliary thrombolysis in the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol*. 1994;23:1–5.
76. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol*. 1997;30:1181–1186.
77. American Heart Association in collaboration with International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science, Part 7: the Era of Reperfusion: Section 1: Acute Coronary Syndromes (Acute Myocardial Infarction). *Circulation.* 2000; 102(suppl I):I-172–I-203.
78. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med*. 2003;349:733–742.
79. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE Study. *Eur Heart J*. 2000;21:823–831.
80. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, Branny M, St'asek J, Formanek P. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial–PRAGUE-2. *Eur Heart J*. 2003;24:94–104.
81. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boullenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P, Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction Study Group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet.* 2002;360:825–829.
82. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation*. 2003;108:1809–1814.
83. Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, Leizorovicz A, Touboul P, Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction Study Group. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation.* 2003;108:2851–2856.
84. Berger PB, Ellis SG, Holmes DR Jr, Granger CB, Criger DA, Betriu A, Topol EJ, Califf RM. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation*. 1999;100:14–20.
85. Canto JG, Every NR, Magid DJ, Rogers WJ, Malmgren JA, Frederick PD, French WJ, Tiefenbrunn AJ, Misra VK, Kiefe CI, Barron HV. The volume of primary angioplasty procedures and survival after acute myocardial infarction. *N Engl J Med*. 2000;342:1573–1580.
86. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. TIMI II A results. The TIMI Research Group. *JAMA*. 1988;260:2849–2858.
87. Simoons ML, Arnold AE, Betriu A, de Bono DP, Col J, Dougherty FC, von Essen R, Lambertz H, Lubsen J, Meier B, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. *Lancet.* 1988;1:197–203.
88. Topol EJ, Califf RM, George BS, Kereiakes DJ, Abbottsmith CW, Candela RJ, Lee KL, Pitt B, Stack RS, O'Neill WW. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med*. 1987;317:581–588.
89. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation*. 1995;91:476–485.
90. Topol EJ. Thrombolytic or angioplasty therapy of evolving myocardial infarction? *J Thromb Thrombolysis*. 1998;5:S125–S131.
91. Jovell AJ, Lau J, Berkey C, Kupelnick B, Chalmers TC. Early angiography and angioplasty following thrombolytic therapy of acute myocardial infarction: metaanalysis of the randomized control trials. *Online J Curr Clin Trials.* 1993; Document No 67.
92. Califf RM, Topol EJ, Stack RS, Ellis SG, George BS, Kereiakes DJ, Samaha JK, Worley SJ, Anderson JL, Harrelson-Woodlief L, Wall TC, Phillips HR III, Abbottsmith CW, Candela RJ, Flanagan WH, Sasahara AA, Mantell SJ, Lee KL. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction: results of thrombolysis and angioplasty in myocardial infarction—Phase 5 randomized trial. *Circulation*. 1991;83:1543–1556.
93. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, Lopez-Mesa J, Fernandez-Vazquez F, Calvo I, Martinez-Elbal L, San Roman JA, Ramos B. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet*. 2004;364: 1045–1053.
94. Bednar F, Widimsky P, Krupicka J, Groch L, Aschermann M, Zelizko M. Interhospital transport for primary angioplasty improves the long-term outcome of acute myocardial infarction compared with immediate thrombolysis in the nearest hospital (one-year follow-up of the PRAGUE-1 study). *Can J Cardiol*. 2003;19:1133–1137.
95. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI- 2). *J Am Coll Cardiol*. 1998;31:1240–1245.
96. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*. 1999;341:625–634.
97. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, LeJemtel TH. One-year survival following early revascularization for cardiogenic shock. *JAMA*. 2001;285:190–192.
98. Emergency department: rapid identification and treatment of patients with acute myocardial infarction. National Heart Attack Alert Program Coordinating Committee, 60 Minutes to Treatment Working Group. *Ann Emerg Med.* 1994;23:311–329.
99. Lambrew CT, Bowlby LJ, Rogers WJ, Chandra NC, Weaver WD. Factors influencing the time to thrombolysis in acute myocardial infarction. Time to Thrombolysis Substudy of the National Registry of Myocardial Infarction-1. *Arch Intern Med.* 1997;157:2577–2582.
