



Jessica L. Mega and David A. Morrow

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The care of patients with ST-elevation myocardial infarction (STEMI) has transformed in conjunction with major shifts in the approach to reperfusion therapy from primarily pharmacologic to catheter-based strategies.<sup>1-4</sup> With simultaneous advances in medical therapy, the case fatality rate for patients with STEMI has continued to decline.<sup>5</sup> Nevertheless, optimal management of patients at high risk for or with established major complications of STEMI remains critical to the care of this condition. A discussion of the management of STEMI can follow the clinical course of the patient. Chapter 42 addresses primary and secondary prevention of coronary artery disease (CAD). This chapter deals with treatment at the time of onset of STEMI (prehospital issues, initial recognition and management in the emergency department, and reperfusion), hospital management (medications, complications, and preparation for discharge), and early secondary prevention after STEMI. Chapter 55 discusses percutaneous coronary intervention (PCI) in patients with STEMI. Chapter 36 describes the use of internal and external automated defibrillators for primary prevention of sudden cardiac death after myocardial infarction (MI).

## PREHOSPITAL MANAGEMENT

Given the progressive loss of functioning myocytes with persistent occlusion of the infarct-related artery in STEMI (see Chapter 51), initial management aims to restore blood flow to the infarct zone as rapidly as possible. Primary PCI (see Chapter 55) is generally the preferred option, provided that an experienced operator and team can perform it in timely fashion.<sup>1,6,7</sup> Missed opportunities for improvement in the care of STEMI include failure to deliver any form of reperfusion therapy in approximately 20% of patients and failure to minimize delays in reperfusion because of inefficient systems of care.<sup>5,8,9</sup> The “chain of survival” for STEMI involves a highly integrated strategy beginning with patient education about the symptoms of MI (see Chapter 50) and early contact with the medical system, coordination of destination protocols in emergency medical service (EMS) systems, efficient practices in emergency departments to shorten door-to-reperfusion time, and expeditious implementation of the reperfusion strategy by a trained team.<sup>10,11</sup> The American Heart Association (AHA) launched a national initiative to engineer

improved health care delivery for STEMI, including implementation of systems that shorten total ischemic time (Tables 52-1 and 52-2) while emphasizing overall quality of care for STEMI.<sup>11,12</sup>

### Prehospital Care

The prehospital care of patients suspected of having STEMI bears directly on the likelihood of survival. Most deaths associated with STEMI occur within the first hour of its onset and usually result from ventricular fibrillation (VF) (see Chapter 39). Hence immediate implementation of resuscitative efforts and rapid transportation of the patient to a hospital have prime importance. Major components of the delay from the onset of ischemic symptoms to reperfusion include the following:<sup>1</sup> (1) the time for the patient to recognize the seriousness of the problem and seek medical attention; (2) prehospital evaluation, treatment, and transportation; (3) the time for diagnostic measures and initiation of treatment in the hospital (e.g., “door-to-needle” time for patients receiving a fibrinolytic agent and “door-to-balloon” time for patients undergoing a catheter-based reperfusion strategy); and (4) the time from initiation of treatment to restoration of flow.

Patient-related factors that correlate with a longer time until deciding to seek medical attention include older age; female sex; black race; low socioeconomic status; low emotional or somatic awareness; history of angina, diabetes, or both; consulting a spouse or other relative; and consulting a physician.<sup>13,14</sup> Health care professionals should heighten the level of awareness of patients at risk for STEMI (e.g., those with hypertension, diabetes, history of angina pectoris).<sup>1</sup> They should use each patient encounter as a “teachable moment” to review and reinforce with patients and their families the need to seek urgent medical attention for a pattern of symptoms that includes chest discomfort, extreme fatigue, and dyspnea, especially if accompanied by diaphoresis or lightheadedness. Patients should also be instructed in the proper use of sublingual nitroglycerin and to call emergency services if the ischemic-type discomfort persists for more than 5 minutes.<sup>1</sup>

### Emergency Medical Service Systems

EMS systems have three major components: emergency medical dispatch, first response, and the EMS ambulance response. The

expanded capability to record a prehospital 12-lead electrocardiogram (ECG) represents a major advance in EMS systems (**Table 52-2**).<sup>15</sup> The ability to transmit such ECGs and to activate the STEMI care team before arrival at the hospital places EMS efforts at the center of the early response to STEMI.<sup>16,17</sup> Ongoing efforts to shorten the time until treatment of patients with STEMI include improvement in the medical dispatch component by expanding 911 coverage,

providing automated external defibrillators to first responders, placing automated external defibrillators in critical public locations, and greater coordination of the EMS ambulance response. Well-equipped ambulances and helicopters staffed by personnel trained in the acute care of patients with STEMI allow definitive therapy to begin during transport to the hospital (**Table 52-3**). Radiotelemetry systems that allow transmission of the electrocardiographic signal to a medical control officer are highly desirable for facilitating the triage of patients with STEMI and are becoming increasingly available in many communities (**Fig. 52-1**).

In addition to prompt defibrillation, the efficacy of prehospital care appears to depend on several factors, including early relief of pain with its deleterious physiologic sequelae, reduction of excessive

**TABLE 52-1 Criteria for a System of Care for ST-Elevation Myocardial Infarction**

1. The system should be registered with Mission: Lifeline.
2. Ongoing multidisciplinary team meetings should occur, including EMS, non-PCI hospitals/STEMI referral centers, and PCI hospitals/STEMI receiving centers, to evaluate outcomes and quality improvement data. Operational issues should be reviewed, problems identified, and solutions implemented.
3. Each STEMI system should include a process for prehospital identification and activation, destination protocols to STEMI receiving centers, and transfer for patients who arrive at STEMI referral centers and are primary PCI candidates, are ineligible for fibrinolytic therapy, and/or are in cardiogenic shock.
4. Each system should have a recognized system coordinator, physician champion, and EMS medical director.
5. Each system component (EMS, STEMI referral centers, and STEMI receiving centers) should meet the appropriate criteria (see [www.americanheart.org/missionlifeline](http://www.americanheart.org/missionlifeline)).

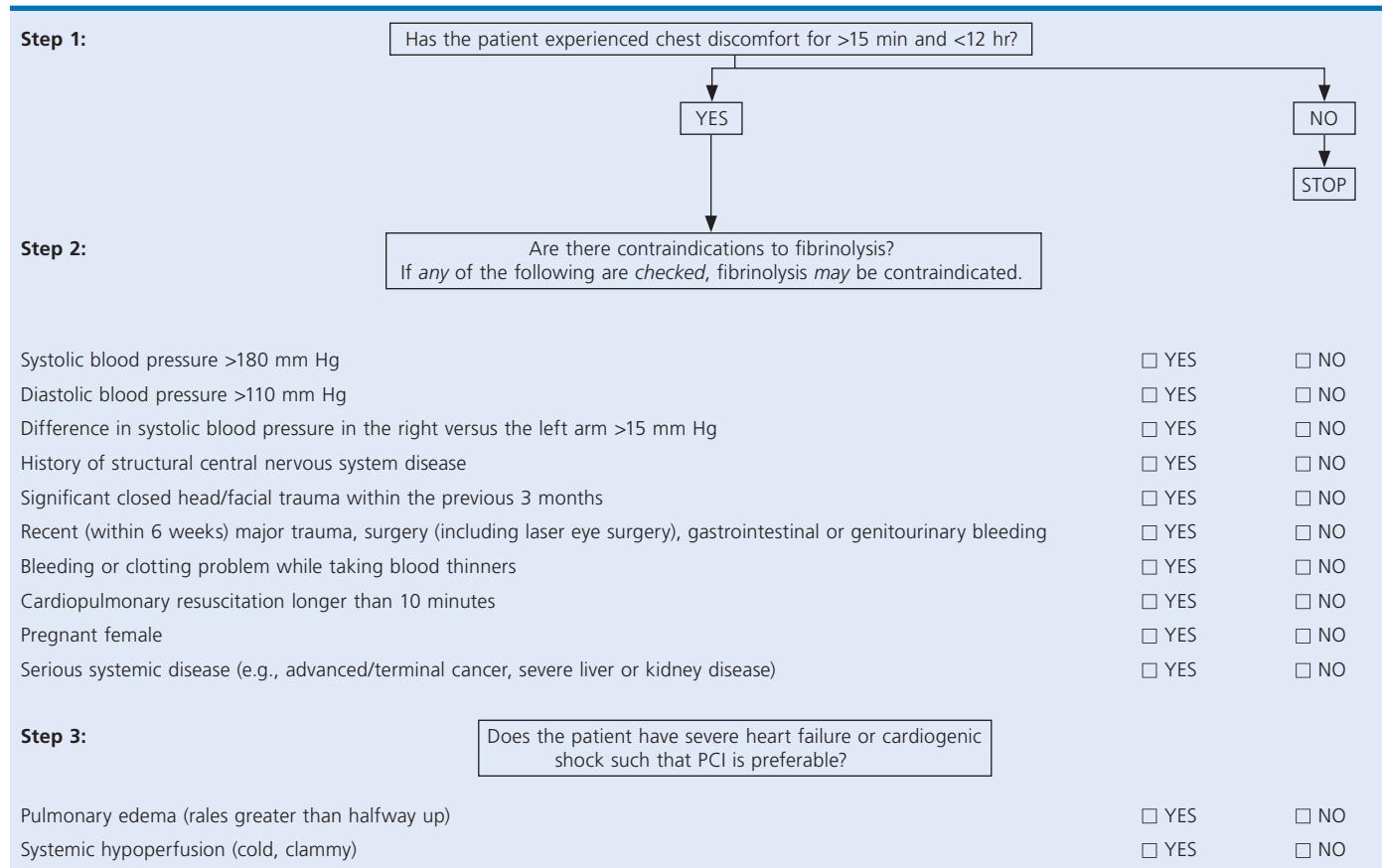
Modified from [www.americanheart.org/missionlifeline](http://www.americanheart.org/missionlifeline).

**TABLE 52-2 Interventions to Improve Door-to-Device Times**

1. A prehospital ECG for diagnosing STEMI is used to activate the PCI team while the patient is en route to the hospital.
2. Emergency physicians activate the PCI team.
3. A single call to a central page operator activates the PCI team.
4. A goal is set for the PCI team to arrive at the catheterization laboratory within 20 minutes after being paged.
5. Timely data feedback and analysis are provided to members of the STEMI care team.

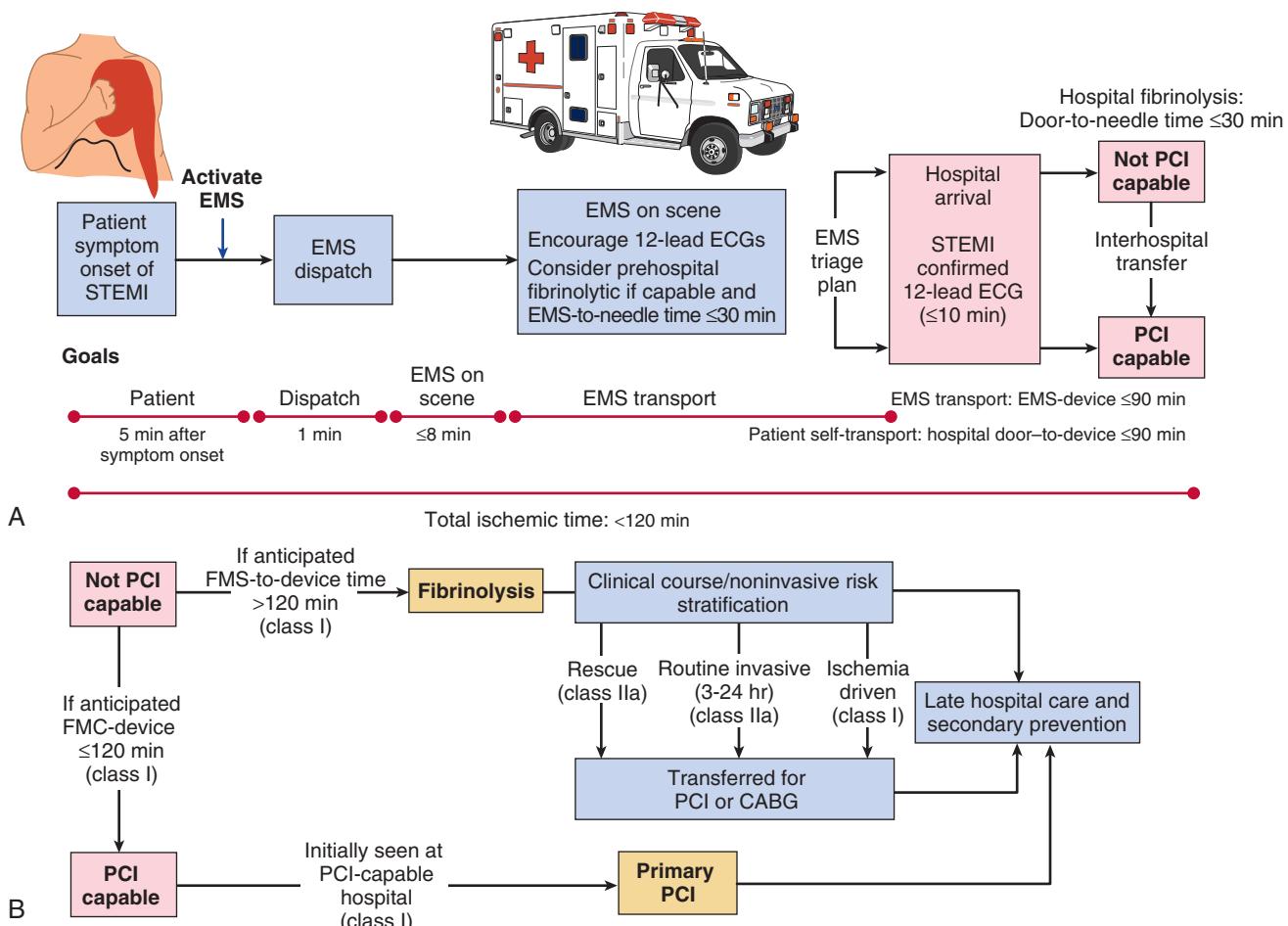
From O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACC/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e78, 2013.

**TABLE 52-3 Prehospital\* Reperfusion Checklist for Evaluation of Patients with ST-Elevation Myocardial Infarction**



\*Note that some of these practical criteria for a prehospital checklist are more inclusive than may subsequently be applied in the hospital if using more refined criteria that differ slightly from the above (see Table 52-4).

From Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 110(9):e82, 2004.



**FIGURE 52-1** System goals and initial reperfusion treatment of patients with STEMI. Reperfusion in patients with STEMI can be accomplished by pharmacologic (fibrinolysis) or catheter-based (primary PCI) approaches and may involve transfer from a non-PCI-capable to a primary PCI-capable center. **A,** Patient transported by the EMS. The STEMI systems goal is to maintain a network of transportation and destination hospitals so that the total ischemic time is kept to less than 120 minutes. In addition to this overall goal, three additional time objectives exist. (1) If the EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis may be considered and, if used, should be started within 30 minutes of arrival of the EMS on scene. (2) For patients transported to a non-PCI-capable hospital where a fibrinolytic is to be administered, the hospital door-to-needle time should be 30 minutes or less. (3) If the patient is transported to a PCI-capable hospital, the time from first medical contact (FMC) to deployment of the first PCI device (FMC-to-device time) should be 90 minutes or less. Patient self-transportation is discouraged. If the patient arrives at a non-PCI-capable hospital and a fibrinolytic is to be administered, the door-to-needle time should be 30 minutes or less. If the patient arrives at a PCI-capable hospital, the door-to-balloon time should be 90 minutes or less. The treatment options and time recommendations after arrival at the hospital are the same. Consideration of emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization is also appropriate if use of a fibrinolytic is contraindicated or PCI can be initiated promptly (anticipated FMC-to-device time ≤120 minutes) or if fibrinolysis is unsuccessful (i.e., “rescue PCI”). Secondary nonemergency interhospital transfer can be considered for recurrent ischemia or routine invasive evaluation 3 to 24 hours after fibrinolysis. **B,** Reperfusion strategies for patients with STEMI, regardless of whether they go to a PCI-capable or to a non-PCI-capable hospital. The optimal strategy depends on the timing of the onset of symptoms, the patient’s eligibility for fibrinolysis, and the options for timely transfer to a PCI-capable hospital. The denoted class I and class II recommendations are from the ACCF/AHA guidelines for the management of STEMI. For patients who receive fibrinolysis, noninvasive risk stratification is recommended to guide decisions regarding delayed coronary revascularization. (Modified from Armstrong PW, Collen D, Antman E: Fibrinolysis for acute myocardial infarction: The future is here and now. *Circulation* 107:2533, 2003; and O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e78, 2013.)

activity of the autonomic nervous system, and treatment of arrhythmias such as ventricular tachycardia (VT)—but these efforts must not delay rapid transfer to the hospital (Fig. 52-1).

### Prehospital Fibrinolysis

Multiple observational studies and several randomized trials have evaluated the potential benefits of prehospital versus in-hospital fibrinolysis.<sup>1,17</sup> Although none of the individual trials showed a significant reduction in mortality with prehospital-initiated fibrinolytic therapy, earlier treatment generally provides greater benefit: a meta-analysis of all the available trials demonstrated a 17% reduction in mortality.<sup>1</sup> The CAPTIM (Comparison of primary Angioplasty and Pre-hospital fibrinolysis In acute Myocardial infarction) trial, for example, reported a trend toward a lower mortality rate in patients with STEMI who received prehospital fibrinolysis than in those who received primary PCI, especially if they were treated within 2 hours of the onset of

symptoms.<sup>1</sup> Prehospital fibrinolysis is reasonable in settings in which substantial time can be saved by prehospital treatment because of long transportation times (i.e., 60 to 90 minutes or longer), physicians are present in the ambulance, or there is a well-organized EMS system with full-time paramedics who can obtain and transmit 12-lead electrocardiographic recordings from the field to an online medical command able to authorize prehospital fibrinolysis (Fig. 52-1).<sup>18</sup>

### MANAGEMENT IN THE EMERGENCY DEPARTMENT

When evaluating patients with chest pain in the emergency department, physicians must confront the difficult tasks of rapidly identifying patients who require urgent reperfusion therapy, triaging lower-risk patients to the appropriate setting within the hospital, and

not discharging patients inappropriately while avoiding unnecessary admissions. A history of ischemic-type discomfort and the initial 12-lead ECG are the primary tools for screening patients with possible acute coronary syndromes (ACSs) for STEMI ([see Chapter 50](#)).<sup>19</sup> Because the 12-lead ECG is at the center of the decision pathway for initiation of reperfusion therapy, it should be obtained promptly ( $\leq 10$  minutes after hospital arrival) in patients with ischemic discomfort.<sup>1</sup> More extensive use of prehospital 12-lead ECGs has also facilitated early triage of patients with STEMI.<sup>15</sup> Because lethal arrhythmias can occur suddenly in patients with STEMI, all patients should have bedside monitoring of the ECG and intravenous access.

The presence of ST-segment elevation on the ECG in a patient with ischemic discomfort highly suggests thrombotic occlusion of an epicardial coronary artery, and it should trigger a well-rehearsed sequence of rapid assessment of the patient for initiation of a reperfusion strategy.<sup>1</sup> If the initial ECG reveals ST-segment elevation of 0.1 mV or greater in at least two contiguous leads or a new or presumably new left bundle branch block, the patient should be evaluated immediately for a reperfusion strategy. Critical factors that weigh into selection of a reperfusion strategy include the time elapsed since the onset of symptoms, the risk associated with STEMI, the risk related to administering a fibrinolytic, and the time required to initiate an invasive strategy ([Fig. 52-1](#)). In non-PCI-capable hospitals, the initial assessment should include evaluation of the contraindications to administration of a fibrinolytic ([Table 52-4](#)). Patients with an initial ECG that reveals new or presumably new ST-segment depression and/or T wave inversion without ST-segment elevation are not considered candidates for immediate reperfusion therapy unless a posterior injury current is suspected ([see Chapter 53](#)).

Given the importance of time to reperfusion,<sup>7</sup> emphasis has shifted to overall medical system goals, starting at the point of first medical

**TABLE 52-4 Contraindications to and Cautions in the Use of Fibrinolysis for Treating ST-Elevation Myocardial Infarction\***

Absolute Contraindications
Any previous intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months except acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 months
Intracranial or intraspinal surgery within 2 months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, previous treatment within the previous 6 months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Significant hypertension at initial evaluation (SBP $> 180$ mm Hg or DBP $> 110$ mm Hg) <sup>†</sup>
History of previous ischemic stroke $> 3$ months
Dementia
Known intracranial pathology not covered in Absolute Contraindications
Traumatic or prolonged ( $> 10$ minutes) cardiopulmonary resuscitation
Major surgery ( $< 3$ weeks)
Recent (within 2 to 4 weeks) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

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

<sup>†</sup>Could be an absolute contraindication in low-risk patients with MI.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

From O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e78, 2013.

contact with the patient.<sup>1,20</sup> Benchmarks for medical systems to use when assessing the quality of their performance are a door-to-needle time of 30 minutes or less for initiation of fibrinolytic therapy and a door-to-device time of 90 minutes or less for percutaneous coronary perfusion ([Fig. 52-1](#)).<sup>14</sup>

In patients with a clinical history suggestive of STEMI ([see Chapter 50](#)) and an initial nondiagnostic ECG (i.e., no ST-segment deviation or T wave inversion), serial tracings should be obtained during evaluation in the emergency department. Emergency department staff can seek the sudden development of ST-segment elevation by periodic visual inspection of the bedside electrocardiographic monitor, by continuous ST-segment recording, or by auditory alarms when the ST-segment deviation exceeds programmed limits. Decision aids such as computer-based diagnostic algorithms, identification of high-risk clinical indicators, rapid determination of cardiac biomarkers, echocardiographic evaluation for regional wall motion abnormalities, and myocardial perfusion imaging have greatest clinical usefulness when the findings on the ECG are not diagnostic.

## General Treatment Measures

### Aspirin ([See also Chapter 82](#))

Aspirin is effective across the entire ACS spectrum and is part of the initial management strategy for patients with suspected STEMI. Because low doses take several days to achieve a full antiplatelet effect, 162 to 325 mg should be administered at the first opportunity after initial medical contact.<sup>1</sup> To achieve therapeutic blood levels rapidly, the patient should chew the tablet to promote buccal absorption rather than absorption through the gastric mucosa.<sup>21</sup>

### Control of Cardiac Pain

Initial management of patients with STEMI should target relief of pain and its associated heightened sympathetic activity. Control of cardiac pain is typically achieved with a combination of analgesics (e.g., morphine) and interventions to favorably improve the balance of myocardial oxygen supply and demand, including oxygen, nitrates, and in appropriately selected patients, beta-adrenergic receptor-blocking agents (beta blockers).<sup>1</sup>

**ANALGESICS.** Although a wide variety of analgesic agents—including meperidine, pentazocine, and morphine—have been used to treat the pain associated with STEMI, morphine remains the drug of choice, except in patients with well-documented morphine hypersensitivity. Doses of 4 to 8 mg administered intravenously and doses of 2 to 8 mg repeated at intervals of 5 to 15 minutes have been recommended<sup>1</sup> until the pain is relieved or side effects emerge—hypotension, depression of respiration, or severe vomiting—that preclude further administration of the drug. Appropriate dosing of morphine sulfate will vary, however, depending on the patient's age, body size, blood pressure, and heart rate.

Reduction of anxiety with successful analgesia diminishes the patient's restlessness and the activity of the autonomic nervous system, with a consequent reduction in the heart's metabolic demands. Morphine has beneficial effects in patients with pulmonary edema caused by peripheral arterial and venous dilation (particularly in those with excessive sympathoadrenal activity); it reduces the work of breathing and slows the heart rate secondary to combined withdrawal of sympathetic tone and augmentation of vagal tone. Observational studies have identified an association between the administration of morphine and adverse outcomes in patients with ACSs; however, it is challenging to disentangle this observation from confounding by indication.

Maintaining the patient in a supine position and elevating the lower extremities if blood pressure falls can minimize hypotension following the administration of nitroglycerin and morphine. Such positioning is undesirable in patients with pulmonary edema, but morphine rarely produces hypotension in these circumstances. Administration of atropine intravenously may be helpful in treating the excessive vagomimetic effects of morphine.

**NITRATES.** By virtue of their ability to enhance coronary blood flow by coronary vasodilation and to decrease ventricular preload by increasing venous capacitance, sublingual nitrates are indicated for

most patients with an ACS. At present, the only groups of patients with STEMI in whom sublingual nitroglycerin should *not* be given are those with suspected right ventricular infarction<sup>22</sup> or marked hypotension (e.g., systolic pressure <90 mm Hg), especially if accompanied by bradycardia.

Once hypotension is excluded, a sublingual nitroglycerin tablet should be administered and the patient observed for improvement in symptoms or change in hemodynamics. If an initial dose is well tolerated and appears to be beneficial, further nitrates should be administered while monitoring vital signs. Even small doses can produce sudden hypotension and bradycardia, a reaction that can usually be reversed with intravenous atropine. Long-acting oral nitrate preparations should be avoided in the early course of STEMI because of the frequently changing hemodynamic status of the patient. In patients with a prolonged period of waxing and waning chest pain, intravenous nitroglycerin may help control the symptoms and correct the ischemia, but frequent monitoring of blood pressure is required. Initiation of a reperfusion strategy in patients with STEMI should not be delayed while assessing the patient's response to sublingual or intravenous nitrates.

**BETA-ADRENERGIC BLOCKING AGENTS.** These drugs aid in the relief of ischemic pain, reduce the need for analgesics in many patients, and reduce infarct size and life-threatening arrhythmias. Avoiding early intravenous blockade in patients with Killip class II or greater is important, however, because of the risk of precipitating cardiogenic shock.<sup>1</sup> Routine use of intravenous beta blockers is no longer recommended in patients with STEMI, but administration of a beta blocker intravenously at the initial evaluation of patients with STEMI who are hypertensive and have ongoing ischemia is reasonable.<sup>1</sup>

A practical protocol for use of a beta blocker in this situation is as follows. (1) Exclude patients with heart failure, hypotension (systolic blood pressure <90 mm Hg), bradycardia (heart rate <60 beats/min), or significant atrioventricular (AV) block. (2) Administer metoprolol in three 5-mg intravenous boluses. (3) Observe the patient for 2 to 5 minutes after each bolus, and if the heart rate falls below 60 beats/min or systolic blood pressure falls below 100 mm Hg, do not administer any further drug. (4) If hemodynamic stability continues 15 minutes after the last intravenous dose, begin oral metoprolol tartrate, 25 to 50 mg every 6 hours for 2 to 3 days as tolerated, and then switch to 100 mg twice daily.<sup>1</sup> Lower doses may be used in patients who have a partial decline in blood pressure with the initial dosing or who appear to be at higher risk (e.g., larger infarction) for the development of heart failure because of poor left ventricular performance. Infusion of an extremely short-acting beta blocker, such as esmolol, 50 to 250 mg/kg/min, may be useful in patients with relative contraindications to the administration of a beta blocker and in whom slowing of the heart rate is considered highly desirable.<sup>23</sup>

**OXYGEN.** Hypoxemia can occur in patients with STEMI and generally results from ventilation-perfusion abnormalities that are sequelae of left ventricular failure; concomitant intrinsic pulmonary disease may be an additional cause of hypoxemia. Treating all patients hospitalized for STEMI with oxygen for at least 24 to 48 hours is common practice based on the empiric assumption of hypoxia and evidence that increased oxygen in the inspired air may protect ischemic myocardium. However, augmentation of the fraction of oxygen in the inspired air does not elevate oxygen delivery significantly in patients who are not hypoxicemic. Furthermore, it may increase systemic vascular resistance and arterial pressure and thereby lower cardiac output slightly.

In view of these considerations, arterial oxygen saturation can be estimated by pulse oximetry, and oxygen therapy can be omitted if the oximetric findings are normal. On the other hand, patients with STEMI and arterial hypoxemia should receive oxygen.<sup>1</sup> In patients with severe pulmonary edema, endotracheal intubation and mechanical ventilation may be necessary to correct the hypoxemia and reduce the work of breathing.

### Limitation of Infarct Size

Infarct size is an important determinant of prognosis in patients with STEMI. Patients who succumb from cardiogenic shock generally

exhibit either a single massive infarct or a small to moderate infarct superimposed on multiple previous infarcts.<sup>24,25</sup> Survivors with large infarcts frequently exhibit late impairment of ventricular function, and their long-term mortality rate is higher than that of survivors with small infarcts, in whom cardiac decompensation tends not to develop.<sup>26</sup> In view of the prognostic importance of infarct size, the possibility of modifying infarct size has attracted much experimental and clinical attention (see Chapter 51, Fig. 51-11).<sup>7,27</sup> Efforts to limit infarct size have been divided among several different (sometimes overlapping) approaches: (1) early reperfusion, (2) reduction of myocardial energy demands, (3) manipulation of energy production sources in the myocardium, and (4) prevention of reperfusion injury.

### Dynamic Nature of Infarction

STEMI is a dynamic process that does not occur instantaneously but rather evolves over a period of hours. The fate of jeopardized, ischemic tissue can be favorably affected by interventions that restore myocardial perfusion, reduce microvascular damage in the infarct zone, decrease myocardial oxygen requirements, inhibit accumulation or facilitate washout of noxious metabolites, augment the availability of substrate for anaerobic metabolism, or blunt the effects of mediators of injury that compromise the structure and function of intracellular organelles and constituents of cell membranes. Strong evidence in experimental animals and suggestive evidence in patients indicate that ischemic preconditioning, a form of endogenous protection against STEMI, before sustained coronary occlusion decreases infarct size and is associated with a more favorable outcome along with decreased risk for extension of infarction and recurrent ischemic events. Brief episodes of ischemia in one coronary vascular bed may precondition myocardium in a remote zone and thereby attenuate the size of infarction in the latter when sustained coronary occlusion occurs.<sup>28</sup>

Perfusion of myocardium in the infarct zone appears to be reduced maximally immediately following coronary occlusion. Spontaneous recanalization of an occluded infarct-related artery occurs in up to a third of patients beginning at 12 to 24 hours. This delayed spontaneous reperfusion may enhance left ventricular function because it improves healing of infarcted tissue, prevents ventricular remodeling, and reperfuses hibernating myocardium. Yet, strategies involving pharmacologically induced and catheter-based reperfusion of the infarct vessel can *maximize* the amount of salvaged myocardium by *accelerating* the process of reperfusion and also implementing it in patients who would otherwise have an occluded infarct-related artery (Fig. 52-1) (see Chapter 55). An overarching concept that applies to all methods of reperfusion is the critical importance of time. Reduction of mortality in patients with STEMI is greatest the earlier the infarct artery is reperfused (Fig. 52-2).<sup>1</sup>

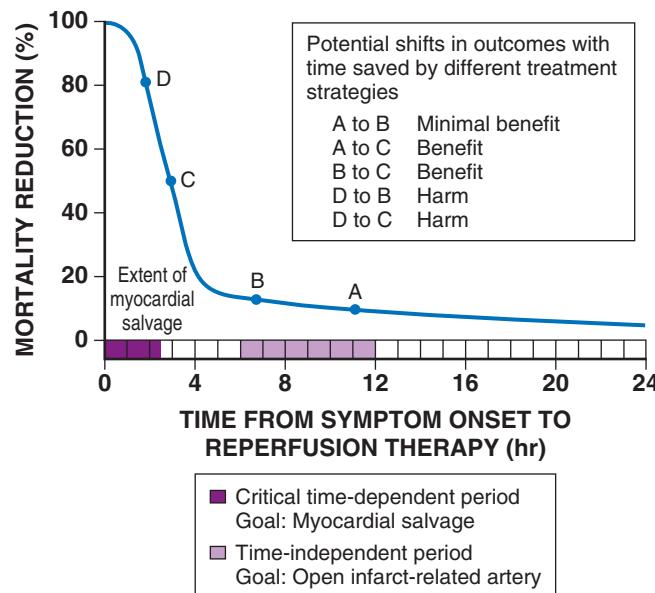
Additional factors that may limit infarct size during reperfusion include relief of coronary spasm, prevention of damage to the microvasculature, improved systemic hemodynamics (augmentation of coronary perfusion pressure and reduced left ventricular end-diastolic pressure), and collateral circulation. Prompt implementation of measures designed to protect ischemic myocardium and support myocardial perfusion may provide sufficient time for the development of compensatory mechanisms that limit the ultimate extent of infarction (see Chapter 51). Interventions designed to protect ischemic myocardium during the initial event may also reduce the extension of infarction or early reinfarction.

### Routine Measures for Limitation of Infarct Size

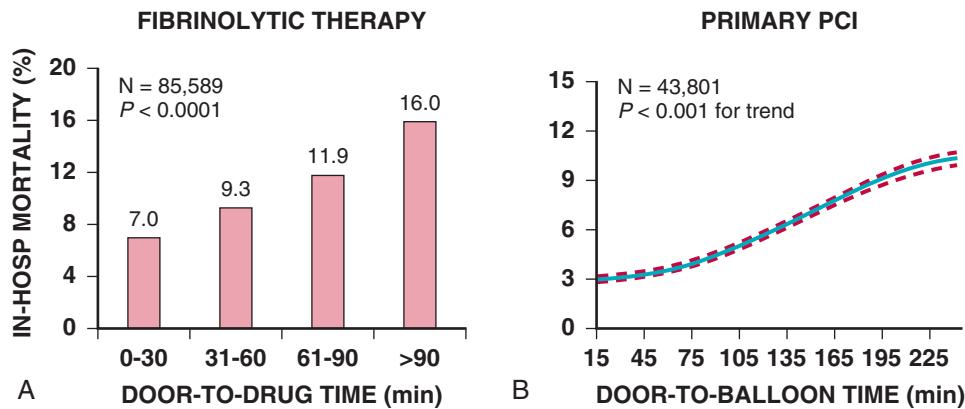
Although timely reperfusion of ischemic myocardium is the most important technique for limiting infarct size, several routine measures to accomplish this goal apply to all patients with STEMI, regardless of whether they receive reperfusion therapy.<sup>1</sup> The treatment strategies discussed in this section can be initiated at first medical contact and be continued throughout the hospital phase of care.

Myocardial oxygen consumption should be minimized by maintaining the patient at rest both physically and emotionally and by using mild sedation and a quiet atmosphere—in addition to the interventions already discussed. Administration of adrenergic agonists

should be avoided whenever possible. All forms of tachyarrhythmia require prompt treatment because they increase myocardial oxygen needs. Heart failure should also be treated swiftly to minimize increases in adrenergic tone and hypoxemia (see the section **Left Ventricular Failure**).



**FIGURE 52-2** The reduction in mortality as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute MI, most likely a consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and the duration of sustained ischemia. After this early period the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. The magnitude of the benefit depends on how far up the curve that the patient can be shifted. The benefit of a shift from point A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. This schematic illustrates how a treatment strategy that delays therapy during the early critical period, such as transfer of a patient for PCI with a long transportation time, could be harmful (shift from point D to point C or point B). (Modified from Gersh BJ, Stone GW, White HD, Holmes DR Jr: Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? *JAMA* 293:979, 2005.)



**FIGURE 52-3** Importance of time to reperfusion in patients undergoing fibrinolysis (A) or primary PCI (B) for STEMI. A, Graph based on data from 85,589 patients treated with fibrinolysis. A progressive increase in the in-hospital mortality rate occurs for every 30-minute delay. B, Based on data from 43,801 patients, this graph depicts the adjusted in-hospital mortality rate as a function of door-to-balloon time. Estimated mortality ranged from 3% with a door-to-balloon time of 30 minutes to 10.3% in patients with a door-to-balloon time of 240 minutes. (Data from Cannon CP, Gibson CM, Lambrew CT, et al: Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 283:2941, 2000; and Rathore SS, Curtis J, Chen J, et al: Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: National cohort study. *BMJ* 338:b1807, 2009.)

If ongoing ischemia occurs, severe anemia should be corrected by the cautious administration of packed red blood cells, accompanied by a diuretic if there is any evidence of left ventricular failure. Associated conditions, particularly infections and accompanying tachycardia, fever, and elevated myocardial oxygen needs, require management.

## REPERFUSION THERAPY

### General Concepts

Although late spontaneous reperfusion occurs in some patients, thrombotic occlusion persists in most patients with STEMI. Timely reperfusion of jeopardized myocardium is the most effective way of restoring the balance between myocardial oxygen supply and demand.<sup>29</sup> The dependence of myocardial salvage on the time elapsed until treatment pertains to patients treated with either fibrinolysis or PCI<sup>1,30,31</sup> (Fig. 52-3; also see Fig. 52-2). The efficacy of fibrinolytic agents decreases as coronary thrombi mature over time (Fig. 52-3). Analyses adjusted for baseline risk, however, demonstrate a statistically significant increase in in-hospital and long-term mortality with progressive delays between the onset of symptoms and PCI.<sup>30,32</sup> Each 30-minute delay from symptom onset to PCI increases the relative risk (RR) for 1-year mortality by 8%.<sup>1</sup>

In some patients, particularly those with cardiogenic shock, tissue damage occurs in a “stuttering” manner rather than abruptly. This concept of the infarction process, as well as the observation that the incidence of complications of STEMI in both the early and late postinfarction periods depends on infarct size, underscores the need for careful history taking to ascertain whether the patient appears to have had repetitive cycles of spontaneous reperfusion and reocclusion. Determining the precise time of onset of the infarction process in these patients, however, can be difficult and sometimes misleading. In such patients with waxing and waning ischemic discomfort, a rigid time interval from the first episode of pain should not be used when determining whether a patient is “outside the window” for benefit from acute reperfusion therapy.

### Pathophysiology of Myocardial Reperfusion

Prevention of cell death by restoration of blood flow depends on the severity and duration of the preexisting ischemia. Substantial experimental and clinical evidence indicates that the earlier blood flow is restored, the more favorably influenced are recovery of left ventricular systolic function, improvement in diastolic function, and reduction in overall mortality.<sup>1</sup> Collateral coronary vessels also appear to influence left ventricular function following reperfusion.<sup>33</sup> They provide sufficient perfusion of myocardium to slow cell death and probably have greater importance in patients undergoing reperfusion later than 1 to 2 hours after coronary occlusion. Even after successful reperfusion and despite the absence of irreversible myocardial damage, a period of posts ischemic contractile dysfunction can occur—a phenomenon referred to as *myocardial stunning*.<sup>34</sup>

### PRIMARY PCI

### Reperfusion Injury

The process of reperfusion, although beneficial in terms of myocardial salvage, may be accompanied by adverse sequelae described by the term *reperfusion injury* (see Chapter 51).<sup>35,36</sup> Several types of reperfusion injury occur in experimental animals: (1) lethal reperfusion injury, which refers to reperfusion-induced death of cells that were still viable at the time of

restoration of coronary blood flow; (2) vascular reperfusion injury, which is progressive damage to the microvasculature such that there is an expanding area of no-reflow and loss of coronary vasodilatory reserve; (3) stunned myocardium, in which salvaged myocytes display a prolonged period of contractile dysfunction following restoration of blood flow because of abnormalities in intracellular metabolism leading to reduced energy production; and (4) reperfusion arrhythmias, which refers to bursts of VT (and on occasion, VF) that occur within seconds of reperfusion.<sup>37</sup> Evidence suggests that vascular reperfusion injury, stunning, and reperfusion arrhythmias can all occur in patients with STEMI. The concept of lethal reperfusion injury to potentially salvageable myocardium remains controversial, both in animals and in humans.<sup>36,38,39</sup>

Microvasculature damage in the reperfused myocardium can lead to a hemorrhagic infarct (see Chapter 51). Fibrinolytic therapy appears more likely than catheter-based reperfusion to produce hemorrhagic infarction. Although concern has been raised that this hemorrhage may lead to extension of the infarct, such does not appear to be the case. Histologic study of patients not surviving despite successful reperfusion has revealed hemorrhagic infarcts, but this hemorrhage does not usually extend beyond the area of necrosis.

### **Protection Against Reperfusion Injury**

A variety of adjunctive therapies have been proposed to mitigate the injury that occurs after reperfusion, including preservation of microvascular integrity by using antiplatelet agents and antithrombins to minimize embolization of atheroembolic debris, prevention of inflammatory damage, and metabolic support of the ischemic myocardium.<sup>36,39,40</sup> The effectiveness of interventions directed against reperfusion injury appears to decline rapidly the later that they are administered after reperfusion. In animal models, no beneficial effect is detectable after 45 to 60 minutes of reperfusion has elapsed. Intriguingly, the phenomenon of induction of transient ischemia in other vascular beds has also been associated with a reduction in reperfusion injury, a concept called *remote conditioning*.<sup>28</sup>

An alternative experimental approach to protection against reperfusion injury is called *postconditioning*, which involves introducing brief, repetitive episodes of ischemia alternating with reperfusion.<sup>41</sup> This appears to activate the cellular protective mechanisms centering around prosurvival kinases.<sup>42</sup> Many of these protective kinases are also activated during ischemic preconditioning. Clinical studies in patients with STEMI undergoing PCI have provided evidence that postconditioning protects the human heart and is associated with reduced infarct size and improvement in myocardial perfusion.<sup>43</sup>

### **Reperfusion Arrhythmias**

Transient sinus bradycardia occurs in many patients with inferior infarcts at the time of acute reperfusion, often accompanied by some degree of hypotension. This combination of hypotension and bradycardia with a sudden increase in coronary flow may involve activation of the Bezold-Jarisch reflex.<sup>44</sup> Premature ventricular contractions, accelerated idioventricular rhythm, and nonsustained VT also commonly follow successful reperfusion. Although some investigators have postulated that early afterdepolarizations participate in the genesis of reperfusion-related ventricular arrhythmias, they are present during both ischemia and reperfusion and therefore not likely to be involved in the development of reperfusion-associated VT or VF.

When present, rhythm disturbances may actually indicate successful restoration of coronary flow, but their specificity for successful reperfusion is limited. In general, clinical features are inaccurate markers of reperfusion, with no single clinical finding or constellation of findings being reliably predictive of angiographically demonstrated coronary artery patency.<sup>1</sup>

Although reperfusion arrhythmias may show a temporal clustering at the time of restoration of coronary blood flow in patients after successful fibrinolysis, this brief “electrical storm” is generally innocuous, and therefore no prophylactic antiarrhythmic therapy is necessary and specific treatment is not indicated, except in rare cases of symptomatic or hemodynamically significant reperfusion arrhythmias.<sup>1</sup>

### **Late Establishment of Patency of the Infarct Vessel**

The improved survival and ventricular function after successful reperfusion may not result entirely from limitation of infarct size.<sup>45</sup> Poorly contracting or noncontracting myocardium in a zone that is supplied by a stenosed infarct-related artery with slow anterograde perfusion may still contain viable myocytes. The function of so-called *hibernating myocardium* can be improved by PCI to augment flow in the infarct-related artery.<sup>46,47</sup>

### **Summary of the Effects of Myocardial Reperfusion**

Disruption of plaque in the culprit vessel and subsequent thrombus formation produces complete occlusion of the infarct-related coronary artery. STEMI occurs with the ensuing development of left ventricular dilation and ultimately cell death through a combination of pump failure and electrical instability (see Chapter 51). Early reperfusion shortens the duration of coronary occlusion, minimizes the degree of ultimate left ventricular dysfunction and dilation, and reduces the probability that pump failure or malignant ventricular tachyarrhythmias will develop in patients with STEMI. Late reperfusion of stenosed infarct arteries may also restore contractile function in hibernating myocardium.

### **Fibrinolysis**

Fibrinolysis recanalizes the thrombotic occlusion associated with STEMI, and restoration of coronary flow reduces infarct size and improves myocardial function and survival over both the short and long term.<sup>48</sup> Patients treated within the first 1 to 2 hours after the onset of symptoms seem to have the greatest potential for long-term improvement in survival with fibrinolysis.<sup>1</sup>

#### **Assessment of Reperfusion**

**TIMI Flow Grade.** To provide a level of standardization both for clinical communication and for studies comparing various reperfusion regimens, most clinicians and investigators describe the flow in the infarct vessel according to the TIMI (Thrombolysis In Myocardial Infarction) trial grading system (Fig. 52-4).<sup>49</sup> Importantly, an angiographic snapshot in time does not reflect the fluctuating status of flow in the infarct vessel, which may undergo repeated cycles of patency and reocclusion before or during fibrinolysis.

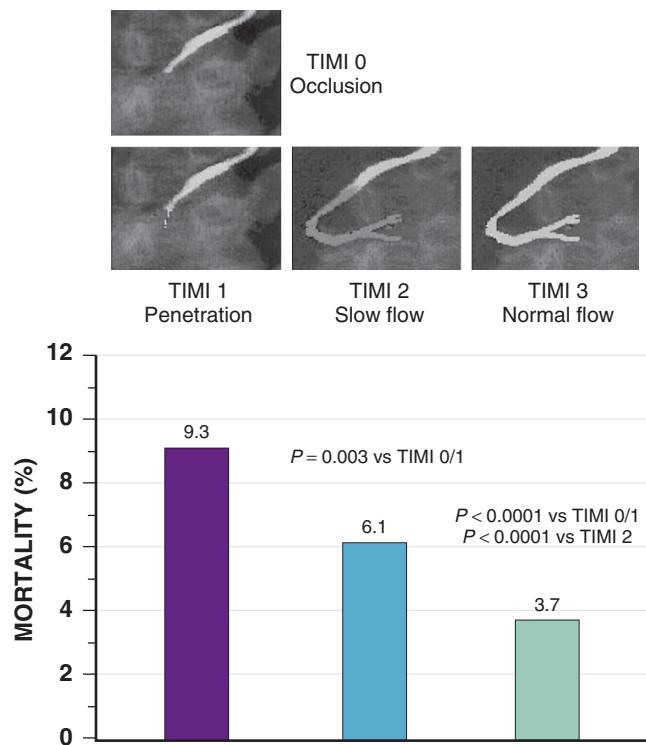
When assessed 60 to 90 minutes after the start of fibrinolytic therapy,<sup>2,48</sup> the finding of TIMI grade 3 flow is far superior to grade 2 in terms of reduction of infarct size and both short-term and long-term mortality benefit. Therefore TIMI grade 3 flow should be the goal when assessing flow in the epicardial infarct artery (Fig. 52-4).

