Part 7: The Era of Reperfusion
Section 1: Acute Coronary Syndromes (Acute Myocardial Infarction)

Major Guidelines Recommendations
Prehospital Care
- Implementation of out-of-hospital 12-lead ECG diagnostic programs is recommended in urban and suburban paramedic systems (Class I).
- Out-of-hospital fibrinolytic therapy is recommended when a physician is present or out-of-hospital transport time is $\geq 60$ minutes (Class IIa).
- When possible, patients at high risk for mortality or severe left ventricular (LV) dysfunction with signs of shock, pulmonary congestion, heart rate $>100$ beats per minute (bpm), plus systolic blood pressure (SBP) $<100$ mm Hg should be triaged to facilities capable of performing cardiac catheterization and rapid revascularization (PCI or coronary artery bypass graft surgery [CABG]). For patients $<75$ years of age, this is a Class I recommendation.

Reperfusion Therapies
- Many clinical trials have established early fibrinolytic therapy as a standard of care for acute ST-segment elevation myocardial infarction (MI) (Class I for patients $<75$ years old and Class IIa for patients $>75$ years old).
- Percutaneous coronary intervention (PCI), including angioplasty/stent, is a Class I recommendation for patients $<75$ years of age with acute coronary syndromes (ACS) and signs of shock.
- Patients in whom fibrinolytic therapy is contraindicated should be considered for transfer to interventional facilities when potential benefit from reperfusion exists (Class IIa).
- Heparin is currently recommended for patients receiving selective fibrinolytic agents (tissue plasminogen activator [tPA]/reteplase [rPA]) (Class IIa).
- Heparin dosing with fibrinolytics is changed to reduce the incidence of intracerebral hemorrhage (ICH) and minimize reocclusion. Give heparin in a 60-U/kg bolus followed by a maintenance infusion of 12 U/kg per hour (with a maximum of 4000 U bolus and 1000 U/h infusion for patients weighing $>70$ kg). The activated partial thromboplastin time should be maintained at 50 to 70 seconds for 48 hours.

New Therapy for Unstable Angina/Non–Q-Wave MI
- Glycoprotein (GP) IIb/IIIa inhibitors are recommended for patients with non–ST-segment elevation MI or high-risk unstable angina (Class IIa).
- GP IIb/IIIa inhibitors have incremental benefit in addition to conventional therapy with unfractionated heparin (UFH) and aspirin (Class IIa).
- Low-molecular-weight heparin (LMWH) is an alternative to UFH for the treatment of non–Q-wave MI and unstable angina.
- Troponin-positive patients are at risk for major adverse cardiac events (MACE) and should be considered for aggressive therapy.

Introduction
Evidence-based data for the management of acute myocardial infarction (AMI) has evolved dramatically in the past decade. AMI and unstable angina are now recognized as part of a spectrum of clinical disease collectively identified as acute coronary syndromes, which have in common a ruptured or eroded atheromatous plaque.1–5 These syndromes include unstable angina, non–Q-wave MI, and Q-wave MI. The ECG presentation of ACS encompasses ST-segment elevation infarction, ST-segment depression (including non–Q-wave MI and unstable angina), and nondiagnostic ST-segment and T-wave abnormalities. The majority of patients with ST-segment elevation will develop Q-wave MI. Only a minority of patients with ischemic chest discomfort at rest who do not have ST-segment elevation will develop Q-wave MI and will eventually be diagnosed as non–Q-wave MI or unstable angina. A significant portion of patients with an initial diagnosis of angina will not have ischemic coronary disease. Sudden cardiac death may occur with each of these syndromes. ACS is the proximate cause of sudden cardiac death in most adult patients.6–10

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The primary goals of therapy for patients with ACS are
- Reduction of myocardial necrosis in patients with ongoing infarction
- Prevention of major adverse cardiac events (death, nonfatal MI, and need for urgent revascularization)
- Rapid defibrillation when ventricular fibrillation (VF) occurs

To date $>750$ 000 patients with ACS have been studied worldwide in randomized clinical trials, producing an abundance of outcome-based data for healthcare providers. Several consensus panels,11–17 including the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines Committees for the Management of Acute Myocardial Infarction and Unstable Angina11–14,16 and the European Society of Cardiology and European Resuscitation...
Council,15,17 have considered the clinical impact of this data and have published guidelines for the management of ACS. The guidelines that follow are a refinement of these international guidelines for healthcare providers who treat patients with ACS within the first several hours after onset of symptoms. These guidelines address out-of-hospital, emergency department (ED), and critical-care issues. Regional practices vary as a result of differences in out-of-hospital and in-hospital resources, availability of healthcare professionals, expertise, and skill. Therefore, these guidelines are designed to provide general directions for care.

Pathogenesis
Understanding the principles of management of ACS requires a knowledge of developing concepts of thrombus initiation and coronary plaque pathobiology.1,18,19 Patients with coronary atherosclerosis in whom these clinical syndromes develop have various degrees of coronary artery occlusion. Typically ACS is caused by rupture of a lipid-laden plaque with a thin cap.1,2 Most of these plaques are not hemodynamically significant before rupture.20,21 However, an inflammatory component present in the subendothelial area further weakens the plaque and predisposes it to rupture.22 Blood flow velocity and turbulence as well as vessel anatomy may also be important contributing factors to plaque disruption. Superficial erosion of a plaque occurs in approximately 25% of patients who also manifest increased systemic markers of inflammation.23 The degree and duration of occlusion, as well as the presence or absence of collateral vessels, determine the type of infarction that occurs.

After plaque rupture or erosion, a monolayer of platelets covers the surface of the ruptured plaque (platelet adhesion). Additional platelets are recruited (platelet aggregation) and activated. Fibrinogen cross-links platelets, and the coagulation system is further activated by thrombin generation. A partially occluding thrombus produces symptoms of ischemia that may be prolonged and may occur at rest. At this stage the thrombus is platelet-rich. Therapy with antiplatelet agents, such as aspirin and GP IIb/IIIa receptor inhibitors, is most effective at this time. Fibrinolytic therapy is not effective and paradoxically may accelerate occlusion by causing the release of clot-bound thrombin, which further activates platelets.24,25

An intermittently occlusive thrombus may cause distal myocyte necrosis in the region supplied by the culprit artery, producing non–Q-wave MI. As the clot enlarges, microemboli originating in the thrombus may embolize and lodge in the coronary microvasculature, causing small elevations of cardiac troponins, new sensitive cardiac markers.10,19,26,27 Microvascular dysfunction is now understood to be an additional determinant of myocardial dysfunction in patients with ACS and those treated with PCI.27–30 Patients with such a thrombus are at highest risk for progression to MI. This process is known as minimal myocardial damage. Other mechanisms for myocardial ischemia and minimal necrosis include intermittent dynamic occlusion and spasm at the thrombus site.31 If the thrombus occludes the coronary vessel for a prolonged period of time, Q-wave MI occurs. The clot causing Q-wave MI is rich in thrombin and fibrin.32 In these patients, fibrinolysis or PCI (eg, angioplasty/stent) may limit the size of the infarct if performed sufficiently early in the course.

