

VIII ACUTE MYOCARDIAL INFARCTION

PETER B. BERGER, M.D.

JAMES L. ORFORD, M.B.CHB., M.P.H.

In the 1970s, coronary angiography demonstrated that almost all cases of acute myocardial infarction were caused by thrombotic occlusion of a coronary artery. This discovery has led to the development of therapies to restore coronary blood flow in the occluded artery, which has dramatically reduced the morbidity and mortality associated with acute myocardial infarction.

Epidemiology

In the past decade, the number of people who die each year of myocardial infarction has decreased significantly. Both in-hospital mortality and out-of-hospital mortality have declined as a result of substantial increases in the use of aspirin, heparin, thrombolytic therapy, and coronary angioplasty, as well as a reduction in the risk factors for coronary artery disease (e.g., hypertension, hyperlipidemia, smoking, and sedentary lifestyle) [see Risk-Factor Modification, *below*]; however, it must be emphasized that there is, unfortunately, persistent discordance between existing guidelines for management of acute coronary artery disease syndromes and current clinical practice.¹²

Despite these advances, approximately 1.5 million people in the United States suffer acute myocardial infarction each year, and nearly 500,000 of these patients die of coronary artery disease.³ Nearly half of these deaths occur before the patients receive medical care either from emergency medical technicians or in a hospital.³⁴

Pathogenesis

The factors responsible for the sudden thrombotic occlusion of a coronary artery have only recently been elucidated.^{5,7} Atherosclerotic plaques rich in foam cells (lipid-laden macrophages) are susceptible to sudden plaque rupture and hemorrhage into the vessel wall, which may result in the sudden partial or total occlusion of the coronary artery. Although severe stenosis of a coronary artery (i.e., stenosis \geq 70% of the diameter of the artery) is generally required to produce anginal symptoms, such stenoses tend to have dense fibrotic caps and are less prone to rupture than mild to moderate stenoses, which are generally more lipid laden. Studies of patients in whom angiography was performed before and after a myocardial infarction revealed that in most cases, acute coronary artery occlusion occurred at sites in the coronary artery circulation with stenoses of less than 70%, as demonstrated on the preinfarction angiogram.⁸ Although patients who have unstable anginal syndromes with increasingly frequent and severe angina are clearly at increased risk for myocardial infarction, the ability of physicians to predict which patients with stable anginal syndromes are likely to experience infarction and which coronary artery stenoses are likely to result in acute thrombotic occlusion is poor.

Diagnosis

According to the World Health Organization, the diagnosis of myocardial infarction requires at least two of the following

three criteria: (1) a clinical history of ischemic-type chest discomfort, (2) serial electrocardiographic tracings indicative of myocardial infarction, and (3) a rise and fall in serum cardiac markers.⁹ However, the advent and widespread adoption of novel diagnostic tools, including highly sensitive and specific serologic biomarkers and precise imaging techniques, have necessitated reevaluation of this established definition. The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction has integrated these diagnostic modalities and published updated definitions of acute myocardial infarction, evolving or recent myocardial infarction, and established myocardial infarction that more accurately reflect current clinical practice [see *Table 1*].¹⁰

CLINICAL MANIFESTATIONS

Patients with acute myocardial infarction often describe a heaviness, pressure, squeezing, or tightness in the chest that has persisted for more than 30 minutes. The discomfort may radiate or be located primarily in the arms, neck, or jaw. Chest pain, particularly severe or stabbing chest pain, and pain that causes writhing are unusual for coronary artery ischemia and should lead the clinician to consider causes other than myocardial infarction. Many patients with acute myocardial infarction, particularly those with inferior infarction, are diaphoretic; nausea and emesis are common as well. Dyspnea is also a common associated symptom. Syncope may occur and is more frequent with inferior than anterior infarction, in part because of the more frequent occurrence of bradyarrhythmias, heart block, and tachyarrhythmias with inferior infarction. Elderly patients with

Table 1 Clinical Definitions of Myocardial Infarction as Determined by the Joint European Society of Cardiology/American College of Cardiology Committee¹⁰

Acute, Evolving, or Recent Myocardial Infarction

Biochemical markers of myocardial necrosis (i.e., typical rise and gradual fall of troponin or more rapid rise and fall of CK-MB) with at least one of the following:

- Ischemic symptoms
- Development of pathologic Q waves on the ECG
- ECG changes indicative of ischemia (ST segment elevation or depression)
- Coronary artery intervention (e.g., primary coronary angioplasty)

Pathologic findings of an acute myocardial infarction

Established Myocardial Infarction

Development of new pathologic Q waves on serial ECGs; the patient may or may not remember previous symptoms; biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed

Pathologic findings of a healed or healing myocardial infarction

CK-MB—creatin kinase—myocardial band

infarction often present with symptoms that differ from the symptoms of infarction in younger patients; more than half of elderly patients present with shortness of breath as their main complaint, and many others present with dizziness or symptoms of arrhythmia rather than the classic symptoms of acute myocardial infarction.¹¹

Approximately two thirds of patients describe the new onset of angina or a change in their anginal pattern in the month preceding infarction.¹² However, in approximately one fourth of patients, myocardial infarction is associated with only mild symptoms or no symptoms at all.¹³

PHYSICAL EXAMINATION

The patient with acute myocardial infarction often appears anxious and in distress. Vital signs are often normal, but sinus tachycardia is not uncommon. The pulse may be rapid or slow if arrhythmias are present. Either hypotension caused by left or right ventricular dysfunction or arrhythmia or hypertension caused by adrenergic discharge may be present. The respiratory rate may be elevated because of anxiety or pain or because of hypoxia in patients with significant congestive heart failure. The jugular venous pressure may be elevated, reflecting right ventricular dysfunction caused by right ventricular involvement (more common with inferior infarction); arrhythmia in which atrioventricular dissociation is present may produce so-called cannon A waves, which are abnormally high jugular venous waves caused by atrial systole occurring when the atrioventricular valves are closed. The lung examination is typically normal, but moist rales indicative of congestive heart failure resulting from left ventricular dysfunction may be present. The cardiac examination may reveal a dyskinctic apical pulsation on palpation; a fourth and, less commonly, a third heart sound may be audible. The murmur of ischemic mitral regurgitation may be present. If a left bundle branch block is present, abnormal splitting of the second heart sound may be heard.

It must be emphasized that the physical examination in acute myocardial infarction is generally most useful in excluding other potentially serious causes of the patient's chest discomfort, including pulmonary embolism, aortic dissection, spontaneous pneumothorax, pericarditis, and cholecystitis, rather than in confirming a diagnosis of acute myocardial infarction.

ELECTROCARDIOGRAPHY

ECG is a valuable tool both in confirming the diagnosis of acute myocardial infarction and in selecting the most appropriate therapy for the patient. Although rhythm and conduction disturbances may be present, the presence and type of repolarization abnormalities are most useful in identifying myocardial infarction. If ST segment elevation is present in a patient with chest pain typical of acute myocardial infarction, the likelihood that the patient has acute myocardial infarction is greater than 90%.¹⁴ Other findings, such as ST segment depression, T wave inversion, and bundle branch block, are less specific but may also support a diagnosis of acute myocardial infarction, particularly when typical symptoms are present [see Figure 1]. Fully 50% of patients with myocardial infarction do not have ST segment elevation on their ECGs, although the ECG is seldom normal even at an early stage.¹⁵ In such patients, the ECG can help predict complications and early mortality.¹⁶ Patients with ST segment depression are at high risk; 30-day mortality in such patients is nearly as high as in patients with anterior ST segment elevation.¹⁷ Patients with other nonspecific ECG abnormalities are at lesser

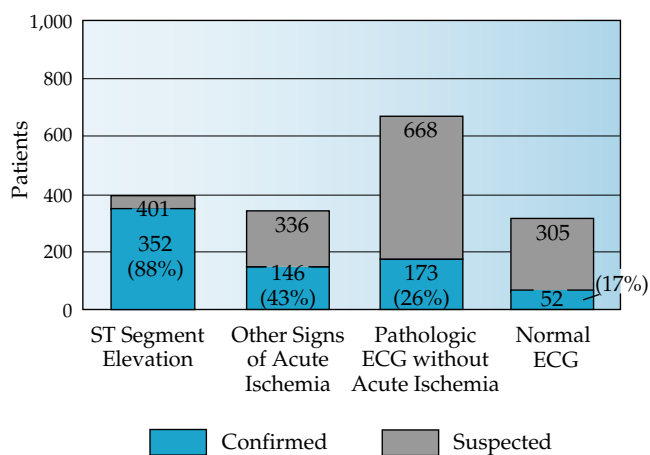


Figure 1 Relation between the initial electrocardiographic changes and the development of infarction in 1,715 patients strongly suspected of having an acute myocardial infarction. Each column shows the total number of patients and the number of patients later found to have had an infarction. Although infarction is less frequently confirmed in patients without ST segment elevation than in those with ST segment elevation, even patients with normal ECG findings may suffer acute myocardial infarction.¹⁴

risk; those with normal ECGs who suffer infarction generally have the best prognosis [see Figure 2]. Regardless of the findings on the initial ECG, the most important element in the evaluation of a patient with suspected acute myocardial infarction is the patient's description of symptoms. All patients suspected of having acute myocardial infarction should be admitted to the hospital and receive rapid and appropriate therapy.

LABORATORY FINDINGS

Injury to myocardial cells results in the release of intracellular enzymes into circulating blood, permitting their detection by blood tests. Traditionally, the serum cardiac marker creatine kinase (CK) and an isoenzyme, creatine kinase-myocardial band (CK-MB), which are found in high concentration in myocardial cells, have been used to diagnose myocardial infarction in its earliest stages.¹⁸ Rapid assays of these enzymes have been developed, permitting the determination of the blood levels of these enzymes within 30 to 60 minutes. Drawbacks to the use of CK-MB include its lack of specificity for cardiac muscle and the time required for CK-MB levels to rise during myocardial infarction. CK and CK-MB usually require at least 3 hours of profound ischemia to rise above normal levels; patients who present early in their infarction would not be expected to have elevated CK levels. Furthermore, patients may have only partial obstruction of the infarct-related artery, or there may be extensive collateralization of the infarct-related artery, which further delays the release of these enzymes. In patients suspected of having acute myocardial infarction, it is not appropriate to delay treatment until an elevation of CK or CK-MB is present, because the goal of treatment is to prevent injury to the myocardium. The challenge facing physicians is to identify patients suffering myocardial infarction even before CK becomes elevated, because these patients require emergency therapy and stand to benefit the most from reperfusion therapy.