**The TIMI Frame Count.** In an effort to provide a more quantitative statement of the briskness of coronary blood flow in the infarct artery and to account for differences in the size and length of vessels (e.g., left anterior descending versus right coronary artery) and interobserver variability, Gibson and coworkers developed the TIMI frame count—a simple count of the number of angiographic frames elapsed until the contrast material arrives in the distal bed of the vessel of interest. This objective and quantitative index of coronary blood flow independently predicts in-hospital mortality from STEMI and also discriminates patients with TIMI grade 3 flow into low-risk and high-risk groups. The TIMI frame count can also be used to quantitate coronary blood flow (mL/sec), as calculated by

$$21 + (\text{Observed TIMI frame count}) \times 1.7$$

(based on Doppler velocity wire data showing that normal flow equals  $1.7 \text{ cm}^3/\text{sec}$ , which is proportional to 21 frames). The calculated coronary perfusion is related to mortality in patients treated with fibrinolysis or primary PCI and serves to assess various modalities for reperfusion in patients with STEMI.

**Myocardial Perfusion.** Despite the priority placed on normalization of flow in the epicardial infarct-related artery, reperfusion in patients with STEMI is ultimately intended to improve actual myocardial perfusion in the infarct zone. Myocardial perfusion cannot be improved adequately without restoration of flow in the occluded infarct-related artery, but even patients with TIMI grade 3 flow may not achieve adequate myocardial perfusion, especially if the delay between the onset of symptoms and restoration of epicardial flow is long.<sup>50,51</sup> The term myocardial “no-reflow” has been used to describe a state with reduced myocardial perfusion after opening of



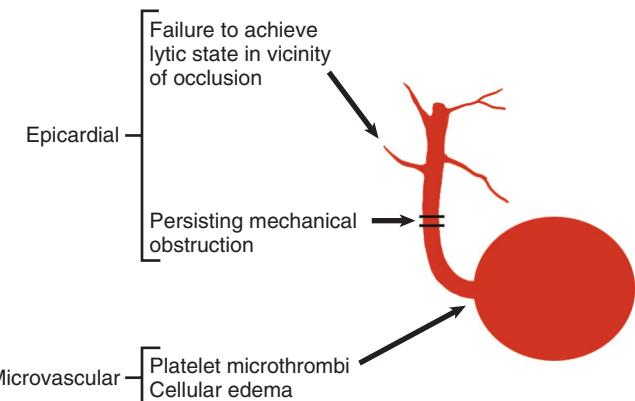
**FIGURE 52-4** Correlation of TIMI flow grade and mortality. A pooled analysis of data from 5498 patients in several angiographic trials of reperfusion for STEMI showed a gradient of mortality when the angiographic findings were stratified by TIMI flow grade. Patients with TIMI 0 or TIMI 1 flow had the highest rate of mortality, TIMI 2 flow associated with an intermediate rate of mortality, and the lowest rate of mortality was observed in patients with TIMI 3 flow. (Courtesy Dr. Michael Gibson, personal communication.)

an epicardial infarct-related artery.<sup>52</sup> The two major impediments to normalization of myocardial perfusion are microvascular damage (Fig. 52-5)<sup>50</sup> and reperfusion injury. Obstruction of the distal microvasculature in the downstream bed of the infarct-related artery results from platelet microemboli and thrombi. Fibrinolysis may actually exacerbate microembolization of platelet aggregates because of the exposure of clot-bound thrombin, an extremely potent platelet agonist. Spasm can also occur in the microvasculature as a consequence of release of substances from activated platelets. Reperfusion injury results in cellular edema, formation of reactive oxygen species, and calcium overload. In addition, cytokine activation leads to the accumulation of neutrophils and inflammatory mediators that contribute to tissue injury.<sup>52</sup>

Several techniques can be used to evaluate the adequacy of myocardial perfusion.

**Electrocardiography.** Electrocardiographic ST-segment resolution strongly predicts outcome in patients with STEMI but is a better predictor of an occluded artery than a patent infarct-related artery.<sup>53,54</sup> The persistence of ST-segment elevation after angiographically successful primary PCI identifies patients with a higher risk for left ventricular dysfunction and mortality, presumably because of microvascular damage in the infarct zone. Thus the 12-lead ECG is a marker of the biologic integrity of myocytes in the infarct zone and can reflect inadequate myocardial perfusion even in the presence of TIMI grade 3 flow.<sup>55</sup> The extent of ST-segment resolution provides powerful prognostic information early in the management of patients with STEMI.<sup>56</sup> Given the dynamic nature of coronary occlusion, continuous ST-segment monitoring may prove more informative than static 12-lead electrocardiographic recordings.

**Noninvasive Imaging.** Defects in perfusion patterns seen with myocardial contrast-enhanced echocardiography correlate with regional wall motion abnormalities and lack of myocardial viability on dobutamine stress echocardiography (see Chapter 14).<sup>57</sup> Contrast-enhanced cardiac magnetic resonance imaging (MRI) can also identify regions of microvascular obstruction, which are associated with an adverse long-term prognosis (see Chapter 17).<sup>58</sup>



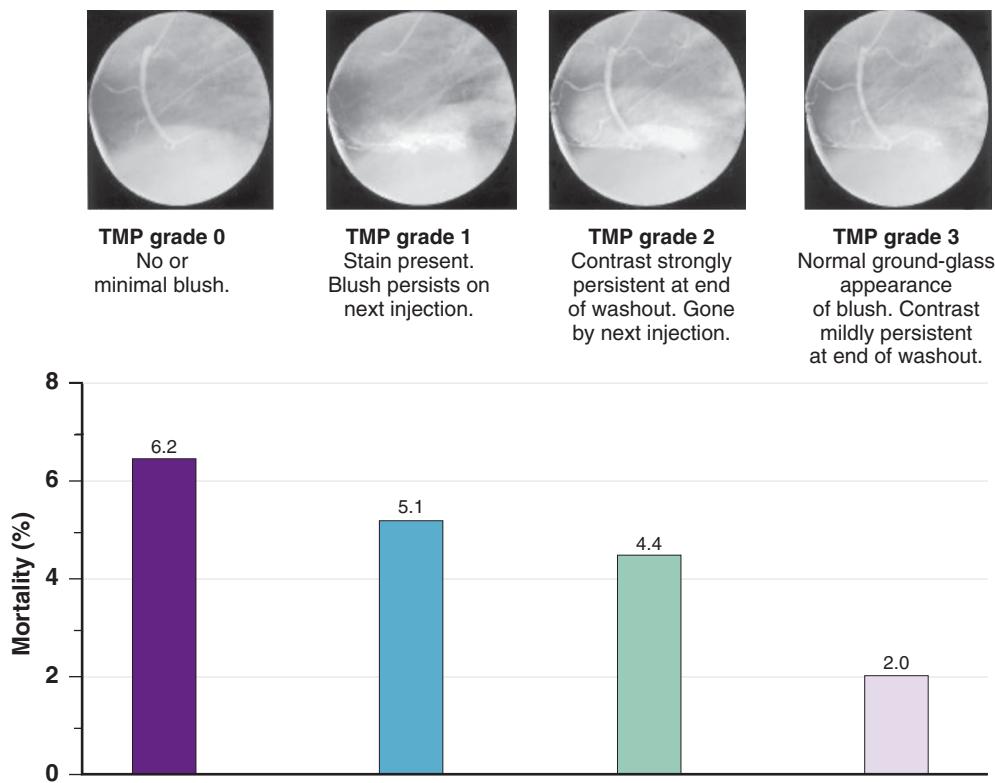
**FIGURE 52-5** Points of possible failure of reperfusion therapy. Complete reperfusion requires successful restoration of normal flow in both the epicardial coronary artery and the distal coronary microvasculature, termed myocardial tissue-level reperfusion. Failure of epicardial reperfusion can result from failure to induce a lytic state or from persistent mechanical obstruction at the site of occlusion. Failure of microvascular reperfusion is caused by a combination of platelet microthrombi followed by endothelial swelling and myocardial edema ("no reflow"). Reperfusion may fail because of persistent occlusion of the epicardial infarct-related artery (TIMI grades 0 and 1), patency of an epicardial artery in the presence of impaired (TIMI grade 2) flow, or microvascular occlusion in the presence of angiographically normal (TIMI grade 3) flow. Successful reperfusion requires a patent artery with an intact microvascular network. (Modified from Davies CH, Ormerod OJ: Failed coronary thrombolysis. *Lancet* 351:1191, 1998.)

**Invasive Assessment.** Doppler flow wire studies can also define abnormalities in myocardial perfusion. In addition, an angiographic method for assessing myocardial perfusion has been developed by Gibson and colleagues: the TIMI myocardial perfusion (TMP) grade (Fig. 52-6).<sup>50,59</sup> Abnormalities associated with increasing myocardial perfusion, as assessed by the TIMI grade, correlate with unfavorable ventricular remodeling and risk for mortality even after adjusting for the presence of TIMI grade 3 flow or a normal TIMI frame count.<sup>50,60</sup>

### Effect of Fibrinolytic Therapy on Mortality

Early intravenous fibrinolysis improves survival in patients with STEMI.<sup>1</sup> The benefit of fibrinolytic therapy appears to be greatest when agents are administered as early as possible, with the most dramatic results occurring when the drug is given less than 1 to 2 hours after symptoms begin.<sup>2</sup>

The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group performed a comprehensive overview of nine trials of thrombolytic therapy, each of which enrolled more than 1000 patients. Absolute mortality rates for the control and fibrinolytic groups stratified by initial features are shown in Figure 52-7. The overall results indicated an 18% reduction in short-term mortality, but as much as a 25% reduction in mortality in the subset of 45,000 patients with ST-segment elevation or bundle branch block. Two trials, LATE (Late Assessment of Thrombolytic Efficacy) and EMERAS (Estudio Multicéntrico Estreptoquinasa Repùblicas de América del Sur), when viewed together, provide evidence that a reduction in mortality may still be observed in patients treated with thrombolytic agents between 6 and 12 hours after the onset of ischemic symptoms. Data from the LATE and EMERAS trials and the FTT overview form the basis for extending the window of treatment with fibrinolitics up to 12 hours after the onset of symptoms. As cited in the American College of Cardiology Foundation (ACCF)/AHA guidelines for the management of ST-elevation MI (referred to hereafter as the guidelines), Boersma and colleagues pooled the trials in the FTT overview, two smaller studies with data on time until randomization, and 11 additional trials.<sup>1</sup> Patients were divided into six time categories from the onset of symptoms to randomization. A nonlinear relationship of treatment benefit to time was observed, with the greatest benefit occurring in the first 1 to 2 hours after the onset of symptoms.<sup>1</sup>



**FIGURE 52-6** Relationship between angiographic assessment of myocardial tissue–level reperfusion categorized by TIMI myocardial perfusion (TMP) grade and mortality. TMP grade 0 or no perfusion of the myocardium is associated with the highest rate of mortality. If a stain of the myocardium is present (grade 1), mortality is also high. A reduction in mortality is seen if the dye enters the microvasculature but is still persistent at the end of the washout phase (grade 2). The lowest mortality rate is observed in patients with normal perfusion (grade 3), with the dye being minimally persistent at the end of the washout phase. (From Gibson CM, Cannon CP, Murphy SA, et al: Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 101:125, 2000.)

The mortality effect of fibrinolytic therapy in elderly patients is of considerable interest and controversy. Although patients older than 75 years were initially excluded from randomized trials of fibrinolytic therapy, they now constitute approximately 15% of those studied in trials of fibrinolysis and approximately 35% of those analyzed in registries of patients with STEMI.<sup>61</sup> Barriers to initiation of therapy in older patients with STEMI include a protracted period of delay in seeking medical care, a lower incidence of ischemic discomfort and greater incidence of atypical symptoms and concomitant illnesses, and an increased incidence of nondiagnostic findings on the ECG.<sup>61</sup> Younger patients with STEMI achieve a slightly greater relative reduction in mortality than elderly patients do, but the higher absolute mortality in elderly patients results in similar absolute reductions in mortality.<sup>62</sup>

Several models have integrated the many clinical variables that affect a patient's risk for mortality before the administration of fibrinolytic therapy. A convenient, simple, bedside risk-scoring system for predicting 30-day mortality at initial evaluation of fibrinolytic-eligible patients with STEMI was developed by Morrow by using the InTIME-II trial database (Fig. 52-8).<sup>63</sup> Modeling of mortality risk cannot cover all clinical scenarios, however, and should supplement clinical judgment in individual cases. For example, patients with inferior STEMI who might otherwise be considered to have a low risk for mortality and for whom many physicians have questioned the benefits of fibrinolytic therapy might be in a higher mortality risk subgroup if their inferior infarction is associated with right ventricular infarction, precordial ST-segment depression, or ST-segment elevation in the lateral precordial leads.

The short-term survival benefit enjoyed by patients who receive fibrinolytic therapy is maintained over the 1- to 10-year follow-up. Room for improvement remains. Advances in adjunctive antiplatelet and antithrombin therapies have led to reductions in the rate of reinfarction after fibrinolysis for STEMI.<sup>2,48</sup>

## Comparison of Fibrinolytic Agents (See Chapter 82)

Comparative features of the approved fibrinolytic agents for intravenous therapy are presented in Table 52-5. All fibrinolytic agents exert their effect by converting the proenzyme plasminogen to the active enzyme plasmin. The so-called fibrin-specific fibrinolitics are those that are relatively inactive in the absence of fibrin but in its presence substantially increase their activity on plasminogen.

The tissue plasminogen activator (t-PA) molecule contains five domains (Fig. 52-9).<sup>64</sup> In the absence of fibrin, t-PA is a weak plasminogen activator; fibrin provides a scaffold on which t-PA and plasminogen are held in such a way that the catalytic efficiency of plasminogen activating t-PA is increased many-fold. A dose regimen of t-PA administered over a 90-minute period produces more rapid thrombolysis than does a 3-hour fixed-rate infusion. Therefore the recommended dosage for t-PA is the 90-minute “accelerated” regimen.

Modifications in the native t-PA structure have yielded a group of fibrinolytic agents with prolonged plasma clearance that allows them to be administered as a bolus (Fig. 52-9 and Table 52-5) rather than as the bolus and infusion by which accelerated-dose t-PA is administered.<sup>64</sup> Reteplase (double fixed-dose bolus) and tenecteplase (single weight-based bolus) have both been compared with accelerated t-PA. Both these newer agents were associated with mortality rates similar to that achieved with accelerated t-PA, but with more convenient dosing. In one large trial, tenecteplase was found to have a lower rate of major bleeding than accelerated t-PA did.

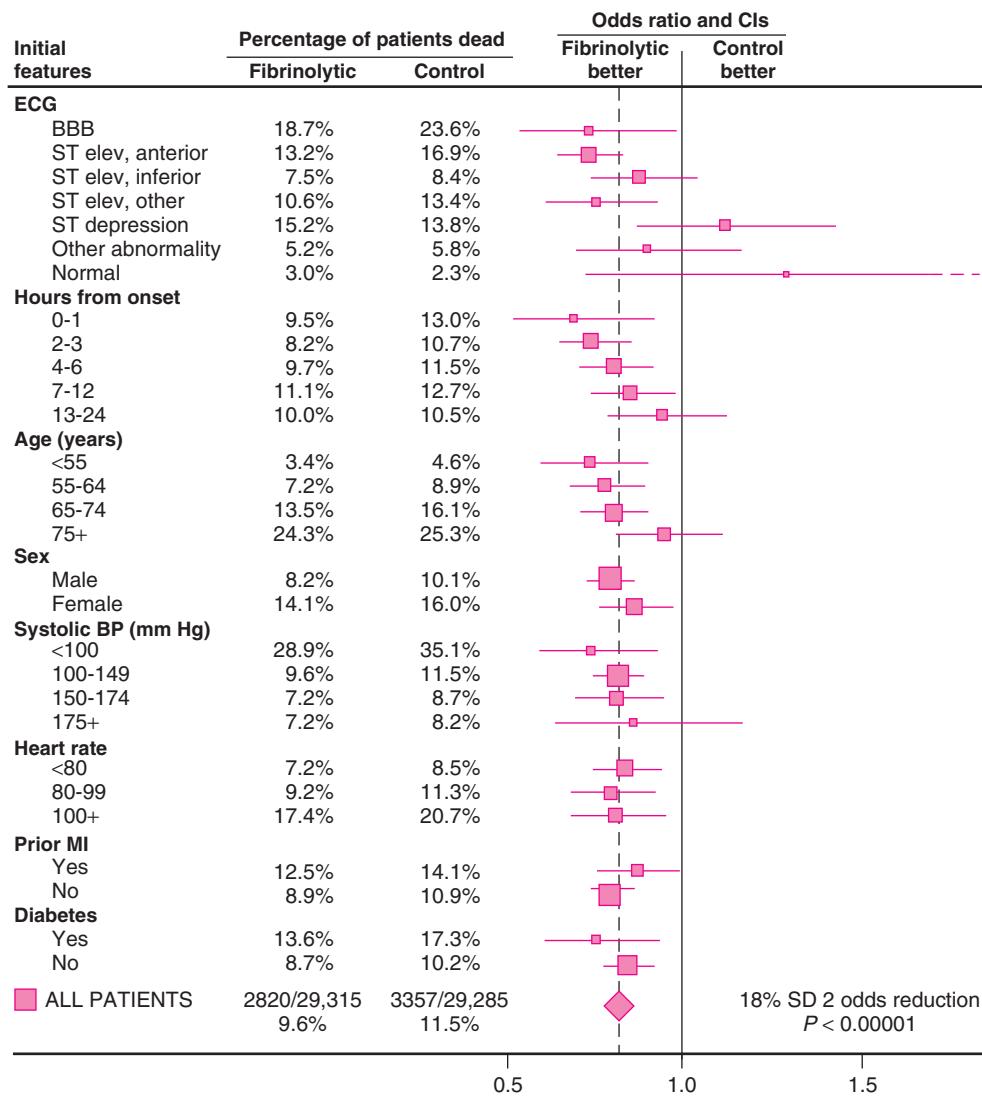
and tenecteplase (single weight-based bolus) have both been compared with accelerated t-PA. Both these newer agents were associated with mortality rates similar to that achieved with accelerated t-PA, but with more convenient dosing. In one large trial, tenecteplase was found to have a lower rate of major bleeding than accelerated t-PA did.

### Other Fibrinolytic Agents

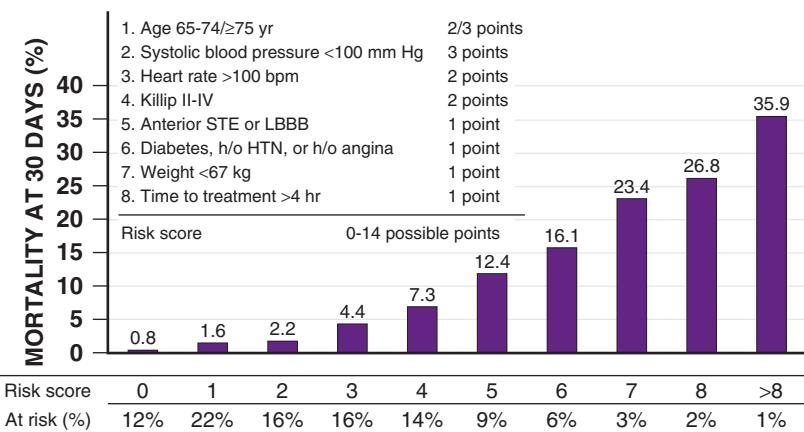
Streptokinase, a protein secreted by several species of streptococci, binds and activates human plasminogen and is an inexpensive and effective fibrinolytic agent that is still used in some regions of the world. Urokinase is used for STEMI on rare occasions as an intracoronary infusion.

### Effect on Left Ventricular Function

As with survival, improvement in global left ventricular function is related to the time of initiation of fibrinolytic treatment, with the greatest improvement occurring with the earliest therapy.<sup>2</sup> Although precise measurements of infarct size would be an ideal endpoint for clinical reperfusion studies, such measures have proved impractical. Attempts to use the left ventricular ejection fraction as a surrogate for infarct size have not been productive because little difference is seen in the ejection fraction between treatment groups that show a significant difference in mortality. Methods of assessing left ventricular function, such as end-systolic volume or quantitative echocardiography, are more revealing because patients with smaller volumes and better-preserved ventricular shape have improved survival. The myocardial salvage index, defined as the difference between the initial perfusion defect (e.g., by sestamibi scintigraphy) and the final perfusion defect, is a useful means for comparing the effectiveness of reperfusion therapies.<sup>65</sup> Characterization of left ventricular volumes concurrently with the extent of scar as revealed by myocardial



**FIGURE 52-7** Differences in mortality during days 0 to 35, subdivided by initial features, in a collaborative overview of results from nine trials of thrombolytic therapy. Absolute mortality rates are shown for the fibrinolytic and control groups in the center of the figure for each of the clinical features at initial encounter, listed on the left side of the figure. The ratio of the odds of death in the fibrinolytic group to that in the control group is shown for each subdivision (colored squares), along with its 99% CI (horizontal line). The summary OR at the bottom of the figure corresponds to an 18% proportional reduction in 35-day mortality and is highly statistically significant. This translates to a reduction of 18 deaths per 1000 patients treated with thrombolytic agents. BBB, bundle branch block; BP, blood pressure; SD, standard deviation. (From Fibrinolytic Therapy Trialists' [FTT] Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet* 343:311, 1994.)



**FIGURE 52-8** TIMI risk score for STEMI predicting 30-day mortality. h/o, history of; HTN, hypertension; LBBB, left bundle branch block. (From Morrow DA, Antman EM, Charlesworth A, et al: The TIMI risk score for ST elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An In TIME II substudy. *Circulation* 102:2031, 2000.)

**TABLE 52-5** Comparison of Approved Fibrinolytic Agents

FIBRINOLYTIC AGENT	DOSE	FIBRIN SPECIFICITY	FIBRINOGEN DEPLETION	ANTIGENIC	PATENCY RATE (90-MIN TIMI 2 OR 3 FLOW)
<b>Fibrin Specific</b>					
Tenecteplase (TNK)	Single IV weight-based bolus <sup>†</sup>	++++	Minimal	No	85%
Reteplase (r-PA)	10 units + 10-unit IV boluses given 30 min apart	++	Moderate	No	84%
Alteplase (t-PA)	90-min weight-based infusion <sup>‡</sup>	++	Mild	No	73-84%
<b>Non-Fibrin Specific</b>					
Streptokinase <sup>\$</sup>	1.5 million units IV given over 30-60 min	No	Marked	Yes <sup>¶</sup>	60-68%

\*Strength of fibrin specificity: ++++ is stronger; ++ is less strong.

**Bolus of 30 mg for weight less than 60 kg, 35 mg for 60 to 69 kg, 40 mg for 70 to 79 kg, 45 mg for 80 to 89 kg, and 50 mg for 90 kg or greater.**

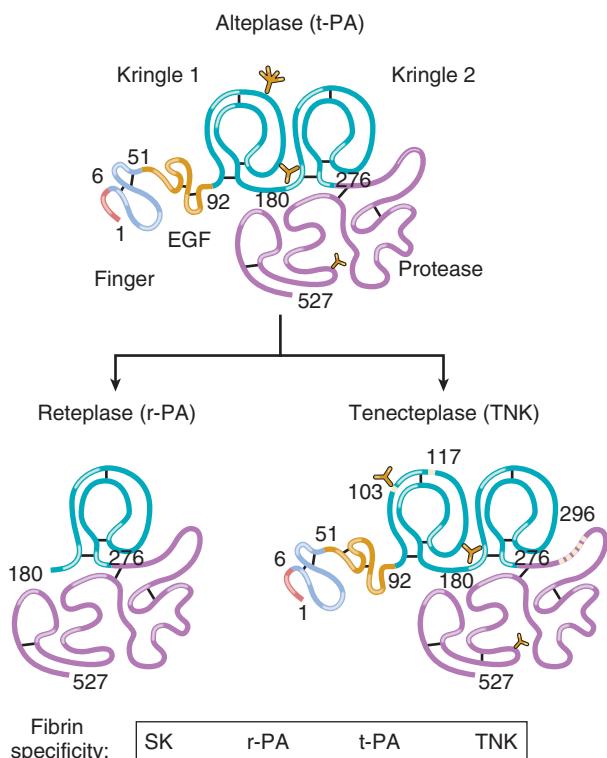
\*Bolus of 15 mg, infusion of 0.75 mg/kg for 30 minutes (maximum, 50 mg), then 0.5 mg/kg (maximum, 35 mg) over the next 60 minutes; the total dose not to exceed 100 mg.

<sup>§</sup>Streptokinase is no longer marketed in the United States but is available in other countries.

<sup>1</sup>Streptokinase is highly antigenic and absolutely contraindicated within 6 months of previous exposure because of the potential for serious allergic reaction.

r-PA = reteplase plasminogen activator; t-PA = tissue plasminogen activator.

From O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 61:e78, 2013.

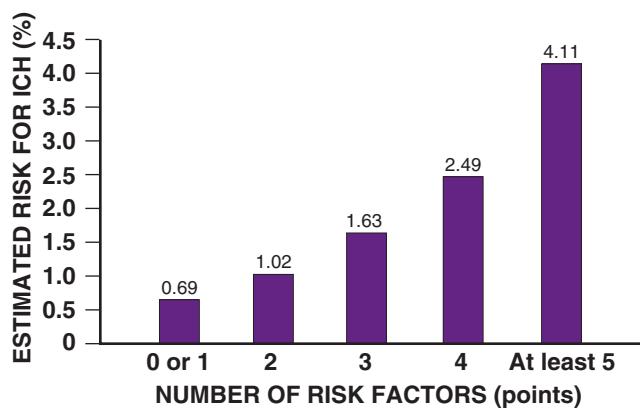


**FIGURE 52-9** Molecular structure of alteplase (t-PA), reteplase (r-PA), and tenecteplase (TNK). Streptokinase (SK) is the least fibrin-specific thrombolytic agent in clinical use; the progressive increase in relative fibrin specificity for the various thrombolytics is shown at the bottom. (Modified from Brener SJ, Topol EJ: Third-generation thrombolytic agents for acute myocardial infarction. In Topol EJ [ed]: Acute Coronary Syndromes. New York, Marcel Dekker, 1998, p 169.)

delayed enhancement, as well as ischemia with adenosine stress perfusion and cardiac MRI, provides significant incremental prognostic information over other clinical variables and is an emerging strategy for risk stratification after STEMI.<sup>66-68</sup>

## Complications of Fibrinolytic Therapy

Bleeding complications are most common, and intracranial hemorrhage is the most serious complication of fibrinolytic therapy; its frequency is generally less than 1% but varies with the clinical



**FIGURE 52-10** Estimation of risk for intracranial hemorrhage (ICH) with fibrinolysis. The number of risk factors is the sum of the points based on criteria established in the studies shown. Although the exact risk factors varied among the studies, common risk factors across each of the studies include increased age, low body weight, and hypertension on admission. See [references](#) for further discussion. (Data from Brass LM, Lichman JH, Wang Y, et al: Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: Results from the Cooperative Cardiovascular Project. *Stroke* 31:1802, 2000.)

characteristics of the patient and the fibrinolytic agent used (**Fig. 52-10**).<sup>1</sup> Intracranial bleeding in the setting of fibrinolysis for STEMI is associated with a high case fatality rate. Nonintracranial bleeding can also result in increased morbidity, but whether it is causal of higher overall mortality, after taking into account the higher-risk clinical characteristics that also predispose patients to bleeding during treatment of STEMI, is uncertain.<sup>69,70</sup>

Reports have demonstrated an "early hazard" with fibrinolytic therapy—that is, an excess of deaths in the first 24 hours in fibrinolytic-treated patients when compared with control subjects (especially in elderly patients treated more than 12 hours after symptom onset). However, this excess early mortality is more than offset by deaths prevented beyond the first day, with an average 18% (range, 13% to 23%) reduction in mortality by 35 days as compared with offering no reperfusion therapy.<sup>1</sup> The mechanisms responsible for this early hazard are not clear but are probably multiple, including an increased risk for myocardial rupture, fatal intracranial hemorrhage, and possible myocardial reperfusion injury.

Recent exposure to streptococci or streptokinase produces some degree of antibody-mediated resistance to streptokinase (and anistreplase) in most patients. Although such resistance is only rarely

of clinical consequence, patients should not receive streptokinase for STEMI if they have been treated with a streptokinase product within the past 6 months.

### Recommendations for Fibrinolytic Therapy

As described in the preceding sections, the benefits of fibrinolytic therapy in patients with STEMI are well established, with a time-dependent improvement in survival rates during the initial 12 hours after the onset of symptoms. When a patient arrives at a PCI-capable facility, primary PCI is the preferred mode of reperfusion therapy (see the section *Selection of Reperfusion Strategy*).<sup>1,4</sup> However, many health care facilities do not have ready access to timely PCI; if the delay from first medical contact to performing primary PCI is anticipated to exceed 120 minutes, administration of a fibrinolytic is indicated for the treatment of STEMI within 12 hours of onset in the absence of contraindications.<sup>1</sup> In addition, even when interhospital transport times are expected to be short, there may be advantages to immediate initiation of fibrinolytic therapy versus incurring any delay until primary PCI in patients with STEMI and low bleeding risk who are initially seen very early in the course.<sup>1</sup>

### Choice of Agent

The choice of fibrinolytic in hospital systems is generally driven by the desire to establish consistent protocols within the health care system by weighing ease of dosing, cost, and other institutional preferences. In patients seen early with acceptable bleeding risk, a high-intensity fibrin-specific regimen, such as accelerated t-PA, reteplase, or tenecteplase, is usually preferable.<sup>1</sup> In patients whose risk for death is low (e.g., a young patient with a small inferior MI) and whose risk for intracranial hemorrhage is increased (e.g., acute hypertension), administration of streptokinase is reasonable, but rarely done in the United States. In patients who are to be treated with a fibrinolytic and in whom t-PA would have been selected as the agent of choice in the past, we believe that clinicians should now consider using a bolus fibrinolytic such as reteplase or tenecteplase. The rationale for this recommendation is that bolus fibrinolysis are easy to administer, have a lower chance of medication errors (and the associated increase in mortality when such errors occur), and are associated with less noncerebral bleeding—as well as offering the potential for prehospital treatment.<sup>64</sup>

### Late Therapy

No mortality benefit was demonstrated in the LATE and EMERAS trials when fibrinolysis were routinely administered to patients between 12 and 24 hours, although we believe that it is still reasonable to consider fibrinolytic therapy when PCI is not available for appropriately selected patients with clinical and/or electrocardiographic evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability. Persistent chest pain late after the onset of symptoms correlates with a higher incidence of collateral or anterograde flow in the infarct zone and is therefore a marker for viable myocardium that might be salvaged. Because elderly patients treated with fibrinolytic agents more than 12 hours after the onset of symptoms have an increased risk for cardiac rupture, we believe that restricting late administration of a fibrinolytic to patients younger than 65 years with ongoing ischemia, especially those with large anterior infarctions, is preferable. An elderly patient with ongoing ischemic symptoms but initially seen late (>12 hours) is probably better managed with PCI than with fibrinolytic therapy.

### General Considerations

Before fibrinolytic therapy is instituted, consideration should be given to the patient's need for intravascular catheterization, as would be required for placement of an arterial pressure monitoring line, a pulmonary artery catheter for hemodynamic monitoring, or a temporary transvenous pacemaker. If any of these are required, ideally they should be placed as expeditiously as possible *before* infusion of the fibrinolytic agent. If such procedures require an additional delay of more than 30 minutes, they should be deferred for as long as possible

after fibrinolytic therapy is begun. In the early hours after institution of fibrinolytic therapy, such catheterization should be performed only if crucial to the patient's survival, and then sites at which excessive bleeding can be controlled should be chosen (e.g., subclavian vein catheterization should be avoided).

Administration of anticoagulant and antiplatelet agents as an adjunct to thrombolysis is discussed in detail in a subsequent section (see *Anticoagulant and Antiplatelet Therapy*).

### Intracoronary Fibrinolysis

In contemporary practice, patients are more likely to be treated with PCI. This evolution has revived the concept of delivering fibrinolytic agents via the intracoronary route, but current efforts are largely restricted to adjunctive use during complicated PCI procedures.<sup>71</sup>

### Catheter-Based Reperfusion Strategies

#### (See also Chapter 55)

Reperfusion of the infarct artery can also be achieved via a catheter-based strategy. This approach has evolved from passage of a balloon catheter over a guidewire to now include potent oral antiplatelet therapy, multiple options for anticoagulants, coronary stents, and thrombectomy.<sup>1</sup> When PCI is used as primary reperfusion therapy in patients with STEMI, it is referred to as direct or primary PCI (see Fig. 52-1). After fibrinolysis has failed to reperfuse the infarct vessel or a severe stenosis is present in the infarct vessel, rescue PCI can be performed (Fig. 52-1). A strategy of routine delayed angiography and PCI after successful fibrinolytic therapy may also be considered (Fig. 52-1).<sup>72,73</sup> Finally, a conservative approach of elective PCI only when spontaneous or exercise-provoked ischemia occurs may be used to manage patients with STEMI, regardless of whether they have received a previous course of fibrinolytic therapy or no initial reperfusion therapy (Fig. 52-1).<sup>1</sup> Primary PCI and the management of significant stenoses in nonculprit coronary arteries are discussed in Chapter 55. This chapter discusses decision making regarding the selection of initial reperfusion therapy and decisions on referral for PCI in patients who have undergone initial fibrinolysis (see also Chapter 55).

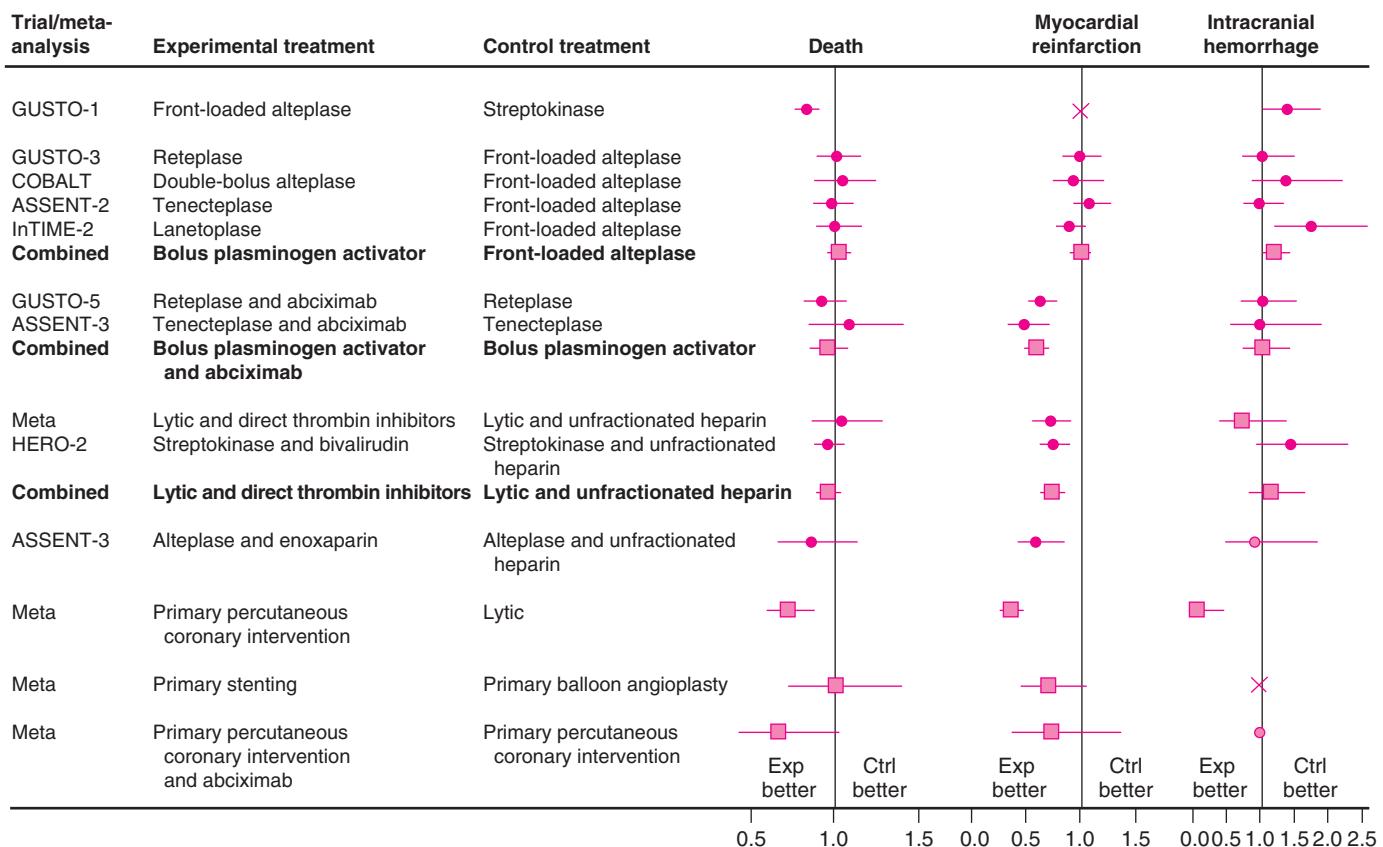
### Surgical Reperfusion

Despite the extensive improvement in intraoperative preservation with cardioplegia and hypothermia and numerous surgical techniques, providing surgical reperfusion in timely fashion is not logistically possible. Therefore patients with STEMI who are candidates for reperfusion should undergo either fibrinolysis or PCI. However, patients with STEMI are currently referred for coronary artery bypass grafting (CABG) for one of the following indications: persistent or recurrent ischemia despite fibrinolysis or primary PCI with residual coronary disease not amenable to PCI, high-risk coronary anatomy (e.g., left main stenosis) discovered at initial catheterization, or a complication of STEMI such as ventricular septal rupture or severe mitral regurgitation caused by papillary muscle dysfunction. STEMI patients with continued severe ischemic and hemodynamic instability will probably benefit from emergency revascularization.

Patients who successfully undergo fibrinolysis but have important residual stenoses and on anatomic grounds are more suitable for surgical revascularization than for PCI have undergone CABG with quite low rates of mortality ( $\approx 4\%$ ) and morbidity, provided that the procedure is carried out more than 24 hours after STEMI; patients requiring urgent or emergency CABG within 24 to 48 hours of STEMI have mortality rates between 12% and 15%.<sup>1</sup> When surgery is performed under urgent conditions with active and ongoing ischemia or cardiogenic shock, operative mortality rates are higher, in large part reflecting the patient's overall condition that necessitated emergency surgery.

### Selection of Reperfusion Strategy

When performed rapidly after arrival at an experienced center, primary PCI is superior to pharmacologic reperfusion therapy.<sup>1,74,75</sup>



**FIGURE 52-11** Relative treatment effect associated with several acute reperfusion modalities in patients with STEMI. Data are ORs and 95% CIs. Ctrl = control; EXP = experimental. (Modified from Boersma E, Mercado N, Poldermans, et al: Acute myocardial infarction. Lancet 361:851, 2003.)

Nevertheless, decision making for individual patients remains complex regarding the optimum form of reperfusion therapy when a delay until PCI can be performed is anticipated, such as in centers without 24-hour availability of primary PCI.<sup>1</sup> This controversy has been difficult to resolve in the context of a dynamic evidence base and the absence of adequately powered definitive trials of reperfusion in patients with STEMI when immediate primary PCI is not an option. Moreover, newer fibrinolytic agents and combinations of adjunctive treatments have improved medical measures to restore and maintain flow in the infarct artery (Fig. 52-11). At the same time, improvements in catheterization laboratory facilities, new stents, evolution of adjunctive antithrombotic therapy, thrombus aspiration devices, and the development of collaborative systems for rapid transfer for invasive therapy have improved the efficacy and safety of primary PCI in patients with STEMI, including those being transferred for primary PCI (see Chapter 55).<sup>76</sup> High-volume operators and centers can consistently achieve better outcomes in patients with STEMI.<sup>77</sup> Selection of the optimal form of reperfusion therapy therefore involves judgments regarding both system resources and individual patient characteristics.

For patients who arrive at an experienced primary PCI center, primary PCI should be performed in those with STEMI who are seen within 12 hours of symptom onset and those with later arrival who have ongoing ischemia or shock. In patients taken to centers that are not PCI capable, the following issues should be considered in choosing the approach to reperfusion (see Fig. 52-1 and Table 52-4):

1. *Time from onset of symptoms to initiation of reperfusion therapy:* PCI is preferable in patients with late arrival, particularly those initially seen more than 12 hours after symptom onset.
2. *Risk for death after STEMI:* The mortality benefit associated with PCI is largest in patients at highest risk for mortality; the mortality benefit of PCI decreases progressively as the patient's risk for death from STEMI decreases such that the mortality advantage of

PCI is no longer evident in patients whose 30-day mortality rate is estimated to be between 2% and 3% if treated with fibrinolytic therapy.

3. *Presence of shock:* Patients in cardiogenic shock have improved survival if they are treated with an early revascularization strategy (PCI and/or CABG as indicated).
4. *Risk for bleeding:* In patients with an increased risk for bleeding, particularly intracranial hemorrhage, therapeutic decision making strongly favors a PCI-based reperfusion strategy (see Fig. 52-10). If PCI is unavailable, the benefit of pharmacologic reperfusion should be balanced against the risk for bleeding. A decision analysis suggests that when PCI is not available, fibrinolytic therapy should still be favored over no reperfusion treatment until the risk for life-threatening bleeding exceeds 4%.
5. *Time required for transportation to a skilled PCI center:* The greatest operational impediment to routine implementation of a PCI reperfusion strategy is the delay required for transportation to a skilled PCI center (Fig. 52-12; also see Fig. 52-1 and Table 52-1).<sup>78</sup> Trials conducted in health care systems with extremely short transportation and door-to-balloon times at PCI centers have demonstrated that referral to a PCI center can be superior to fibrinolysis administered at a local hospital.<sup>78,79</sup> If the delay to implementation of primary PCI is substantial, however, the mortality advantage over administration of a fibrin-specific agent is lost. The best estimate of the time delay at which this advantage is lost is 1 to 2 hours, but it may vary depending on the timing of initial evaluation and the extent of myocardium at risk.<sup>78</sup>

Based on the aforementioned considerations, clinicians should make an integrated assessment of the time since the onset of symptoms (see Figs. 52-1, 52-2, and 52-3), risk for death after STEMI (see Fig. 52-8), risk for bleeding if a fibrinolytic is administered (see Fig. 52-10), and time required for transportation to a skilled PCI center (see Fig. 52-1 and 52-3). Reducing this decision making to a



“one-size-fits-all” approach is not possible. Primary PCI is generally preferred, except when a patient with low bleeding risk arrives very early after the onset of symptoms (1 to 2 hours) at a non-PCI-capable hospital and the delay in transfer for primary PCI is anticipated to be long (Fig. 52-12). When fibrinolysis is performed early, particularly in the prehospital setting, and is followed by coronary angiography and PCI when appropriate, the 1-year survival rate is comparable to that achieved with primary PCI.<sup>80</sup> Importantly, when the diagnosis of STEMI is in doubt, an invasive strategy is clearly the preferred strategy because it not only provides key diagnostic information regarding the patient’s symptoms but does so without the risk for intracranial hemorrhage associated with fibrinolysis.

### Referral for Angiography with the Intent of Revascularization after Initial Fibrinolysis

Patients with STEMI who are initially managed by fibrinolysis at a non-PCI-capable center may be appropriate for transfer for coronary angiography because of the development of cardiogenic shock or severe heart failure, for failed reperfusion with a fibrinolytic, or as part of an invasive strategy in stable patients with the intention of performing PCI 3 to 24 hours after fibrinolysis (Table 52-6; also see Fig. 52-1). Performance of PCI in patients with STEMI and shock has been discussed.

Studies of patients undergoing angiography and PCI after suspected failure of reperfusion with fibrinolysis have demonstrated a trend toward a lower mortality rate and significantly lower rates of recurrent MI and heart failure in those treated with rescue PCI versus continued medical therapy, including readministration of a fibrinolytic agent. In the REACT (Rapid Early Action for Coronary Treatment) study, patients with suspected failed reperfusion at 90 minutes by electrocardiographic criteria were randomly assigned to one of three treatment arms: rescue PCI, conservative care, or repeated fibrinolytic therapy. The composite of death, reinfarction, stroke, or severe heart failure at 6 months was significantly lower in patients randomly assigned to rescue PCI than in the two other treatment groups.<sup>1</sup> More minor bleeding, however, occurred in patients randomly assigned to rescue PCI.