Out-of-Hospital Management
Early Defibrillation
Half of the patients who die of AMI do so early, before reaching a hospital (see Figure 1). In most of these deaths the presenting rhythm is ventricular tachycardia (VT)/VF.33–35 The major risk of VF occurs during the first 4 hours after onset of symptoms.36,37,37a VF that occurs during the acute phase (usually within the first few hours) of an MI is called “primary VF”; it occurs in 4% to 18% of patients with infarction.37a,38,39 Once the patient is admitted to the hospital, the incidence of in-hospital VF is approximately 5%.40 VF incidence appears to be declining even further in the modern era of reperfusion. Investigators in the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico Study (GISSI) found a 3.6% incidence of early VF and a 0.6% incidence of late VF. Fibrinolytic therapy reduced the occurrence of VF primarily within the first 3 hours; the occurrence of VF did not predict reperfusion.41,42 The presence of primary VF increases in-hospital mortality and complications41,43 but does not appear to increase long-term mortality.44

All emergency medical services (EMS) and dispatch systems should have a trained and dedicated staff to respond to cardiac emergencies. Because the incidence of VF is highest out of hospital, every emergency vehicle that responds to cardiac emergencies should carry a defibrillator with staff skilled in its use. The AHA, the European Resuscitation Council, and the International Liaison Council on Resuscitation endorse the position that all emergency personnel, including first responders both in-hospital and in the field, should be trained to operate a defibrillator.45,46 Automated external defibrillators (AEDs) have been used safely and effectively by first responders with minimal
training.47–51 Whether greater availability of AEDs and access to them will increase survival is the subject of ongoing evaluation.52–54 The AHA public health initiative public access defibrillation proposes to achieve more widespread early defibrillation through placement of AEDs throughout the community, making them available to a large number of trained lay community and nontraditional emergency responders. (See “Part 4: The Automated External Defibrillator.”)

Ideally an EMS system should have enough trained personnel that a first responder can be at a victim’s side anywhere in the system within 5 minutes. Early access is promoted by an emergency phone system with a dedicated number for that area (or region or country), with dispatchers trained to prioritize responses to these calls (see “Part 3: Adult Basic Life Support,” Emergency Medical Dispatchers). Because patients with AMI have a high risk of sudden cardiac death during the first hour after onset of symptoms, an out-of-hospital EMS system that can provide immediate defibrillation is mandatory. Every ambulance that transports cardiac patients should be equipped with a defibrillator and personnel proficient in its use. If VF occurs under observation and immediate defibrillation is available, many patients will survive (see Figure 1).

When patients with ACS, including MI and other ischemic syndromes, reach the ED and hospital critical care unit (CCU), their risk of sudden cardiac death due to lethal arrhythmias falls dramatically.40 This decline in risk stems from a combination of early reperfusion, administration of β-blockers, and other adjunctive agents used in the reperfusion era.55,56 The deaths that do occur during this period are due to VF/VT, LV power failure with congestive heart failure (CHF) and cardiogenic shock, reoclusion with extension of the infarct, or mechanical complications of cardiac rupture and structural damage (Figure 1). For these reasons, healthcare professionals should focus on limiting the size of the infarct, treating arrhythmias, and preserving LV function.

Patient Education and Delays in Therapy

Delays in therapy after the onset of symptoms for ACS occur during 3 periods: during the interval from onset of symptoms to patient recognition, during out-of-hospital transport, and during in-hospital evaluation. Potential delay during the in-hospital evaluation period may occur from door to data, from data (ECG) to decision, and from decision to drug; these 4 major points of in-hospital therapy are commonly referred to as the “4 D’s.”57

Because myocardial salvage is time dependent, with the greatest potential benefit in the first few hours of ACS, it is imperative that patients arrive at the treating hospital and receive evaluation and therapy as quickly as possible. Delay by patients, EMS personnel, and hospitals significantly prolongs the time to reperfusion therapy,58,59 reducing the effectiveness of fibrinolytic therapy and increasing mortality.

Patient delay to symptom recognition constitutes the longest period of delay to treatment. Prodromal symptoms are common among patients with ACS,60 but these symptoms are frequently denied or misinterpreted. The elderly, women, persons with diabetes, and hypertensive patients are most likely to delay, partly because they tend to have atypical symptoms or unusual presentations.61–64 In the US Rapid Early Action for Coronary Treatment (REACT) trial, the median out-of-hospital delay was ≥2 hours in non-Hispanic blacks, the elderly and disabled, homemakers, and Medicaid recipients. The decision to use an ambulance was an important variable that reduced out-of-hospital delay and persisted after correction for variables associated with severity of symptoms.65 Other factors that have an impact on the patient’s arrival at the hospital include time of day, location (eg, work or home), and the presence of a family member.66a,69 The REACT trial also found that community members recognized the value of EMS systems and warning signs of heart attack when they were involved as bystanders but often failed to act on their own behalf when having similar symptoms.66a

Out-of-hospital transport time constitutes only 5% of delay to treatment time, whereas in-hospital evaluation constitutes 25% to 33% of delay to treatment.67,68 EMS systems, hospitals, and communities should educate patients about symptoms of cardiac ischemia, rapidly triage patients to appropriate care, and provide rapid defibrillation and medical care to patients with ischemic-type chest discomfort.

Education of patients is the primary intervention to reduce denial or misinterpretation of symptoms. The physician and family members of patients with known coronary disease should reinforce the need to seek medical attention when symptoms recur, because these patients paradoxically present later than patients with no known disease. Public education campaigns have been effective in increasing public awareness and knowledge of the symptoms and signs of heart attack.69 The results of these campaigns, however, have been transient and unrewarding. An educational program emphasizing early recognition of symptoms and reasons for misinterpretation or denial of symptoms is important. Physicians should also educate their patients about the local EMS system and encourage early activation for appropriate symptoms.70 Physicians should discuss prompt and appropriate use of nitroglycerin (glyceryl trinitrate in Europe) and aspirin, EMS activation, and location of the nearest hospital that offers 24-hour emergency cardiac care.

Out-of-Hospital Fibrinolysis

Clinical trials have shown the benefit of initiating fibrinolysis as soon as possible after onset of ischemic-type chest pain. Because the potential for myocardial salvage is greatest very early in AMI, a number of researchers have studied administration of fibrinolytics during the out-of-hospital period. Several studies demonstrated the feasibility and safety of out-of-hospital fibrinolytic administration,71,72 but early small trials yielded conflicting results about the efficiency and efficacy of this strategy.73–78

Physicians in the Grampian Region Early Anistreplase Trial (GREAT) administered fibrinolytic therapy to patients at home 130 minutes earlier than to patients at the hospital and noted a 50% reduction in mortality in those treated earlier.77 At the 5-year follow-up examination, investigators found that fewer patients (25%) in the out-of-hospital treatment group had died compared with a greater number (36%)
in the hospital treatment group (log-rank test, \( P < 0.025 \)).\(^79\)

Delaying fibrinolytic treatment by 30 minutes reduced average life expectancy by approximately 1 year. Delaying fibrinolytic treatment by 1 hour increased the hazard ratio of death by 20%, which is equivalent to the loss of 43 lives per 1000 patients within the next 5 years.

The European Myocardial Infarction Project group (EMIP) found that patients in the out-of-hospital treatment group received fibrinolytic therapy a median of 55 minutes earlier than those in the in-hospital treatment group.\(^72,77\) Death due to cardiac causes was significantly less common in the group treated out of hospital than in the group treated in-hospital (8.3% versus 9.8%; reduction in risk, 16%; 95% CI, 0% to 29%; \( P = 0.049 \)). Only a nonsignificant reduction in overall mortality was observed at 30 days in the out-of-hospital group (9.7% versus 11.1% in the hospital group; reduction in risk 13%; 95% CI, –1% to 26%; \( P = 0.08 \)).

