AHA Medical/Scientific Statement

Special Report

ACC/AHA Guidelines for the Early Management of Patients With Acute Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients With Acute Myocardial Infarction)

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Preamble

It is becoming more apparent each day that despite a strong national commitment to excellence in health care, the resources and personnel are finite. It is, therefore, appropriate that the medical profession examine the impact of developing technology on the practice and cost of medical care. Such analysis, carefully conducted, could potentially have an impact on the cost of medical care without diminishing the effectiveness of that care.

To this end, the American College of Cardiology and the American Heart Association in 1980 established a Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures with the following charge:

The Task Force of the American College of Cardiology and the American Heart Association shall define the role of specific noninvasive and invasive procedures in the diagnosis and management of cardiovascular disease.

The Task Force shall address, when appropriate, the contribution, uniqueness, sensitivity, specificity, indications, contraindications, and cost-effectiveness of such specific procedures.

The Task Force shall include a Chairman and six members, three representatives from the American Heart Association and three representatives from the American College of Cardiology. The Task Force may select ad hoc members as needed upon the approval of the Presidents of both organizations. Recommendations of the Task Force are forwarded to the President of each organization.

The members of the Task Force are: George A. Beller, MD, Roman W. DeSanctis, MD, Harold T.
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This document was reviewed by the officers and other responsible individuals of the two organizations and received final approval in March 1990. It is being published simultaneously in Circulation and the Journal of the American College of Cardiology. The potential impact of this document on the practice of cardiology and some of its unavoidable shortcomings are clearly set out in the introduction.

Charles Fisch, MD, FACC

Introduction to Acute Myocardial Infarction

Coronary artery disease is the leading cause of death in the United States. Despite an encouraging 47% reduction in age-adjusted coronary mortality rates over the past 25 years, coronary disease caused 514,000 deaths in 1987.1 There were approximately 750,000 patients admitted to hospitals with acute myocardial infarction during 1987 in the United States.2 There are roughly 7 million patients with diagnosed coronary disease in this country and many more with clinically silent coronary atherosclerosis. Morbidity and mortality in patients with coronary artery disease in general, and in heart attack victims in particular, are in large part determined by the extent of heart muscle damage as well as the number and severity of coronary atherosclerotic lesions.

Developments in Treatment of Myocardial Infarction

From the time the myocardial infarction syndrome was first related to coronary thrombosis in 1912 through the 1940s, treatment progressed slowly, with no landmark changes except, perhaps, the introduction of oral anticoagulant therapy. There were inerminable debates about digitalis usage and the length of absolute bed rest needed in the treatment of such patients. In the late 1950s, coronary care units were developed. With development of direct current defibrillators and closed chest cardiopulmonary resuscitation in the 1960s, a significant impact was made on the early mortality rate of myocardial infarction. The 1960s also saw the development of hemodynamic monitoring of patients with myocardial infarction and recognition of hypovolemia as a correctable cause of shock in a percentage of such patients. Finally, the development of counterpulsation improved survival in the patients with pump failure, but only to a minimal extent. The 1970s witnessed more universal training of medical and nonmedical personnel in cardiopulmonary resuscitation and deployment of mobile coronary care units (first developed by Pantridge and Geddes in 1967). The 1970s saw use of pharmacologic methods for myocardial preservation by improvement of nutrient supply to the myocardium through interstitial diffusion using hyaluronidase or glucose-insulin-potassium solution and decrease in myocardial oxygen requirements with use of β-adrenergic blockers and unloading agents.

Physicians in Spokane, Washington, made the next major leap forward by providing reperfusion through early coronary artery bypass surgery.4 DeWood et al5 presented convincing evidence that there was thrombosis of the coronary artery early in myocardial infarction and this thrombus likely had spontaneous lysis over the ensuing hours in some patients. The surgical experiences in Spokane and later in Iowa6 were outstanding tours de force in reperfusion by surgical thrombectomy and coronary bypass, but did not lead to universal application because of logistic impracticality.

In 1976, Chazov et al7 reported on intracoronary fibrinolysis in acute myocardial infarction. Rentrop et al8 used catheter-directed reperfusion by mechanically opening the artery and then using intracoronary thrombolytic agents. As time went on, it became clear that the delay while waiting for intracoronary thrombolytic agents was using up the time window for best myocardial salvage by reperfusion. Thus, the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) trial,9 the first large scale study of early intravenous thrombolysis, is the milestone that marks the beginning of the era of routine thrombolysis in patients with early acute myocardial infarction. The development of the second generation thrombolytic agents that are more clot-specific may well improve the safety and efficacy of thrombolysis. The third generation, which may be represented by single chain pro-urokinase, could further improve safety and efficacy; however, despite hope for further improvements, there is little doubt that patients who receive thrombolytic reperfusion early in acute myocardial infarction and are not excluded from thrombolytic therapy by specific contraindicators show significantly improved survival9–12 and ventricular function.13

Current Guidelines for Treatment

In this review, it is incumbent to establish as best we can current guidelines for treatment of acute myocardial infarction, including the current use of thrombolytic agents. We recognize that we are shooting at a moving target, but enough has been established that we think guidelines can be developed appropriately and must be developed at this time. These guidelines should not be considered rigid; rather they are guides to be modified by clinical judgment and individual patient needs. The next major step may well be newer methods of preserving or preventing further destruction of the myocardium after temporary occlusion using such agents as oxygen-free radical scavengers. However, these interventions are still in the discovery phase and are not appropriate for our guidelines at this time.

Throughout this report, we have used the following classification of indications for diagnostic procedures and therapeutic interventions:

Class I: Usually indicated, always acceptable, and considered useful/effective
Class II: Acceptable, of uncertain efficacy, and may be controversial
   a: Weight of evidence in favor of usefulness/efficacy
   b: Not well established by evidence, can be helpful, and probably not harmful

Class III: Not indicated, may be harmful

Role of Patient Education in Early Treatment

Patients with acute myocardial infarction can receive optimal medical management only when they seek medical care early in the course of the illness. Many current strategies for care, including thrombolytic therapy, are most effective when started early in the course of infarction. Treatment for life-threatening complications of infarction, including ventricular fibrillation and cardiogenic shock, is, of course, available only to patients who are under medical observation when these events occur. Because of the extreme importance of early medical care in the treatment of acute myocardial infarction, the portion of the adult population at risk of having an acute infarction must be educated about the symptoms of infarction and how to seek emergency cardiac care in their community. It is the obligation of physicians who care for patients with known coronary artery disease as well as those receiving medical care for illnesses that increase the risk of myocardial infarction (for example, diabetes, hypertension, and peripheral vascular disease) to educate their patients about the recognition of and response to symptoms of infarction.

Emergency Care Systems

Each community must take the responsibility of developing a plan for the early management and triage of patients with suspected acute myocardial infarction. When possible, the emergency care system should have a group of well trained emergency medical technicians who have a physician-directed plan for the care of these patients.

Evaluation of patients in the field should be carried out with a specific protocol. Patients should be evaluated rapidly and transferred to a nearby hospital equipped to manage patients with acute myocardial infarction. Patients who are critically ill, such as those who have had a cardiac arrest, have repetitive episodes of ventricular tachyarrhythmias, or severe bradycardia or are in shock, should be taken to a hospital with cardiac catheterization and cardiac surgery facilities instead of to a smaller community hospital without such facilities if this will not require excessive transport time. Plans for the triage of critically ill patients to a tertiary hospital should be part of every community plan.

Emergency departments must be able to rapidly assess patients with suspected myocardial infarction. The emergency department must make every effort to identify patients with suspected acute myocardial infarction when they enter the department. Patients with chest pain, chest tightness, acute epigastric distress, and other symptoms suggestive of acute myocardial infarction must be evaluated quickly and, when appropriate, placed on a protocol. These patients should have electrocardiographic (ECG) monitoring from the time of entry, an immediate full ECG, frequent vital signs, and be seen by a physician within the first few minutes of arrival in the emergency department. Delays in evaluation and treatment related to hospital administrative procedures, such as establishing insurance coverage, must not be allowed to occur.

In patients in whom the clinical presentation and ECG are characteristic (classic) of acute myocardial infarction, the initial therapy, including appropriate use of thrombolytic therapy, should be begun by the appropriately trained emergency department physician and staff. When the diagnosis of acute myocardial infarction is less certain, consultation with an immediately available cardiologist or internist should be obtained. Prolonged efforts to consult with the patient's private physician are inappropriate if this is likely to result in a significant delay in initiating specific therapy.

In rural communities, patients with acute myocardial infarction will often receive their initial care in hospitals with limited special facilities and without physicians with special training in acute cardiac care. In this situation, plans should be developed with nearby medical centers for rapid telephone consultation and appropriate patient transfer to a tertiary medical center. In many circumstances, protocols for the initiation of thrombolytic therapy in the rural hospital before transfer are appropriate and have been shown to be safe and effective.

Other Considerations

In this document we only touch on treatment of arrhythmias and do not discuss modification of risk factors. This should not reflect their lack of importance, but rather a decision that they have been treated well elsewhere and are outside the scope of this document.

Oxygen

Even with uncomplicated myocardial infarction, some patients are modestly hypoxemic initially. Although the exact mechanism for this hypoxemia is uncertain and may be complex, it is likely that ventilation-perfusion mismatch plays a prominent role. Patients with associated congestive heart failure have more severe hypoxemia.

Supplemental oxygen should be provided at least in the initial hours for all patients suspected of having acute ischemic pain. Oxygen should not be withheld during transportation to the hospital, even if there is evidence of chronic pulmonary disease; however, lower flow rates may be prudent in these patients.

Patients with severe congestive heart failure, pulmonary edema, or a mechanical complication of acute myocardial infarction may fail to correct significant hypoxemia with supplemental oxygen alone.
Nitroglycerin

For more than 100 years nitroglycerin has relieved the pain of myocardial ischemia for patients suffering from coronary artery disease. This benefit is achieved by the actions of nitroglycerin to dilate epicardial conductance arteries, increase collateral blood flow to ischemic myocardium, and decrease left ventricular preload.

Initial Use of Nitroglycerin

Patients presenting with ischemic pain should receive sublingual nitroglycerin unless the initial systolic blood pressure is <90 mm Hg. Even if the systolic blood pressure is <90 mm Hg, a single sublingual nitroglycerin tablet may be tried in the hospital, provided there is evidence of ongoing ischemic pain and an intravenous line has been inserted. Nitroglycerin should be avoided in the presence of marked bradycardia or tachycardia, especially if relative hypotension is present.16 Careful and frequent observation of vital signs is necessary for several minutes after the initial dose.

Long-acting oral nitrate preparations should be avoided in the management of early acute myocardial infarction. Sublingual or transdermal nitroglycerin can be used, but intravenous infusion of nitroglycerin allows for more precise minute to minute control of this agent. Intravenous nitroglycerin can be successfully titrated by frequent measurement of cuff blood pressure and heart rate. Although invasive hemodynamic monitoring is not mandatory, it may be preferable if high doses of vasodilating agents are required, blood pressure instability ensues, or there is clinical doubt about the adequacy of the left ventricular filling pressure.17

Preventing Adverse Effects

Nitroglycerin frequently causes headache. It also may aggravate hypoxemia by increasing ventilation-perfusion mismatch. Unquestionably, however, inadvertent systemic hypotension with resulting worsening of myocardial ischemia is the most serious potential complication of nitroglycerin therapy in patients with acute myocardial infarction.18 Nitroglycerin should be carefully titrated in patients with inferior wall myocardial infarction and used with extreme caution, if at all, in patients with suspected right ventricular infarction. Such patients are especially dependent on adequate right ventricular preload to maintain cardiac output and can experience profound hypotension during nitrate administration. If nitroglycerin administration results in excessive bradycardia and hypotension, discontinuation of the drug, leg elevation, rapid fluid administration, and atropine are appropriate therapies.

Effect of Intravenous Nitroglycerin on Infarct Size and Mortality

There is experimental and clinical evidence18–20 that intravenous nitroglycerin may reduce infarct size in some patients. As with all interventions designed to salvage myocardium, the best results occur when treatment begins early. Nitroglycerin may decrease susceptibility to ventricular fibrillation during both acute myocardial ischemia and reperfusion.21 Meta-analysis of the pooled results of 10 studies seemed to demonstrate that intravenous nitrates also reduce mortality by 10% to 30%.22 One recent randomized trial20 on intravenous nitroglycerin in 310 patients demonstrated improved hospital survival (mortality rate 14% versus 26%, p<0.01) that was limited to patients with anterior infarction. This benefit was sustained for 1 year.20 Despite these considerations, however, there are inadequate data at present to recommend infusion of intravenous nitroglycerin in all patients with uncomplicated acute myocardial infarction.

Whatever its theoretic value in reducing infarct size and mortality, however, intravenous nitroglycerin is of uncontested value in suppressing ongoing myocardial ischemic pain. Its benefit is also well established when acute myocardial infarction is complicated by congestive heart failure or pulmonary edema.17

Dosage

When titrating intravenous nitroglycerin, begin with a 15 μg bolus injection and a pump-controlled infusion of 5 to 10 μg/min and increase the dosage by 5 to 10 μg/min every 5 to 10 minutes while carefully monitoring hemodynamic and clinical responses. Titration end points are the control of clinical symptoms or a decrease in mean arterial pressure of 10% in normotensive patients or 30% in hypertensive patients (but never a systolic blood pressure <90 mm Hg), an increase in heart rate >10 beats/min (but not usually >110 beats/min) or a decrease in pulmonary artery end-diastolic pressure of 10% to 30%. Although there is no absolute upper dosage limit, doses >200 μg/min are associated with an increased risk of hypotension and alternative therapy should be considered. Prolonged infusion may result in relative nitrate tolerance. The combination of intravenous nitroglycerin with a β-adrenergic blocker in appropriate patients is well tolerated and theoretically attractive because the risk of undesired tachycardia may be reduced. As tolerance develops, the infusion rate can be increased, but if it becomes necessary to administer >200 μg/min, another vasodilator such as a calcium channel blocker should be substituted with the knowledge that effectiveness of nitroglycerin usually returns after 12 hours of removal from nitroglycerin.

Analgesia

The frequent clinical observation of rapid and complete relief of pain after early reperfusion with
thrombolytic therapy has made it clear that the pain of acute myocardial infarction is due to continuing ischemia of living jeopardized myocardium rather than to the effects of completed myocardial necrosis. Efforts to control pain, therefore, may reasonably involve utilization of anti-ischemic interventions, including, in addition to reperfusion, the use of oxygen, nitrates, β-adrenergic blocking agents, and, under some circumstances, intra-aortic balloon counterpulsation. Effective analgesia should be promptly administered at the time of diagnosis, however, and not unreasonably delayed to evaluate the results of anti-ischemic therapy.17

Available Agents

The agents available to suppress the pain of acute myocardial infarction include morphine sulfate, hydromorphone, and meperidine. Meperidine has been recommended for inferior wall infarction because of its vagolytic properties. When equipotent analgesic doses are given, however, it seems to have no clear advantage over morphine.23 Except in patients with documented hypersensitivity to its use, morphine sulfate remains the drug of choice to suppress the pain of myocardial infarction. It is administered intravenously in small repeated doses of 2 to 5 mg every 5 to 30 minutes as needed. Relatively large cumulative doses of 2 to 3 mg/kg are occasionally required.

Morphine blocks sympathetically effenter discharge at a central nervous system level, resulting in peripheral venous and arterial dilation.24 As a consequence, there is a reduction in both preload and afterload and a decrease in myocardial oxygen demand. Pain is relieved and anxiety decreased, leading to a decrease in circulating catecholamines and a possible reduction in associated arrhythmia.25

Side Effects

Hypotension associated with inappropriate bradycardia has been reported to occur rarely. Leg elevation, fluids, and atropine will correct the hemodynamic status. Respiratory depression with aggravation of hypoxemia is a risk, especially in patients with chronic lung disease. Respiratory depression is rarely encountered in the setting of severe chest pain or pulmonary edema.26 If it does occur, its effects can be reversed with naloxone, although its administration may reverse pain relief as well.

Countershock

About 65% of deaths from recognizable acute myocardial infarction occur in the first hour of the attack and most are caused by ventricular fibrillation.25 If basic life support is initiated by a bystander within 4 minutes and if defibrillation occurs within 8 minutes of the cardiac arrest, 40% of patients will live to be discharged from the hospital. When minimally trained “first-responding rescuers” (such as police and firefighters) were permitted to defibrillate ventricular fibrillation before paramedic arrival, marked improvement in neurologic recovery was documented.26 As many as 85% of episodes of ventricular fibrillation will be corrected by a single shock of 200 J.

An organized treatment protocol for the resuscitation of patients with ventricular tachycardia and ventricular fibrillation has been established27 and recently updated.28 Blind defibrillation in a pulseless patient may be attempted. In a monitored setting with a defibrillator present, the occurrence of witnessed ventricular fibrillation or pulseless ventricular tachycardia should lead to immediate nonsynchronized defibrillation at 200 J without intervening basic life support.28 If a pulse is not rapidly restored, subsequent shocks at 200 to 300 J and again at 360 J should follow. It is important to remember that ventricular fibrillation has a “vector” and, depending on the ECG lead and the amplitude of the fibrillatory waves, the ECG during ventricular fibrillation may appear to record ventricular asystole. The diagnosis of “asystole,” therefore, should always be confirmed in at least two ECG leads or, if the distinction between fine ventricular fibrillation and asystole is in doubt, delivery of a countershock to the unconscious patient is appropriate.28

Atropine

By its parasympatholytic (anticholinergic) activity, atropine sulfate reduces vagal tone, enhances the rate of discharge of the sinus node, and facilitates atrioventricular (AV) conduction.29 It is frequently given as an adjunct to morphine administration to reduce nausea and vomiting. During the early moments to hours of acute ischemia or acute myocardial infarction, atropine is particularly useful in treating sinus bradycardia with associated reduced cardiac output and signs of peripheral hypoperfusion, including arterial hypotension, confusion, faintness and grayish pallor, or frequent premature ventricular contractions.30 In this setting, leg elevation and the intravenous administration of atropine may be lifesaving.

Atropine for Atrioventricular Block, Sinus Bradycardia, or Ventricular Asystole

Atropine is the drug of choice for the occasional treatment of type I second-degree AV block, especially when complicating inferior myocardial infarction. It is rarely useful in third-degree AV block. When AV block or sinus bradycardia is associated with congestive heart failure, hypotension, or frequent and complex ventricular arrhythmias, atropine may improve AV conduction and increase the sinus rate and may avert the need for immediate insertion of a transvenous pacemaker.31 As a rule, however, in the absence of hemodynamic compromise, treatment of sinus bradycardia and AV block is not indicated. Similarly, atropine is rarely, if ever, the drug of choice for management of type II second-degree AV block. On occasion, while failing to improve AV block, atropine may increase the sinus rate and, in fact, enhance the block.
The recommended dosage of atropine for bradycardia is 0.5 mg intravenously, repeated if needed every 5 minutes to a total dose of no more than 2 mg, the amount that produces complete vagal blockade. Atropine may also be therapeutic in ventricular asystole, for which the recommended dose is 1 mg intravenously, to be repeated in 5 minutes (while cardiopulmonary resuscitation continues) if asystole persists. The total cumulative dose should not exceed 2.5 mg over 2.5 hours. The peak action of atropine given intravenously is observed within 3 minutes.

**Side Effects**

Atropine in doses of <0.5 mg or when administered other than intravenously may result in a paradoxic effect (namely, bradycardia and depression of AV conduction). The effects are due either to central reflex stimulation of the vagus or to peripheral parasympathomimetic effect on the heart.

Repeated administration of atropine may produce adverse central nervous system effects, including hallucinations and fever. Careful observation is necessary after the administration of atropine because the sinus tachycardia that follows may increase ischemia. Rarely, ventricular tachycardia and fibrillation occur after the intravenous administration of atropine.

Pacemaker insertion is the treatment of choice for symptomatic bradycardia not responding promptly to atropine administration (see elsewhere).

**Recommendations for Atropine Use**

The following indications are applicable in the early moments to 6 or 8 hours after onset of acute myocardial infarction.

**Class I**

1. Sinus bradycardia with evidence of low cardiac output and peripheral hypoperfusion or frequent premature ventricular contractions at the onset of symptoms of acute myocardial infarction.
2. Acute inferior infarction with symptomatic type I second-degree AV block.
3. Bradycardia and hypotension after nitroglycerin administration.
4. For nausea and vomiting associated with morphine administration.
5. Asystole.

**Class IIa**

1. Administration concomitantly with (before or after) morphine administration in the presence of sinus bradycardia, even without evidence of low cardiac output or peripheral hypoperfusion.
2. Asymptomatic patients with inferior infarction and type I second-degree heart block or third-degree heart block at the level of the AV node (see Class III-2).