To overcome these limitations and more accurately and rapidly identify patients in need of emergency reperfusion therapy,

other blood tests have been developed to help identify patients with ischemia. Myoglobin is a low-molecular-weight heme protein found in cardiac muscle. Its advantage for diagnosis is that it is released more rapidly from infarcted myocardium than is CK-MB. However, myoglobin is also found in skeletal muscle, and the lack of specificity is a drawback.¹⁹ Troponin is a cardiac-specific marker for acute myocardial infarction; an increase in serum levels of troponin occurs soon after myocardial cell injury. An elevated cardiac troponin level on admission is a predictor of subsequent cardiac events.^{20,21} Changes to the definition of acute myocardial infarction reflect the increased emphasis on these specific biomarkers of myocardial injury [see Table 1].¹⁰

IMAGING STUDIES

Echocardiography

Echocardiography may be useful in identifying patients with myocardial infarction in the emergency department. Regional wall motion abnormalities occur within seconds of coronary occlusion and well before myocyte necrosis,²²⁻²⁶ and most patients with acute myocardial infarction have regional wall motion abnormalities readily seen on echocardiography. However, echocardiographic evidence of myocardial infarction is not required in patients with symptoms and electrocardiographic evidence typical of acute myocardial infarction, and treatment should not be delayed, so that an echocardiogram can be performed. Similarly, wall motion abnormalities are not specific for acute myocardial infarction and may be caused by ischemia or prior infarction. Echocardiography may be useful in patients with left bundle branch block or abnormal ECGs without ST segment elevation whose symptoms are atypical and in whom the diagnosis is uncertain.²⁷

Radionuclide Imaging

Perfusion imaging with both thallium and sestamibi in the emergency department has been reported to be both sensitive and specific in the evaluation of patients in whom the diagnosis is uncertain.²⁷⁻²⁹ A prospective randomized trial of 2,475 patients found that resting technetium-99m sestamibi imaging reduced unnecessary hospitalization in patients with acute ischemia without reducing admission of patients with acute ischemia.³⁰

Emergent Therapy

Treatments have been developed that reduce the morbidity and mortality of acute myocardial infarction, particularly when initiated early; it is therefore important to avoid delay in administering therapy.^{4,31} Much of the emphasis on reducing delay has focused on the time between a patient's presentation to the emergency department and the administration of reperfusion therapy. The 2004 ACC/AHA guidelines recommended that all initial therapy be carried out in the emergency department based upon a predetermined, institution-specific, written protocol.³¹ A patient with symptoms suggestive of myocardial infarction should be evaluated within 10 minutes after arrival in the emergency department. Early steps should include the assessment of hemodynamic stability by measurement of the patient's heart rate and blood pressure; the performance of a 12-lead ECG; and the administration of oxygen by nasal prongs, I.V. analgesia (most commonly morphine sulfate), oral aspirin, and sublingual nitroglycerin if the blood pressure is greater than 90 mm Hg. The challenge facing physicians who work in emergency departments is that more than 90% of patients who present to the emergency department complaining of chest pain are not suffering myocardial infarction; many do not have a cardiac etiology for their chest pain.

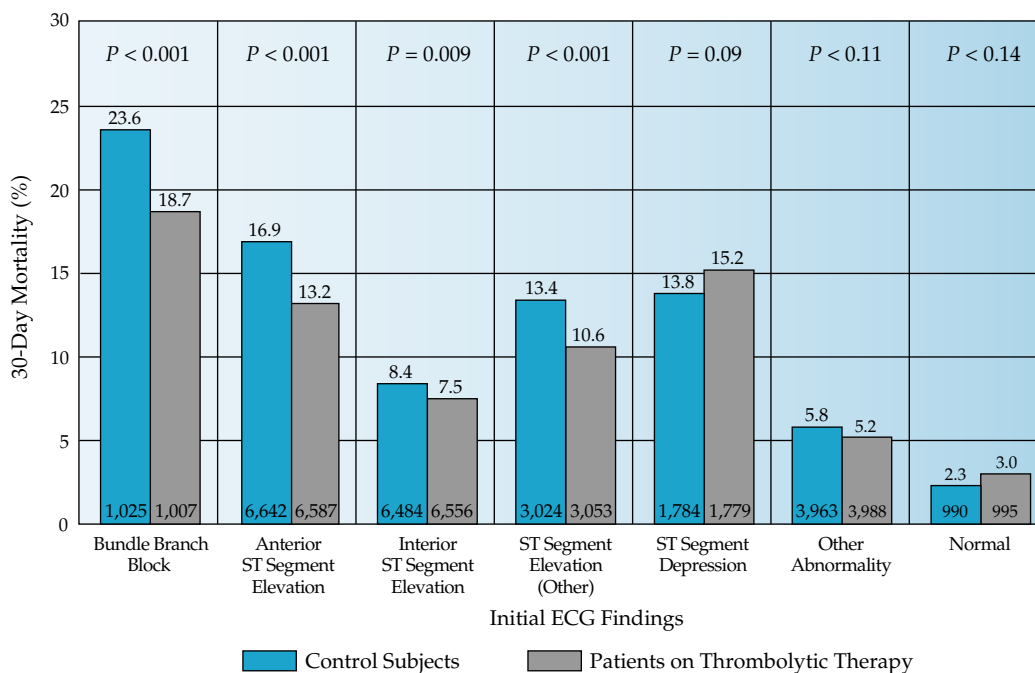


Figure 2 Thirty-day mortality in patients with suspected acute myocardial infarction from placebo-controlled trials of thrombolytic therapy on the basis of their initial ECGs. Patients with ST segment depression are at high risk, nearly as high as patients with anterior ST segment elevation. The mortality among such patients is not reduced (and may be increased) by thrombolytic therapy. Patients with other nonspecific electrocardiographic abnormalities are at lesser risk, and those with normal ECG findings have the best prognosis.

All patients with definite or suspected myocardial infarction should be admitted to the hospital, undergo preparation for I.V. access, and be placed on continuous ECG monitoring. High-risk patients should be admitted to a coronary care unit. In many hospitals, patients at low risk for major complications are admitted to a telemetry unit, where emergency medical care can be quickly administered, rather than to a coronary care unit. Tachyarrhythmias and bradyarrhythmias may occur even in low-risk patients, particularly in the first 24 hours. Lidocaine, atropine, an external or internal pacemaker, and a defibrillator should be readily available.

OXYGEN

Oxygen is generally recommended for all patients with acute myocardial infarction for the first several hours after admission and is mandatory for patients with pulmonary congestion or evidence of oxygen desaturation.

ASPIRIN

Aspirin should be given to all patients as soon as a diagnosis of myocardial infarction is made.¹⁷ In the second International Study of Infarct Survival (ISIS-2), aspirin was found to be nearly as effective as streptokinase, reducing 30-day mortality 23% in 17,000 patients with acute myocardial infarction; the benefit was additive in patients receiving both aspirin and streptokinase [see Figure 3].¹⁷ Other studies have revealed similar benefit from immediate aspirin therapy.³²

Patients should be maintained on aspirin indefinitely. Prolonged administration of aspirin in patients with a history of myocardial infarction is associated with a 25% reduction in death, nonfatal reinfarction, and stroke.³²

ANALGESIA

Pain relief should be among the initial therapies offered to patients with acute myocardial infarction. Persistent chest discomfort is generally caused by ongoing myocardial ischemia; although the ultimate goal of therapy is to eliminate ischemia, analgesia should be administered without delay. In addition to making patients more comfortable, pain relief may reduce the outpouring of catecholamines characteristic of the early stages of acute myocardial infarction and thereby reduce myocardial oxygen demand. Intravenous morphine sulfate is commonly used for pain relief in this setting.

Reperfusion Therapy

Reperfusion may be achieved by percutaneous coronary intervention (PCI) (previously referred to as primary coronary angioplasty, percutaneous transluminal coronary angioplasty [PTCA], or balloon angioplasty) or thrombolytic therapy.

REPERFUSION STRATEGIES AND OUTCOMES

Importance of Time to Reperfusion

Many important predictors of early clinical outcome in myocardial infarction are independent of treatment. Most of the early mortality is explained by factors such as the age of the patient, initial heart rate and blood pressure, initial Killip classification [see Table 2], and infarct location. However, the time to administration of reperfusion therapy is a critical determinant of outcome and one of the few determinants of early clinical outcome under the control of the physician. Many studies have revealed

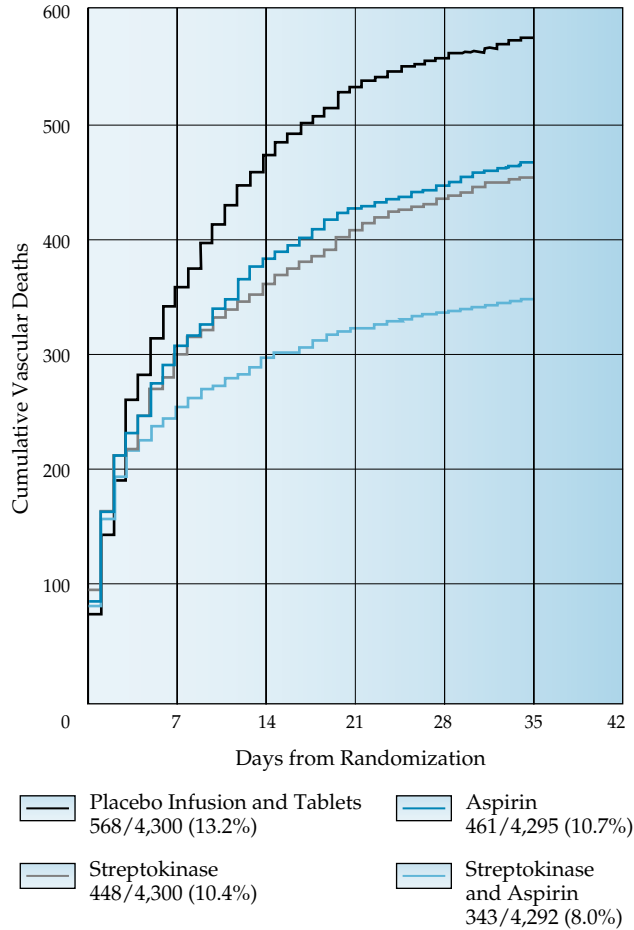


Figure 3 Mortality at 35 days in 17,187 cases of suspected acute myocardial infarction in the second International Study of Infarct Survival (ISIS-2). In this study, aspirin reduced 30-day mortality by 23% and was nearly as effective as streptokinase; the benefit was additive in patients receiving both aspirin and streptokinase.¹⁷

that patients with myocardial infarction treated most rapidly have a lower mortality and, among survivors, reduced infarct size [see Figure 4].³³ This observation has led to recommendations that the time between a patient's presentation to the emergency department and the administration of thrombolytic therapy not exceed 60 minutes; ideally, this period should not exceed 30 minutes.³⁴ The most critical interval is the time between symptom onset and the achievement of reperfusion, not the time to the ini-

Table 2 Killip Classification of Acute Myocardial Infarction

Class I	No clinical heart failure
Class II	Findings consistent with mild or moderate heart failure (e.g., isolated S ₃ gallop, bilateral rales in up to 50% of lung fields)
Class III	Pulmonary edema, rales in all lung fields, acute mitral regurgitation
Class IV	Cardiogenic shock (e.g., stuporous state of consciousness, systolic blood pressure < 90 mm Hg, decreased urine output, pulmonary edema, and cold, clammy skin)

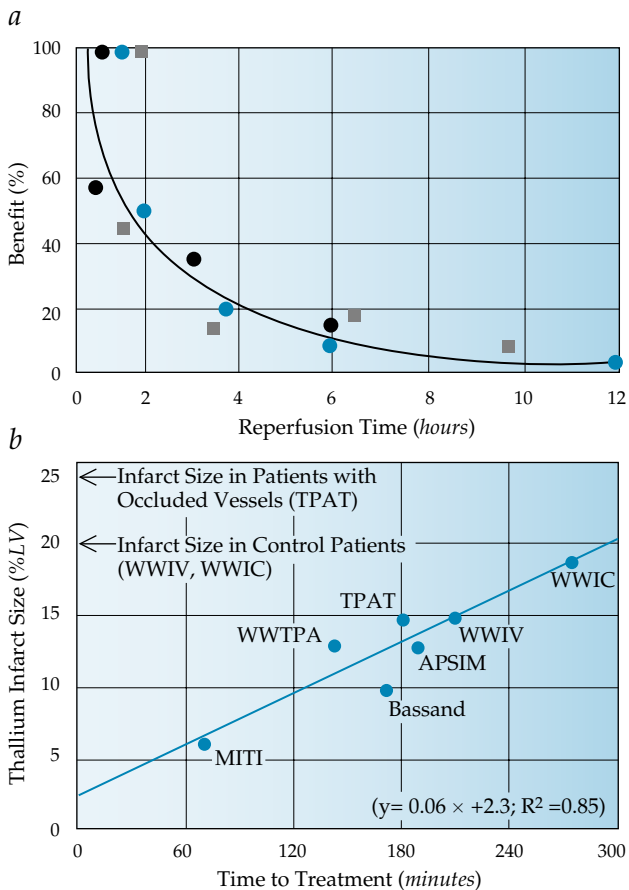


Figure 4 Many studies have revealed lower mortality (a) and reduced infarct size among survivors (b) of myocardial infarction treated most rapidly. The equation shows the linear relation between infarct size and time to treatment.³³ (APSIM—APSAC dans l’Infarctus du Myocarde; Bassand—Bassand study; MITI—Myocardial Infarction Triage and Intervention; TPAT—Tissue Plasminogen Activator, Toronto trial; WWIC—Western Washington Intracoronary streptokinase trial; WWIV—Western Washington Intravenous streptokinase trial; WWTPA—Western Washington Tissue Plasminogen Activator trial)

tiation of therapy. Thus, therapy that takes longer to initiate may actually be superior if it achieves reperfusion more rapidly than another therapy that can be initiated more rapidly (e.g., thrombolytic therapy). The ACC/AHA task force gave a class I recommendation to the use of PCI for any patient with an acute ST-segment elevation myocardial infarction (STEMI) who presents within 12 hours of symptom onset and who can undergo the procedure within 90 minutes of presentation by clinicians skilled in the procedure.³¹ When primary PCI is not available or its implementation is delayed, use of thrombolytic therapy is recommended. The ACC/AHA task force gave a class I recommendation to the use of thrombolytic therapy for any patient with an acute STEMI without contraindications for thrombolysis, who presents to a facility without the capability for expert, prompt intervention with primary PCI within 90 minutes of first medical contact.³¹ The delay from patient arrival to administration of thrombolytics should be less than 30 minutes.³¹ Reperfusion therapy, whether PCI or thrombolytics, should not await the availability of results of cardiac biomarkers. The immediate implementation of reperfusion therapy without awaiting biomarker data was given a class I recommendation.³¹