In the Myocardial Infarction Triage and Intervention (MITI) trial,\(^7\) no significant difference in mortality between out-of-hospital and in-hospital fibrinolysis was observed. In a retrospective analysis, however, researchers noted that any patient treated within a median time of 70 minutes, whether before or after hospital arrival, had a significantly improved outcome. A confounding variable in this trial was advance notification of hospital staff and the shortening of hospital treatment times compared with historic controls.\(^8\)\(^0\)

A meta-analysis of out-of-hospital fibrinolytic trials summarized by the EMIP group found a 17% relative improvement in outcome associated with out-of-hospital fibrinolytic therapy. The greatest improvement was observed when therapy was initiated 60 to 90 minutes earlier than in the hospital.\(^8\)\(^1\) More recently a meta-analysis evaluated time to therapy and impact of prehospital fibrinolysis on all-cause mortality. Pooled results of 6 randomized trials with >6000 patients found a significant 58-minute reduction in time to administration (\( P = 0.007 \)) and decreased all-cause hospital mortality (OR 0.83; CI 0.70 to 0.98).\(^8\)\(^2\) Although fibrinolytic therapy initiated out of hospital results in earlier treatment, the time savings can be offset in most instances by an improved hospital triage with a door-to-needle time ≤30 minutes.

In summary, administration of fibrinolytics during the out-of-hospital period appears to reduce mortality when transport times are long (Figure 2). The 1996 ACC/AHA Task Force on Practice Guidelines recommended that out-of-hospital systems focus on early diagnosis and that fibrinolytics be administered in the field when a physician is present or transport time is >90 minutes.\(^8\)\(^3\) The European Society of Cardiology and the European Resuscitation Council recommend out-of-hospital fibrinolysis when transport time is ≥30 minutes or hospital door-to-needle time (beginning infusion of a fibrinolytic agent) is expected to be ≥60 minutes.\(^8\)\(^4\) The AHA Committee on Emergency Cardiovascular Care, the Evidence Evaluation Conference, and the international Guidelines 2000 Conference expert panels evaluated these recommendations and recent data and practice. We recommend out-of-hospital fibrinolytic therapy only when a physician is present or out-of-hospital transport time is ≥60 minutes (Class IIa). Observations from trials of out-of-hospital fibrinolysis suggest that most EMS systems should focus on early diagnosis and rapid transport instead of delivery of therapy.

### Out-of-Hospital ECGs

Out-of-hospital performance of electrocardiography and transmission of the ECG to the ED speeds the care of patients with AMI. Multiple studies have shown the feasibility of obtaining a 12-lead ECG during the out-of-hospital period.\(^7\)\(^1,8\)\(^3\)–\(^8\)\(^5\) Diagnostic-quality ECGs can be successfully transmitted for approximately 85% of patients with chest pain who are eligible for 12-lead ECGs.\(^8\)\(^4\) Recording an ECG increases the time spent at the scene of an emergency by only to 4 minutes.\(^7\)\(^1,8\)\(^7\)\(^9\) In addition, there is no difference between the quality of information collected out-of-hospital and that received by cellular transmission at the base station.\(^8\)\(^3\) A diagnosis of AMI can be made sooner when the 12-lead ECG is obtained before the patient arrives in the hospital than if the ECG is performed after arrival.

The use of out-of-hospital ECGs and a chest pain evaluation form leads to more rapid initiation of reperfusion therapy without substantially delaying out-of-hospital time. A 12-lead ECG transmitted to the hospital speeds diagnosis and shortens time to fibrinolysis.\(^8\)\(^5,8\)\(^6,9\)\(^3,9\)\(^4\) Many studies have shown significant reductions in hospital-based time to treatment with fibrinolytic therapy in patients with AMI identified before arrival by a 12-lead ECG.\(^8\)\(^7\)–\(^8\)\(^9\)\(^5\) Time savings in these studies ranged from 20 to 55 minutes.\(^8\)\(^7\)–\(^8\)\(^9\)\(^\)\(^5\) Patients with an AMI identified by an out-of-hospital 12-lead ECG were more frequently treated in the ED than the CCU, and a trend toward more rapid ED and CCU treatment was demonstrated.\(^9\)\(^6\) The US National Heart Attack Alert Program recommends that EMS systems provide out-of-hospital 12-lead ECGs to facilitate early identification of AMI and that all advanced lifesaving vehicles be able to transmit a 12-lead ECG to the hospital.\(^9\)\(^7\)

A retrospective study of the US National Registry of Myocardial Infarction database showed a mortality benefit (reduction in mortality) for patients with AMI identified by an out-of-hospital 12-lead ECG.\(^9\)\(^8\) Canto et al evaluated the treatment and outcome of patients with and without an out-of-hospital 12-lead ECG. Although the median time from onset of infarction to arrival at the hospital was longer among
Cardiogenic Shock and Out-of-Hospital Facility Triage

Controversy continues over whether fibrinolytic therapy or PCI is the best method of reperfusion (see below). Mortality among patients with cardiogenic shock is high in reported studies.99–102 In recent years an increasing body of evidence has suggested that early hemodynamic stabilization is beneficial and reduces mortality in certain patients. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) investigators retrospectively evaluated patients with cardiogenic shock after MI. The incidence of cardiogenic shock in the study was 11%, and an aggressive strategy (PCI) was associated with a lower mortality than that associated with fibrinolytic therapy.103 The use of early invasive interventions is more common in the United States than in other countries, but patients who underwent revascularization had better survival in all countries.104 In the Second National US Registry of Myocardial Infarction, the mortality rate in patients with AMI and shock was lower in those treated with PCI as a primary strategy than in those treated with fibrinolysis.105 In a large registry of patients with shock, mortality was also lower in AMI patients who received early revascularization with either PCI or CABG.106

A recently completed randomized trial found reduced mortality among patients with cardiogenic shock treated aggressively with intra-aortic balloon pulsation (IABP) and mechanical or surgical revascularization. In the SHOCK trial 152 patients were randomly assigned to an early revascularization strategy (ERV) and 150 patients were assigned to a strategy of initial medical stabilization (IMS).106a The initial medical management strategy was aggressive for both the ERV and IMS groups; intra-aortic balloon pump (IABP) support was used in 86% of both groups. Sixty-three percent of the IMS group received fibrinolytic agents, and 25% underwent delayed revascularization. Of the ERV group of patients who underwent emergency early revascularization, >60% received PCI and 40% had surgical revascularization. The 30-day mortality rate for ERV patients was lower but not significantly lower than those with IMS. A secondary end point, mortality rate at 6 months, was significantly lower in the ERV group (50.3% versus 63.1%, P=0.027). In this study a prespecified subgroup analysis was performed for patients <75 years old. The analysis showed a 15.4% reduction in 30-day mortality with early revascularization (IMS group, 56.8% versus ERV group, 41.4%, P<0.01). Outcome for patients >75 years old was worse for the ERV group. These results were thought to mirror those in the SHOCK registry.107

The 1999 update of the ACC/AHA Guidelines for the Management of Patients With Myocardial Infarction was revised to indicate a Class I recommendation for PCI in patients with shock who are <75 years of age. These recommendations were supported at the Guidelines 2000 Conference.13 Use of IABP followed by diagnostic cardiac catheterization and, where anatomically appropriate, coronary revascularization with either PCI or CABG may reduce mortality.108–112

When possible, transfer patients at high risk for mortality or severe LV dysfunction with signs of shock, pulmonary congestion, heart rate >100 bpm, and SBP <100 mm Hg to facilities capable of cardiac catheterization and rapid revascularization (PCI or CABG) (for patients <75 years old, Class I). An out-of-hospital checklist can also identify patients who have contraindications to fibrinolytic therapy. Patients with contraindications to fibrinolytic therapy should be considered for transfer to interventional facilities when benefit from reperfusion exists (Class IIa).