**Class III**

1. Sinus bradycardia >40 beats/min without signs or symptoms of hypoperfusion or frequent premature ventricular contractions.
2. AV block at the His-Purkinje level (that is, type II AV block and third-degree AV block with new wide QRS complex).

**Indications for Monitoring**

**Electrocardiographic Monitoring**

Continuous ECG monitoring must be established as rapidly as possible when a patient with suspected acute myocardial infarction comes to medical attention. Emergency medical technicians working in the prehospital environment should be capable of establishing ECG monitoring as well as diagnosing and initiating therapy for life-threatening arrhythmias. Once ECG monitoring has been established, it should be continuous and uninterrupted until the patient’s condition has become stable and the responsible medical staff have discharged the patient from intensive cardiac care. In most patients, a single anterior chest lead provides adequate ECG monitoring.

**Recommendations for Electrocardiographic Monitoring in Acute Myocardial Infarction**

**Class I**

1. Patients with acute myocardial infarction during the initial 48 to 72 hours.
2. Patients >72 hours after acute myocardial infarction who have hemodynamic instability, persistent ischemia, or arrhythmia.
3. Patients with suspected myocardial infarction ("rule out" myocardial infarction) during the initial 12 to 36 hours.
4. Patients who have had insertion of a temporary transvenous pacemaker.

**Class IIa**

1. Patients >72 hours after acute myocardial infarction who have a high likelihood of intermittent ischemia or complex ventricular arrhythmias.
2. Patients with chest pain in whom there is a low likelihood of myocardial infarction.

**Class IIb**

1. Monitoring >72 hours after myocardial infarction, particularly if the patient has undergone thrombolysis or angioplasty.

**Class III**

1. Patients with or without known heart disease in whom there is no evidence of myocardial ischemia, recent infarction, or arrhythmia.

**Balloon Flotation Right Heart Catheter Monitoring**

The balloon flotation catheter is of great value in the management of patients with acute myocardial infarction who have an unstable hemodynamic state, including low cardiac output, hypotension, cardiogenic shock, and pulmonary edema. This technique is most helpful when it identifies patients with acute myocardial infarction who have low cardiac output and hypotension due to low left ventricular filling.
pressures. The condition of patients often stabilizes rapidly with simple fluid therapy. Unfortunately, the great majority of patients with low cardiac output, hypotension, or shock have high left ventricular filling pressures and often are in pulmonary edema. In these individuals, the balloon flotation catheter can be used to monitor therapeutic efforts directed toward adjusting the filling pressure so as to maximize cardiac output at the lowest possible wedge pressure. These sophisticated manipulations of the patient’s hemodynamic state would not be possible without readily available measurements of right atrial, pulmonary artery, and pulmonary wedge pressures as well as frequent and convenient determinations of cardiac output.

The balloon flotation catheter is a relatively safe device, but nonetheless is associated with a low risk of serious complications, including pulmonary hemorrhage or infarction. It also results in increased discomfort and immobilization for the patient. There are many opportunities for the pressure recorded from the tip of the balloon flotation catheter to be distorted. These artifactual pressures are most readily identified when displayed with a strip chart recorder. The coronary care unit monitoring equipment should, therefore, have the capacity to record as well as display the pressure waveforms. Digital display of the pressure may be inaccurate and misleading and cannot be relied on. A radiographic check of catheter placement should be made after pressure recording is established. As with all invasive diagnostic techniques, it is essential to have a clear patient management goal before balloon flotation catheter monitoring is initiated. Many patients with acute myocardial infarction now receive thrombolytic therapy early in the course of the illness. Because central venous catheterization by means of the subclavian or internal jugular vein is a relative contraindication to thrombolytic therapy, these sites of catheter insertion should not be used until the need for thrombolytic therapy has been established. If the balloon flotation catheter is indicated, it should be inserted at a compressible site. Because of the risk of infection, balloon flotation catheters generally should not remain in the same site for >48 to 72 hours and no longer than clinically indicated.

**Recommendations for Balloon Flotation Right Heart Catheterization in Acute Myocardial Infarction**

**Class I**

1. Severe or progressive congestive heart failure.
2. Cardiogenic shock or progressive hypotension.
3. Mechanical complications of acute infarction, such as a ventricular septal defect or papillary muscle rupture.

**Class IIa**

1. Hypotension not responding rapidly to fluid administration in a patient without evidence of pulmonary congestion.

2. Before giving a fluid challenge in a patient with circulatory insufficiency and suspected pulmonary congestion.
3. As a diagnostic tool when there is suspicion of an intracardiac shunt, acute mitral insufficiency, or pericardial tamponade.

**Class IIb**

1. Patients with acute myocardial infarction who are hemodynamically stable, but have evidence of mild pulmonary congestion.

**Class III**

1. Patients with acute myocardial infarction who are hemodynamically stable and without evidence of cardiac or pulmonary complications.

**Arterial Pressure Monitoring**

All cardiac intensive care units should have the equipment and trained staff to monitor intra-arterial pressure. Arterial monitoring is useful in the management of hypotensive patients and is required in patients who are in cardiogenic shock. Long-term arterial pressure monitoring is most safely accomplished with a small catheter placed in the radial artery, but other arterial sites, including the femoral and brachial arteries, are acceptable and may be more easily catheterized in a hypotensive patient. The arterial circulation of the limb or hand distal to the arterial catheterization site must be carefully and periodically examined for evidence of tissue ischemia. Because of the risk of arterial thrombosis and infection, intra-arterial catheters generally should not remain in the same arterial site for prolonged periods of time, certainly no longer than is clinically necessary and never for >48 to 72 hours without being changed. Large artery (brachial or femoral) catheters placed without a sheath during an emergency should not be left in place for >6 hours.

**Recommendations for Intra-arterial Pressure Monitoring in Acute Myocardial Infarction**

**Class I**

1. Patients with severe hypotension (systolic <80 mm Hg) or cardiogenic shock.
2. Patients receiving vasopressor agents.

**Class IIa**

1. Patients receiving intravenous nitroprusside or other powerful arterial dilating agents.
2. Hemodynamically stable patients receiving intravenous vasodilators for myocardial ischemia.
3. Patients receiving intravenous inotropic agents.
4. Patients with life-threatening arrhythmias.

**Class III**

1. Patients with acute myocardial infarction who are hemodynamically stable.

*Comment:* In patients in cardiogenic shock or in those receiving vasopressor agents, the radial artery
pressure may be artificially low because of constriction of peripheral arteries. This can be recognized by the poor waveform and, in these patients, a more central arterial pressure may be required.

**Lidocaine**

In the presence of acute myocardial infarction, lidocaine is the drug of choice for the management of ventricular ectopic beats and arrhythmia, including ventricular tachycardia and ventricular fibrillation.\(^{35}\)

Suppression of premature ventricular contractions applies the concept that with myocardial ischemia, the threshold for ventricular fibrillation is reduced and premature ventricular contractions may trigger ventricular fibrillation. Even though premature ventricular contractions in the presence of myocardial ischemia may be successfully suppressed, ventricular fibrillation may still occur. Moreover, although lidocaine reduces the incidence of ventricular arrhythmia, including ventricular fibrillation, trials\(^{36,37}\) have failed to demonstrate that suppression of premature ventricular contractions significantly reduces overall mortality in acute myocardial infarction. There appears to be an increased incidence of asystole with lidocaine and this may obscure the favorable influence of suppression of premature ventricular beats.\(^{38}\)

Generally accepted indications for the use of lidocaine in acute myocardial infarction include ventricular premature beats that are 1) frequent (>6/min), 2) closely coupled (R on T phenomenon), 3) multiform in configuration, or 4) occur in short bursts of three or more in succession. Lidocaine should also be used for the treatment of ventricular tachycardia and ventricular fibrillation that is resistant to defibrillation.

**Dosage**

A loading dose or multiple bolus injections are necessary to initiate lidocaine therapy and to achieve therapeutic blood levels rapidly.\(^{39}\) An initial intravenous bolus injection of 1 mg/kg, not to exceed 100 mg, is recommended. Additional bolus injections of 0.5 mg/kg can be given every 8 to 10 minutes if necessary, to a total of 4 mg/kg. Maintenance of blood levels is accomplished by the administration of 20 to 50 \(\mu g/kg/min\) (1.4 to 3.5 \(\mu g/min\) in a 7 kg patient). This produces blood levels of 2 to 5 \(\mu g/ml\) of blood.\(^{40}\) Patients who require more than one bolus dose of lidocaine to effect suppression of extrasystoles may require higher maintenance doses of lidocaine as well (up to 40 to 50 \(\mu g/kg/min\)).\(^{41}\) The elimination is almost exclusively by the liver. Its half-life averages 1 to 2 hours in normal subjects, >4 hours in patients with relatively uncomplicated myocardial infarction, >20 hours in patients with myocardial infarction complicated by cardiac failure, and even longer in the presence of cardiogenic shock and therefore there will be a need to reduce the infusion rate of lidocaine appropriately in these patients.\(^{41}\)

Patients treated with an initial bolus injection followed by a maintenance infusion may experience transient subtherapeutic plasma concentration at 30 to 120 minutes after initiation of therapy. A second bolus injection of 0.5 mg/kg without increasing the maintenance infusion rate reestablishes a therapeutic serum concentration. If arrhythmia recurs after 6 to 10 hours (that is, at a steady rate of infusion), a similar bolus injection should be given and the maintenance infusion rate increased. Increasing the maintenance infusion rate without an additional bolus injection results in a very slow increase in plasma lidocaine concentration, taking >6 hours to reach a new plateau.\(^{41}\) The half-life of lidocaine increases after 24 to 48 hours\(^{42,43}\) so the dose should be reduced by 1 mg/min, preferably at 12 hours but at least by 24 hours or blood levels should be monitored, or both.

**Toxic reactions should be recognized by frequent and careful clinical assessment.** Reactions are manifested by central nervous system symptoms such as nausea, drowsiness, perioral numbness, dizziness, confusion, slurred speech, numbness of lips or tongue, muscle twitching, respiratory depression or arrest, double vision, tremor, and altered consciousness\(^{44}\) and cardiovascular effects such as bradycardia, sinus arrest, and hypotension.

Only bolus therapy should be used in the setting of cardiac arrest. Bolus therapy may be given every 2 to 3 minutes as needed. When ventricular fibrillation is present, an initial dose of 100 mg is recommended. It might take 2 minutes for lidocaine to reach the central circulation.\(^{45}\) In these doses, lidocaine has no detrimental hemodynamic effects.

**Prophylactic Administration of Lidocaine in Patients With Suspected or Proved Myocardial Infarction**

This has been recommended but is controversial.\(^{46}\) The adverse effects of lidocaine used prophylactically may offset any benefits.\(^{47}\) If routine prophylactic lidocaine administration is to be utilized, its use should be in those patients at highest risk of developing ventricular fibrillation. These include younger patients without prior history of heart failure and who present within the first 6 hours of infarction. Older patients (>70 years) who are at higher risk of developing lidocaine toxicity probably should not receive prophylaxis routinely and patients who are seen >6 hours after the onset of myocardial infarction are less likely to develop ventricular fibrillation and do not need prophylaxis. Prophylactic use employs a program of initial repeat small bolus therapy of 0.5 to 1.0 mg/kg every 5 minutes to a total of 200 to 300 mg, followed by an infusion of 2 mg/min. Prophylactic therapy should be discontinued after the first 12 to 24 hours unless other therapeutic indications are present.

An overview,\(^{38}\) or meta-analysis, of 14 randomized trials of prophylactic lidocaine in patients with suspected acute myocardial infarction indicates that treatment may reduce the incidence of ventricular fibrillation by 33%, but provides no evidence of any mortality benefit.
**Preventing Lidocaine Toxicity**

1. Administration on basis of lean body weight.
2. Caution and reduced infusion rates in:
   a. Patients >70 years of age.
   b. Patients with congestive heart failure, cardiogenic shock, or hepatic dysfunction.
   c. Patients with severe renal dysfunction.
   d. Patients with premature atrial complexes.
3. Measurement of serum levels with prolonged or high infusion rates or change in neurologic condition.

When premature ventricular contractions persist despite administration of lidocaine, procainamide intravenously in bolus doses of 1 to 2 mg/kg over intervals of 5 minutes to a cumulative dose of approximately 1,000 mg, followed by maintenance therapy with an intravenous infusion (20 to 80 μg/kg/min), may be effective.36

**Recommendations for Lidocaine Use**

**Class I**

1. In patients with acute myocardial ischemia or infarction, or both, with ventricular premature beats that are:
   a. Frequent (>6/min).
   b. Closely coupled (R on T).
   c. Multiform in configuration.
   d. Occurring in short bursts of three or more in succession.
2. In the patient with ventricular tachycardia or ventricular fibrillation, or both, in association with defibrillation and cardiopulmonary resuscitation as indicated.

**Class IIa**

1. In patients with suspected acute myocardial infarction or ischemia, or both, with indications as in Class I.

**Class IIb**

1. Prophylactic administration in the presence of uncomplicated acute myocardial ischemia or infarction, or both, without ventricular premature beats in patients <70 years of age and within the first 6 hours of onset of symptoms.

**Class III**

1. Patients with proved allergic or hypersensitivity reactions to lidocaine.

Although the treatment of choice for ventricular arrhythmias during the acute phase of myocardial infarction is lidocaine, an occasional patient may be refractory to lidocaine or the arrhythmia may persist past the acute phase. Discussion of the pharmacotherapy of these arrhythmias is beyond the scope of this report, other than to suggest that procainamide and quinidine are probably the drugs of choice. For discussion of the indications for electrophysiologic study for selection of drugs, the reader is referred to the ACC/AHA Guidelines for Clinical Intracardiac Electrophysiologic Studies.48

Similarly, for indications for implantable defibrillators, the reader is referred to the ACC/AHA Guidelines for Permanent Cardiac Pacemaker Implantation (in press).

Supraventricular arrhythmias, although relatively frequent, are rarely life-threatening. When complicating acute infarction, their management as a rule does not differ from that for similar arrhythmias complicating other cardiac disorders. The discussion of therapy of these arrhythmias is similarly beyond the scope of this report.

**Use of Pacemakers in Acute Myocardial Infarction**

Although it is difficult to demonstrate statistically significant improvement in survival with use of temporary pacing in acute myocardial infarction, there are accepted indications and the general impression that some patients are saved.49 Patients with progressive heart block usually have a large infarct and it is the loss of myocardium that leads to death in many temporarily saved by pacing. There is a small but significant incidence of complications from temporary pacing and this includes induction of arrhythmias, ventricular perforation, pneumothorax, hemotorax, arterial injury, and infection.50 Practical external pacemakers that can be used for standby indications or in an emergency until transvenous pacing can be established are now available.51 Temporary pacemakers are also useful for overdrive pacing of ventricular tachycardias and conversion of supraventricular tachycardias such as atrial flutter.52 When ventricular function is severely compromised, AV sequential pacing to preserve atrial augmentation should be considered.

**Recommendations for Temporary Pacemaker in Acute Myocardial Infarction**

**Class I**

1. Asystole.
2. Complete heart block.
3. Right bundle branch block with left anterior or left posterior hemiblock developing in acute myocardial infarction.
4. Left bundle branch block developing in acute myocardial infarction.
5. Type II second-degree AV block.
6. Symptomatic bradycardia not responsive to atropine.

**Class IIa**

1. Type I second-degree AV block with hypotension not responsive to atropine. During ventricular pacing, if ventricular atrial conduction causes the atrial contraction to fall within ventricular contraction, atrial or AV sequential pacing may be necessary.
2. Sinus bradycardia with hypotension not responsive to atropine.
3. Recurrent sinus pauses not responsive to atropine.
4. Atrial or ventricular overdrive pacing for incessant ventricular tachycardia.

Class IIb
1. Left bundle branch block with first-degree heart block of unknown duration.
2. Bifascicular block of unknown duration.

Class III
1. First-degree heart block.
2. Type I second-degree AV block with normal hemodynamics.
3. Accelerated idioventricular rhythm causing AV dissociation.
4. Bundle branch block known to exist before the myocardial infarction.

For the use of permanent pacemakers following acute myocardial infarction, the reader is referred to the ACC/AHA Guidelines for Permanent Cardiac Pacemaker Implantation, which have recently been revised and are in press.

Transportation
Although these guidelines focus predominantly on interhospital transportation, the problem of initially transporting a patient with suspected acute myocardial infarction to the hospital is highly important. If paramedics are available, it is most advisable to call for their help. Stabilization of the patient’s condition at the scene by the paramedical team and direct communication with a physician at the receiving hospital emergency room can both be accomplished. Transportation in a fully equipped ambulance or mobile coronary care unit further enhances safety. Transportation in an automobile may be hazardous and should be avoided.

Because time is critical for our current therapies, it is recommended that each community organize a transportation system to bring the patient quickly for immediate care, which might include thrombolysis. If the hospital designated for initial care is not equipped for more definitive treatment, a more sophisticated transportation system should be developed for transfer of patients to a hospital where such facilities exist.

Hospital Plans
Each hospital should have an approved plan for treating early acute myocardial infarction. When notified by the paramedical team that a patient with suspected acute infarction is on the way, the proper personnel and equipment should be mobilized and the physician qualified to make the decisions as to use of thrombolytic or other aggressive therapy should be called in.

Each hospital referring patients or receiving referrals of patients for completion of definitive or staged early therapy of acute myocardial infarction must have approved plans for transportation. If interhospital transfer is necessary, the patient should be referred to the most appropriate regional hospital on the basis of medical needs, facilities, and expertise available and consistent with patient choice. A patient in unstable condition should be transferred only when the receiving hospital has special skills, services, and equipment required by the patient’s condition but not available at the sending hospital. Transfer should be arranged on a physician to physician basis. The patient must be accompanied by a complete medical record.

Emergency transportation must be in a vehicle equipped and staffed for advanced life support. Inordinate delays at the sending facility should be avoided, but stabilization of the patient’s condition should be achieved to the extent possible before and during transportation of the patient to the receiving hospital. A physician need not accompany the patient during transportation, but must see to it that the patient is in stable condition before transfer and will be treated quickly by a physician on arrival at the receiving hospital.

Direct voice communication with the receiving hospital is essential during transportation. Radio contact assures rapid access to medical direction. Electrocardiographic monitoring and emergency medications are essential. Equipment for endotracheal intubation and suction, esophageal obturator airway maintenance, direct current defibrillation, and external pacing are necessary.

Patients who should be transferred include (but are not limited to) those who have undergone acute thrombolysis and continue to experience angina or other evidence of continuing ischemia of viable myocardium. These patients should be in a facility with the staff and equipment required to perform coronary angioplasty and emergency cardiac surgery.

Air Versus Surface Transportation
During transportation, safety of the patient and personnel are of foremost importance. If the patient’s condition has been stabilized and if thrombolytic therapy has been given, haste in the transportation process is secondary to safety. Whether transportation is by surface or by air will depend on the distance and local capabilities. Studies of helicopter transfer of patients with acute myocardial infarction who have or have not received intravenous fibrinolytic therapy have indicated that this can be done safely. Arrhythmias, hypotension, and bleeding have been treated during transit without mortality.

The advantage of helicopter transport pertains as much if not more to the personnel and equipment for communication as to this specific mode of transportation. Aircraft safety is an important and controversial issue and cost/benefit ratio is still being determined. Crashes, deaths, and injuries have occurred during aeromedical transport of critically ill patients.

If surface transportation to the receiving hospital required >90 to 120 minutes, air transportation should be considered. Transportation has been performed safely by ambulance for approximately 60
miles with a paramedic but no physician in attendance.\textsuperscript{57} In one series,\textsuperscript{57,58} 33% of patients developed complications including ventricular arrhythmias requiring cardioversion, myocardial infarction, or hypotension requiring treatment during transport; only 1 of 50 patients died.

It is important to utilize the following pretransfer checklist to avoid mishap and anticipate problems:\textsuperscript{59}

- Review reasons for transfer with the patient, patient's family, and accepting physician.
- Discuss transfer and plans for the patient at the receiving hospital with appropriate physicians, hospital administrators, and coordinators.
- Duplicate appropriate portions of the patient's medical record.
- Review patient care with authorized representatives of transporting team and carrier.
- Provide for continuation of therapy during transportation.
- Assure that appropriate medical supplies are available during transportation and that equipment is functional.
- Select suitable medical and support staff to accompany the patient.
- Formulate a realistic and efficient transfer schedule and arrange for timely linking or support vehicles if more than one mode of transfer en route is necessary. Police escort through intracity transfer may be indicated.