The importance of avoiding hospital delay in performing pri-

mary coronary angioplasty was evident in the Global Use of Strategies to Open Occluded Arteries (GUSTO-IIb) substudy, which compared primary coronary angioplasty with tissue plasminogen activator (t-PA) therapy.³⁵ There was a clear relation between the length of time until angioplasty was performed after enrollment in the study and 30-day mortality [see Figure 5]. Analysis of 27,080 patients in the second National Registry of Myocardial Infarction also revealed a relation between time to treatment with primary PTCA and survival, even after adjusting for other mortality risk factors.³⁶ In that study, the volume of patients treated with angioplasty at the hospital was also a predictor of outcome; a lower mortality was seen at hospitals in which a high number of patients with acute myocardial infarction were treated with coronary angioplasty. There have been studies in which unacceptably high mortality was seen at hospitals when primary angioplasty was not performed rapidly; reducing delay led to a reduction in mortality.³⁷ Therefore, as is the case with thrombolytic therapy, the speed with which reperfusion is achieved appears to be an important determinant of clinical outcome. The best reperfusion therapy (coronary angioplasty or thrombolytic therapy) is not necessarily the one that can be most rapidly initiated but, rather, the one that achieves coronary patency most rapidly. In general, the therapy that restores flow most rapidly should be preferred.³⁸⁻⁴⁰

Transfer for Primary Angioplasty versus Immediate Thrombolytic Therapy

Time to reperfusion is an important modifiable predictor of clinical outcome for both thrombolysis and primary angioplasty, although it has the greatest impact on patients treated with thrombolytic therapy. An alternative treatment strategy for patients with STEMI initially assessed at a hospital without on-site cardiac surgery facilities is immediate transfer for primary PCI.

The PRAGUE-2 investigators randomized 850 patients with acute STEMI presenting within 12 hours to a hospital without a catheterization laboratory to either immediate thrombolysis or transfer for primary PCI.⁴¹ The investigators determined that in the acute phase of STEMI, long-distance transport from a community hospital to a facility with PCI is safe and is associ-

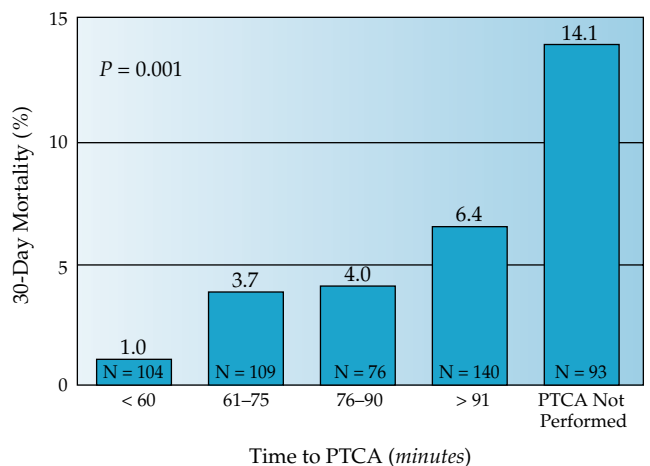


Figure 5 Relation between the time from study enrollment to the first balloon inflation and 30-day mortality in the GUSTO-IIb substudy. Patients assigned to angioplasty in whom angioplasty was not performed are also shown.³⁵ (PTCA—percutaneous transluminal coronary angioplasty)

ated with decreased mortality in patients presenting more than 3 hours after symptom onset. Similarly, the Danish Trial in Acute Myocardial Infarction (DANAMI)-2 trial investigators concluded that immediate transfer for primary PCI, in preference to immediate thrombolysis, was safe and efficacious.⁴²

However, data from these trials need to be understood within the context of the individual trial designs and their actual conduct. The maximum transport distance in the PRAGUE-2 trial was 120 kilometers, and the time from transport to balloon inflation was only 97 ± 27 minutes. In the DANAMI-2 trial, the time from arrival to initiation of treatment in the thrombolysis arm of the study was 51 minutes, whereas the time required to transfer patients for primary PCI was 155 minutes ($P < 0.0001$). It is reasonable to assume that the reported benefit associated with this particular treatment strategy in the aforementioned randomized, controlled clinical trials (i.e., PRAGUE-2 and DANAMI-2) can be realized only if similar transfer times and door-to-balloon times are reproduced in clinical practice; the findings of the NRM1 4 investigators are not reassuring in this regard.

Coronary Angiography after Uncomplicated Myocardial Infarction

The role of coronary angiography after uncomplicated myocardial infarction remains controversial for patients who have received thrombolytic therapy. Coronary angiography in patients initially treated with thrombolytic agents has been studied in the second Thrombolysis in Myocardial Infarction (TIMI II) study, the Should We Intervene Following Thrombolysis? (SWIFT) study, the Treatment of Post-thrombolytic Stenoses (TOPS) study, and, most recently, a German study.⁴³⁻⁴⁶ It is clear from these studies that patients treated with thrombolytic therapy in whom complications do not occur are at low risk for reinfarction and death after discharge and that the routine performance of coronary angiography and coronary angioplasty does not reduce the occurrence of these adverse events. Despite the publication of these well-designed studies, there has been considerable reluctance among physicians to accept their results, and there remains considerable variability throughout the United States and the world in the frequency with which coronary angiography is performed in such patients.

Many cardiologists feel more comfortable caring for patients who have suffered a myocardial infarction if the patient's coronary anatomy is known. Patients at low risk may be discharged from the hospital more rapidly. Patients who have left mainstem or multivessel disease, particularly those who have reduced ventricular function, may be referred for coronary artery bypass surgery or percutaneous revascularization. Patients with persistent occlusion of the infarct-related artery may benefit from revascularization because of favorable effects on remodeling, a reduction in ventricular arrhythmia, and the improved ability of the infarct-related artery to provide collateral blood flow to other coronary arteries in the future. Nonetheless, until the benefits of cardiac catheterization are demonstrated in asymptomatic patients after an uncomplicated myocardial infarction, a conservative strategy is recommended in patients who have been given thrombolytic therapy, and coronary angiography is recommended only for patients with hemodynamic instability or for patients in whom spontaneous or exercise-induced ischemia occurs; such a strategy is safe and is associated with a good clinical outcome.

Patients who are not given thrombolytic therapy are at higher risk for reinfarction and death than those receiving thrombolytic therapy. The role of coronary angiography in patients with acute

myocardial infarction not receiving thrombolytic therapy has not been studied. In such patients whose infarctions are complicated by hemodynamic compromise or postinfarction chest pain or in patients in whom multivessel disease or reduced ventricular function is believed to be present, coronary angiography is probably helpful. It remains unclear whether coronary angiography should be performed in patients not treated with thrombolytic therapy who do not have these high-risk characteristics. It is impossible to be definitive about recommendations in the absence of appropriate studies, and not surprisingly, practice patterns vary widely throughout the United States and the world in such patients.

Reperfusion Therapy in Patients without ST Segment Elevation

Primary PTCA has not been appropriately studied in patients without ST segment elevation, and it is not possible to be definitive about its use in this setting. However, regardless of the findings on ECG, PTCA is widely believed to be beneficial in patients with ischemic-type chest discomfort that persists despite medical therapy. Many patients with prolonged chest pain without ST segment elevation are not suffering from myocardial infarction; the likelihood that infarction is present is increased if repolarization abnormalities are present on the ECG and the patient has risk factors for coronary artery disease. In patients with critical coronary artery stenoses, immediate PTCA or bypass surgery may be appropriate. In patients without significant coronary artery disease, immediate angiography can also be extremely useful and can lead to the withdrawal of cardiac med-

Table 3 Class I Recommendations for the Use of an Invasive Strategy in the Management of Patients with Unstable Angina or Non-ST Segment Elevation Myocardial Infarction

An early invasive strategy is recommended for patients who have unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) without serious comorbidity and who have any of the following high-risk indicators (level of evidence: A):

- Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy
- Elevated levels of troponin T or troponin I
- New or presumably new ST segment depression
- Recurrent angina/ischemia with symptoms of congestive heart failure, an S₃ gallop, pulmonary edema, worsening rales, or new or worsening mitral regurgitation
- High-risk findings on noninvasive stress testing
- Depressed left ventricular systolic function (e.g., ejection fraction < 0.40 on noninvasive study)
- Hemodynamic instability
- Sustained ventricular tachycardia
- Percutaneous coronary intervention within 6 mo
- Prior coronary artery bypass grafting

In the absence of any of these findings, an early conservative strategy or an early invasive strategy may be offered in hospitalized patients without contraindications for revascularization (level of evidence: B)

Note: Class I recommendations pertain to conditions for which there is evidence or general agreement that a given procedure is useful and effective. Level A evidence (highest)—Derived from multiple randomized clinical trials. Level B evidence (intermediate)—Derived from limited number of randomized clinical trials, nonrandomized studies, or observational registries.

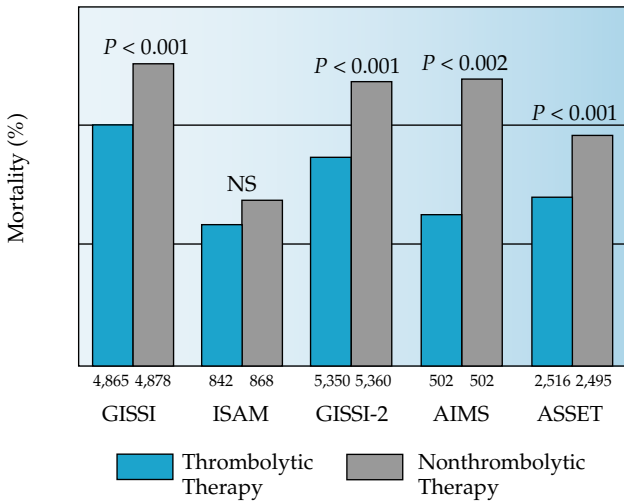


Figure 6 Data from five controlled megatrials of thrombolytic therapy large enough to detect a mortality difference between the thrombolytic and nonthrombolytic control arms of the trials. Pooled data from these five trials (not shown) reveal a 29% mortality reduction in patients treated within 6 hours of symptom onset.⁵³ (AIMS—APSA International Mortality Study; ASSET—Anglo-Scandinavian Study of Early Thrombolysis; GISSI—Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico; GISSI-2—Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico; ISAM—Intravenous Streptokinase in Acute Myocardial Infarction; NS—not significant)

ications, discharge from the coronary care unit, and appropriate diagnostic evaluation, in many cases as an outpatient. Immediate angiography is recommended in all patients with hypotension, severe congestive heart failure, or cardiogenic shock regardless of the initial ECG results, because immediate revascularization appears to reduce mortality in this setting.⁴⁷ In addition, there is a compelling case to be made for routine invasive evaluation of all patients who are admitted with unstable angina or non-ST segment elevation myocardial infarction (NSTEMI).⁴⁸

In the TIMI-IIIb study, an early intervention strategy was compared with a conservative strategy in 3,000 patients with either unstable angina, recent non-Q wave myocardial infarction, or prolonged chest pain without ST segment elevation on ECG.⁴⁹ Patients were randomized to receive either early angiography or medical therapy; only those patients who subsequently experienced recurrent chest pain or had an exercise test underwent angiography. Although death and myocardial infarction occurred with similar frequency in the two groups, the study showed that the initial hospitalization was longer and the need for rehospitalization more frequent in the group receiving conservative therapy. More recently, in the second Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC-II) trial, an early invasive strategy was shown to reduce both mortality and myocardial infarction at 1 year.⁵⁰ In the Treat Angina with Aggrastat [tirofiban] and Determine Cost of Therapy with Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction-18 (TACTICS-TIMI-18) study, an early invasive strategy was found to reduce the combined end point of death or myocardial infarction.⁵¹ In both the FRISC-II and TACTICS-TIMI-18 studies, patients at greatest risk, such as those with positive troponin values and with ST segment depression at study entry, had the highest event rates and derived the greatest benefit from an invasive strategy.