The option of administration of a fibrinolytic agent at non-PCI-capable hospitals, followed by routine transfer for angiography and PCI if indicated, has been advanced as an attractive strategy to offer timely reperfusion therapy and arrange a “nonemergency” transfer

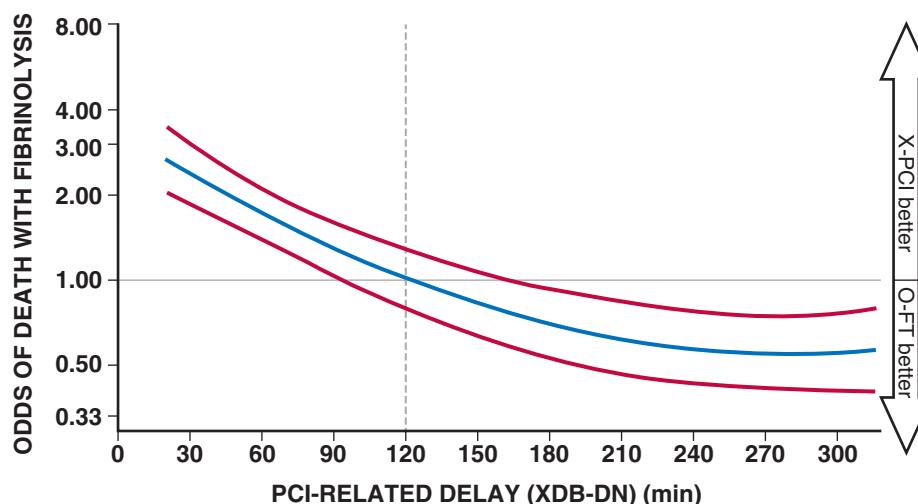
for subsequent procedures to reduce the risk for subsequent reinfarction. This approach is supported indirectly by retrospective analyses of trials of fibrinolytic therapy that suggest a lower risk for recurrent MI and a lower 2-year mortality rate in patients who subsequently undergo early PCI. The limited randomized trials evaluating a strategy of routine catheterization after fibrinolysis have provided mixed results. Nevertheless, overall, these trials have suggested improvement in clinical outcomes in patients transferred for early catheterization, particularly those at higher risk for death and recurrent ischemia (Fig. 52-13).<sup>1</sup> In the largest of these studies, TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; N = 1059), immediate transfer for angiography versus conservative care reduced the composite endpoint of death, recurrent MI, recurrent ischemia, new or worsening heart failure, or shock at 30 days.<sup>73</sup> In a meta-analysis that included seven randomized trials of early transfer for catheterization, a strategy of routine early catheterization after fibrinolysis was associated with a statistically significant reduction in the incidence of death or MI at 30 days and at 1 year without an increase in the risk for major bleeding.<sup>81</sup> Notably, the clinical trials that assessed routine invasive evaluation after initial fibrinolysis used a time window of 0 to 24 hours for the “early invasive” strategy, thus supporting earlier transfer after administration of fibrinolytic therapy, even for patients without high-risk features. Although we believe that there will probably be continued benefit even beyond 24 hours in patients with a patent but stenotic infarct artery after initial successful reperfusion, later time windows have not been directly examined. Because of the associated increased bleeding risk, very early (<2 to 3 hours) catheterization after the administration of fibrinolytic therapy with the intent to perform revascularization should be reserved for patients with evidence of failed fibrinolysis and significant myocardial jeopardy, for whom rescue PCI would be appropriate. In addition, when STEMI is suspected to have occurred by a mechanism other than thrombotic occlusion at the site of atherosclerotic plaque, coronary angiography may provide diagnostic information and direct specific therapy.

In summary, delayed coronary angiography with PCI of the infarct artery is indicated in patients initially treated with a noninvasive strategy (i.e., with fibrinolysis or without reperfusion therapy) who become unstable after cardiogenic shock, acute severe heart failure, or unstable postinfarction angina develops, provided that invasive management is not considered futile or inappropriate (Table 52-6).

Delayed PCI also appears to be reasonable in patients with failed fibrinolysis or reocclusion of the infarct artery or in those who demonstrate significant residual ischemia during hospitalization after initial noninvasive management. The benefits of routine (non-ischemia-driven) PCI on an angiographically significant stenosis in a patent infarct artery more than 24 hours after STEMI are less well established, and delayed PCI on a totally occluded infarct artery longer than 24 hours after STEMI should not be undertaken in clinically stable patients without evidence of severe ischemia.<sup>1</sup>

### Patients Not Eligible for Reperfusion Therapy

Aspirin and antithrombin therapy can be prescribed for patients who are not candidates for acute reperfusion because of lack of availability of PCI and contraindications to fibrinolysis. In the setting of absolute contraindications to fibrinolysis (see Table 52-4) and lack of access to PCI facilities, antithrombotic therapy should be initiated because of the small but finite chance



**FIGURE 52-12** Relationship between PCI-related delay (minutes) during transfer from a non-PCI-capable hospital to a PCI-capable hospital and in-hospital mortality. The dotted line represents 95% CIs. XDB-DN indicates transfer delay (transfer door-to-balloon minus door-to-needle time). With delays longer than 120 minutes between administration of a fibrinolytic on-site and balloon (or device) time at a receiving hospital, the on-site fibrinolytic strategy becomes preferable with respect to mortality risk when compared with transfer for PCI. O-FT = On-site fibrinolytic therapy. X-PCI = transfer PCI. (From Pinto DS, Frederick PD, Anjan K, et al: Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic as delays increase. Circulation 124:2518, 2011.)

**TABLE 52-6** Indications for Coronary Angiography in Patients Who Were Managed with Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

RECOMMENDATION	COR	LOE
Cardiogenic shock or acute severe HF that develops after initial evaluation	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B
Spontaneous or easily provoked myocardial ischemia	I	C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B
Stable* patients after successful fibrinolysis—before discharge and ideally between 3 and 24 hr	IIa	B

\*Although individual circumstances vary, clinical stability is defined as the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR = class of recommendation; HF = heart failure; LOE = level of evidence.

From O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 61:e78, 2013.

(≈10%) of restoring TIMI grade 3 flow in the infarct vessel and decreasing the chance of thrombotic complications of STEMI.

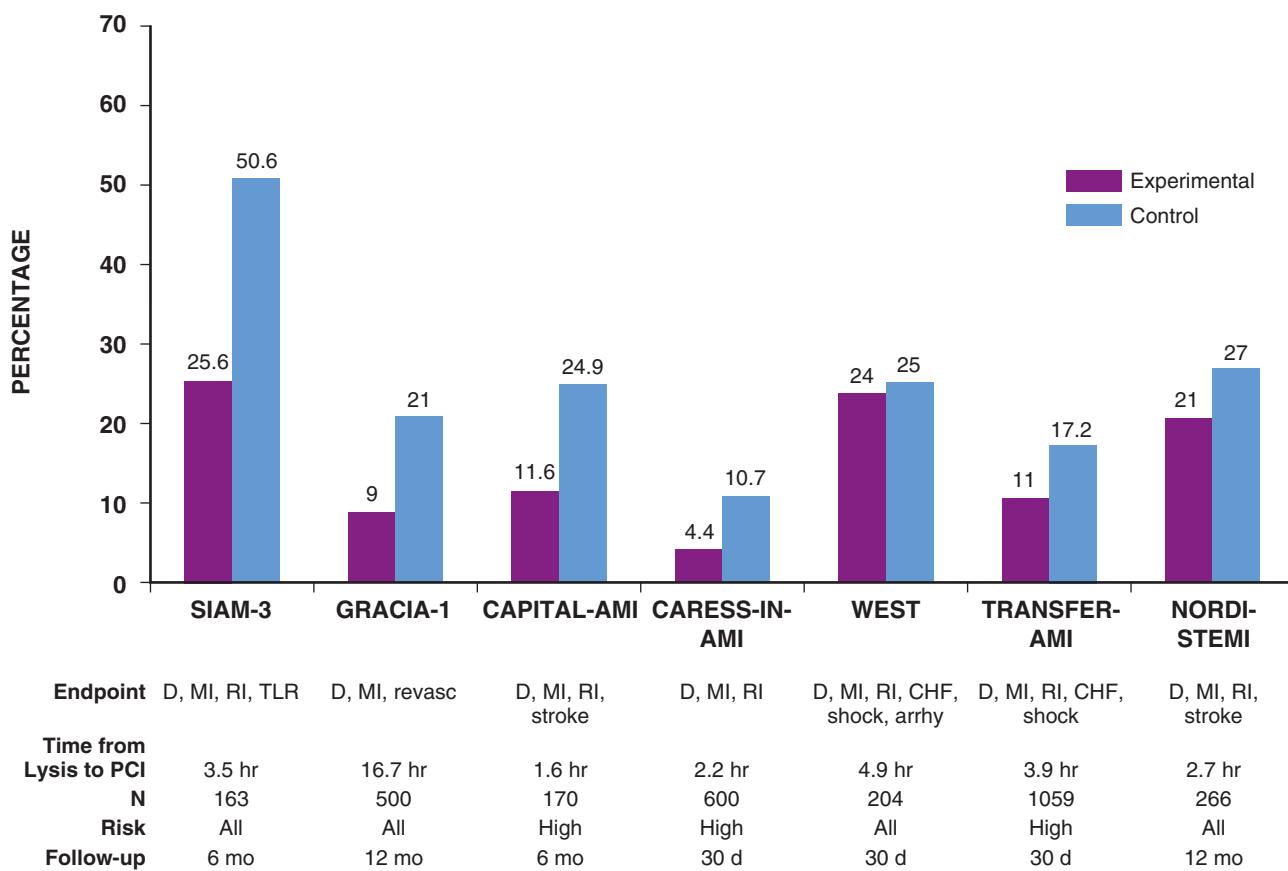
## Anticoagulant and Antiplatelet Therapy

### Anticoagulant Therapy

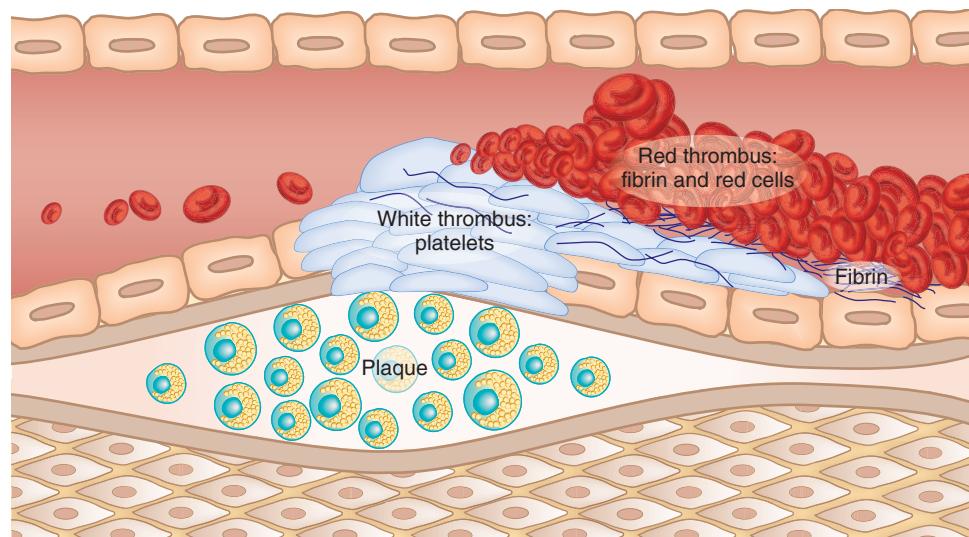
The rationale for administering anticoagulant therapy acutely to patients with STEMI includes establishing and maintaining patency of the infarct-related artery, regardless of whether a patient receives fibrinolytic therapy (Fig. 52-14), and preventing deep venous thrombosis, pulmonary embolism, ventricular thrombus formation, and cerebral embolization.

### Effect of Heparin on Mortality

Randomized trials of patients with STEMI conducted in the prefibrinolytic era showed a lower risk for reinfarction, pulmonary embolism, and stroke in those who received intravenous heparin, thus supporting the administration of heparin to STEMI patients not treated with fibrinolytic therapy. With the introduction of the fibrinolytic era and, importantly, after publication of the ISIS-2 (Second International Study of Infarct Survival) trial, the situation became more complicated because of strong evidence of a



**FIGURE 52-13** Primary outcome of trials of routine versus ischemia-driven (or delayed) catheterization and PCI after fibrinolytic therapy. Trials comparing routine early catheterization after fibrinolytic therapy with either an ischemia-driven approach or routine delayed catheterization generally showed a consistent pattern of benefit with a strategy of routine transfer for invasive evaluation. The darker bars represent patients who underwent routine early catheterization after fibrinolytic therapy. The lighter bars represent patients who underwent either an ischemia-guided or routine delayed catheterization approach. arrhy = arrhythmia; CAPITAL-AMI = Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction; CARESS-in-AMI = Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction; CHF = congestive heart failure; D = death; GRACIA = Grupo de Análisis de la Cardiopatía Isquémica Aguda; NORDISTEMI = Norwegian study on District treatment of ST-Elevation Myocardial Infarction; revasc = ischemia-driven revascularization; RI = recurrent ischemia; SIAM-3 = Southwest German Interventional Study In Acute Myocardial Infarction; TLR = target lesion revascularization; TRANSFER-AMI = Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction; WEST = Which Early ST-Elevated Myocardial Infarction Therapy. (Modified from O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e383, 2013.)



**FIGURE 52-14** Targets for therapy during reperfusion of patients with STEMI. This figure shows a schematic view of a longitudinal section of an infarct-related artery at the level of the obstructive thrombus. Following rupture of a vulnerable plaque (bottom center), the coagulation cascade is activated, which ultimately leads to the deposition of fibrin strands; platelets are activated and begin to aggregate. Platelets that aggregate with incorporation of relatively few red cells form a white thrombus. The mesh of fibrin strands and platelet aggregates obstructs flow in the infarct-related artery. Pharmacologic reperfusion is a multipronged approach consisting of fibrinolytic agents that digest fibrin, anticoagulants that prevent the formation of thrombin and inhibit the activity of formed thrombin, and antiplatelet therapy. (Modified from Jackson SP: Arterial thrombosis—insidious, unpredictable, and deadly. *Nat Med* 17:1423, 2011.)

substantial reduction in mortality with aspirin alone and confusing and conflicting data regarding the risk-benefit ratio of heparin used as an adjunct to aspirin or in combination with aspirin and a fibrinolytic agent.<sup>1</sup> Nevertheless, a meta-analysis of trials in the fibrinolytic era suggested that for every 1000 patients treated with heparin versus aspirin alone, five fewer deaths ( $P = 0.03$ ) and three fewer recurrent infarctions ( $P = 0.04$ ) occur, but at the expense of three more major bleeding episodes ( $P = 0.001$ ).<sup>82</sup>

**OTHER EFFECTS OF HEPARIN.** Several angiographic studies have examined the role of heparin therapy in establishing and maintaining patency of the infarct-related artery in patients with STEMI. Although evidence favoring the use of heparin for enhancing patency of the infarct artery when a fibrin-specific fibrinolytic agent is prescribed is not conclusive, the suggestion of a mortality benefit and amelioration of left ventricular thrombi after STEMI indicates that use of heparin for at least 48 hours after fibrinolysis is prudent.<sup>1</sup>

The most serious complication of anticoagulant therapy is bleeding (see Chapter 82), especially intracranial hemorrhage, when fibrinolytic agents are prescribed.<sup>83</sup> Major hemorrhagic events occur more frequently in patients with low body weight, advanced age, female sex, marked prolongation of the activated partial thromboplastin time (APTT) (>90 to 100 seconds), and performance of invasive procedures. Frequent monitoring of the APTT reduces the risk for major hemorrhagic complications in patients treated with heparin. It should be noted, however, that during the first 12 hours following fibrinolytic therapy, the APTT may be elevated as a result of the fibrinolytic agent alone (particularly if streptokinase is administered), thus making it difficult to accurately interpret the effects of a heparin infusion on the patient's coagulation status.

### Newer Antithrombotic Agents

Potential disadvantages of unfractionated heparin include dependency on antithrombin III for inhibition of thrombin activity, sensitivity to platelet factor 4, inability to inhibit clot-bound thrombin, marked interpatient variability in therapeutic response, and the need for frequent monitoring of the APTT. Even with standardized weight-based dosing nomograms, less than 35% of initial APTT measurements are within the therapeutic range.<sup>84</sup> An effort to circumvent these disadvantages of unfractionated heparin has stimulated interest in the development of alternative anticoagulants.

### HIRUDIN AND BIVALIRUDIN.

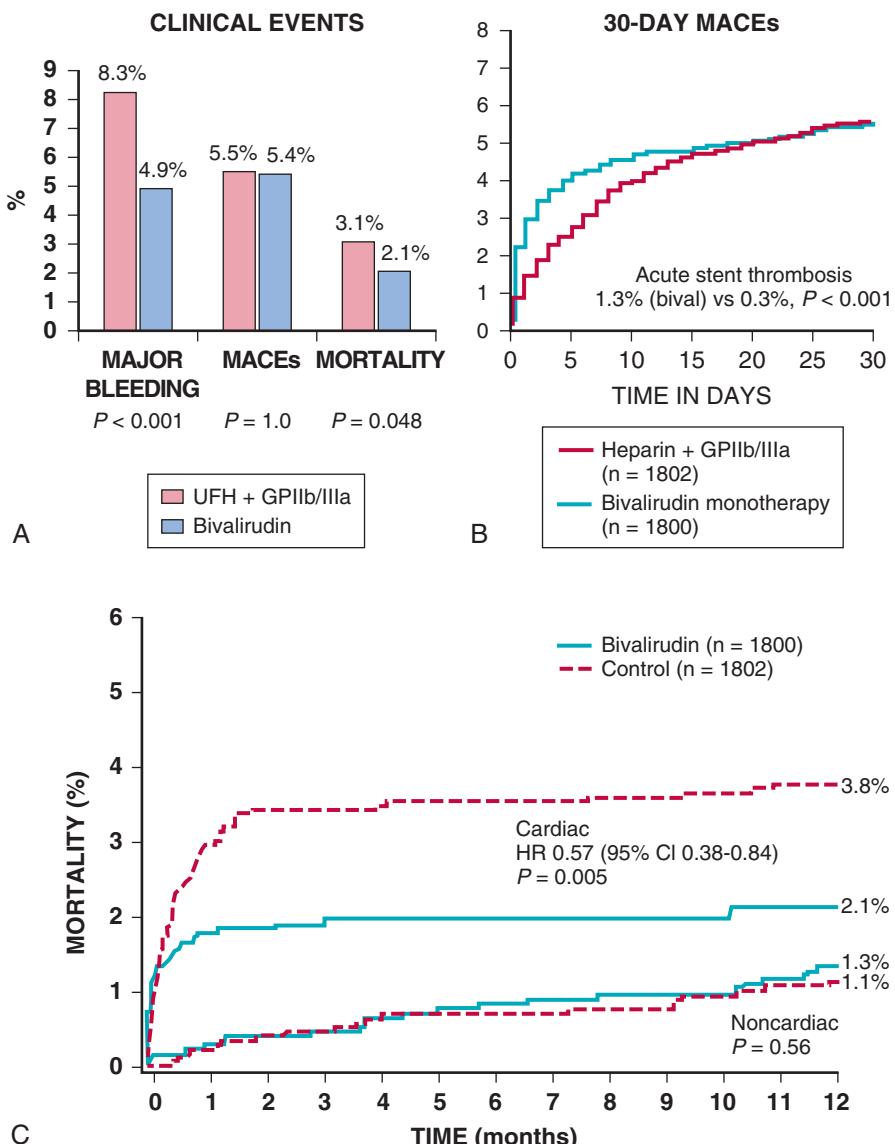
In patients undergoing fibrinolysis, direct thrombin inhibitors such as hirudin or bivalirudin reduce the incidence of recurrent MI by 25% to 30% when compared with heparin but have not reduced mortality. In addition, both hirudin and bivalirudin cause higher rates of major bleeding than heparin does when used with fibrinolytic agents.<sup>85</sup> In contrast, when administered for a short period as an adjunct to primary PCI in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, bivalirudin (open label), versus heparin plus glycoprotein (GP) IIb/IIIa inhibitors, resulted in a reduced 30-day rate of major bleeding or major adverse cardiovascular events, including death, reinfarction, target vessel revascularization for ischemia, and stroke (RR, 0.76; 95% confidence interval [CI], 0.63 to 0.92;  $P = 0.005$ ), driven by a significant 40% reduction in major bleeding. Importantly, treatment with bivalirudin significantly reduced mortality at 30 days and at 1 year (Fig. 52-15).<sup>86</sup> Bivalirudin

was associated with an increased early risk for stent thrombosis, thus demonstrating an early trade-off of bleeding and antithrombotic efficacy.<sup>87</sup> Additional studies have observed this increased early risk for stent thrombosis, with mixed results in terms of bleeding.<sup>87a,87b</sup>

**LOW-MOLECULAR-WEIGHT HEPARINS.** Advantages of low-molecular-weight heparins (LMWHs) include a stable, reliable anticoagulant effect, high bioavailability permitting administration via the subcutaneous route, and a high anti-Xa-to-anti-IIa ratio producing blockade of the coagulation cascade in an upstream location and resulting in a marked decrement in thrombin generation. When compared with unfractionated heparin, the rate of early (60 to 90 minutes) reperfusion of the infarct artery, assessed either angiographically or by noninvasive means, is not enhanced by the administration of LMWH. Rates of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events, however, appear to be reduced with LMWH.<sup>88</sup> This effect may underlie the significant reduction in recurrent MI with a strategy of extended anticoagulation with LMWHs, or a factor Xa antagonist versus standard therapy, in patients with STEMI undergoing fibrinolysis.

When compared with placebo, the LMWH reviparin significantly reduced the incidence of death, recurrent MI, or stroke at 30 days in 15,570 patients with STEMI, 73% of whom received a fibrinolytic (predominantly a non-fibrin-specific agent).<sup>89</sup> This important finding demonstrates not only that LMWHs are clinically effective for STEMI but also that a clinical anticoagulant therapy provides benefit as part of a pharmacologic reperfusion strategy in the fibrinolytic era.<sup>89</sup>

Several trials have compared a LMWH with unfractionated heparin as part of a pharmacologic reperfusion strategy and demonstrated the LMWH to be superior.<sup>89</sup> In the ASSENT (Assessment of the Safety and Efficacy of a New Thrombolytic) 3 trial, enoxaparin (30-mg intravenous bolus, followed by subcutaneous injections of 1 mg/kg every 12 hours until discharge from the hospital)<sup>90</sup> reduced 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia when compared with unfractionated heparin (RR, 0.74; 95% CI, 0.63 to 0.87). The rate of intracranial hemorrhage was similar with unfractionated heparin and enoxaparin (0.93% versus 0.88%;  $P = 0.98$ ). The EXTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction [25]) trial tested in a double-blind, double-dummy design the hypothesis that a strategy of enoxaparin (adjusted for age and renal function) administered for the duration of the index



**FIGURE 52-15** Results of an open-label randomized clinical trial comparing bivalirudin versus unfractionated heparin (UFH) and a GP IIb/IIIa receptor antagonist as adjunctive medical therapy to support primary PCI in patients with STEMI. **A**, Treatment with bivalirudin was associated with significantly lower rates of major bleeding and mortality at 30 days. **B**, Kaplan-Meier curves of the cumulative incidence of major adverse cardiac events (MACEs) did not differ between the two strategies at 30 days. **C**, Acute stent thrombosis during the first 24 hours was higher in patients treated with bivalirudin alone, but cardiovascular mortality was reduced in the bivalirudin group after 1 year of follow-up, thus providing strong evidence for this treatment strategy. (From Stone GW, Witzenbichler B, Guagliumi G, et al: Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 358:2218, 2008; and Mehran R, Lansky AJ, Witzenbichler B: Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomized controlled trial. *Lancet* 374:1149, 2009.)

hospitalization was superior to the conventional antithrombin strategy of administration of unfractionated heparin for 48 hours after fibrinolysis.<sup>91</sup> The primary endpoint of death or recurrent nonfatal MI through 30 days was reduced by 17% ( $P = 0.001$ ; Fig. 52-16A) with enoxaparin as compared with unfractionated heparin, with a 33% reduction ( $P = 0.001$ ) in reinfarction and a nonsignificant favorable trend on overall mortality ( $P = 0.11$ ). This improvement in recurrent MI was balanced against an increase in the incidence of major bleeding (1.4% and 2.1%,  $P = 0.001$ ). In a meta-analysis of trials of LMWH versus unfractionated heparin, LMWH clearly reduced recurrent MI but with a pattern of increased bleeding (Fig. 52-16B).

**PARENTERAL FACTOR Xa ANTAGONISTS.** The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial evaluated the specific factor Xa antagonist fondaparinux (2.5 mg subcutaneously) in 12,092 patients with STEMI.<sup>92</sup> The trial design

compared fondaparinux given for 8 days with placebo in patients when the treating physician thought that unfractionated heparin was not indicated (stratum I) and with unfractionated heparin for 48 hours when the treating physician thought that heparin was indicated (stratum II). Fondaparinux reduced the composite of death or reinfarction in stratum I (hazard ratio [HR], 0.79; 95% CI, 0.68 to 0.92), but not in stratum II (HR, 0.96; 95% CI, 0.81 to 1.13). Thus fondaparinux was superior to placebo (stratum I) but yielded results similar to those achieved with unfractionated heparin (stratum II). The outcome of patients in stratum II who underwent PCI tended to be worse when fondaparinux was used than when unfractionated heparin was used, probably because of an increased risk for catheter thrombosis.

**ORAL FACTOR IIA AND FACTOR Xa ANTAGONISTS.** See the section *Secondary Prevention of Acute Myocardial Infarction*.

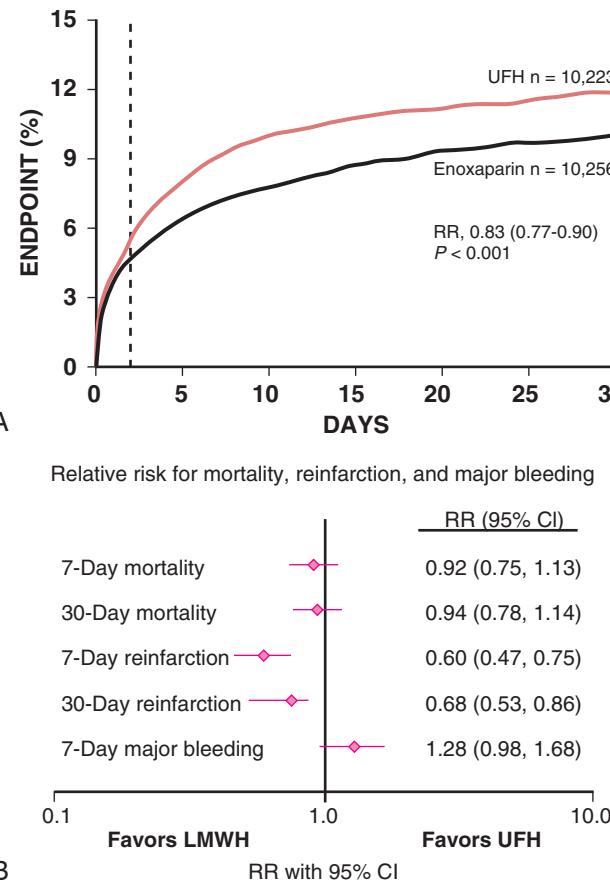
### Recommendations for Anticoagulant Therapy

**ANTICOAGULATION WITH FIBRINOLYSIS.** Given the pivotal role of thrombin in the pathogenesis of STEMI, antithrombotic therapy remains an important intervention (see Fig. 55-14). A regimen of an intravenous unfractionated heparin bolus of 60 units/kg to a maximum of 4000 units, followed by an initial infusion at 12 units/kg/hr to a maximum of 1000 units/hr for 48 hours, adjusted to maintain the APTT at 1.5 to 2 times control ( $\sim$ 50 to 70 seconds), is effective in patients receiving fibrinolytic therapy. However, infusions of unfractionated heparin are cumbersome to administer and provide unreliable levels of anticoagulation that require frequent measurements of the APTT to adjust the infusion rate.<sup>93</sup> In addition, because of the risk for heparin-induced thrombocytopenia with prolonged administration of unfractionated heparin, alternative anticoagulant regimens are preferred if administered for longer than 48 hours.<sup>1</sup>

Both the ExTRACT-TIMI 25 and OASIS-6 trials indicated that prolonged administration of an anticoagulant for the duration of hospitalization is beneficial when compared with the previous practice of administering unfractionated heparin only for 48 hours unless clear-cut indications for continued anticoagulation were present. Accordingly, patients managed with pharmacologic reperfusion therapy should receive anticoagulant therapy for a minimum

of 48 hours and preferably for the duration of hospitalization after STEMI, up to 8 days. Enoxaparin or fondaparinux is preferred when administration of an anticoagulant for longer than 48 hours is planned in patients with STEMI treated with a fibrinolytic.<sup>1</sup> Enoxaparin should be administered according to age, weight, and creatinine clearance and be given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization. Fondaparinux should be administered as an initial intravenous dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is higher than 30 mL/min. If PCI is performed in a patient treated with fondaparinux, coadministration of an additional antithrombin agent with anti-factor IIa activity is required.

In patients with a known history of heparin-induced thrombocytopenia, bivalirudin in conjunction with streptokinase is a useful



**FIGURE 52-16** Comparison of enoxaparin with unfractionated heparin (UFH) as adjunctive therapy in patients with STEMI receiving fibrinolysis. **A**, Primary results from the EXTRACT-TIMI 25 trial showing that the rate of the primary endpoint (death or nonfatal MI) at 30 days was significantly lower in the enoxaparin group than in the UFH group (9.9% versus 12%,  $P < 0.001$  by the log-rank test). The dashed vertical line indicates the comparison at day 2 (direct pharmacologic comparison), at which time a trend in favor of enoxaparin was seen. **B**, Results of a meta-analysis of seven randomized controlled clinical trials of LMWH versus UFH, including 27,577 patients with STEMI. Individual outcomes of all-cause death, reinfarction, and major bleeding through 7 days are shown. (From Antman EM, Morrow DA, McCabe CH, et al: Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354:1477, 2006; and Singh S, Bahekar A, Moinar J, et al: Adjunctive low molecular weight heparin during fibrinolytic therapy in acute ST-elevation myocardial infarction: A meta-analysis of randomized control trials. *Clin Cardiol* 32:358, 2009.)

alternative to heparin.<sup>1</sup> For patients who are referred for CABG, unfractionated heparin is the preferred antithrombin. When an alternative antithrombin has been used, it should be discontinued at a sufficiently long interval before surgery to avoid double anticoagulation when the patient enters the operating room and receives unfractionated heparin.

**ADJUNCTIVE ANTICOAGULATION FOR PRIMARY PERCUTANEOUS CORONARY INTERVENTION (See Chapter 55).** Either unfractionated heparin or bivalirudin is recommended as an anticoagulant to support primary PCI, with bivalirudin being preferred in patients at high risk for bleeding.<sup>1,86</sup> Fondaparinux is not recommended as the sole anticoagulant in this setting.<sup>1</sup> LMWH has not had sufficient evaluation in primary PCI to formulate recommendations for treatment. Some investigators who have used enoxaparin to support primary PCI for STEMI administer 0.5 mg/kg intravenously at the time of the procedure.

**PATIENTS TREATED WITHOUT REPERFUSION THERAPY.** Treatment with an anticoagulant is reasonable, and agents shown to be more effective than unfractionated heparin in other groups with STEMI may be preferable. For example, in patients with STEMI not receiving reperfusion therapy, fondaparinux reduces the composite

of death or recurrent MI without an increase in severe bleeding when compared with placebo or unfractionated heparin.<sup>94</sup>

### Antiplatelet Therapy

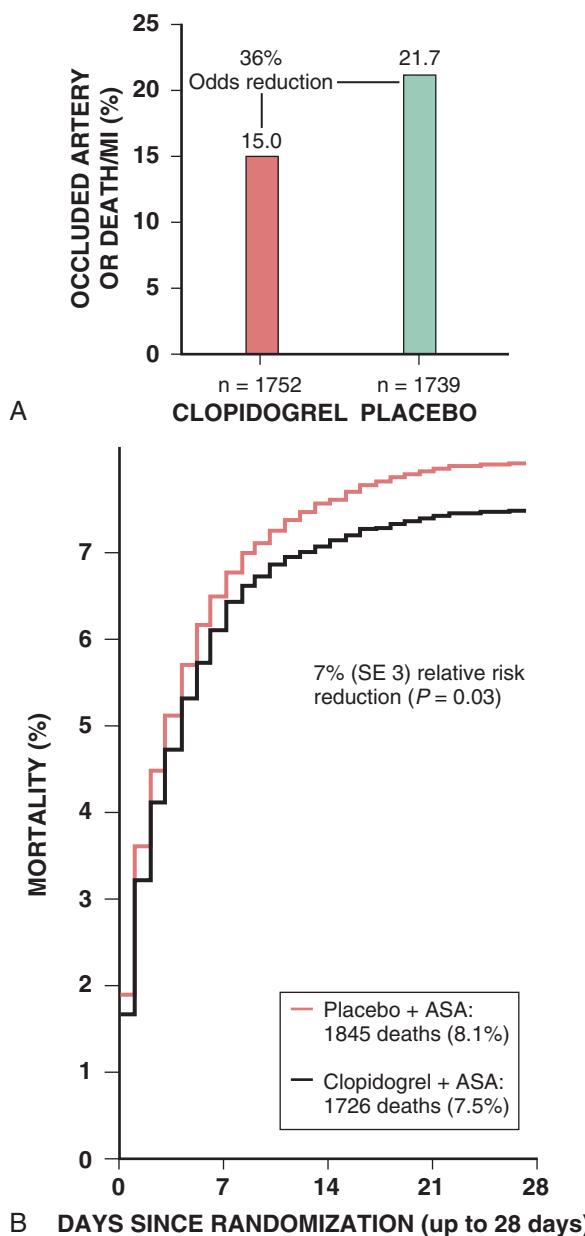
Platelets play a major role in the response to disruption of coronary artery plaque, especially in the early phase of thrombus formation. Platelets are also activated in response to fibrinolysis, and platelet-rich thrombi are more resistant to fibrinolysis than are fibrin and erythrocyte-rich thrombi (see Fig. 52-14). Thus a sound scientific basis exists for inhibiting platelet aggregation in *all* patients with STEMI, regardless of the reperfusion management strategy. The agent most extensively tested has been aspirin, and treatment with aspirin and a second antiplatelet agent—such as clopidogrel, prasugrel, or ticagrelor—has become the standard of care for patients with STEMI.

### Antiplatelet Therapy with Fibrinolysis

The ISIS-2 study was the largest trial of aspirin in patients with STEMI; it provided the single strongest piece of evidence that aspirin reduces mortality in such patients.<sup>95</sup> In contrast to the observations of a time-dependent mortality effect of fibrinolytic therapy, the reduction in mortality with aspirin was similar in patients treated within 4 hours (25% reduction in mortality), between 5 and 12 hours (21% reduction), and between 13 and 24 hours (21% reduction). An overall 23% reduction in mortality with aspirin occurred in ISIS-2 that was largely additive to the 25% reduction in mortality from streptokinase, so patients receiving both therapies experienced a 42% reduction in mortality. The reduction in mortality was as high as 53% in patients who received both aspirin and streptokinase within 6 hours of symptoms.

Obstructive platelet-rich arterial thrombi resist fibrinolysis and have an increased tendency for reocclusion after initial successful reperfusion in patients with STEMI. Despite inhibition of cyclooxygenase (COX) by aspirin, platelet activation leading to platelet aggregation and increased thrombin formation continues through thromboxane A<sub>2</sub>-independent pathways.<sup>21</sup> Adding other antiplatelet agents to aspirin has benefited patients with STEMI. Inhibitors of the P2Y<sub>12</sub> adenosine diphosphate receptor help prevent the activation and aggregation of platelets. In the CLARITY-TIMI (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction) 28 trial, addition of the P2Y<sub>12</sub> inhibitor clopidogrel to background treatment with aspirin in patients with STEMI who were younger than 75 years and received fibrinolytic therapy reduced the risk for clinical events (death, reinfarction, stroke) and reocclusion of a successfully reperfused infarct artery (Fig. 52-17).<sup>96</sup> An ST Resolution (STRes) electrocardiographic sub-study from CLARITY-TIMI 28 provided insight into the mechanism of the benefit of clopidogrel in STEMI. No difference was seen in the rate of complete STRes between the clopidogrel and placebo groups at 90 minutes (38.4% versus 36.6%). When patients were stratified by STRes category, treatment with clopidogrel resulted in greater benefit in those with evidence of early STRes, with greater odds of having an open artery at late angiography in patients with partial (odds ratio [OR], 1.4;  $P = 0.04$ ) or complete (OR, 2;  $P = 0.001$ ) STRes, but no improvement in those with no STRes evident at 90 minutes (OR, 0.89;  $P = 0.48$ ) ( $P$  for interaction = 0.003). Clopidogrel was also associated with a significant reduction in the odds for in-hospital death or MI in patients who achieved partial (OR, 0.30;  $P = 0.003$ ) or complete STRes at 90 minutes (OR, 0.49;  $P = 0.056$ ), whereas clinical benefit was not apparent in patients who had no STRes (OR, 0.98;  $P = 0.95$ ) ( $P$  for interaction = 0.027). Thus it appears that clopidogrel did not increase the rate of complete opening of occluded infarct arteries when fibrinolysis was administered but was highly effective in preventing reocclusion of an initially reperfused infarct artery.

In COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial), 45,852 patients with suspected MI were randomly assigned to clopidogrel, 75 mg/day (without a loading dose), or placebo in addition to aspirin, 162 mg/day (Fig. 52-17).<sup>96</sup> Patients in the clopidogrel group had a lower rate of the composite endpoint of death, reinfarction, or stroke (9.2% versus 10.1%;  $P = 0.002$ ). They also had a significantly lower rate of death (7.5% versus 8.1%;  $P = 0.03$ ). No excessive bleeding with clopidogrel occurred in this trial.



**FIGURE 52-17** Impact of the addition of clopidogrel to aspirin (ASA) in patients with STEMI. **A**, Effects of the addition of clopidogrel in patients receiving fibrinolysis for STEMI. Patients in the clopidogrel group ( $n = 1752$ ) had a 36% reduction in the odds of dying, sustaining a recurrent infarction, or having an occluded infarct artery in comparison to the placebo group ( $n = 1739$ ) in the CLARITY-TIMI 28 trial. **B**, Effect of the addition of clopidogrel on in-hospital mortality after STEMI. These time-to-event curves show a 0.6% reduction in mortality in the group receiving clopidogrel plus aspirin ( $n = 22,961$ ) versus placebo plus aspirin ( $n = 22,891$ ) in the COMMIT trial. (**A**, Modified from Sabatine MS, Cannon CP, Gibson CM, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352:1179, 2005; **B**, modified from Chen ZM, Jiang LX, Chen YP, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet* 366:1607, 2005.)

### Combination Pharmacologic Reperfusion

Several studies evaluated the combination of platelet GP IIb/IIIa inhibitors and fibrinolytics. Trials of GP IIb/IIIa inhibitors combined with either full or reduced doses of fibrinolytics showed improvements in reperfusion, including myocardial perfusion as reflected in enhanced ST-segment resolution and faster angiographic frame counts. However, subsequent large outcomes trials revealed no significant effect on survival and reductions in reinfarction that were outweighed

by the increases in bleeding.<sup>90</sup> The combination of a GP IIb/IIIa inhibitor and a fibrinolytic as a pharmacologic reperfusion regimen is therefore not recommended.<sup>1</sup>

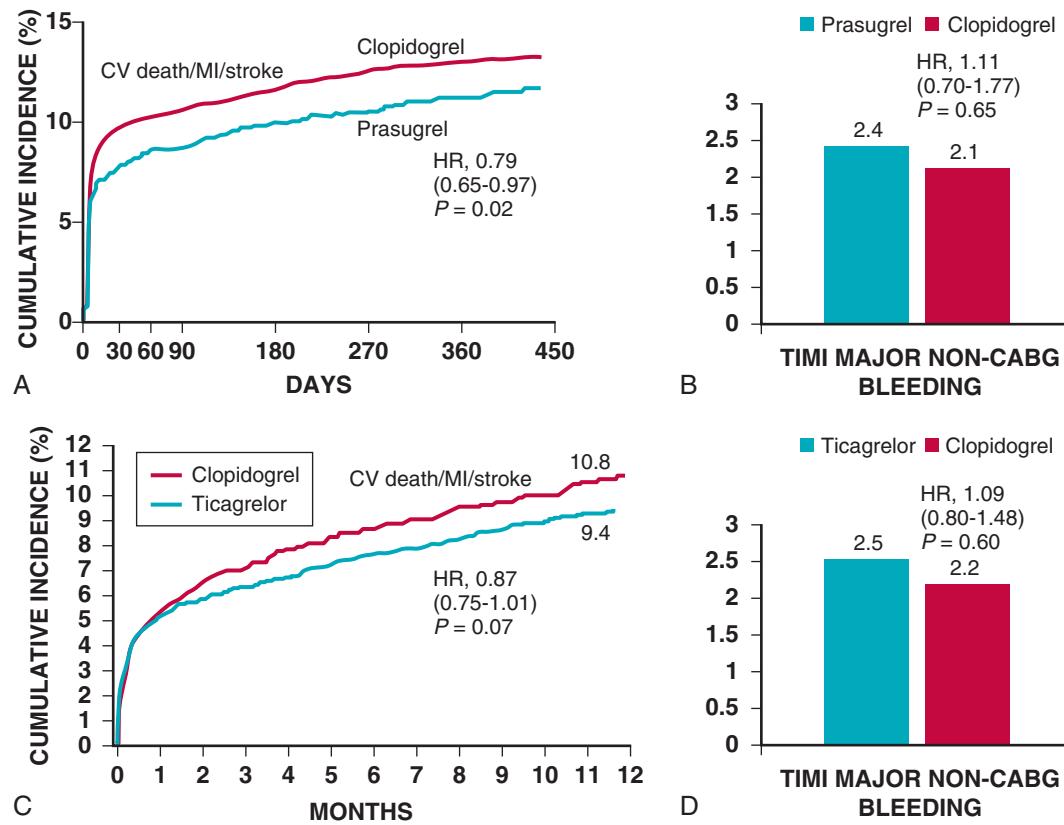
### Antiplatelet Therapy for Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction (See Chapter 55)

All patients with STEMI should receive aspirin as soon as possible after initial encounter in the absence of contraindications. Adding the P2Y<sub>12</sub> inhibitor clopidogrel to aspirin appears to offer additional benefit in patients undergoing PCI after STEMI. An analysis of the subgroup of patients who underwent PCI in the CLARITY-TIMI 28 trial showed that pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, MI, or stroke following PCI (3.6% versus 6.2%;  $P = 0.008$ ).<sup>1,97</sup> Pretreatment with clopidogrel also reduced the incidence of MI or stroke before PCI (4% versus 6.2%;  $P = 0.03$ ). There was no significant excess in rates of TIMI major or minor bleeding (2% versus 1.9%;  $P = 0.99$ ). As part of the PCI-CLARITY (PCI-Clopidogrel as Adjunctive Reperfusion Therapy) study, the investigators performed a meta-analysis of PCI-CLARITY, PCI-CURE (PCI-Clopidogrel in Unstable angina to prevent Recurrent Events), and CREDO (Clopidogrel for the Reduction of Events During Observation) and found that pretreatment with clopidogrel significantly reduced the risk for 30-day cardiovascular death or MI. A subsequent meta-analysis included data from randomized trials and registries of patients with CAD (stable or with an ACS) undergoing catheterization for potential revascularization to evaluate the association between pretreatment with clopidogrel and outcomes after PCI. Higher-risk STEMI patients had a lower risk for major coronary events with clopidogrel pretreatment, but not a reduction in mortality or an increase in bleeding.<sup>98</sup> Regarding dose, in CURRENT-OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Syndromes), which included a population in which 29% had STEMI, doubling the standard dose of clopidogrel (loading dose of 600 mg, daily dose of 150 mg) for the first 7 days did not improve outcome in the overall ACS population referred for an invasive strategy, but there was benefit in ACS patients who actually underwent PCI.<sup>99,100</sup>

In patients undergoing either primary PCI or delayed PCI after initial therapy for STEMI, the more potent P2Y<sub>12</sub> inhibitor prasugrel has been superior to clopidogrel in reducing the risk for cardiovascular death, MI, or stroke.<sup>101</sup> In the subgroup of patients with STEMI enrolled in TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) ( $N = 3534$ ), this endpoint was lowered by 32% at 30 days with prasugrel as compared with aspirin (6.5% versus 9.5%;  $P = 0.0017$ ) and by 21% at 15 months (10.0% versus 12.4%;  $P = 0.022$ ) (Fig. 52-18).<sup>102</sup> Prasugrel reduced definite or probable stent thrombosis by 42% when compared with clopidogrel.<sup>102</sup> Analogously, in the PLATO (Platelet Inhibition and Patient Outcomes) trial, when compared with clopidogrel, treatment with the reversible P2Y<sub>12</sub> inhibitor ticagrelor in patients with STEMI undergoing primary PCI ( $N = 7544$ ) tended to reduce the primary endpoint of cardiovascular death, recurrent MI, or stroke by 13%, a magnitude similar to that for the overall trial population (Fig. 52-18); there was a 26% reduction in definite or probable stent thrombosis and an 18% reduction in all-cause mortality also occurred.<sup>103</sup> A discussion of the use of GP IIb/IIIa inhibitors as part of adjunctive therapy for patients with STEMI undergoing PCI is presented in Chapter 55.