\textbf{Recommendations for Transportation}

Transfer to a tertiary care facility equipped for angioplasty and cardiovascular surgery is indicated in:

\textbf{Class I}

1. Patients with recurrent pain.
2. Patients who have hemodynamic instability as manifested by persistent congestive heart failure, arterial hypotension, or cardiogenic shock.
3. Patients with resistant, recurrent ventricular arrhythmias (ventricular tachycardia or fibrillation).

\textbf{Class IIa}

1. Patients with high risk myocardial infarction and contraindications to thrombolytic therapy, but in whom it is reasonable to expect that reperfusion can be accomplished by percutaneous transluminal coronary angioplasty or coronary artery bypass grafting within 6 hours.
2. Patients who are stable late in the initial hospitalization, but who are to be evaluated for angioplasty or bypass grafting before discharge.
3. Patients in the early hours of acute myocardial infarction who have had prior bypass grafting and who are thought to be candidates for angioplasty or regrafting.

\textbf{Class IIb}

1. Patients who are in stable condition in the early hours of acute myocardial infarction after thrombolysis, but are in a facility in which coronary angioplasty or surgery cannot be performed.

2. Stable patients with early acute transmural infarction and extensive ST-T changes.

\textbf{Detection and Quantification of Acute Myocardial Infarction}

A strong history of the typical manifestations of myocardial ischemia and positive risk factors coupled with salient physical findings of acute myocardial infarction are of inestimable value in diagnosis. With a suggestive history, the probability of infarction is enhanced in the presence of detectable ventricular ectopic activity, sinus tachycardia, bradycardia, or accelerated idioventricular rhythm. Findings that more directly reflect myocardial injury are palpable dyskinesia, pulsus alternans, hypotension, a soft S\textsubscript{1}, paradoxic splitting of S\textsubscript{2}, an accentuated S\textsubscript{4} or an S\textsubscript{5}, murmur of mitral regurgitation, and signs and symptoms of congestive heart failure. Manifestations of excessive autonomic nervous system activity support the diagnosis. Involvement of the right ventricle in patients with inferior infarction is often recognizable by ST segment changes in ECG leads V\textsubscript{1}, V\textsubscript{2}, and V\textsubscript{3}, elevated venous pressure, and hypotension disproportionate to left heart failure. The Killip classification has been useful for clinical assessment of the severity of infarction. However, more objective and definitive information can be acquired with noninvasive techniques (for example, two-dimensional echocardiography or radionuclide ventriculography) that permit serial assessment, quantification and localization of regional wall motion abnormalities, and delineation of global left and right ventricular function.\textsuperscript{60}

Definitive diagnosis is based on objective criteria; despite the occasional occurrence of electrocardiographically silent infarction, there are frequently nondiagnostic ECG changes and, therefore, sequential ECG changes remain a mainstay of early diagnosis. Infarction cannot be established with certainty in the absence of alterations of the QRS complex, but ST segment deviation, T wave abnormalities, intraventricular conduction delays, changes indicative of right ventricular infarction in right-sided precordial leads, and nonspecific changes in rate and rhythm are suggestive of infarction.

\textbf{Laboratory Criteria}

\textit{Detection of the release of macromolecules from irreversibly injured myocardium.} This has evolved as the definitive diagnostic criterion of infarction. Enzymes that egress from ischemic myocardium within several hours after the onset of irreversible injury include aspartate aminotransferase, lactate dehydrogenase, and creatine kinase (CK). Elevated activity in plasma is a sensitive diagnostic criterion, although its specificity is somewhat limited because of potential liberation of enzyme from skeletal muscle or other tissues. The MB isoenzyme of creatine kinase has become a cornerstone of diagnosis because it is much more abundant in myocardium
than in most other human tissues.\textsuperscript{61} Necrosis of \textless{}0.1 g of myocardium can be recognized. Assessment of posttranslational conversion of individual isoenzymes of creatine kinase to subforms (isoforms) provides criteria for even earlier detection of infarction and permits recognition of recanalization by increased washout of the tissue subform into plasma.\textsuperscript{62–64} Analysis of isoenzymes of other enzymes such as lactate dehydrogenase provides less specific information. These macromolecules are elaborated from components of the inflammatory response accompanying infarction and hemorrhage within the heart as well as from the myocytes themselves.

Assays of macromolecules such as myosin light chains\textsuperscript{65} and myoglobin.\textsuperscript{66} Such assays may be valuable in clarifying elusive diagnoses because of their characteristic rates of appearance and disappearance. Interpretation of changes in plasma concentrations of macromolecular markers of infarction may be obscured when rates of release are altered by recanalization or profound ischemia. When appearance rates are very slow compared with disappearance rates, dilution of the marker in plasma may mask elevations that otherwise would be apparent.\textsuperscript{61} Sequential changes in plasma concentrations of macromolecular markers such as creatine kinase are useful in estimating the extent of infarction.\textsuperscript{61} In view of the specificity and sensitivity of the MB isoenzyme of creatine kinase in plasma as a marker of myocardial injury, assay of other plasma enzymes is generally not necessary. These assays may be useful when a patient with suspected infarction is admitted several days or more after the onset of symptoms, by which time MB CK elevations may no longer persist, or if the time of onset of infarction is uncertain.\textsuperscript{61}

Isoform analyses. Recent recognition\textsuperscript{62–64} of isoforms and characterization of the kinetics of their formulation in plasma by proteolysis of isoforms released from the myocardium underlie an approach for very early detection of infarction and noninvasive detection of reperfusion. Although creatine kinase isoform and myoglobin analyses are still investigational, likely uses are monitoring the efficacy of pharmacologic thrombolysis, defining the need for invasive studies or interventions, and facilitating interpretation of episodes of chest pain. Elevations of the ratio of the tissue MM CK isof orm (MM\textsubscript{i}) to the fully converted form in plasma (MM\textsubscript{c}) or of myoglobin in samples obtained within 1 hour after such an episode compared with values in samples obtained before the episode are consistent with recurrent infarction.

Ventricular Performance

Assessment by echocardiography and radionuclide and contrast ventriculography. Regional hypokinesia or dyskinesia may be a manifestation of a condition other than infarction and certain infarcts may not be reflected by detectable or proportional wall motion abnormalities. Despite these provisos, both the sensitivity and the specificity of abnormal wall motion as a criterion of acute myocardial infarction exceed 90\% with several imaging methods.

Two-dimensional echocardiography consistently localizes impaired wall motion associated with anterior infarcts and that associated with inferior infarcts in >90\% of patients.\textsuperscript{67} Contrast echocardiography may permit estimation of the extent of infarction by delineating hyperperfusion in the region at risk, although its use for this purpose is primarily in research and its implementation requires a practiced technique and dedicated instrumentation.\textsuperscript{68} Wall thinning or the lack of wall thickening is an important ancillary finding. Global measures of left ventricular performance are less sensitive and specific than assessments of regional wall motion in detecting, localizing, and qualifying the extent of ischemic insults.

Assessment of global and regional ventricular performance by radionuclide ventriculography has a sensitivity and specificity comparable with those of echocardiography and provides estimates even in patients with anatomic features precluding adequate echocardiographic examination. Cost and radiation exposure are considerations.\textsuperscript{69}

Sensitivity, specificity, spatial resolution, and quantitative power of contrast ventriculography are superior to those with any conventional noninvasive method. Expense, radiation exposure and risk associated with left heart catheterization and administration of radiographic contrast agents are disadvantages.

Assessment by cine computed tomography and nuclear magnetic resonance imaging. Several novel techniques have been developed for delineating abnormal ventricular function indicative of acute myocardial infarction, including ultrafast (cine) computed tomography.\textsuperscript{70} Instrumentation is expensive, radiation burdens are significant, and applicability is limited. Gated nuclear magnetic resonance (NMR) imaging with or without paramagnetic contrast agents such as gadolinium-DTPA detects reversible and irreversible myocardial injury induced by ischemia in experimental animals and patients.\textsuperscript{71} Spin-echo images show increased signal intensity corresponding with dyskinetic segments, reflecting acute myocardial infarction\textsuperscript{72} or zones with diminished perfusion evident in contrast studies.\textsuperscript{71} NMR imaging provides excellent spatial resolution, but the costs of instrumentation, the current need for relatively long imaging intervals and the difficulties inherent in imaging patients instrumented with metallic devices are disadvantages that often preclude its use for diagnosis of acute myocardial infarction. However, rapid speed NMR imaging may soon be available to enhance the capability for imaging cardiac dynamics.

Scintigraphic Methods for Detecting Infarction and Ischemia

Infarct-avid agents such as technetium-99m pyrophosphate detect infarction sensitively and define its locus (infarct scintigraphy). Disadvantages include the lack of accumulation of tracer in tissue early
during the course of infarction and, hence, reliable detection only 24 hours or more after onset. Radiolabeled monoclonal anti-myosin antibodies (Fab fragments labeled with indium 111 or technetium 99m) bind to myosin in irreversibly injured cells and yield excellent images of an infarction. However, positive results can be obtained only after injury has evolved, and uptake of tracer may be influenced markedly by the hypoperfusion in the infarct zone. Decreased uptake of potassium analogs such as thallium 201 indicative of hypoperfused or necrotic tissue can be implemented earlier, and differentiation of reversible from irreversible injury can be accomplished by acquisition of "redistribution" images in which differences between accumulation of tracer in normal zones and those with initially depressed accumulation vanish, in part because of differential washout rates (perfusion scintigraphy). As a current research scintigraphic method, the use of technetium-99m isonitrile, which does not redistribute, may become a useful method for assessing the initial zone at risk and the success of reperfusion.

Echocardiographic Methods for Assessment of Patients With Infarction

Echocardiography is of considerable value in the assessment of patients with acute myocardial infarction for acquisition of prognostic information as well as for characterization of ventricular function. In patients with apparent complications of infarction, echocardiography is particularly useful in determining the presence or absence of pericardial effusion compromising cardiac performance; characterizing factors that contribute to otherwise unexplained tachycardia, hemodynamic instability or pulmonary congestion suggestive of pump failure; assessing the severity of and identifying factors that may require alteration of medical management of infarction, such as coexisting valvular or congenital heart disease; and defining the extent to which potentially catastrophic complications may be contributing to sudden deterioration in the clinical course, such as mitral insufficiency, ventricular septal rupture, cardiomyosis with hemopericardium or ventricular aneurysm. In patients with extensive anterior myocardial infarction (ECG criteria and peak MB CK >150 IU/l [or total CK >1000 IU/l]), echocardiography may be particularly helpful in assessing hypokinesia or dyskinesia predisposing to left ventricular mural thrombi, detecting thrombi already present and facilitating assessment of the predisposition of thrombi for embolization. In patients in whom left bundle branch block, a paced rhythm, posterior infarction, or non–Q wave infarction is present, the diagnostic power of the ECG for infarction may be somewhat limited. Under these circumstances, detection of infarction and delineation of its locus and extent can be facilitated greatly by echocardiography.

Diagnosis of Acute Myocardial Infarction

In addition to history and physical examination, patients with suspected acute myocardial infarction should be evaluated with a chest X-ray study, serial ECGs, possibly several within a few hours, and MB CK determinations. Subsequent ECGs are needed daily until the nature of evolution of infarction is defined and more frequently if complications occur. Plasma MB CK (or total CK if MB assays are not available) should be measured at 6 hour intervals for the first 24 hours and then daily until the diagnosis is established or, in the absence of complications, until values have returned to baseline. Determination of levels of other plasma enzymes, such as aspartate aminotransferase and lactate dehydrogenase, are not necessary except in unusual circumstances such as when admission is days after suspected infarction at a time lactate dehydrogenase may still be elevated but MB CK has returned to normal.

Indications for Assessment of Left Ventricular Function in the Early Phase of Acute Myocardial Infarction

Assessments of left ventricular function can be made expeditiously by echocardiography, radionuclide ventriculography, and other imaging techniques. The selection of the particular modality used in a given institution should depend in part on the familiarity and expertise of the institution with each specific method. It is inappropriate to acquire duplicate information with different methods unless specifically indicated.

Recommendations for Echocardiography in the Early Phase of Acute Myocardial Infarction

Class I

1. Myocardial infarction associated with shock or profound pump failure consistent with extensive myocardial dysfunction or a potentially surgically remediable lesion such as ventricular septal rupture, free wall rupture, profound mitral regurgitation, or left ventricular true or pseudoaneurysm.

2. Myocardial infarction associated with extensive infarction (ECG localization and peak MB CK >150 IU/l [or total CK >1,000 IU/l]) in which valuable prognostic information and information regarding the need for anticoagulant therapy for prevention or treatment of ventricular thrombi can be acquired.

3. Myocardial infarction accompanied by clinical complications such as tachycardia, hemodynamic instability, pulmonary congestion suggestive of pump failure, refractory angina, or pericardial tamponade.

4. Myocardial infarction associated with valvular or congenital heart disease.

5. Suspected pericarditis or pericardial effusion that may complicate acute myocardial infarction.

6. Myocardial infarction in patients being or to be treated with calcium antagonists or β-adrenergic blocking agents in whom left ventricular function may be compromised so that risks and potentially...
deleterious effects of therapy can be anticipated or recognized promptly.

**Class IIa**

1. Myocardial infarction superimposed on previous infarction or associated with ECG phenomena such as left bundle branch block or posterior locus that may obscure diagnosis, in which case delineation of regional wall motion abnormalities may help confirm the diagnosis and provide prognostically important information.

2. Myocardial infarction with suspected concomitant right ventricular infarction (such as true posterior infarction) to define the severity of right ventricular involvement as a guide to management and exclude pericardial tamponade.

**Class IIb**

1. Myocardial infarction of modest extent without clinical complications for evaluation of prognosis.

**Use of β-Blockers in Acute Myocardial Infarction**

β-blocker therapy in acute infarction requires consideration in relation to two goals:

1. Limitation of myocardial damage or mortality, or both, when administered during the first few hours of infarction.

2. Reduction of the risk of reinfarction or mortality, or both, when administered after completed infarction.

**Limitation of Myocardial Damage or Mortality, or Both, When β-Blocker Therapy Is Started During the First Few Hours of Infarction**

Studies of reperfusion have convincingly demonstrated that the amount of myocardial damage is not fixed during the first few hours of acute infarction. β-Blocking agents can potentially reduce myocardial oxygen demand during this period by reducing heart rate and arterial pressure or myocardial contractility, or both, and have a favorable influence on myocardial blood flow distribution. The prolongation of diastole resulting from a reduction in heart rate may augment the amount of coronary flow reaching injured but not irreversibly damaged myocardium (particularly in the subendocardium). One might therefore expect that β-blockade could increase the amount of myocardium salvaged by reperfusion if it was achieved sufficiently early in the course of infarction. There is evidence that β-blockade can reduce the extent of infarction or the complications of infarction, or both, in the absence of thrombolytic therapy.

Nearly 30 randomized trials have now been reported using an initial intravenous dose of a β-blocker in acute infarction without concomitant thrombolytic therapy. In the largest of these, in which >16,000 patients were accepted within 12 hours of the onset of symptoms, the 7-day mortality rate was reduced from 4.3% to 3.7% (p<0.02). Favorable trends of similar magnitude were also apparent for reinfarction and cardiac arrest (or ventricular fibrillation). The 14% mortality difference between the treated and nontreated groups was apparent by the end of day 1 and remained essentially constant thereafter. β-Blockade was initiated in this study as 5 to 10 mg of atenolol (intravenously) and continued at a level of 100 mg orally/day for 1 week. In the second largest study, the 15-day mortality rate in >5,700 patients was reduced from 4.9% to 4.3%, with the difference in mortality between treated and placebo groups again evident at day 1. It was suggested that the beneficial effect of β-blockade was largest in “high-risk” subgroups, as defined by either prestudy risk predictors or a multivariate risk model. The β-blocker employed was metoprolol in a dose of up to 15 mg intravenously in three divided doses (with 2-minute intervals between) and, starting 15 minutes after completion of the intravenous dosage, 50 mg orally every 6 hours for 48 hours then 100 mg twice daily thereafter.

Assessment of effects of acute β-blockade on indexes of infarct size are complicated by differences in study design (for example, frequency of enzyme sampling, time of initiation of β-blockade in relation to onset of symptoms, approaches to ECG evaluation) and study size. Review of available studies is consistent with the view that modest favorable effects occur. Thrombolytic agents were not administered in these studies.

A recent trial of early β-blockade in conjunction with thrombolytic therapy showed no adverse effect of the combined therapy and a suggested reduction in frequency of reinfarction compatible with findings in the larger studies.

Because several β-blocking agents (both cardioselective and nonselective) have been employed in the studies cited, beneficial effects of β-blocking agents do not seem limited to any particular member of the drug group. Agents having intrinsic sympathomimetic activity as well as β-blocking activity may be less desirable and should be avoided. Intravenous β-blocking agents with extremely short durations of activity may prove advantageous in selected patients.

**Contraindications to β-Blockade**

Heart rate <60 beats/min.

Systolic blood pressure <100 mm Hg.

Moderate to severe left ventricular failure.

Signs of peripheral hypoperfusion.

AV conduction abnormalities: PR interval >0.22, type I and II AV block or complete heart block.

Severe chronic obstructive pulmonary disease.

**Relative Contraindications to β-Blockade**

History of asthma.

Current use of β-blockade (may require modification of initial intravenous dosage).

Current use of calcium channel blockers (verapamil and diltiazem).
Severe peripheral vascular disease.
Difficult-to-control insulin-dependent diabetes.

Recommendations for Early Intravenous β-Blockade
Class I
1. Patients, including those receiving thrombolytic therapy, with reflex tachycardia or systolic hypertension, or both, without signs of congestive heart failure or contraindication to β-blockade.
2. Patients with continuing or recurrent ischemic pain, tachyarrhythmias such as atrial fibrillation with a rapid ventricular response or an enzyme elevation thought to represent recurrent injury who are without contraindication to β-blockade.
3. Postinfarction angina while awaiting study in patients without contraindications.

Class IIa
1. Other patients without contraindication to β-blockade who can be treated within the first 12 hours from the onset of chest pain.
2. Non-Q wave myocardial infarction.

Class III
1. Patients with moderate to severe left ventricular failure and other contraindications to β-blockade.

Reduction of the Risk of Reinfarction or Mortality, or Both, When Maintenance β-Blocker Therapy Is Given After Completed Infarction

A number of placebo-controlled secondary prevention trials involving >35,000 patients indicate that chronic β-blockade begun in the early phase of infarction improves survival and decreases the incidence of reinfarction for at least the first several months after the acute event. The improved survival appears to include a reduction in the frequency of sudden cardiac death. Patients with compensated or mild congestive heart failure appear to benefit as greatly as patients without heart failure and may show a significant reduction in the frequency of sudden cardiac death. Patients with an uncomplicated course after an initial infarction, good residual left ventricular function, no angina or arrhythmia and no evidence of ischemia during functional testing are recognized to have a very favorable 1-year mortality rate, making the benefit of secondary prevention by long-term blockade less clear in this group.

The absolute reduction in the 2-year mortality rate effected by long-term β-blockade in patients without contraindication to this therapy appears to be 2% to 3% (for example, a reduction in one major trial from 9.8% to 7.2% over an average 25-month follow-up period). The favorable effect of β-blockade again occurs with both cardioselective and nonselective agents. However, agents with intrinsic sympathomimetic activity should be avoided. Daily dosages in the studies demonstrating beneficial effects of β-blockade have again been relatively high (for example, 180 to 240 mg of propranolol and 20 mg of timolol), but there is no evidence that the same results cannot be achieved with lower doses. Whether or not low-risk patients should be routinely treated with β-blockade has been a subject of some debate because there is concern about side effects of these agents and the greatest effect can be demonstrated most readily in the high-risk patients. Side effects (fatigue, depression or sexual dysfunction, nightmares, and insulin dosage difficulty) may be frequent enough in low-risk patients to outweigh benefits. Goldman et al presented cost-effectiveness data suggesting that even low-risk patients derive significant benefit; however, this theoretic analysis did not take into account the psychosocial costs of the side effects. Finally, none of the studies cited addresses the question as to if and when the recommendations should be modified in patients who have had successful revascularization after myocardial infarction.

Recommendations for Long-Term β-Blockade for Secondary Prevention in Patients Without Myocardial Revascularization
Class I
1. All but low-risk patients who do not have a clear contraindication to β-blockade. Treatment should ordinarily begin within the first few days of infarction and should be continued for at least 2 years.

Class IIa
1. Low-risk patients who do not have a clear contraindication to β-blockade. Treatment to begin within the first few days of infarction and continued for at least 2 years. Decisions concerning β-blockade withdrawal (or dose reduction) because of drug side effects should take into account the risk status of the individual patient (that is, the decision to reduce or discontinue should be controlled by weighing side effects more heavily as one moves from high- to low-risk patients).

Class III
1. Patients with contraindications to β-blockade.