The 2002 ACC/AHA unstable angina guideline update has summarized the data regarding early invasive versus early conservative strategies in patients with unstable angina or NSTEMI and issued an updated set of recommendations to guide clinical decision making in this setting [see Table 3].⁵²

THROMBOLYTIC THERAPY

Thrombolytic therapy has been widely studied in prospective, randomized, controlled trials involving more than 50,000 patients and has been proved to reduce mortality 29% in patients with ST segment elevation treated within 6 hours after the onset of chest pain [see Figure 6].⁵³ The survival benefit of thrombolytic therapy is maintained for years.⁵⁴ The benefit of thrombolytic therapy is achieved through rapid restoration of blood flow in an occluded coronary artery.⁵⁵⁻⁵⁷

Thrombolytic therapy is strongly recommended for patients with ST segment elevation in two or more contiguous leads who have had less than 6 hours of chest pain; for patients with classic symptoms of infarction in whom a bundle branch block precludes detection of ST segment elevation⁵³; and for patients presenting with 6 to 12 hours of chest pain, although the expected benefits for this last group of patients are fewer. The potential benefits should be weighed against the potential risks in patients with relative contraindications to thrombolytic therapy (see below).^{17,58} It is important to calculate the duration of infarction as the time from the last pain-free interval. The infarct-related artery often opens and closes spontaneously during the early stages of infarction, which the patient may experience as alternating pain-free and painful intervals; the window of benefit from thrombolytic therapy may be greater than 12 hours if antegrade flow was even briefly restored.

Contraindications to Thrombolytic Therapy

Contraindications to thrombolytic therapy include all conditions that predispose a patient to significant bleeding. The most feared bleeding complication is intracerebral hemorrhage, which is fatal in over half of cases. Risk factors for intracerebral bleeding include advanced age, low body weight, hypertension, warfarin use, and previous stroke.^{53,59} Patients with gastrointestinal bleeding and those who have recently undergone surgery are also at increased risk for bleeding. Even when risk factors for bleeding are present, however, the potential benefits of thrombolytic therapy may still outweigh the risks. For example, although the elderly have a higher risk of intracerebral bleeding than younger patients, elderly patients should certainly be considered candidates for thrombolytic therapy, because their increasing absolute mortality results in a greater reduction in absolute mortality with thrombolytic therapy than is seen in younger patients.⁵³

In patients with ECG findings other than ST segment elevation or bundle branch block, thrombolytic therapy has been found to be either of no use or deleterious; its use is not recommended in such patients.^{17,53}

Choice of Thrombolytic Agent

Many different thrombolytic regimens have been proved effective for the treatment of acute myocardial infarction, and many more are being studied. In principle, the preferred thrombolytic regimen would restore normal antegrade blood flow to an occluded coronary artery most rapidly and in the greatest number of patients, would have the lowest reocclusion rate, and would be associated with the lowest risk of severe hemorrhagic

complications. The first Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO-I) trial evaluated four thrombolytic regimens to determine which was associated with the greatest overall survival and stroke-free survival at 30 days: (1) a regimen of front-loaded, weight-adjusted t-PA and I.V. heparin, (2) a regimen of streptokinase and I.V. heparin, (3) a regimen of streptokinase and subcutaneous heparin, and (4) a combination of I.V. t-PA and streptokinase given concurrently with I.V. heparin. Front-loaded t-PA was found to be moderately superior to the other thrombolytic regimens [see Figure 7].⁵⁶ However, because of the approximately 10 times greater cost of t-PA than I.V. streptokinase and the low margin of superiority of t-PA (one life saved per thousand patients treated), some physicians prefer the less expensive streptokinase therapy, particularly for patients at low risk of dying (such as those with uncomplicated inferior infarctions) and the elderly, who are more likely to have hemorrhagic complications with t-PA than with streptokinase; t-PA is associated with a greater frequency of intracerebral hemorrhage than streptokinase.⁵⁶ The recommendation of streptokinase in these patient groups is largely driven by its lower cost; if the costs of t-PA and streptokinase were similar, t-PA would most likely be the preferred therapy in all patient subgroups, with the possible exception of those at increased risk for intracerebral hemorrhage, in whom streptokinase might be preferred.

Streptokinase therapy is contraindicated in patients who have recently received a dose of streptokinase because of antibodies that form against the drug; these antibodies limit the efficacy of repeat doses and increase the risk of allergic reactions. It has been suggested that the drug not be readministered for at least 2 years.

New thrombolytic agents are continuously being developed in the hope of finding safer and more effective therapies. One such agent, reteplase, is a recombinant tissue plasminogen activator (rt-PA) that is a mutant of alteplase. Reteplase is easier to administer than alteplase; because of its longer half-life, it can be administered as two 10 mU boluses given 30 minutes apart, with concomitant aspirin and I.V. heparin administration. Several pilot studies suggest that reteplase has an early patency rate that is superior to the patency rates of streptokinase and alteplase. In the International Joint Efficacy Comparison of Throm-

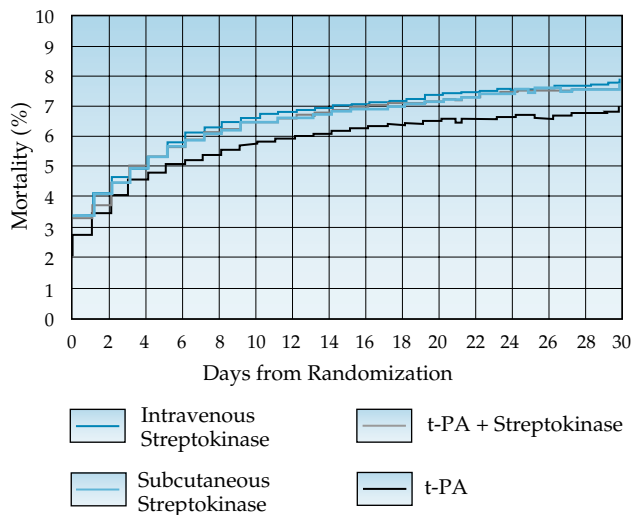


Figure 7 The frequency of death or disabling stroke in the 30 days after enrollment in 41,021 patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO-I) trial. Front-loaded t-PA was found to be superior to the other thrombolytic regimens.⁵⁶

bolytics (INJECT) trial, 6,010 patients with acute myocardial infarction received either reteplase or streptokinase within 12 hours after the onset of symptoms.⁶⁰ Mortality at 35 days, the primary end point of the study, was 9.02% for patients given reteplase, compared with 9.53% for patients given streptokinase, a nonsignificant difference (95% confidence interval, 1.98 to 0.96). This lack of significant difference indicates that reteplase was at least as effective as streptokinase.

In the GUSTO-III trial, reteplase was compared with t-PA in 15,059 patients with acute myocardial infarction who presented within 6 hours of symptom onset.⁶¹ Patients received either reteplase or an accelerated infusion of t-PA. For patients receiving reteplase, the mortality at 30 days was 7.47%, compared with 7.24% for patients receiving t-PA ($P = 0.54$; odds ratio, 1.03; 95%



Figure 8 (a) Left anterior oblique view of an occluded left anterior descending artery in a patient suffering an acute anterior myocardial infarction. (b) Patency was restored with direct coronary angioplasty 17 minutes after the patient had arrived in the catheterization laboratory, and the patient had immediate resolution of his symptoms.

confidence interval, 0.91 to 1.18). The mortality rates with the two agents were therefore similar, and the two agents are probably, although not definitely, equivalent in efficacy.

Combination Therapy

Combination therapy, defined as the use of a thrombolytic agent and a glycoprotein IIb/IIIa inhibitor, has been proposed as an alternative to thrombolytic therapy alone for the primary treatment of STEMI. This strategy is supported by data from a number of trials that demonstrated improved rates of TIMI-3 flow after combination therapy, as compared with thrombolytic therapy alone.^{62,63} However, the results of two randomized, controlled trials evaluating clinical outcomes after the respective aforementioned reperfusion strategies have been somewhat disappointing.

The GUSTO-V trial randomized 16,588 patients who presented within 6 hours after symptom onset with STEMI to either standard-dose reteplase or half-dose reteplase and full-dose abciximab.⁶⁴ At 30 days, the incidence of death in the reteplase arm was 5.9%, compared with 5.6% in the combination-therapy arm ($P = 0.43$), suggesting no mortality benefit associated with combination therapy. However, five of 16 prespecified secondary end points were reduced to a statistically significant degree ($P < 0.05$), suggesting a beneficial impact of combination therapy on the incidence of recurrent ischemic events and the mechanical and electrical complications of acute myocardial infarction (e.g., nonfatal reinfarction, recurrent ischemia, ventricular fibrillation, sustained ventricular tachycardia, and atrioventricular block). However, these clinical benefits were offset by an increased incidence of bleeding of any kind (13.7% with monotherapy versus 24.6% with combination therapy; $P < 0.0001$); severe or moderate, spontaneous, nonintracranial bleeding (1.9% versus 4.3%, $P < 0.0001$); severe bleeding (0.5% versus 1.1%; $P < 0.0001$), and bleeding sufficient to require blood transfusion (4.0% versus 5.7%; $P < 0.0001$). Furthermore, there were subgroups of patients in whom intracranial bleeding was increased by combination therapy; there was a significant ($P = 0.033$) association between age (< 75 or ≥ 75 years) and intracranial hemorrhage in the combination-therapy arm.

The Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 trial randomized 6,095 patients to one of

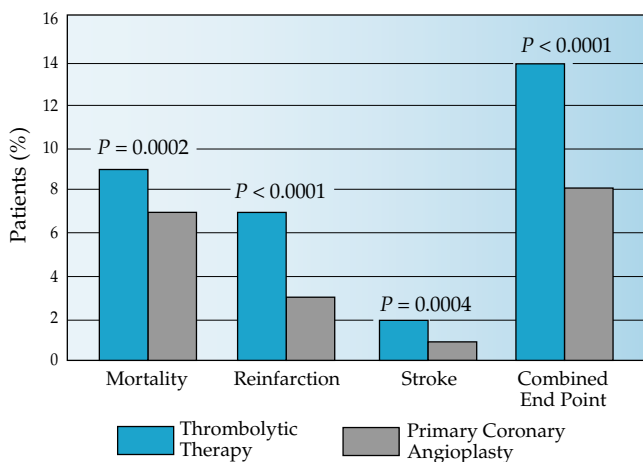


Figure 9 Results from a quantitative review of 23 randomized trials of primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction.⁷² Clinical outcome was improved in patients who received angioplasty.