### Recommendations for Antiplatelet Therapy

Patients who have not taken aspirin before the development of STEMI should chew non-enteric-coated aspirin, and the dose should be 162 to 325 mg initially. During the maintenance phase of antiplatelet therapy following STEMI, the dose of aspirin is preferably reduced to 75 to 162 mg to minimize the risk for bleeding.<sup>1</sup> Lower doses are preferable because of the increased risk for bleeding with higher



**FIGURE 52-18** **A**, Efficacy of prasugrel in the subgroup of patients with STEMI enrolled in a randomized clinical trial of prasugrel versus clopidogrel in patients undergoing PCI after an ACS. Treatment with prasugrel was associated with a 21% relative reduction in the risk for cardiovascular (CV) death, MI, or stroke during 15 months of follow-up. **B**, Major bleeding (TIMI non-CABG) increased with prasugrel in the trial overall, but not in patients with STEMI. **C**, Efficacy results for ticagrelor (versus clopidogrel) in patients with STEMI enrolled in the PLATO trial. Ticagrelor reduced the primary endpoint (incidence of MI, stroke, or vascular death) versus clopidogrel from 11.0% to 9.3% (HR, 0.85; 95% CI, 0.74 to 0.97; P = 0.02). **D**, Rates of major bleeding (TIMI non-CABG) are shown. (**A, B**, From Montalescot G, Wiviott SD, Braunwald E, et al: Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction [TRITON-TIMI 38]: Double-blind, randomised controlled trial. Lancet 373:723, 2009; **C, D**, from Steg PG, James S, Harrington RA, et al: Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 122:2131, 2010.)

doses reported in several studies; the CURRENT-OASIS 7 trial did not find differences in terms of efficacy or safety in STEMI patients randomly assigned to 81 versus 325 mg of aspirin. If true aspirin allergy is present, other antiplatelet agents such as clopidogrel or ticlopidine can be substituted.

The addition of a P2Y<sub>12</sub> inhibitor to aspirin is warranted in most patients with STEMI.<sup>1</sup> Based on the results of the COMMIT and CLARITY-TIMI 28 trials, clopidogrel, 75 mg/day orally, is an option for all patients with STEMI regardless of whether they receive fibrinolytic therapy, undergo primary PCI, or do not receive reperfusion therapy. The data available suggest that a loading dose of 300 mg of clopidogrel should be given to patients younger than 75 years who receive fibrinolytic therapy. Data are insufficient in elderly patients to recommend a loading dose in those 75 years or older who receive a fibrinolytic.

When primary PCI is the mode of reperfusion therapy, an oral loading dose of 600 mg of clopidogrel before stent implantation is an established treatment, followed by 75 mg daily.<sup>1,6</sup> Notably, interpatient variability in the response to clopidogrel can occur, and individuals with lesser degrees of platelet inhibition are at increased risk for death and ischemic complications.<sup>104</sup> One potential source of this variability is the metabolism of clopidogrel, which is a prodrug that requires absorption and biotransformation to become an active antiplatelet compound. Cytochrome P-450 (CYP) enzymes play a role in the metabolism, and carriers of particular genetic variants in CYP2C19 (~30% of the population) have lower active clopidogrel metabolite levels, diminished platelet inhibition, and higher rates of adverse

cardiovascular events than do noncarriers in the setting of PCI.<sup>105-107</sup> The response to clopidogrel may also vary as a function of a patient's clinical characteristics, such as age or diabetic status.<sup>104</sup>

Prasugrel and ticagrelor generally achieve greater degrees of platelet inhibition than clopidogrel does and can be used to treat patients with STEMI. On the basis of the results of TRITON-TIMI 38, prasugrel administered as an oral loading dose of 60 mg and 10 mg daily thereafter demonstrated benefit in patients with STEMI, but should not be used in patients with a history of cerebrovascular disease who are at higher risk for life-threatening bleeding.<sup>101,102</sup> Ticagrelor also reduced cardiovascular events when compared with clopidogrel, and in PLATO, ticagrelor was administered as an oral loading dose of 180 mg and 90 mg twice daily.<sup>103,108</sup> When using ticagrelor, the recommended maintenance dose of aspirin is 81 mg daily.<sup>1</sup>

## HOSPITAL MANAGEMENT

### Coronary Care and Intermediate Care Units

Development of the coronary care unit (CCU) has facilitated continuous monitoring of cardiac rhythm by highly trained nurses with the skills and authority to initiate immediate treatment of arrhythmias in the absence of physicians and with the availability of specialized equipment (defibrillators, pacemakers) and drugs.<sup>109</sup> The clustering of patients with STEMI in the CCU greatly enhanced efficient use of the trained personnel, facilities, and equipment to improve patient outcomes.<sup>109</sup> These benefits of geographic clustering contribute to the

optimal care of patients with STEMI, and in some hospitals, such care can be provided in “intermediate care” telemetry units with well-trained staff outside the CCU. Such intermediate care units, when equipped with continuous electrocardiographic monitoring and resuscitation equipment, may be appropriate for initial admission of patients with a low risk for mortality from STEMI. This strategy has proved cost-effective and may reduce CCU use by a third, shorten hospital stays, and have no deleterious effect on patients’ recovery.<sup>1</sup>

With increasing attention directed to limitations on resources and to the economic impact of intensive care, the proportion of appropriately selected patients with STEMI cared for in an intermediate care unit is likely to increase. Nevertheless, a dedicated CCU is the environment most often used to provide care for patients with STEMI, and it plays a pivotal role in the management of patients with major complications of STEMI, who may require treatment of refractory arrhythmias, use of invasive hemodynamic monitoring, or mechanical circulatory support.<sup>10</sup> Facilities in which patients can undergo diagnostic and therapeutic angiographic procedures are often integrated into the structure of a coronary care team.<sup>11</sup> The capacity for early detection of problems following STEMI and the social and educational benefits of grouping such patients together strongly argue for continued use of CCUs and intermediate care units with experienced multidisciplinary staff.

In patients with STEMI managed in a CCU, those with an uncomplicated status, such as patients without congestive heart failure, hypotension, heart block, hemodynamically compromising ventricular arrhythmias, or persistent ischemic-type discomfort, can be safely transferred out of the CCU within 24 to 36 hours. In patients with complicated STEMI, the duration of the CCU stay should be dictated by the need for “intensive” care—that is, hemodynamic monitoring, close nursing supervision, intravenous vasoactive drugs, and frequent changes in the medical regimen.

### General Measures

The managing clinical staff should be sensitive to patient concerns about prognosis and future productivity. A calm, quiet atmosphere can help allay anxiety and reduce sympathetic tone, thereby potentially reducing hypertension, tachycardia, and arrhythmias. Use of anxiolytic medications may be appropriate in some cases. To reduce the risk for nausea and vomiting early after infarction and to decrease the risk for aspiration, patients should receive either nothing by mouth or a clear liquid diet during the first 4 to 12 hours after admission. Thereafter, dietary intervention is an important component of an overall strategy for secondary prevention (see Chapters 42 and 46).

The results of laboratory tests should be scrutinized for any derangements potentially contributing to arrhythmias, such as hypoxemia, hypovolemia, or disturbances in acid-base balance or electrolytes. Delirium can be provoked by medications frequently used in the hospital, including antiarrhythmic drugs, H<sub>2</sub> blockers, narcotics, and beta blockers. Use of potentially offending agents should be discontinued in patients with an abnormal mental status. Haloperidol, a butyrophenone, can be used safely in patients with STEMI. Stool softeners should be considered to prevent constipation and straining.

### Physical Activity

In the absence of complications, stabilized patients with STEMI need not be confined to bed for more than 12 hours, and unless they are hemodynamically compromised, they may use a bedside commode shortly after admission. Progression of activity should be individualized depending on the patient’s clinical status, age, and physical capacity. In patients without hemodynamic compromise, early mobilization—including sitting in a chair, standing, and walking around the bed—does not usually cause important changes in heart rate, blood pressure, or pulmonary wedge pressure. As long as the blood pressure and heart rate are monitored, early mobilization offers considerable psychological and physical benefit without any clear medical risk.

## Pharmacologic Therapy

### Beta Blockers

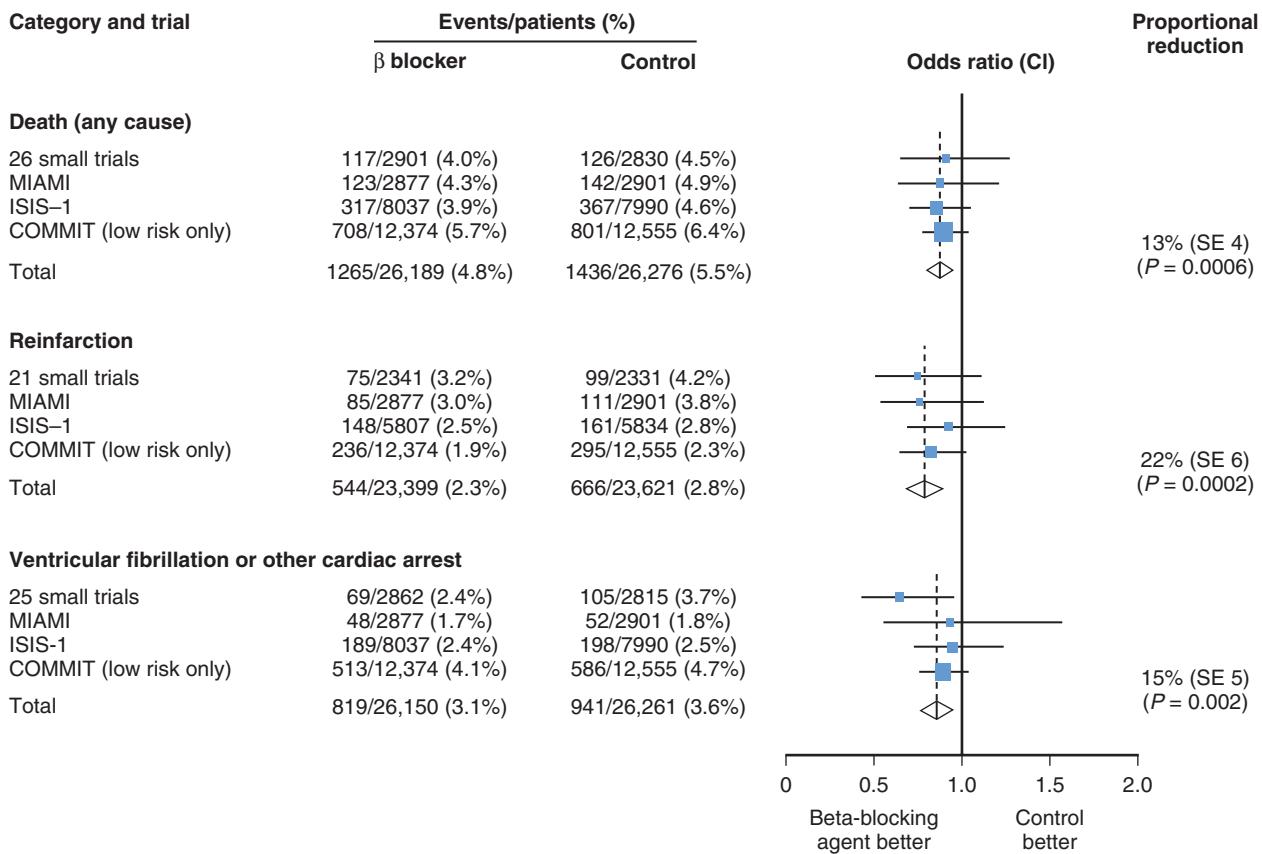
Use of beta blockers for the treatment of patients with STEMI can cause both immediate effects (when the drug is given early in the course of infarction) and long-term effects (secondary prevention). Immediate intravenous administration of beta blockers reduces the cardiac index, heart rate, and blood pressure.<sup>12</sup> The net effect is a reduction in myocardial oxygen consumption per minute and per beat. Favorable effects of acute intravenous administration of beta blockers on the balance of myocardial oxygen supply and demand are reflected in reductions in chest pain, in the proportion of patients with threatened infarction in whom STEMI actually evolves, and in the development of ventricular arrhythmias. Because beta-adrenergic blockade diminishes circulating levels of free fatty acids by antagonizing the lipolytic effects of catecholamines and because elevated levels of fatty acids augment myocardial oxygen consumption and probably increase the incidence of arrhythmias, these metabolic actions of beta blockers may also benefit the ischemic heart. As noted earlier, because early administration of intravenous beta blockers can cause detrimental effects in some patients, the present guidelines omit this therapy for most patients.<sup>1</sup>

More than 52,000 patients have been randomly assigned to treatment in clinical trials studying beta-adrenergic blockade for acute MI.<sup>1</sup> These trials cover a range of beta blockers and timing of administration and were largely conducted in the era before reperfusion strategies were developed for STEMI. Data available in the pre-reperfusion era suggested favorable trends toward a reduction in mortality, reinfarction, and cardiac arrest. In the reperfusion era, adding an intravenous beta blocker to fibrinolytic therapy was not associated with a reduction in mortality but helped reduce the rate of recurrent ischemic events. Concern arose regarding the potential risk of provoking cardiogenic shock if early intravenous followed by oral beta-adrenergic blockade was routinely administered to all patients with STEMI. The largest trial of beta blockade in patients with acute MI was COMMIT, which randomly assigned 45,852 patients within 24 hours of MI to metoprolol given as sequential intravenous boluses of 5 mg up to 15 mg, followed by 200 mg/day orally, or to placebo.<sup>1</sup> The rate of the composite endpoint of death, reinfarction, or cardiac arrest in the metoprolol group (9.4%) did not differ from that in the placebo group (9.9%). Significant reductions occurred in reinfarction and episodes of VF in the metoprolol group, which translated into 5 fewer events for each of these endpoints per 1000 patients treated; yet there were 11 more episodes of cardiogenic shock in the metoprolol group per 1000 patients treated. Risk for the development of cardiogenic shock (which was recorded as part of the COMMIT protocol in contrast to earlier studies) was greatest in patients with moderate to severe left ventricular dysfunction (Killip class II or greater).

The combined results of the low-risk patients from COMMIT and data from earlier trials provide an overview of the effects of early intravenous therapy followed by oral therapy with beta blockers (Fig. 52-19). A 13% reduction occurred in all-cause mortality (7 lives saved per 1000 patients treated), along with a 22% reduction in reinfarction (5 fewer events per 1000 patients treated) and a 15% reduction in VF or cardiac arrest (5 fewer events per 1000 patients treated). To achieve these benefits safely, early administration of beta blockers to patients with relative contraindications should be avoided, as outlined in Table 52-7.

### Recommendations

Given the evidence of a benefit of early administration of beta-blocking agents for STEMI, patients without a contraindication, irrespective of the administration of concomitant fibrinolytic therapy or performance of primary PCI, should receive *oral* beta blockers within the first 24 hours (Table 52-7). Prompt intravenous administration of beta-blocking therapy to patients with STEMI is also reasonable if a tachyarrhythmia or hypertension is present, in the absence of signs of heart failure/low output, increased risk for the development of



**FIGURE 52-19** Meta-analysis of the effects of intravenous and then oral beta-blocker therapy on death, reinfarction, and cardiac arrest during the scheduled treatment periods in 26 small randomized trials, MIAMI, ISIS-1, and the low-risk subset of COMMIT. For COMMIT, data are included only for patients with a systolic blood pressure higher than 105 mm Hg, a heart rate greater than 65 beats/minute, and Killip class I (as in MIAMI). Five small trials included in the ISIS-1 report did not have any data on reinfarction. In the ISIS-1 trial, data on reinfarction in the hospital were available for the last three quarters of the study and involved 11,641 patients. ORs in each (blue squares with the area proportional to the number of events) were determined by comparing outcomes in patients allocated to beta-blocker therapy with those in patients allocated to control, along with 99% CIs (horizontal lines). Overall ORs and 95% CIs are plotted by the diamonds, with value and significance given alongside. (From Chen ZM, Pan HC, Chen YP, et al: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet 366:1622, 2005.)

**TABLE 52-7** Recommendations for Beta Blocker Therapy for ST-Elevation Myocardial Infarction

RECOMMENDATION	COR	LOE
Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: Signs of heart failure or evidence of a low-output state Increased risk for cardiogenic shock*: Age > 70 years Systolic blood pressure <120 mm Hg Sinus tachycardia >110 beats/min or heart rate <60 beats/min Increased time since the onset of symptoms of STEMI Other contraindications to use of oral beta blockers: PR interval longer than 0.24 second Second- or third-degree heart block Active asthma or reactive airways disease	I	B
Beta blockers should be continued during and after hospitalization for all patients with STEMI and no contraindications to their use.	I	B
Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility.	I	C
It is reasonable to administer IV beta blockers at initial encounter to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.	IIa	B

\*The greater the number of risk factors present, the higher the risk for development of cardiogenic shock.

COR = class of recommendation; LOE = level of evidence.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 61:e78, 2013.

shock, indicators of high risk for the development of shock, or other relative contraindications to beta blockers.<sup>1</sup>

Beta blockers are especially helpful in STEMI patients with significant residual unrevascularized CAD and evidence of recurrent ischemia or tachyarrhythmias early after the onset of infarction.<sup>113</sup> If adverse effects of beta blockers develop or if patients have complications of infarction that are contraindications to beta blockade, such as heart failure or heart block, beta blockers should be withheld. Unless there are contraindications (Table 52-7), beta blockade probably should be continued in patients in whom STEMI develops. Moreover, patients who initially have contraindications to a beta blocker, such as heart failure, should be reevaluated with respect to their candidacy for such therapy after 24 hours.<sup>1</sup>

### Selection of Beta Blockers

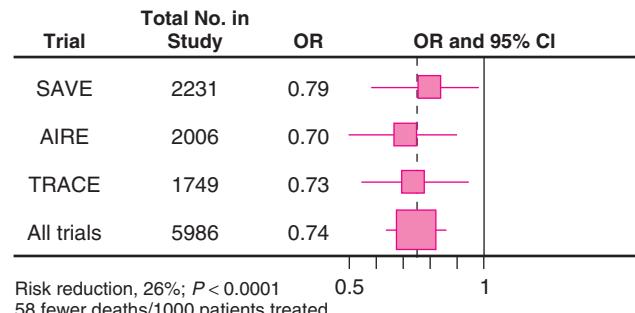
Favorable effects have been reported with metoprolol, atenolol, carvedilol, timolol, and alprenolol; these benefits probably occur with propranolol and with esmolol, an ultrashort-acting agent, as well. In the absence of any favorable evidence supporting the benefit of agents with intrinsic sympathomimetic activity, such as pindolol and oxprenolol, and with some unfavorable evidence for these agents in secondary prevention, beta blockers with intrinsic sympathomimetic activity should probably not be chosen for treatment of STEMI. The CAPRICORN (CArvedilol Post infarction survIval COntrol in left ventricular dysfunction) trial randomly assigned 1959 patients with MI and systolic dysfunction (ejection fraction <40%) to carvedilol or placebo in addition to contemporary pharmacotherapy, including angiotensin-converting enzyme (ACE) inhibitors in 98% of patients. All-cause mortality was reduced over a mean follow-up of 1.3 years by 23% with carvedilol in comparison to placebo ( $P = 0.031$ ), with a similar pattern noted during the first 30 days.<sup>114</sup> Thus CAPRICORN confirmed the benefit of administration of a beta blocker in addition to ACE inhibitor therapy in patients with transient or sustained left ventricular dysfunction after MI.

Occasionally, clinicians may wish to proceed with therapy with a beta blocker even in patients with relative contraindications, such as a history of mild asthma, mild bradycardia, mild heart failure, or first-degree heart block. In this situation a trial of esmolol may help determine whether the patient can tolerate beta-adrenergic blockade. Because the hemodynamic effects of this drug, which has a half-life of 9 minutes, disappear in less than 30 minutes, it offers an advantage over longer-acting agents when the risk for complications with a beta blocker is relatively high.

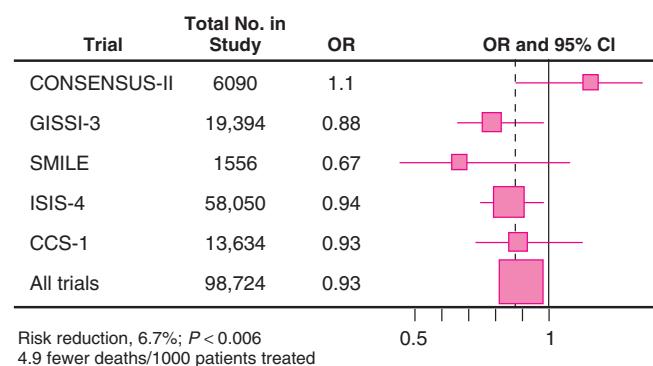
### Inhibition of the Renin-Angiotensin-Aldosterone System

The rationale for inhibition of the renin-angiotensin-aldosterone system (RAAS) includes experimental and clinical evidence of a favorable impact on ventricular remodeling, improvement in hemodynamics, and a reduction in the incidence of congestive heart failure. Unequivocal evidence from randomized, placebo-controlled trials has shown that ACE inhibitors reduce the rate of mortality from STEMI.<sup>1</sup> These trials can be grouped into two categories. The first group selected MI patients for randomization on the basis of features indicative of increased mortality, such as left ventricular ejection fraction lower than 40%, clinical signs and symptoms of congestive heart failure, anterior location of infarction, and abnormal wall motion score index (Fig. 52-20). The second group consisted of unselective trials that randomized all patients with MI provided that they had a minimum systolic pressure of approximately 100 mm Hg (ISIS-4, GISSI-3 [Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico], CONSENSUS II [Cooperative New Scandinavian Enalapril Survival Study II], and the Chinese Captopril Study) (Fig. 52-21). With the exception of the SMILE (Survival of Myocardial Infarction Long-Term Evaluation) study, all the selective trials initiated ACE inhibitor therapy between 3 and 16 days after MI and maintained it for 1 to 4 years, whereas the unselective trials all initiated treatment within the first 24 to 36 hours and maintained it for only 4 to 6 weeks.

A consistent survival benefit was observed in all the trials already noted, except for CONSENSUS II, the one study that used an



**FIGURE 52-20** Effect of ACE inhibitors on mortality after MI—results from long-term trials. (From Gornik H, O’Gara PT: Adjunctive medical therapy. In Manson JE, Buring JE, Ridker PM, Gaziano JM [eds]: Clinical Trials in Heart Disease: A Companion to Braunwald’s Heart Disease. Philadelphia, Saunders, 2004, p 114.)



**FIGURE 52-21** Effects of ACE inhibitors on mortality after MI—results from short-term trials. (From Gornik H, O’Gara PT: Adjunctive medical therapy. In Manson JE, Buring JE, Ridker PM, Gaziano JM [eds]: Clinical Trials in Heart Disease: A Companion to Braunwald’s Heart Disease. Philadelphia, Saunders, 2004, p 114.)

intravenous preparation early in the course of MI. An estimate of the mortality benefit of ACE inhibitors in the unselective trials with a short duration of therapy was 5 lives saved per 1000 patients treated. Analysis of these unselective short-term trials indicates that approximately a third of the lives saved occurred within the first 1 to 2 days. Certain subgroups, such as patients with anterior infarction, showed proportionately greater benefit with the early administration (11 lives saved per 1000) of ACE inhibitors. Not unexpectedly, greater survival benefits of 42 to 76 lives saved per 1000 patients treated were obtained in the selective trials with a long duration of therapy. Of note, a general 20% reduction in the risk for death attributable to ACE inhibitor treatment occurred in the selective trials. The reduction in mortality with ACE inhibitors was accompanied by significant reductions in the development of heart failure, thus supporting the underlying pathophysiological rationale for administering this class of drugs to patients with STEMI. In addition, some data suggest that chronic administration of ACE inhibitors after STEMI reduces the incidence of ischemic events, including recurrent infarction and the need for coronary revascularization.<sup>29</sup>

The mortality benefits of ACE inhibitors are additive to those achieved with aspirin and beta blockers. The benefits of ACE inhibition appear to be a class effect inasmuch as several agents have been associated with reduced mortality and morbidity. To replicate these benefits in clinical practice, however, physicians should select a specific agent and prescribe the drug according to the protocols used in the successful clinical trials reported to date.<sup>115</sup>

The major contraindications to the use of ACE inhibitors in patients with STEMI include hypotension in the setting of adequate preload, known hypersensitivity, and pregnancy. Adverse reactions include hypotension, especially after the first dose, and intolerable cough; much less commonly, angioedema can occur.

An alternative method of pharmacologic inhibition of the RAAS is the administration of angiotensin II receptor-blocking agents (ARBs). The VALIANT (VALsartan In Acute myocardial infarction) trial compared the effects of the ARB valsartan, valsartan and captopril, and captopril alone on mortality in patients with acute MI complicated by left ventricular systolic dysfunction and/or heart failure within 10 days of MI.<sup>29</sup> Rates of mortality were similar in the three treatment groups: 19.9% with valsartan, 19.3% with valsartan plus captopril, and 19.5% with captopril alone.

Aldosterone blockade is another pharmacologic strategy for inhibition of the RAAS. The EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival) trial randomly assigned 6642 patients with acute MI complicated by left ventricular dysfunction and heart failure to the selective aldosterone-blocking agent eplerenone or placebo in conjunction with contemporary postinfarction pharmacotherapy.<sup>116,117</sup> During a mean follow-up period of 16 months, a 15% reduction occurred in the RR for mortality in favor of eplerenone (Fig. 52-22). Eplerenone also reduced cardiovascular mortality or hospitalization for cardiovascular events. Serious hyperkalemia (serum potassium concentration, 6 mmol/liter) occurred in 5.5% of patients in the eplerenone group as compared with 3.9% in the placebo group ( $P = 0.002$ ).

### Recommendations

After administration of aspirin and initiation of reperfusion strategies and, when appropriate, beta blockers, *all* patients with STEMI should be considered for inhibition of the RAAS. Although few disagree with the recommendation that high-risk STEMI patients (elderly, anterior infarction, previous infarction, Killip class II or greater, and asymptomatic patients with evidence of depressed global ventricular function on an imaging study) should receive life-long treatment with ACE inhibitors, some have proposed short-term (4 to 6 weeks) therapy for a broader group of patients on the basis of the pooled results of the unselective mortality trials.<sup>1,115</sup>

Considering all the data available, we favor a strategy of an initial trial of oral ACE inhibitors in all patients with STEMI and congestive heart failure, as well as in hemodynamically stable patients with ST-segment elevation or left bundle branch block, commencing within the first 24 hours. ACE inhibition therapy should be continued indefinitely in patients with congestive heart failure, evidence of a reduction in global function, or a large regional wall motion abnormality. In patients without these findings, long-term treatment with ACE inhibitors is based on other considerations related to the potential benefits on secondary prevention (see Chapter 42). ARBs are a

clinically effective alternative to ACE inhibitors. The choice between ACE inhibition and an ARB following STEMI should be based on physician experience with the agents, patient tolerability, safety, convenience, and cost. Finally, long-term aldosterone blockade should be instituted in high-risk patients following STEMI (ejection fraction <40%, clinical heart failure, diabetes mellitus) who are already receiving an ACE inhibitor and beta blocker and do not have contraindications. Given the small but definite increase in the risk for serious hyperkalemia when aldosterone blockade is prescribed, particularly when other measures for RAAS inhibition are used concurrently, periodic monitoring of the serum potassium level should be undertaken.<sup>117</sup>

### Nitrates

The potential for reductions in ventricular filling pressure, wall tension, and cardiac work, coupled with improvement in coronary blood flow, especially in ischemic zones, and antiplatelet effects, makes nitrates a logical and attractive pharmacologic intervention in patients with STEMI.<sup>1</sup> Administration of nitrates reduces pulmonary capillary wedge pressure and systemic arterial pressure, left ventricular chamber volume, infarct size, and the incidence of mechanical complications. Nevertheless, routine administration of nitrates does not alter survival in patients with STEMI.

Although a meta-analysis of 10 trials conducted in the pre fibrinolytic era showed nitrate therapy to be associated with a reduction in mortality,<sup>82</sup> two megatrials of nitrate therapy conducted in the reperfusion era demonstrated no benefit on major cardiovascular outcomes.<sup>1</sup> In GISSI-3 and ISIS-4, no independent effect of nitrates on short-term mortality was detected.

Intravenous nitroglycerin can be administered safely to patients with evolving STEMI as long as the dose is titrated to avoid induction of reflex tachycardia or systemic arterial hypotension. Patients with inferior wall infarction may be sensitive to an excessive fall in preload, particularly with concurrent right ventricular infarction.<sup>1</sup> In such cases, nitrate-induced venodilation could impair cardiac output and reduce coronary blood flow, thus worsening rather than improving myocardial oxygenation.

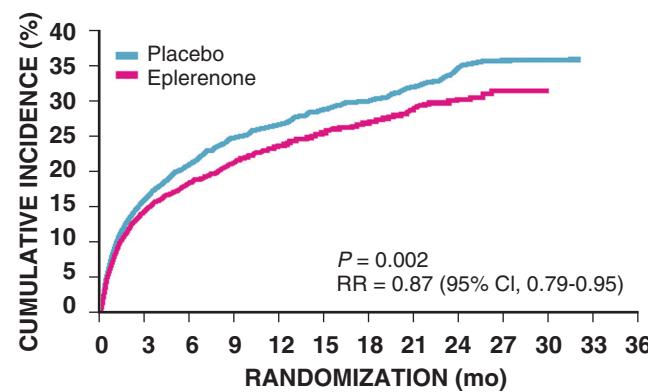
Clinically significant methemoglobinemia, although rare, can develop when unusually large doses of nitrates are administered. This problem is important not only for its potential to cause symptoms of lethargy and headache but also because elevated methemoglobin levels can impair the oxygen-carrying capacity of blood and potentially exacerbate ischemia. Dilation of the pulmonary vasculature supplying poorly ventilated lung segments may produce a ventilation-perfusion mismatch. Tolerance to intravenous nitroglycerin (as manifested by increasing nitrate requirements) develops in many patients, often as soon as 12 hours after the infusion is started.

### Recommendations

Nitroglycerin is indicated for the relief of persistent pain and as a vasodilator in patients with infarction associated with left ventricular failure or hypertension. In the absence of recurrent angina or heart failure, we do not routinely prescribe nitrates for patients with STEMI. Long-term nitrates have no clear benefit in asymptomatic patients, and we therefore do not prescribe them beyond the first 48 hours in patients without angina or ventricular failure.

### Calcium Channel Antagonists

Despite sound experimental and clinical evidence of an anti-ischemic effect, calcium antagonists have not been helpful in the acute phase of STEMI, and several systematic overviews have raised concern about an increased risk for mortality when these agents—and particularly short-acting dihydropyridines—are prescribed on a routine basis. Nondihydropyridine calcium channel-blocking agents (verapamil and diltiazem) can be given to slow a rapid ventricular response in atrial fibrillation in patients for whom beta blockers are ineffective. They should be avoided in patients with Killip class II or greater hemodynamic findings.



**FIGURE 52-22** Effect of a selective aldosterone receptor-blocking agent (eplerenone) after MI. Kaplan-Meier estimates of the rate of death from cardiovascular causes or hospitalization for cardiovascular events in the EPHESUS trial are depicted. (From Pitt B, Remme W, Zannad F, et al: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [abstract]. *N Engl J Med* 348:14, 2003.)

## Other Therapies

### Magnesium

A functional deficit in available magnesium may develop in patients with STEMI. Because of the risk for cardiac arrhythmias when electrolyte deficits are present in the early phase of infarction, patients with STEMI should have their serum magnesium measured on admission. We advocate repleting magnesium deficits to maintain a serum magnesium level of 2 mEq/liter or greater. In the presence of hypokalemia, the serum magnesium level should be rechecked and repleted if necessary because it is often difficult to correct a potassium deficit in the presence of a concurrent magnesium deficit. There is no indication for routine intravenous administration of magnesium to patients with STEMI.

### Glucose Control During ST-Elevation Myocardial Infarction (See also Chapter 61)

During the acute phase of STEMI, catecholamine levels increase in both the blood and ischemic myocardium. Insulin levels remain low, whereas cortisol, glucagon, and free fatty acid levels increase. These factors may contribute to an elevation in the blood glucose level, which should be measured routinely on admission. Intensive insulin therapy to strictly control blood glucose is no longer recommended routinely for patients with MI.<sup>118</sup> Blood glucose levels should be maintained below 180 mg/dL if possible while avoiding hypoglycemia.<sup>1</sup>

Routine administration of infusions of glucose-insulin-potassium (GIK) to patients with STEMI was proposed to reduce mortality. A series of small trials suggested that GIK infusions were beneficial, but the CREATE-ECLA (Clinical Trial of MEtabolic Modulation in Acute Myocardial Infarction Treatment-Estudios Cardiologicos Latinoamerica) investigators randomly assigned 20,201 patients with STEMI (83% of whom received reperfusion therapy) to GIK or placebo and found no impact on mortality (30-day mortality, 9.7% in control patients and 10% in GIK patients).<sup>119,120</sup> In addition, prehospital administration of GIK did not improve the primary endpoint of progression to MI in patients with ACSs.<sup>121</sup> Thus in the contemporary era of management of STEMI in which other effective therapies (reperfusion, aspirin, ACE inhibitors) are administered, routine use of GIK infusions appears to have no benefit.

### Other Agents

Multiple adjunctive pharmacotherapies to prevent inflammatory damage in the infarct zone have been investigated but have not shown clinical benefit.<sup>122</sup> For example, pexelizumab, a monoclonal antibody against the C5 component of complement, had no effect on infarct size in patients with STEMI treated with either fibrinolytics or PCI or on mortality in patients treated with primary PCI.<sup>123</sup> Intravenous administration of adenosine to reduce myocardial injury in patients with STEMI has been studied. Although administration of high-dose adenosine has been associated with a reduction in infarct size, neither high-dose nor low-dose adenosine improves clinical outcomes such as death or the development of heart failure when compared with placebo.<sup>124</sup>

## HEMODYNAMIC DISTURBANCES

### Hemodynamic Assessment

Patients with clinically uncomplicated STEMI do not require invasive hemodynamic monitoring because clinical evaluation can be used to assess the status of the circulation. Routine assessments in patients with STEMI should include monitoring of the heart rate and rhythm, repeated measurement of systemic arterial pressure by cuff, repeated auscultation of the lung fields for pulmonary congestion, measurement of urine output, examination of the skin for evidence of the adequacy of perfusion, and monitoring for hypoxemia.

In patients with STEMI who have clinical signs and symptoms of heart failure, assessment of the degree of hemodynamic compromise is important. Central venous pressure reflects right rather than left

ventricular function. Right ventricular function—and therefore systemic venous pressure—may be normal or almost so in patients with significant left ventricular failure. Conversely, patients with right ventricular failure caused by right ventricular infarction or pulmonary embolism may exhibit elevated right atrial and central venous pressure despite normal left ventricular function. Low values for right atrial and central venous pressure imply hypovolemia, whereas elevated right atrial pressure usually results from right ventricular failure secondary to left ventricular failure, pulmonary hypertension, right ventricular infarction, or less commonly, tricuspid regurgitation or pericardial tamponade.

In patients with complicated STEMI it may be useful to establish invasive monitoring with an intra-arterial catheter and a pulmonary artery catheter for measurement of pulmonary artery, pulmonary artery occlusive (equivalent to pulmonary wedge), and right atrial pressure, as well as cardiac output. In patients with hypotension, a Foley catheter provides accurate and continuous measurement of urine output.

### Monitoring of Pulmonary Artery Pressure

**Table 52-8** describes circumstances when to consider invasive monitoring. Patients most likely to benefit from pulmonary artery catheter monitoring include those whose STEMI is complicated by (1) hypotension that is not easily corrected by fluid administration, (2) hypotension in the presence of congestive heart failure, (3) hemodynamic compromise severe enough to require intravenous vasopressors or vasodilators or intra-aortic balloon counterpulsation, (4) mechanical lesions (or suspected ones) such as severe mitral regurgitation and a ruptured ventricular septum, and (5) right ventricular infarction.<sup>125</sup> Other possible indications for hemodynamic monitoring include assessment of the effects of mechanical ventilation, differentiating pulmonary disease from left ventricular failure as the cause of hypoxemia, and management of septic shock (Table 52-8).

Before inserting a pulmonary artery catheter into a patient with STEMI, the physician must believe that the potential benefit of the information that can be obtained outweighs any potential risks. Accumulating evidence from settings other than STEMI suggests that invasive hemodynamic monitoring does not improve outcomes.<sup>126</sup> Major complications from pulmonary artery catheters are not common, but severe problems can occur—including sepsis, pulmonary infarction, and pulmonary artery rupture. Minimized duration of catheterization and strict adherence to aseptic technique can diminish the risk. Using antiseptic-impregnated dressings can also reduce catheter-related bloodstream infections.<sup>127</sup> Noninvasive methods of determination of cardiac output, such as pulse contour analysis and thoracic electrical bioimpedance, are also available.<sup>128,129</sup>

**TABLE 52-8** Indications for Hemodynamic Monitoring in Patients with ST-Elevation Myocardial Infarction

Management of complicated acute MI
Hypovolemia versus cardiogenic shock
Ventricular septal rupture versus acute mitral regurgitation
Severe left ventricular failure
Right ventricular failure
Refractory ventricular tachycardia
Difficulty differentiating severe pulmonary disease from left ventricular failure with available noninvasive data
Assessment of cardiac tamponade
Assessment of therapy in selected individuals
Afterload reduction in patients with severe left ventricular failure
Inotropic agent therapy
Beta-blocking agent therapy
Temporary pacing (ventricular versus AV)
Intra-aortic balloon counterpulsation
Mechanical ventilation

From Gore JM, Zwerin PL: Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS (eds): *Modern Coronary Care*. Boston, Little, Brown, 1990, p 138.

Accurate determination of hemodynamics by clinical assessment can be difficult in critically ill patients. Use of a pulmonary artery catheter thus often leads to important changes in therapy. Of note, some reports have shown that complication and mortality rates may be higher in patients who undergo pulmonary artery catheterization, although such patients are often at higher risk initially. These observations emphasize the importance of patient selection, meticulous technique, and correct interpretation of the data obtained.<sup>129</sup>

### Hemodynamic Abnormalities

In 1976, Swan, Forrester, and associates measured cardiac output and wedge pressure simultaneously in a large series of patients with acute MI and identified four major hemodynamic subsets of patients (**Table 52-9**): (1) patients with normal systemic perfusion and without pulmonary congestion (normal cardiac output and normal wedge pressure), (2) patients with normal perfusion and pulmonary congestion (normal cardiac output and elevated wedge pressure), (3) patients with decreased perfusion but without pulmonary congestion (reduced cardiac output and normal wedge pressure), and (4) patients with decreased perfusion and pulmonary congestion (reduced cardiac output and elevated wedge pressure). This classification, which overlaps with a crude clinical classification

proposed earlier by Killip and Kimball (**Table 52-9**), has proved quite useful, but it should be noted that patients frequently pass from one category to another with therapy and sometimes apparently even spontaneously.

### Hemodynamic Subsets

A patient's clinical status typically reflects these subsets. Hypoperfusion usually becomes evident clinically when the cardiac index falls below approximately 2.2 liters/min/m<sup>2</sup>, whereas pulmonary congestion is noted when the wedge pressure exceeds approximately 18 mm Hg. However, approximately 25% of patients with cardiac indices lower than 2.2 liters/min/m<sup>2</sup> and 15% of patients with elevated pulmonary capillary wedge pressure are not recognized clinically. Discrepancies in the hemodynamic and clinical classification of patients with STEMI arise for a variety of reasons. Patients may exhibit "phase lags" as clinical pulmonary congestion develops or resolves, symptoms secondary to chronic obstructive pulmonary disease may be confused with those resulting from pulmonary congestion, or longstanding left ventricular dysfunction may mask signs of hypoperfusion because of compensatory vasoconstriction.

The hemodynamic findings shown in **Tables 52-9** and **52-10** allow rational approaches to therapy. The goals of hemodynamic therapy include maintenance of ventricular performance, blood pressure support, and protection of jeopardized myocardium. Because these goals may occasionally be at cross-purposes, recognition of the hemodynamic profile, as assessed clinically or as available from hemodynamic monitoring, may be needed to design an optimal therapeutic management strategy.

**TABLE 52-9** Hemodynamic Classifications of Patients with Acute Myocardial Infarction

A. BASED ON CLINICAL EXAMINATION		B. BASED ON INVASIVE MONITORING	
Class	Definition	Subset	Definition
I	Rales and S <sub>3</sub> absent	I	Normal hemodynamics PCWP <18, CI >2.2
II	Crackles, S <sub>3</sub> gallop, elevated jugular venous pressure	II	Pulmonary congestion PCWP >18, CI >2.2
III	Frank pulmonary edema	III	Peripheral hypoperfusion PCWP <18, CI <2.2
IV	Shock	IV	Pulmonary congestion and peripheral hypoperfusion PCWP >18, CI <2.2

CI = cardiac index; PCWP = pulmonary capillary wedge pressure.

**A**, Modified from Killip T, Kimball J: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 20:457, 1967;

**B**, from Forrester J, Diamond G, Chatterjee K, et al: Medical therapy of acute myocardial infarction by the application of hemodynamic subsets. *N Engl J Med* 295:1356, 1976.

### Hypotension in the Prehospital Phase

Hypotension associated with bradycardia often reflects excessive vagotonia. Relative or absolute hypovolemia is often present when hypotension occurs with a normal or rapid heart rate. Marked diaphoresis, reduction of fluid intake, or vomiting during the period preceding and accompanying the onset of STEMI may all contribute to the development of hypovolemia. Even if the effective vascular volume is normal, relative hypovolemia may be present because ventricular compliance is reduced in cases of STEMI, and a left ventricular filling pressure as high as 20 mm Hg may be necessary to provide optimal preload.

**MANAGEMENT.** In the absence of heart failure and the presence of hypotension suspected of being due to excessive vagotonia, patients should be placed in the reverse Trendelenburg position, and in patients with sinus bradycardia and hypotension, atropine should be administered (0.3 to 0.6 mg intravenously, repeated at 3- to 10-minute intervals up to 2 mg). If these measures do not correct the hypotension, normal saline should be administered intravenously (e.g., beginning with a bolus of 100 mL, followed by 50-mL increments every 5 minutes) while monitoring for signs of heart

**TABLE 52-10** Hemodynamic Patterns for Common Clinical Conditions

CARDIAC CONDITION	RA	RV	CHAMBER PRESSURE (mm Hg)		
			PA	PCW	CI
Normal	0-6	25/0-6	25/0-12	6-12	≥2.5
AMI without LVF	0-6	25/0-6	30/12-18	≤18	≥2.5
AMI with LVF	0-6	30-40/0-6	30-40/18-25	>18	>2.0
Biventricular failure	>6	50-60/>6	50-60/25	18-25	>2.0
RVMI	12-20	30/12-20	30/12	≤12	<2.0
Cardiac tamponade	12-16	25/12-16	25/12-16	12-16	<2.0
Pulmonary embolism	12-20	50-60/12-20	50-60/12	<12	<2.0

AMI = acute MI; CI = cardiac index; LVF = left ventricular failure; PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrium; RV = right ventricle; RVMI = right ventricular MI.

From Gore JM, Zwernet PL: Hemodynamic monitoring of acute myocardial infarction. In Francis GS, Alpert JS (eds): *Modern Coronary Care*. Boston, Little, Brown, 1990, pp 139-164.

failure. Because of the poor correlation between left ventricular filling pressure and mean right atrial pressure, assessment of systemic (even central) venous pressure can be of limited value as a guide to fluid therapy. Administration of positive inotropic agents is indicated during the prehospital phase if systemic hypotension persists despite correction of hypovolemia.

### The Hyperdynamic State

When infarction is not complicated by hemodynamic impairment, no therapy other than general supportive measures and treatment of arrhythmias is necessary. However, if the hemodynamic profile involves a hyperdynamic state—that is, elevation of the sinus rate, arterial pressure, and cardiac index, occurring singly or together in the presence of a normal or low left ventricular filling pressure—and if infection and other causes of tachycardia such as fever can be excluded, treatment with beta blockers is indicated. Presumably, the increased heart rate and blood pressure result from inappropriate activation of the sympathetic nervous system, possibly because of augmented release of catecholamines triggered by pain and/or anxiety.

### Left Ventricular Failure

Left ventricular dysfunction is the single most important predictor of mortality following STEMI (Fig. 52-23).<sup>130-133</sup> In patients with STEMI, either systolic dysfunction alone or both systolic and diastolic dysfunction can occur. Left ventricular diastolic dysfunction leads to pulmonary venous hypertension and pulmonary congestion. Clinical manifestations of left ventricular failure become more common as the extent of injury to the left ventricle increases. In addition to infarct size, other important predictors of the development of symptomatic left ventricular dysfunction include advanced age and diabetes.<sup>132,134</sup> Mortality increases in association with the severity of the hemodynamic deficit.