Calcium Channel Blockers

A wealth of published data have accumulated describing the efficacy of calcium channel blocking drugs as anti-ischemic agents effective in the treatment of stable and unstable angina pectoris resulting from fixed stenoses of coronary atherosclerosis and from coronary vasospasm. The known cardiovascular properties of these drugs suggest a rationale for their use in the treatment of acute myocardial infarction and in the prevention of secondary complications after myocardial infarction. Although some new calcium channel blocking drugs are under investigation, this discussion will be limited to those now in clinical use—verapamil, nifedipine, and diltiazem. All three reduce systemic vascular resistance and, therefore, are utilized as antihypertensive agents. They have been shown to influence the ionic calcium currents that
regulate action potential. Diltiazem and verapamil both reduce myocardial contractility, thereby diminishing myocardial oxygen consumption, as does nifedipine if reflex sympathetic stimulation is blocked. Diltiazem and verapamil have potent effects on the AV node, producing slowing of the ventricular response to atrial flutter and fibrillation, terminating paroxysmal supraventricular arrhythmias, and occasionally producing AV block.

Despite these multiple cardiovascular effects of the calcium channel blockers, there have been only a few reports evaluating their use in acute myocardial infarction.

**Diltiazem**

The Diltiazem Reinfarction Study Group reported that in the dose of 90 mg every 6 hours, initiated within 24 to 72 hours after onset of infarction, diltiazem was effective in preventing early reinfarction and recurrent angina in patients with non-Q wave infarction (formerly designated nontransmural or subendocardial infarction). The study of long-term diltiazem therapy in patients with both Q wave and non-Q wave myocardial infarction failed to demonstrate a beneficial effect of diltiazem. Although there were slightly fewer recurrent cardiac events overall in the diltiazem group as opposed to the placebo group, this did not reach statistical significance. In patients receiving diltiazem, there appeared to be an adverse effect in the small group of patients with left ventricular dysfunction and this may have obscured the favorable effects in patients with normal ventricular function, but this was not tested prospectively. Thus, the efficacy of routine diltiazem treatment after acute myocardial infarction in patients with preservation of left ventricular function is not yet established.

**Verapamil**

This agent may be beneficial in the setting of acute myocardial infarction for the treatment of acute supraventricular arrhythmias, particularly if other antiarrhythmic drugs (such as digoxin) are inadvisable and neither ventricular function nor the conduction system is in jeopardy. Care should be exercised in patients receiving β-blockers.

**Nifedipine**

Muller et al reported the results of a trial to determine whether early nifedipine therapy could prevent progression or extension of infarction as determined by MB CK values and whether nifedipine would limit necrosis in patients with ongoing acute myocardial infarction with a primary end point being the serum enzyme determination of infarct size. The results showed no reduction in the progression to infarction or a reduction of infarct size, but the nifedipine group had a significantly higher 2-week mortality rate than the placebo group (p<0.02).

Thus, there is no clear evidence to support the routine use of calcium channel blockers in the treatment of acute myocardial infarction, except in the subset of patients with non-Q wave infarction, in whom diltiazem was found effective in preventing early reinfarction and recurrent severe angina.

**Recommendations for Use of Calcium Channel Blockers in Acute Myocardial Infarction**

**Class I**

1. Symptomatic treatment of postinfarction angina while awaiting cardiac catheterization and therapy based on angiographic findings.

**Class IIa**

1. Diltiazem in patients with non-Q-wave infarction in whom no contraindication exists. It should be started during the first 48 hours and continued through the hospital phase and the first postinfarction year.

2. After angioplasty, a calcium channel blocker to prevent coronary vasospasm.

**Class IIb**

1. A calcium channel blocker may be used in transmural (Q wave) infarction for treatment of postinfarction angina, especially if contraindications to proceeding with coronary arteriography and more definitive treatment exist.

**Class III**

1. Calcium channel blockers that suppress ventricular function in patients with myocardial infarction complicated by pulmonary congestion or left ventricular dysfunction.

**Thrombolytic Therapy in Patients With Acute Myocardial Infarction**

**Background**

Approximately 66% of heart attack victims at hospital entry have ST segment elevation, making it likely that the process is caused by an occlusive coronary clot. In patients with this finding, clot-dissolving therapy in the form of intravenous streptokinase (SK [Streptase/Kabikinase]), recombinant tissue-type plasminogen activator (rt-PA [Activase]) or anisoylated plasminogen streptokinase activator complex (APSAC [Anistreplase]) can dissolve the clot and restore flow, interrupt the infarction, reduce myocardial necrosis, and improve survival if therapy is delivered within 6 hours of the onset of the attack.

**Results of Clinical Trials**

The use of thrombolytic therapy in acute myocardial infarction ST segment elevation rests on reductions in mortality observed in randomized controlled trials (Table 1).

**GISSI**. The first large study reported was conducted in Italy and is known by the acronym GISSI. In this trial, 11,712 patients presenting within 12 hours of onset of acute infarction and free of contraindications to thrombolytic therapy were randomly assigned to treatment with a 1-hour intra-
venous infusion of 1.5 million units of streptokinase or to conventional care with no streptokinase. The 21-day mortality rate in the streptokinase group was 10.7%, compared with 13.0% in the control group, a significant 18% reduction (p = 0.0002). No benefit was observed in patients receiving streptokinase >6 hours after the onset of symptoms. However, in those treated within 6 hours, the mortality rate at 21 days was 12.8% in the control group and 10.2% in the streptokinase-treated group (a 20% reduction in mortality). The earlier treatment was started, the more effective it was. For example, in patients whose treatment started within 3 to 6 hours, streptokinase resulted in a 17% reduction in mortality (from 14.1% to 11.7%); in the 0- to 3-hour treatment group, it reduced mortality by 23% (from 12.0% to 9.2%) and in those treated within 1 hour of symptoms by 47% (from 15.4% to 8.2%). The survival curves from 21 days to 1 year are parallel (7% mortality rate in both treated and untreated groups between hospital discharge and 1 year), demonstrating extended benefit in a group of patients marked by very infrequent use of percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery.

**ISIS-2.** The investigators participating in the Second International Study of Infarct Survival (ISIS-2) have reported baseline and outcome data in 17,187 patients with suspected myocardial infarction who were recruited within 24 hours of the onset of chest pain. These patients were randomized to intravenous streptokinase (1.5 mU over 60 minutes), oral aspirin (160 mg/day for 1 month), to both or to neither in a double-blind fashion by means of matching placebos. Patients were excluded from the trial if >24 hours had elapsed from the onset of symptoms, whereas most other trials used either a 6-hour or 12-hour exclusion, and there was no age limit, which ranged from 70 to 75 years in other trials. The issues to be tested were the effect of streptokinase on the vascular mortality rate at 5 weeks and later and the effect of aspirin on the 5-week vascular mortality rate. In addition, a subsidiary analysis was planned of the effect of streptokinase on the vascular mortality rate in those treated <4 hours after the onset of pain, 4 to 12 hours after pain, and at 12 to 24 hours.

When the data were analyzed for mortality at 5 weeks after trial entry, the ISIS-2 investigators observed that the 8,592 patients assigned to streptokinase treatment experienced 786 (9.1%) vascular deaths compared with 1,016 such deaths (11.8%) in the 8,595 patients assigned to receive placebo, a 23% reduction (p < 0.00001). This difference is similar to the overall 18% reduction noted in the GISSI trial. In the interval between 5 weeks and 1 year, the estimated vascular mortality rate in the streptokinase and placebo groups was 5.7% and 6.2%, respectively, also similar to that in the GISSI trial (7% mortality in both groups in the interval from 3 weeks to 1 year). The observed 5-week vascular mortality rate in the streptokinase and placebo groups was, respectively, 8.2% and 12.1% (32%) reduction in those treated within 4 hours, 10.3% and 11.8% (13% reduction) in those treated between 4 and 12 hours, and 8.7% and 10.8% (19% reduction) in those treated between 12 and 24 hours. In patients treated within 1 hour, the 5 week vascular mortality rate was reduced by 42% in the streptokinase group (similar to the 3-week reduction of 47% in the GISSI trial). Thus, the overall ISIS-2 findings confirm the GISSI results. Earlier treatment appears more effective than late treatment, with substantial benefit to at least 6 hours.

### Table 1. Selected Controlled Trials of Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Short-term mortality</th>
<th>Follow-up interval (days)</th>
<th>% Reduction</th>
<th>% Reduction in subgroups by time to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GISSI (SK)</td>
<td>11,712</td>
<td>10.7</td>
<td>13.0</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-6 hours — 17</td>
</tr>
<tr>
<td>ISIS-2 (SK +/- aspirin)</td>
<td>17,187</td>
<td>9.1</td>
<td>11.8</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-12 hours — 32</td>
</tr>
<tr>
<td>ASSET (rt-PA)</td>
<td>5,011</td>
<td>7.2</td>
<td>9.8</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Eur Coop (rt-PA + aspirin)</td>
<td>721</td>
<td>2.8</td>
<td>5.7</td>
<td>14</td>
<td>51*</td>
</tr>
<tr>
<td>AIMS (APSAC)</td>
<td>1,004</td>
<td>6.4</td>
<td>12.2</td>
<td>30</td>
<td>47</td>
</tr>
</tbody>
</table>

*p = 0.06—secondary end point. †Preliminary report. These trials of thrombolytic therapy are presented to show differences in entry criteria as reflected in control-related mortality rate. This table should not be used to compare treatment-related mortality rates among trials. AIMS, APSAC Intervention Mortality Study; APSAC, anisoylated plasminogen streptokinase activator; ASSET, Anglo-Scandinavian Study of Early Thrombolysis; Eur Coop, European Cooperative Study; GISSI, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; ISIS-2, Second International Study of Infarct Survival; rt-PA, recombinant tissue-type plasminogen activator; SK, streptokinase; +/-, with or without.
The ISIS-2 entry criteria did not require ST segment elevation. Review of ISIS-2 entry ECGs revealed that only 56% of the 17,187 patients had ST segment elevation. The remainder had ST depression (8%), bundle branch block (6%), Q waves or T wave inversions (22%), or both, or had a normal study (2%).

ISIS-2 tested 160 mg of aspirin daily for 35 days as an adjunct to thrombolytic therapy. The first dose was given immediately after trial entry. In the 8,587 patients assigned to receive aspirin, there were 800 (9.3%) vascular deaths by 5 weeks compared with 1,002 such deaths (11.7%) in the 8,600 given placebo; this 21% reduction ($p<0.00001$) is similar in magnitude to the result with streptokinase. The vascular mortality rate between 5 weeks and 1 year was similar (6.0% and 5.8% in the aspirin and the placebo group, respectively). Finally, a comparison of the group assigned to receive both streptokinase and aspirin with the group assigned to neither revealed a 5-week vascular mortality rate of 7.9% (341 of 4,292 patients) and 13.0% (557 of 4,300 patients), a 39% reduction ($p<0.00001$). In addition to confirmation of the GISSI findings with respect to streptokinase, ISIS-2 provides very strong evidence for a similar and additive effect of aspirin on subsequent mortality in patients with infarction.

**Short-term mortality.** Mortality data from the GISSI and ISIS-2 studies, with similar smaller supporting trials carried out in The Netherlands, Federal Republic of Germany, New Zealand, and Washington (state) and the ISIS-2 pilot study, provide conclusive evidence that intravenous streptokinase given early in the course of myocardial infarction to patients without contraindications reduces the short-term mortality rate by 20% to 30%. The smaller supporting trials, in which left ventricular function and infarct size were assessed, reveal myocardial salvage as assessed by these two indirect measures of infarct size, supporting the hypothesis that the major mechanism of action of streptokinase is limitation of infarct size by reperfusion. Intravenous streptokinase was approved by the Food and Drug Administration for use in patients with myocardial infarction in 1987.

**New thrombolytic agents. European Cooperative Study and TIMI.** A new generation of thrombolytic agents that activate plasminogen preferentially on the surface of clot rather than in the general circulation (as is the case with streptokinase) has been employed in clinical trials during the last 5 years. One of these agents, recombinant tissue-type plasminogen activator (rt-PA), was approved by the Food and Drug Administration in 1987 for use in patients with acute myocardial infarction. Two other agents, anisoylated plasminogen streptokinase activator complex (APSAC [Anistreplase]) and single chain urokinase-type plasminogen activator (SCUPA), are under active investigation. The former has just been approved by the Food and Drug Administration, but SCUPA has not as yet been approved for general use in the United States.

In two independent randomized trials, the patency or reperfusion rate, or both, after intravenous rt-PA were compared with those with intravenous streptokinase. In the European cooperative Study, 129 patients were given either rt-PA or streptokinase intravenously an average of 3 hours after the onset of myocardial infarction. Patency of the infarct-related artery observed approximately 90 minutes after initiation of infusion was 70% and 55% for the rt-PA and the streptokinase groups, respectively ($p=0.058$). The investigators in the National Heart, Lung, and Blood Institute Thrombolysis in Myocardial Infarction (TIMI) study used a slightly higher dose of rt-PA and encountered a longer delay in starting thrombolytic infusion because of required pretreatment arteriography. They noted a patency rate of 70% and 43%, respectively, 90 minutes after onset of rt-PA and streptokinase infusion in 290 patients treated an average of 4.75 hours after pain onset. Thus, the patency rates noted by the two groups of investigators were identical for rt-PA (70%) and varied minimally (55% in the European Cooperative Study and 43% in the TIMI trial) in the streptokinase groups.

The declared TIMI study end point was, however, the proportion of patients entering with closed coronary arteries who experienced reperfusion 90 minutes after initiation of thrombolytic infusion. In 232 TIMI patients with a closed infarct-related artery, the 90-minute reperfusion rate was 62% and 31% for rt-PA and streptokinase, respectively. In addition, as noted in both the European and TIMI studies, perturbation of elements of the clotting system was less marked with rt-PA, although hemorrhagic complications were similar in the streptokinase and rt-PA groups and largely due to hematoma formation at the arterial catheterization site.

**Studies after changed formulation of rt-PA.** Shortly after completion of the European and TIMI comparisons of rt-PA and streptokinase, the rt-PA production process was changed. The new product, predominantly single-chained, had pharmacokinetic properties that made 100 mg of the new product roughly equivalent to 80 mg of the product used in the TIMI study. The rt-PA studies discussed next used the more recent formulation, which is the rt-PA preparation approved for use by the Food and Drug Administration.

Investigators participating in the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) randomized 5,011 patients with suspected myocardial infarction within 5 hours of onset to either 100 mg of rt-PA (10 mg bolus injection, 50 mg in the first hour, 20 mg in the second and third hours) or placebo. Aspirin was not given. The ASSET investigators made no ECG entry criteria, but excluded patients >75 years of age. Approximately 18% of ASSET patients had a normal ECG at trial entry. At 1 month, the total mortality rate in the rt-PA–assigned group was 7.2% compared with 9.8% in those assigned placebo, a 26% reduction ($p=0.0011$).
The European Cooperative Group reported a randomized, double-blind, controlled trial comparing rt-PA (100 mg given over 3 hours) with placebo in 721 patients with chest pain and ST segment elevation entered within 5 hours of symptom onset. Both groups received aspirin and heparin. The study was designed to detect a difference in left ventricular function. Death at 14 days and death at 3 months were declared as secondary end points. The 14-day mortality rate was 2.8% (10 of 355) in the group assigned to rt-PA and 5.7% (21 of 366) in the placebo group. This observed 51% mortality reduction is of borderline statistical significance (p=0.06). Thus, the European collaborative group noted a substantial reduction in the 14-day mortality rate, but this was of borderline statistical significance in a trial not designed to test a mortality difference. Ejection fraction, the declared primary end point, was 2.2 ejection fraction points higher (95% confidence interval, 0.3 to 4.0) in the rt-PA group compared with the placebo group (30.7 versus 48.5, respectively). Infarct size as assessed by cumulative release of hydroxybutyrate dehydrogenase was reduced by 20% in the rt-PA group compared with the placebo group (p=0.0018).

Neither of these two trials designed to compare patency or reperfusion of streptokinase and rt-PA was sufficiently large to detect a statistically significant mortality difference. Thus, these trials that have directly compared rt-PA and streptokinase demonstrated that at 90 minutes and with the doses given, rt-PA is a more effective coronary thrombolytic agent with less consumption of clotting factors. The recent comparison of streptokinase and rt-PA reported from New Zealand was designed to test the effect of the two agents on ventricular function. The study was a double-blind trial comparing the effect of rt-PA with streptokinase on subsequent (3 week) ventricular function in 270 patients admitted within 3 hours of their first myocardial infarction. A similar ejection fraction was noted (0.58 in both rt-PA– and streptokinase-assigned groups), but mean ejection fraction was not adjusted for patients with an undetermined ejection fraction (such as patients who died before the scheduled ejection fraction determination). The mortality rate at 30 days was 3.7% in the rt-PA group and 7.4% in the streptokinase group (p>0.2). Although there were fewer deaths in the rt-PA group than in the streptokinase group, the trial was too small to draw conclusions about mortality.

The mechanism of mortality reduction with both rt-PA and streptokinase is likely to be thrombolysis with resultant reperfusion, limitation of infarct size, and improved left ventricular remodeling. Accordingly, one might anticipate myocardial salvage and mortality reduction with rt-PA similar to and perhaps larger than that observed with streptokinase, given the observed reperfusion advantage observed with rt-PA. There are currently two large randomized trials involving a direct comparison of streptokinase and rt-PA using death as an end point. GISSI-2 is nearing completion and will probably report data in 1990, while ISIS-3 is early in patient recruitment. Until these large trials are completed, clinicians must shoulder the burden of choosing between streptokinase and rt-PA without conclusive comparative data on relative morbidity and mortality, bearing in mind the substantial cost and reperfusion differential.

The AIMS Trial Study Group. This group, in the United Kingdom, conducted a multicenter, double-blind, placebo-controlled evaluation of APSAC (30 units intravenously over 5 minutes) in patients <70 years of age admitted with ≥30 minutes but not >6 hours of chest pain associated with ST segment elevation. A data monitoring committee recommended early termination of the trial during its second interim data analysis after 50% of the anticipated sample size had been entered. A preliminary report on 1,004 patients revealed a 30-day mortality rate of 12.2% (61 of 502 deaths) in the placebo group and 6.4% (32 of 502 deaths) in patients assigned to APSAC (p=0.0016). The overall mortality reduction was 47%, with the patients entered between 4 and 6 hours having nominally larger reduction than those entered at <4 hours (52% versus 41%, respectively). The overall benefit of therapy appears to persist and perhaps increase between the 30-day and 1-year follow-up evaluations. The estimated 1-year mortality is 19.4% and 10.8% in the placebo and APSAC groups, respectively, a 44% reduction (p=0.0006). At this time, APSAC is a promising thrombolytic drug and it joins streptokinase and rt-PA as a useful therapeutic alternative. Again, direct comparisons between rt-PA and APSAC have not been made, but recently reported trials comparing streptokinase and APSAC show them to be of equal efficacy, with APSAC showing a trend to higher early patency and having an advantage in ease of administration.

Thrombolytic therapy and infarct site. The two largest trials, GISSI and ISIS-2, as well as many of the small trials, have evaluated the efficacy of thrombolytic therapy relative to the location of infarction. This is important because it is nearly always possible to predict the location of infarction as being anterior, lateral, inferior, or overlapping these areas based on the location of ST segment elevation on the initial ECG. It is much more difficult to distinguish the presence of true posterior Q wave infarction in patients presenting with anterior ST segment depression, but this location of infarction is infrequent. It is now established by GISSI and other trials that anterior infarction has the highest mortality rate and benefits most from thrombolytic therapy; the efficacy of therapy in patients with inferior infarction is less clear. Patients with inferior infarction did not have a significant reduction in the mortality rate in the GISSI trial, but did benefit from streptokinase and aspirin therapy in ISIS-2. Likewise, patients with prior infarction did not benefit in the GISSI trial, but did benefit in ISIS-2. A recent publication from GISSI has demonstrated that the size of the infarct as judged by the number of ECG leads with ST elevation rather
than location alone is predictive of benefit from streptokinase therapy. Many clinicians believe that thrombolytic therapy is indicated in patients who are hypotensive or are in cardiogenic shock, especially those who have an evolving inferior infarction with associated right ventricular ischemic dysfunction or infarction, or both. The efficacy of thrombolytic therapy in these patients is not as yet established.

**Contraindications to Thrombolytic Therapy**

The major side effect of all thrombolytic agents is hemorrhage. The contraindications to thrombolytic therapy include:

**Absolute Contraindications**

1. Active internal bleeding.
2. Suspected aortic dissection.
3. Prolonged or traumatic cardiopulmonary resuscitation.
4. Recent head trauma or known intracranial neoplasm.
5. Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic condition.
7. Previous allergic reaction to the thrombolytic agent (streptokinase or APSAC).
8. Recorded blood pressure >200/120 mm Hg.
9. History of cerebrovascular accident known to be hemorrhagic.