100. Bleeker JK, Simoons ML, Erdman RA, Leenders CM, Kruyssen HA, Lamers LM, van der Does E. Patient and doctor delay in acute myocardial infarction: a study in Rotterdam, The Netherlands. *Br J Gen Pract*. 1995;45:181–184.
101. Goldberg RJ, McGovern PG, Guggina T, Savageau J, Rosamond WD, Luepker RV. Prehospital delay in patients with acute coronary heart disease: concordance between patient interviews and medical records. *Am Heart J*. 1998;135(pt 1):293–299.
102. Goodacre SW, Angelini K, Arnold J, Revill S, Morris F. Clinical predictors of acute coronary syndromes in patients with undifferentiated chest pain. *QJM*. 2003;96:893–898.
103. Goodacre S, Locker T, Morris F, Campbell S. How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med*. 2002;9:203–208.
104. Everts B, Karlson BW, Wahrborg P, Hedner T, Herlitz J. Localization of pain in suspected acute myocardial infarction in relation to final diagnosis, age and sex, and site and type of infarction. *Heart Lung*. 1996;25:430–437.

105. McSweeney JC, Cody M, O'Sullivan P, Elberson K, Moser DK, Garvin BJ. Women's early warning symptoms of acute myocardial infarction. *Circulation*. 2003;108:2619–2623.
106. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342–1349.
107. Svensson L, Axelsson C, Nordlander R, Herlitz J. Elevation of biochemical markers for myocardial damage prior to hospital admission in patients with acute chest pain or other symptoms raising suspicion of acute coronary syndrome. *J Intern Med*. 2003;253:311–319.
108. Gust R, Gust A, Bottiger BW, Bohrer H, Martin E. Bedside troponin T testing is not useful for early out-of-hospital diagnosis of myocardial infarction. *Acta Anaesthesiol Scand*. 1998;42:414–417.
109. Newman J, Aulick N, Cheng T, Faynor S, Curtis R, Mercer D, Williams J, Hobbs G. Prehospital identification of acute coronary ischemia using a troponin T rapid assay. *Prehosp Emerg Care*. 1999;3:97–101.
110. Svensson L, Axelsson C, Nordlander R, Herlitz J. Prognostic value of biochemical markers, 12-lead ECG and patient characteristics amongst patients calling for an ambulance due to a suspected acute coronary syndrome. *J Intern Med*. 2004;255:469–477.
111. Schuchert A, Hamm C, Scholz J, Klimmeck S, Goldmann B, Meinertz T. Prehospital testing for troponin T in patients with suspected acute myocardial infarction. *Am Heart J*. 1999;138:45–48.
112. Tanaka K, Seino Y, Ohbayashi K, Takano T. Cardiac emergency triage and therapeutic decisions using whole blood rapid troponin T test for patients with suspicious acute coronary syndrome. *Jpn Circ J*. 2001;65: 424–428.
113. Ng SM, Krishnaswamy P, Morrissey R, Clopton P, Fitzgerald R, Maisel AS. Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol*. 2001;88:611–617.
114. Ng SM, Krishnaswamy P, Morrisey R, Clopton P, Fitzgerald R, Maisel AS. Mitigation of the clinical significance of spurious elevations of cardiac troponin I in settings of coronary ischemia using serial testing of multiple cardiac markers. *Am J Cardiol.* 2001;87:994–999.
115. al-Mubarak N, Rogers WJ, Lambrew CT, Bowlby LJ, French WJ. Consultation before thrombolytic therapy in acute myocardial infarction. Second National Registry of Myocardial Infarction (NRMI 2) Investigators. *Am J Cardiol.* 1999;83:89–93.
116. Topol EJ. Inflammation and embolization in ischemic heart disease. *J Invasive Cardiol.* 2000;12(suppl B):2B–7B.
117. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. 2002;106:1893–1900.
118. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE III, Steward DE, Theroux P, Alpert JS, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO, Smith SC Jr. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2000; 36:970–1062.
119. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation.* 1994;89:1545–1556.
120. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr. ACC/AHA guidelines for coronary angiography: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. *Circulation*. 1999;99:2345–2357.
121. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969.
122. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. British Cardiac Society Guidelines and Medical Practice Committee and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. *Heart.* 2001; 85:133–142.
123. Clinical policy: critical issues in the evaluation and management of adult patients presenting with suspected acute myocardial infarction or unstable angina. American College of Emergency Physicians. *Ann Emerg Med.* 2000;35:521–525.
124. Doukky R, Calvin JE. Risk stratification in patients with unstable angina and non-ST segment elevation myocardial infarction: evidence-based review. *J Invasive Cardiol*. 2002;14:215–220.
125. Doukky R, Calvin JE. Part II: risk stratification in patients with unstable angina and non-ST segment elevation myocardial infarction: evidence-based review. *J Invasive Cardiol*. 2002;14:254–262.
126. Braunwald E, Jones RH, Mark DB, Brown J, Brown L, Cheitlin MD, Concannon CA, Cowan M, Edwards C, Fuster V, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation*. 1994;90:613–622.
127. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835–842.
128. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, Kuntz RE, Popma JJ, Schaff HV, Williams DO, Gibbons RJ, Alpert JP, Eagle KA, Faxon DP, Fuster V, Gardner TJ, Gregoratos G, Russell RO. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation*. 2001; 103:3019–3041.
129. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet.* 1988;2:349–360.
130. Gurfinkel EP, Manos EJ, Mejail RI, Cerda MA, Duronto EA, Garcia CN, Daroca AM, Mautner B. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol*. 1995;26:313–318.
131. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86.
132. Collaborative overview of randomised trials of antiplatelet therapy–I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration [published correction appears in *BMJ.* 1994;308: 1540]. *BMJ.* 1994;308:81–106.
133. Feldman M, Cryer B. Aspirin absorption rates and platelet inhibition times with 325-mg buffered aspirin tablets (chewed or swallowed intact) and with buffered aspirin solution. *Am J Cardiol*. 1999;84:404–409.
134. Sagar KA, Smyth MR. A comparative bioavailability study of different aspirin formulations using on-line multidimensional chromatography. *J Pharm Biomed Anal*. 1999;21:383–392.
135. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet.* 1995;345: 669–685.
136. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343:311–322.
137. A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med.* 1997;337:1118–1123.
138. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial.

Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. *Lancet.* 1999;354:716–722.
139. Franzosi MG, Santoro E, De Vita C, Geraci E, Lotto A, Maggioni AP, Mauri F, Rovelli F, Santoro L, Tavazzi L, Tognoni G. Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 study. The GISSI Investigators. *Circulation*. 1998;98:2659–2665.
140. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet.* 1986;1:397–402.
141. Brodie BR, Stuckey TD, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. 1996;28:319–325.
142. Puma JA, Sketch MHJ, Thompson TD, Simes RJ, Morris DC, White HD, Topol EJ, Califf RM. Support for the open-artery hypothesis in survivors of acute myocardial infarction: analysis of 11,228 patients treated with thrombolytic therapy. *Am J Cardiol*. 1999;83:482–487.
143. de Lemos JA, Antman EM, Gibson CM, McCabe CH, Giugliano RP, Murphy SA, Coulter SA, Anderson K, Scherer J, Frey MJ, Van Der Wieken R, Van De Werf F, Braunwald E. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. *Circulation*. 2000;101: 239–243.
144. Claeys MJ, Bosmans J, Veenstra L, Jorens P, De R, Vrints CJ. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: importance of microvascular reperfusion injury on clinical outcome. *Circulation*. 1999; 99:1972–1977.
145. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, McCabe CH, Cannon CP, Van de Werf F, Braunwald E. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation*. 1999;99:1945–1950.
146. Brouwer MA, Martin JS, Maynard C, Wirkus M, Litwin PE, Verheugt FW, Weaver WD. Influence of early prehospital thrombolysis on mortality and event-free survival (the Myocardial Infarction Triage and Intervention [MITI] Randomized Trial). MITI Project Investigators. *Am J Cardiol*. 1996;78:497–502.
147. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med.* 1993;329:673–682.
148. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. *Lancet.* 1993;342:767–772.
149. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet.* 1993; 342:759–766.
150. Hillis LD, Forman S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. The Thrombolysis in Myocardial Infarction (TIMI) Phase II Co-Investigators. *J Am Coll Cardiol*. 1990;16:313–315.
151. Simoons ML, Maggioni AP, Knatterud G, Leimberger JD, de Jaegere P, van Domburg R, Boersma E, Franzosi MG, Califf R, Schroder R, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet.* 1993;342:1523–1528.
152. Mahaffey KW, Granger CB, Sloan MA, Thompson TD, Gore JM, Weaver WD, White HD, Simoons ML, Barbash GI, Topol EJ, Califf RM. Risk factors for in-hospital nonhemorrhagic stroke in patients with acute myocardial infarction treated with thrombolysis: results from GUSTO-I. *Circulation*. 1998;97:757–764.
153. Gore JM, Granger CB, Simoons ML, Sloan MA, Weaver WD, White HD, Barbash GI, Van de Werf F, Aylward PE, Topol EJ, et al. Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation.* 1995;92:2811–2818.
154. White HD, Barbash GI, Califf RM, Simes RJ, Granger CB, Weaver WD, Kleiman NS, Aylward PE, Gore JM, Vahanian A, Lee KL, Ross AM, Topol EJ. Age and outcome with contemporary thrombolytic therapy: results from the GUSTO-I trial. Global Utilization of Streptokinase and TPA for Occluded coronary arteries trial. *Circulation*. 1996;94: 1826–1833.
155. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. *Circulation.* 2000; 101:2239–2246.
156. Aylward PE, Wilcox RG, Horgan JH, White HD, Granger CB, Califf RM, Topol EJ. Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction: a randomized trial. GUSTO-I Investigators. *Ann Intern Med*. 1996;125:891–900.
157. Kennedy JW, Martin GV, Davis KB, Maynard C, Stadius M, Sheehan FH, Ritchie JL. The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial. *Circulation*. 1988;77: 345–352.
158. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. AIMS Trial Study Group. *Lancet.* 1988;1:545–549.
159. Timmis AD, Griffin B, Crick JC, Sowton E. Anisoylated plasminogen streptokinase activator complex in acute myocardial infarction: a placebo-controlled arteriographic coronary recanalization study. *J Am Coll Cardiol*. 1987;10:205–210.
160. Verstraete M, Bernard R, Bory M, Brower RW, Collen D, de Bono DP, Erbel R, Huhmann W, Lennane RJ, Lubsen J, et al. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction: report from the European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator. *Lancet*. 1985;1:842–847.
161. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet*. 1988;2:525–530.
162. Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, Chernoff R, Christie LG, Feldman RL, Seals AA, Weaver WD. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II Investigators. *Circulation*. 1996;94:891–898.
163. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. International Joint Efficacy Comparison of Thrombolytics. *Lancet.* 1995;346:329–336.
164. Van de Werf F, Cannon CP, Luyten A, Houbracken K, McCabe CH, Berioli S, Bluhmki E, Sarelin H, Wang-Clow F, Fox NL, Braunwald E. Safety assessment of single-bolus administration of TNK tissue-plasminogen activator in acute myocardial infarction: the ASSENT-1 trial. The ASSENT-1 Investigators. *Am Heart J*. 1999;137:786–791.
165. Collins R, Peto R, Parish S, Sleight P. ISIS-3 and GISSI-2: no survival advantage with tissue plasminogen activator over streptokinase, but a significant excess of strokes with tissue plasminogen activator in both trials [letter]. *Am J Cardiol*. 1993;71:1127–1130.
166. The EPISTENT Investigators (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting). Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet.* 1998;352:87–92.
167. Selker HP, Griffith JL, D'Agostino RB. A tool for judging coronary care unit admission appropriateness, valid for both real-time and retrospective use: a time-insensitive predictive instrument (TIPI) for acute cardiac ischemia: a multicenter study. *Med Care*. 1991;29:610–627.
168. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. *N Engl J Med.* 1997;336:1621–1628.
169. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, DeWood MA, Ribichini F. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review [published correction appears in *JAMA*. 1998;279:1876]. *JAMA*. 1997;278: 2093–2098.
170. Berger AK, Schulman KA, Gersh BJ, Pirzada S, Breall JA, Johnson AE, Every NR. Primary coronary angioplasty vs thrombolysis for the management of acute myocardial infarction in elderly patients. *JAMA*. 1999; 282:341–348.

171. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20.
172. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. 2003;92:824–826.
173. Zijlstra F, Patel A, Jones M, Grines CL, Ellis S, Garcia E, Grinfeld L, Gibbons RJ, Ribeiro EE, Ribichini F, Granger C, Akhras F, Weaver WD, Simes RJ. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J*. 2002;23:550–557.
174. Holmes DR Jr, Bates ER, Kleiman NS, Sadowski Z, Horgan JH, Morris DC, Califf RM, Berger PB, Topol EJ. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1995;26:668–674.
175. Califf RM, Bengtson JR. Cardiogenic shock. *N Engl J Med*. 1994;330:1724–1730.
176. Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M, Just H. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med*. 1993;328:981–988.
177. Berger PB, Ruocco NA Jr, Ryan TJ, Jacobs AK, Zaret BL, Wackers FJ, Frederick MM, Faxon DP. Frequency and significance of right ventricular dysfunction during inferior wall left ventricular myocardial infarction treated with thrombolytic therapy (results from the thrombolysis in myocardial infarction [TIMI] II trial). The TIMI Research Group. *Am J Cardiol*. 1993;71:1148–1152.
178. Goldstein JA, Barzilai B, Rosamond TL, Eisenberg PR, Jaffe AS. Determinants of hemodynamic compromise with severe right ventricular infarction. *Circulation*. 1990;82:359–368.
179. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
180. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533.
181. Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation*. 2003;107:966–972.
182. Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi MG. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation*. 2002;106:1622–1626.
183. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation*. 2003;108:1682–1687.
184. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation*. 2004;110:1202–1208.
185. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348:1329–1339.
186. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411–2420.
187. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352:1179–1189.
188. Hjalmarson A, Herlitz J, Holmberg S, Ryden L, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Waldenstrom J, Wedel H, Wilhelmsen L, Wilhelmsson C. The Goteborg metoprolol trial: effects on mortality and morbidity in acute myocardial infarction: limitation of infarct size by beta blockers and its potential role for prognosis. *Circulation*. 1983;67(suppl I):I26–I32.
189. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J.* 1985;6:199–226.
190. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet.* 1986;2:57–66.
191. Rehnqvist N, Olsson G, Erhardt L, Ekman AM. Metoprolol in acute myocardial infarction reduces ventricular arrhythmias both in the early stage and after the acute event. *Int J Cardiol*. 1987;15:301–308.
192. Herlitz J, Edvardsson N, Holmberg S, Ryden L, Waagstein F, Waldenstrom A, Swedberg K, Hjalmarson A. Goteborg Metoprolol Trial: effects on arrhythmias. *Am J Cardiol.* 1984;53:27D–31D.
193. Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC, Willerson JT, Knatterud GL, Forman S, Passamani E, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation.* 1991;83:422–437.
194. Brieger DB, Mak KH, Kottke-Marchant K, Topol EJ. Heparin-induced thrombocytopenia. *J Am Coll Cardiol*. 1998;31:1449–1459.
195. Ryan TJ, Antman EM, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel B, Russell RO, Smith EE III, Weaver WD, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Garson A Jr, Gregoratos G, Smith SC Jr. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol.* 1999;34:890–911.
196. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, Bayes De Luna A, Fox K, Lablanche JM, Radley D, Premmereur J, Braunwald E. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593–1601.
197. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAxiparine in Ischaemic Syndrome). *Eur Heart J.* 1999;20:1553–1562.