### Therapeutic Implications

Classification of patients with STEMI by hemodynamic subsets has therapeutic relevance. As already noted, patients with normal wedge pressure and hypoperfusion may benefit from infusion of fluids because the peak stroke volume value is not usually attained until left ventricular filling pressure reaches 18 to 24 mm Hg. However, a low level of left ventricular filling pressure does not necessarily imply that the left ventricular damage is slight. Such patients may be relatively hypovolemic and/or may have suffered a right ventricular infarct with or without severe left ventricular damage.

The relationship between ventricular filling pressure and cardiac index when preload is increased by infusion of fluid can provide valuable hemodynamic information in addition to that obtained from

baseline measurements. For example, the ventricular function curve rises steeply (marked increase in cardiac index, small increase in filling pressure) in patients with normal left ventricular function and hypovolemia, whereas the curve rises gradually or remains flat in patients with a combination of hypovolemia and depressed cardiac function. Invasive hemodynamic monitoring can help guide therapy in patients with severe left ventricular failure (pulmonary capillary wedge pressure >18 mm Hg and cardiac index <2.2 liters/min/m<sup>2</sup>). Although positive inotropic agents can be useful, they do not represent the initial therapy of choice for patients with STEMI. Instead, heart failure is managed most effectively first by reducing ventricular preload and then, if possible, by lowering afterload. Arrhythmias can contribute to hemodynamic compromise and should be treated promptly in patients with left ventricular failure.

### Hypoxemia

In STEMI complicated by heart failure, hypoxemia caused by a combination of pulmonary vascular engorgement (and in some cases, pulmonary interstitial edema), diminished vital capacity, and in some patients, contributory respiratory depression from narcotic analgesics characteristically develops. Hypoxemia can impair the function of ischemic tissue at the margin of the infarct and thereby contribute to establishing or perpetuating the vicious cycle (see Chapter 51). The ventilation-perfusion mismatch that results in hypoxemia requires careful attention to ventilatory support. Increasing fractions of inspired oxygen ( $\text{FiO}_2$ ) via facemask should be used initially, but if oxygen saturation cannot be maintained above 85% to 90% with 100%  $\text{FiO}_2$ , strong consideration should be given to endotracheal intubation and positive-pressure ventilation. The improvement in arterial oxygenation and hence myocardial oxygen supply may help restore ventricular performance. Positive end-expiratory pressure may diminish systemic venous return and reduce effective left ventricular filling pressure. This effect may require reducing the amount of positive end-expiratory pressure, normal saline infusions to maintain left ventricular filling pressure, adjustment of the rate of infusion of vasodilators such as nitroglycerin, or some combination of these factors. Because myocardial ischemia frequently occurs during the return to unsupported spontaneous breathing, weaning should be accompanied by observation for signs of ischemia and may benefit from a period of supported ventilation before extubation in patients who are not already revascularized.

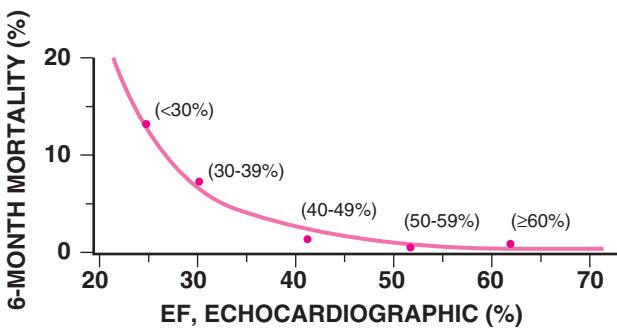
### Diuretics

Mild heart failure in patients with STEMI frequently responds well to diuretics such as furosemide administered intravenously in doses of 10 mg to 40 mg, repeated at 3- to 4-hour intervals if necessary. The resultant decrease in pulmonary capillary pressure reduces dyspnea, and the lowering of left ventricular wall tension that accompanies the reduction in left ventricular diastolic volume diminishes myocardial oxygen requirements and may lead to improvement in contractility and augmentation of the ejection fraction, stroke volume, and cardiac output. The reduction in elevated left ventricular filling pressure may also enhance myocardial oxygen delivery by diminishing the impedance to coronary perfusion attributable to the elevated ventricular wall tension. It may also improve arterial oxygenation by reducing pulmonary vascular congestion.

Intravenous administration of furosemide reduces pulmonary vascular congestion and pulmonary venous pressure within 15 minutes, before renal excretion of sodium and water has occurred; presumably this action results from a direct dilating effect of this drug on the systemic arterial bed. Left ventricular filling pressure should not be reduced much below 18 mm Hg, the lower range being associated with optimal left ventricular performance in patients with STEMI, because this may reduce cardiac output further and cause arterial hypotension. Excessive diuresis may also result in hypokalemia.

### Afterload Reduction

Myocardial oxygen requirements depend on left ventricular wall stress, which in turn is proportional to the product of the



**FIGURE 52-23** Impact of left ventricular function on survival following MI. The curvilinear relationship between the left ventricular ejection fraction (EF) in patients treated in the reperfusion era is shown. In patients with a left ventricular EF below 40%, the rate of mortality markedly increases at 6 months. (Modified from Volpi A, De Vita C, Franzosi MG, et al: Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad Hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. Circulation 88:416, 1993.)

peak developed left ventricular pressure, volume, and wall thickness. Intravenous vasodilator therapy should be considered in patients with STEMI complicated by (1) heart failure unresponsive to treatment with diuretics, (2) hypertension, (3) mitral regurgitation, or (4) ventricular septal defect. In these patients, treatment with vasodilator agents increases stroke volume and may reduce myocardial oxygen requirements and thereby lessen ischemia. Hemodynamic monitoring of systemic arterial and, in many cases, pulmonary capillary wedge (or at least pulmonary artery) pressure and cardiac output in patients treated with these agents is generally indicated. Improvement in cardiac performance and energetics requires three simultaneous effects: (1) reduction of left ventricular afterload, (2) avoidance of excessive systemic arterial hypotension to maintain effective coronary perfusion pressure, and (3) avoidance of excessive reduction of ventricular filling pressure with consequent diminution of cardiac output. In general, pulmonary capillary wedge pressure should be maintained at approximately 18 mm Hg and arterial pressure higher than 90/60 mm Hg in patients who were normotensive before the development of STEMI.

Vasodilator therapy is particularly useful when STEMI is complicated by mitral regurgitation or rupture of the ventricular septum. In such patients, vasodilators alone or in combination with intra-aortic balloon counterpulsation can sometimes serve as a "holding maneuver" and provide sufficient hemodynamic stabilization to permit definitive catheterization and angiographic studies, as well as to prepare the patient for early intervention. Because of the precarious state of patients with complicated infarction and the need for meticulous adjustment of dosage, therapy is best initiated with agents that can be administered intravenously and have a short duration of action, such as nitroprusside or nitroglycerin. After initial stabilization, the medication of choice is generally an ACE inhibitor, but long-acting nitrates given by mouth can also be useful.

### Nitroglycerin

This drug has been shown in animal experiments to be less likely than nitroprusside to produce "coronary steal" (i.e., diversion of blood flow from the ischemic to the nonischemic zone). Therefore apart from consideration of its routine use in STEMI patients discussed earlier, it may be a particularly useful vasodilator in patients with STEMI complicated by left ventricular failure. A dosage of 10 to 15 mg/min is infused, and the dose is increased by 10 mg/min every 5 minutes until the desired effect (improvement in hemodynamics or relief of ischemic chest pain) is achieved or a decline in systolic arterial pressure to 90 mm Hg or by more than 15 mm Hg has occurred. Although both nitroglycerin and nitroprusside lower systemic arterial pressure, systemic vascular resistance, and the heart rate–systolic blood pressure product, the reduction in left ventricular filling pressure is more prominent with nitroglycerin because of its relatively greater effect than nitroprusside on venous capacitance vessels. Nevertheless, in patients with severe left ventricular failure, cardiac output often increases despite the reduction in left ventricular filling pressure produced by nitroglycerin.

### Oral Vasodilators

The use of oral vasodilators for the treatment of chronic congestive heart failure is discussed in [Chapter 25](#). Patients with STEMI and persistent heart failure should receive long-term RAAS inhibition.<sup>1</sup> The reduced ventricular load decreases the left ventricle remodeling that occurs commonly in the period after STEMI and thereby reduces the development of heart failure and risk for death.<sup>135,136</sup>

### Digitalis (See Chapter 25)

Although digitalis increases the contractility and oxygen consumption of normal hearts, when heart failure is present, the diminution in heart size and wall tension frequently results in a net reduction of myocardial oxygen requirements. In animals, it fails to improve ventricular performance immediately following experimental coronary occlusion, but salutary effects are elicited when it is administered several days later. The absence of early beneficial effects may be caused by the inability of ischemic tissue to respond to digitalis or

the already maximal stimulation of contractility of the normal heart by circulating and neuronally released catecholamines.

Although the issue is still controversial, the incidence of arrhythmias can be increased by digitalis glycosides when they are given to patients in the first few hours after the onset of STEMI, particularly in the presence of hypokalemia. Undesirable peripheral systemic and coronary vasoconstriction can also result from the rapid intravenous administration of rapidly acting glycosides such as ouabain.

Administration of digitalis to patients with STEMI in the hospital phase should generally be reserved for the management of supraventricular tachyarrhythmias, such as atrial flutter and fibrillation, in the setting of poor left ventricular function and heart failure persisting despite treatment with diuretics or vasodilators. There is no indication for the use of digitalis as an inotropic agent in patients without clinical evidence of left ventricular dysfunction, and it is too weak an inotropic agent to be relied on as the principal cardiac stimulant in patients with overt pulmonary edema or cardiogenic shock.

### Beta-Adrenergic Agonists

When left ventricular failure is severe, as manifested by marked a reduction in the cardiac index (<2.2 liters/min/m<sup>2</sup>), and pulmonary capillary wedge pressure is at optimal (18 to 24 mm Hg) or excessive (>24 mm Hg) levels despite therapy with diuretics, beta-adrenergic agonists are indicated.<sup>137</sup> Dopamine and dobutamine can be useful in patients with STEMI and reduced cardiac output, increased left ventricular filling pressure, pulmonary vascular congestion, and hypotension. Fortunately, the potentially deleterious alpha-adrenergic vasoconstrictor effects exerted by dopamine occur only at higher doses than those required to increase contractility. The vasodilating actions of dopamine on renal and splanchnic vessels and its positive inotropic effects generally improve hemodynamics and renal function. In patients with STEMI and severe left ventricular failure, this drug may be started at a dose of 3 mg/kg/min and be increased stepwise to 20 mg/kg/min to reduce pulmonary capillary wedge pressure to approximately 18 mm Hg and elevate the cardiac index to exceed 2 liters/min/m<sup>2</sup>.

Dobutamine has a positive inotropic action comparable to that of dopamine but a slightly less positive chronotropic effect and less vasoconstrictor activity.<sup>137</sup> It can be administered at a starting dose of 2 mg/kg/min and be increased stepwise to a maximum of 30 mg/kg/min. Both dopamine and dobutamine must be given carefully and with constant monitoring of the ECG, systemic arterial pressure, and pulmonary artery or pulmonary artery occlusive pressure and, if possible, with frequent measurements of cardiac output. The dose should be reduced if significant tachycardia develops, if supraventricular or ventricular tachyarrhythmias occur, or if ST-segment deviations increase.

Norepinephrine increases myocardial oxygen consumption because of its peripheral vasoconstrictor and positive inotropic actions and thus had previously been thought best not to be used in patients with MI and shock.<sup>137</sup> However, a randomized trial that compared norepinephrine with dopamine showed efficacy similar to or better than that of dopamine, with fewer adverse effects.<sup>138</sup> Use of norepinephrine in patients with cardiogenic shock has therefore increased.

Although isoproterenol is a potent cardiac stimulant that improves ventricular performance, it should be avoided in patients with STEMI. It also causes tachycardia and augments myocardial oxygen consumption and lactate production; in addition, it reduces coronary perfusion pressure by causing systemic vasodilation, and in animals it increases the extent of experimentally induced infarction.

### Other Positive Inotropic Agents

Milrinone is a noncatecholamine, nonglycoside, phosphodiesterase inhibitor with inotropic and vasodilating actions.<sup>137</sup> It is useful in selected patients whose heart failure persists despite treatment with diuretics, who are not hypotensive, and who are likely to benefit from both an enhancement in contractility and afterload reduction. Milrinone should be given as a loading dose of 0.5 mg/kg/min administered over a 10-minute period, followed by a maintenance infusion of

0.375 to 0.75 mg/kg/min. The loading dose may be reduced or omitted if the patient has borderline hypotension.

## Cardiogenic Shock

Cardiogenic shock is the most severe clinical expression of left ventricular failure and is associated with extensive damage to the left ventricular myocardium in more than 80% of STEMI patients in whom it occurs; the remainder have a mechanical defect such as ventricular septal or papillary muscle rupture or predominant right ventricular infarction.<sup>130,132</sup> This low-output state is characterized by elevated ventricular filling pressure, low cardiac output, systemic hypotension, and evidence of vital organ hypoperfusion (e.g., clouded sensorium, cool extremities, oliguria, acidosis). Patients with cardiogenic shock caused by STEMI are more likely to be older; to have a history of diabetes mellitus, previous MI, or congestive heart failure; and to have sustained an anterior infarction at the time of development of shock. In the past, cardiogenic shock was reported to occur in up to 20% of patients with STEMI, but estimates from recent large trials and observational data bases report an incidence rate in the range of 5% to 8%.<sup>130,132,139</sup> When shock occurs, the prognosis remains poor and few interventions, with the exception of prompt coronary revascularization, conclusively provide benefit.<sup>131</sup>

## Pathologic Findings

At autopsy, more than two thirds of patients with cardiogenic shock demonstrate multivessel coronary disease, usually including the left anterior descending coronary artery. Almost all patients with cardiogenic shock exhibit thrombotic occlusion of the artery supplying the major region of recent infarction, with loss of 40% or more of left ventricular mass.<sup>130</sup> Patients who die of cardiogenic shock often have “piecemeal” necrosis—that is, progressive myocardial necrosis from marginal extension of the infarct into an ischemic zone bordering on the infarction. This finding is generally associated with persistent elevation of cardiac biomarkers. Such extensions and focal lesions probably result in part from the shock state itself. Early deterioration of left ventricular function secondary to apparent extension of the infarction in some cases may result from expansion of the necrotic zone of myocardium without actual extension of the necrotic process. The hydrodynamic force that develops during ventricular systole can disrupt necrotic myocardial muscle bundles with resultant expansion and thinning of the akinetic zone of myocardium, which in turn results in deterioration of overall left ventricular function.

Other causes of cardiogenic shock in patients with STEMI include mechanical defects such as rupture of the ventricular septum, a papillary muscle, or a free wall with tamponade; right ventricular infarction; or a marked reduction in preload caused by conditions such as hypovolemia.<sup>130,132</sup>

## Pathophysiology

The shock state in patients with STEMI appears to be the result of a vicious cycle, as demonstrated in Figure 51-14 (see Chapter 51).

## Diagnosis

Cardiogenic shock is characterized by marked and persistent (>30 minutes) hypotension with systolic arterial pressure lower than 90 mm Hg and a reduction in the cardiac index (<2.2 liters/min/m<sup>2</sup>) in the presence of elevated left ventricular filling pressure (pulmonary capillary wedge pressure >18 mm Hg). Spurious estimates of left ventricular end-diastolic pressure based on measurements of pulmonary artery wedge pressure can occur in patients with marked mitral regurgitation, in which the tall *v* wave in the left atrial (and pulmonary artery wedge) pressure tracing elevates the mean pressure above left ventricular end-diastolic pressure. Accordingly, mitral regurgitation and other mechanical lesions such as ventricular septal defect, ventricular aneurysm, and pseudoaneurysm must be excluded before the diagnosis of cardiogenic shock caused by impairment of left ventricular function can be established. Mechanical complications should be suspected in any patient with STEMI in whom circulatory collapse occurs. Immediate hemodynamic, angiographic, and

echocardiographic evaluations are necessary in patients with cardiogenic shock. It is important to exclude mechanical complications because primary therapy for such lesions usually requires immediate invasive treatment with intervening support of the circulation by intra-aortic balloon counterpulsation.

## Medical Management

When the aforementioned mechanical complications are not present, cardiogenic shock is caused by impairment of left ventricular function. Inotropic and vasopressor agents may be used as pharmacologic support and should be administered at the lowest possible doses. Although dopamine or dobutamine generally improves hemodynamics in these patients, unfortunately, neither appears to improve hospital survival significantly. Similarly, vasodilators have been used in an effort to elevate cardiac output and to reduce left ventricular filling pressure, but by lowering the already markedly reduced coronary perfusion pressure, myocardial perfusion can be compromised further and accelerate the vicious cycle illustrated in Figure 51-14. Vasodilators may nonetheless be used in conjunction with intra-aortic balloon counterpulsation (see the section **Mechanical Support**) and inotropic agents to increase cardiac output while sustaining or elevating coronary perfusion pressure.

Patients with cardiogenic shock usually have elevated systemic vascular resistance, but occasionally resistance is normal, and in a few cases vasodilation actually predominates. When systemic vascular resistance is not elevated (i.e., <1800 dynes/sec/cm<sup>5</sup>) in patients with cardiogenic shock, norepinephrine, which has both alpha- and beta-adrenergic agonist properties (in doses ranging from 2 to 10 mg/min), can increase diastolic arterial pressure, maintain coronary perfusion, and improve contractility. Alpha-adrenergic agents such as phenylephrine are contraindicated in patients with cardiogenic shock (unless systemic vascular resistance is inordinately low). Calcium-sensitizing agents, such as levosimendan, may have some beneficial effects on cardiovascular outcomes, but these medications have shown little incremental value in randomized trials.<sup>140</sup>

## Mechanical Support (See Chapter 29)

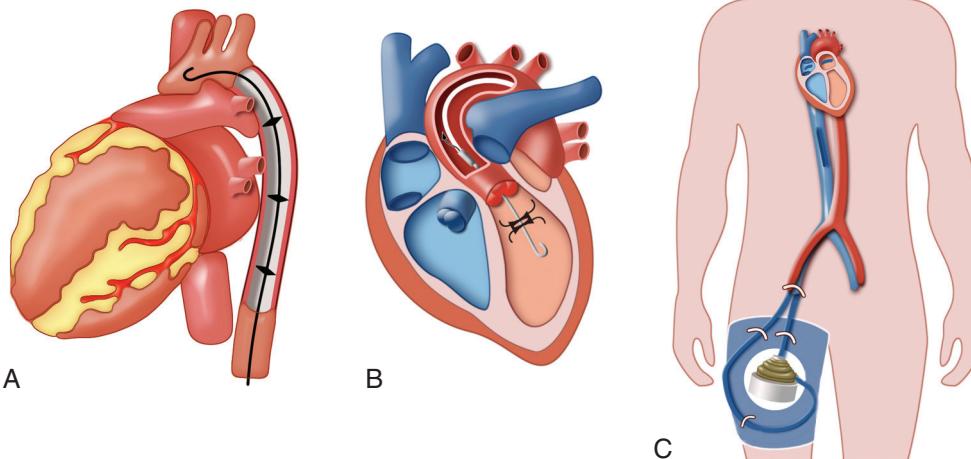
In patients in whom pharmacologic support is failing because of end-organ hypoperfusion, initiation of mechanical circulatory support is reasonable (Fig. 52-24), but no definitive evidence has yet shown that this strategy improves outcomes.<sup>141</sup>

## Intra-Aortic Balloon Counterpulsation

Intra-aortic balloon counterpulsation is used for the treatment of STEMI in three groups of patients: (1) those whose conditions are hemodynamically unstable and in whom support of the circulation is required for the performance of cardiac catheterization and angiography carried out to assess lesions that are potentially correctable surgically or by angioplasty, (2) those with cardiogenic shock that is unresponsive to medical management, and rarely, (3) those with refractory ischemia that is unresponsive to other treatments or who are waiting for definitive revascularization. In experimental animals, intra-aortic balloon counterpulsation decreases preload, increases coronary blood flow, and improves cardiac performance. Unfortunately, the improvement is often only temporary in patients with cardiogenic shock. Although a response to intra-aortic balloon counterpulsation correlates with better outcomes in observational studies and small randomized trials, in the largest randomized trial conducted to date, counterpulsation alone did not improve overall survival in patients with cardiogenic shock secondary to MI (Fig. 52-25).<sup>142</sup> Nor was a benefit observed in any clinically relevant subgroups. Nevertheless, intra-aortic balloon counterpulsation is reasonable in patients with cardiogenic shock whose condition does not stabilize with other interventions and as a bridge to recovery or more advanced therapies.<sup>1</sup>

## Percutaneous Left Ventricular Assist Devices

Temporary mechanical support with left ventricular assist devices may allow time for recovery of stunned or hibernating myocardium.<sup>143</sup> A percutaneous left ventricular assist device may be placed by



**FIGURE 52-24** Schematic representation of examples of major categories of nonsurgical mechanical circulatory support. **A**, Intra-aortic balloon pump inserted into the descending aorta between the arch vessels and renal arteries. **B**, Impella Recover (Abiomed, Aachen, Germany). This rotational flow device is percutaneously inserted via the femoral artery and positioned across the aortic valve, with flow intake in the left ventricle and outflow in the aorta. **C**, TandemHeart (CardiacAssist, Inc., Pittsburgh). A cannula is inserted percutaneously through the right femoral vein and advanced toward the right atrium, where it is introduced by transatrial septal perforation, to establish inflow into an external rotational motor. A cannula in either femoral artery then provides the outflow. (Modified from Desai NR, Bhatt DL: Evaluating percutaneous support for cardiogenic shock: Data shock and sticker shock. Eur Heart J 30:2073, 2009.)

cannulation of the left femoral vein and advancement to the left atrium via transseptal puncture. Blood from the left atrium is then returned by a nonpulsatile motor into the femoral artery. This system may provide up to 5 liters/min of flow. Small randomized trials have not revealed any mortality advantage over intra-aortic balloon counterpulsation,<sup>130,141,143</sup> but hemodynamic improvement is greater with the percutaneous left ventricular assist device. Another percutaneous alternative is a motorized device placed across the aortic valve that delivers continuous flow of blood from the left ventricle into the aorta and provides hemodynamic support superior to that achieved with an intra-aortic balloon pump in patients with MI.<sup>144</sup> Additionally, lactate levels have been reduced with these devices, thus suggesting improved organ perfusion, although 30-day mortality remains high.<sup>145</sup> Surgically placed left ventricular devices as a bridge to transplantation or as a destination therapy are discussed in Chapter 29.

### Complications

Complications of intra-aortic balloon counterpulsation include damage to or perforation of the aortic wall, ischemia distal to the site of insertion of the balloon in the femoral artery, thrombocytopenia, hemolysis, atheroemboli, infection, and mechanical failure such as rupture of the balloon, as well as complications stemming directly from the anticoagulation required. Because of the potential for vascular bleeding complications, physicians have been reluctant to use intra-aortic pumps in patients who have undergone fibrinolytic therapy. However, despite the increased bleeding risk, this modality should be considered in selected patients who are candidates for an aggressive approach to revascularization because of the poor outcome in those with shock following thrombolysis (usually associated with ineffective thrombolysis). In addition to vascular complications, percutaneous left ventricular assist devices are associated with the development of systemic inflammatory response syndrome in some patients.<sup>146</sup>

### Revascularization

Of the five therapies frequently used to treat patients with cardiogenic shock (vasopressors, mechanical support, fibrinolysis, PCI, and CABG), the first two are useful temporizing maneuvers. Revascularization, however, appears to improve survival.

The SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shock?) study evaluated early revascularization for the treatment of patients with MI complicated by cardiogenic

shock.<sup>130</sup> Patients with shock caused by left ventricular failure complicating STEMI were randomly assigned to emergency revascularization ( $n = 152$ ) accomplished by either CABG or angioplasty or to initial medical stabilization ( $n = 150$ ). In 86% of patients in both groups, intra-aortic balloon counterpulsation was performed. The primary endpoint was all-cause mortality at 30 days; a secondary endpoint was mortality at 6 months. At 30 days the overall mortality rate was 46.7% in the revascularization group—not significantly different from the 56% mortality rate observed in the medical therapy group ( $P = 0.11$ ). Subgroups of patients in the SHOCK study who showed benefit from the early revascularization strategy (i.e., reduced 6-month mortality) were those younger than 75 years, those with a previous MI, and those randomly assigned less than 6 hours from the onset of infarction. Long-term survival improved significantly in patients with cardiogenic shock

who underwent early revascularization (Fig. 52-26). A subsequent observational study of patients with MI complicated by shock indicated that well-selected elderly patients undergoing PCI had a 1-year survival similar to that in younger patients undergoing early revascularization.<sup>147</sup>

### Recommendations

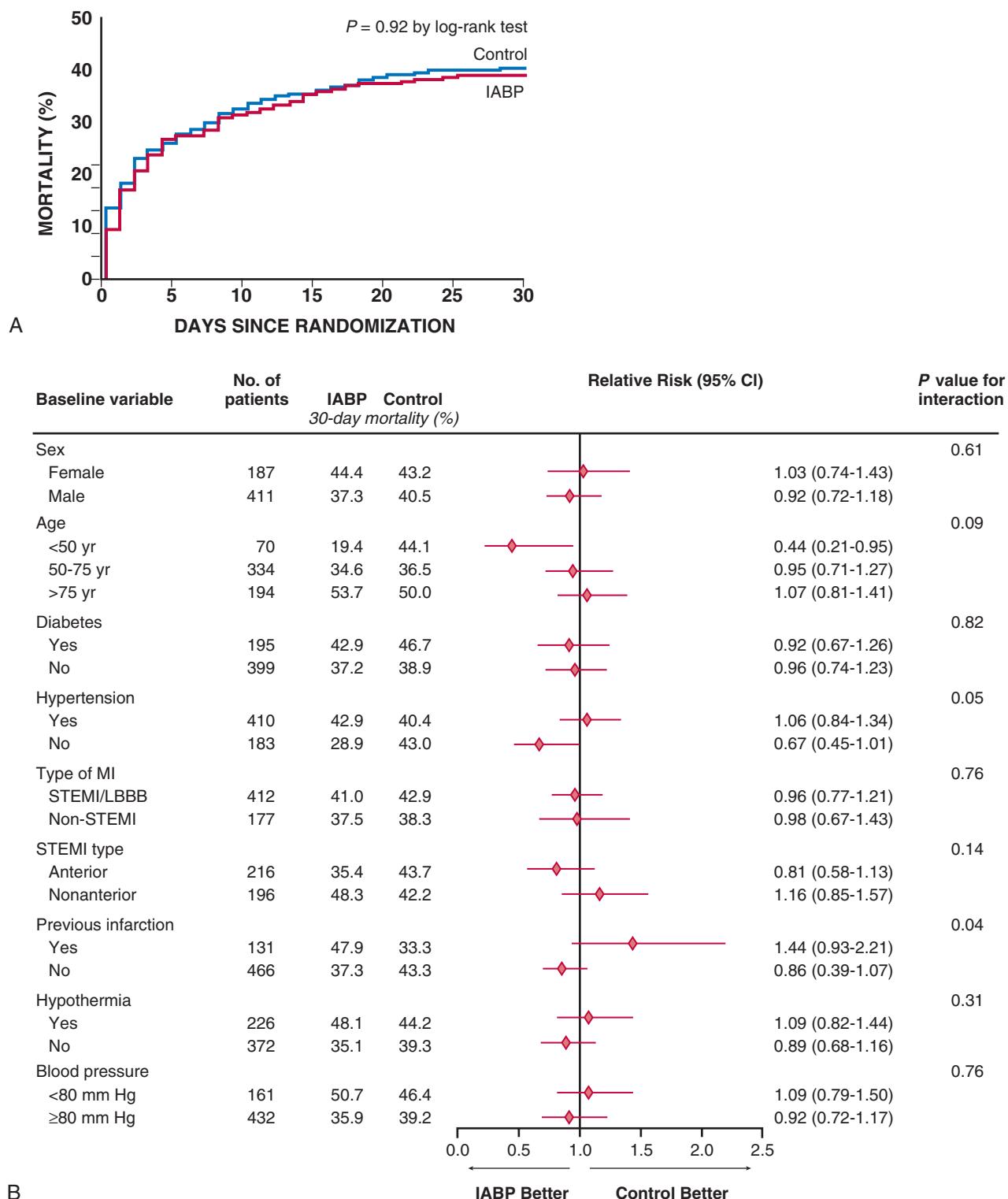
We recommend individualized assessment of patients to determine their desire for aggressive care and overall candidacy for further treatment (e.g., age, mental status, comorbid conditions). Patients with shock who are potential candidates for revascularization should be revascularized, which may include revascularization of significant stenoses in non-culprit arteries, with PCI and/or CABG. In patients with STEMI and shock, in whom PCI or CABG is not suitable, fibrinolytic agents can be given unless they have a contraindication.<sup>1</sup> Intra-aortic balloon counterpulsation and left ventricular assist devices may be considered in patients with refractory shock whose condition does not stabilize with other therapies.

### Right Ventricular Infarction

The clinical features of right ventricular infarction range from mild right ventricular dysfunction to cardiogenic shock. Characteristic electrocardiographic manifestations and hemodynamic patterns (Fig. 52-27) have been observed in patients with clinically significant right ventricular infarction, which accompanies approximately a third of inferior left ventricular infarctions. Right-sided heart filling pressures (central venous, right atrial, and right ventricular end-diastolic) are elevated, whereas left ventricular filling pressure is normal or only slightly raised; right ventricular systolic and pulse pressures are decreased, and cardiac output is often markedly depressed.

### Diagnosis

Many patients with the combination of a normal left ventricular filling pressure and depressed cardiac index have right ventricular infarcts (with accompanying inferior left ventricular infarcts). The hemodynamic picture may superficially resemble that seen in patients with pericardial disease (see Chapter 71) and includes elevated right ventricular filling pressure; a steep, right atrial y descent; and an early diastolic drop and plateau (resembling the square root sign) in the right ventricular pressure tracing. Moreover, patients with right ventricular infarction may display the Kussmaul sign (an increase in

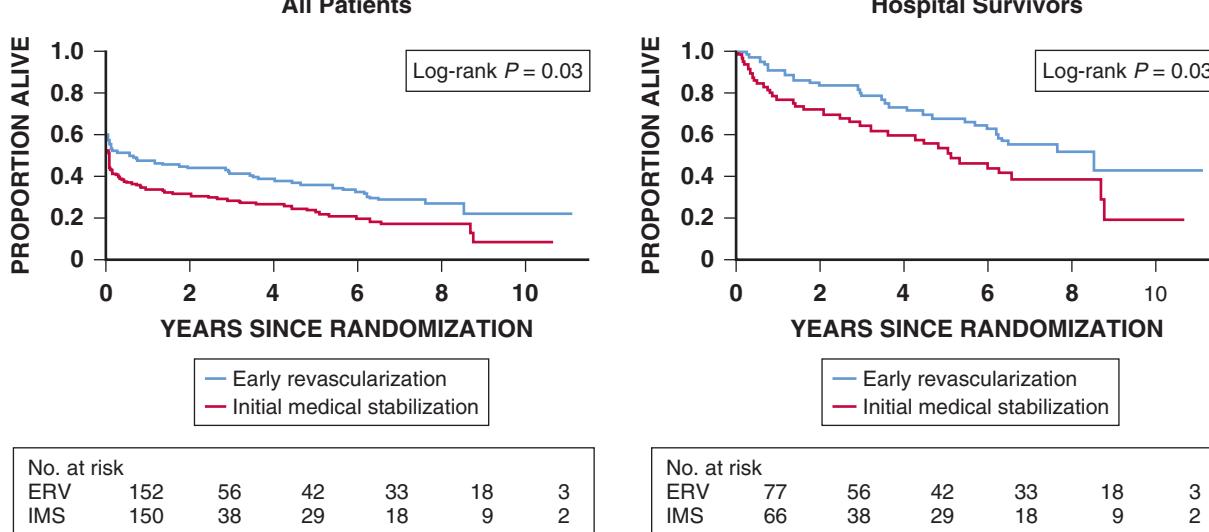


**FIGURE 52-25** Primary result of a randomized trial of routine insertion of an intra-aortic balloon pump (IABP) versus standard care in patients with acute MI and cardiogenic shock. **A**, In this randomized trial of 600 patients, the primary endpoint of death from any cause did not differ between the randomized treatment groups. **B**, There was no convincing benefit of the routine use of IABP for shock in any of the major subgroups examined. LBBB = left bundle branch block. (From Thiele H, Zeymer U, Neumann FJ, et al: Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 367:1287, 2012.)

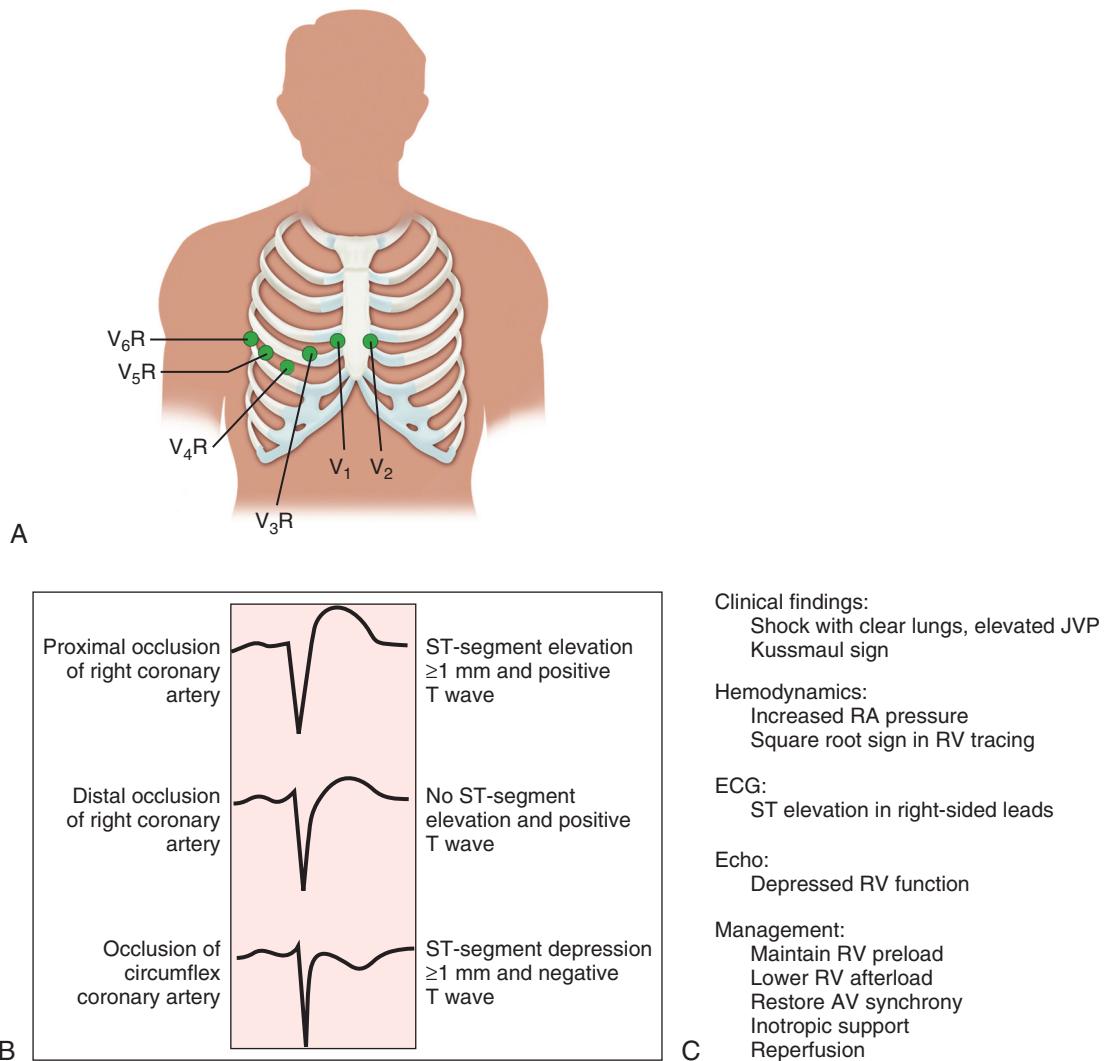
jugular venous pressure with inspiration) and pulsus paradoxus (a fall in systolic pressure >10 mm Hg with inspiration) (Fig. 52-27). In fact, the Kussmaul sign in the setting of inferior STEMI is highly predictive of right ventricular involvement.

The ECG can provide the first clue to right ventricular involvement in patients with inferior STEMI (Fig. 52-27). Most patients with right ventricular infarction have ST-segment elevation in lead V<sub>4</sub>R (right

precordial lead in the V<sub>4</sub> position).<sup>1</sup> Transient elevation of the ST segment in any of the right precordial leads can occur with right ventricular MI, and the presence of ST-segment elevation of 0.1 mV or greater in any one or a combination of leads V<sub>4</sub>R, V<sub>5</sub>R, and V<sub>6</sub>R in patients with the clinical picture of acute MI points to the diagnosis of right ventricular MI. In addition to noting the presence or absence of convex upward ST elevation in V<sub>4</sub>R, clinicians should determine



**FIGURE 52-26** Impact of revascularization in patients in the SHOCK trial. Among all patients, survival rates in the early revascularization (ERV) and initial medical stabilization (IMS) groups, respectively, were 41.4% and 28.3% at 3 years and 32.8% and 19.6% at 6 years. Among hospital survivors, survival rates in the ERV and IMS groups, respectively, were 78.8% and 64.3% at 3 years and 62.4% and 44.4% at 6 years. (From Hochman JS, Sleeper LA, Webb JG, et al: Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 295:2511, 2006.)



**FIGURE 52-27** Right ventricular infarction: diagnosis, clinical features, and management. **A**, Placement of right-sided leads for electrocardiographic evaluation of right ventricular infarction. **B**, ST elevation is seen in the right-sided ECG leads, with variation in the repolarization pattern depending on the infarct artery and the location of the occlusion. **C**, Patients with hemodynamically significant right ventricular infarction have shock but clear lungs and elevated jugular venous pressure. Management is directed at maintaining adequate right ventricular preload and lowering pulmonary artery pressure to unload the right ventricle. Inotropic therapy may be necessary in some cases. Echo = echocardiogram; JVP = jugular venous pressure; RA = right atrial; RV = right ventricular. (Modified from Wellens HJ: The value of the right precordial leads of the electrocardiogram. *N Engl J Med* 340:381, 1999; and Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction]. *Circulation* 2004;110(9):e82.)

whether the T wave is positive or negative—such distinctions help distinguish proximal versus distal occlusion of the right coronary artery versus occlusion of the left circumflex artery (Fig. 52-27). Elevation of the ST segments in leads V<sub>1</sub> through V<sub>4</sub> caused by right ventricular infarction can be confused with elevation caused by anteroseptal infarction. Although the elevated ST segments are oriented anteriorly in both cases, the frontal plane can provide important clues—the ST segments are oriented to the right with right ventricular infarction (e.g., +120 degrees), whereas they are oriented to the left with anteroseptal infarction (e.g., -30 degrees).

### Noninvasive Assessment

Echocardiography helps in the differential diagnosis because in patients with right ventricular infarction, in contrast to pericardial tamponade, little or no pericardial fluid accumulates. The echocardiogram shows abnormal wall motion of the right ventricle, as well as right ventricular dilation and depression of the right ventricular ejection fraction.<sup>148</sup> MRI can also aid in recognition of right ventricular infarction.<sup>149</sup> Impaired right ventricular function delineated by either modality has been associated with increased mortality after MI.<sup>150</sup> Additionally, shock from isolated right ventricular dysfunction carries almost as high a mortality risk as left ventricular shock does; serial studies have shown, however, that some degree of ventricular recovery is more common with right ventricular infarction than with left ventricular infarction.<sup>150</sup>

### Treatment

Because of their ability to reduce preload, medications routinely prescribed for left ventricular infarction may produce profound hypotension in patients with right ventricular infarction. Specifically, nitrates and diuretics should be avoided. In patients with hypotension caused by right ventricular MI, hemodynamics can be improved by a combination of expansion of plasma volume to augment right ventricular preload and cardiac output and, when left ventricular failure is present, arterial vasodilators.<sup>1</sup> If hypotension has not responded to

brisk administration of 1 or more liters of fluid, however, consideration should be given to hemodynamic monitoring with a pulmonary artery catheter because further volume infusion may be of little use and could produce pulmonary congestion. Arterial vasodilators reduce the impedance to left ventricular outflow and, in turn, left ventricular diastolic, left atrial, and pulmonary (arterial) pressure—thereby lowering impedance to right ventricular outflow and enhancing right ventricular output.

In patients requiring pacing, ventricular pacing may fail to increase cardiac output, and AV sequential pacing may be needed. Right ventricular infarction is common in patients with inferior left ventricular infarction. Therefore otherwise unexplained systemic arterial hypotension with diminished cardiac output or marked hypotension in response to small doses of nitroglycerin in patients with inferior infarction should lead to prompt consideration of this diagnosis. Patients requiring pacing should undergo atrial or AV sequential pacing. Successful reperfusion of the right coronary artery significantly improves right ventricular mechanical function and lowers in-hospital mortality in patients with right ventricular infarction. Replacement of the tricuspid valve and repair of the valve with annuloplasty rings have been performed for the treatment of severe tricuspid regurgitation caused by right ventricular infarction.

### Mechanical Causes of Heart Failure

The most dramatic complications of STEMI involve tearing or rupture of acutely infarcted tissue (see Fig. 52-33). The clinical characteristics of these lesions vary considerably and depend on the site of rupture, which may involve the free wall of either ventricle, the interventricular septum, or the papillary muscles. The overall incidence of these complications, although difficult to assess because clinical and autopsy series differ considerably, appears to be decreasing with the increasing use of reperfusion therapy.<sup>151,152</sup> Table 52-11 shows the comparative clinical profile of these complications, as gathered from different studies.

**TABLE 52-11** Characteristics of Ventricular Septal Rupture, Rupture of the Ventricular Free Wall, and Papillary Muscle Rupture

CHARACTERISTIC	VENTRICULAR SEPTAL RUPTURE	RUPTURE OF THE VENTRICULAR FREE WALL	PAPILLARY MUSCLE RUPTURE
Incidence	1-3% without reperfusion therapy, 0.2-0.34% with fibrinolytic therapy, 3.9% in patients with cardiogenic shock	0.8-6.2%; fibrinolytic therapy does not reduce risk; primary PTCA seems to reduce risk	~1% (the posteromedial more frequent than the anterolateral papillary muscle)
Time course	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days	Bimodal peak; within 24 hr and 3-5 days; range, 1-14 days
Clinical manifestations	Chest pain, shortness of breath, hypotension	Anginal, pleuritic, or pericardial chest pain; syncope; hypotension; arrhythmia; nausea; restlessness; hypotension; sudden death	Abrupt onset of shortness of breath and pulmonary edema; hypotension
Physical findings	Harsh holosystolic murmur, thrill (+), S <sub>3</sub> , accentuated second heart sound, pulmonary edema, RV and LV failure, cardiogenic shock	Jugular venous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic shock	A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock
Echocardiographic findings	Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload	>5 mm pericardial effusion not visualized in all cases; layered, high-acoustic echoes within the pericardium (blood clot); direct visualization of tear; signs of tamponade	Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography
Right-heart catheterization	Increase in oxygen saturation from the RA to RV, large v waves	Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures in the cardiac chambers)	No increase in oxygen saturation from the RA to RV, large v waves,* very high pulmonary capillary wedge pressure

\*Large v waves are from the pulmonary capillary wedge pressure.

LV = left ventricle/left ventricular; PTCA = percutaneous transluminal coronary angioplasty; RA = right atrium; RV = right ventricle/right ventricular.

From Antman EM, Anbe DT, Armstrong PW, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). ([www.acc.org/clinical/guidelines/stemi/index.pdf](http://www.acc.org/clinical/guidelines/stemi/index.pdf)). Accessed April 19, 2006.

## Free Wall Rupture

The clinical course of rupture varies from catastrophic, with an acute tear leading to tamponade and immediate death, to subacute, with nausea, hypotension, and pericardial discomfort being the major clinical clues to its presence (Table 52-11). The tear is usually preceded by a large infarct with subsequent expansion, sometimes with a dissecting hematoma, and occurs near the junction of the infarct and normal muscle. Rupture is more common in the left ventricle (specifically, the anterior or lateral wall) than in the right ventricle and seldom occurs in the atria. Other features associated with rupture include reperfusion with a fibrinolytic agent versus PCI, older age, female sex, hypertension, the absence of collateral circulation, and a first MI.<sup>152</sup> Survival depends on recognition of this complication, on hemodynamic stabilization of the patient—usually with inotropic agents and/or an intra-aortic balloon pump—and most importantly, on prompt surgical repair.<sup>1</sup>

## Pseudoaneurysm

Incomplete rupture of the heart may occur when organizing thrombus and hematoma, together with pericardium, seal a rupture of the left ventricle and thus prevent the development of hemopericardium (Fig. 52-28). With time, this area of organized thrombus and pericardium can become a pseudoaneurysm (false aneurysm) that maintains communication with the cavity of the left ventricle. In contrast to true aneurysms, which always contain some myocardial elements in their walls, the walls of pseudoaneurysms are composed of organized hematoma and pericardium and lack any elements of the original myocardial wall. Pseudoaneurysms can become quite large, even equaling the true ventricular cavity in size, and they communicate with the left ventricular cavity through a narrow neck. Frequently, pseudoaneurysms contain significant quantities of old and recent thrombi, the superficial portions of which can cause arterial emboli. Pseudoaneurysms can drain off a portion of each ventricular stroke volume, exactly as true aneurysms do. The diagnosis of pseudoaneurysm can usually be made by echocardiography and contrast-enhanced angiography,<sup>150</sup> although differentiation between a true aneurysm and a pseudoaneurysm can sometimes be difficult with any imaging technique.