**Relative Contraindications***

1. Recent trauma or surgery >2 weeks; trauma or surgery more recent than 2 weeks which could be a source of rebleeding, is an absolute contraindication.
2. History of chronic severe hypertension with or without drug therapy.
3. Active peptic ulcer.
4. History of cerebrovascular accident.
5. Known bleeding diathesis or current use of anticoagulants.
6. Significant liver dysfunction.
7. Prior exposure to streptokinase or APSAC (this contraindication is particularly important in the initial 6- to 9-month period after streptokinase or APSAC administration and applies to reuse of any streptokinase-containing agent, but does not apply to rt-PA or urokinase).

**Hemorrhagic complications.** The major nonreversible complication of thrombolytic therapy is intracranial hemorrhage. With currently used doses of streptokinase (1.5 million units over 1 hour), the risk of intracranial hemorrhage has been reported as 1–10/1,000 patients treated. In addition, gastrointestinal hemorrhage of varying severity can be expected in 5% and genitourinary bleeding in a similar number. However, most hemorrhagic complications in clinical trials have occurred at the site of vascular invasion. Venous and arterial puncture should be kept to an absolute minimum in patients treated with thrombolytic agents and should be cared for meticulously thereafter.

Intracranial hemorrhage after rt-PA may be dose-related. Estimated event rates with 150 mg are on the order of 15–20/1,000 and with a dose of 100 mg, the rate is 5–10/1,000.109 Intracranial hemorrhage after APSAC has not been well defined.

**Thrombolytic Therapy in Older Patients**

Mortality and case fatality rates with myocardial infarction increase steeply with age. In fact, nearly 50% of all deaths in patients hospitalized for acute infarction occur in those >75 years of age.110 Trials of thrombolytic therapy, with the exception of ISIS-2 and GISSI (which had no age exclusion), have excluded patients >70 years of age (AIMS) or >75 years (ASSET, European Cooperative Study) largely because of a fear of hemorrhagic complications. The ISIS-2 reported a 16% reduction in the 5-week vascular mortality rate (18.2% versus 21.6%) in the streptokinase group >70 years of age at entry, a 26% reduction (10.6% versus 14.4%) in the streptokinase group in those 60 to 69 years and a 28% reduction (4.2% versus 5.8%) in the streptokinase group in <60 years.

The GISSI trial noted a 13% reduction in mortality at 3 weeks in those >75 years, an 8% reduction in those 65 to 75 years, and a 26% reduction in those ≤65 years. The reduction in mortality did not reach statistical significance in the two older categories. Risk of bleeding complications was not tabulated by age in the ISIS-2 or GISSI reports. Given the attenuation of streptokinase effect with increasing age reported in the ISIS-2 and GISSI trials and the paucity of data on use of rt-PA and APSAC in the elderly patient, the administration of thrombolytic therapy to older patients should be judicious with careful screening for potential bleeding risk.

**Recommendations for Administration of Thrombolytic Therapy to Patients With Myocardial Infarction**

**Patients Without Contraindications to Thrombolytic Therapy**

**Class I**

1. Patients <70 years of age who present with chest pain consistent with the diagnosis of acute myocardial infarction and at least 0.1 mV of ST segment elevation in at least two contiguous ECG leads in whom treatment can be initiated within 6 hours of pain onset.

**Class IIa**

1. Patients between ages 70 and 75 years who present with chest pain consistent with the diagnosis

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*These should be considered on a case by case analysis of risk versus benefit. In instances where these contraindications (particularly 1 to 5) have paramount importance, such as more recent trauma or surgery or active peptic ulcer with history of bleeding, they become absolute contraindications when weighed against a less than life-threatening, evolving acute myocardial infarction.
of acute myocardial infarction and at least 0.1 mV of ST segment elevation in at least two contiguous ECG leads in whom treatment can be initiated within 6 hours of pain onset.

2. Patients with acute myocardial infarction >6 hours after symptom onset but with a “stuttering” pattern of pain.

3. Patients who suffer clinically apparent reinfarction in the days after administration of thrombolytic therapy.

Class IIb

1. Patients who present with chest pain consistent with the diagnosis of acute myocardial infarction and at least 0.1 mV of ST segment elevation in at least two contiguous ECG leads in whom treatment can be initiated between 6 and 24 hours after pain onset.

2. Patients >75 years of age who present with chest pain consistent with the diagnosis of acute myocardial infarction and at least 0.1 mV of ST segment elevation in at least two contiguous ECG leads in whom treatment can be initiated within 6 hours of pain onset where the impending infarction is extensive.

3. Patients who present with chest pain consistent with the diagnosis of acute myocardial infarction with ECG changes less profound than 0.1 mV of ST segment elevation in two contiguous leads who can be treated within 24 hours.

Class III

Patients who have had chest pain when:

1. Treatment cannot be initiated within 24 hours of onset of chest pain and pain has not recurred.

2. Chest pain onset is unknown and has receded.

3. The cause of the chest pain is unclear.

Follow-up Therapy After Thrombolysis

Very few data are available regarding management after thrombolytic therapy. Information regarding the effects of various therapeutic agents often used during the acute stage of myocardial infarction (such as β-blockers, nitroglycerin, and calcium channel blockers) is based on findings from randomized clinical trials that were carried out in patient cohorts that did not receive thrombolytic therapy. The question arises whether one can assume that if an agent was beneficial in clinical trials of myocardial infarction in the absence of reperfusion, it would be similarly beneficial in patients who have received thrombolytic treatment. There are theoretic reasons for believing that this may not be the case. For example, randomized clinical trials of β-blockers given to patients in the early hours of a myocardial infarction suggest that early mortality rates may be reduced. In contrast, randomized clinical trials comparing calcium channel blockers with placebo in cases with ST segment elevation and transmural infarction have shown no benefit. However, one could postulate that the opposite might be true in the patient who has had successful reperfusion. Recanalization may enhance vasomotor activity in the infarct-related artery consequent to the liberation of vasoactive substances from platelet aggregation. Under these circumstances, a calcium channel blocker such as nifedipine that inhibits coronary vasospasm might be preferable to a β-adrenergic receptor blocking drug, which theoretically might result in enhanced coronary vasospasm, reflecting unopposed α-adrenergic activity. This is purely speculative, but serves to emphasize that only a small amount of randomized clinical trial data after reperfusion are currently available.

β-Blocker Therapy

The TIMI-2 trial examined management alternatives in patients after thrombolytic therapy. One arm of that trial dealt with the specific question as to the effect of β-blockers after thrombolysis. Patients were randomized to receive a β-blocker immediately or at the end of the first week of hospitalization. Left ventricular ejection fraction was the end point. No statistically significant difference was demonstrated in the group randomized to immediate intervention with a β-blocker compared with those in whom oral administration was begun at approximately 1 week; however, it was noted that if β-blockers were given within the first 4 hours after hospitalization, a significant improvement in the rate of nonfatal reinfarction and recurrent ischemia was observed. For patients with infusions started within 2 hours of symptom onset, death or recurrent myocardial infarction occurred significantly less frequently in those treated with intravenous β-blockade. It thus seems reasonable to use β-blockers as one might in the patient who has not undergone thrombolysis (that is, in patients who demonstrate increased adrenergic activity manifested by tachycardia or hypertension in whom β-blockers are not otherwise contraindicated). Additionally, patients demonstrating continuing ischemia characterized by recurrent chest pain after thrombolytic therapy presumably will benefit from administration of a β-blocker; however, these patients are also candidates for immediate study in the cardiac catheterization laboratory with a view toward the performance of angioplasty or bypass graft surgery. Finally, if the patient develops atrial fibrillation with a fast ventricular response or develops reflex tachycardia from the use of other agents such as calcium channel blockers or nitrates after thrombolytic therapy, a β-blocker may prove highly useful in slowing heart rate.

Intravenous Nitroglycerin

This is a highly effective agent in the patient who has not received thrombolytic therapy, and after thrombolysis it appears to have the same rationale for its use. The coronary vasodilating effects of nitrates and their preload-reducing effects appear to justify their routine use during the first day or two after thrombolytic therapy.
Calcium Channel Blockers

Reocclusion after recanalization is a serious limitation to the benefits of thrombolysis. Spasm has been proposed as playing a role in promoting recurrent occlusion after reperfusion. Hyperreactivity of the coronary vessels exists, as noted earlier, and the particular effectiveness of calcium channel blockers in combating spasm is well documented. A similar experience has been observed in patients after angioplasty. Therefore, although spasm has not been proved as causative in early reocclusion, calcium channel blockade has been suggested. Any of the calcium channel blockers would seem suitable under these circumstances, although the widest experience has been gained with the use of nifedipine, which is the agent that produces the greatest increase in sympathetic tone, and may have to be combined with a β-blocker to offset the reflex tachycardia. Their use appears reasonable in patients with preserved left ventricular function and coronary artery spasm not responsive to the usual dose of nitrates.

Heparin and Aspirin

One major effort directed to the prevention of rethrombosis is the administration of intravenous heparin. Some physicians begin heparin concomitant with the start of the administration of rt-PA, whereas others give heparin after completion of the rt-PA infusion or after the usual 30-minute to 1-hour infusion of streptokinase. Heparin is normally started in a dose of 600 to 800 IU/hr, often preceded by a bolus injection of 5,000 IU, with the dosage subsequently adjusted to maintain the active partial thromboplastin time between 1.5 and 2 times control values.

It is generally accepted that the usual pathophysiological basis of acute coronary occlusion leading to acute myocardial infarction is plaque rupture with subsequent thrombus formation. Successful fibrinolysis restores patency of the lumen, but the underlying vascular injury and residual thrombus persist and have active surfaces. For this reason, it is advisable that patients receive both heparin and aspirin. It must be appreciated that the combination of heparin and aspirin may increase the likelihood of a bleeding complication. Low dose aspirin may prove to be effective and the ISIS-2 data indicate the daily dose to be 160 mg. Over the next several days if the patient has an uncomplicated course, heparin can be discontinued, although aspirin should be continued indefinitely. An alternative strategy in those who cannot take aspirin is to switch to coumadin before hospital discharge with the view toward long-term oral anticoagulant therapy.

Recommendations for Follow-up Therapy After Thrombolysis

Class I

1. Intravenous infusion of heparin over several days begun with or after thrombolytic therapy.
2. A 160 mg aspirin tablet daily, beginning immediately.
3. Intravenous or topical nitroglycerin for 24 to 48 hours.
4. Early intravenous β-blocker, followed by oral administration if patient is hypertensive, demonstrates reflex tachycardia, has atrial fibrillation with rapid ventricular response or develops post-infarction angina, provided usual contraindications to β-blocker therapy are not present.
5. Early coronary arteriography if the patient develops evidence of recurrent myocardial infarction.

Class IIa

1. Early routine intravenous β-blocker in patients without contraindications.
2. Calcium channel blocker while hospitalized to protect against episodic coronary vasospasm, except in patients with pulmonary congestion or left ventricular dysfunction.

Anticoagulants and Platelet Inhibitory Agents

The goals of antithrombotic therapy during and early after acute myocardial infarction include 1) prevention of deep venous thrombosis and pulmonary embolism, 2) prevention of arterial embolization, 3) reduction of early recurrence or extension of myocardial infarction and death, 4) reduction of early reocclusion and death after successful reperfusion with thrombolytic therapy, and 5) secondary prevention of late recurrence of myocardial infarction and death.

Prevention of Deep Venous Thrombosis and Pulmonary Embolism

Introduction. As assessed by indium-125-labeled fibrinogen, the incidence of deep venous thrombosis in the lower limbs of patients with acute myocardial infarction ranges from 17% to 38%, which is similar to the incidence in patients after operation. These observations and the increased risk of recurrent myocardial infarction within 3 months of a previous infarction in patients undergoing noncardiac surgery may indicate a hypercoagulable state early after acute myocardial infarction similar to that after major surgery. Deep venous thrombi form early after the myocardial infarction (≤50% within 3 days), with an incidence that is increased after massive or recurrent infarction with heart failure or cardiogenic shock, prolonged immobilization, and certain characteristics, especially age >70 years.

Low dose heparin started within 12 to 18 hours of the onset of symptoms of acute myocardial infarction and continued for 10 days has successfully reduced the incidence of venous thrombosis in three randomized trials from a mean of 23% in 145 control patients to 4% in 138 treated patients. This significant benefit is particularly apparent in high risk subgroups that can be identified within the first 24 to 48 hours. One small trial of low dose heparin after myocardial infarction showed no benefit, but the time of initiation of therapy in relation to the onset of symptoms was unclear.
Current Recommendations

Class I

1. Immediate subcutaneous heparin (5,000 units every 12 hours) for the first 24 to 48 hours unless full dose anticoagulant therapy has been initiated in association with thrombolytic therapy or for prevention of systemic emboli (vide infra).

2. Continued low dose subcutaneous heparin in high risk patients (age >70 years, large acute myocardial infarction, previous myocardial infarction, heart failure or shock, necessity for immobilization for >3 days, prior deep venous thrombosis or pulmonary emboli, obesity, or evidence of chronic venous insufficiency) until fully ambulatory.

Prevention of Arterial Embolism

Introduction. The overall incidence of mural thrombus is approximately 20% in acute myocardial infarction, approximately 40% in anterior myocardial infarction, and approximately 60% in large anterior myocardial infarction. However, the incidence of clinically apparent systemic embolism is only about 2%, 4%, and 6%, respectively.

Based on three large prospective studies, the incidence of left ventricular mural thrombus at postmortem examination in patients who died after acute myocardial infarction was 40% to 50% in patients not treated with anticoagulants versus 22% to 24% in those treated with anticoagulants. For the prevention of mural thrombus over a short period of 10 days, high dose subcutaneous heparin (12,500 units every 12 hours) has recently been found to be of significant benefit when compared with low dose subcutaneous heparin (5,000 units every 12 hours). The overall incidence of nonhemorrhagic stroke in this early period was <1% in those initially treated with high dose heparin and 4% in the low dose group. Because of insufficient sample size and low event rates, this difference did not reach statistical significance. Patients treated with heparin and followed up for up to 1 month with administration of oral anticoagulants at relatively low doses had a reduction in the incidence of cerebral embolism from about 3% to 1% when compared with no anticoagulant therapy. Anticoagulant therapy has been effective if given on admission to the hospital; delay until a mural thrombus is demonstrated echocardiographically may miss the time in which therapy can be most valuable. Most systemic emboli occur within the first 2 to 3 months and particularly within the first 10 days. Accordingly, a strategy of administering heparin, subcutaneously or intravenously, in a dosage sufficient to prolong the activated partial thromboplastin time to 1.5 to 2.0 times the control value is advocated for patients with a large anteroapical infarction, beginning immediately after the onset of infarction and continued for a period of about 10 days. In some patients (for example, those with ventricular mural thrombus or large akinetic regions identified by ECG), it is appropriate to continue with oral anticoagulants for approximately 3 months. Warfarin should be used in dose sufficient to prolong prothrombin time, using rabbit brain thromboplastin to an internationally normalized ratio (INR) of 2.0 to 3.0, or 1.3 to 1.5 times control. The INR is defined as the prothrombin time ratio result that would be obtained if the World Health Organization primary international reference thromboplastin (IRP) was used to test the plasma sample.

In patients with chronic left ventricular aneurysm but preserved wall motion outside the zone of infarction, the embolic risk appears considerably lower after 3 months and routine long-term anticoagulation beyond 3 months may not be justified. Conversely, in those patients with chronic diffuse left ventricular dysfunction, continued oral anticoagulant therapy beyond 3 months may be justified.

Current Recommendations

Class I

1. Immediate high dose subcutaneous or intravenous heparin in a dosage sufficient to prolong the activated partial thromboplastin time to 1.5 to 2.0 times control in patients with a large anterior transmural myocardial infarction. Heparin should be continued until discharge.

2. Oral anticoagulants administered at a dose sufficient to prolong the prothrombin time to 1.3 to 1.5 times the control value (INR=2.0 to 3.0) after heparin in patients who have a ventricular mural thrombus or a large akinetic region of the apex of the left ventricle. Anticoagulant therapy should be continued for at least 3 months.

Class IIa

1. Long-term (indefinite) oral anticoagulant therapy in patients with a diffusely dilated and poorly contracting left ventricle. (Prolong prothrombin time to 1.3 to 1.5 times the control value, or INR=2.0 to 3.0.)

Class IIb

1. In patients with anterior myocardial infarction requiring anticoagulation up to 3 months for the prevention of systemic emboli, low-dose aspirin (80 to 160 mg/day) to prevent coronary events may be added to the anticoagulants and then continued alone indefinitely.

Reduction of Early Recurrence or Extension of Myocardial Infarction and Mortality in Patients Not Receiving Thrombolytic Therapy

Introduction. Extension or recurrence of myocardial infarction ranges from 14% to 30% as recognized by a secondary increase in MB CK and is comparable with the incidence of 17% found at necropsy. Recurrence during hospitalization is more common in patients with a smaller infarct (lower plasma
enzyme levels). More than half of the early recurrences occur within 10 days and the remainder occur within 14 to 18 days after the initial infarction. In >85% of patients studied, the ECG site of early recurrent infarction has been the same as the initial site. Thus, early recurrence and extension of infarction are nearly synonymous. There is evidence of frequent spontaneous reperfusion after myocardial infarction and a known incidence of reocclusion after reperfusion, particularly in patients with high-grade residual lesions. The reason for reocclusion may be related to the association of high-grade residual stenosis or residual thrombus providing a very thrombogenic surface, or both.

**Anticoagulant and antiplatelet therapy.** During and early after hospitalization, can the early recurrence and extension of infarction be prevented by short-term anticoagulant therapy? In the late 1960s and early 1970s, three randomized, controlled, prospective studies using heparin followed by low dose anticoagulant therapy (with the equivalent of an INR=2.0 to 3.0), for up to 1 month were significant enough to assess its value. In regard to mortality and reinfarction rates in these three studies, there was only a trend to beneficial results in the patients who had undergone anticoagulant therapy. Chalmers et al analyzed all of the reported, adequately designed, randomized trials of oral anticoagulants in acute infarction and found, when case fatality ratios were pooled, the small differences in mortality rate in each study became significant by simple chi-square analysis: the overall reduction in mortality rate was 21%; the reduction in the incidence of reinfarction was about 30%. It was suggested that all patients without specific contraindications be given anticoagulants during hospitalization for myocardial infarction.

The role of platelet inhibitors in the reduction of the early mortality rate and recurrence (extension) of myocardial infarction was confirmed by the recently reported ISIS-2 study. The 5-week vascular mortality (mostly cardiac mortality) rate was reduced by 23% with aspirin alone and was reduced a further 19% when aspirin and streptokinase were both given. Furthermore, aspirin alone reduced the incidence of early recurrence of nonfatal reinfarction by 49%. Thus, irrespective of whether or not thrombolytic therapy is employed, the use of aspirin during the acute phase of myocardial infarction appears to be justified.

**Current Recommendations**

**Class I**

1. Short-term aspirin begun immediately and continued for at least 1 month at a dose of 160 mg/day. After 1 month, aspirin should be continued at a dose of 160 to 325 mg/day.

**Class IIa**

1. Heparin followed by oral anticoagulant therapy for at least 1 month after infarction (prolong prothrombin time to 1.3 to 1.5 times control value).

**Reduction in Early Reocclusion and Mortality After Successful Reperfusion With Thrombolytic Therapy**

**Introduction.** After thrombolysis, significant residual thrombus contributes to the stenosis visualized at angiography, and such a thrombotic surface also contributes to more thrombogenicity and reocclusion. Recently, reocclusion after thrombolysis has been reported in 5% to 15% of patients, rates that are lower than reported in previous years, probably because of more aggressive postlysis antithrombotic approaches.

The TIMI-I investigators observed that after thrombolysis, reocclusion occurred despite continued heparin infusion (activated partial thromboplastin time 1.5 to 2.0 times control value) for 7 to 10 days. Reocclusion was not concentrated within the first few days, but rather occurred throughout the hospitalization. However, in the recent study from Johns Hopkins University, no reocclusion during hospitalization occurred when therapy with heparin (activated partial thromboplastin time 2.0 to 3.0 times control value) plus aspirin (325 mg/day) and calcium channel blockade were used. Thus, the role of heparin in adequate dosage plus aspirin appears important for the reduction of reocclusion after thrombolysis.

**Current Recommendations**

**Class I**

1. Aspirin (160 mg/day) should be started as soon as the patient is admitted and given daily until discharge from the hospital, at which time it can be continued at a dose of 160 to 325 mg daily.

2. Heparin should be administered together with or immediately after thrombolysis to maintain the activated partial thromboplastin time approximately 1.5 to 2.0 times the control value for 24 to 72 hours.