Initial General Measures

Immediately begin continuous cardiac monitoring for patients with suspected ischemic-type chest pain and obtain intravenous access. Administer morphine, oxygen, nitroglycerin, and aspirin (“MONA”) to patients without contraindications. Determine the immediate treatment necessary, rapidly assess reperfusion eligibility, and administer necessary adjunctive treatments (Table 1 and Figure 3).

Oxygen

Administer oxygen to all patients complaining of ischemic-type chest discomfort. Also administer oxygen, usually by
Initial general treatment (memory aid: “MONA”)

- Morphine, 2 to 4 mg repeated every 5 to 10 min to provide adequate analgesia (diamorphine may be used instead of morphine in some countries)
- Oxygen, 4 L/min; continue if arterial oxygen saturation <90%
- Nitroglycerin, sublingual or spray, followed by IV for persistent or recurrent discomfort
- Aspirin, 160 to 325 mg (chew and swallow)

Specific treatments

- Target times for reperfusion therapy
  - Fibrinolytic agents: door-to-needle time <30 min
  - Primary PCI: door-to-dilatation time 90–30 min
- Conjugate therapy (combined with fibrinolytic agents)
  - Aspirin
  - Heparin (especially with fibrin-specific lytics)
- Adjunctive therapies
  - β-Blocker if no contraindications
  - IV nitroglycerin (for recurrent ischemia, large anterior MI, heart failure, antihypertensive effects)
- ACE inhibitor (especially large anterior wall MI, heart failure without hypotension [SBP >100 mm Hg], previous MI)

Patients with ST-segment elevation or new or presumably new bundle-branch block are candidates for reperfusion therapy.

nasal cannula, to all patients with suspected ACS. Experimental evidence suggests that breathing supplemental oxygen may limit ischemic myocardial injury. There is also evidence that oxygen reduces the amount of ST-segment elevation, although it is not known whether this therapy reduces morbidity or mortality among patients with AMI. Results of early experimental studies aimed at reducing the size of the infarct suggested that oxygen might be beneficial. In addition, oxygen can reduce ST-segment elevation among patients with anterior infarction.113,114

If a patient has overt pulmonary congestion or if oxygen saturation is <90%, continue oxygen therapy until the patient’s condition has stabilized. If hypoxemia is persistent and respiratory muscle fatigue develops, consider early intubation with assisted mechanical ventilation and a higher fraction of inspired oxygen (FiO₂). Hypoxemia and respiratory insufficiency can tax a marginal cardiac output substantially, leading to increased infarct size and cardiovascular collapse. No clinical studies, however, have shown a reduction in morbidity or mortality with the routine use of supplemental oxygen and current treatment regimens. In the absence of compelling indications in uncomplicated cases, there is little justification for continued use of oxygen beyond 2 to 3 hours.

NITROGLYCERIN (OR GLYCEROL TRINITRATE)

Nitroglycerin (glyceryl trinitrate in Europe) is an effective analgesic for ischemic-type chest discomfort. Nitrates also have beneficial hemodynamic effects, including dilation of the coronary arteries (particularly in the region of plaque disruption) and the peripheral arterial bed and venous capacitance vessels. Administer sublingual or aerosol nitroglycerin; repeat twice at 5-minute intervals until pain is relieved or low blood pressure limits its use. Initially administer nitrates to all patients with suspected ischemic-type pain unless SBP is <90 mm Hg.

The most significant potential complication of nitroglycerin therapy is systemic hypotension; this complication should be avoided when possible. Also avoid use of nitroglycerin in patients with extreme bradycardia (<50 bpm) or tachycardia. Administer nitrates with extreme caution, if at all, to patients with suspected right ventricular (RV) infarction.

Routine use of nitroglycerin has not been shown to be beneficial in AMI. In trials conducted before the fibrinolytic era, intravenous nitrates reduced infarct size. An analysis of subgroups in the largest of these studies showed that most of this benefit was in large anterior wall infarcts,115 and a meta-analysis concluded that nitroglycerin was effective in reducing mortality.116 In the Fourth International Study of Infarct Survival (ISIS-4) and GISSI-3, no conclusive evidence was presented to recommend routine use of oral or topical nitrile therapy in patients with AMI.117

Nitroglycerin is indicated for the initial management of pain and ischemia with AMI without hypotension (SBP <90 mm Hg), except in patients with RV infarction. Nitroglycerin should be used cautiously in patients with inferior wall MI with possible RV involvement (see below). Evidence does not support the routine administration of nitroglycerin in patients with uncomplicated AMI. In patients with recurrent ischemia, nitrates are indicated in the first 24 to 48 hours. They may be useful in patients with hypertension, CHF, and large anterior wall MI. In the absence of these indications, use of nitrates should be carefully considered, especially when lower blood pressure precludes the use of other agents shown to be effective in reducing morbidity and mortality, eg, β-blockers and angiotensin-converting enzyme (ACE) inhibitors (ACEIs). The continued use of nitroglycerin beyond 48 hours is indicated for patients with recurrent angina or persistent pulmonary congestion. Initially avoid the use of long-acting nitrates, including topical preparations whose absorption may be altered as skin blood flow changes in response to neurohumoral alterations during the peri-infarction period. Instead use intravenous preparations, which can be controlled more precisely during periods of hemodynamic lability.

MORPHINE

Although nitroglycerin effectively relieves ischemic-type chest discomfort due to ACS, it should not be used as a substitute for narcotic analgesia, which is often necessary to relieve pain associated with MI. Morphine is indicated for continuing pain unresponsive to nitrates. Morphine is also effective in patients with vascular congestion complicating AMI because of its favorable hemodynamic effects. Mor-
Figure 3. Acute ischemic chest pain protocol. Although local evaluation, diagnosis, and treatment may vary, core concepts involve the prompt treatment of ischemic-type chest pain with oxygen, nitrates, and morphine. The ECG is central to the initial triage of patients and allows identification of patients at high, intermediate, or low risk, who may then be further evaluated. Patients with ST-segment elevation should be rapidly assessed for reperfusion therapy (fibrinolytic; PCI). ST-segment depression identifies a group of patients at high short-term risk for cardiac events, and aggressive antiplatelet therapy is indicated whether a medical or invasive strategy is chosen. Some patients at increased risk also have nondiagnostic or normal ECGs, and the use of cardiac markers, C-reactive protein, and functional studies allows additional risk stratification.
Phenobarbital reduces ventricular preload and oxygen requirements primarily by venodilation. For this reason it should not be used in patients who may have hypovolemia. If hypotension develops, elevation of the patient’s legs and volume infusion with saline will usually reverse adverse hemodynamics. Pain associated with MI may be due to continuing ischemia of viable myocardium in the evolving infarct region. 