## Diagnosis

Myocardial free wall rupture is usually accompanied by sudden profound shock, often rapidly leading to pulseless electrical activity caused by pericardial tamponade. Immediate pericardiocentesis can confirm the diagnosis and relieve the pericardial tamponade, at least momentarily. If the patient's condition is relatively stable, echocardiography may help in establishing the diagnosis of tamponade.<sup>150</sup>

## Treatment

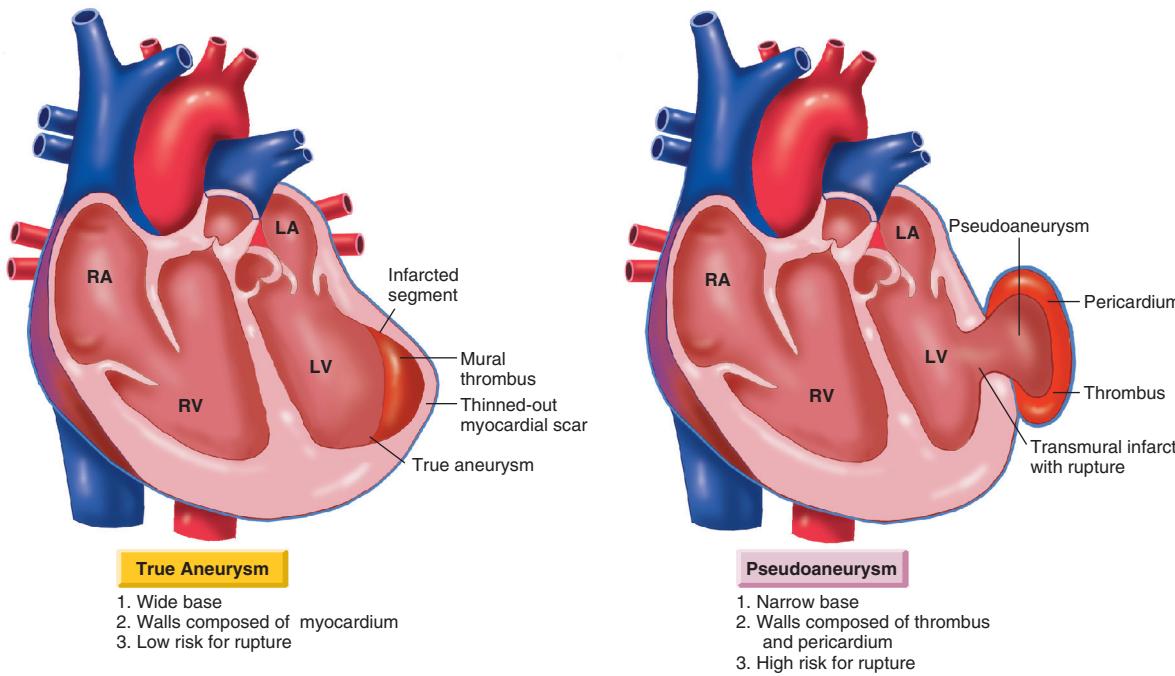
In patients with critically compromised hemodynamics, establishment of the diagnosis should be followed immediately by surgical resection of the necrotic and ruptured myocardium with primary reconstruction. When the rupture is subacute and a pseudoaneurysm is suspected or present, prompt elective surgery is indicated because rupture of the pseudoaneurysm can occur relatively frequently.<sup>153</sup>

## Rupture of the Interventricular Septum

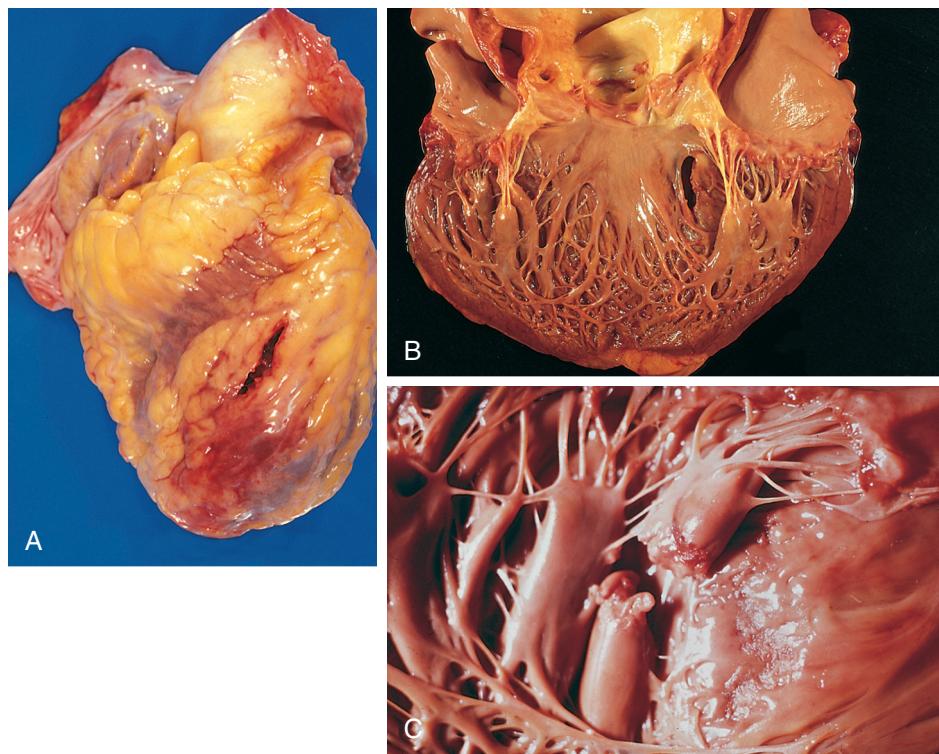
As in rupture of the free wall of the ventricle, transmural infarction underlies rupture of the ventricular septum. The perforation can range in length from one to several centimeters (Fig. 52-29). It can be a direct through-and-through opening or more irregular and serpiginous. Rupture of the septum with an anterior infarction tends to be apical in location, whereas inferior infarctions are associated with perforation of the basal septum and have a worse prognosis than do those in an anterior location.

Clinical features associated with increased risk for rupture of the interventricular septum include lack of development of a collateral network, advanced age, female sex, and chronic kidney disease (Table 52-12). Because previous ischemia induces myocardial preconditioning, thereby decreasing the likelihood of transmural myocardial necrosis and septal rupture, patients with evidence of hypertension, diabetes mellitus, chronic angina, or previous MI are less likely to experience rupture.<sup>132</sup>

A ruptured interventricular septum is characterized by the appearance of a new harsh, loud holosystolic murmur that is heard best at the lower left sternal border and is usually accompanied by a thrill. Biventricular failure generally ensues within hours to days. The defect can also be recognized by echocardiography with color flow Doppler



**FIGURE 52-28** Differences between a pseudoaneurysm and a true aneurysm. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. (From Shah PK: Complications of acute myocardial infarction. In Parmley W, Chatterjee K [eds]: Cardiology. Philadelphia, JB Lippincott, 1987.)



**FIGURE 52-29** Cardiac rupture syndromes complicating STEMI. **A**, Anterior myocardial rupture in an acute infarct. **B**, Rupture of the ventricular septum. **C**, Complete rupture of a necrotic papillary muscle. (From Schoen FJ: *The heart*. In Kumar V, Abbas AK, Fausto N [eds]: *Robbins & Cotran Pathologic Basis of Disease*. 7th ed. Philadelphia, WB Saunders, 2005.)

**TABLE 52-12** Cardiac Arrhythmias and Their Management During Acute Myocardial Infarction

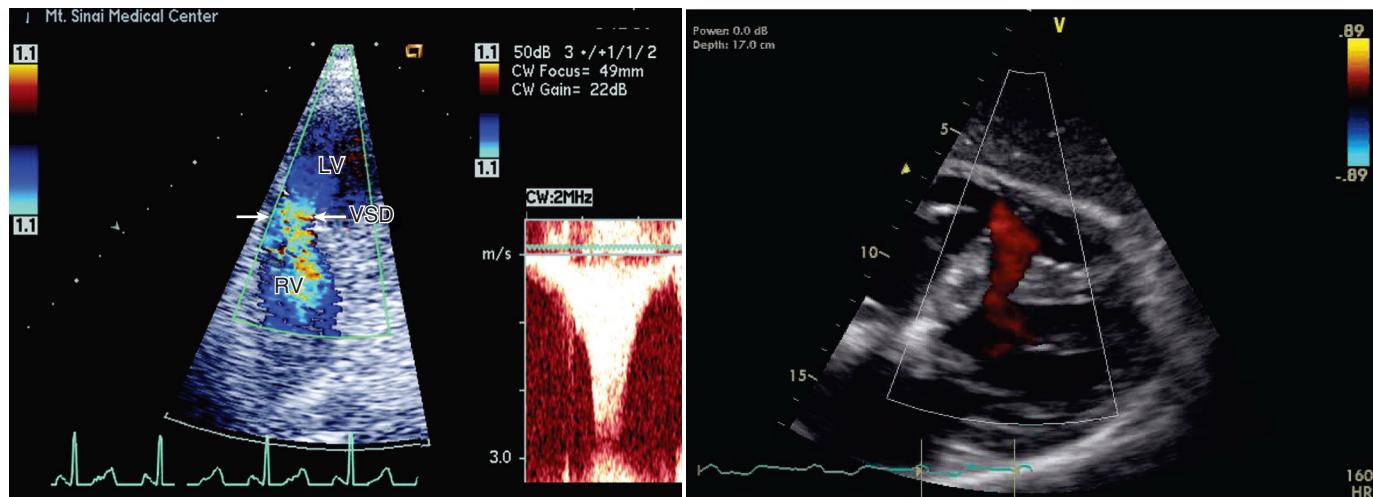
CATEGORY	ARRHYTHMIA	OBJECTIVE OF TREATMENT	THERAPEUTIC OPTIONS
1. Electrical instability	Ventricular premature beats Ventricular tachycardia  Ventricular fibrillation Accelerated idioventricular rhythm Nonparoxysmal AV junctional tachycardia	Correction of electrolyte deficits and increased sympathetic tone Prophylaxis against ventricular fibrillation, restoration of hemodynamic stability Urgent reversion to sinus rhythm Observation unless hemodynamic function is compromised Search for precipitating cause (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Potassium and magnesium solutions, beta blocker Antiarrhythmic agents, beta blocker; cardioversion/defibrillation Defibrillation; amiodarone, lidocaine Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication present
2. Pump failure/excessive sympathetic stimulation	Sinus tachycardia  Atrial fibrillation and/or atrial flutter Paroxysmal supraventricular tachycardia	Reduce heart rate to diminish myocardial oxygen demands  Reduce ventricular rate; restore sinus rhythm Reduce ventricular rate; restore sinus rhythm	Antipyretics; analgesics; consider beta-blocking agent unless congestive heart failure present Verapamil, digitalis glycosides; amiodarone; treat heart failure; cardioversion Vagal maneuvers; verapamil, cardiac glycosides, beta-adrenergic blocking agents; cardioversion
3. Bradyarrhythmias and conduction disturbances	Sinus bradycardia  Junctional escape rhythm  AV block and intraventricular block	Acceleration of the heart rate only if hemodynamic function is compromised Acceleration of the sinus rate only if loss of atrial "kick" causes hemodynamic compromise  Insertion of a pacemaker	Atropine; atrial pacing Atropine; atrial pacing  Insertion of a pacemaker

Modified from Antman EM, Rutherford JD (eds): *Coronary Care Medicine: A Practical Approach*. Boston, Martinus Nijhoff, 1986, p 78.

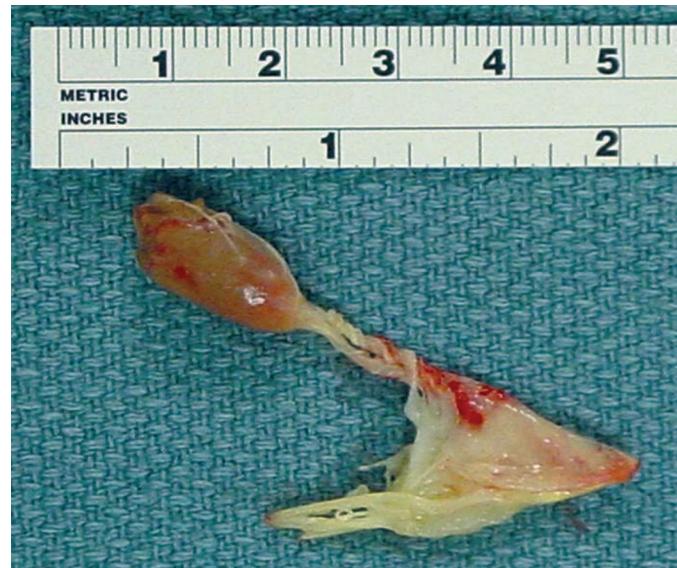
imaging (Fig. 52-30) or by insertion of a pulmonary artery balloon catheter to document the left-to-right shunt. Rupture of the interventricular septum after STEMI confers high 30-day mortality.<sup>152</sup> The likelihood of survival depends on the degree of impairment of ventricular function and the size of the defect, but because the rupture site can expand, prompt surgical repair is necessary even in hemodynamically stable patients.<sup>1,154</sup>

### Rupture of a Papillary Muscle

Partial or total rupture of a papillary muscle is a rare but often fatal complication of transmural MI (see Fig. 52-29).<sup>155</sup> Complete transection of a left ventricular papillary muscle is incompatible with life because the sudden massive mitral regurgitation that develops cannot be tolerated. Rupture of a portion of a papillary muscle, usually the tip or head of the muscle, that results in severe, although



**FIGURE 52-30** Echocardiography of two ventricular septal defects (VSDs) that developed after STEMI. A close-up of the ventricular septum in an apical four-chamber view demonstrates turbulent systolic color flow Doppler across a VSD and continuous-wave Doppler demonstrates systolic flow across a VSD (**left**). (From Kamran M, Attari M, Webber G: Images in cardiovascular medicine. Ventricular septal defect complicating an acute myocardial infarction. Circulation 112:e337, 2005.) A subcostal view demonstrates color flow Doppler across a VSD (**right**). (From Brigham and Women's Hospital, 2013.) LV = left ventricle; RV = right ventricle.



**FIGURE 52-31** Surgical specimen showing a papillary muscle (**top left**), chordae, and anterior mitral leaflet (**bottom right**) from a patient who had a partial rupture of the papillary muscle and underwent mitral valve replacement for severe mitral regurgitation after STEMI. (Courtesy Dr. John Byrne, Brigham and Women's Hospital, Boston.)

not necessarily overwhelming mitral regurgitation is much more frequent and is not immediately fatal (Fig. 52-31). Inferior wall infarction can lead to rupture of the posteromedial papillary muscle, which because of its singular blood supply, occurs more commonly than does rupture of the anterolateral muscle, a consequence of anterolateral MI. Unlike rupture of the ventricular septum, which occurs with large infarcts, papillary muscle rupture occurs with a relatively small infarction in approximately half of cases. These patients can sometimes have a modest extent of CAD as well. Rupture of a right ventricular papillary muscle is unusual but can cause massive tricuspid regurgitation and right ventricular failure. In a small number of patients, rupture of more than one cardiac structure is noted clinically or at postmortem examination; all possible combinations of rupture of the left ventricular free wall, the interventricular septum, and the papillary muscles can occur.

As with patients who have a ruptured ventricular septal defect, those with papillary muscle rupture manifest a new holosystolic murmur and have increasingly severe heart failure.<sup>155</sup> In both conditions the murmur may become softer or disappear as arterial pressure falls. Mitral regurgitation secondary to partial or complete rupture of a papillary muscle can be recognized promptly with echocardiography. Color flow Doppler imaging is particularly helpful in distinguishing acute mitral regurgitation from a ventricular septal defect in the setting of STEMI (Table 52-11).<sup>1,154</sup> An echocardiogram should therefore be obtained immediately for any patient in whom the diagnosis is suspected because hemodynamic deterioration can ensue rapidly. Echocardiography also often permits differentiation of papillary muscle rupture from other, generally less severe forms of mitral regurgitation that occur with STEMI.

### Differentiation Between Ventricular Septal Rupture and Mitral Regurgitation

Distinguishing on clinical grounds between acute mitral regurgitation and rupture of the ventricular septum in patients with STEMI in whom a loud systolic murmur suddenly develops may be difficult.<sup>155</sup> Such differentiation can be made most readily by color flow Doppler echocardiography. In addition, right-heart catheterization with a balloon-tipped catheter can readily distinguish between these two complications. Patients with ventricular septal rupture demonstrate a "step-up" in oxygen saturation in blood samples from the right ventricle and pulmonary artery as compared with those from the right atrium. Patients with acute mitral regurgitation lack this step-up; they may demonstrate tall *c-v* waves in both the pulmonary capillary and pulmonary arterial pressure tracings.

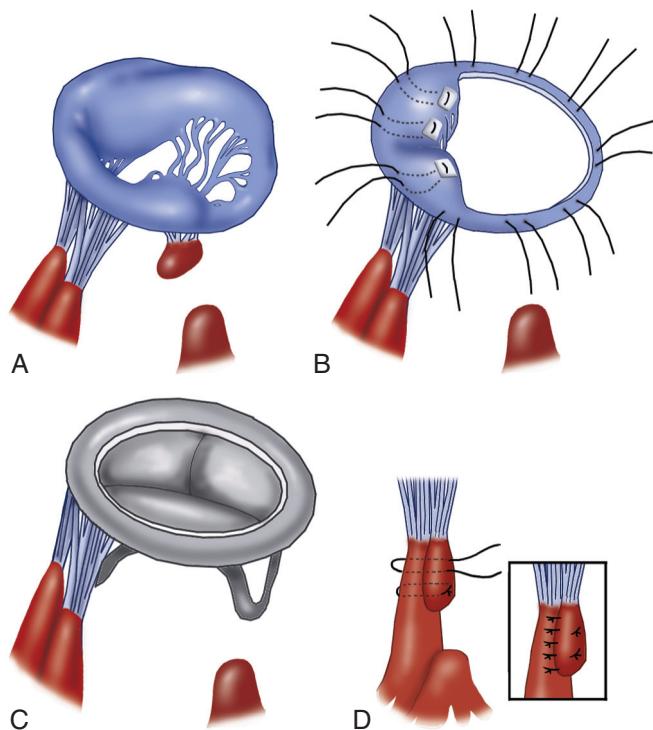
### Management

Invasive monitoring is generally indicated on recognition of a major mechanical complication of STEMI. Right and left ventricular filling pressures (right atrial pressure and pulmonary capillary wedge pressure) guide fluid administration or the use of diuretics, whereas measurements of cardiac output and mean arterial pressure permit calculation of systemic vascular resistance to direct vasodilator therapy. For acute mitral regurgitation and ventricular septal defects, unless systolic pressure is below 90 mm Hg, this therapy, which generally involves nitroglycerin or nitroprusside, should be instituted as soon as possible once hemodynamic monitoring is available. Inotropes may also be needed to support adequate cardiac output. These interventions may be critically important for stabilizing the patient's condition in preparation for further diagnostic studies and

repair. If pharmacologic therapy is not tolerated or if it fails to achieve hemodynamic stability, intra-aortic balloon counterpulsation should be instituted rapidly. Intra-aortic balloon counterpulsation should be considered for most patients with acute mechanical complications of STEMI.

Operative intervention is most successful in patients with STEMI and circulatory collapse when a surgically correctable mechanical lesion such as a ventricular septal defect or ruptured papillary muscle can be identified and addressed. In most cases, surgery should not be delayed in patients with a correctable lesion who agree to an aggressive management strategy and require pharmacologic and/or mechanical (counterpulsation) support.<sup>1</sup> In such patients a serious complication frequently develops—*infection, adult respiratory distress syndrome, extension of the infarct, or renal failure—if surgery is delayed*. Surgical survival is predicted by early surgery, short duration of shock, and mild degrees of right and left ventricular impairment.<sup>152,156</sup> In a subset of patients whose hemodynamic status remains stable, the operation may be postponed for 2 to 4 weeks to allow some healing of the infarct. Such decisions regarding the optimal timing of surgery are complicated and require integration of multiple aspects of the clinical course, as well as the anatomy of the mechanical complication, by a multidisciplinary team. Surgical repair involves correction of mitral regurgitation, insertion of a prosthetic mitral valve, or closure of a ventricular septal defect, usually accompanied by coronary revascularization (**Figs. 52-32 and 52-33**).

Catheter-based options for repair of ventricular septal defects may be appropriate in patients who are not candidates for early definitive surgical correction.<sup>146,157</sup> Because complete closure of the defect, however, requires time for the device to thrombose and endothelialize, in most patients with hemodynamically significant mechanical complications, surgical management is the best established management option.<sup>1</sup>



**FIGURE 52-32** Surgical management of mitral regurgitation caused by a ruptured papillary muscle. **A**, An acute papillary muscle rupture results in severe mitral regurgitation as a result of leaflet and commissural prolapse. Mitral valve replacement is usually necessary. **B**, Mitral debridement with retention of the unruptured commissural and leaflet segment is performed to preserve partial continuity of the annular papillary muscle. **C**, Mitral valve replacement is then performed. **D**, Occasionally, mitral valve repair can be performed by transfer of a papillary head to a nonruptured segment. (Courtesy Dr. David Adams, Mt. Sinai Hospital, New York.)

## ARRHYTHMIAS (See also Chapters 37 Through 39)

Arrhythmias that can complicate the course of patients with STEMI, as well as their prevention and treatment in this setting, are discussed here and summarized in **Table 52-12**. Many serious arrhythmias develop before hospitalization, even before the patient is monitored. Some abnormality in cardiac rhythm also occurs in many patients with STEMI treated in the hospital. These arrhythmias can include both tachycardic and bradycardic episodes, both of which have the ability to provoke hemodynamic consequences.

### Hemodynamic Consequences

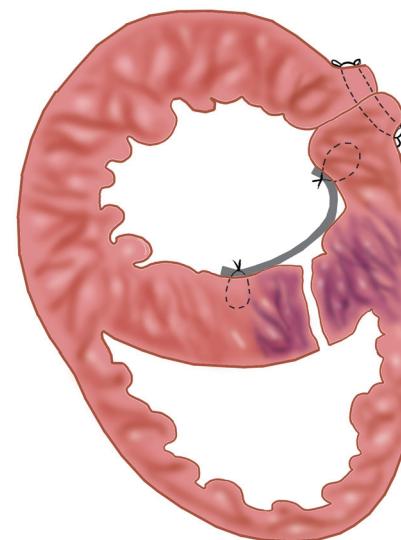
Patients with significant left ventricular dysfunction have a relatively fixed stroke volume and depend on changes in the heart rate to alter cardiac output. However, the range of heart rate with maximal cardiac output is narrow: either faster or slower rates can cause reductions in output. Thus all forms of tachycardia and bradycardia can depress cardiac output in patients with STEMI. Although optimal cardiac output may require a rate higher than 100 beats/min, because heart rate is one of the major determinants of myocardial oxygen consumption, more rapid heart rates elevate myocardial energy needs to levels that can adversely affect ischemic myocardium. In patients with STEMI, therefore, the optimal rate is usually lower—in the range of 60 to 80 beats/min.

A second factor to consider in assessing the hemodynamic consequences of a particular arrhythmia is loss of the atrial contribution to ventricular preload. Studies of patients without STEMI have demonstrated that loss of atrial transport decreases left ventricular output by 15% to 20%. In patients with reduced diastolic left ventricular compliance of any cause (including STEMI), however, atrial systole is of greater importance for left ventricular filling. In patients with STEMI, atrial systole boosts end-diastolic volume by approximately 15%, end-diastolic pressure by 30%, and stroke volume by 35%.

## Ventricular Arrhythmias (See Chapters 37 and 39)

### Ventricular Premature Depolarizations

Before the widespread use of reperfusion therapy, aspirin, beta-blocking agents, and intravenous nitrates for the management of STEMI, frequent ventricular premature complexes (VPCs) (more than



**FIGURE 52-33** Repair of an ischemic ventricular septal defect. The infarct typically involves a free wall and septum. Repair of the defect is performed through an incision in the ventricular wall infarct. The septal defect is closed with a prosthetic patch, and a second patch is used to close the incision in the free wall. (Courtesy Dr. David Adams, Mt. Sinai Hospital, New York.)



five per minute), VPCs with a multiform configuration, early coupling (the “R-on-T” phenomenon), and repetitive patterns in the form of couplets or salvos were thought to presage VF. It is now clear, however, that as many patients in whom fibrillation does not develop as those in whom it does have such “warning arrhythmias.” Several reports have shown that primary VF (see later) occurs without antecedent warning arrhythmias and may even develop despite suppression of warning arrhythmias. Both primary VF and VPCs, especially R-on-T beats, occur during the early phase of STEMI, when considerable heterogeneity in electrical activity is present. Although R-on-T beats expose this heterogeneity and can precipitate VF in a small minority of patients, the ubiquitous nature of VPCs in patients with STEMI and the extremely infrequent nature of VF in the current era of STEMI management produce unacceptably low sensitivity and specificity of the electrocardiographic patterns observed on monitoring systems for identifying patients at risk for VF.

### Management

The incidence of VF in patients with STEMI seen in CCUs over the past three decades appears to have declined. The previous practice of prophylactic suppression of ventricular premature beats with antiarrhythmic drugs is not indicated and may actually increase the risk for fatal bradycardic and asystolic events.<sup>1</sup> We therefore pursue a conservative course when VPCs are observed in patients with STEMI and do not routinely prescribe antiarrhythmic drugs, other than beta blockers, but instead determine whether recurrent ischemia or electrolyte or metabolic disturbances are present.<sup>1</sup> When VPCs accompany sinus tachycardia at the inception of an infarction, augmented sympathoadrenal stimulation often contributes and can be treated by beta-adrenergic blockade. In fact, early administration of an intravenous beta blocker effectively reduces the incidence of VF in cases of evolving MI.<sup>158</sup>

### Accelerated Idioventricular Rhythm

An accelerated idioventricular rhythm typically occurs during the first 2 days, with about equal frequency in anterior and inferior infarctions. Most episodes are of short duration. Accelerated idioventricular rhythm is often observed shortly after successful reperfusion has been established with fibrinolytic therapy. However, the frequent occurrence of this rhythm in patients without reperfusion limits its reliability as a marker of the restoration of patency of the infarct-related coronary artery and may have different implications following primary PCI.<sup>159</sup> In contrast to rapid VT, accelerated idioventricular rhythm is thought not to affect prognosis, and we do not routinely treat accelerated idioventricular rhythms.

### Ventricular Tachycardia and Ventricular Fibrillation

A leading hypothesis for a major mechanism of ventricular arrhythmias in the acute phase of coronary occlusion is reentry caused by inhomogeneity of the electrical characteristics of ischemic myocardium.<sup>160</sup> The cellular electrophysiologic mechanisms for reperfusion arrhythmias appear to include washout of various ions such as lactate and potassium and toxic metabolic substances that have accumulated in the ischemic zone. VT and/or VF occurring late in the course of STEMI is more common in patients with transmural infarction and left ventricular dysfunction and is more frequently associated with hemodynamic deterioration.

### Prophylaxis

Because hypokalemia can increase the risk for development of VT, low serum potassium levels should be identified quickly after admission for STEMI and should be treated promptly.<sup>161</sup> Despite the lack of a consistent relationship between hypomagnesemia and ventricular arrhythmias, magnesium deficits may still be linked to risk because patients with STEMI have reduced intracellular magnesium levels not adequately reflected by serum measurements. As noted earlier, magnesium should be repleted to achieve a serum level of 2 mEq/liter. Early beta blocker use has reduced VF and can be instituted in patients without contraindication. Lidocaine prophylaxis to prevent primary VF is no longer advised.<sup>1</sup>

### Management

Treatment of unstable VT or VF consists of electrical cardioversion implemented as rapidly as possible. Successful interruption of unstable ventricular arrhythmias or prevention of refractory recurrent episodes can also be facilitated by the intravenous administration of amiodarone. We do not usually administer bicarbonate injections to correct acidosis because of the high osmotic load that they impose and because hyperventilation of the patient is probably a more suitable means of clearing the acidosis. After reversion to sinus rhythm, every effort should be made to correct any underlying abnormalities such as hypoxia, hypotension, acid-base or electrolyte disturbances, and digitalis excess. Urgent attempts at revascularization are warranted if ventricular arrhythmias are ongoing and caused by ischemia. The use of extended antiarrhythmic drug therapy, such as amiodarone or lidocaine, is discussed in Chapter 37. In patients with sustained VT or VF successfully treated at a time after successful reperfusion, we generally continue antiarrhythmic drug therapy, most often amiodarone, until a defibrillator is placed.

Failure of electrical cardioversion to restore an effective cardiac rhythm is almost always caused by rapidly recurrent VT or VF, by electromechanical dissociation, or rarely, by electrical asystole. When synchronous cardiac electrical activity is restored by countershock but contraction is ineffective (i.e., pulseless electrical activity), the underlying cause is usually extensive myocardial ischemia or necrosis or rupture of the ventricular free wall or septum.

The highest rates of successful treatment of VT/VF occur in the intensive care setting. When ventricular arrhythmias occur outside an intensive care unit, resuscitative efforts are much less likely to be successful, primarily because the time interval between onset of the episode and institution of definitive therapy tends to be prolonged.

### Prognosis

Among patients who underwent fibrinolytic therapy in the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) study, approximately 10% experienced VT/VF. In the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) study, which included patients treated with primary PCI, sustained VT/VF developed in 5.7%. Clinical outcomes were worse in patients with VT/VF than in those without VT/VF. Additionally, mortality rates were worse in those with early versus late VT/VF; specifically, when compared with patients without VT/VF, the risk for mortality at 90 days increased twofold in patients with both early and late VT/VF, respectively.<sup>158</sup> In patients in whom sustained VT/VF develops later in the course after STEMI (e.g., after more than 48 hours) without evidence of a reversible cause, implantable cardioverter-defibrillator (ICD) therapy for secondary prevention should be considered before discharge.<sup>1</sup> This situation differs from that in patients with VT/VF before reperfusion therapy, in whom antiarrhythmic therapy other than a beta blocker is not indicated. Indications for insertion of an ICD for *primary* prevention in patients with a reduced left ventricular ejection fraction after STEMI are discussed later in this chapter.

## Bradyarrhythmias (See Chapters 36 and 37)

### Sinus Bradycardia

Sinus bradycardia occurs commonly during the early phases of STEMI, particularly in patients with inferior and posterior infarctions. On the basis of data obtained from experimental infarction and from some clinical observations, the increased vagal tone that produces sinus bradycardia during the early phase of STEMI may actually be beneficial, perhaps because it reduces myocardial oxygen demand. Thus the acute mortality rate in patients with sinus bradycardia appears to be similar to that in those without this arrhythmia.<sup>1</sup>

### Management

Isolated sinus bradycardia, unaccompanied by hypotension or ventricular ectopy, should be observed rather than treated initially. In the first 4 to 6 hours after infarction, if the sinus rate is extremely low (<40 to 50 beats/min) and associated with hypotension, intravenous

atropine in doses of 0.3 to 0.6 mg every 3 to 10 minutes (with a total dose not exceeding 3 mg) can be administered to bring the heart rate up to approximately 60 beats/min.

### Atrioventricular and Intraventricular Block

Ischemic injury can produce conduction block at any level of the AV or intraventricular conduction system. Such blocks can occur in the AV node and the bundle of His and produce various grades of AV block, in either main bundle branch and produce right or left bundle branch block, and in the anterior and posterior divisions of the left bundle and produce left anterior or left posterior (fascicular) divisional blocks. Conduction disturbances can, of course, occur in various combinations. The clinical features of proximal and distal AV conduction disturbances in patients with STEMI are summarized in **Table 52-13**.

#### First-Degree Atrioventricular Block

A first-degree AV block does not generally require specific treatment. Beta blockers and calcium antagonists (other than dihydropyridines) prolong AV conduction and may be responsible for first-degree AV block as well, but discontinuation of the use of these drugs in the setting of STEMI could increase ischemia and ischemic injury. Therefore we do not decrease the dosage of these drugs unless the PR interval is greater than 0.24 second. Use of these agents should be stopped only if a higher-degree block or hemodynamic impairment occurs. If the block is a manifestation of excessive vagotonia and is associated with sinus bradycardia and hypotension, administration of atropine, as already outlined, may be helpful. Continued

electrocardiographic monitoring is important in such patients in view of the possibility of progression to higher degrees of block.

#### Second-Degree Atrioventricular Block

First-degree and type I second-degree AV blocks do not appear to affect survival, are most commonly associated with occlusion of the right coronary artery, and are caused by ischemia of the AV node (**Table 52-13**). Specific therapy is not required in patients with second-degree type I AV block when the ventricular rate exceeds 50 beats/min and PVCs, heart failure, and bundle branch block are absent. If these complications develop, however, or if the heart rate falls below approximately 50 beats/min and the patient is symptomatic, immediate treatment with atropine (0.3 to 0.6 mg) is indicated; temporary pacing systems are almost never needed in the management of this arrhythmia.

Type II second-degree AV block in the setting of inferior/posterior STEMI is usually temporary and is manifested as a narrow-complex/junctional escape rhythm. These arrhythmias can typically be managed conservatively. With anterior/lateral STEMI, a type II second-degree AV block usually originates from a lesion in the conduction system below the bundle of His (**Table 52-13**). Because of its potential for progression to complete heart block, type II second-degree AV block in this setting should be treated with a temporary external or transvenous demand pacemaker.<sup>1</sup>

#### Complete (Third-Degree) Atrioventricular Block

Complete AV block can occur in patients with either inferior or anterior infarction, although it is more common in the inferior than in the anterior location. Complete heart block in patients with inferior

**TABLE 52-13** Atrioventricular Conduction Disturbances in Acute Myocardial Infarction

	LOCATION OF AV CONDUCTION DISTURBANCE	
	Proximal	Distal
Site of block	Intranodal	Intranodal
Site of infarction	Inferoposterior	Anteroseptal
Compromised arterial supply	RCA (90%), LCX (10%)	Septal perforators of the LAD
Pathogenesis	Ischemia, necrosis, hydropic cell swelling, excessive parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
Predominant type of AV nodal block	First-degree (PR >200 msec) Mobitz type I second-degree	Mobitz type II second-degree Third-degree
Common premonitory features of third-degree AV block	First- or second-degree AV block Mobitz I pattern	Intraventricular conduction block Mobitz II pattern
Features of escape rhythm following third-degree block		
Location	Proximal conduction system (His bundle)	Distal conduction system (bundle branches)
QRS width	<0.12/sec*	>0.12/sec
Rate	45-60/min but may be as low as 30/min	Often <30/min
Stability of escape rhythm	Rate usually stable; asystole uncommon	Rate often unstable with moderate to high risk for ventricular asystole
Duration of high-grade AV block	Usually transient (2-3 days)	Usually transient but some form of AV conduction disturbance and/or intraventricular defect may persist
Associated mortality rate	Low unless associated with hypotension and/or with power failure or ventricular arrhythmias	High because of extensive infarction associated congestive heart failure
Pacemaker therapy		
Temporary	Rarely required; may be considered for bradycardia associated with left ventricular power failure, syncope, or angina	Should be considered in patients with anteroseptal infarction and acute bifascicular block
Permanent	Almost never indicated because the conduction defect is usually transient	Indicated for patients with high-grade AV block and block in the His-Purkinje system and those with a transient advanced AV block and associated bundle branch block

\*Some studies suggest that a wide QRS escape rhythm (>0.12 second) following high-grade AV block in inferior infarction is associated with a worse prognosis.

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery.

Modified from Antman EM, Rutherford JD (eds): *Coronary Care Medicine: A Practical Approach*. Boston, Martinus Nijhoff, 1986; and Dreifus LS, Fisch C, Griffin JC, et al: Guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. *J Am Coll Cardiol* 18:1, 1991.



infarction usually develops gradually, often progressing from a first-degree or type I second-degree block.<sup>162</sup> The escape rhythm is typically stable without asystole and often junctional, with a rate exceeding 40 beats/min and a narrow QRS complex in 70% of cases and a slower rate and wide QRS complex in the others. This form of complete AV block is often transient, may respond to pharmacologic antagonism of adenosine with methylxanthines, and resolves in most patients within a few days (*Table 52-13*).

Patients with inferior infarction often have concomitant ischemia or infarction of the AV node secondary to hypoperfusion of the AV node artery, but the His-Purkinje system usually escapes injury in such individuals. Patients with inferior STEMI and AV block have larger infarcts and more depressed right ventricular and left ventricular function than do patients with an inferior infarct and no AV block. As already noted, junctional escape rhythms with narrow QRS complexes occur commonly in this setting.

Pacing is not generally necessary in patients with inferior wall infarction and complete AV block because it is often transient in nature, but it is indicated if symptoms related to a ventricular rate emerge, if ventricular arrhythmias or hypotension is present, or if pump failure develops; atropine only rarely proves adequate in these patients. Only when complete heart block develops in less than 6 hours after the onset of symptoms is atropine likely to abolish the AV block or cause acceleration of the escape rhythm. In such cases the AV block is more likely to be transient and to be related to increases in vagal tone, as opposed to the more persistent block seen later in the course of STEMI, which generally requires cardiac pacing.

In patients with anterior infarction, third-degree AV block can occur suddenly 12 to 24 hours after the onset of infarction, although it is usually preceded by an intraventricular block and often a type II (not first-degree or type I) AV block. Such patients typically have unstable escape rhythms with wide QRS complexes and rates less than 40 beats/min; ventricular asystole may occur quite suddenly. In patients with anterior infarction, AV block generally develops as a result of extensive septal necrosis involving the bundle branches. The high rate of mortality in this group of patients with a slow idioventricular rhythm and wide QRS complex is the consequence of extensive myocardial necrosis resulting in severe left ventricular failure and frequently shock (*Table 52-13*).

Whether temporary transvenous pacing per se improves survival in patients with anterior STEMI remains controversial. Some physicians contend that ventricular pacing is of limited efficacy when used to correct a complete AV block in patients with anterior infarction in view of the poor prognosis in this group regardless of therapy. However, pacing protects against asystole and may protect against transient hypotension, with its attendant risks of extending the infarction and precipitating malignant ventricular tachyarrhythmias.

### **Intraventricular Block**

The right bundle branch and the left posterior division have a dual blood supply from the left anterior descending and right coronary arteries, whereas the left anterior division is supplied by septal perforators originating from the left anterior descending coronary artery. Not all conduction blocks in patients with STEMI are complications of infarcts because almost half are already present at the time that the first ECG is recorded, and they may represent antecedent conduction abnormalities. When compared with patients without conduction defects, those with STEMI and bundle branch blocks have higher peak biomarker levels, lower ejection fractions, and increased in-hospital and long-term mortality rates.<sup>163</sup> In the prefibrinolytic era, intraventricular conduction disturbances (i.e., block within one or more of the three subdivisions [fascicles] of the His-Purkinje system [the anterior and posterior divisions of the left bundle and the right bundle]) occurred in 5% to 10% of patients with STEMI. More recent series in the reperfusion era suggest that intraventricular blocks occur in approximately 2% to 5% of patients with MI.<sup>163</sup>

### **Isolated Fascicular Blocks**

An isolated left anterior divisional block is unlikely to progress to a complete AV block. Mortality is increased in these patients, although

not as much as in those with other forms of conduction block. The posterior fascicle is larger than the anterior fascicle, and in general, a larger infarct is required to block it. As a consequence, mortality is markedly increased. Complete AV block is not a frequent complication of either form of isolated divisional block.

### **Right Bundle Branch Block**

This conduction defect alone can lead to AV block because it is often a new lesion associated with anteroseptal infarction. Isolated right bundle branch block is associated with an increased risk for mortality in patients with anterior STEMI even if complete AV block does not occur, but this appears to be the case only if accompanied by congestive heart failure.

### **Bifascicular Block, Including Left Bundle Branch Block**

The combination of right bundle branch block with either left anterior or posterior divisional block or the combination of left anterior and posterior divisional blocks (i.e., left bundle branch block) is known as *bidivisional* or *bifascicular block*. If a new block occurs in two of the three divisions of the conduction system, the risk for development of a complete AV block is quite high. Mortality is also high because of the occurrence of severe pump failure secondary to the extensive myocardial necrosis required to produce such an extensive intraventricular block.<sup>164</sup>

Preexisting bundle branch block or divisional block is less often associated with the development of complete AV block in patients with STEMI than are conduction defects acquired during the course of the infarct. Bidivisional block in the presence of prolongation of the PR interval (first-degree AV block) may indicate disease of the third subdivision rather than disease of the AV node and is associated with a greater risk for complete heart block than if first-degree AV block is absent.

Complete bundle branch block (either left or right), the combination of right bundle branch block and left anterior divisional (fascicular) block, and any of the various forms of trifascicular block are all more often associated with anterior than with inferoposterior infarction. All these forms are more frequent with large infarcts and in older patients and have a higher incidence of other accompanying arrhythmias than seen in patients without bundle branch block.

### **Use of Pacemakers in Patients with Acute Myocardial Infarction (See Chapter 36)**

#### **Temporary Pacing**

Just as is the case for complete AV block, transvenous ventricular pacing has not resulted in a statistically demonstrable improvement in prognosis in patients with STEMI in whom intraventricular conduction defects develop. Temporary pacing is advisable in some of these patients, however, because of the high risk for development of a complete AV block. This category includes patients with new bilateral (bifascicular) bundle branch block (i.e., right bundle branch block with left anterior or posterior divisional block and alternating right and left bundle branch block); first-degree AV block adds to this risk. An isolated new block in only one of the three fascicles, even with PR prolongation and preexisting bifascicular block and a normal PR interval, poses somewhat less risk; these patients should be monitored closely, with insertion of a temporary pacemaker deferred unless a higher-degree AV block occurs.

#### **Asystole**

The presence of apparent ventricular asystole on monitor displays of continuously recorded ECGs may be misleading in that the rhythm may actually be fine VF. The predominance of VF as the cause of cardiac arrest in this setting suggests electrical countershock as initial therapy, even if definitive electrocardiographic documentation of this arrhythmia is not available.

#### **Permanent Pacing**

The advisability of permanent pacemaker insertion is complicated because not all sudden deaths in patients with STEMI and conduction defects are caused by high-grade AV block. A high incidence of late

VF occurs in CCU survivors with anterior STEMI complicated by either right or left bundle branch block. Therefore VF rather than asystole caused by failure of AV conduction and infranodal pacemakers could be responsible for late sudden death.

Long-term pacing is often helpful when complete heart block persists throughout the hospital phase in a patient with STEMI, when sinus node function is markedly impaired, or when type II second-degree or third-degree block occurs intermittently.<sup>165</sup> When high-grade AV block is associated with newly acquired bundle branch block or other criteria for conduction system impairment, prophylactic long-term pacing may be justified as well. Additional considerations that drive the decision to insert a permanent pacemaker include whether the patient is a candidate for an ICD or has severe heart failure that might be improved with biventricular pacing ([see Chapters 25 and 26](#)).

## Supraventricular Tachyarrhythmias

([See Chapters 37 and 38](#))

### Sinus Tachycardia

This arrhythmia is typically associated with augmented sympathetic activity and may provoke transient hypertension or hypotension. Common causes are anxiety, persistent pain, left ventricular failure, fever, pericarditis, hypovolemia, pulmonary embolism, and the administration of drugs such as atropine, epinephrine, or dopamine; rarely, it occurs in patients with atrial infarction. Sinus tachycardia is particularly common in patients with anterior infarction, especially in those with significant accompanying left ventricular dysfunction. It is an undesirable rhythm in patients with STEMI because it results in augmentation of myocardial oxygen consumption, as well as a reduction in the time available for coronary perfusion, thereby intensifying the myocardial ischemia and/or external myocardial necrosis. Persistent sinus tachycardia can signify persistent heart failure and, in these circumstances, connotes a poor prognosis and excess mortality. An underlying cause should be sought and appropriate treatment instituted, such as analgesics for pain; diuretics for heart failure; oxygen, beta blockers, and nitroglycerin for ischemia; and aspirin for fever or pericarditis. Treating sinus tachycardia caused by pain, anxiety, or fever with beta blockers is reasonable, but beta blockers are contraindicated in patients who are tachycardic because of pump failure.