**Secondary Prevention of Late Recurrence of Myocardial Infarction and Death**

**Introduction.** Ten large trials using platelet inhibitor drugs in postmyocardial infarction patients, mostly within the first 2 years, have been conducted. They involved large numbers of patients and were randomized, double blind, and placebo controlled. In eight of these trials, aspirin (at a dose of 300 to 1,500 mg/day) was used alone or combined with dipyridamole. The pooled analysis suggests a significant reduction in the mortality and reinfarction rates (15% and 31%, respectively) in the aspirin group. In patients with unstable angina, the beneficial effect of aspirin in reducing cardiac events continues for the subsequent 2 years, even after the patient becomes stable. Finally, in patients with non-Q wave infarction, long-term treatment with aspirin plus dipyridamole produced a 53% reduction in coronary events. In regard to the use of long-term oral anticoagulants after infarction, an International Anticoagulant Review Group attempted to overcome the problem of inadequate numbers by pooling data from nine controlled trials. Using the pooled data, the
review group concluded that death after myocardial infarction was reduced by 20% by use of long-term anticoagulants and that the reinfarction rate was reduced by >30%.126

**Long-term Anticoagulant Therapy.** In 1980, the Sixty Plus Reinfarction Study127 from the Netherlands revived the issue of the value of long-term anticoagulant therapy, this time >6 months after myocardial infarction. In six centers, ambulant patients >60 years of age were studied; all patients were receiving anticoagulant therapy for ≥6 months after documented myocardial infarction; the average follow-up period was 6 years. Eligible patients were randomized to continue on anticoagulant therapy or discontinue the anticoagulant and substitute a placebo. There was a dramatic 55% reduction in the incidence of fatal and nonfatal recurrent myocardial infarction in the group that received an anticoagulant. The greater benefit of anticoagulants in this trial might be related to the better control of the anticoagulant therapy and the relative stability of the group of patients studied 6 years after infarction. Moreover, in contrast to the first 1 to 2 years after infarction, recurrent thrombotic events rather than myocardial factors dictate the long-term prognosis (high specificity for antithrombotic therapy). Despite the impressive results reported in this study,127 it is unlikely that clinicians will be enthusiastic about routine use of long-term oral anticoagulation after myocardial infarction, simply because the risk of hemorrhage is much higher with anticoagulants than with aspirin, which may be of similar benefit.128

**Current Recommendations**

**Class I**

1. Aspirin (160 to 325 mg daily) if not associated with significant side effects.

**Class IIa**

1. Oral anticoagulant therapy with warfarin (prothrombin time 1.3 to 1.5 times the control value or INR = 2.0 to 3.0) rather than aspirin for long-term prevention of recurrence of myocardial infarction.

**Summary**

Anticoagulation therapy using subcutaneous low dose heparin is recommended for all patients with acute myocardial infarction not receiving thrombolytic therapy. This is begun on admission and discontinued at 48 hours unless the patient is not a candidate for or capable of early ambulation. Those patients with a large anterior infarction, particularly involving the apex of the left ventricle, should be given full dose heparin and switched to an oral anticoagulant (warfarin) when need for invasive evaluation or therapy is no longer contemplated. Oral anticoagulants should be continued for 3 months.

To prevent reocclusion after thrombolysis and for prevention of early and late reinfarction, long-term aspirin therapy should be given as a platelet inhibitor to all patients who can tolerate it. However, in the subgroup of patients with a large anterior myocardial infarction, warfarin may be needed for the prevention of systemic emboli and has benefit for the prevention of early and late reinfarction. Thus, in this subgroup of patients, it may be reasonable to postpone the use of aspirin until anticoagulants are discontinued once the risk of emboli has ceased.

**Percutaneous Transluminal Coronary Angioplasty**

**Introduction**

The guidelines for the use of percutaneous transluminal coronary angioplasty have been previously published in an ACC/AHA Task Force Report.129 That report outlines the immediate and long-term effects of elective angioplasty, its risks and contraindications, the selection of patients, and current indications for its use. The present report will elaborate on the indications for angioplasty in patients with acute infarction. The use of angioplasty alone in evolving acute myocardial infarction will be considered separately from the use of angioplasty as an adjunct to thrombolytic therapy.

**Primary Coronary Angioplasty**

Along with the increasing interest in thrombolysis for the treatment of acute myocardial infarction, there has been interest in mechanical reperfusion by coronary angioplasty. There have been a number of reports130–135 describing the use of angioplasty alone in the treatment of acute myocardial infarction. These have all been relatively small series and only one134 has been randomized in comparison with an alternative therapy (streptokinase). These studies have generally reported a beneficial effect on left ventricular function, but there has been no good large-scale randomized study comparing this form of treatment with either conventional supportive therapy or the most effective forms of thrombolytic therapy given early during acute infarction.

Percutaneous transluminal coronary angioplasty as the primary treatment strategy suffers from the need to have facilities and personnel for cardiac catheterization and a physician qualified to perform angioplasty available at all times. Because of this, intravenous thrombolysis has become established as the first line of therapy in acute myocardial infarction in suitable patients.

With this background, angioplasty should be considered as primary therapy in acute myocardial infarction only when facilities are available for expeditious transfer to a cardiac catheterization laboratory and where the personnel have the technical expertise and experience in performing angioplasty in this acute situation. Primary coronary angioplasty may appropriately be considered when a hospitalized patient has acute myocardial infarction, a patient presents within 4 hours after onset of symptoms to an
Institution where adequate facilities and personnel are available, or when thrombolytic therapy is contraindicated. Patients presenting in cardiogenic shock are a special group that may benefit from emergency angioplasty (vide infra).

Although intracoronary thrombolytic therapy is not usually as practical as primary therapy, the use of adjunctive intracoronary thrombolytic therapy during or after an angioplasty procedure may be appropriate when there is evidence of residual thrombus in the artery. In this situation, a smaller dose can be used than that used intravenously (such as 50,000 to 500,000 units of streptokinase or urokinase). Using a smaller dose, particularly <100,000 units, has the advantage of avoiding a systemic lytic effect, therefore minimizing bleeding complications resulting from thrombolytic therapy.

**Recommendations for Primary Angioplasty of Infarct-Related Artery Only**

**Class I**

1. Patients presenting within 6 hours of onset of pain and who meet the criteria for thrombolysis but in whom thrombolytic therapy is clearly contraindicated and only if facilities and personnel are immediately available. This recommendation is operative only when data indicate a large amount of myocardium is at risk.

**Class IIa**

1. Intermittent continuous pain indicating the possibility of “stuttering” infarction, especially if there are ECG changes, but without clear indication for thrombolytic therapy.
2. Within 18 hours of acute infarction in patients developing cardiogenic shock or pump failure.
3. Patients who have had previous coronary artery bypass graft surgery in whom recent occlusion of a vein graft is suspected.

**Class IIb**

1. Patients with known coronary anatomy in whom thrombolytic therapy is not contraindicated, but who develop symptoms and ECG evidence of acute infarction in hospital at a time when rapid access to a catheterization laboratory with personnel experienced in performing expeditious angioplasty for acute myocardial infarction is available (completion within 1 hour).
2. Patients in whom thrombolytic therapy is not contraindicated who present within 4 hours of onset of symptoms of acute infarction at a facility where rapid access to a catheterization laboratory with personnel experienced in performing expeditious angioplasty for acute myocardial infarction is available (completion within 1 hour).

**Class III**

This category applies to patients with acute myocardial infarction who do not fulfill the Class I or II criteria. For example:

1. Patients with severe left main coronary artery disease when instrumentation of a more distal occluded artery may be hazardous.
2. Patients in whom only a small area of myocardium is involved, as evidenced by clinical data or previously known coronary anatomy.
3. Dilation of vessels other than the infarct-related artery within the early hours of infarction. (This may not apply to the patient in shock or pump failure.)

**Angioplasty After Thrombolytic Therapy**

**Immediate angioplasty.** Although intravenous thrombolysis offers the promise of early reperfusion in up to 75% of patients,136 more complete reperfusion may be possible by performing angioplasty in those with a high-grade residual stenosis of the infarct-related artery and those who failed intravenous thrombolysis. Three well-controlled, relatively large prospective trials79,136,137 have, however, cast doubt on the utility of this strategy when applied early after thrombolysis and in the absence of continued or recurrent ischemia. The TAMI trial,136 European Cooperative Study,137 and TIMI-IIA79 trial of urgent angioplasty failed to demonstrate a significant improvement in global or regional ventricular function in patients undergoing emergency (immediate) angioplasty of infarct-related vessels with a residual stenosis after administration of tissue plasminogen activator compared with patients receiving intravenous tissue plasminogen activator alone and undergoing elective angioplasty (TAMI trial), delayed angioplasty (TIMI-IIA trial), or no angioplasty (European Cooperative Study). The incidence of complications and death associated with emergency angioplasty was significantly greater in those undergoing emergency angioplasty after intravenous rt-PA than in those undergoing intravenous rt-PA administration without emergency angioplasty in the summed results of the three trials. It therefore appears that urgent angioplasty of infarct-related vessels with a residual stenosis after rt-PA therapy has no significant benefit, but does have a significant increase in risk. The failure of angioplasty immediately after thrombolysis may be related to an increased risk of hemorrhagic infarction when angioplasty is performed after administration of tissue plasminogen activator or to an increased risk of restenosis. Thrombolytic agents such as streptokinase, urokinase, or tissue plasminogen activator have been shown to cause platelet activation and release of thromboxane A₂.138,139 Because thrombolysis is incomplete 1.5 to 3 hours after the administration of an intravenous thrombolytic agent such as tissue plasminogen activator, it is not surprising that angioplasty performed under these circumstances may further predispose to platelet deposition on the residual thrombosis, with subsequent, distal platelet embolization, reocclusion, and death. Whether a similar risk exists with other thrombolytic agents remains to be determined.
Delayed angioplasty. In view of the increased risk of urgent angioplasty after thrombolysis, attention has focused on the role of delayed and elective angioplasty. The need for further revascularization after intravenous thrombolysis relates to the often incomplete thrombolysis and the high incidence of residual stenosis in the infarct-related artery after intravenous thrombolysis. This is in part due to the presence of residual thrombosis and in part to the underlying atherosclerotic lesion. Patients undergoing thrombolysis alone, such as in the GISSI trial9 or the Western Washington trial,19 had a higher incidence of reocclusion and reinfarction than those not given a thrombolytic agent. The significant advantages of early reperfusion in patients with anterior myocardial infarction in the Western Washington trial of intra-coronary streptokinase were lost over a year follow-up as a result of reocclusion of the infarct-related artery and reinfarction. In a recent study, Mathey et al40 reported that patients undergoing coronary artery bypass graft surgery after reperfusion with streptokinase had a better survival rate than patients undergoing thrombolysis alone. The ISIS-2 study, in which aspirin was given in conjunction with intravenous streptokinase, suggested a reduced incidence of reinfarction compared with that from intravenous streptokinase alone.10 The beneficial result of the use of aspirin in conjunction with intravenous streptokinase in regard to survival, reocclusion, and reinfarction may modify the need for delayed angioplasty. Nevertheless, a high-grade residual stenosis with the potential for recurrent ischemia and infarction persists in many patients after intravenous thrombolysis, suggesting a potential role for delayed or elective angioplasty.

In The Johns Hopkins University trial121 of delayed angioplasty, patients were first randomized to receive tissue plasminogen activator or placebo and then after 48 to 72 hours were rerandomized to undergo or not undergo angioplasty. At follow-up study before hospital discharge, patients undergoing angioplasty had a significant improvement in exercise ejection fraction but not rest left ventricular ejection fraction compared with those not undergoing angioplasty. The risk of angioplasty under these circumstances 48 to 72 hours after infarction does not appear to be appreciably greater than that for elective angioplasty. The advantages of this strategy include avoiding the risk of early angiography, avoiding the risk of emergency angioplasty and achieving a high incidence of final reperfusion, a decrease in the incidence of recurrent ischemic events, and an improvement in exercise-stressed ventricular function. A disadvantage of this strategy is the possible overuse of angioplasty in low risk individuals.

The TIMI-IIB investigators79 examined the strategy of delayed angioplasty in a relatively large number of patients and demonstrated that there was no advantage of this strategy on rest left ventricular ejection fraction or survival compared with a noninvasive strategy in which angioplasty was performed only for postinfarction angina or the development of ischemia on stress testing before hospital discharge.79 The noninvasive strategy avoids the risk of early angiography and urgent angioplasty. It restricts the use of coronary angioplasty to those at increased risk of ischemic events. The disadvantage of this strategy relates to the failure to identify coronary anatomy and the argument that a submaximal prehospital discharge stress test may not reliably predict recurrent ischemic events, reinfarction, and death.

In view of the failure of available data to demonstrate an advantage of salvage or rescue angioplasty and the failure to show a benefit of routine urgent or delayed angioplasty after successful thrombolysis, it appears that an elective or noninvasive strategy is preferred. Until further data are available from prospective controlled trials, a conservative approach after intravenous thrombolytic therapy seems indicated. This would reserve angiography and angioplasty for patients with postinfarction angina, severe left ventricular dysfunction, or stress-induced myocardial ischemia detected before hospital discharge.

**Recommendations for Angioplasty After Intravenous Thrombolysis**

**Class I**

Dilation of a significant lesion suitable for coronary angioplasty in the infarct-related artery in patients who are in the low risk group for angiographic-related morbidity and mortality who have a type A lesion (see ACC/AHA Task Force Report on coronary angioplasty129) and:

1. Have recurrent episodes of ischemic chest pain particularly if accompanied by ECG changes (postinfarction angina).
2. Show evidence of myocardial ischemia while on optimal medical therapy during submaximal stress testing performed before hospital discharge or on maximal stress testing in the early posthospital period.
3. Have recurrent ventricular tachycardia or ventricular fibrillation, or both convincingly related to ischemia while on antiarrhythmic therapy.

**Class IIa**

Dilation of significant lesions in patients who:

1. Are similar to those in class I but who have type B lesions (anticipated success rate 60% to 85%) (see ACC/AHA Task Force Report on coronary angioplasty129).
2. Are within 18 hours of onset of acute infarction and have cardiogenic shock or pump failure. These patients should be studied and undergo reperfusion as soon as possible.
3. Before hospital discharge in those who have survived cardiogenic shock or pump failure.

**Class IIb**

Dilation of a lesion in patients who:

1. Have an occluded coronary artery after attempted thrombolytic therapy.
2. Require multivessel angioplasty.
3. Have >90% diameter proximal narrowing of an infarct-related artery with a large area of viable myocardium still at risk.

**Class III**

All patients in the immediate postinfarct period (during initial hospitalization) who do not fulfill Class I or II criteria. For example:
1. Dilation in patients who are within the early hours of an evolving myocardial infarction and have <50% residual stenosis of the infarct-related artery after receiving a thrombolytic agent.
2. Dilation of lesions in vessels other than the infarct-related artery within the early hours of infarction.
3. Dilation of residual lesions that are borderline in severity (50% to 70% diameter narrowing) of the infarct-related artery without demonstration of ischemia on functional testing.
5. Undertaking angioplasty in patients in the high risk group for morbidity and mortality (see ACC/AHA Task Force Report on coronary angioplasty for definition). 129

**Pump Failure and Shock in Acute Myocardial Infarction and Use of Intra-aortic Balloon Counterpulsation and Other Circulatory Assist Devices**

Pump failure and shock represent a clinical spectrum more easily defined than treated. The clinical syndrome includes a weak pulse, poor peripheral perfusion with cool cyanotic limbs, obtundation, and oliguria. Blood pressure taken by cuff is usually low and there are variable degrees of pulmonary congestion. The heart sounds are usually quiet and a third heart sound may have a variable degree of prominence. Because the best treatment is prevention, relieving the load on the left ventricle and improving the myocardial oxygen supply/demand ratio in patients showing early evidence of hemodynamic deterioration should be vigorously undertaken. It is most probable that the current use of hemodynamic monitoring and early use of afterload-reducing and oxygen-sparing agents are the reason we see the shock syndrome less frequently than in the past. 141

Before defining the various subsets of pump failure, we must be certain that the filling pressure of the ventricle is adequate. There are several reasons for volume depletion in patients with acute myocardial infarction, including overwhelming diuresis, volume loss through the gastrointestinal tract at the onset of the syndrome, use of pressor agents, and a period of cardiac arrest during which intravascular volume may be diverted into the third space. 34,142 If the filling pressure of the left ventricle is <15 mm Hg, it is hard to define pump failure, and before more active intervention, it is useful to challenge intravascular volume sufficiently to bring the filling pressure of the left ventricle to 18 mm Hg. This must be done as a challenge infusion over a short period of time because prolonged infusion can lead to pulmonary congestion without elevation of left ventricular filling pressure.

The treatment of pump failure should be divided according to hemodynamic subsets and patients may move from one subset to another, requiring change in the therapeutic regimen. 17

**Subset 1. Left ventricular filling pressure >15 mm Hg, systolic arterial pressure >100 mm Hg and cardiac index <2.5 l/min/m².** This subset has left ventricular failure; the arterial pressure is sufficiently high to allow for afterload reduction as the first line of therapy. 143 It is a subset that, within itself, has a spectrum from hypertension and pulmonary edema to systolic pressures approaching 100 mm Hg, less prominent pulmonary congestion, and more marked evidence of peripheral hypoperfusion. The two vasodilator agents most commonly used are nitroprusside and nitroglycerin. Nitroprusside has the benefit of more active afterload reduction. 144 Nitroglycerin has a greater degree of venodilator effect and also relieves ischemia by dilating epicardial coronary arteries. When ischemia is not prominent and the epicardial coronary artery dilator effect of nitroglycerin is not needed, nitroprusside becomes the agent of choice. Conversely, in the early hours of acute infarction when ischemia plays a prominent role in ventricular dysfunction, nitroglycerin may be the more appropriate agent. When using nitroprusside, the patient should be monitored for arterial and left ventricular filling pressures. The initial dose should not exceed 10 µg/min and increase by 5 µg/min every 10 minutes. If cardiac output increases and the shock syndrome abates, the infusion should be continued. If arterial pressure decreases, tachycardia develops or the cardiac output increase is insufficient, or both, one should add dobutamine beginning at 5 µg/kg/min and increase the dose to a maximum of 15 µg/kg/min. 145 Intravenous amrinone with its vasodilating and inotropic effects can also be considered. If arterial pressure decreases more precipitously, dopamine should be substituted for dobutamine. Throughout this period of treatment, use of the intra-aortic balloon pump for counterpulsation should be considered because it is the only treatment that increases coronary blood flow and simultaneously reduces work for the left ventricle. Even in the patient with hypertension who is in pulmonary edema, the balloon pump will tend to lower arterial pressure by its inherent vasodilating effect through double bombardment of the baroreceptors. As one stabilizes the patient with this syndrome, gentle use of diuretic drugs may be indicated if pulmonary congestion continues to be a problem. Pulmonary congestion can often be monitored better by measurement of blood gases combined with changes in wedge pressure than by appearance of rales.
Subset 2. Arterial pressure <90 mm Hg, left ventricular filling pressure >15 mm Hg, and cardiac output <2.5 l/min/m². This subset defines the classic hypotensive shock patient with acute myocardial infarction who has a 20% prognosis for survival. It should be obvious to the reader that we have excluded the patient with systolic pressure between 90 and 100 mm Hg to allow for clinical judgment as to whether the patient is moving toward subset 2 or subset 1 and the design of therapy on that clinical assessment. Once the patient is defined to be in this subset of pump failure, the balloon pump team should be mobilized and the catheterization laboratory should be prepared to accept the patient. If the patient is markedly hypotensive, norepinephrine is the agent of choice until systolic arterial pressure is brought in the range of 80 to 90 mm Hg. At that point, a switch to dopamine should be attempted. If the pressure is in the range of 70 to 90 mm Hg, dopamine can be the initial agent, beginning with doses from 5 to 15 μg/kg/min. When 20 to 30 μg/kg/min is exceeded to maintain arterial pressure, the major effect of the agent is peripheral α-adrenergic stimulation and administration of norepinephrine, which has less chronotropic effect, is better. If the patient can be stabilized so that arterial pressure is no longer the problem, the best agent is dobutamine and this can be given simultaneously with the dopamine in the attempt to reduce the dopamine requirement. However, dobutamine is not an agent to be used alone in the severely hypotensive patient.