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\beta\text{-Adrenergic receptor blocking agents are effective anti-ischemic agents that often also reduce or control the pain of infarction.}
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![Figure 4. The Acute Coronary Syndromes Algorithm.](image-url)
Aspirin

Although a time-dependent effect of aspirin is not supported by evidence, aspirin should be given as soon as possible to all patients with suspected ACS unless the patient is allergic to it. A dose of 160 to 325 mg causes rapid and near-total inhibition of thromboxane A2 production. This inhibition reduces coronary reocclusion and recurrent events after fibrinolytic therapy. Aspirin alone reduced death from MI in the Second International Study of Infarct Survival (ISIS-2), and its effect was additive to that of streptokinase. In a review of 145 trials involving aspirin, the Antiplatelet Trialists Collaboration reported a reduction in vascular events from 14% to 10% in patients with MI. In high-risk patients, aspirin reduced nonfatal MI by 30% and vascular death by 17%. Aspirin is also effective in patients with unstable angina. For this reason, aspirin should be part of the early treatment of all patients with suspected ACS. Aspirin is relatively contraindicated for patients with active peptic ulcer disease and a history of asthma.

Chewable aspirin is absorbed more quickly than swallowed tablets in the early hours after infarction, particularly if morphine has been given. Aspirin suppositories (325 mg) are safe and recommended for patients with severe nausea, vomiting, or disorders of the upper gastrointestinal tract.

Risk Stratification, Initial Therapy, and Evaluation for Reperfusion in the ED

The Ischemic Chest Pain Algorithm (Figure 3) provides an overview of the recommended approach to patients presenting with ACS. Such an organized and interdisciplinary protocol is essential for efficient, effective treatment of these patients. The initial clinical history and ECG are used to triage patients into risk categories and choose a treatment strategy. Patients with ischemic-type chest discomfort and ST-segment elevation should be rapidly identified and considered for reperfusion therapy. If an ECG was not obtained during the out-of-hospital period, one should be obtained and reviewed by the senior physician treating the patient within 10 minutes of the patient’s arrival in the ED. If the patient meets the criteria for reperfusion therapy, a door-to-needle time (beginning of infusion of a fibrinolytic agent) of 30 minutes is consistent with the urgent need for reperfusion.

TABLE 2. Patients With Chest Pain Suggestive of Ischemia: Probability of Significant CAD Based on Clinical Features and Presenting ECG

<table>
<thead>
<tr>
<th>High Risk (≥1 of the Following Features)</th>
<th>Intermediate Risk (No High-Risk Features Plus 1 of the Following)</th>
<th>Low Risk (No High- or Intermediate-Risk Features Plus 1 of the Following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI or life-threatening arrhythmia episode</td>
<td>Definite clinical angina in young age</td>
<td>Possible angina</td>
</tr>
<tr>
<td>Known CAD</td>
<td>Definite clinical angina</td>
<td>Probable angina in older age</td>
</tr>
<tr>
<td>Dynamic ST-segment changes with chest symptoms</td>
<td>Possible angina</td>
<td>1 risk factor, not diabetes</td>
</tr>
<tr>
<td>Marked T-wave changes in anterior precordial leads</td>
<td>ST-segment depression ≤1 mm</td>
<td>Normal ECG</td>
</tr>
<tr>
<td></td>
<td>T-wave inversion &lt;1 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabete</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 other risk factors</td>
<td></td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease. Modified from Reference 14.

Figure 5. The TIMI investigators found that baseline characteristics, including age, sex, previous or anterior MI, indicators of LV dysfunction such as rales and hypotension/tachycardia, atrial fibrillation, or diabetes were predictive of mortality at 30 days. Mortality increased from 1.4% with no risk factors to ≥22% when ≥4 risk factors were present. From Cannon CP, et al. J Am Coll Cardiol. 1999;33(suppl A):396A.

The first physician who encounters a patient with MI should be able to determine the need for fibrinolysis and direct its administration. Protocols for rapid evaluation and treatment should be available. Consultation with a cardiologist or the patient’s personal physician delays therapy, is associated with increased hospital mortality, and is recommended only in equivocal or uncertain cases. Patients with ST-segment elevation and new or presumably new left bundle-branch block should be quickly screened for indications and contraindications to fibrinolytic therapy. See Figure 4, The Acute Coronary Syndromes.

Risk Stratification With the First 12-Lead ECG

Use the 12-lead ECG to triage patients into 1 of 3 groups:

1. ST-segment elevation
2. ST-segment depression (≥1 mm)
3. Nondiagnostic or normal ECG

Patients with ischemic-type pain but normal or nondiagnostic ECGs or ECGs consistent with ischemia (ST-segment depression only) do not benefit from fibrinolytic therapy. These patients are not candidates for fibrinolytic agents. In
TABLE 3. Patients With Chest Pain Suggestive of Ischemia: Short-Term Risk of Death and Nonfatal MI

<table>
<thead>
<tr>
<th>High Risk of Death or Nonfatal AMI (≥1 of the Following)</th>
<th>Intermediate Risk of Death or Nonfatal AMI (No High-Risk Features Plus 1 of the Following)</th>
<th>Low Risk of Death or Nonfatal AMI (No High- or Intermediate-Risk Features Plus 1 of the Following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged continuing pain not relieved by rest (&gt;20 min)</td>
<td>Prolonged angina (&gt;20 min) but resolved at time of evaluation; moderately high likelihood of CAD</td>
<td>Angina increased in frequency, severity, or duration</td>
</tr>
<tr>
<td>Pulmonary edema related to ischemia</td>
<td>Rest angina &gt;20 min or relieved with nitroglycerin</td>
<td>Lower activity threshold before angina</td>
</tr>
<tr>
<td>S$_3$ or rales</td>
<td>Age &gt;65 y</td>
<td>1 risk factor, not diabetes</td>
</tr>
<tr>
<td>Hypotension with angina</td>
<td>Dynamic T-wave changes and angina</td>
<td>New-onset angina &gt;2 wk to 2 mo before presentation</td>
</tr>
<tr>
<td>Rest angina with dynamic ST-segment changes &gt;1 mm</td>
<td>Pathological Q waves or ST-segment depression &lt;1 mm multiple-lead groups</td>
<td>Normal or unchanged ECG</td>
</tr>
<tr>
<td>Elevated serum troponin T or I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Although the ECG is nondiagnostic in approximately 50% of patients with chest discomfort, it is central and helpful in risk stratification of patients with suspected ACS. The terms transmural MI and subendocardial MI have been replaced by Q-wave MI and non–Q-wave MI. However, physicians in the ED will not be able to determine whether an infarction will evolve into a Q-wave or non–Q-wave MI. Initial triage and reperfusion decisions are therefore based on the presence of ST-segment elevation, ST-segment depression, and nondiagnostic ST-segment and T-wave abnormalities on the ECG.

Patients with ischemic-type chest pain and ST-segment elevation ≥1 mm in 2 contiguous leads have a 45% sensitivity but a 98% specificity for AMI. In the TIMI IIIB registry of patients with unstable angina/non–Q-wave MI, the ECG ancillary study found that 60% of patients with ischemic pain had no ECG changes. Patients traditionally thought to be at high risk with >1 mm ST-segment depression constituted 12.4% of patients and had an 11% 1-year rate of death or nonfatal MI. However, patients with 0.5-mm ST-segment depression were also found to be at high risk, and death or MI occurred in 16.3% at 1 year, suggesting that the more traditional use of 1 mm ST-segment depression warrants review. T-wave inversion did not add to the clinical history or significantly increase the 1-year event rate. Although patients presenting with left bundle-branch block had a low hospital event rate (1%), with no significant coronary disease in >34%, they had the highest 1-year mortality rate and more heart failure. Careful follow-up and more intensive medical therapy are appropriate.