198. Suvarna TT, Parikh JA, Keshav R, Pillai MG, Pahlajani DB, Gandhi MJ. Comparison of clinical outcome of fixed-dose subcutaneous low molecular weight heparin (tinzaparin) with conventional heparin in unstable angina: a pilot study. *Indian Heart J*. 1997;49:159–162.
199. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, Kereiakes DJ, Langer A, Mahaffey KW, Nessel CC, Armstrong PW, Avezum A, Aylward P, Becker RC, Biasucci L, Borzak S, Col J, Frey MJ, Fry E, Gulba DC, Guneri S, Gurfinkel E, Harrington R, Hochman JS, Kleiman NS, Leon MB, Lopez-Sendon JL, Pepine CJ, Ruzyllo W, Steinhubl SR, Teirstein PS, Toro-Figueroa L, White H. 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;292:45–54.
200. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, Langer A, Califf RM, Fox KA, Premmereur J, Bigonzi F. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med*. 1997;337:447–452.
201. Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004;292:89–96.
202. Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. *Cochrane Database Syst Rev*. 2004;2:2.

203. Antman EM, Cohen M, Radley D, McCabe C, Rush J, Premmereur J, Braunwald E. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602–1608.
204. Antman EM, Cohen M, McCabe C, Goodman SG, Murphy SA, Braunwald E. Enoxaparin is superior to unfractionated heparin for preventing clinical events at 1-year follow-up of TIMI 11B and ESSENCE. *Eur Heart J*. 2002;23:308–314.
205. Le Nguyen MT, Spencer FA. Low molecular weight heparin and unfractionated heparin in the early pharmacologic management of acute coronary syndromes: a meta-analysis of randomized clinical trials. *J Thromb Thrombolysis*. 2001;12:289–295.
206. Malhotra S, Bhargava VK, Grover A, Pandhi P, Sharma YP. A randomized trial to compare the efficacy, safety, cost and platelet aggregation effects of enoxaparin and unfractionated heparin (the ESCAPEU trial). *Int J Clin Pharmacol Ther*. 2001;39:110–115.
207. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis [published correction appears in *Lancet*. 2000;356:600]. *Lancet*. 2000;355:1936–1942.
208. Clark SC, Vitale N, Zacharias J, Forty J. Effect of low molecular weight heparin (Fragmin) on bleeding after cardiac surgery. *Ann Thorac Surg*. 2000;69:762–764.
209. Brieger D, Solanki V, Gaynor M, Booth V, MacDonald R, Freedman SB. Optimal strategy for administering enoxaparin to patients undergoing coronary angiography without angioplasty for acute coronary syndromes. *Am J Cardiol*. 2002;89:1167–1170.
210. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation*. 2003;107:238–244.
211. Kovar D, Canto JG, Rogers WJ. Safety and effectiveness of combined low molecular weight heparin and glycoprotein IIb/IIIa inhibitors. *Am J Cardiol*. 2002;90:911–915.
212. Cohen M, Theroux P, Borzak S, Frey MJ, White HD, Van Mieghem W, Senatore F, Lis J, Mukherjee R, Harris K, Bigonzi F. Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with tirofiban and aspirin: the ACUTE II study. The Antithrombotic Combination Using Tirofiban and Enoxaparin. *Am Heart J*. 2002;144:470–477.
213. Cohen M, Theroux P, Weber S, Laramee P, Huynh T, Borzak S, Diodati JG, Squire IB, Deckelbaum LI, Thornton AR, Harris KE, Sax FL, Lo MW, White HD. Combination therapy with tirofiban and enoxaparin in acute coronary syndromes. *Int J Cardiol*. 1999;71:273–281.
214. Ferguson J. Low-molecular-weight heparins and glycoprotein IIb/IIIa antagonists in acute coronary syndromes. *J Invasive Cardiol*. 2004;16:136–144.
215. Wallentin L, Bergstrand L, Dellborg M, Fellenius C, Granger CB, Lindahl B, Lins LE, Nilsson T, Pehrsson K, Siegbahn A, Swahn E. Low molecular weight heparin (dalteparin) compared to unfractionated heparin as an adjunct to rt-PA (alteplase) for improvement of coronary artery patency in acute myocardial infarction—the ASSENT Plus study. *Eur Heart J*. 2003;24:897–908.