Subset 3. Right ventricular infarction, elevated right atrial and right ventricular diastolic pressures (>10 mm Hg), <2.5 l/min/m², systolic pressure <100 mm Hg, and left ventricular filling pressure normal or elevated. These patients are important to recognize because they are very sensitive to volume depletion and frequently respond to volume infusion. They usually, but not always, have inferior wall infarction. There may be varying degrees of left ventricular dysfunction. The principles of therapy differ from those for subset 2 in that right ventricular filling pressure must be increased by rapid administration of fluids until blood pressure is stabilized, left ventricular filling pressure is >20 mm Hg or right atrial pressure is >20 mm Hg. Venodilator agents (such as nitroglycerin) and diuretic drugs (such as furosemide) should be avoided and dobutamine is much preferred to dopamine because the latter tends to increase pulmonary vascular resistance. If volume replacement and mild inotropic support is insufficient, it is useful to know that these patients do respond to intra-aortic balloon counterpulsation and represent a group of patients who, with appropriate therapy (including counterpulsation if necessary), can be discharged in New York Heart Association functional class I. Right ventricular infarction must be differentiated from cardiac tamponade, which is sometimes hemodynamically similar.

All of these patients with pump failure, particularly if seen in the first 12 to 24 hours, deserve immediate transfer to a facility equipped for catheterization, angioplasty, and cardiovascular surgery. Angioplasty performed in the patient in shock seen within the first 18 hours of symptom onset has resulted in a survival rate in the range of 50%, a marked improvement over any reports using pharmacologic agents and counterpulsation. It is also important to define the anatomic and physiologic abnormalities. Occasionally, severe mitral insufficiency even without a murmur is present in these patients. If global left ventricular dysfunction is due to ischemia, reperfusion is important for the salvage of myocardium. If it appears that the dysfunction is due to irreversible myocardial damage, the patient may be a candidate for heart transplantation, and if so, a left ventricular assist device or mechanical heart implantation should be considered in centers so equipped. It must be emphasized again that patients with pump failure or shock need to be studied angiographically early so that intervention with angioplasty or surgery can be undertaken at a time early enough to reverse hemodynamic deterioration.

Recommendations for Intra-aortic Balloon Counterpulsation or Other Circulatory Assist Devices

Class I

1. Cardiogenic shock or pump failure not responding promptly to pharmacologic therapy.
2. Right ventricular infarction with pump failure or shock not responding to volume infusion and appropriate pharmacologic therapy.
3. Refractory postinfarction angina for stabilization before and during angiography.
4. Intractable recurrent tachycardia in patients with hemodynamic instability during the arrhythmia.

Class IIa

1. Ventricular septal rupture.
2. Acute mitral insufficiency.
3. Persistent ischemic pain.
4. Progressive congestive heart failure despite pharmacologic therapy, particularly as a bridge to more definitive therapy.

Class III

1. A patient who is reasonably stable and in whom balloon insertion may delay more definitive therapy.
2. Severe peripheral vascular disease and fewer indications than in Class I.

Surgical Intervention in Acute Myocardial Infarction

Introduction

Guidelines for the surgical interventions associated with acute myocardial infarction follow the indications as classified elsewhere in this report. In addition, surgical intervention may be grouped chron-
Cardiac Arrhythmias

There are no class I emergency indications for surgery in this subset of patients. Emergency introduction of the intra-aortic balloon pump for cardiac arrhythmias that are incessant or produce hypotension has been helpful in some instances.\(^{151}\) In patients with aneurysmal expansion of the infarction associated with persistent ventricular tachycardia and failure of medical therapy, surgical resection of the aneurysm and endocardial scar incision along with coronary artery bypass grafting has been successful.\(^{152}\) In general, intraoperative mapping, revascularization, and surgical ablation of reentry areas are reserved as elective procedures and are indicated only if drug therapy has failed. The surgical mortality rate is 10% to 20% and the freedom from recurrent arrhythmias and sudden death has been reported to be 75%,\(^ {153,154}\)

Failed Percutaneous Transluminal Coronary Angioplasty

Coronary artery bypass grafting may occasionally be performed as an emergency procedure in a patient with acute myocardial infarction and persistent pain or hemodynamic instability after failed percutaneous transluminal coronary angioplasty. Surgical intervention within 4 hours (optimally 2 hours) can often lead to patient survival and minimal loss of ventricular function.\(^ {155}\) Survival varies with the severity of the pump failure, urgency of the operative procedure, and skill of the operative team. Brahos et al\(^ {156}\) report a 4.4% and 3.1% mortality rate for urgent and elective groups.

The most common urgent or elective surgical intervention after failed coronary angioplasty is in the presence of a closed vessel with new or persistent symptoms of ischemia. Goldberg et al\(^ {157}\) reported two deaths in 81 patients requiring surgery within 24 hours after angioplasty. There were 75 major complications in 52 patients. Reul et al\(^ {158}\) reported an overall surgical mortality rate of 3.3% in 184 patients 1 week to 19 months after angioplasty, with one death in 57 patients who were unstable.

Postthrombolytic Therapy

In the patient who has received thrombolytic therapy, there are no indications for emergency surgical revascularization. Urgent operation in patients not suitable for angioplasty is indicated for persisting pain or evolving infarction despite thrombolytic therapy. Skinner et al\(^ {159}\) reported a 17% mortality rate and blood use of 8.2 units/patient in 24 such cases.

Elective surgical intervention after thrombolytic therapy is indicated in patients with persisting symptoms and closed or stenotic coronary arteries not suitable for angioplasty. Additionally, elective coronary artery bypass graft surgery must be considered in those patients with other elective indications for cardiac surgery.\(^ {160}\) These indications include a markedly positive exercise test, a correctable mechanical derangement, left main coronary artery disease, and three- or two-vessel coronary artery disease not better treated with angioplasty.\(^ {161}\)

Recurrent Ischemia

Urgent operation should be considered indicated when there are ST-T wave changes with pain after and during the same hospitalization as the initial myocardial infarction, presuming the coronary anatomy in this type of patient is not amenable to angioplasty. The results of urgent revascularization in this group of patients are highly correlated with ejection fraction. In those patients with an ejection fraction >50%, survival is nearly equal to that of elective revascularization. With increasingly depressed left ventricular function, survival after urgent surgical revascularization is somewhat less but very similar to that of elective bypass surgery in patients with depressed ventricular function.\(^ {162,163}\)

Surgery for Evolving Myocardial Infarction

Emergency operation (within 6 hours) for evolving infarction has been evaluated by Phillips et al,\(^ {155}\) DeWood et al,\(^ {164}\) and Flameng et al.\(^ {165}\) In each report, surgical treatment appeared to improve survival or result in better salvage of myocardium, or both, than occurred in matched retrospective control groups. However, surgical reperfusion is available less quickly in the evolution of infarction than is thrombolyis or angioplasty. Therefore, except in those communities where this has been established, emergency bypass is not indicated until future studies show that this approach is superior to thrombolyis and coronary angioplasty.

Non-Q Wave Infarction

Although DeWood et al\(^ {164}\) have shown improved survival in a nonrandomized group of patients with non-Q wave infarction treated by emergency bypass surgery as compared with conventional medical treatment, emergency operation in this group of patients is controversial. Urgent operation may be indicated in patients with unstable rhythms, unstable angina, unstable ECG changes, pulmonary venous hypertension, or significant left main coronary artery disease. At particular risk are those patients with transient ECG changes and postinfarction angina. This, in practicality, defines patients with two or three vessel coronary artery disease not ordinarily treated with coronary angioplasty who have persisting symptoms or are developing congestive heart failure.

Elective operation in those patients who have had a non-Q wave infarction is indicated if there is left main or three vessel disease, two vessel disease where the proximal left anterior coronary artery is significantly narrowed or with two-vessel disease and ejection fraction <40%. In these patients, elective surgery would be expected to prolong survival.\(^ {161,165,166}\)
Mechanical Derangements After Myocardial Infarction

Papillary muscle rupture producing acute mitral incompetence is an infrequent but catastrophic complication of myocardial infarction. Emergency coronary artery bypass graft surgery and mitral valve replacement are indicated. Tepe and Edmunds reported 5 survivors of 11 such patients operated on within 1 month of myocardial infarction.

Severe mitral insufficiency due to papillary muscle dysfunction or chordal rupture should be treated with intra-aortic balloon counterpulsation or afterload reduction, or both. Surgery can be urgent, elective, or not needed, depending on the hemodynamic consequences, although with chordal or papillary muscle rupture, surgery will almost always be indicated. Coronary artery bypass graft surgery and mitral valve repair or replacement are indicated.

Ventricular free wall rupture presenting as a pseudoaneurysm should be treated as an emergency unless it is discovered late in the clinical course, in which case it should be treated urgently. Surgical intervention consists of revascularization, aneurysmectomy, and closure of the ventricular defect.

Ventricular septal rupture with resulting left to right shunt, pulmonary venous and pulmonary arterial hypertension, and low cardiac output is often life-threatening and is an indication for operation. It should be treated as an emergency if pulmonary congestion, congestive heart failure of pulmonary edema occur, or there are manifestations of cardiogenic shock. Urgent operation is indicated in the absence of conditions as just stipulated. However, there is emerging information that emergency operation rather than urgent or elective intervention is appropriate for ventricular septal rupture even if the patient is stable and particularly if the diagnosis is made early in the course of infarction. The initial smaller rupture may be predictive of more severe septal or free wall rupture.

Left ventricular aneurysm, defined as a demarcated diastolic deformity of the left ventricle appearing on left ventricular angiography with systolic dyskinesia, may be associated with congestive heart failure or important ventricular arrhythmias. There are no emergency indications for operation. Urgent operation may be required when left ventricular aneurysm is associated with intractable ventricular tachycardia or intractable heart failure. The operative mortality rate may be 6% to 15%. Operation can take the form of map-directed ventricular tachycardia surgery, left ventricular aneurysm resection, mitral valve repair or replacement, or coronary revascularization. The indication for operation in left ventricular aneurysm is the presence of intractable congestive heart failure, ventricular tachyarrhythmias not responsive to drug therapy, and embolization despite anticoagulant therapy. In 1,131 patients reported from the Coronary Artery Surgery Study (CASS) Registry, the surgical mortality rate was 7.9%. However, surgical priority (emergency and urgent) was a significant operative risk factor. Cardiac transplantation may be appropriate for this and other mechanical derangements when ventricular function is poor or after failure of conventional operative approaches.

Pump Failure and Cardiogenic Shock

In this situation, emergency intra-aortic balloon counterpulsation and coronary artery bypass surgery have led to a better survival rate and greater salvage of myocardium than has treatment by conventional pharmacologic means, but should be deferred to angioplasty where feasible.

Recommendations for Surgery in the Early Management of Myocardial Infarction

Recommendations for Emergency or Urgent Coronary Bypass Surgery

Class I
1. Failed angioplasty with persistent pain or hemodynamic instability.
2. Postinfarct angina with left main or three-vessel disease or where coronary angioplasty is not indicated, with two-vessel disease involving the proximal left anterior descending coronary artery or two-vessel disease and poor left ventricular function.

Class IIa
1. At the time of surgical repair of ventricular septal defect or acute mitral insufficiency.
2. Cardiogenic shock not suitable for angioplasty.

Class III
1. Where the available surgical mortality rate exceeds the mortality rate associated with appropriate medical therapy.

Recommendations for Emergency or Urgent Cardiac Repair

Class I
1. Papillary muscle rupture (emergency).
2. Ventricular septal defect or free wall rupture (urgent).
3. Aneurysmal infarction with intractable ventricular arrhythmias or pump failure (urgent), or both.
4. Acute mitral insufficiency with intractable failure (urgent).
5. Intractable ventricular tachycardia (urgent).

Class IIa
1. Ventricular septal defect or free wall rupture (emergency).
2. Severe mitral insufficiency with controlled failure (urgent).

Class III
1. Acute infarctectomy in hemodynamically stable patients.
2. Surgery where the operative mortality rate exceeds the expected mortality rate associated with conservative therapy.
Recommendations for Implantable Ventricular Assist Devices

Class I

None.

Class IIb

1. As a bridge in a patient who has intractable pump failure and who would be a reasonable candidate for cardiac transplantation.

Predischarge Evaluation in Acute Myocardial Infarction

Patients with acute myocardial infarction require serial evaluation by their managing physician. These daily clinical assessments are usually combined with various diagnostic studies performed during recovery or just before discharge. Such an evaluation will allow the division of patients into high and low risk groups and aid in choosing patients who will benefit from myocardial revascularization in addition to risk factor management and anti-ischemic, antiarrhythmic, or antifailure therapy as appropriate. The prognosis after acute myocardial infarction is most directly related to the extent of left ventricular dysfunction, the presence of residual myocardial ischemia, and the degree of electrical instability of the myocardium. Many of the techniques that can be used to define these factors are duplicative and the clinician must choose those that are cost-effective, most accurate in his or her own environment, and will lead to clinical decisions that can modify outcome or at least make a major impact on prog nostication.

Clinical Assessment

There are certain clinical attributes already present on admission that yield prognostic information. By clinical assessment, patients at high risk who should have angiography before discharge and thus may not need additional high technology assessment can be identified. Infarct-related mortality increases with age, approaching 50% in patients > 80 years of age. A history of prior acute myocardial infarction or chronic angina pectoris is associated with an increased acute mortality rate and a doubling of the mortality rate in the first 2 years after infarction. Although men have a higher incidence of acute myocardial infarction, women have a poor prognosis. A history of hypertension increases the late mortality rate for several years after infarction. Diabetes mellitus increases the mortality rate by threefold to fourfold. Cigarette smoking is associated with an increased risk of death in those who continue to smoke. One study of 818 patients described an index based on clinical information available in the first 24 hours (including maximal blood-urea-nitrogen, history of prior myocardial infarction, age, displaced left ventricular apex on physical examination, and bradycardia) to be strongly predictive of subsequent death in the year after discharge.

Other predictive characteristics become apparent as the infarction evolves. Anterior infarcts carry a higher short- and long-term mortality rate than do inferior infarcts, even when corrected for infarct size. Non-Q wave infarctions have an initial mortality rate about half of that of Q wave infarctions, but an increased incidence of late extension and reinfarction and a comparable mortality rate at 1 year. An estimate of infarct size by analysis of creatine kinase or MB CK release has significant prognostic information. The presence of congestive heart failure correlates roughly with infarct size and ultimate prognosis. Certain atrial arrhythmias (especially atrial fibrillation) appearing after the first 48 hours are associated with left ventricular failure and an increased risk of death. Runs of three or more consecutive premature ventricular complexes are independent predictors of early death. Postinfarction angina predicts nonfatal reinfarction in the following year. Rest ST segment depression that persists denotes an increased 1-year mortality rate.

The clinical characteristics just described identify a number of patients at increased risk before a formal predischarge risk assessment. Patients with a complicated clinical course manifested by significant congestive heart failure (Killip class III or IV), hypotension, ongoing ischemia, malignant arrhythmia, or suspicion of a mechanical defect are generally candidates for cardiac catheterization without further extensive noninvasive evaluation. Approximately 60% to 80% of all patients who survive their first infarct to leave the hospital will be free of these indications by the fifth postinfarction day. These relatively uncomplicated patients can be further stratified into high and low risk subgroups by the application of the following technologies.

Exercise Testing

The role of exercise testing in evaluating patients after acute myocardial infarction has been extensively discussed in a prior ACC/AHA guideline report. The risk of symptom-limited exercise testing is low in properly selected patients at 10 to 14 days after infarction. In predischarge-limited exercise testing at 6 to 10 days after infarction, however, a submaximal test should be used. Five METS is a useful end point in the absence of limiting symptoms such as angina, dyspnea, or fatigue. However, arbitrary limits of 120 to 130 beats/min or 70% of maximal predicted heart rate for age have been used to establish the safety of early exercise testing. Safety is likewise maximized when three or more consecutive premature ventricular complexes, ST segment depression > 2 mm, or development of exertional hypotension to below baseline are taken as indications for termination of exercise.

Patients who have ST segment depression > 1 mm during exercise have a 3 to 20 times higher risk of subsequent cardiac events. The 1-year mortality rate
in this group is as high as 15%. Patients able to achieve a high peak work load generally have less ischemia and left ventricular dysfunction than patients capable of only low work loads. Inability to achieve a treadmill work load of 4 METS on symptom-limited exercise testing 3 weeks after infarction is associated with a sixfold increase in the risk of cardiac death, nonfatal ventricular fibrillation, or recurrent infarction in the subsequent 12 months. Inability to achieve a peak systolic pressure of ≥110 mm Hg, increase systolic pressure by 10 mm Hg over baseline values, or decrease systolic pressure below baseline values also implies a poor prognosis. In contrast, exertional hypotension (a decrease >10 mm Hg from the highest value achieved during earlier exercise) occurring on the predischarge exercise test is a relatively common and nonspecific finding and usually does not warrant further immediate investigation. Many of these patients will have more normal blood pressure and heart rate responses on follow-up exercise testing 4 to 7 weeks later.

The best time to perform the exercise test varies, depending on physician preferences, patient characteristics, and local laboratory expertise. There are strong arguments that symptom-limited maximal exercise testing at 3 weeks after myocardial infarction is a cost-effective alternative to submaximal predischarge testing at 10 to 14 days and can be used for prognostication as well as evaluation of functional capacity. Because the trend to earlier discharge decreases the hospital stay for an uncomplicated infarction patient to ≤6 to 10 days, the safety of predischarge testing is less well established. Symptom-limited testing at 3 weeks, however, is proved to be safe and the delay seems to be associated with very few instances of intercurrent death or reinfarction in properly selected patients. Patients having a negative ECG response to ≥6 METS work load at 3 weeks have a 1-year mortality rate of <2%, .

When a patient has difficulty in returning for exercise testing, either because of transportation considerations, inadequate compliance, or other causes of uncertain follow-up, predischarge submaximal testing may be preferred. In addition, all patients who have had thrombolytic therapy should have an exercise test before discharge. The addition of thallium-201 imaging or radionuclide ventriculography improves the predictive value of the submaximal predischarge exercise test and may be considered if locally available. A second treadmill exercise test performed to symptom limitation at 4 to 8 weeks may be necessary if clearance is required before returning to work or resuming strenuous leisure activities.

In uncomplicated patients being discharged at 10 to 14 days and properly selected as clinically at low risk, a symptom-limited exercise test with a thallium-201 perfusion scan or radionuclide ventriculogram can identify most of the patients in that group who are still at risk and therefore need angiography.

If a patient is selected for earlier discharge at 6 to 10 days, a heart rate or 5 METS-limited submaximal exercise test could be used before early discharge, with a follow-up symptom-limited stress test at 3 to 8 weeks. A recent study that failed to show additional prognostic value gained by the follow-up maximal stress test used a submaximal test at 8 to 10 days. It suggested that a second symptom-limited test at 6 to 8 weeks be reserved for patients who develop new symptoms or require functional capacity clearance for an active lifestyle.

Supplemental Imaging (Table 2)

Thallium-201 myocardial perfusion scanning is frequently performed in association with exercise testing in patients with conditions that compromise interpretation of the ECG (bundle branch block, rest ST-T wave abnormalities, digitalis therapy). In a study of 140 patients after infarction, thallium-201 scintigraphy detected 94% of those who had a late cardiac event and was more reliable than ECG changes on submaximal predischarge exercise testing in defining high and low risk subgroups. Thallium-201 defects in multiple vascular regions, redistribution abnormalities, or pulmonary uptake of thallium-201 identified more high risk patients than did ST segment depression or angina. Recently, rest thallium-201 imaging performed before discharge has been shown to give prognostic information that, in one study, was a better predictor of outcome than either rest ejection fraction by radionuclide ventriculography or 24-hour Holter monitoring. This technique can be considered for risk stratification in patients after infarction who are judged to be unable to perform exercise. Dipyridamole thallium-201 imaging has also been advocated for the same exercise-restricted patients. At present, it remains a promising investigational technique awaiting further confirmation.

Radionuclide ventriculography measured at rest and during exercise provides useful prognostic information. When the rest ejection fraction is normal, a decrease in ejection fraction during exercise correlates well with thallium perfusion defects in the same patients. Therefore, it is likely that the exertional decrease in ejection fraction reflects myocardial ischemia. In one study, the predictive accuracy of a failure to increase ejection fraction by 5 percentage units during submaximal exercise was 95% for any cardiac event during a 10-month follow-up period. In another study, exercise ventriculography during maximal symptom-limited testing at 3 weeks correctly predicted >90% of episodes of death, nonfatal ventricular fibrillation, or reinfarction in the subsequent year. There has been no direct comparison of the predictive value of thallium-201 versus radionuclide ventriculography when performed with a submaximal treadmill exercise test before discharge. When the two techniques were compared with maximal stress testing at 3 weeks, radionuclide ventriculography was
of superior prognostic value in patients with a rest ejection fraction >40%.192

Wall motion abnormalities due to exercise-induced myocardial ischemia can also be detected by two-dimensional echocardiography either at peak bicycle exercise or, more conveniently, immediately after treadmill exercise testing.201 New or worsening wall motion abnormality on maximal stress testing soon after myocardial infarction (average 13 days) identified a high risk subgroup with greater sensitivity and specificity than did echocardiographic abnormalities alone.202 Another study203 reported similar prognostic value of echocardiography when exercise was submaximal with a heart rate limitation. Exercise echocardiography is a versatile and inexpensive imaging technique, the validity of which is being established.204

**In summary,** the principle of predischARGE or early postdischarge exercise evaluation is based on first selecting out the patients who on clinical grounds are at high risk for ischemic events and directing them to invasive evaluation. Then the patients who have myocardium in jeopardy of ischemic injury need to be identified with highest accuracy and those who would undertake strenuous exertion be provided a functional evaluation after partial or complete rehabilitation.