Patients with normal or nondiagnostic ECGs should be reevaluated for the cause of their symptoms. Coronary angiographic studies have shown that as many as 20% of patients with unstable angina will have normal or nonsignificant coronary artery disease. In the Women’s Ischemia Symptom Evaluation (WISE) trial, 70% of women had normal arteries or no significant obstructive disease (<50% closed). A prior ECG for comparison is useful when the initial ECG is consistent with ischemia or infarction. Diagnostic accuracy and triage decisions are improved by reducing the admission of patients without ACS (increased specificity) without reducing the admission of patients with these diagnoses (unchanged sensitivity). A repeat ECG with pain or after initial assessment may be helpful when the initial ECG is normal or nondiagnostic and should be obtained approximately 1 hour after admission or sooner if clinically indicated.

The presence of Q waves does not preclude the use of reperfusion therapy but predicts a worse outcome. In fact, Q waves may develop quite early in ACS. In 1 study, 53% of patients presenting within 1 hour of onset of symptoms already displayed abnormal Q waves. This early development of Q waves appears to predict the size of the infarct but may not negate beneficial effects of fibrinolytic therapy on mortality or myocardial salvage.

Failure of reperfusion with fibrinolytics has been difficult to evaluate with clinical parameters. More recently, studies evaluating resolution of ST-segment elevation following fibrinolysis have shown a strong correlation with infarct patency and therapeutic efficacy.

Risk Stratification and Clinical Variables

When combined with clinical information, the ECG helps triage patients into treatment and risk profile groups. The TIMI-II and TIMI-9 studies found that clinical risk factors, including age, female sex, history of MI, anterior MI, rales, hypotension and increased heart rate, diabetes, and atrial fibrillation, were incremental and predicted mortality at 30 days (Figure 5). The hospital mortality rate was 1.6% in patients with no risk factors and 22.3% in those with >4 risk factors. Clinical variables can be used to assess the probability of coronary artery disease (Table 2) and the risk of a major adverse cardiac event in the presence of unstable angina (Table 3). Patients with unstable angina can be placed into high-, intermediate-, and low-risk groups for more aggressive treatment strategies and newer therapies in a cost-effective manner.
manner. Most recently, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) investigators have also found that, in addition to age, ST-segment depression and signs of heart failure, and positive cardiac markers predicted mortality or myocardial (re)infarction.

New cardiac markers more sensitive than the myocardial muscle creatine kinase isoenzyme are useful in risk stratification and determination of prognosis. An elevated level of troponin correlates with an increased risk of death, and greater elevations predict greater risk. An elevated level of troponin also has incremental value beyond that of the ECG and clinical variables. In addition, elevated troponin levels have predicted the benefits of newer treatment therapies, including GP IIb/IIIa inhibitors and LMWH. Patients with increased troponin levels have increased thrombus burden and microvascular embolization. In the absence of troponin elevation, inflammatory markers help identify chest pain patients with unstable plaques and active inflammation. C-reactive protein has independent prognostic utility and is incremental when troponin levels are considered. C-reactive protein appears to predict 6-month but not short-term major cardiac events in ACS. More clinical studies are needed to determine whether C-reactive protein can identify patients who will benefit from aggressive medical treatment strategies or early coronary intervention.

**ST-Segment Elevation MI**

Patients with ST-segment elevation should be rapidly evaluated for reperfusion therapy. Strategies for reperfusion include the administration of fibrinolytics and primary PCI.

**Reperfusion Therapy: Fibrinolytics**

Perhaps the most significant advance in treatment of cardiovascular disease in the last decade is reperfusion therapy for AMI. Many clinical trials have established early fibrinolytic therapy as a standard of care (Class I for persons <75 years of age and Class IIa for persons >75 years of age) for acute ST-segment elevation MI. In addition, the era of reperfusion has enriched our understanding of MI and other ACS.

The first megatrial to show a reduction in mortality associated with fibrinolytic therapy was the GISSI-1 trial, which randomly assigned 17,721 patients to streptokinase or placebo and found a significant reduction in 21-day mortality in the streptokinase-treated group. This effect on mortality has recently been documented to persist for up to 10 years. The GISSI-1 trial also found the greatest benefit when treatment occurred during the first 3 hours after onset of symptoms. This trial predicted a maximum reduction in mortality of 47% for patients treated in the first hour. The landmark ISIS-2 study convincingly showed that antiplatelet therapy with aspirin (OR 23%) or fibrinolytic therapy with streptokinase (OR 25%) alone reduced mortality in patients with MI (see Figure 6). The effect of combining these 2 treatments was additive; mortality was reduced by 42%. Most of this reduction (53%) occurred if therapy was provided during the first 4 hours after the onset of symptoms. An overview of all available randomized trials in 1990 noted a reduction in short-term mortality of 24% (treated 12.8%; placebo 10%; P<0.0001) with a maintained benefit in the 2 largest trials. The reperfusion era had come of age.

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

- Short time to reperfusion
- Early and sustained patency of the infarct-related artery with normal flow (TIMI grade 3)
- Normal microvascular perfusion

Early studies in laboratory animals suggested that the infarct was substantially complete within 6 hours. Results of early fibrinolytic trials in humans were similar: Most reduction in mortality occurred when therapy was initiated in the first few hours after infarction. In GISSI-1 a 50% reduction in mortality was found in patients treated within the first hour. Results of the Myocardial Infarction Triage and Intervention (MITI) trial supported this finding and showed that patients treated within the first 70 minutes of onset of symptoms had a >50% reduction in infarct size and a reduction in mortality from 8.7% to 1.2%. These studies led to the initial US recommendation that all patients with ST-segment elevation infarction within 6 hours of onset of symptoms be considered candidates for fibrinolytic therapy.

Additional studies have suggested that the benefit of treatment may extend up to 12 hours. Reduction in mortality was confirmed in a large meta-analysis, which showed an 18% proportional reduction (P<0.0001) in mortality, leading to a reduction in mortality of 18 deaths per 1000 patients treated. Subsequent recommendations have expanded treatment indications and increased the time window for patients in whom the risk-benefit ratio is favorable.

The early benefit results from myocardial salvage. This “saving of muscle” is due to early rapid patency and complete restoration of normal flow (“time is muscle”). An additional late benefit of infarct-artery patency is the mortality benefit, which occurs independent of ventricular function. This late benefit appears to come from a reduction of scar formation and from attenuation of ventricular dilation and infarct remodeling. Attenuation of remodeling of the infarcted myocardium reduces the development of CHF, promotes electrical stability of the infarct substrate, and increases the likelihood of recovery of watershed (“penum-
Areas of ischemia. This is particularly true for areas of the myocardium that depend on collateral circulation.

Risk/Benefit of Fibrinolytic Therapy

Physicians who administer fibrinolytic agents should be aware of the indications, contraindications, benefits, and major risks of administration. Most of the reluctance to administer fibrinolytic agents is related to the risks of hemorrhage and intracranial bleeding. In addition, a number of patients are considered marginal, which makes it difficult to apply eligibility criteria. Familiarity with these risk/benefit principles will allow the physician at the bedside to weigh the net clinical benefit for each patient.