### Atrial Flutter and Fibrillation

Atrial flutter and atrial fibrillation are usually transient in patients with STEMI; they are typically a consequence of augmented sympathetic stimulation of the atria and often occur in patients with left ventricular failure, pulmonary emboli in which the arrhythmia intensifies hemodynamic deterioration, or atrial infarction ([see Table 52-12](#)). The increased ventricular rate and loss of the atrial contribution to left ventricular filling can result in a significant reduction in cardiac output. Atrial fibrillation during STEMI is associated with increased mortality and stroke, particularly in patients with anterior wall infarction<sup>166</sup>—but because it is more common in patients with clinical and hemodynamic manifestations of extensive infarction and a poor prognosis, atrial fibrillation is probably a marker of a poor prognosis with only a small independent contribution to increased mortality.<sup>166</sup>

### Management

Atrial flutter and fibrillation in patients with STEMI are treated in a manner similar to these conditions in other settings ([see Chapter 38](#)). If the arrhythmia is causing ongoing hypotension, ischemia, or heart failure, cardioversion should be considered. In stabilized patients and in the absence of contraindications, a beta blocker should be administered after STEMI; in addition to several other benefits, these agents help slow the ventricular rate should atrial fibrillation recur. Digitalis may also help slow the ventricular rate when atrial fibrillation develops after STEMI in the setting of ventricular dysfunction.<sup>167</sup> In addition, amiodarone may be considered in this situation. Patients with recurrent episodes of atrial fibrillation should be treated

with oral anticoagulants (to reduce the risk for stroke), even if sinus rhythm is present at the time of hospital discharge, because no antiarrhythmic regimen can be relied on to completely suppress atrial fibrillation.

## OTHER COMPLICATIONS

### Recurrent Chest Discomfort

Evaluation of postinfarction chest discomfort is sometimes complicated by previous abnormalities on the ECG and a vague description of the discomfort by the patient, who either may be exquisitely sensitive to fleeting discomfort or may deny a potential recrudescence of symptoms. The critical task for clinicians is to distinguish recurrent angina or infarction from nonischemic causes of discomfort that might be caused by infarct expansion, pericarditis, pulmonary embolism, and non–cardiac-related conditions. Ischemic causes to consider include acute reocclusion of an initially recanalized or stented vessel, mechanical or thrombotic occlusion of a side branch or distal vessel during an initial PCI, new ischemia in a non–infarct-related coronary artery that was also stenosed but not occluded, and coronary spasm. Important diagnostic maneuvers include repeated physical examination, repeated ECG, and assessment of the response to sublingual nitroglycerin, 0.4 mg. (The use of noninvasive diagnostic evaluation for recurrent ischemia in patients whose symptoms appear only with moderate or higher levels of exertion is discussed elsewhere in this chapter.)

### Recurrent Ischemia and Reinfarction

The incidence of postinfarction angina with and without reinfarction is significantly reduced in patients undergoing primary PCI for STEMI versus fibrinolysis. Additionally, in high-risk patients with STEMI who were treated with fibrinolysis, transfer for PCI within 6 hours after fibrinolysis is also associated with significantly fewer ischemic complications than is treatment with fibrinolysis alone.<sup>72</sup> More effective antiplatelet and antithrombin therapies have also reduced the rate of recurrent ischemic events following STEMI.<sup>1</sup> Consequently, the incidence of early recurrent ischemic events in STEMI patients treated by immediate or delayed PCI is now in a range of less than 5%.

### Diagnosis

Extension of the original zone of necrosis or reinfarction into a separate myocardial zone can be a difficult diagnosis, especially within the first 24 hours after the index event. Diagnostic criteria have been established,<sup>168</sup> but discrimination of a new myocardial infarction discrete from the initial STEMI is often challenging because both cardiac markers may remain elevated as a result of the initial infarction and distinguishing changes of the normal evolution after the index infarction from those caused by recurrent infarction may not be possible on the ECG. Recurrent infarction should be strongly considered, however, when dynamic recurrent ST-segment elevation is noted on the ECG.

Pericarditis should also be considered in such patients. The presence of a rub and lack of responsiveness to nitroglycerin may be useful in distinguishing pericardial discomfort, but doing so on clinical grounds is frequently challenging, and diagnostic coronary angiography may be necessary to exclude acute native vessel or stent thrombosis. The predominant angiographic predictors of reinfarction in patients undergoing primary PCI include a final coronary stenosis greater than 30%, post-PCI coronary dissection, and post-PCI intracoronary thrombus.<sup>169</sup>

### Prognosis

Regardless of whether postinfarction angina is persistent or limited, its presence is important because of the associated higher short-term morbidity rate. Reinfarction is linked to higher rates of in-hospital complications (congestive heart failure, AV block) and early and long-term mortality.<sup>170</sup> Presumably, the higher mortality rate is related to the larger mass of myocardium, the function of which becomes compromised.



## Management

Patients with ST-segment re-elevation and the appropriate clinical findings should be referred for urgent catheterization and PCI (see Fig. 52-1) unless pericarditis or other post-MI complications are the cause; repeated fibrinolysis can be considered if PCI is not available. In patients believed to have recurrent ischemia in the absence of ST elevation concerning for ongoing injury and who do not have evidence of hemodynamic compromise, an attempt should be made to control symptoms with sublingual or intravenous nitroglycerin and intravenous beta blockade to slow the heart rate to 60 beats/min. When hypotension, congestive heart failure, or ventricular arrhythmias develop during recurrent ischemia, urgent catheterization and revascularization are indicated.

High-risk patients with STEMI who undergo fibrinolysis may benefit from a strategy of routine referral for catheterization and revascularization (3 to 24 hours; see Fig. 52-13).<sup>72</sup> Trials that compared primary PCI with PCI performed as soon as possible after a preparatory pharmacologic regimen had been administered, however, have not shown such a facilitated PCI approach to be more effective than primary PCI, and mortality may even increase because of excessive bleeding in the facilitated PCI group.<sup>1</sup>

Finally, with increasing use of PCI for the management of patients with STEMI, clinicians should be alert to the problem of stent thrombosis as a cause of recurrent ischemia. Stent thrombosis can occur acutely (hours to days after deployment of a stent) or in a more subacute fashion (many months after deployment of a stent) (see Chapter 55).

## Pericardial Effusion and Pericarditis

(See Chapter 71)

### Pericardial Effusion

Effusions are generally detected echocardiographically, and their incidence varies with technique, criteria, and laboratory expertise.<sup>171</sup> Effusions are more common in patients with anterior STEMI and with larger infarcts and when congestive failure is present. Most pericardial effusions that occur following STEMI do not cause hemodynamic compromise. The reabsorption rate of a postinfarction pericardial effusion is slow, with resolution often taking several months. The presence of an effusion does not indicate that pericarditis is present; although they may occur together, most effusions develop without other evidence of pericarditis. When tamponade does occur, it is usually caused by ventricular rupture or hemorrhagic pericarditis.

### Pericarditis

Pericarditis can produce pain as early as the first day and as late as 8 weeks after STEMI. The pain of pericarditis may be confused with that resulting from postinfarction angina, recurrent infarction, or both. An important distinguishing feature is radiation of the pain to either trapezius ridge, a finding that is nearly pathognomonic of pericarditis and rarely seen with ischemic discomfort. Additionally, the discomfort of pericarditis usually becomes worse during a deep inspiration, but it can be relieved or diminished when the patient sits up and leans forward.

Transmural MI, by definition, extends to the epicardial surface and can cause local pericardial inflammation. An acute fibrinous pericarditis (pericarditis epistenoocardica) occurs commonly after transmural infarction, but most patients do not report any symptoms from this process. Although transient pericardial friction rubs are relatively common within the first 48 hours in patients with transmural infarction, pain or electrocardiographic changes occur much less often. The development of a pericardial rub, however, appears to correlate with a larger infarct and greater hemodynamic compromise.

Although anticoagulation clearly increases the risk for hemorrhagic pericarditis early after STEMI, this complication does not occur with sufficient frequency during heparinization or following fibrinolytic therapy to warrant absolute prohibition of such agents when a rub is present. Nevertheless, detection of a pericardial effusion on echocardiography is usually an indication for discontinuation of anticoagulation. In patients in whom continuation or initiation of

anticoagulant therapy is strongly indicated (e.g., during cardiac catheterization), heightened monitoring of clotting parameters and observation for clinical signs of possible tamponade are necessary. Late pericardial constriction caused by anticoagulant-induced hemopericardium has been reported.

Treatment of pericardial discomfort consists of aspirin, but usually in doses higher than prescribed routinely following infarction—doses of 650 mg orally as often as every 4 hours may be necessary. Nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids should be avoided because they may interfere with myocardial scar formation.<sup>172</sup>

### Dressler Syndrome

Also known as *post-myocardial infarction syndrome*, Dressler syndrome usually occurs 1 to 8 weeks after infarction. Dressler cited an incidence of 3% to 4% of all patients with MI in 1957, but the incidence has decreased dramatically since that time. Clinically, patients with Dressler syndrome have malaise, fever, pericardial discomfort, leukocytosis, an elevated sedimentation rate, and a pericardial effusion. At autopsy, individuals with this syndrome usually demonstrate localized fibrinous pericarditis containing polymorphonuclear leukocytes. The cause of this syndrome is not clearly established, although detection of antibodies to cardiac tissue has raised the notion of an immunopathologic process. Treatment is with aspirin, 650 mg as often as every 4 hours, and in large doses this is effective.<sup>172</sup> Glucocorticosteroids and NSAIDs are best avoided in patients with Dressler syndrome within 4 weeks of STEMI because of their potential to impair infarct healing, cause ventricular rupture, and increase coronary vascular resistance.<sup>172</sup>

## Venous Thrombosis and Pulmonary Embolism

Almost all peri-MI pulmonary emboli originate from thrombi in the veins of the lower extremities; much less commonly, they originate from mural thrombi overlying an area of right ventricular infarction. Bed rest and heart failure predispose to venous thrombosis and subsequent to pulmonary embolism, and both these conditions occur commonly in patients with STEMI, particularly in those with large infarcts. At a time when patients with STEMI were routinely subjected to prolonged periods of bed rest, significant pulmonary embolism was found in more than 20% of individuals with STEMI examined at autopsy, and massive pulmonary embolism accounted for 10% of deaths from MI. In contemporary practice, with early mobilization and the widespread use of low-dose anticoagulant prophylaxis, especially with LMWH, pulmonary embolism has become an uncommon cause of death in patients with STEMI. When pulmonary embolism does occur in patients with STEMI, management is generally along the lines described for patients without infarction (see Chapter 73).

## Left Ventricular Aneurysm

The term *left ventricular aneurysm* (often termed *true aneurysm*) is generally reserved for a discrete, dyskinetic area of the left ventricular wall with a broad neck (to differentiate it from a pseudoaneurysm caused by a contained myocardial rupture). Dyskinetic or akinetic areas of the left ventricle are far more common than true aneurysms after STEMI. True left ventricular aneurysms probably develop in less than 5% of all patients with STEMI.<sup>173</sup> The wall of a true aneurysm is thinner than the wall of the rest of the left ventricle (see Fig. 52-29), and it is usually composed of fibrous tissue, as well as necrotic muscle occasionally mixed with viable myocardium.

### Pathogenesis

Aneurysm formation presumably occurs when intraventricular tension stretches the noncontracting infarcted heart muscle and thus produces expansion of the infarct, a relatively weak, thin layer of necrotic muscle, and fibrous tissue that bulges with each cardiac contraction. With the passage of time, the wall of the aneurysm

becomes more densely fibrotic, but it continues to bulge with systole and causes some of the left ventricular stroke volume during each systole to be ineffective.

Total occlusion of a poorly collateralized left anterior descending coronary artery is generally associated with aneurysm formation after anterior STEMI. An aneurysm rarely occurs with multivessel disease when either extensive collaterals or a nonoccluded left anterior descending artery is present. Aneurysms usually range from 1 to 8 cm in diameter. They occur approximately four times more often at the apex and in the anterior wall than in the inferoposterior wall. The overlying pericardium generally adheres densely to the wall of the aneurysm, which may even become partially calcified after several years. True left ventricular aneurysms (in contrast to pseudoaneurysms) rarely rupture soon after development. Late rupture, when the true aneurysm has become stabilized by the formation of dense fibrous tissue in its wall, almost never occurs.

## Diagnosis

The presence of persistent ST-segment elevation in an electrocardiographic area of infarction, classically thought to suggest aneurysm formation, indicates a large infarct with a regional wall motion abnormality but does not necessarily imply an aneurysm. The diagnosis of aneurysm is best made noninvasively by an echocardiographic study, by MRI, or by left ventriculography at the time of cardiac catheterization.

## Prognosis and Treatment

A left ventricular aneurysm increases the risk for mortality, even when compared with that in patients with a comparable left ventricular ejection fraction. Death in these patients is frequently sudden and presumably related to the relatively high incidence of ventricular tachyarrhythmias that occur with aneurysms.<sup>174</sup> With loss of shortening from the area of the aneurysm, the remainder of the ventricle may become hyperkinetic to compensate, but with relatively large aneurysms, complete compensation is impossible. Stroke volume falls, or if maintained, it is at the expense of an increase in end-diastolic volume, which in turn leads to increased wall tension and myocardial oxygen demand. Heart failure may ensue, and angina may appear or worsen.

Aggressive management of STEMI, including prompt reperfusion, may diminish the incidence of ventricular aneurysms. Surgical aneurysmectomy generally succeeds only if contractile performance in the nonaneurysmal portion of the left ventricle is relatively preserved. In such circumstances, when the operation is performed for worsening heart failure or angina, operative mortality is relatively low and clinical improvement can be expected. Several surgical techniques for ventricular reconstruction have been developed to maintain as normal a left ventricular shape as possible.<sup>175</sup> Because of the risk for mural thrombosis and systemic embolization, long-term oral anticoagulation with warfarin may be considered in patients with a residual left ventricular aneurysm after STEMI.

## Left Ventricular Thrombus and Arterial Embolism

Endocardial inflammation and the relative stasis of blood during the acute phase of infarction probably provide a thrombogenic surface for clots to form in the left ventricle. With extensive transmural infarction of the septum, however, mural thrombi may overlie infarcted myocardium in both ventricles. The incidence of left ventricular thrombus formation after STEMI appears to have dropped from approximately 20% to 5% with more aggressive use of antithrombotic strategies, but varying imaging techniques will influence detection rates.<sup>176</sup> Prospective studies have suggested that patients in whom a mural thrombus develops early (within 48 to 72 hours of infarction) have an extremely poor early prognosis, with a high rate of mortality from the complications of a large infarction (shock, reinfarction, rupture, and ventricular tachyarrhythmia), rather than emboli from the left ventricular thrombus.

Even though a mural thrombus adheres to the endocardium overlying the infarcted myocardium, superficial portions of it can become

detached and produce systemic arterial emboli. Although estimates vary because of patient selection, approximately 10% of mural thrombi result in systemic embolization. Echocardiographically detectable features suggesting that a given thrombus is more likely to embolize include increased mobility and protrusion into the ventricular chamber, visualization on multiple views, and contiguous zones of akinesis and hyperkinesis. MRI techniques can also be used to characterize left ventricular thrombi and assist in prediction of the risk for embolism.<sup>176</sup>

## Management

Data from previous trials with limited sample sizes suggested that anticoagulation (intravenous heparin or high-dose subcutaneous heparin) reduces the development of left ventricular thrombi by 50%, but because of the low event rate, demonstrating a reduction in the incidence of systemic embolism was not possible. Fibrinolysis reduces the rate of thrombus formation and the character of the thrombi so that they are less protuberant. Of note, however, the data from fibrinolytic trials are difficult to interpret because of the confounding effect of antithrombotic therapy with heparin. Recommendations for anticoagulation vary considerably, and fibrinolysis has precipitated fatal embolization. Moreover, few data from the era of dual antiplatelet therapy after primary PCI are available to make decisions. Nevertheless, anticoagulation for 3 to 6 months with warfarin is reasonable for many patients with demonstrable mural thrombi. For patients with STEMI and anterior apical akinesis or severe dyskinesia, a limited course of anticoagulant therapy may also be considered.<sup>1</sup>

## CONVALESCENCE, DISCHARGE, AND POST-MYOCARDIAL INFARCTION CARE

The transition to outpatient care after STEMI is a critical one. Post-hospital systems of care designed to reduce hospital readmissions should be used to facilitate coordinated, evidence-based outpatient care for all patients with STEMI.<sup>1,177</sup>

### Timing of Hospital Discharge

In practice, the timing of discharge from the hospital is variable. Patients with STEMI are at risk for late in-hospital mortality from recurrent ischemia or infarction, hemodynamically significant ventricular arrhythmias, and severe congestive heart failure. Risk indicators for mortality in the hospital include significant congestive heart failure as evidenced by persistent sinus tachycardia and pulmonary congestion, recurrent VT and VF, new atrial fibrillation or flutter, intraventricular conduction delays or heart block, anterior location of infarction, and recurrent episodes of angina with marked ST-segment abnormalities at low activity levels (see the section **Risk Stratification after ST-Elevation Myocardial Infarction**).

Aggressive reperfusion protocols with PCI or fibrinolysis can reduce the length of hospital stay without compromising mortality after discharge.<sup>178,179</sup> In patients believed to have successfully undergone reperfusion, the absence of early sustained ventricular tachyarrhythmias, hypotension, or heart failure, coupled with a well-preserved left ventricular ejection fraction, predicts a low risk for late complications in the hospital. Such patients appear to be suitable candidates for discharge from the hospital in less than 5 days from the onset of symptoms.<sup>179</sup> Most complications that would preclude early discharge occur within the first 3 days of admission; therefore patients suitable for early discharge can be identified early during the hospitalization. Several controlled trials and many uncontrolled trials of early discharge after STEMI have failed to show any increase in risk in patients appropriately selected for early discharge.<sup>178,179</sup>

Following STEMI, patients are often eager for information, anxious, in need of reassurance, confused by misinformation and previous impressions, and capable of counterproductive denial. The hospitalization after STEMI provides ample opportunities to begin the rehabilitation process. The decision regarding timing of discharge in

patients with uncomplicated STEMI should take into account the patient's psychological state after STEMI, the adequacy of dose titration for essential drugs such as beta blockers and inhibitors of the RAAS, and the availability and timing of follow-up with visiting nurses and the patient's primary care physician. In patients who have experienced a complication, discharge is deferred until their condition has been stable for several days and it is clear that they have responded appropriately to any interventions.

### Counseling

Before discharge from the hospital, all patients should receive detailed instruction concerning physical activity. Initially, this should consist of walking at home but avoidance of isometric exercise such as lifting. In addition, the patient should be given fresh nitroglycerin tablets and be instructed in their use (see Chapter 54) and should receive instructions for any other medications prescribed. Graded resumption of activity should be encouraged, ideally as part of a monitored cardiac rehabilitation program (see Chapters 47 and 79). Many approaches have been used, ranging from formal rigid guidelines to general advice advocating moderation and avoidance of any activity that evokes symptoms. Sexual counseling, often overlooked during recovery from STEMI, should be included in the educational process.<sup>180</sup> In addition, physicians should explicitly discuss the risk associated with continued smoking and offer assistance in cessation, along with nicotine replacement therapy in appropriate patients.<sup>1,181</sup>

Some evidence indicates that behavioral alteration is possible after recovery from STEMI and that this may improve the prognosis. Patients with STEMI should be referred to a postdischarge cardiac rehabilitation program with supervised physical exercise and an educational component.<sup>182</sup> Given the relationship between depression and STEMI, psychosocial intervention programs can decrease symptoms of depression and are a useful adjunct to standard cardiac rehabilitation programs after STEMI<sup>183</sup> (see Chapters 47 and 86).

## Risk Stratification after ST-Elevation Myocardial Infarction

The process of risk stratification following STEMI occurs in several stages: initial findings, in-hospital course (CCU, intermediate care unit), and at the time of hospital discharge. The tools used to form an integrated and dynamic assessment of the patient consist of baseline demographic information; serial ECGs and serum and plasma cardiac biomarker measurements; hemodynamic monitoring data; a variety of noninvasive tests; and if performed, the findings at cardiac catheterization. These findings, integrated with the occurrence of in-hospital complications, can provide information regarding survival.

### Initial Findings

Certain demographic and historical factors portend a worse prognosis in patients with STEMI, including age older than 65 years, a history of diabetes mellitus, previous angina pectoris, and previous MI (see Fig. 52-8). Diabetes mellitus, in particular, appears to confer a more than 40% increase in adjusted risk for death by 30 days (see Chapter 61).<sup>184</sup> Surviving diabetic patients also experience a more complicated post-MI course, including a greater incidence of postinfarction angina, infarct extension, and heart failure. These higher rates of complications probably relate to the extensive accelerated atherosclerosis and higher risk for thrombosis and heart failure associated with diabetes mellitus.

In addition to playing a central role in the decision pathway for the management of patients with ACSs based on the presence or absence of ST-segment elevation, the 12-lead ECG carries important prognostic information.<sup>63</sup> Mortality is greater in patients experiencing anterior wall STEMI than in those with inferior STEMI, even when corrected for infarct size. Patients with right ventricular infarction complicating inferior infarction, as suggested by ST-segment elevation in V<sub>4R</sub>, have greater mortality rate than do patients sustaining an inferior infarction without right ventricular involvement. Patients with multiple leads showing ST elevation and a high sum of ST-segment elevation

have an increased mortality rate, especially if their infarct is anterior in location. Patients whose ECGs demonstrate persistent advanced heart block (e.g., type II second-degree or third-degree AV block) or new intraventricular conduction abnormalities (bifascicular or trifascicular) in the course of STEMI have a worse prognosis than do patients without these abnormalities. The influence of high degrees of heart block has particular importance in patients with right ventricular infarction because such patients have a markedly increased mortality risk.<sup>63</sup> Other electrocardiographic findings that augur poorly are persistent horizontal or downsloping ST-segment depression, Q waves in multiple leads, evidence of right ventricular infarction accompanying inferior infarction, ST-segment depression in anterior leads in patients with inferior infarction, and atrial arrhythmias (especially atrial fibrillation).

Several validated clinical risk stratification tools may be used at initial evaluation to assess the short- and long-term risk for death after MI.<sup>63</sup> In addition to the patient's age and historical factors such as diabetes and previous MI, clinical signs of heart failure, including tachycardia and hypotension, are common in many of these clinical risk assessment scores.

### Hospital Course

Hospital mortality from STEMI depends directly on the severity of left ventricular dysfunction. Risk stratification via physical findings, estimation of infarct size, and in appropriate patients, invasive hemodynamic monitoring provides an assessment of the likelihood of a complicated hospital course and may also identify important abnormalities, such as hemodynamically significant mitral regurgitation, that convey an adverse long-term prognosis (see Table 52-9). In particular, the development of heart failure after MI entails a higher risk for sudden cardiac death.<sup>185</sup> Recurrent infarction and new stroke during hospitalization for STEMI also, not surprisingly, confer a higher risk for death.

### Assessment at Hospital Discharge

Both short- and long-term survival after STEMI depend on three major factors: resting left ventricular function, residual potentially ischemic myocardium, and susceptibility to serious ventricular arrhythmias. The most important of these factors is the state of left ventricular function (see Fig. 52-23).<sup>63</sup> The second most important factor is how the severity and extent of the obstructive lesions in the coronary vascular bed perfusing residual viable myocardium affect the risk for recurrent infarction, additional myocardial damage, and serious ventricular arrhythmias. Thus survival is related to the quantity of myocardium that has become necrotic and the quantity at risk of becoming necrotic. At one end of the spectrum, the prognosis is best for patients with normal intrinsic coronary vessels whose completed infarction constitutes a small fraction (5%) of the left ventricle as a consequence of a coronary embolus and who have no jeopardized myocardium. At the other extreme are patients with a massive infarct and left ventricular failure whose residual viable myocardium is perfused by markedly obstructed vessels. Progression of atherosclerosis or lowering of perfusion pressure in these vessels impairs the function and viability of the residual myocardium on which left ventricular function depends. Revascularization may reduce the threat to the jeopardized myocardium even in such patients. The third risk factor, susceptibility to serious arrhythmias, is reflected in ventricular ectopic activity and other indicators of electrical instability, such as reduced heart rate variability or baroreflex sensitivity and abnormal findings on a signal-averaged ECG.<sup>63</sup> All these factors identify patients at increased risk for death.

### Assessment of Left Ventricular Function

The left ventricular ejection fraction may be the most easily assessed measurement of left ventricular function and is extremely useful for risk stratification (see Fig. 52-23). However, imaging of the left ventricle at rest may not adequately distinguish among infarcted, irreversibly damaged, and stunned or hibernating myocardium. To circumvent this difficulty, various techniques have been investigated to assess the extent of residual viable myocardium—including

exercise and pharmacologic stress echocardiography, stress radionuclide ventricular angiography, perfusion imaging in conjunction with pharmacologic stress, positron emission tomography, and gadolinium-enhanced MRI.<sup>186,187</sup> All these techniques can be performed safely in postinfarction patients. Because no study has clearly shown one imaging modality to be superior to the others, clinicians should be guided in their selection of ventricular imaging technique by the availability and level of expertise with a given modality at their local institution.<sup>188</sup>

### **Assessment of Myocardial Ischemia**

Because of the adverse consequences of recurrent MI after STEMI, assessing a patient's risk for future ischemia and infarction is important. Predischarge noninvasive testing for ischemia provides valuable information about the presence of residual ischemia in patients who have not undergone coronary angiography during the initial management of STEMI and may also be useful in assessing the functional significance of any angiographically significant coronary stenoses identified at angiography but not revascularized (see Table 52-6). In the latter case, stress imaging to localize ischemia may be useful.

**EXERCISE TESTING.** An exercise test also offers an opportunity to formulate a more precise exercise prescription and helps boost patients' confidence in their ability to conduct their daily activities after discharge. Patients who are unable to exercise can be evaluated via a pharmacologic stress protocol with echocardiography or perfusion imaging. Treadmill exercise testing after STEMI has traditionally used a submaximal protocol that requires the patient to exercise until symptoms of angina appear, electrocardiographic evidence of ischemia is seen, or a target workload (5 metabolic equivalents) has been reached, whichever comes first (see Chapter 47). Symptom-limited exercise tests can be performed safely before discharge in patients with an uncomplicated course after infarction. Variables derived from exercise tests after STEMI that have been evaluated for their ability to predict the occurrence of death or recurrent nonfatal infarction include the development and magnitude of ST-segment depression, the development of angina, exercise capacity, and the systolic blood pressure response during exercise.<sup>189</sup>

### **Assessment for Electrical Instability**

After STEMI, patients are at greatest risk for the development of sudden cardiac death caused by malignant ventricular arrhythmias in the first 1 to 2 years.<sup>63</sup> Multiple techniques have been proposed to stratify patients into those who are at increased risk for sudden death following STEMI: measurement of QT dispersion (variability in QT intervals between ECG leads), ambulatory ECGs for detection of ventricular arrhythmias (Holter monitoring), invasive electrophysiologic testing, recording of a signal-averaged ECG (a measure of delayed, fragmented conduction in the infarct zone), and measurement of heart rate variability (beat-to-beat variability in R-R intervals) or baroreflex sensitivity (slope of a line relating beat-to-beat change in the sinus rate in response to alteration of blood pressure), but none of these approaches have proved sufficiently useful for routine practice.<sup>63</sup>

Despite the increased risk for arrhythmic events following STEMI in patients who are found to have abnormal results on one or more of the noninvasive tests described earlier, several points should be emphasized. The low positive predictive value (<30%) of the noninvasive screening tests limits their usefulness when viewed in isolation. Although the predictive value of screening tests can be improved by combining several of them together, the therapeutic implications of an increased risk profile for arrhythmic events have not been established. The reductions in mortality achievable with the general use of beta blockers, ACE inhibitors, aspirin, and revascularization when appropriate after infarction, coupled with concerns about the efficacy and safety of antiarrhythmic drugs and the cost of implanted defibrillators, leave considerable uncertainty about the therapeutic implications of an abnormal noninvasive test result for electrical instability in an asymptomatic patient. Action by clinicians on the results of an abnormal finding in asymptomatic patients should await additional data on patient outcomes. Management of patients with

sustained, hemodynamically compromising arrhythmias is discussed in Chapters 35 through 38.

### **Prophylactic Antiarrhythmic Therapy**

Although antiarrhythmic therapy can control atrial and ventricular arrhythmias effectively in many patients, routine use of prophylactic antiarrhythmic drug therapy, with the exception of beta blockers, does not improve outcome and, with some agents, increases the risk for death.<sup>1</sup> The most notable postinfarction trial in this area was CAST (Cardiac Arrhythmia Suppression Trial), which tested whether encainide, flecainide, or moricizine for suppression of ventricular arrhythmias detected on ambulatory electrocardiographic monitoring would reduce the risk for cardiac arrest and death; however, CAST was stopped prematurely because of increased mortality in the active treatment groups. The SWORD (Survival With ORal D-sotalol) trial was similarly stopped prematurely because of increased mortality in the active treatment group. In contrast, CAMIAT (Canadian Amiodarone Myocardial Infarction Trial) showed that amiodarone reduces the frequency of ventricular premature depolarization in patients with recent MI and that this reduction correlated with lowering of arrhythmic death or resuscitation from VF. However, 42% of patients discontinued use of amiodarone during maintenance therapy in CAMIAT because of intolerable side effects. EMIAT (European Amiodarone Myocardial Infarction Trial) showed a reduction in arrhythmic death after MI in patients with depressed left ventricular function, but total mortality and other cardiovascular-related mortality did not decrease.

The routine use of antiarrhythmic agents (including amiodarone) therefore cannot be recommended. Although trials that included post-STEMI patients in the study population have shown significant reductions in mortality in those randomly assigned to ICD implantation versus conventional medical therapy (see Chapter 36), early implantation of an ICD in the first few weeks after MI has not shown benefit.<sup>189</sup> Routine risk stratification to guide ICD placement early after STEMI is therefore not recommended; reassessment of left ventricular function 40 days or longer after STEMI may be used to guide consideration of an ICD for primary prevention of sudden cardiac death (Fig. 52-34).<sup>189,190</sup> Trials of strategies for prevention and treatment of arrhythmias, including the use of wearable external defibrillators,<sup>191</sup> during the early period after STEMI are ongoing.

### **Secondary Prevention of Acute Myocardial Infarction (See Chapters 42 and 45)**

Patients who survive the initial course of STEMI still have considerable risk for recurrent events, thus rendering efforts imperative to reduce this risk.

### **Cardiac Rehabilitation**

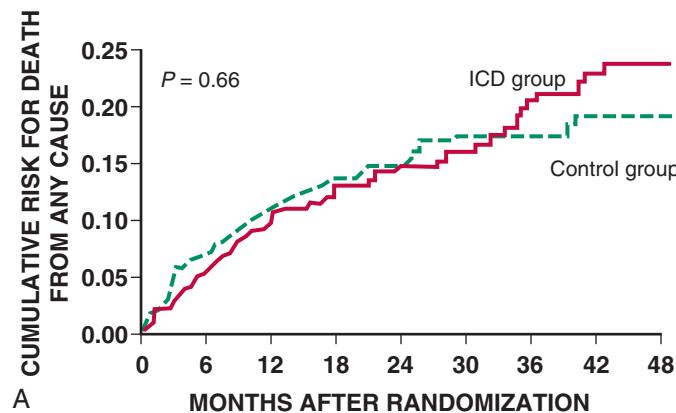
Contemporary exercise-based cardiac rehabilitation after STEMI is aimed at increasing functional capacity, reducing disability, improving quality of life, modifying coronary risk factors, and reducing morbidity and mortality rates.<sup>192-194</sup> The key components of cardiac rehabilitation include patient assessment; ongoing medical surveillance; nutritional counseling; management of hypertension, lipids, and diabetes mellitus; cessation of smoking; psychosocial counseling; physical activity counseling; exercise training; and pharmacologic treatment, as appropriate.<sup>195</sup> When compared with usual care, cardiac rehabilitation is associated with lower total and cardiac mortality, but despite these outcomes, cardiac rehabilitation services remain vastly underused.<sup>1</sup>

### **Lifestyle Modification**

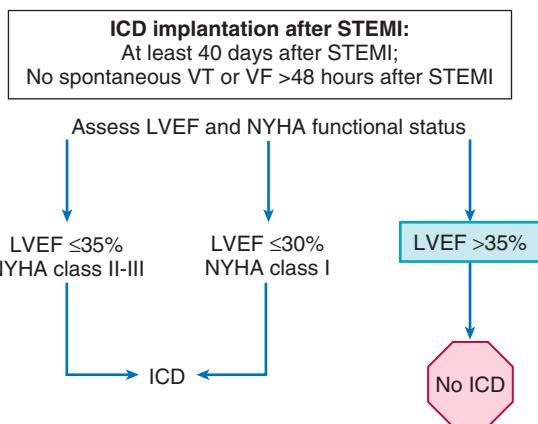
Efforts to improve survival and quality of life after MI that relate to lifestyle modification of known risk factors are considered in Chapter 42. Of these, cessation of smoking and control of hypertension are probably the most important. Use of hospital-based smoking cessation programs and referral to cardiac rehabilitation programs have led to successful smoking cessation.<sup>196</sup>

## Depression (See Chapter 86)

Physicians caring for patients following STEMI need to be sensitive to the prevalence of major depression after infarction.<sup>197</sup> This problem is independently associated with higher risk for death. In addition, lack of an emotionally supportive network in the patient's environment after discharge is associated with an increased risk for recurrent cardiac events. The precise mechanisms relating depression and lack of social support to a worse prognosis after STEMI are not clear, but one possibility is lack of adherence to prescribed treatments, a behavior that has been associated with increased risk for mortality after infarction. Therefore a comprehensive cardiac rehabilitation program that includes primary health care personnel who counsel patients and make home visits can reduce the rate of rehospitalization for recurrent ischemia and infarction.<sup>198</sup>



A



B

**FIGURE 52-34 A,** DINAMIT trial and algorithm for implantation of an ICD in patients with STEMI but without VF or sustained VT more than 48 hours after STEMI. DINAMIT was a randomized, open-label study comparing ICD with no ICD therapy 6 to 40 days after an MI in 674 patients who also had a left ventricular ejection fraction (LVEF) of 35% or less and impaired cardiac autonomic function. The study concluded that ICD therapy was associated with a reduction in the rate of death from arrhythmias but that this advantage was offset by an increase in deaths from other causes. **B,** The appropriate management path is based on measurement of LVEF; measurements obtained 3 days or less after STEMI should be repeated before proceeding with the algorithm. Patients with an LVEF of less than 30% to 40% at least 40 days after STEMI are referred for insertion of an ICD if they are in New York Heart Association (NYHA) class II or III. Patients with a more depressed LVEF of less than 30% to 35% are referred for ICD implantation even if they are NYHA class I because of their increased risk for sudden cardiac death. Patients with preserved left ventricular function (LVEF > 40%) do not receive an ICD and are treated with medical therapy after STEMI. (**A,** From Hohnloser SH, Kuck KH, Dorian P, et al: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 351:2481, 2004; **B,** modified from Zipes DP, Camm AJ, Borggrefe M, et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death]. Developed in collaboration with the European Rhythm Association and the Heart Rhythm Society. *Circulation* 114:e385, 2006.)

## Modification of Lipid Profile (See Chapters 42 and 45)

A target low-density lipoprotein cholesterol level of less than 100 mg/dL with an optimal target of less than 70 mg/dL has been recommended in patients with clinically evident CAD.<sup>199</sup> High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.<sup>1</sup> Obtaining a lipid profile on admission is reasonable in all patients admitted with acute infarction. Total cholesterol levels may fall 24 to 48 hours after infarction.

## Antiplatelet Agents (See also Chapter 82)

On the basis of compelling data from the Antiplatelet Trialists' Collaboration of a 22% reduction in the risk for recurrent infarction, stroke, or vascular death in high-risk vascular patients receiving prolonged antiplatelet therapy, in the absence of true aspirin allergy all patients with STEMI should receive 75 to 325 mg of aspirin daily indefinitely, with 81 mg being the preferred maintenance dose.<sup>1,154</sup> Additional benefits of long-term aspirin therapy that can accrue in patients with STEMI include an increased likelihood of patency of the infarct artery and smaller infarcts if MI recurs. Patients with true aspirin allergy can be treated with clopidogrel (75 mg once daily) on the basis of experience in patients with unstable angina/non-ST-segment elevation MI. In the absence of contraindications, all patients after STEMI should receive a platelet inhibitor in addition to aspirin for 12 months according to one of the following regimens: clopidogrel (75 mg/day) in patients with STEMI treated with or without PCI, prasugrel (10 mg/day) in patients treated with PCI, or ticagrelor (90 mg twice daily) in patients to be treated with PCI.<sup>1</sup> In patients treated with PCI, prasugrel and ticagrelor have been found to be superior to clopidogrel and are recommended as preferred in some professional guidelines.<sup>4</sup> However, in some practice environments, economic or formulary barriers may render access to prasugrel or ticagrelor difficult for some patients. Given the critical importance of dual antiplatelet therapy in patients who have received drug-eluting stents, access to a P2Y<sub>12</sub> inhibitor must be ensured. The twice-daily dosing regimen for ticagrelor should be considered for patients with concern regarding adherence to this regimen. The optimum duration of treatment with dual antiplatelet therapy remains uncertain. Nonetheless, its benefit has continued after 30 days, and for now, a P2Y<sub>12</sub> inhibitor along with aspirin should be administered to most patients for at least 1 year after STEMI, with aspirin treatment being maintained indefinitely.<sup>1</sup>

## Inhibition of the Renin-Angiotensin-Aldosterone System

See Inhibition of the Renin-Angiotensin-Aldosterone System in the section Pharmacologic Therapy. To prevent late remodeling of the left ventricle and to decrease the likelihood of recurrent ischemic events, we advocate indefinite therapy with an ACE inhibitor in patients with heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality, even in the presence of a normal global ejection fraction. Other candidates for long-term management with ACE inhibitors or ARBs are discussed in **Chapter 54**.

## Beta-Adrenergic Blocking Agents

Meta-analyses of trials from the prethrombolytic era involving more than 24,000 patients who received beta blockers in the convalescent phase of STEMI have shown a 23% reduction in long-term mortality. In most patients who have beta blockade initiated during the convalescent phase of STEMI, the reduction in long-term mortality is probably caused by the combination of an antiarrhythmic effect (prevention of sudden death) and prevention of reinfarction.

Given the well-documented benefits of therapy with a beta blocker, it is disturbing that this form of treatment continues to be underused, especially in high-risk groups such as older adults. Patients with a relative contraindication to beta blockers (e.g., bradycardia) should undergo a monitored trial of therapy in the hospital. The dosage should be sufficient to blunt the heart rate response to stress or exercise. Much of the impact of beta blockers in preventing mortality occurs in the first weeks; consequently, treatment should commence as soon as possible. Programs that provide physician feedback to improve adherence to guidelines should be used.

Some controversy exists regarding how long patients should be treated. The collective data from five trials that provided information on long-term follow-up of patients treated with beta blockers after infarction suggest that therapy should be continued for at least 2 to 3 years. At that time, if the beta blocker is well tolerated and there is no reason to discontinue therapy, such therapy probably should be continued in most patients (see Chapter 54).

### Nitrates

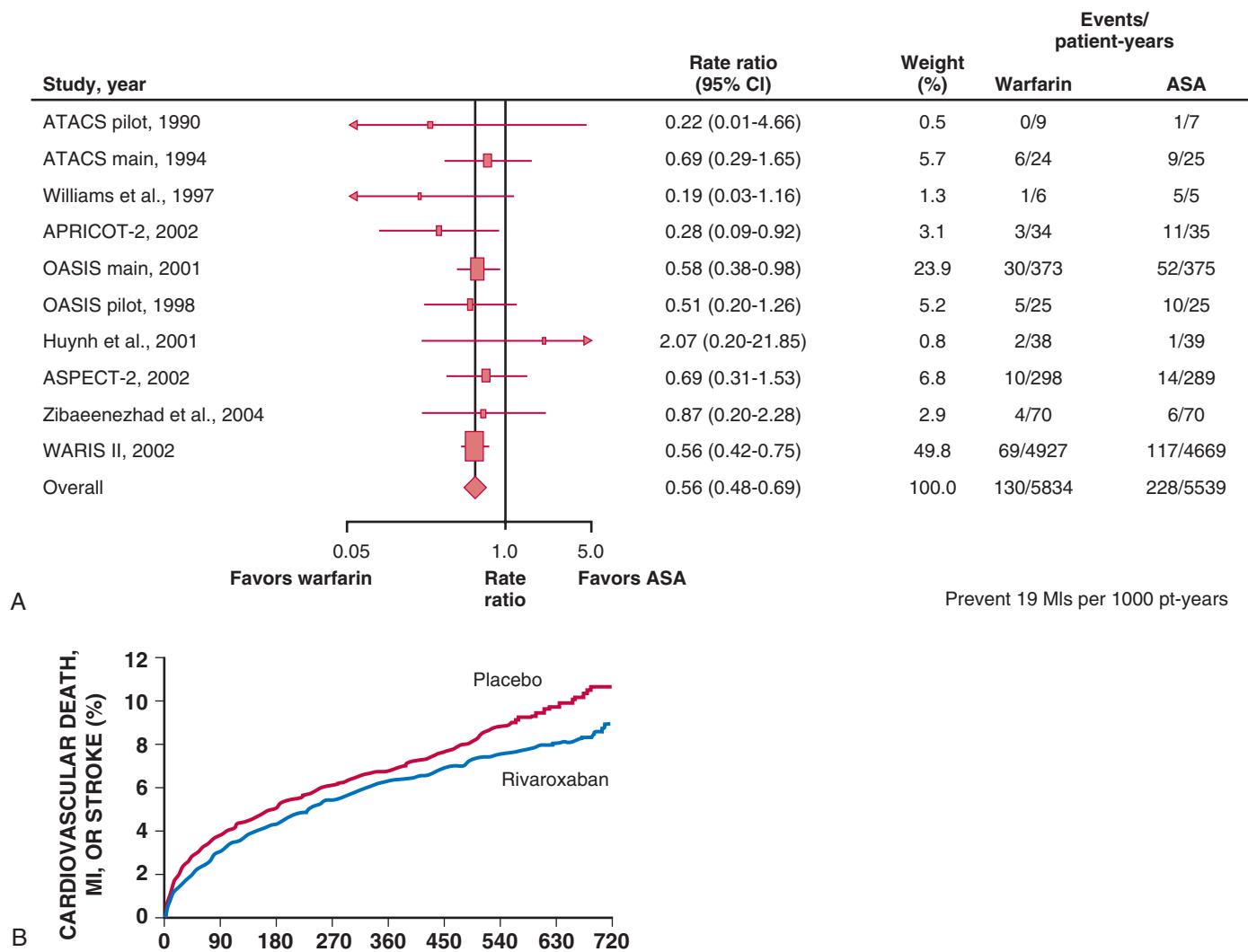
Although these agents are suitable for the management of specific conditions after STEMI (such as recurrent angina) or as part of a treatment regimen for congestive heart failure, little evidence indicates that they reduce mortality over the long term when prescribed on a routine basis to all patients with infarction.

### Anticoagulants

After several decades of evaluation, the weight of evidence now suggests that anticoagulants have a favorable effect on late mortality, stroke, and reinfarction in patients hospitalized with STEMI (Fig. 52-35). Given the complexities of combining long-term warfarin therapy with antiplatelet therapy, clinicians must weigh the need for warfarin based on established indications for anticoagulation, the use of other antithrombotic therapies, and the risk for bleeding.<sup>83</sup>

At least three theoretical reasons exist for anticipating that anticoagulants might be beneficial in the long-term management of patients after STEMI. (1) Because the coronary occlusion responsible for STEMI is often caused by a thrombus, anticoagulants might be expected to halt progression, slow progression, or prevent the development of new thrombi elsewhere in the coronary arterial tree; (2) anticoagulants might be expected to diminish the formation of mural thrombi and resultant systemic embolization; and (3) anticoagulants might be expected to reduce the incidence of venous thrombosis and pulmonary embolization.

Alternative oral anticoagulants that have the advantage of more predictable anticoagulation with stable oral dosing, such as the oral factor Xa inhibitors, have undergone evaluation in patients with ACSs, including STEMI patients treated with background antiplatelet therapies. ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction) tested two low doses of the oral factor Xa inhibitor rivaroxaban versus placebo. Rivaroxaban at doses of both 2.5 and 5 mg twice daily significantly reduced cardiovascular death, MI, or stroke in comparison to placebo (8.9% versus 10.7%;  $P = 0.008$ ; Fig. 52-35).<sup>200</sup> Both doses also reduced stent thrombosis. The group receiving the 2.5-mg dose demonstrated a significant reduction in cardiovascular mortality



**FIGURE 52-35** Outcomes with extended oral anticoagulant therapy for secondary prevention in patients with STEMI. **A**, Meta-analysis of trials of warfarin versus placebo with respect to the outcome of recurrent MI showing the potential to prevent 19 MIs per 1000 patients treated. **B**, Primary result of the ATLAS ACS 2-TIMI 51 trial, in which 15,526 patients with ACSs were randomly assigned to one of two doses of the oral factor Xa inhibitor rivaroxaban or placebo for a mean of 13 months. Rivaroxaban lowered the rate of cardiovascular death, MI, or stroke by 16%. This benefit was present in patients with STEMI ( $n = 7727$ ), among whom a 15% reduction in the primary endpoint occurred.

(2.7% versus 4.1%;  $P = 0.002$ ) when compared with placebo, which was not seen with 5 mg. Rivaroxaban resulted in an increase in major bleeding (2.1% versus 0.6%;  $P < 0.001$ ) without a significant increase in fatal bleeding.