**One strategy** is to perform a symptom-limited exercise test, perhaps with thallium scanning or radionuclide ventriculography at 10 to 14 days. This could serve to determine prognosis and identify most patients in the clinically low risk group who have residual ischemia and therefore need invasive evaluation. No additional exercise testing is needed in those who do well on this early exercise test unless the patient wants to undertake strenuous activity and needs a test for functional evaluation after rehabilitation.

A **second strategy** is to perform a submaximal exercise test at 6 to 10 days after the infarction and just before early discharge. This strategy requires very careful clinical assessment to identify patients for early discharge, and there are too few published data on early exercise testing to assess its prognostic validity. For those patients identified as having ischemia, it starts the process of invasive evaluation early, whereas those who do well still need a symptom-limited exercise test—perhaps with thallium—for prognosis and function assessment at 4 to 8 weeks.

A **third strategy** is to discharge the clinically low risk patient at 7 to 14 days and perform the symptom-limited exercise, perhaps with thallium or radionuclide ventriculographic evaluation at 3 weeks for prognostic as well as functional evaluation. This has the advantage of requiring only one exercise evaluation, but has the disadvantage of delaying invasive evaluation for 3 weeks in those patients identified to have ischemia. There is also a possibility of postinfarction events occurring before this test.

If there is doubt about the exercise/thallium interpretation, exercise ventriculography by radionuclide scanning or echocardiography can increase the sensitivity of the test by identifying exercise-induced wall motion abnormalities.

### Table 2. Strategies for PredischARGE or Early Postdischarge Exercise Evaluation

<table>
<thead>
<tr>
<th>Clinical indicators of high risk at predischARGE</th>
<th>Cardiac catheterization</th>
<th>Medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy I</strong></td>
<td>Symptom-limited exercise at 10–14 days with thallium</td>
<td>Strenuous leisure activity or occupation</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Strategy II</strong></td>
<td>Uncomplicated course + submaximal exercise at 6–10 days</td>
<td>Symptom-limited exercise at 4–8 weeks with thallium</td>
</tr>
<tr>
<td>+</td>
<td>Cardiac catheterization</td>
<td>+</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Strategy III</strong></td>
<td>Discharge at 7–14 days</td>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td>+</td>
<td>–</td>
<td>Medical treatment</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>+</td>
<td>Medical treatment</td>
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</tbody>
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**ACC/AHA Task Force Management of Acute Myocardial Infarction** 697

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Recommendations for Noninvasive Evaluation of Patients at Low Risk by Clinical Indicators

Class I

1. Stress ECG.
   a. Before discharge for prognostic assessment (submaximal at 6 to 10 days or symptom-limited at 10 to 14 days).
   b. Early after discharge for prognostic assessment and functional capacity (3 weeks).
   c. Late after discharge (3 to 8 weeks) for functional capacity and prognosis if early stress was submaximal.
2. Exercise thallium-201 scintigraphy (whenever baseline abnormalities of the ECG compromise its interpretation).

Class IIa

1. Exercise thallium-201 scintigraphy; before discharge for prognostic assessment with symptom-limited exercise at 10 to 14 days.
2. Dipyridamole thallium-201 scintigraphy (before discharge for prognostic assessment in patients judged to be unable to perform exercise) (pending expected Food and Drug Administration approval).
3. Exercise radionuclide ventriculography predischARGE AT 10 TO 14 DAYS OR EARLY AFTER DISCHARGE FOR PROGNOSTIC ASSESSMENT.
4. Exercise two-dimensional echocardiography (before discharge or early after discharge for prognostic assessment).

Class IIb

1. Stress ECG.
   a. At any time to evaluate patients with a class I indication, but baseline ECG abnormalities or coexisting medical problems that limit ability to achieve maximal exertion. In some of these patients, exercise testing may still yield clinically valuable information (duration of exercise, blood pressure response, production of chest discomfort, etc.).
   b. Before discharge or early after discharge to evaluate patients who have sustained a complicated myocardial infarction, but who have subsequently “stabilized” and for whom a decision for invasive evaluation has not been made.
2. Exercise thallium-201 myocardial scintigraphy (late after discharge at 6 to 8 weeks for prognostic assessment).
3. Dipyridamole thallium or dobutamine thallium before discharge in patients judged unable to exercise (not approved by the Food and Drug Administration for this indication).

Class III

1. Stress ECG.
   a. Within 72 hours of acute myocardial infarction.
   b. At any time to evaluate patients having unstable postinfarction angina pectoris.
   c. At any time to evaluate patients with acute myocardial infarction who have uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit their ability to exercise.
   d. Before discharge to evaluate patients who have already been selected for cardiac catheterization. In this situation, an exercise test may be useful after catheterization to evaluate function or identify ischemia in distribution of a coronary lesion of borderline severity.

Rest Radionuclide Ventriculography

Guidelines for cardiac radionuclide imaging have been previously published. The most widely available techniques include first pass and equilibrium radionuclide ventriculography. Because ventricular dysfunction is a major predictor of infarction-related death, an accurate measurement of left ventricular ejection fraction would be expected to aid in postinfarction risk stratification. An assessment of ventricular function can be obtained by two-dimensional echocardiography at rest. At present, however, radionuclide ventriculography is more commonly utilized. A progressive increase in the 1-year mortality rate occurs as left ventricular ejection fraction (measured by radionuclide ventriculography) decreases <40%. Some have suggested that a cutoff level of 45% is more sensitive and reveals a high risk subgroup of more reasonable size. When radionuclide ventriculography was performed late (1 to 2 months postinfarction), end-systolic volume was the best predictor of survival over a 6-year follow-up period, being superior to ejection fraction when ejection fraction was low.

Recommendations for Rest Radionuclide Ventriculography

Class I

1. PredischARGE REST RADIONUCLEIDE VENTRICULOGRAPHY TO DETERMINE THE HIGH RISK SUBSET UNLESS DETERMINATION OF VENTRICULAR FUNCTION HAS BEEN MADE BY OTHER MEANS.

Class IIa

1. For shunt detection in patients with suspected ventricular septal defect (pulmonary artery injection).

Class III

1. PredischARGE RADIONUCLEIDE VENTRICULOGRAPHY TO DETECT LEFT VENTRICULAR THROMBUS.
2. WHERE SIMILAR INFORMATION CAN BE DERIVED FROM OTHER TESTS ALREADY PERFORMED OR SCHEDULED.

Two-Dimensional Echocardiography at Rest

Guidelines for the general use of echocardiography will be the subject of a future ACC/AHA Subcommittee publication. In the setting of acute myocardial infarction, two-dimensional echocardiography at rest has proved useful in the assessment of left ventricular
function and risk stratification. Estimates of left ventricular systolic and diastolic volume and ejection fraction can be obtained by several techniques. Left ventricular function is more commonly and more usefully represented as a semiquantitative “wall motion index,” wherein a numeric value representing hypokinesia, akinesia, or dyskinesia is visually assigned to wall segments.200 Predischarge two-dimensional echocardiography at rest can identify patients at higher risk of death, recurrent infarction, or development of congestive heart failure in the following 17 to 21 months.202,207 More importantly, a normal wall motion index early in infarction identifies a low risk subgroup that remained free of complications with a negative predictive accuracy of 95%.208

Unlike radionuclide ventriculography, two-dimensional echocardiography detects wall thinning as well as abnormal wall motion. Disproportionate infarction expansion and ventricular dilation can be detected and are associated with a significant 2-month mortality rate.209 Furthermore, the detection of asynery remote from the area of infarction on an echocardiogram identifies patients with multivessel disease and residual myocardium in jeopardy from ischemia.210 Two-dimensional echocardiography can readily detect the following complications of infarction: rupture of the ventricular septum, papillary muscle or left ventricular free wall, left ventricular aneurysm or pseudoaneurysm, mural thrombus formation, infarct extension or expansion, and right ventricular infarction.211

The advantages of two-dimensional echocardiography include its portability and ease of performance. It can be used in the coronary care unit on very sick patients and can be repeated as necessary. It is painless and relatively inexpensive. Limitations include technical difficulties in obtaining interpretable studies in some patients with unusual body habitus or overriding lung tissue obscuring the echocardiographic window.211 In addition, wall motion scores, though clearly predictive, have largely been of research interest and clinicians have little direct experience in using such indexes for day-to-day patient management decisions.

**Recommendations for Two-Dimensional Echocardiography at Rest**

**Class I**

1. Detection or confirmation of suspected complications of infarction: Tissue rupture, aneurysm or pseudoaneurysm formation, infarct extension or expansion, mural thrombus, and right ventricular infarction.

**Class IIa**

1. For evaluation of left ventricular function in predicting a low risk subgroup for ambulation and early discharge from the coronary care unit.

**Class IIb**

1. Prediction of patients with multivessel coronary artery disease by the detection of remote asynery.

**Class III**

1. Where similar information has been obtained from other tests already performed or scheduled.

**Ambulatory Continuous Electrocardiographic Monitoring**

Guidelines for ambulatory electrocardiography have been previously published.212 Twenty-four-hour Holter monitoring before discharge detects less than one premature ventricular complex per hour in >50% of patients after infarction. These low risk patients have a 2-year mortality rate of about 5%.20 The 15% to 25% of postinfarction patients found to have ≥10 premature ventricular complexes per hour on Holter monitoring have a 2-year mortality rate >20%.217 Even as few as one to three premature ventricular complexes per hour and certainly more than three premature ventricular complexes or a single ventricular premature couplet in a 24-hour recording markedly increases the risk of death over a follow-up period of several years.213,214 Increasing complexity of the ventricular arrhythmia (pairs and runs of ventricular tachycardia) is associated with decreasing survival.180,190,215

Although ventricular ectopic activity is strongly associated with left ventricular dysfunction, multiple regression analysis in several large studies175,180,212–215 has shown it to be an independent risk factor for death after acute myocardial infarction. Furthermore, although the risk of death is greatest in patients with both complex ectopic activity and left ventricular dysfunction, the risk ratio was higher in patients with complex ectopic beats, even if they were at low risk by all other criteria. In these clinically uncomplicated patients, ectopic activity was infrequent, but when present it quadrupled the risk of death.215

**Electrophysiologic testing.** This has also been utilized to stratify patients with ventricular ectopic activity and coronary artery disease. When programmed ventricular stimulation induced sustained ventricular tachyarrhythmia, the 1-year mortality rate, even on antiarrhythmic therapy, exceeded 30% versus 2% for patients with noninducible arrhythmias.216 Because there are no randomized trials available to support the validity of this approach, however, the application of electrophysiologic study to evaluate ventricular ectopic activity occurring late after acute myocardial infarction remains controversial.48 There is no indication for the use of electrophysiologic study to evaluate ventricular tachycardia or cardiac arrest in the acute phase of myocardial infarction (≤48 hours).48 Signal-averaged electrocardiography is another promising technique that may prove beneficial in defining a subset of patients at high risk for sustained ventricular tachycardia.217

Whether antiarrhythmic therapy with encainide, flecainide, or moricizine can be expected to improve the survival of patients with significant ventricular arrhythmias is the subject of a randomized multicenter study, the Cardiac Arrhythmia Suppression Trial (CAST/NHLBI).218 Preliminary results from
that trial reveal an increased incidence of sudden death in patients treated with encainide or flecainide as compared with placebo-treated control subjects. All patients had demonstrated suppression of the ventricular arrhythmias before randomization to drug or placebo. Only 20% of the patients had nonsustained ventricular tachycardia and most had isolated premature ventricular beats. This study shows that these class IC antiarrhythmic agents should not be used in postmyocardial infarction patients with asymptomatic ventricular arrhythmias.\textsuperscript{218} The study does not provide any evidence that suppression of such arrhythmias has a positive therapeutic effect despite the evidence that these arrhythmias define a group of patients at increased risk of sudden death. There is no evidence that any drug, with the possible exception of $\beta$-blockers, alters the incidence of sudden death.

The Holter recording contains other information of value beyond documenting the frequency of premature ventricular complexes. The Holter monitor can be programmed to compute heart rate variability (standard deviation of all RR intervals in sinus rhythm). In a large trial,\textsuperscript{219} heart rate variability had the strongest univariate correlation with mortality of all the variables analyzed (greater than any grade of premature ventricular complexes, rales, and left ventricular ejection fraction <30%). This probably represents decreased vagal tone and increased sympathetic activity during ischemia, which would tend to promote ventricular fibrillation. ST segment shifts detected on calibrated continuous ambulatory ECG recording after infarction seem to represent ischemia that is frequently silent. Such changes are associated with a significantly increased 1-year mortality rate.\textsuperscript{220}

**Recommendations for 24-Hour Ambulatory Continuous Electrocardiography**

**Class IIa**

1. After myocardial infarction, patients with moderate to severe left ventricular dysfunction for prognostic assessment.
2. After myocardial infarction, patients with significant ventricular ectopic activity in the coronary care unit or stepdown telemetry unit for prognostic assessment.

**Class IIb**

1. After myocardial infarction, patients to determine heart rate variability for prognostic assessment.
2. High risk postmyocardial infarction patients as a screen for silent ischemia.

**Class III**

1. Uncomplicated ambulatory patients after discharge as a routine screen.

**Summary**

As noted at the beginning of this section, many of the described techniques are duplicative and the clinician must choose the tests that are cost-effective, are most accurate in his or her environment, and will lead to clinical decisions that can modify outcome or at least make a major impact on prognostication. One needs to decide if cardiac catheterization is indicated during the initial hospitalization or early convalescence and this frequently can be done by clinical assessment and data collected early in the initial hospitalization. Patients with an uncomplicated course and not considered for early catheterization need evaluation of left ventricular function either by echocardiography or radionuclide ventriculography and a search for evidence of myocardium at risk for new infarction by use of one of the three exercise strategies proposed.

If there is electrical instability manifested by complex ectopic beats or frequent ventricular premature beats during the later course of the infarction, a 24-hour ambulatory ECG recording is indicated. If there are runs of ventricular tachycardia, further electrophysiologic studies may be indicated, but it must be realized that there are no large trials to support the efficacy of antiarrhythmic therapy in the asymptomatic group of such patients after myocardial infarction. Studies showing efficacy of suppression of inducible sustained ventricular tachycardia have all been done in patients with chronic ischemic heart disease.

There are those who recommend routine convalescent cardiac catheterization and coronary angiography. This would eliminate the need for much of the noninvasive testing and eliminate exercise testing strategies in those selected immediately for surgical or angioplasty intervention. Cost-effectiveness is used as an argument, but we are not ready to recommend such a routine course because outcome data are not available as yet to support this aggressive strategy.

**Coronary Angiography**

Guidelines for the utilization of coronary angiography have been previously published.\textsuperscript{221} In essence, all of the risk stratification efforts described using clinical assessment, exercise testing, radionuclide imaging, echocardiography, and Holter monitoring have been directed at defining a subset of patients after infarction at high risk for complications or premature death who would be candidates for coronary angiography to determine the potential for revascularization. The prognosis in the first year after infarction is directly related to the extent of coronary obstruction and the degree of left ventricular dysfunction documented at angiography.\textsuperscript{176,222} The cost-effectiveness of various management alternatives after uncomplicated myocardial infarction has been analyzed using a theoretic model.\textsuperscript{223} The most cost-effective strategy was that which screened patients with treadmill exercise testing (with thallium added where indicated) and recommended coronary angiography and revascularization in all but those patients who had unequivocally negative studies.
Early Evolving Myocardial Infarction (Initial Hours of Myocardial Infarction)

Class I
1. All patients developing pump failure/shock syndrome.
2. All patients suspected of developing an acute ventricular septal defect.
3. Persistent or recurrent ischemia, or both, despite thrombolytic therapy.

Class IIa
1. When coronary angiography can be performed within the first 6 hours after the onset of chest pain in patients who are candidates for revascularization therapy utilizing percutaneous transluminal coronary angioplasty or coronary artery bypass surgery (but who are not candidates for thrombolytic therapy).
2. Patients who have had a previous aortocoronary vein graft if the graft is to the suspected infarct-related vessel.

Class IIb
1. Patients who can be taken quickly for angioplasty or bypass surgery in a facility set up and qualified for these emergency procedures.

Class III
1. As a routine after early intravenous thrombolytic therapy.
2. Patients with uncomplicated myocardial infarction having no evidence of ongoing ischemia.

Late Evolving Myocardial Infarction (After the Initial 6 Hours up to But Not Including Predischarge Evaluation)

Class I
1. Patients with recurrent episodes of ischemic chest pain, particularly if accompanied by ECG changes.
2. Patients suspected of having acute mitral regurgitation or a ruptured interventricular septum causing heart failure or shock.
3. Patients suspected of developing subacute cardiac rupture (pseudoaneurysm).
4. Patients with cardiogenic shock or severe pump failure.

Class IIa
1. Patients with congestive heart failure during intensive medical therapy.
2. Patients with recurrent ventricular tachycardia or ventricular fibrillation, or both, during intensive antiarrhythmic therapy.

Class IIb
1. Asymptomatic patients who have received thrombolytic therapy during the evolving phase.

Class III
1. Patients with uncomplicated completed myocardial infarction in whom no acute mechanical or surgical intervention is contemplated.

Convalescent Myocardial Infarction (Immediate Predischarge up to 8 Weeks After Discharge)

Class I
1. Postinfarction angina pectoris.
2. Patients with evidence of myocardial ischemia on laboratory testing: exercise-induced ischemia (with or without exercise-induced angina pectoris), manifested by ≥1 mm of ST segment depression or exercise-induced reversible thallium perfusion defect or defects, increased lung thallium uptake, or exercise-induced reduction of the ejection fraction or wall motion abnormalities on radionuclide ventriculography or two-dimensional echocardiography.

Class IIa
1. Patients with the need to return to unusually active and vigorous physical employment.
2. Patients with a left ventricular ejection fraction <40%.

Class IIb
1. As a routine in patients receiving thrombolytic therapy during the evolving phase of infarction.
2. Otherwise uncomplicated and asymptomatic patients who are <45 years of age.
3. Patients with uncomplicated non-Q wave myocardial infarction not otherwise manifesting evidence of myocardial ischemia on noninvasive laboratory testing.

Class III
1. Patients judged to have a debilitating disease or conditions that preclude their being candidates for invasive intervention.
2. Patients with coexisting disease judged to be primarily responsible for the patient's prognosis, with a greatly shortened life expectancy unless revascularization is determined to be necessary to facilitate treatment of the underlying disease.
3. Patients with very advanced left ventricular dysfunction (ejection fraction <20%) in the absence of angina pectoris or evidence of ischemia. An exception is the patient who is a candidate for aneurysmectomy or cardiac transplantation.
4. Patients with ventricular arrhythmias who have no evidence of ischemia symptomatically or during exercise testing, well preserved exercise tolerance and no suggestion of aneurysm formation. An exception may be the patient with inducible sustained ventricular tachycardia.

Follow-up Care
The Subcommittee decided to not include any detail regarding modification of coronary artery disease risk
factors in this report. We believe strongly that this is a major task for the clinician discharging and following up the patient after monitoring his or her infarction, but because of space limitations we have left this task to other reports. We urge clinicians to become involved in treatment of lipid abnormalities, stopping smoking, treating hypertension, weight control, exercise, prescriptions, and seeing that this modification is a lifestyle change rather than just a temporary change induced by the fright of the acute episode.

References


27. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1986; 255:2905–2989.


97. ISIS Pilot Study Investigators: Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. Eur Heart J 1987;8:634–642


139. Sebuski RJ, Ohi stein EH: Attenuation of platelet responsiveness to prostacyclin (PGI₂) after tissue plasminogen activator (t-PA) (abstract). *Circulation* 1987;76(suppl IV):IV-338


199. Guidelines for clinical use of cardiac radionuclide imaging: A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic
and Therapeutic Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 1968;8:1471–1483
201. Applegate RJ, Dell’Italia LJ, Crawford MH: Usefulness of two-dimensional echocardiography during low-level exercise testing after uncomplicated acute myocardial infarction. Am J Cardiol 1987;60:10–14
ACC/AHA guidelines for the early management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (subcommittee to develop guidelines for the early management of patients with acute myocardial infarction).


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