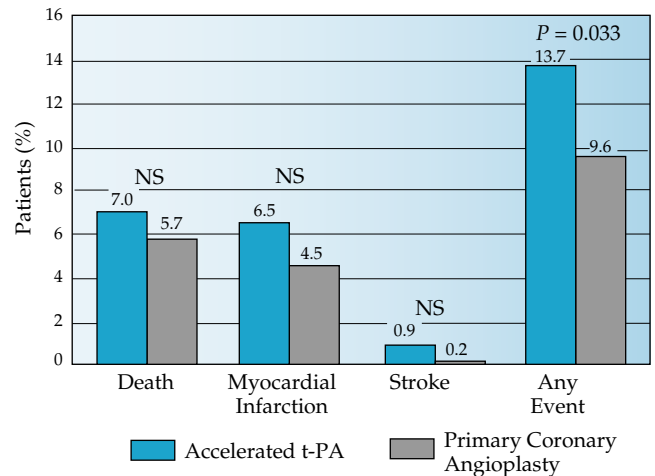


Figure 10 Results from the GUSTO-IIb substudy trial comparing primary coronary angioplasty and accelerated t-PA indicate that primary angioplasty was associated with a lower mortality, reinfarction rate, and frequency of stroke in the 30 days after enrollment than was accelerated t-PA.⁷³ (NS—not significant)

three treatment regimens: full-dose tenecteplase and enoxaparin, half-dose tenecteplase and weight-adjusted low-dose unfractionated heparin infusion plus 12-hour infusion of abciximab, or full-dose tenecteplase and weight-adjusted unfractionated heparin infusion for 48 hours.⁶⁵ In-hospital mortality was not significantly different between the three groups. The abciximab treatment regimen reduced in-hospital rates of reinfarction and refractory ischemia. Although rates of intracranial hemorrhage were similar, other types of major bleeding were significantly higher in the abciximab arm of the trial. The enoxaparin arm suggested that there is a higher rate of intracranial bleeding in the elderly; this finding was corroborated by the ASSENT-PLUS study, which necessitated a change in dose of enoxaparin when administered with a thrombolytic agent in elderly patients.⁶⁶

PRIMARY CORONARY ANGIOPLASTY

In prospective, randomized trials comparing primary coronary angioplasty [see Figure 8] with different thrombolytic agents, primary coronary angioplasty was associated with a lower morbidity and mortality than thrombolytic therapy.⁶⁷⁻⁷¹ Although most of the individual trials were too small to detect statistically significant differences in mortality, pooled data from these trials suggest that primary coronary angioplasty is the preferred therapy for acute myocardial infarction at institutions where it can be performed without delay [see Figure 9].⁷²

The GUSTO-IIb trial was designed to be large enough to confirm the reduction in mortality found in the smaller randomized trials.⁷³ The results of the study indicate that compared with thrombolytic therapy, primary coronary angioplasty is associated with a lower mortality, reinfarction rate, and frequency of stroke in the 30 days after enrollment [see Figure 10]. However, the degree of benefit associated with primary coronary angioplasty was much smaller than that seen in the earlier randomized studies; this finding was in part related to the lower frequency with which patients assigned to undergo angioplasty in GUSTO-IIb actually underwent the procedure and in part related to the lower frequency with which normal antegrade coronary blood flow was achieved in patients who did undergo coronary angioplasty.

The consistency of the results favoring primary coronary angioplasty and the greater speed and frequency with which coronary angioplasty can restore flow to an occluded coronary artery support the conclusion that primary coronary angioplasty is preferable to thrombolytic therapy at institutions where it can be performed quickly with a high success rate.⁷⁴ Studies have shown that excessive delay in performing primary coronary angioplasty and operator inexperience lead to a higher mortality than that seen when primary coronary angioplasty is performed rapidly by experienced operators.³⁶ It has been recommended that primary angioplasty be performed only in hospitals where a high success rate and low complication rate can be demonstrated and where primary angioplasty is performed in at least 80% to 90% of patients in whom acute myocardial infarction is confirmed.^{72,75} The need for surgical backup is controversial, as excellent results have been obtained at centers without surgical backup.⁷⁶ However, surgical backup is recommended because approximately 5% of patients with acute myocardial infarction who undergo immediate coronary angiography require emergency surgery either for angioplasty that has failed or, more commonly, because lethal coronary anatomy precludes primary angioplasty.

Immediate transfer for primary angioplasty is an alternative treatment strategy for patients with STEMI initially assessed at a hospital without on-site cardiac surgery facilities.

Antiplatelet Therapy

Aspirin and clopidogrel therapy Aspirin should be given to patients with suspected STEMI as early as possible and continued indefinitely. True aspirin allergy is the only exception to this recommendation.³¹ The 2004 ACC/AHA guidelines gave a class I recommendation to the use of clopidogrel in all patients treated with primary PCI.³¹ Clopidogrel may be given in a loading dose of 300 mg or 600 mg; limited trial data suggest that 600 mg works within 2 to 3 hours and that outcomes may be better than with 300 mg. There are no data available regarding the combination of fibrinolytic agents and clopidogrel, but ongoing trials will provide this information. However, clopidogrel is probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.

Glycoprotein IIb/IIIa inhibitor therapy The 2004 ACC/AHA guidelines gave a class IIa recommendation to treatment with abciximab as early as possible prior to PCI (with or without implantation of stents) in patients with STEMI.³¹ This recommendation was based on several studies including the Randomized, Placebo-Controlled Trial of Abciximab with Primary Angioplasty for Acute Myocardial Infarction (RAPPORT), the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) study, the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) study, and, most recently, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study.⁷⁷⁻⁸⁰ The results of the four studies differ, in part because the trials used different end points, in part because of the high frequency of noncompliance with the protocol in some trials, and in part because of differences in the treatments utilized (balloon angioplasty alone versus balloon angioplasty followed by stent placement).

The largest of the four studies, the CADILLAC study, found that abciximab is beneficial at reducing major adverse events, but the benefit appeared to be limited to patients undergoing

balloon angioplasty without stent placement. The apparent lack of benefit following treatment with abciximab in patients in the CADILLAC trial who received a coronary stent is contrary to the results of the ISAR-2 and ADMIRAL trials, in which abciximab was found to be beneficial in patients receiving stents. There are data suggesting that stent placement in the setting of acute myocardial infarction slightly reduces the frequency with which normal antegrade blood flow in the infarct-related artery is achieved.⁸¹ This would suggest that glycoprotein IIb/IIIa inhibitors should be beneficial in this setting. Taken together, the results of these studies that are currently available suggest that abciximab is beneficial in patients with acute myocardial infarction but that the benefit in patients undergoing balloon angioplasty alone may differ from that in patients who undergo balloon angioplasty with stent placement. Clearly, however, stents markedly reduce the frequency with which a repeat revascularization procedure is needed in the months after the angioplasty procedure.⁸¹ The combined use of stents and platelet glycoprotein inhibitors may maximize the frequency with which normal antegrade blood flow is achieved while reducing the need for repeat procedures in the following year.

One study compared the outcome of thrombolytic therapy using t-PA with that of primary angioplasty utilizing both stents and abciximab.⁸² The reduction in infarct size was far greater in the group undergoing primary angioplasty; the clinical outcome was also better in the patients who underwent angioplasty.

CORONARY ARTERY BYPASS SURGERY

Coronary artery bypass surgery can restore blood flow in an occluded infarct-related artery. However, because of the time required to perform coronary angiography and to transport patients to the operating room, reperfusion is achieved more slowly with bypass surgery than with thrombolytic therapy and primary coronary angioplasty.⁸³ Emergency coronary artery bypass surgery should generally be reserved for patients in whom immediate angiography reveals coronary anatomy that precludes primary coronary angioplasty; for patients in whom angioplasty has failed; and for patients with a ventricular septal defect, severe mitral regurgitation, or myocardial rupture.

RESCUE CORONARY ANGIOPLASTY

Depending on the regimen used, only 33% to 60% of patients treated with thrombolytic therapy have restoration of normal antegrade flow in the infarct-related artery 90 minutes after the initiation of therapy.⁸⁵ Accordingly, immediate coronary angiography has been studied to determine whether patients with persistent occlusion of the infarct-related artery benefit from coronary angioplasty; this procedure has been termed rescue angioplasty. A single small, randomized trial has examined the clinical outcome of patients with anterior infarction and coronary occlusion that persist despite thrombolytic therapy.⁸⁴ Patients were randomized to either undergo rescue coronary angioplasty or receive continued medical therapy alone. The results of the trial suggested improved outcome with rescue angioplasty, although the benefits were not compelling. Three additional randomized trials evaluated the role of rescue angioplasty.⁸⁵⁻⁸⁷ Analyzed together, the four trials suggest that rescue angioplasty offers benefit, although the data are not compelling. Although use of coronary stents and platelet glycoprotein inhibitors improves the results of percutaneous revascularization procedures and would be expected to further increase the benefit of angioplasty after failed thrombolytic therapy, this has not

yet been proved. There are insufficient data to recommend immediate angiography and angioplasty in all patients early after thrombolytic therapy. Immediate angiography is most likely to be beneficial in patients with large myocardial infarctions in whom persistent pain, ST segment elevation, or hemodynamic compromise is present more than 90 minutes after the administration of a thrombolytic agent.

The routine performance of angioplasty immediately after the administration of thrombolytic therapy in all patients with a significant residual stenosis (not just those patients with occluded coronary arteries) has been well studied in three prospective, randomized trials and has been found to be either of no benefit or deleterious.^{43,88} Angioplasty should not be routinely performed in such patients.

Stents appear to improve the ability to achieve arterial patency early after thrombolytic therapy, as compared with balloon angioplasty alone⁸⁹; therapy with a glycoprotein IIb/IIIa inhibitor may also do so, although an increase in bleeding has been seen when glycoprotein IIb/IIIa inhibitors are used early after full-dose thrombolytic therapy.⁹⁰ Data from several pilot studies suggest that the combination of a fibrin-specific thrombolytic agent, either t-PA or reteplase, combined with the glycoprotein IIb/IIIa inhibitor abciximab, may actually facilitate the performance of angioplasty rather than reduce its safety and efficacy, as was seen when balloon angioplasty was performed after thrombolytic therapy.^{62,63} Hence, the term facilitated angioplasty has been coined for the routine performance of angioplasty after the combination of half-dose thrombolytic therapy with a glycoprotein IIb/IIIa inhibitor.

The Plasminogen-activator Angioplasty Compatibility Trial (PACT) investigators randomized 606 patients to a reduced dose of a short-acting fibrinolytic regimen (50 mg bolus of reteplase) or a placebo followed by immediate angiography with angioplasty, if needed.⁹¹ In the group receiving reduced-dose reteplase, there was no increase in the incidence of stroke or major bleeding, and convalescent left-ventricular ejection fraction was higher, as evidenced by a patent infarct-related artery (TIMI-3 flow) on arrival in the catheterization laboratory (62%) or a TIMI-3 flow that was achieved by angioplasty within 1 hour after administration of the drug bolus (58%). However, only 12% of successful angioplasty procedures resulted in a patent infarct-related artery within 1 hour, because of routine delay in transfer to the catheterization laboratory, and there was no difference between the two treatment groups by a traditional intention-to-treat analysis.

The Southwest German Study in Acute Myocardial Infarction III (SIAM III) investigators randomized 163 patients initially treated with thrombolysis at a community hospital with no on-site PCI facilities either to hospital transfer and immediate stenting within 6 hours of thrombolysis or to delayed, elective stenting approximately 2 weeks after acute myocardial infarction.⁹² Transfer and immediate stenting were associated with a statistically significant reduction in the incidence of the composite primary end point (i.e., death, reinfarction, ischemic events, and target-lesion revascularization at 6 months), as compared with delayed stenting (25.6% versus 50.6%; $P = 0.001$). The difference in outcome was driven by events occurring during the 2 weeks that patients waited for elective stenting in the deferred PCI group. This trial design does not address whether PCI performed 1 to 2 days after thrombolytic therapy, as is usual in the United States, is as effective as PCI performed immediately after thrombolytic therapy. A randomized trial that analyzed the use of combination therapy

(half-dose thrombolytic therapy with full-dose abciximab) before routinely performing primary PCI was reported.⁹³ In the Bavarian Reperfusion Alternatives Evaluation (BRAVE) Trial, patients with STEMI were randomly assigned to receive either half-dose reteplase and full-dose abciximab or abciximab alone, and all patients underwent PCI as rapidly as possible. No advantage was seen with combination therapy; in fact, more bleeding complications occurred in this group. The results argue against the use of a facilitated PCI approach using the combination regimen of reteplase and abciximab.