Despite similar findings in the ACS phase II studies with rivaroxaban (ATLAS ACS-TIMI 46)<sup>201</sup> and with another oral factor Xa inhibitor, apixaban (APPRAISE [Apixaban for Prevention of Acute Ischemic Events]),<sup>202</sup> the phase III APPRAISE-2 study, which tested apixaban versus placebo in patients following an ACS, was terminated early because of an increase in major bleeding without a significant improvement in efficacy.<sup>203</sup> The divergent results of the ATLAS ACS 2-TIMI 51 and APPRAISE-2 studies may be related to the baseline risk of the patients in that APPRAISE-2 enrolled older patients with more comorbid conditions than the other three trials did. Consequently, these patients may have experienced competing risks and diseases not necessarily modified by anticoagulant therapy. Additionally, APPRAISE-2 included patients with a previous stroke or transient ischemic attack, and recent studies have illustrated that this group of patients may not benefit from further intensification of antithrombotic therapy. Finally, APPRAISE-2 studied higher degrees of anticoagulation than ATLAS ACS 2-TIMI 51 did.

### Calcium Channel Antagonists

At present we do not recommend the routine use of calcium antagonists for secondary prevention of infarction. A possible exception is a patient who cannot tolerate a beta-blocker because of adverse effects on bronchospastic lung disease but who has well-preserved left ventricular function; such patients may be candidates for a rate-slslowing calcium antagonist such as diltiazem or verapamil.

### Hormone Therapy (See also Chapters 42 and 77)

The decision to prescribe hormone therapy is often a complex one that involves the desire to suppress postmenopausal symptoms versus the risk for breast and endometrial cancer and vascular events. At present we recommend that hormone therapy with estrogen plus progestin not be started after STEMI and be discontinued in postmenopausal women after STEMI.

### Antioxidants

#### (See Chapter 46)

Dietary supplementation with omega-3 polyunsaturated fatty acids has been associated with a reduction in death from coronary heart disease and nonfatal reinfarction in patients within 3 months of MI. Contemporary randomized studies, however, have shown no convincing benefit in the context of guidelines-based medical therapy.<sup>204,205</sup> Presently available data therefore do not support the use of antioxidant therapy for secondary prevention after STEMI.

### Nonsteroidal Anti-Inflammatory Drugs

Evidence has emerged that COX-2-selective drugs and NSAIDs that have varying COX-1/COX-2 inhibitory ratios promote a prothrombotic state and that their use is associated with an increased risk for atherothrombotic events.<sup>206,207</sup>

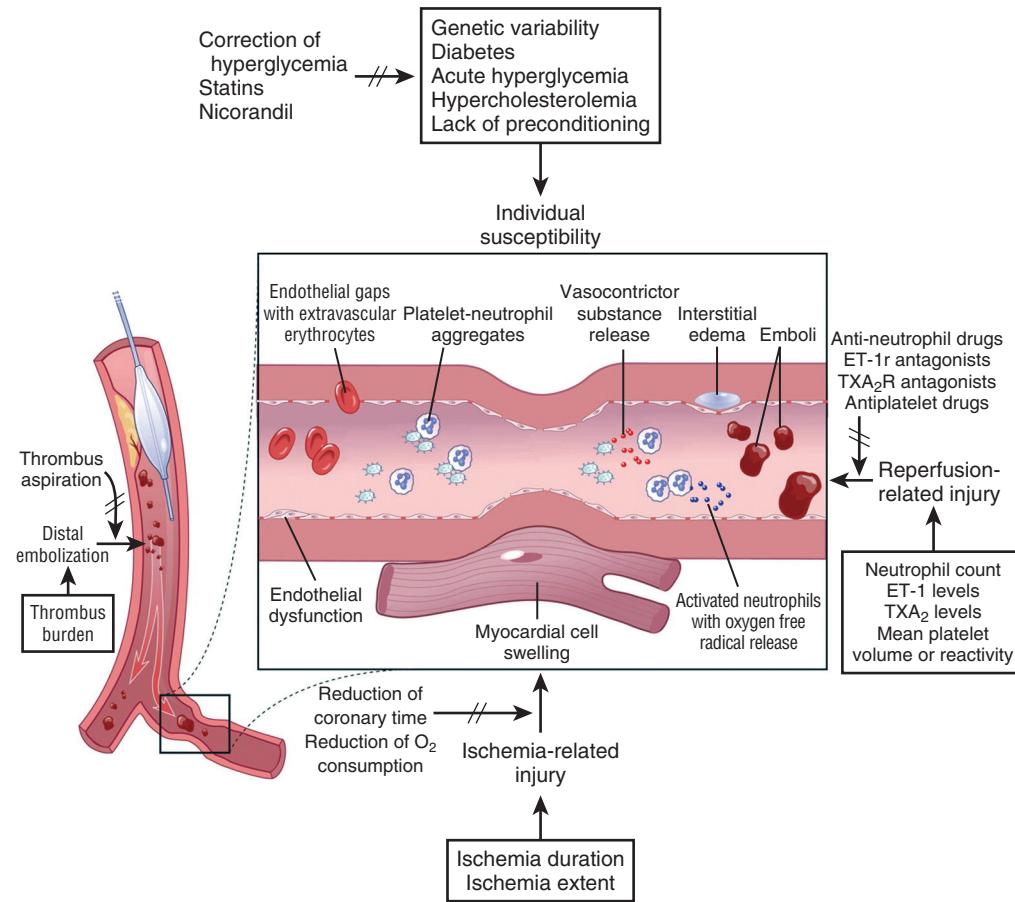
Given the increased risk for atherothrombosis related to the index STEMI event, the desire not to interfere with the beneficial pharmacologic actions of low-dose aspirin after STEMI, and reports of increased mortality and reinfarction when they are used after MI, clinicians should avoid prescribing NSAIDs to patients recovering from STEMI.<sup>1</sup> If NSAIDs must be prescribed for relief of pain, the lowest dose required to control symptoms should be administered for the shortest time required.<sup>208</sup>

## FUTURE DIRECTIONS AND EMERGING THERAPIES

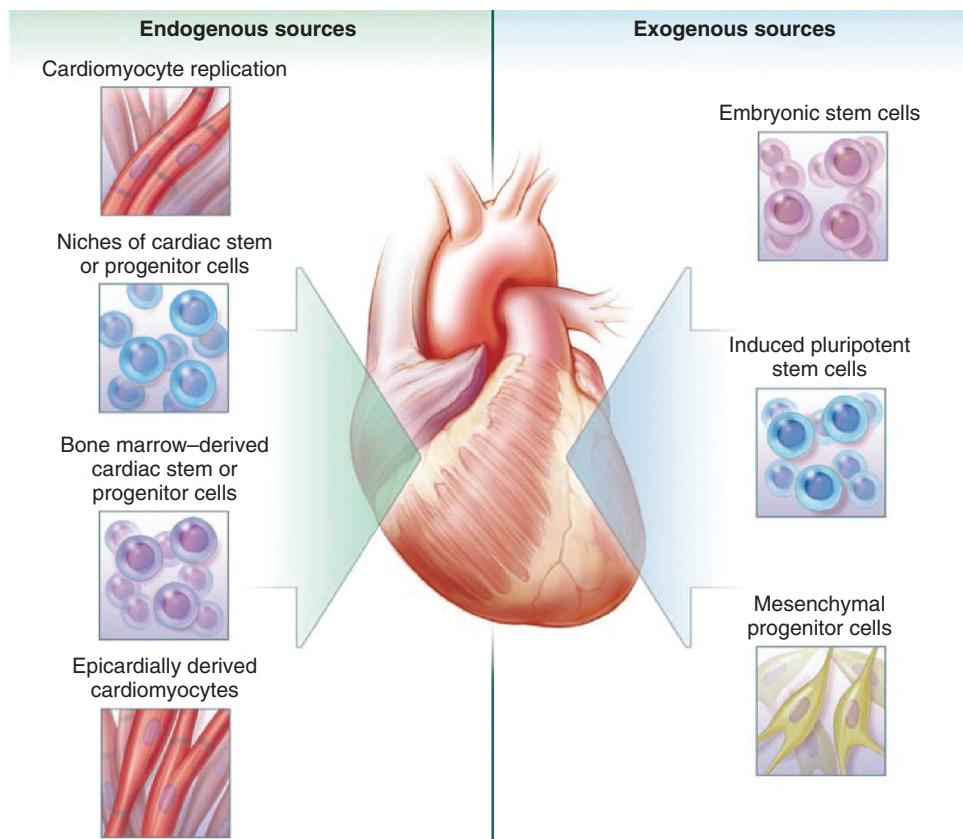
Although the case fatality of patients with STEMI has declined substantially, considerable opportunities for improvement remain. Of these, we emphasize four major directions: (1) evidence-based development of systems for care of patients with STEMI, (2) mitigation of reperfusion injury and impaired myocardial tissue perfusion, (3) management of cardiogenic shock after STEMI, and (4) amelioration of the adverse remodeling.

The widespread adoption of regional systems of care for patients with STEMI across diverse areas has remained challenging, and inappropriate delays to initiation of reperfusion therapy are regrettably common. Comparative effectiveness research is needed to directly test the implementation of prehospital EMS protocols, management of patients with out-of-hospital cardiac arrest, practical triage, and transfer algorithms to get patients to expert PCI services rapidly.<sup>10,11,80,209</sup>

Although PCI usually restores flow through epicardial arteries, many patients do not achieve adequate nutrient flow at the myocardial level in the infarct zone because of impaired microvascular flow (Fig. 52-36; see also Fig. 52-5).<sup>52</sup> Despite effective restoration of



**FIGURE 52-36** Multiple mechanisms involved in the pathogenesis of no-reflow that might be targeted by appropriate therapy. ET = endothelin; TXA<sub>2</sub> = thromboxane A<sub>2</sub>. (Modified from Niccoli G, Burzotta F, Galiuto L, Crea F: Myocardial no-reflow in humans. *J Am Coll Cardiol* 54:281, 2009.)



**FIGURE 52-37** The demonstration that some cardiomyocytes are regenerated after birth highlights the promise and challenges of future regenerative cardiac therapies. Autologous and allogeneic sources of cells that may give rise to cardiomyocytes are under investigation. (From Parmacek MS, Epstein JA: Cardiomyocyte renewal. *N Engl J Med* 361:86, 2009.)

flow in the culprit epicardial artery, patients with impaired microvascular reperfusion have impaired survival.<sup>50</sup> Identification of therapies that reliably improve microvascular perfusion in the setting of primary PCI and pharmacologic reperfusion has proven challenging. The benefits of thrombus aspiration before stenting in patients undergoing primary PCI appear to be mitigated in part by improving microvascular perfusion; however, the proportion of patients with impaired microvascular flow because of distal embolization and abnormal vasomotor regulation in the distal vessels remains substantial. These abnormalities in vasomotor function are derived in part from the intense release of oxidative species and inflammatory cytokines that occurs during reperfusion of the necrotic area. This consequence of successful reperfusion, which underlies the phenomenon of reperfusion injury, can also lead to extension of myocardial injury beyond the initial ischemic zone. To date, multiple candidate interventions to reduce reperfusion injury that have appeared promising in initial studies have failed in definitive randomized trials.<sup>36</sup> Amelioration of the reperfusion injury that contributes to long-term myocardial dysfunction remains an unmet clinical need.<sup>39,122</sup> Therefore processes that contribute to both microvascular obstruction<sup>210</sup> and reperfusion injury are potential therapeutic targets that merit ongoing investigation.

Even if reperfusion is achieved in timely fashion and microvascular obstruction is minimized, patients with STEMI inevitably lose some myocytes. When ventricular failure or severe mechanical disruption results, cardiogenic shock may ensue. Mortality from cardiogenic shock remains in excess of 40%. Improvement in the outcomes of patients in whom shock develops after STEMI remains a vexing clinical challenge.<sup>131</sup> The disappointing results of recent trials of percutaneous mechanical support have challenged commonly held clinical assumptions.<sup>142,211,212</sup> Novel therapies and strategies for the management of shock are a critical area for substantial investment in research.<sup>132</sup>

In addition to the early risk for ventricular failure because of acute myocardial injury, secondary damage to the left ventricle can also

occur in the long term as a result of ventricular remodeling after STEMI.<sup>123,213</sup> Treatments to minimize ventricular remodeling include the standard approaches to disruption of the RAAS and potential new therapies such as renin inhibition, reducing the amount of central nervous system generation of aldosterone, enhancing the synthesis of endothelial nitric oxide synthase, modulating beta-adrenergic signaling, and minimizing the processes that lead to cardiac apoptosis.<sup>123,213</sup> Novel approaches using biologic and mechanical interventions to improve ventricular structure are under investigation.<sup>214-216</sup> Moreover, myocytes are capable of entering the cell cycle and dividing (see Chapter 30).<sup>217</sup> The burgeoning field of cardiac regenerative medicine holds promise to support amelioration of the adverse ventricular remodeling by using both endogenous and exogenous sources of cells that give rise to myocytes (Fig. 52-37).<sup>218</sup>

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## GUIDELINES

### Management of Patients with ST-Elevation Myocardial Infarction

Stephen D. Wiviott

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) updated guidelines for the diagnosis and management of patients with ST-elevation myocardial infarction (STEMI) in 2013.<sup>1</sup> As with other ACCF/AHA guidelines, indications for interventions are classified into the following four groups:

Class I—For generally accepted indications

Class IIa—When indications are controversial but the weight of evidence is supportive

Class IIb—When usefulness or efficacy is less well established

Class III—When there is consensus against the usefulness of the intervention

The guidelines use a convention for rating the level of evidence (LOE) on which recommendations have been based, as follows:

Level A—Derived from data from multiple randomized clinical trials

Level B—Derived from a single randomized trial or nonrandomized studies

Level C—Based on the consensus opinion of experts or standard of care

### DEFINITION AND DIAGNOSIS

STEMI is defined by symptoms of myocardial ischemia associated with persistent electrocardiographic evidence of ST elevation and subsequent elevation of biologic markers of myocardial necrosis. According to the universal definition of myocardial infarction (MI), ST elevation in the absence of either left bundle branch block (LBBB) or left ventricular (LV) hypertrophy is defined as new ST elevation of at least 2 mm in men or 1.5 mm in women in at least two contiguous leads.<sup>2</sup> New or presumably new LBBB at initial evaluation should not be considered diagnostic of MI. Interpretation of the electrocardiogram (ECG) may be obscured by previous LBBB, paced rhythm, LV hypertrophy, or Brugada syndrome.

### ONSET OF MYOCARDIAL INFARCTION

Time until treatment is paramount in the management of STEMI, and early recognition, transport, and treatment can improve outcomes in patients with this syndrome.

### Patient-Related Delays and Initial Treatment

Time delays in seeking care tend to be longer in women, blacks, and older adults. Reasons for delays may include failure to recognize symptoms, uncertainty of the severity of symptoms, and lack of understanding of the importance of rapid treatment. The STEMI guidelines emphasize the importance of health care providers making anticipatory plans, including the need to activate the emergency medical service (EMS) system and institution of early aspirin use. Patients should learn warning systems, develop a survival plan, and discuss risk reduction with their physicians to improve potential outcomes.

### Mode of Transport to the Hospital

Patients with ischemic symptoms should be transported to the hospital by ambulance rather than by friends or family. Ambulance transport is associated with earlier recognition of STEMI, faster times to

reperfusion, and lower mortality. The benefits of ambulance transport are increased by prehospital communication of the diagnosis of STEMI and by preference for transfer to hospitals capable of performing percutaneous coronary intervention (PCI).

### Community Preparedness and Systems Goals for Reperfusion Therapy

Time until appropriate reperfusion therapy is one key to the treatment of STEMI. Goals of achieving rapid reperfusion should be facilitated by community-based systems designed for the rapid management of patients with STEMI. **Figure 52G-1** outlines the major strategies and decision points for the management of patients with STEMI.

Class I recommendations include the following:

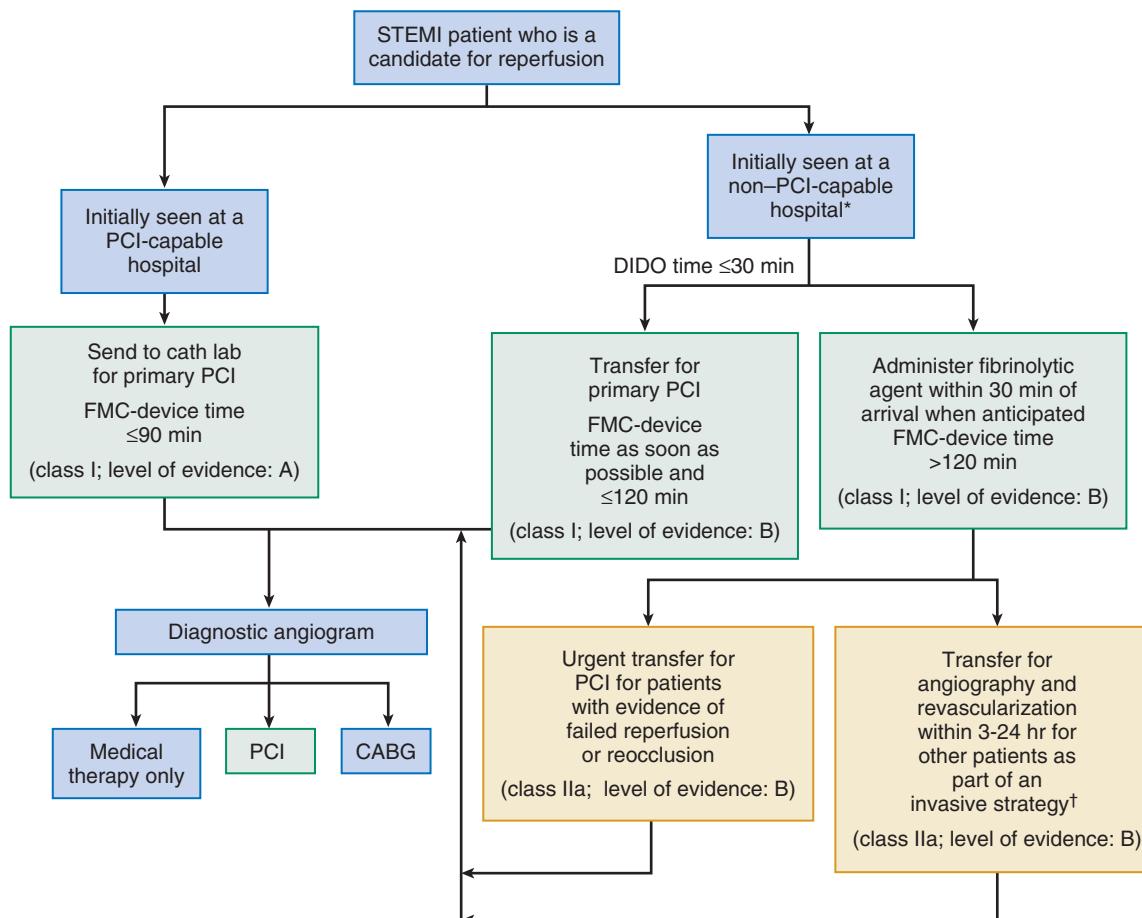
- Communities should create and maintain regional systems of STEMI care that includes assessment and quality improvement of EMS and hospital-based activities (Level of evidence: B).
- A 12-lead ECG should be performed by EMS personnel at the site of first medical contact (FMC) in patients with symptoms consistent with STEMI (Level of evidence: B).
- Reperfusion therapy should be administered to all eligible patients with STEMI in whom the onset of symptoms began within the previous 12 hours (Level of evidence: A).
- Primary PCI is the recommended method of reperfusion when experienced operators can perform it within timely fashion (Level of evidence: A).
- EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal FMC-to-device time goal of 90 minutes or less (Level of evidence: B).
- Immediate transfer to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI who initially arrive at or are transported to a non-PCI-capable hospital, with an FMC-to-device time goal of 12 minutes or less (Level of evidence: B).
- Without contraindications, fibrinolytic therapy should be administered to patients with STEMI at non-PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays (Level of evidence: B).
- When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival (Level of evidence: B).

When selecting reperfusion therapy, the provider must consider several features in relation to these recommendations, including time from the onset of symptoms, risk for STEMI-related complications, risk for bleeding, presence of heart failure or shock, and time required for the administration of fibrinolysis versus the time needed for transfer to a PCI-capable hospital. Patients best suited for transfer to PCI-capable hospitals include those with congestive heart failure (CHF) or shock, high bleeding risk, longer than 3 to 4 hours after onset of symptoms, and short transfer times to PCI-capable hospitals. Those best suited for initial fibrinolytic therapy include patients with low bleeding risk, very early after the onset of symptoms, and longer delays until the performance of PCI.

### Relationship Between Sudden Cardiac Death and ST-Elevation Myocardial Infarction

STEMI is inexorably linked to sudden cardiac death. Indeed, some 70% of deaths attributable to coronary heart disease occur with out-of-hospital arrest. Comprehensive management of out-of-hospital arrest extends beyond the scope of this chapter, but the STEMI guidelines offer key recommendations for the evaluation and management of patients with STEMI and out-of-hospital cardiac arrest, including the following class I recommendations:

- Therapeutic hypothermia should be started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest caused by ventricular fibrillation or pulseless ventricular tachycardia, including patients who undergo primary PCI (Level of evidence: B).



**FIGURE 52G-1** Reperfusion therapy for patients with STEMI. The bold arrows and boxes are the preferred strategies. Performance of PCI is dictated by an anatomically appropriate culprit stenosis. \*Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of the delay in time after the onset of MI (class I; Level of evidence: B). †Angiography and revascularization should not be performed within the first 2 to 3 hours after the administration of fibrinolytic therapy. DIDO = door in-door out. (Modified from O’Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.)

- Immediate angiography and PCI, when indicated, should be performed in resuscitated patients with out-of-hospital cardiac arrest whose initial ECG shows STEMI (Level of evidence: B).

with low-volume operators. Potential adverse effects of primary PCI include arterial access site complications and contrast agent- and antithrombotic-related complications. A summary of the recommendations is encapsulated in **Table 52G-1**.

## REPERFUSION AT A HOSPITAL CAPABLE OF PERFORMING PERCUTANEOUS CORONARY INTERVENTIONS

The 2013 STEMI guidelines are divided into sections describing appropriate care at PCI-capable hospitals versus non-PCI-capable hospitals.<sup>1</sup>

### Primary Percutaneous Coronary Intervention

Primary PCI is generally preferable to fibrinolytic therapy when time until treatment is short and the patient arrives at a high-volume, well-equipped center with experienced operators and support staff. When compared with fibrinolysis, primary PCI produces higher rates of TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow and patent infarct-related arteries and lower rates of recurrent ischemia, urgent revascularization, recurrent MI, and death. Primary PCI, when successful, also results in early hospital discharge and return to activities. Such improvements are less or absent in low-volume centers or

### Procedural Considerations

The 2013 STEMI guidelines offer a class IIa recommendation for manual aspiration thrombectomy in patients undergoing primary PCI, although subsequent trial data do not show that this procedure reduces 30-day mortality in patients with STEMI.<sup>3</sup> Class I indications are given for the use of intracoronary stents at the time of primary PCI (Level of evidence: A). Either drug-eluting stents (DESs) or bare metal stents (BMSs) can be used, but when patients are anticipated to be at high bleeding risk or are probably not compliant with dual antiplatelet therapy (DAPT) for other reasons, a class I indication is given for the use of BMSs and a class III indication for DESs—because of the risk for delayed stent thrombosis in DESs with premature discontinuation of DAPT. **Table 52G-2** summarizes the adjunctive anti-thrombotic therapy for primary PCI, including antiplatelet therapy and anticoagulant therapy.

For antiplatelet therapy, class I recommendations include aspirin and P2Y<sub>12</sub> receptor antagonists.

#### Aspirin

- Aspirin (162 to 325 mg) should be given before primary PCI (Level of evidence: B).

**TABLE 52G-1 Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction**

	COR	LEVEL OF EVIDENCE
Ischemic symptoms <12 hr	I	A
Ischemic symptoms <12 hr and contraindications to fibrinolytic therapy irrespective of delay in time after FMC	I	B
Cardiogenic shock or acute severe HF irrespective of delay in time after the onset of MI	I	B
Evidence of ongoing ischemia 12-24 hr after the onset of symptoms	IIa	B
PCI on a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III: Harm	B

COR = class of recommendation; HF = heart failure.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

**TABLE 52G-2 Adjunctive Antithrombotic Therapy to Support Reperfusion with Primary Percutaneous Coronary Intervention**

	COR	LEVEL OF EVIDENCE
<b>Antiplatelet Therapy</b>		
<b>Aspirin</b>		
• 162- to 325-mg loading dose before the procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
<b>P2Y<sub>12</sub> Inhibitors</b>		
Loading Doses		
• Clopidogrel: 600 mg as early as possible or at the time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at the time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at the time of PCI	I	B
Maintenance Doses and Duration of Therapy		
DES placed: Continue therapy for 1 year with		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
BMS <sup>†</sup> placed: Continue therapy for 1 year with		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
DES placed:		
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 year	IIb	C
• Patients with STEMI and previous stroke or TIA: prasugrel	III: Harm	B
<b>Intravenous Glycoprotein IIb/IIIa Receptor Antagonists in Conjunction with Unfractionated Heparin or Bivalirudin in Selected Patients</b>		
• Abciximab: 0.25-mg/kg IV bolus, then 0.125 µg/kg/min (maximum, 10 µg/min)	IIa	A
• Tirofiban (high bolus dose): 25-µg/kg IV bolus, then 0.15 µg/kg/min	IIa	B
• In patients with CrCl <30 mL/min, reduce the infusion by 50%		
• Eptifibatide (double bolus): 180-µg/kg IV bolus, then 2 µg/kg/min; a second 180-µg/kg bolus is administered 10 min after the first bolus	IIa	B
• In patients with CrCl < 50 mL/min, reduce the infusion by 50%		
• Avoid in patients on hemodialysis		
• Pre-catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B
• Intracoronary abciximab: 0.25-mg/kg bolus	IIb	B

*Continued*

**TABLE 52G-2** Adjunctive Antithrombotic Therapy to Support Reperfusion with Primary Percutaneous Coronary Intervention—cont'd

	COR	LEVEL OF EVIDENCE
<b>Anticoagulant Therapy</b>		
• UFH		
• With a GP IIb/IIIa receptor antagonist planned: 50- to 70-unit/kg IV bolus to achieve therapeutic ACT <sup>+</sup>	I	C
• With no GP IIb/IIIa receptor antagonist planned: 70- to 100-unit/kg bolus to achieve a therapeutic ACT <sup>§</sup>	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75-mg/kg/hr infusion with or without previous treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed	I	B
• Reduce the infusion to 1 mg/kg/hr with estimated an CrCl <30 mL/min		
• Preferred over UFH with a GP IIb/IIIa receptor antagonist in patients at high risk for bleeding	IIa	B
• Fondaparinux: not recommended as the sole anticoagulant for primary PCI	III: Harm	B

\*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

<sup>†</sup>Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide P2Y<sub>12</sub> inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone according to the recommendations listed for BMSs (Level of evidence: C).

<sup>‡</sup>The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 seconds.

<sup>§</sup>The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 seconds (HemoTec device) or 300 to 350 seconds (Hemochron device). ACT = activated clotting time; rCrI = creatinine clearance; COR = class of recommendation; GP = glycoprotein; IV = intravenous.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

- After PCI, aspirin should be continued indefinitely (Level of evidence: B). *Note:* An 81-mg dose of aspirin is recommended for maintenance (class IIa; Level of evidence: B) instead of higher doses.

### P2Y<sub>12</sub> Antagonists

- A loading dose of a P2Y<sub>12</sub> receptor inhibitor should be given as early as possible or at the time of primary PCI in patients with STEMI (Level of evidence: B), with options including clopidogrel, 600 mg (Level of evidence: B); prasugrel, 60 mg (Level of evidence: B); or ticagrelor, 180 mg (Level of evidence: B).
- A P2Y<sub>12</sub> antagonist should be prescribed for 1 year to patients with STEMI after primary PCI when they receive a stent. Options include clopidogrel, 75 mg daily (Level of evidence: B); prasugrel, 10 mg daily (Level of evidence: B); or ticagrelor, 90 mg twice daily (Level of evidence: B). *Note:* Prasugrel should not be used (class III, Level of evidence: B) in patients with a history of transient ischemic attack (TIA) or stroke.
- For anticoagulant therapy, key recommendations include supportive anticoagulation with unfractionated heparin (UFH), with dosing being based on the activated clotting time (class I, Level of evidence: C), or with bivalirudin in patients who have not been treated previously with UFH (class I; Level of evidence: B). In patients with a high risk for bleeding, bivalirudin is generally recommended instead of heparin plus a glycoprotein IIb/IIIa receptor antagonist (class IIa; Level of evidence: B), and fondaparinux should not be used as the sole anticoagulant (class III; Level of evidence: B).

## REPERFUSION AT A HOSPITAL NOT CAPABLE OF PERFORMING PERCUTANEOUS CORONARY INTERVENTIONS

The guidelines categorize the management of patients at a non-PCI-capable hospital into three phases: fibrinolytic therapy, assessment of patency, and transfer to a PCI-capable hospital.

### Fibrinolytic Therapy When the Delay Anticipated Is Within 120 Minutes

The key recommendations for the indications for fibrinolytic therapy with a delay of longer than 120 minutes from FMC to primary PCI are summarized in **Table 52G-3**.

**TABLE 52G-3** Indications for Fibrinolytic Therapy When the Delay from First Medical Contact to Primary Percutaneous Intervention Is Longer than 120 Minutes

	COR	LEVEL OF EVIDENCE
Ischemic symptoms <12 hr	I	A
Evidence of ongoing ischemia 12-24 hr after the onset of symptoms and a large area of myocardium at risk or hemodynamic instability	IIa	C
ST depression except if true posterior (inferobasal) MI is suspected or when associated with ST-elevation in lead aVR	III: Harm	B

COR = class of recommendation.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

The 2013 STEMI guidelines recommend fibrin-specific agents over non-fibrin-specific agents when available.<sup>1</sup> Fibrin-specific regimens include single-bolus tenecteplase (TNK tissue plasminogen activator [t-PA]), double-bolus reteplase (r-PA), or infusion of alteplase (t-PA). Streptokinase administered over a 30- to 60-minute period is the only nonspecific agent recommended. The choice of fibrinolytic agent depends on a risk-benefit analysis that integrates time from the onset of symptoms, clinical features, comorbid conditions, delay until performance of PCI, and potential contraindications (**Table 52G-4**). **Table 52G-5** summarizes antithrombotic therapy for STEMI treated with fibrinolytic therapy.

### Antiplatelet Therapy

- A loading dose of aspirin (162 to 325 mg) and clopidogrel (300 mg in patients ≤75 years of age; 75 mg in patients >75 years of age) should be administered with fibrinolytic therapy (class I; Level of evidence: A).
- Aspirin should be continued indefinitely, and clopidogrel should be continued for at least 14 days and up to 1 year (class I; Level of evidence: A). *Note:* A dose of 81 mg of aspirin is preferred instead of higher maintenance dosing (class IIa; Level of evidence: B).

## Anticoagulant Therapy

Patients with STEMI treated with fibrinolytic therapy for reperfusion should receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of hospitalization, up to 8 days or until revascularization is performed (class I, Level of evidence: A). Acceptable regimens include UFH for up to 48 hours (Level of evidence: C), enoxaparin for up to 8 days (Level of evidence: A), or fondaparinux for up to 8 days (Level of evidence: B).

## Assessment of Reperfusion after Fibrinolysis

Sudden and complete relief of chest pain, coupled with greater than 70% ST resolution, is highly correlated with normal coronary artery blood flow in the infarct-related artery and suggests reperfusion.

**TABLE 52G-4 Contraindications to Fibrinolytic Therapy for ST-Elevation Myocardial Infarction**

### Absolute Contraindications

Any previous intracranial hemorrhage  
Known structural cerebral vascular lesion  
Known malignant intracranial neoplasm  
Ischemic stroke within 3 months (except ischemic stroke within 4.5 hours)  
Suspected aortic dissection  
Active bleeding or bleeding diathesis  
Significant closed-head or facial trauma within 3 months  
Intracranial or intraspinal surgery within 2 months  
Severe uncontrolled hypertension (not responsive to emergency therapy)  
For streptokinase, previous treatment within 6 months

### Relative Contraindications

History of chronic, severe, poorly controlled hypertension  
Significant hypertension at initial evaluation (systolic blood pressure >180 mm Hg, diastolic blood pressure >110 mm Hg)  
History of ischemic stroke >3 months  
Dementia  
Known intracranial pathology not covered in Absolute Contraindications  
Traumatic or prolonged cardiopulmonary resuscitation (>10 minutes)  
Major surgery within 3 weeks  
Recent internal bleeding (within 2-4 weeks)  
Noncompressible vascular puncture  
Pregnancy  
Active peptic ulcer  
Oral anticoagulant therapy

## Transfer to a Hospital Capable of Performing Percutaneous Coronary Interventions after Fibrinolytic Therapy

Key recommendations for transfer to a PCI-capable hospital for angiography are summarized in **Table 52G-6**. The only class I indication for immediate transfer in the 2013 STEMI guidelines is for patients with severe heart failure or cardiogenic shock, but the general recommendation is for all patients who have failed reperfusion or suffered reocclusion (class IIa; Level of evidence: B) to be transferred urgently and for stable patients to be transferred routinely (class IIa; Level of evidence: B).

## DELAYED INVASIVE MANAGEMENT

### Coronary Angiography and Percutaneous Coronary Intervention in Patients Initially Managed with Fibrinolytic Therapy or in Those with No Reperfusion

Key recommendations for indications for coronary angiography and PCI are summarized in **Table 52G-7**. PCI should be performed when angiography identifies significant stenosis in the infarct-related arteries. Class I indications relate to high-risk clinical features (cardiogenic shock, severe CHF), recurrent spontaneous or provoked ischemia, or high-risk features on noninvasive testing. PCI on non-infarct-related arteries should be based on spontaneous symptoms (class I; Level of evidence: C) or high-risk features on noninvasive testing (class IIa; Level of evidence: B) suggestive of ischemia in the territory of the non-infarct-related artery. One study published after the guidelines suggested a benefit of PCI on non-infarct-related arteries.<sup>4</sup>

### Adjunctive Antithrombotic Agents to Support Delayed Percutaneous Coronary Intervention

Adjunctive antiplatelet therapy and anticoagulant therapy to support delayed PCI are summarized in **Table 52G-8**. Antiplatelet and anticoagulant therapies in patients in whom PCI is delayed are similar to those in patients who undergo PCI early, but the timing and dosing of P2Y<sub>12</sub> antagonists differ depending on the time interval and type of fibrinolytic agent given. Notably, a loading dose of 300 mg of clopidogrel should be administered (if not already given with fibrinolysis) within 24 hours of PCI and a 600-mg loading dose

**TABLE 52G-5 Adjunctive Antithrombotic Therapy to Support Reperfusion with Fibrinolytic Therapy**

	COR	LEVEL OF EVIDENCE
<b>Antiplatelet Therapy</b>		
<b>Aspirin</b>		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
<b>P2Y<sub>12</sub> Receptor Inhibitors</b>		
• Clopidogrel:	I	A
• Age ≤ 75 yr: 300-mg loading dose		
Followed by 75 mg daily for at least 14 days and up to 1 yr in the absence of bleeding	I	A (14 days) C (up to 1 yr)
• Age > 75 yr: no loading dose, give 75 mg	I	A
Followed by 75 mg daily for at least 14 days and up to 1 yr in the absence of bleeding	I	A (14 days) C (up to 1 yr)

Continued

**TABLE 52G-5** Adjunctive Antithrombotic Therapy to Support Reperfusion with Fibrinolytic Therapy—cont'd

	COR	LEVEL OF EVIDENCE
<b>Anticoagulant Therapy</b>		
• UFH:	I	C
• Weight-based IV bolus and infusion adjusted to obtain an APTT of 1.5-2.0 times control for 48 hr or until revascularization. IV bolus of 60 units/kg (maximum, 4000 units) followed by an infusion of 12 units/kg/hr (maximum, 1000 units) initially, adjusted to maintain the APTT at 1.5-2.0 times control ( $\approx$ 50-70 sec) for 48 hr or until revascularization		
• Enoxaparin:	I	A
• If age < 75 yr: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 hr (maximum, 100 mg for the first 2 doses)		
• If age $\geq$ 75 yr: no bolus, 0.75 mg/kg subcutaneously every 12 hr (maximum, 75 mg for the first 2 doses)		
• Regardless of age, if CrCl < 30 mL/min, 1 mg/kg subcutaneously every 24 hr		
• Duration: For the index hospitalization, up to 8 days or until revascularization		
• Fondaparinux:	I	B
• Initial dose of 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 days or until revascularization		
• Contraindicated if CrCl < 30 mL/min		

APTT = activated partial thromboplastin time; COR = class of recommendation; CrCl = creatinine clearance.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

**TABLE 52G-6** Indications for Transfer for Angiography after Fibrinolytic Therapy

	COR	LEVEL OF EVIDENCE
Cardiogenic shock or acute severe heart failure that develops after initial evaluation	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B
Spontaneous or easily provoked myocardial ischemia	I	C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B
Stable* patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hr	IIa	B

\*Although individual circumstances vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR = class of recommendation.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

**TABLE 52G-7** Indications for Percutaneous Coronary Intervention on an Infarct Artery in Patients Who Were Managed with Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LEVEL OF EVIDENCE
Cardiogenic shock or acute severe heart failure	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	C
Spontaneous or easily provoked myocardial ischemia	I	C
Patients with evidence of failed reperfusion or with reocclusion after fibrinolytic therapy (as soon as possible)	IIa	B
Stable* patients after successful fibrinolysis, ideally between 3 and 24 hr	IIa	B
Stable* patients >24 hr after successful fibrinolysis	IIb	B
Delayed PCI on a totally occluded infarct artery >24 h after STEMI in stable patients	III: No benefit	B

\*Although individual circumstances vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

COR = class of recommendation.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

**TABLE 52G-8** Adjunctive Antithrombotic Therapy to Support Percutaneous Intervention after Fibrinolytic Therapy

	COR	LEVEL OF EVIDENCE
<b>Antiplatelet Therapy</b>		
<b>Aspirin</b>		
• 162- to 325-mg loading dose given with a fibrinolytic agent (before PCI)	I	A
• 81- to 325-mg daily maintenance dose after PCI (indefinite)	I	A
• 81 mg daily is the preferred daily maintenance dose	IIa	B
<b>P2Y<sub>12</sub> Receptor Inhibitors</b>		
Loading Doses		
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:		
• Continue clopidogrel, 75 mg daily, without an additional loading dose	I	C
For patients who have not received a loading dose of clopidogrel:		
• If PCI is performed ≤24 hr after fibrinolytic therapy: clopidogrel, 300-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 hr after fibrinolytic therapy: clopidogrel, 600-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 hr after treatment with a fibrin-specific agent or >48 hr after a non-fibrin-specific agent: prasugrel, 60 mg at the time of PCI	IIa	B
For patients with previous stroke/TIA: prasugrel	III: Harm	B
Maintenance Doses and Duration of Therapy		
DES placed: Continue therapy for at least 1 yr with		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
BMS* placed: Continue therapy for at least 30 days and up to 1 yr with		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
<b>Anticoagulant Therapy</b>		
• Continue UFH throughout PCI while administering additional IV boluses as needed to maintain a therapeutic ACT, depending on use of a GP IIb/IIIa receptor antagonist <sup>†</sup>	I	C
• Continue enoxaparin throughout PCI:		
• No additional drug if the last dose was given within the previous 8 hr	I	B
• 0.3-mg/kg IV bolus if the last dose was given 8-12 hr earlier		
• Fondaparinux:	III: Harm	C
• As sole anticoagulant for PCI		

\*Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide P2Y<sub>12</sub> inhibitor therapy to patients with STEMI undergoing balloon angioplasty after fibrinolysis alone according to the recommendations listed for BMSs (Level of evidence: C).

<sup>†</sup>The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 seconds (HemoTec device) or 300 to 350 seconds (Hemochron device). ACT = activated clotting time; COR = class of recommendation; IV = intravenous.

Modified from O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.

thereafter. Prasugrel should be used at standard dosing, but not within 48 hours of fibrinolytic therapy. Anticoagulant therapy can consist of UFH (class I; Level of evidence: C) or enoxaparin (class I; Level of evidence: B), but fondaparinux should not be used as a stand-alone anticoagulant (class III; Level of evidence: B).

## CORONARY ARTERY BYPASS GRAFT SURGERY

The 2013 STEMI guidelines accord coronary artery bypass grafting (CABG) a relatively limited role in the management of patients with STEMI. The only class I indications for CABG in patients with STEMI include the management of those whose coronary anatomy is not amenable to PCI; those who have ongoing or recurrent ischemia, shock, severe heart failure, or other high-risk features (Level of

evidence: B); and patients at the time of operative repair of mechanical defects, such as a ventricular septal defect (Level of evidence: B).

In general, aspirin should be continued throughout the pre-CABG and peri-CABG periods. With the understanding that CABG is often urgent in the setting of STEMI, clopidogrel or ticagrelor should be discontinued for at least 24 hours when possible. In stable settings, clopidogrel and ticagrelor should be stopped for 5 days and prasugrel stopped for 7 days before CABG, but earlier surgery may be considered if the benefits outweigh the risks (class IIb).

## ROUTINE MEDICAL THERAPIES

Pharmacologic management of STEMI is covered in the chapter accompanying these guidelines. **Table 52G-9** summarizes the indications and cautions for routine medical therapies in patients following STEMI, as based on the 2013 guidelines.

**TABLE 52G-9 Indications and Cautions for Adjunctive Medical Therapies for Patients with ST-Elevation Myocardial Infarction**

Beta-adrenergic receptor-blocking agents	Oral: All patients without contraindication IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Signs of CHF Low-output state Increased risk for cardiogenic shock Prolonged first-degree or high-grade atrioventricular block Reactive airways disease
Angiotensin-converting enzyme (ACE) inhibitors	Anterior MI and EF ≤ 0.40 or CHF All patients without contraindication	Hypotension Renal failure Hyperkalemia
Angiotensin receptor-blocking agents (ARBs)	Intolerant of ACE inhibitors	Hypotension Renal failure Hyperkalemia
Statins	All patients without contraindications	With drugs metabolized via CYP3A4, fibrates Monitor for myopathy, hepatotoxicity Adjust dose for lipid targets
Nitroglycerin	Ongoing chest pain Hypertension and CHF	Suspected right ventricular infarction SBP < 90 (or 30 mm Hg below baseline) Recent use of a type 5 PDE inhibitor
Oxygen	Clinically significant hypoxemia ( $\text{SpO}_2 < 90$ ) CHF Dyspnea	Chronic obstructive pulmonary disease and $\text{CO}_2$ retention
Morphine	Pain Anxiety Pulmonary edema	Lethargic or moribund patient Hypotension Bradycardia Known hypersensitivity

EF = ejection fraction; PDE = phosphodiesterase; SBP = systolic blood pressure.

## RISK ASSESSMENT AFTER ST-ELEVATION MYOCARDIAL INFARCTION

Post-STEMI risk assessment allows the clinician's initial impression to be updated based on data occurring during the hospital stay, such as successful reperfusion, angiographic parameters, clinical heart failure or arrhythmia, and ventricular function; noninvasive testing may be helpful. Testing for the presence of residual ischemia may be helpful in patients following STEMI. The only class I recommendation is to use noninvasive testing for ischemia before discharge in patients who did not undergo angiography and who did not have high-risk features for which coronary angiography would be warranted. (Level of evidence: B.)

Because LV function strongly predicts outcome in patients with STEMI, it is recommended with a class I indication that all patients with STEMI undergo measurement of their LV ejection fraction (LVEF). Echocardiography is the most commonly used modality and can assess for mechanical complications, in addition to ventricular function. In general, this assessment can be performed on day 2 to 3 following MI, and in patients with significant ventricular dysfunction it should be repeated more than 40 days after MI to evaluate the potential need for an implantable cardioverter-defibrillator (ICD).

In the absence of a reversible cause, late (defined as >48 hours after MI) in-hospital sustained ventricular tachycardia or ventricular fibrillation is an indication (class I; level of evidence: B) for ICD therapy. In patients who do not have an indication for ICD therapy based on late life-threatening arrhythmias, evaluation of LVEF to determine the need for an ICD for primary prevention of sudden cardiac death should be performed with sufficient time to allow any LV stunning to resolve. Based on the 2013 STEMI guidelines, patients with an LVEF of 0.40 or lower should have echocardiography repeated more than 40 days after MI. If the LVEF remains 0.35 or lower and the patient has a class II or III New York Heart Association classification of CHF or an LVEF of 0.30 or lower independent of symptoms, an ICD is indicated.

## POSTHOSPITALIZATION PLAN OF CARE

Transition from hospital to outpatient care requires a careful discharge and follow-up plan. Class I indications for posthospital care planning include the following:

- Posthospital systems of care designed to prevent hospital readmission should be used to facilitate the transition to effective, coordinated outpatient care for all patients with STEMI. (Level of evidence: B.)
- Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI. (Level of evidence: B.)
- A clear, detailed, evidence-based plan of care that promotes adherence to medication, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI. (Level of evidence: C.)
- Encouragement and advice to stop smoking and to avoid secondhand smoke should be provided to patients with STEMI. (Level of evidence: A.)

Key components in the plan of care should include medications, physical activity/rehabilitation, risk factor modification, lifestyle interventions, attention to management of comorbid conditions and psychosocial factors, provider follow-up, patient and family education, and socioeconomic factors.

## References

1. O'Gara PT, Kushner FG, Ascheim DD, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 127:e362, 2013.
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4. Wald DS, Morris JK, Wald NJ, et al, for the PRAMI Investigators: Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 369:1115, 2013.