216. Ross AM, Molhoek P, Lundergan C, Knudtson M, Draoui Y, Regalado L, Le Louer V, Bigonzi F, Schwartz W, De Jong E, Coyne K. Randomized comparison of enoxaparin, a low-molecular-weight heparin, with unfractionated heparin adjunctive to recombinant tissue plasminogen activator thrombolysis and aspirin: second trial of Heparin and Aspirin Reperfusion Therapy (HART II). *Circulation*. 2001;104:648–652.
217. Van de Werf FJ, Armstrong PW, Granger C, Wallentin L. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605–613.
218. Theroux P, Welsh RC. Meta-analysis of randomized trials comparing enoxaparin versus unfractionated heparin as adjunctive therapy to fibrinolysis in ST-elevation acute myocardial infarction. *Am J Cardiol*. 2003;91:860–864.
219. Baird SH, Menown IB, McBride SJ, Trouton TG, Wilson C. Randomized comparison of enoxaparin with unfractionated heparin following fibrinolytic therapy for acute myocardial infarction. *Eur Heart J*. 2002;23:627–632.
220. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, Bogaerts K, Danays T, Lindahl B, Makijarvi M, Verheugt F, Van de Werf F. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135–142.
221. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med.* 1998;339:436–443.
222. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879–1887.
223. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation*. 2001;104:2767–2771.
224. Bosch X, Marrugat J. Platelet glycoprotein IIb/IIIa blockers for percutaneous coronary revascularization, and unstable angina and non-ST-segment elevation myocardial infarction. *Cochrane Database Syst Rev*. 2001;CD002130.
225. Boersma E, Harrington RA, Moliterno DJ, White H, Theroux P, Van de Werf F, de Torbal A, Armstrong PW, Wallentin LC, Wilcox RG, Simes J, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials [published correction appears in *Lancet*. 2002;359:2120]. *Lancet*. 2002;359:189–198.
226. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet*. 2001;357:1915–1924.
227. Ottervanger JP, Armstrong P, Barnathan ES, Boersma E, Cooper JS, Ohman EM, James S, Topol E, Wallentin L, Simoons ML. Long-term results after the glycoprotein IIb/IIIa inhibitor abciximab in unstable angina: one-year survival in the GUSTO IV-ACS (Global Use of Strategies To Open Occluded Coronary Arteries IV—Acute Coronary Syndrome) Trial. *Circulation*. 2003;107:437–442.
228. Ryan T, Anderson J, Antman E, Braniff B, Brooks N, Califf R, Hillis L, Hiratzka L, Rapaport E, Riegel B, Russell R, Smith E Jr, Weaver W. ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol*. 1996;28:1328–1428.
229. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet.* 1995;345:669–685.
230. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet.* 1994;343:1115–1122.
231. Chinese Cardiac Study (CCS-1) Collaborative Group. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicenter, randomized, double-blind, placebo controlled clinical trial. *Chin Med J.* 1997;110:834–838.
232. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction: the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. *N Engl J Med.* 1995;332:80–85.
233. Borghi C, Marino P, Zardini P, Magnani B, Collatina S, Ambrosioni E. Short- and long-term effects of early fosinopril administration in patients with acute anterior myocardial infarction undergoing intravenous thrombolysis: results from the Fosinopril in Acute Myocardial Infarction Study. FAMIS Working Party. *Am Heart J*. 1998;136:213–225.

234. Oral captopril versus placebo among 13,634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet.* 1995;345:686–687.
235. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicenter, randomized, double-blind, placebo controlled clinical trial. Chinese Cardiac Study (CCS-1) Collaborative Group. *Chin Med J (Engl).* 1997;110:834–838.
236. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet.* 1994;343:1115–1122.
237. Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT, Menapace FJ Jr, Rapaport E, Ridker PM, Rouleau JL, Solomon SD, Hennekens CH. Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The Healing and Early Afterload Reducing Therapy Trial. *Circulation.* 1997;95:2643–2651.
238. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation.* 1998;97:2202–2651.