Adjunctive Medical Therapy

INTRAVENOUS HEPARIN

The need for I.V. heparin after thrombolytic therapy varies with the thrombolytic agents used. A retrospective analysis of the GUSTO-I trial suggested that I.V. heparin with a partial thromboplastin time of 50 to 70 seconds was associated with the best clinical outcome in patients treated with t-PA.⁹⁴ Data from GUSTO-I also suggest that I.V. heparin is not required when I.V. streptokinase is used, although heparin is recommended in patients with large anterior infarctions to prevent the development of apical mural thrombus and embolization.⁵⁶ In patients in whom I.V. heparin is not administered, subcutaneous heparin should be administered during the period of bed rest to reduce the risk of deep vein thrombosis.⁹⁵

The optimal duration of I.V. heparin therapy is unclear. Standard practice was to administer I.V. heparin for 3 to 5 days, although patients are now often discharged after only 3 days. It is recommended that heparin be discontinued more than 24 hours before patient discharge from the hospital because of the possibility of a rebound effect and recurrent thrombosis within 24 hours after cessation of heparin therapy.⁹⁶

Randomized studies from the prethrombolytic era suggested that administration of I.V. heparin reduces mortality and reinfarction in patients not treated with thrombolytic agents.⁹⁵ Aspirin and beta blockers were not routinely administered in those early trials; consequently, the true benefits of heparin when these drugs are administered are unknown. However, on the basis of the early data, I.V. heparin is generally recommended for patients with suspected myocardial infarction who are not treated with thrombolytic therapy.⁷⁵

LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparins (depolymerized unfractionated heparin with a mean molecular weight of approximately 5,000) have a number of potential pharmacokinetic advantages over the parent molecule, including decreased binding to plasma proteins, decreased sensitivity to platelet factor 4, enhanced factor Xa activity, and improved bioavailability. These factors are associated with a predictable dose-response relationship and, combined with the ease of administration (once or twice daily S.C. dosing regimens) and lower rates of heparin-induced thrombocytopenia, have increased investigators' interest in low-molecular-weight heparins in preference to unfractionated heparin for the treatment of myocardial infarction. The results of four large randomized trials comparing three different low-molecular-weight heparins with unfractionated heparin have suggested that low-molecular-weight heparin is at least as effective in reducing ischemic events in patients with NSTEMI acute coronary syndromes. Following patients with STEMI, the second tri-

al of Heparin and Aspirin Reperfusion Therapy (HART II) and the Acute Myocardial Infarction–Streptokinase (AMI-SK) trial demonstrated evidence of improved rates of reperfusion when the low-molecular-weight heparin enoxaparin was combined with t-PA or streptokinase, respectively.^{97,98} The ASSENT-3 trial compared three regimens: full-dose tenecteplase and enoxaparin, full-dose tenecteplase and unfractionated heparin, and half-dose tenecteplase and abciximab for the treatment of thrombolytic-eligible STEMI; the study revealed that enoxaparin fared better than unfractionated heparin in terms of 30-day mortality, in-hospital reinfarction, and in-hospital refractory ischemia ($P = 0.0001$) at 30 days.⁹⁹ However, at 1 year, the benefits had diminished, and the mortality with enoxaparin was identical to that with unfractionated heparin. In addition, when the data from ASSENT-3 and ASSENT-3-PLUS (a study examining the administration of tenecteplase with enoxaparin in the prehospital setting) were pooled, a marked and prohibitive increase in the risk of intracerebral hemorrhage was seen in the elderly.^{66,99} As a result, ongoing trials utilizing enoxaparin with a fibrinolytic agent have adjusted the dose of enoxaparin downward in elderly patients. At present, the adjunctive anticoagulant that should be administered with fibrinolytic therapy and its optimal dose are not known.

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors are an attractive alternative to indirect thrombin inhibitors, such as heparin or low-molecular-weight heparins, particularly because they block both circulating and clot-bound thrombin. A collaborative meta-analysis of phase-3 trials of direct thrombin inhibitors for the treatment of acute coronary artery syndromes demonstrated superiority over unfractionated heparin for the prevention of the composite end point of death or myocardial infarction.¹⁰⁰ The Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial demonstrated a similar benefit in a comparison of bivalirudin with heparin in patients with STEMI.¹⁰¹ Bivalirudin was associated with a 30% reduction in the incidence of reinfarction, but mortality did not decrease; however, the bivalirudin arm of the study exhibited a trend toward more bleeding events.

BETA BLOCKERS

The 2004 ACC/AHA guidelines recommended that oral beta blockers be administered to all STEMI patients for whom treatment is not contraindicated, irrespective of whether they are undergoing fibrinolytic therapy or primary PCI.³¹ Early administration of beta blockers is recommended because it may reduce infarct size by reducing heart rate, blood pressure, and myocardial contractility, all of which diminish myocardial oxygen demand. Meta-analysis of the effects of early administration of I.V. beta blockers in 27,486 patients with acute myocardial infarction enrolled in 28 randomized trials revealed a 14% reduction in mortality during the first week of therapy; reinfarction was reduced by 18%.¹⁰²

The TIMI-II study compared immediate beta-blocker therapy with deferred beta-blocker therapy in acute myocardial infarction; all patients also received I.V. t-PA.¹⁰³ Results indicated that immediate beta-blocker therapy reduced the incidence of nonfatal reinfarction and recurrent ischemia, compared with oral metoprolol therapy begun on the sixth hospital day; as in earlier studies, only about 40% of patients with acute myocardial infarction were eligible for acute beta-blocker therapy.⁴³ There are also data suggesting that immediate beta-blocker

therapy reduces the risk of intracranial hemorrhage after lytic therapy.¹⁰⁴

In patients in whom contraindications preclude early beta-blocker therapy, reevaluation should take place before discharge. Many patients will no longer have contraindications at the time of discharge. Patients without contraindications should be routinely started on beta-blocker therapy before discharge from the hospital. The optimal duration of benefit remains unclear, but it appears that the benefit of beta-blocker therapy is maintained for years. Patients with the largest infarctions benefit the most from the use of beta blockers. Current recommendations are that beta-blocker therapy be continued indefinitely in the absence of contraindications or side effects.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Several large randomized, controlled clinical trials evaluating the use of angiotensin-converting enzyme (ACE) inhibitors early after acute myocardial infarction have been performed; all but one trial revealed a significant reduction in mortality. Meta-analysis of these large trials and many smaller trials, which together included over 100,000 patients, suggested a 6.5% reduction in deaths, with an absolute reduction in mortality of 4.6 deaths per 1,000 patients among those treated with an ACE inhibitor.¹⁰⁵ All patients with significant ventricular dysfunction (an ejection fraction < 40%) without contraindications should be treated with an ACE inhibitor; treatment should begin within the first 48 hours of infarction and be increased cautiously to avoid hypotension. If hypotension results from the early administration of ACE inhibitors, short-term mortality may be increased.¹⁰⁶

The benefit of ACE inhibitors is clear in patients with large anterior infarctions and an ejection fraction less than 40%; whether patients with an ejection fraction greater than 40% benefit from ACE inhibitor therapy is less clear. However, the results of two large trials suggest that patients with a normal ejection fraction after myocardial infarction, as well as even patients with coronary artery disease without a previous myocardial infarction, have a reduction in mortality when treated with an ACE inhibitor. In the Heart Outcomes Prevention Evaluation (HOPE) study, 9,297 patients 55 years of age or older with vascular disease (or with diabetes and another cardiovascular risk factor) without a low ejection fraction or congestive heart failure were randomly assigned to receive either the ACE inhibitor ramipril or placebo for a mean of 5 years.¹⁰⁷ The reduction in the combined end point of death from cardiovascular causes, myocardial infarction, or stroke with ramipril was remarkable; it occurred in 17.7% of placebo-treated patients versus 14.1% of patients receiving ramipril (relative risk, 0.78; 95% confidence interval, 0.70 to 0.86; $P < 0.001$). A statistically significant reduction was also present in the individual end points of cardiovascular death, myocardial infarction, and stroke. The study was stopped prematurely by the Data Safety Monitoring Board when clear evidence of a beneficial effect of ramipril was found. These findings are supported by the results of the European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA) trial, which randomized 12,218 patients with stable coronary artery disease and no evidence of congestive heart failure to 8 mg of perindopril or conventional therapy.¹⁰⁸ Treatment with perindopril was associated with a highly statistically significant reduction in the incidence of fatal and nonfatal myocardial infarction at 4 years. Whether these favorable results are unique to tissue-specific ACE inhibitors or represent a class effect is unknown.

INTRAVENOUS NITROGLYCERIN

Randomized studies examining the role of I.V. nitroglycerin in acute myocardial infarction revealed beneficial effects on left ventricular function and a reduction in infarct size and mortality.¹⁰⁹ However, these studies were small and were performed before the reperfusion era. To determine whether nitroglycerin therapy is beneficial in patients treated with reperfusion, 58,050 patients with acute myocardial infarction in the fourth International Study of Infarct Survival (ISIS-4) were randomized to receive either oral controlled-release mononitrate therapy or placebo; thrombolytic therapy was administered to patients in both groups.¹⁰⁵ The results of this study revealed no benefit to the routine administration of oral nitrate therapy in this setting. Similar results were seen among 19,000 patients in the third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) study, in whom I.V. nitroglycerin was administered for the first 24 hours, followed by transdermal nitrates.¹¹⁰ Whether these disappointing results in the ISIS-4 and GISSI-3 trials were caused by the routes of administration of the nitroglycerin preparation or the administration of thrombolytic therapy is unknown. However, on the basis of existing data, it does not appear that the routine administration of nitroglycerin to patients receiving early thrombolytic therapy is beneficial. I.V. nitroglycerin is probably most likely to be beneficial in patients with persistent or recurrent chest pain after reperfusion therapy and in patients in whom reperfusion therapy is not administered.

PROPHYLACTIC ANTIARRHYTHMIC THERAPY

Previously, routine prophylactic antiarrhythmic therapy with I.V. lidocaine was recommended for all patients in the early stages of acute myocardial infarction. However, studies have revealed that prophylactic therapy with lidocaine does not reduce and may actually increase mortality because of an increase in the occurrence of fatal bradyarrhythmia and asystole.¹¹¹ Neither I.V. lidocaine nor other antiarrhythmic agents are recommended as prophylactic therapy for patients without malignant ventricular ectopy.^{111,112}

STATIN THERAPY

Statin therapy in the early management of acute myocardial infarction is under investigation; current evidence indicates such therapy may be beneficial. A study of more than 300,000 patients in the National Registry of Myocardial Infarction found that statin use within the first 24 hours of admission for acute myocardial infarction was associated with a significantly lower rate of early complications and in-hospital mortality.¹¹³ Statin therapy in the follow-up management of acute myocardial infarction is recommended.^{31,114,115} The 2004 ACC/AHA gave a class I recommendation to the initiation of statin therapy prior to hospital discharge in all STEMI patients [*see Secondary Prevention, below*].^{31,114,115}

CALCIUM CHANNEL ANTAGONISTS

Calcium channel antagonists should not be routinely administered for acute myocardial infarction. Calcium channel antagonists have been studied in prospective, double-blind, placebo-controlled trials; and neither verapamil,^{116,117} nifedipine,^{118,119} nor diltiazem¹²⁰ appears to reduce postinfarction mortality. Verapamil and diltiazem may be useful in patients with preserved left ventricular function and no heart failure in whom contraindications to beta blockers exist.^{121,122} However, the data are insufficient to recommend the routine administration of these agents. On the basis

of existing data, treatment with calcium channel blockers should be reserved for patients with ischemia that persists despite use of aspirin, beta blockers, nitrate therapy, and I.V. heparin and for patients with other indications for their administration.