A large body of evidence confirms that patients who present with ischemic pain and ST-segment elevation (≥0.1 mV in ≥2 contiguous leads) within 12 hours of onset of persistent pain receive the greatest benefit from fibrinolytic therapy. The initial ECG can be prognostic as well as diagnostic, with useful information for the clinician evaluating the patient for risk and benefit. The GISSI investigators found that stratification of patients by both infarct site (inferior, anterior, lateral, multiple) and the number of leads with ST-segment elevation predicted both benefit from fibrinolysis and mortality. Mortality was almost linearly related to the number of leads with ST-segment elevation (Figure 7).

The Fibrinolytic Therapy Trialists’ (FTT) Collaborative Group evaluated 9 major randomized trials with >1000 patients each (45 000 total patients) to determine the safety and benefit of fibrinolytic therapy in a wide variety of patient subgroups (Figure 8). Treatment was helpful regardless of patients’ sex, presenting blood pressure (if SBP was <180 mm Hg), previous MI, or diabetes. Although cardiogenic shock was not specifically identified, patients with low blood pressure and tachycardia also benefited. Therapeutic benefit was seen for up to 12 hours but was greatest when fibrinolytics were administered in the first 3 hours. The benefits were less impressive in inferior wall infarction, except when it was associated with RV infarction (ST-segment elevation in lead V_{1,R} or anterior ST-segment depression). Older patients had a higher absolute risk of death, but absolute benefit in older patients was similar to that in younger patients. Fewer numbers of older patients (>75 years old) were included in the analysis, however, and most patients had been treated with streptokinase.

Although age is not a contraindication to fibrinolytic therapy and absolute benefit remains, the incidence of stroke increases with advancing age, and the relative benefit of fibrinolytic therapy is reduced. Older age is the most important baseline variable predicting nonhemorrhagic stroke. Investigators from the Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO-I) trial recently reported lower mortality and net clinical benefit with accelerated administration of tPA in patients <85 years old; this treatment also resulted in lower mortality at 1 year. Too few patients >85 years old were included in the clinical trial for analysis. A recent retrospective analysis of the US Medicare database of patients >75 years of age treated with fibrinolytic therapy found no specific survival advantage and possible risk for patients >75 years old. Additional studies are needed to clarify risk-benefit parameters in the elderly. A careful review of associated risks and potential benefits in the elderly is needed, and recent clinical trials with larger numbers of elderly subjects have recorded an increased incidence of stroke. Elderly patients should be carefully assessed.

One method for expressing the time-dependent benefit of fibrinolytic therapy is the concept of “lives saved per 1000
TABLE 4. Comparison of Fibrinolytic Therapy With Standard Therapy

<table>
<thead>
<tr>
<th>Fibrinolytics Started</th>
<th>Additional Lives Saved per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the first hour</td>
<td>65</td>
</tr>
<tr>
<td>In the second hour</td>
<td>37</td>
</tr>
<tr>
<td>In the third hour</td>
<td>29</td>
</tr>
<tr>
<td>Between hours 3 and 6</td>
<td>26</td>
</tr>
<tr>
<td>Between hours 6 and 12</td>
<td>18</td>
</tr>
<tr>
<td>Between hours 12 and 24</td>
<td>9</td>
</tr>
</tbody>
</table>

patients treated.165 The method assumes 1000 patients treated with fibrinolytics and 1000 patients treated with standard care that does not include fibrinolytics. The analysis calculates the number of additional lives saved (or the number of deaths) per 1000 people. This recent study pooled findings from 22 randomized, controlled trials of fibrinolytic therapy published from 1983 to 1993. The study results are summarized in Table 4.

**Intracerebral Hemorrhage**

Fibrinolytic therapy is associated with a small but definite increase in the risk of hemorrhagic stroke, which contributes to the early hazard of therapy in the first day (increased mortality).24 More intensive fibrinolytic regimens using tPA (alteplase) and heparin pose a greater risk than streptokinase and aspirin.166,167 Clinical risk factors that may help risk-stratify patients at the time of presentation are age (>65 years), low body weight (<70 kg), initial hypertension (180/110 mm Hg), and use of tPA. The number of risk factors can be used to estimate the frequency of stroke, which ranges from 0.25% with no risk factors to 2.5% with 3 risk factors.159

Fibrinolytic therapy is not recommended if >12 hours has passed since the onset of symptoms. In patients who present >12 hours after onset of symptoms with extensive infarction and ongoing ischemic pain, however, fibrinolytic therapy may be considered (Class IIb). Fibrinolytic therapy is contraindicated and may be harmful when continuous, persistent pain has been present for >24 hours, even in the presence of ST-segment elevation. There is only a small trend for benefit after a delay of 12 to 24 hours since symptom onset.

The presence of high blood pressure (SBP >175 mm Hg) at presentation to the ED increases the risk of stroke.168 Current clinical practice is directed at lowering blood pressure before administration of fibrinolytic agents, although this has not been proved to reduce the risk of stroke.168 Fibrinolytic treatment of patients who present with an SBP >180 mm Hg or a diastolic blood pressure >110 mm Hg is relatively contraindicated. The risk-benefit ratio should be carefully considered. Patients with AMI precipitated by cocaine use can be safely treated with fibrinolytics.169

Patients with ST-segment depression are a heterogeneous population with a high mortality rate who do not benefit from fibrinolytic treatment.170 Whether a subgroup of these patients could benefit from therapy was a question raised by a retrospective analysis of the Late Assessment of Thrombolytic Efficacy (LATE) trial.171 More precise selection of patients based on new diagnostic strategies (eg, cardiac markers) will be the subject of future prospective trials. Fibrinolytic therapy for patients with ST-segment depression and ischemic pain at rest (unstable angina or non–Q-wave infarction) is currently not recommended.12

**Treatment Regimens**

Initial trials demonstrated the efficacy of currently approved fibrinolytic agents: streptokinase,118,145,172 anistreplase,173,174 alteplase,175,176 retapase,177,178 and tenecteplase.143,179 These trials differed in enrollment, time to treatment, patient demographics, and conjunctive therapy, particularly use of heparin. The GUSTO trial subsequently tested 4 fibrinolytic regimens in >40 000 patients.166 Thirty-day mortality was lowest with the alteplase and intravenous heparin regimen, but a small increase in the number of hemorrhagic strokes occurred in patients treated with this accelerated protocol. Nevertheless, an overall net benefit of 9 fewer deaths per 1000 patients treated was achieved. The GUSTO-I angiographic substudy found differences in early (90-minute) patency among the 4 subgroups that closely predicted survival, suggesting that earlier reperfusion was the physiological mechanism responsible for outcome.155

Studies have shown that complete restoration of arterial flow (TIMI grade 3) rather than partial restoration of flow (TIMI grade 1 and 2) correlates with improved outcome.180 The accelerated alteplase regimen used in GUSTO currently appears to provide the earliest and most complete reperfusion, supporting the treatment goal of very early and complete restoration of vessel patency. Recent findings also stress the importance of microvascular dysfunction, which limits myocardial function and recovery, and the numerous factors involved in optimal myocardial function.181

A paradoxical effect of fibrinolytic administration is platelet activation. Newer regimens that include more effective platelet inhibitors, such as direct GP IIb/IIIa receptor inhibitors, increase the incidence and speed of reperfusion.182–184 Large clinical trials are now evaluating the newer fibrinolytic agents143,185,186 and combination therapies for AMI. Novel fibrinolytic regimens can be expected for both AMI and unstable angina.187,188

After GUSTO-I several clinical applications of the risk-benefit ratio have attempted to compare the cost-benefit ratio, risk of ICH, and mortality benefits in subgroups of patients. Alteplase (tPA) appears to have the greatest benefit in patients with large infarctions and appears to pose a low risk of ICH in younger patients who present early. Streptokinase appears to provide greater benefit in older patients with a smaller amount of myocardium at risk who present later and those with a greater risk of ICH. In addition, streptokinase appears to be most effective in the first 3 hours before the clot organizes. In EDs these facts should lead to a careful evaluation of risk and benefit.