239. Teo KK, Yusuf S, Pfeffer M, Torp-Pedersen C, Kober L, Hall A, Pogue J, Latini R, Collins R. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet.* 2002;360:1037–1043.
240. Borghi C, Ambrosioni E. Double-blind comparison between zofenopril and lisinopril in patients with acute myocardial infarction: results of the Survival of Myocardial Infarction Long-term Evaluation-2 (SMILE-2) study. *Am Heart J.* 2003;145:80–87.
241. Latini R, Maggioni AP, Flather M, Sleight P, Tognoni G. ACE inhibitor use in patients with myocardial infarction: summary of evidence from clinical trials. *Circulation.* 1995;92:3132–3137.
242. Latini R, Tognoni G, Maggioni AP, Baigent C, Braunwald E, Chen ZM, Collins R, Flather M, Franzosi MG, Kjekshus J, Kober L, Liu LS, Peto R, Pfeffer M, Pizzetti F, Santoro E, Sleight P, Swedberg K, Tavazzi L, Wang W, Yusuf S. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group. *J Am Coll Cardiol.* 2000;35:1801–1807.
243. Lu CY. [Treatment of acute myocardial infarction with oral captopril. A randomized, double blind and placebo controlled pilot study.] *Zhonghua Xin Xue Guan Bing Za Zhi.* 1993;21:74–76, 121–122.
244. Ray SG, Pye M, Oldroyd KG, Christie J, Connelly DT, Northridge DB, Ford I, Morton JJ, Dargie HJ, Cobbe SM. Early treatment with captopril after acute myocardial infarction. *Br Heart J.* 1993;69:215–222.
245. Di Pasquale P, Paterna S, Cannizzaro S, Bucca V. Does captopril treatment before thrombolysis in acute myocardial infarction attenuate reperfusion damage? Short-term and long-term effects. *Int J Cardiol.* 1994;43:43–50.
246. Spinar J, Vitovec J, Pluhacek L, Spinarova L, Fischerova B, Toman J. First dose hypotension after angiotensin converting enzyme inhibitor captopril and angiotensin II blocker losartan in patients with acute myocardial infarction. *Int J Cardiol.* 2000;75:197–204.
247. Wagner A, Herkner H, Schreiber W, Bur A, Woisetschlager C, Stix G, Laggner AN, Hirschl MM. Ramipril prior to thrombolysis attenuates the early increase of PAI-1 in patients with acute myocardial infarction. *Thromb Haemost.* 2002;88:180–185.
248. Mehta PM, Przyklenk K, Kloner RA. Cardioprotective effects of captopril in myocardial ischaemia, ischaemia/reperfusion and infarction. *Eur Heart J.* 1990;(suppl B):94–99.
249. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med.* 2003;349:1893–1906.
250. Kayikcioglu M, Can L, Kultursay H, Payzin S, Turkoglu C. Early use of pravastatin in patients with acute myocardial infarction undergoing coronary angioplasty. *Acta Cardiol.* 2002;57:295–302.
251. Kayikcioglu M, Can L, Evrengul H, Payzin S, Kultursay H. The effect of statin therapy on ventricular late potentials in acute myocardial infarction. *Int J Cardiol.* 2003;90:63–72.
252. Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ, Sasiela WJ, Szarek M, Libby P, Ganz P. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation.* 2003;108:1560–1566.
253. Correia LC, Sposito AC, Lima JC, Magalhaes LP, Passos LC, Rocha MS, D'Oliveira A, Esteves JP. Anti-inflammatory effect of atorvastatin (80 mg) in unstable angina pectoris and non-Q-wave acute myocardial infarction. *Am J Cardiol.* 2003;92:298–301.
254. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K, Tai J, Orlandini A, Pogue J, Liu L. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA.* 2005;293:437–446.
255. Timmer J. Glucose-insulin-potassium study in patients with ST-elevation myocardial infarction without signs of heart failure: the Gips-II Trial. Paper presented at: Late-Breaking Clinical Trials III, American College of Cardiology Scientific Sessions; March 9, 2005; Orlando, Fla.
256. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction: an overview of results from the randomized, controlled trials. *JAMA.* 1988; 260:1910–1916.