MAGNESIUM

Magnesium has been studied in many prospective, randomized trials of acute myocardial infarction, and the results have been conflicting. Magnesium is involved in hundreds of enzymatic steps and produces systemic and coronary vasodilatation, inhibits platelet function, and reduces reperfusion injury. Meta-analysis of seven prospective, randomized trials revealed a significant reduction in mortality with the use of magnesium (odds ratio, 0.44; confidence interval, 0.27 to 0.71).¹²³ In ISIS-4, in which 58,050 patients were randomized to receive either I.V. magnesium or no magnesium, there was no reduction in 30-day mortality.¹⁰⁵ It is possible that the later administration of magnesium in this study, compared with the previous studies, and the concomitant use of thrombolytic therapy in 70% of patients contributed to the lack of efficacy of magnesium in ISIS-4; only one third of patients in the LIMIT-2 study received thrombolytic therapy. Therefore, on the basis of the existing evidence, current recommendations are that magnesium not be routinely given to patients in whom reperfusion therapy is administered. It is possible that magnesium is of benefit, particularly in patients not receiving reperfusion therapy. Magnesium is clearly indicated in patients with myocardial infarction who have torsade de pointes-type ventricular tachycardia and in patients with magnesium deficiency.

Complications of Acute Myocardial Infarction

VENTRICULAR ARRHYTHMIAS

Ventricular arrhythmias are a frequent cause of death in the earliest stages of acute myocardial infarction. The development of coronary care units, continuous ECG surveillance, and defibrillators in the 1960s led to a reduction in mortality from acute myocardial infarction through the prompt identification and treatment of ventricular arrhythmia; and emergency medical technicians have reduced outpatient mortality in the earliest minutes of myocardial infarction. In cities with well-developed emergency response systems, such as Seattle, Washington, and Rochester, Minnesota, where the average response time is less than 5 minutes, survival of patients with myocardial infarction complicated by cardiac arrest has increased.⁴ In fact, long-term survival of patients who have undergone rapid defibrillation after out-of-hospital cardiac arrest is similar to that of age-, sex-, and disease-matched patients who did not have out-of-hospital cardiac arrest; the quality of life of the majority of survivors is similar to that of the general population.¹²⁴

Ventricular Fibrillation

In the setting of acute myocardial infarction, ventricular fibrillation is often described as either primary, when it occurs in the absence of hypotension or heart failure, or secondary, when hypotension or heart failure is present. Primary ventricular fibrillation occurs in approximately 3% to 5% of patients with acute myocardial infarction; the peak incidence is in the first 4 hours of infarction. Primary ventricular fibrillation is infrequent more than 24 hours after symptom onset. Mortality is increased in patients who suffer this complication.^{125,126} In patients who are suc-

cessfully resuscitated and survive to hospital discharge, however, the long-term prognosis does not appear to be affected.¹²⁵ Although lidocaine was shown to reduce the occurrence of primary ventricular fibrillation, mortality in patients receiving lidocaine increased because of an increase in fatal bradycardia and asystole; therefore, prophylactic lidocaine is no longer recommended if defibrillation can rapidly be performed.¹¹¹ Beta blockers may reduce the early occurrence of ventricular fibrillation and should be administered to patients who have no contraindications.

Hypokalemia is a risk factor for primary ventricular fibrillation and should be rapidly corrected if present. When ventricular fibrillation occurs, rapid defibrillation with 200 to 300 joules should be attempted, and repeated shocks of 360 joules should be administered. The Advanced Cardiac Life Support (ACLS) guidelines recommend medical therapy, including epinephrine, lidocaine, and bretylium; in addition, I.V. amiodarone should be considered in patients in whom defibrillation is initially unsuccessful.

Secondary ventricular fibrillation is associated with a high mortality, in part because of the underlying hypotension and heart failure. Treatment must be aimed not only at terminating the arrhythmia but also at treating the hemodynamic abnormalities and their causes.

Ventricular Tachycardia

Ventricular tachycardia (three or more consecutive ventricular ectopic beats) is common in patients with acute myocardial infarction; however, short runs of nonsustained ventricular tachycardia are no longer believed to predispose a patient to sustained ventricular tachycardia or ventricular fibrillation. In patients in whom sustained or hemodynamically significant ventricular tachycardia occurs, prompt electrical cardioversion should be performed. If the ventricular tachycardia is monomorphic, synchronic cardioversion with 100 joules should first be attempted. As with ventricular fibrillation, polymorphic ventricular tachycardia should be treated with unsynchronized discharge. Prolonged runs of asymptomatic ventricular tachycardia can be initially treated with I.V. lidocaine, procainamide, or amiodarone. These medications may also be helpful in reducing recurrent ventricular tachycardia.

ATRIAL ARRHYTHMIA

Atrial Fibrillation

Atrial fibrillation is the most common atrial arrhythmia in acute myocardial infarction, occurring in 10% to 16% of patients. Atrial fibrillation may result either from an acute increase in left atrial pressure caused by left ventricular dysfunction or from atrial ischemia as a result of occlusion of a coronary artery (usually the right coronary artery) proximal to the origin of atrial branches. The incidence of atrial fibrillation is decreased in patients given thrombolytic therapy.⁵⁶

The treatment of atrial fibrillation in acute myocardial infarction should be similar to the treatment of atrial fibrillation in other settings. When there is hemodynamic compromise caused by loss of atrial systole or a rapid ventricular response with a reduction in cardiac output, cardioversion should be performed immediately. In patients with preserved left ventricular function in whom the atrial fibrillation is well tolerated, beta-blocker therapy is indicated. Verapamil and diltiazem may also be effective in such patients. In patients with congestive heart failure, digoxin is a reasonable alternative and may slow the ventricular response. If

atrial fibrillation recurs, antiarrhythmic agents may be used, although their impact on clinical outcomes is unproved. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators randomized 4,060 patients to either rhythm-control or rate-control treatment strategies.¹²⁷ The rhythm-control strategy achieved no survival advantage over the rate-control strategy and there were both fewer hospital admissions and fewer adverse drug reactions in the rate-control group.

BRADYARRHYTHMIAS AND HEART BLOCK

Sinus bradycardia is common in acute myocardial infarction, particularly in patients with inferior myocardial infarction. However, treatment with atropine and a temporary pacemaker is required infrequently and, generally, only in patients with significant hemodynamic compromise manifested by increased angina, hypotension, or congestive heart failure.

High-degree (second- or third-degree) heart block occurs in approximately 20% of patients with inferior infarction; it is uncommon with infarction at other sites.¹²⁸ About half of the cases of heart block seen with inferior infarction are Wenckebach-type second-degree heart block; the remainder are cases of third-degree heart block. The heart block is often easily treated with atropine, but a temporary pacemaker is required in as many as 50% of cases. The heart block generally lasts for hours to days; placement of a permanent pacemaker is needed in fewer than 1% of cases. However, the development of heart block with inferior infarction is associated with a threefold to fourfold increase in in-hospital mortality over inferior infarction without heart block.^{128,129} The increased mortality appears to result from the association between heart block and more severe left and right ventricular infarction rather than from the heart block itself or treatment of the heart block.

Heart block during anterior infarction is uncommon, occurring in fewer than 1% of cases. It is generally associated with extensive left ventricular myocardial infarction involving the conduction system below the atrioventricular node and carries a very poor prognosis.

MITRAL REGURGITATION

Mitral regurgitation may result from injury to any of the components of the mitral valve apparatus, including the papillary muscles and ventricular walls to which they attach. Mild mitral regurgitation is common in acute myocardial infarction and is present in nearly 50% of patients. Severe mitral regurgitation caused by acute myocardial infarction is rare and generally results from partial or complete rupture of a papillary muscle. The characteristic murmur of severe chronic mitral regurgitation may not be present with acute rupture of a papillary muscle. Instead, a decrescendo systolic murmur is often present, extending less throughout systole as systemic arterial pressure falls and left arterial pressure rises. In many cases, the significance of the murmur is not recognized. The blood supply of the anterior papillary muscle arises from branches of both the left anterior descending and the circumflex arteries; therefore, rupture of the anterior papillary muscle is rare. However, the posterior papillary muscle receives blood only from the dominant coronary artery (the right coronary artery in nearly 90% of patients); thrombotic occlusion of this artery may cause rupture of the posterior papillary muscle, resulting in severe mitral regurgitation. Severe mitral regurgitation is 10 times more likely to occur with inferior infarction than with anterior infarction. Acute severe mitral regurgitation is poorly tolerated and generally results in pul-

monary edema, often with cardiogenic shock. Prompt surgical repair is recommended. Although the mortality associated with mitral valve surgery is high in this setting, approaching 50%, survival appears to be greater than with medical therapy alone. Therapy aimed at reducing left ventricular afterload, such as use of I.V. nitroprusside and an intra-aortic balloon pump, reduces the regurgitant volume and increases forward blood flow and cardiac output and may be helpful as a temporizing measure.

VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects are slightly more frequent in patients with anterior infarction than in patients with inferior infarction. The characteristic holosystolic murmur of ventricular septal defects may be difficult to distinguish from that of severe mitral regurgitation; however, ventricular septal defects are generally better tolerated and less frequently result in severe congestive heart failure. Surgical repair is recommended and results in the best outcome when repaired emergently in the hemodynamically compromised patient. As with acute severe mitral regurgitation, therapy aimed at reducing afterload, including I.V. nitroprusside and an intra-aortic balloon pump, may be beneficial. Repair of the septum is generally more difficult when associated with inferior infarction, because there may not be a viable rim of myocardial tissue beneath the defect to facilitate repair. The surgical mortality associated with repair of a postinfarction ventricular septal defect is approximately 20% but is largely related to the age of the patient, whether cardiogenic shock is present, the infarction site, and the severity of the underlying coronary artery disease.

MYOCARDIAL RUPTURE

As more and more patients survive the acute phase of myocardial infarction because reperfusion therapy reduces myocardial infarct size, myocardial rupture has increased in frequency as a cause of early death. Myocardial rupture has been reported to account for more than 20% of in-hospital deaths in some series in the thrombolytic era. Physicians must have a heightened awareness of the diagnosis if a patient is to survive this catastrophic occurrence, because emergency surgery is required. Symptoms suggestive of rupture include repetitive vomiting, pleuritic chest pain, restlessness, and agitation. ECG evidence of rupture includes a deviation from the normal pattern of ST segment and T wave evolution. Resolution of ST segment elevation and T wave inversion, with maximal T wave negativity in the leads with maximal ST segment elevation, should normally occur; however, in patients with rupture, there is progressive or recurrent ST segment elevation and persistently positive T wave deflections or reversal of initially inverted T waves.¹³⁰ Echocardiography can quickly confirm the diagnosis. Even when emergency surgery is performed, fewer than 50% of patients survive to discharge.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in approximately one third of patients with acute inferior left ventricular infarction and is hemodynamically significant in approximately 50% of affected patients.¹³¹ Hemodynamically significant right ventricular infarction associated with anterior infarction or isolated right ventricular infarction is rare. The classic findings associated with hemodynamically significant right ventricular infarction are hypotension with clear lung fields and an elevated jugular venous pressure, often with the Kussmaul sign. Although nearly all patients with right ventricular infarction suffer both right and left ventricular infar-

tion, the characteristic hemodynamic findings of right ventricular infarction generally dominate the clinical course and must be the main focus of therapy. Right ventricular involvement during inferior myocardial infarction is associated with a significant increase in mortality, and aggressive attempts at early reperfusion should be pursued.^{128,131} Prompt recognition of right ventricular involvement is clinically important because therapy that reduces right ventricular filling, such as use of nitrates or diuretics, should be avoided. Volume therapy should be administered to maintain cardiac output; in patients whose hypotension is refractory to volume therapy, dopamine may be beneficial. Heart block, which occurs in as many as 50% of patients with right ventricular infarction, should be treated rapidly, and maintenance of atrioventricular synchrony with dual atrial and ventricular pacing is often required to maintain filling of the ischemic noncompliant right ventricle and an adequate cardiac output.

Cardiogenic shock resulting from right ventricular infarction is generally reversible with these measures. Improvement in right ventricular function generally occurs over time, particularly in patients in whom reperfusion therapy was successful in achieving vessel patency.¹²⁵ In patients who survive the initial hospitalization, left ventricular function is the most potent predictor of long-term outcome.

STROKE

Extensive infarction of the anterior wall and apex of the left ventricle leads to thrombus formation in the apex of the left ventricle in approximately 30% of patients; systemic embolization occurs in about 15% of these patients. Left ventricular thrombus formation is much less common after inferior infarction. The thrombus generally appears within the first several days after infarction; it is more likely to embolize and cause stroke if it is pedunculated, protrudes into the left ventricular cavity, or is mobile. Left ventricular thrombus is an indication for anticoagulation with I.V. heparin, followed by warfarin therapy for 3 to 6 months.

Therapy that reduces infarct size, such as thrombolytic therapy, reduces the frequency of thrombus formation and therefore the risk of systemic embolization and stroke. However, in 0.3% to 1.0% of patients, thrombolytic therapy causes hemorrhagic stroke, most commonly in the 24 hours after its administration, which is fatal in more than 50% of cases. Hemorrhagic stroke is rare in acute myocardial infarction except as a consequence of thrombolytic therapy, although an ischemic stroke may become hemorrhagic because of thrombolytic, antiplatelet, and anticoagulation therapy. Hemorrhagic stroke, the most feared complication of thrombolytic therapy, is more likely in elderly patients; in patients with low body weight, with hypertension, or who have previously had a stroke; and in those on warfarin.^{33,39} Although thrombolytic therapy decreases the risk of ischemic stroke, there is a slight net increase in the overall risk of stroke because of the risk of hemorrhagic stroke. Primary coronary angioplasty is believed to reduce the incidence of ischemic stroke without increasing the risk of hemorrhagic stroke.

Predischarge Exercise Testing

In patients with spontaneous postinfarction angina, congestive heart failure, hypotension, or malignant ventricular arrhythmia, exercise testing should generally be deferred and coronary angiography should be performed. However, in patients without these high-risk characteristics, exercise testing is generally recommended before discharge from the hospital to assess a pa-

tient's functional capacity and ability to return to activities of daily living and work.¹³² Most data indicating that predischarge exercise testing can identify patients at increased risk for cardiac events after discharge are from the prethrombolytic era, when the risk of adverse cardiac events was much higher. In the modern era, in which thrombolytic therapy or primary coronary angioplasty is frequently performed and in which aspirin, beta blockers, ACE inhibitors, and lipid-lowering agents are routinely administered—all of which reduce the frequency of adverse events in the years after discharge—it is difficult to identify patients at risk, because the adverse event rate is so low. Nonetheless, exercise testing is generally recommended to provide a measure of comfort to both the patient and the physician, to help determine the appropriateness of medical therapy, and to facilitate entry of the patient into a cardiac rehabilitation program.

Although predischarge exercise testing has been the standard of care in the United States for some time, only recently has a study examined whether therapy based on the results of a predischarge exercise test improves clinical outcome. The Danish Trial in Acute Myocardial Infarction (DANAMI) was the first study to examine the usefulness of exercise testing in patients treated with thrombolytic agents (a low-risk group) and to provide support for what has been the standard of care in the United States [see Figure 11].¹³³ The results of this study revealed that clinical outcome was improved in patients who received angiography and coronary angioplasty, compared with those who received medical therapy alone. Use of the results of exercise testing to decide whether or not to employ revascularization in patients without spontaneous angina is less common outside of the United States.

Patients with acute myocardial infarction who do not receive thrombolytic therapy or do not undergo primary angioplasty are at greater risk for adverse events after discharge from the hospital, and predischarge exercise testing is of even greater utility in such patients.

Prognostic variables indicating increased risk during exercise testing are exercise-induced angina or ST segment depression, particularly when it occurs during exercise at a low work load, and an abnormal drop in systolic blood pressure. However, electrocardiographic, symptomatic, and scintigraphic risk markers of ischemia (e.g., ST segment depression, angina, or a reversible perfusion defect) are less sensitive for identifying morbid and fatal outcomes than markers of left ventricular dysfunction or heart failure (e.g., exercise duration, impaired systolic blood pressure response, and peak left ventricular ejection fraction).¹³⁴ The patients at greatest risk are those unable to exercise; such patients have the highest mortality after discharge.¹³⁵

The type of exercise test that should be performed has been the subject of controversy. It is generally recommended that only simple treadmill testing be performed before discharge; in patients with abnormalities in the baseline ECG, stress testing with perfusion imaging or stress echocardiography may be helpful. In patients without widespread abnormalities on the ECG, perfusion imaging or stress echocardiography is generally deferred until at least 4 weeks after discharge, when a more vigorous exercise test can be performed. Whether the predischarge treadmill test should be a low-level test or a more vigorous symptom-limited test is unclear. It has been shown that a symptom-limited Bruce protocol exercise test detects ischemia more frequently than a submaximal test; however, it is not known which test has the greater positive and greater negative predictive value for identifying patients at risk. Currently, a lower-level exercise test

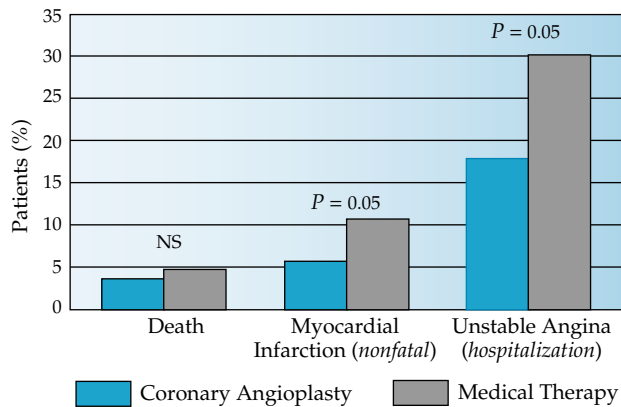


Figure 11 In the Danish Acute Myocardial Infarction (DANAMI) study, 1,008 patients treated with thrombolytic therapy in whom exercise-induced ischemia was present on a predischarge exercise test were randomized to receive either coronary angioplasty or medical therapy alone. Clinical outcome was improved in patients in the invasive arm of the study. (NS—not significant)

is preferred, although a more vigorous test may be appropriate in patients likely to resume a more active and vigorous lifestyle shortly after discharge and in whom a low-level test may not cause the patient to expend the amount of energy he or she will be using during activities of daily living.

There has been concern that the use of beta blockers before the predischarge exercise test may mask the presence of significant coronary artery disease and prevent the identification of high-risk patients. This concern does not appear to be significant enough to outweigh the benefits of early beta-blocker therapy.

Secondary Prevention

PHARMACOTHERAPY

Lipid-Lowering Therapy

Recent studies have demonstrated that in patients with coronary artery disease, lipid-lowering therapy with HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors reduces not only fatal and nonfatal infarction but also mortality from all causes. The Scandinavian Simvastatin Survival Study revealed a 42% reduction in cardiac mortality and a 30% reduction in all-cause mortality in 4,444 men and women with coronary artery disease over the 5.4 years of the study.¹³⁶ The reductions in mortality were similar in patients in the lowest and those in the highest quartiles of serum low-density lipoprotein (LDL) cholesterol. It has been demonstrated that postinfarction patients with an LDL cholesterol level at or above 130 mg/dl benefit from lipid-lowering therapy within as little as 2 years after the initiation of such therapy.¹³⁷ Initial measurement of cholesterol should be made within 24 hours after myocardial infarction; measurement of lipids 24 hours or more after myocardial infarction can be misleading in that cholesterol levels may be reduced below baseline levels during this period and remain low for up to 1 month. Early initiation of statins may be more beneficial than later initiation.¹³⁸ Exercise, weight reduction in overweight patients, avoidance of dietary saturated fat and cholesterol, and smoking cessation have all been reported to favorably influence blood lipid levels and should be recommended

whether or not lipid-lowering medications are prescribed [see CE: III Reducing Risk of Injury and Disease and see CE: IV Diet and Exercise].

Anticoagulation Therapy

Several prospective, randomized trials revealed that warfarin therapy reduces mortality after discharge from the hospital in patients with acute myocardial infarction. However, in these studies, in which warfarin therapy was compared with placebo, aspirin was not administered in either arm of the study.^{139,140} The Coumadin Aspirin Reinfarction Study (CARS) revealed that the risk of reinfarction in patients treated with aspirin alone was similar to that in patients treated with aspirin and either low-dose (1 mg) or higher-dose (3 mg) warfarin.¹⁴¹ Warfarin is also ineffective at preventing coronary reocclusion in patients in whom thrombolytic therapy was successful.¹⁴² Routine warfarin therapy is not currently recommended to prevent reinfarction in patients who have survived myocardial infarction.

Antiarrhythmic Therapy

Although Holter monitoring before discharge can help identify patients at increased risk for sudden cardiac death, antiarrhythmic therapy has not been shown to decrease the risk of death in such patients, and in fact, it increased mortality in the Cardiac Arrhythmia Suppression Trial (CAST).¹⁴³ Since CAST, several prospective, randomized studies have been performed that have examined the role of amiodarone in patients at increased risk for sudden death. Taken together, the results of those studies do not indicate that amiodarone reduces mortality. Further studies are needed before the routine use of amiodarone can be recommended in high-risk patients, such as those included in these trials.

Automated, Implantable Cardioverter-Defibrillator

Automated implantable cardioverter-defibrillators are of proven benefit in patients with coronary artery disease, reduced left ventricular ejection fraction, nonsustained ventricular tachycardia, and inducible ventricular tachycardia.¹⁴⁴ It has been proposed that patients with a prior myocardial infarction and advanced left ventricular dysfunction may benefit from prophylactic implantation of a defibrillator (in the absence of electrophysiologic testing to induce arrhythmias). The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II investigators randomized 1,232 patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less to an implantable defibrillator or conventional medical therapy. During an average follow-up of 20 months, the mortality rates were 19.8% in the conventional-therapy group and 14.2% in the defibrillator group ($P = 0.016$). Prophylactic implantation of a defibrillator is a recommended therapy in this patient population.¹⁴⁵

RISK-FACTOR MODIFICATION

An important and often neglected aspect of medical care after a myocardial infarction is the identification and modification of risk factors for atherosclerosis. Hypertension and hypercholesterolemia should be treated. Cessation of smoking has been shown to prolong life in patients who have survived a myocardial infarction; behavior modification and group therapy can increase the likelihood of kicking the habit. Cardiac rehabilitation and the establishment of a healthier lifestyle with an exercise program¹⁴⁶ can further reduce the likelihood of a return to smok-

ing. Hypercholesterolemia should be aggressively treated as described above.

Although there are few data that conclusively indicate that patients who participate in a cardiac rehabilitation program after discharge have increased survival, an exercise rehabilitation program appears to improve a patient's sense of well-being and hasten return to work and leisure activities. A cardiac rehabilitation program can also help improve diet and aid weight reduction in overweight patients, help smokers refrain from smoking, and help establish an exercise program that the patient can maintain long after the formal rehabilitation program has ended. In summary, participation in a cardiac rehabilitation program often leads to the establishment of a healthier lifestyle.

Long-term Prognosis

Long-term prognosis after myocardial infarction is determined primarily by the severity of left ventricular dysfunction, the presence and degree of residual ischemia, and the potential for malignant ventricular arrhythmia. These adverse prognostic factors are related to each other but are also independently associated with death after discharge. Age is also an important determinant of outcome. Most deaths that occur in the first year after discharge occur in the first 3 months, a fact that stresses the importance of assessing risk and optimizing therapy before discharge from the hospital. However, there can be substantial improvement in ventricular function in the weeks and months after acute myocardial infarction, particularly in patients in whom early reperfusion was achieved. Therefore, measurement of ventricular function 2 to 3 months after myocardial infarction is a more accurate predictor of long-term prognosis than measurement of left ventricular function in the acute stages.

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