**Reperfusion Therapy: PCI**

Clinical trials support the finding that direct coronary angioplasty is potentially superior to fibrinolytic therapy in the restoration of infarct patency (Figure 9).189,190 Coronary angioplasty provides higher rates of TIMI grade 3 flow, is successful in >90% of patients, and is associated with lower
Myocardial Infarction trial 192 were recently reported. At 2
years patients undergoing primary angioplasty had less recur-
rent ischemia and lower rates of reintervention and hospital
readmission than those treated with fibrinolysis. The com-
pared end point of death or reinfarction was 14.9% in patients
with ST-segment depression, fibrinolytic therapy provides no
benefit. The available data does not support routine use of
fibrinolytic therapy as a treatment option in patients with
ST-segment depression or nondiagnostic ECGs with elevated
cardiac markers.

Triage by EMS personnel of patients with large anterior
infarction and those with severe LV dysfunction may attenu-
ate this problem. Door-to-balloon times are suboptimal, but
experienced centers can reduce this delay so that reperfusion
times may be comparable to those of fibrinolytic therapy.

When possible, triage patients at high risk for mortality or
severe LV dysfunction with signs of shock, pulmonary conges-
tion, heart rate >100 bpm, and SBP <100 mm Hg to facili-
ties capable of performing cardiac catheterization and rapid
revascularization (PCI or CABG). For patients <75 years of age, this is a Class I recommendation. When
available without delay, consider primary PCI for patients
who are reperfusion candidates but have a risk of bleeding
that contraindicates use of fibrinolytic therapy (Class IIa).

**ST-Segment Depression: Non—Q-Wave MI/High-Risk Unstable Angina**

Non—Q-wave MI and unstable angina presenting with ST-
segment depression constitute a pathological process on the
continuum between chronic stable angina and typical Q-wave
MI. These patients with ST-segment depression on presenta-
tion constitute a high-risk subgroup. In some patients non—
Q-wave MI will evolve. Recent registries suggest that the
incidence of non—Q-wave MI is increasing as the population
of older patients with more advanced disease increases. The
widespread use of fibrinolytics, aspirin, and β-blockers may
also contribute to this increase.

Despite the relatively high mortality rate among patients
with ST-segment depression, fibrinolytic therapy provides no
benefit. The available data does not support routine use of
fibrinolytic therapy as a treatment option in patients with
ST-segment depression or nondiagnostic ECGs with elevated
cardiac markers.

Treat patients with ST-segment depression or T-wave
inversion with ischemic-type chest pain with aspirin and
heparin (see Figure 10). Administer nitrates for recurrent
angina. Initiate or optimize β-blockade. If patients have
persistent symptoms despite adequate β-blockade or cannot
tolerate this therapy, add a calcium antagonist. Consider
coronary angiography for high-risk patients with recurrent
ischemia, depressed LV function, widespread changes on the
ECG, or prior MI. Consider revascularization with PCI or
CABG for patients with a suitable anatomy. Continue med-
cal therapy in patients who are clinically stable. Further
stratify risk with stress tests when appropriate.

Aggressive medical therapy is indicated for patients at high
risk for major adverse cardiac events. The TIMI-III investi-
gators have defined high-risk clinical indicators.199 TIMI III
evaluated clinically useful predictors to help distinguish
patients with non—Q-wave MI from those with unstable
angina at the time of presentation. *Four baseline character-
istics independently predict non—Q-wave MI:
ST-Segment Depression, Dynamic T-Wave Changes: Non–Q-Wave Infarction — Unstable Angina

Recommendations for Initial Management and Therapy

1. Absence of prior coronary angioplasty (OR 3.3; \( P < 0.001 \))
2. Duration of pain ≥60 minutes (OR 2.9; \( P < 0.001 \))
3. ST-segment deviation on the admission ECG (OR 2.0; \( P < 0.001 \))
4. Recent-onset angina (OR 1.7; \( P < 0.002 \))

Non–Q-wave AMI developed in 7.0%, 19.6%, 24.4%, 49.9%, and 70.6% of patients with 0, 1, 2, 3, and 4 risk factors, respectively (\( P < 0.001 \)). Aggressive medical therapy is indicated in high-risk patients; such therapy includes use of heparin, aspirin, nitrates (administered intravenously), \( \beta \)-blockers, and GP IIb/IIIa inhibitors. Whether patients benefit most from a conservative or initially invasive strategy is the subject of recent studies and continuing discussion. Many clinicians will elect to perform angiography in higher-risk patients, especially those with recurrent or persistent symptoms on medical therapy.

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Figure 10. Recommendations for initial management and therapy of ST-segment depression, dynamic T-wave changes, non–Q-wave infarction, and unstable angina.
GP IIb/IIIa Inhibitors in PCI and ACS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Placebo</th>
<th>GP IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>2099</td>
<td>10.1%</td>
<td>7.0%</td>
</tr>
<tr>
<td>IMPACT-II</td>
<td>4010</td>
<td>8.4%</td>
<td>7.1%</td>
</tr>
<tr>
<td>EPILOG</td>
<td>2792</td>
<td>9.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1325</td>
<td>9.0%</td>
<td>4.8%</td>
</tr>
<tr>
<td>RESTORE</td>
<td>2139</td>
<td>5.3%</td>
<td>6.1%</td>
</tr>
<tr>
<td>EPISEPENT</td>
<td>2399</td>
<td>10.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>PRISM</td>
<td>3221</td>
<td>7.0%</td>
<td>5.7%</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>1570</td>
<td>11.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>PARAGON</td>
<td>2282</td>
<td>11.7%</td>
<td>11.3%</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>10 948</td>
<td>15.7%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Overall</td>
<td>30 338</td>
<td>0.79 (0.63, 0.98)</td>
<td>11.1%  9.0%</td>
</tr>
</tbody>
</table>


Optimal medical management of unstable angina and non–ST-segment elevation MI is rapidly evolving. Fibrinolysis releases thrombin and, paradoxically, increases the tendency toward thrombosis, a possible explanation for fibrinolytic failure in patients with non-Q-wave MI/unstable angina. Patients with a clot composed predominantly of platelets require antithrombin and antiplatelet therapy. New drugs and treatment strategies have focused on this pathogenesis, and new therapies have evolved.

**GP IIb/IIIa Inhibitors**

After plaque rupture in the coronary artery, tissue factor in the lipid-rich core is exposed and forms complexes with factor VIIa, promoting generation of factor Xa. In the coagulation cascade, relatively low concentrations of factor Xa lead to production of large amounts of thrombin, with deposition of fibrin strands and activation of platelets. Platelet adhesion, activation, and aggregation may result in formation of an arterial thrombus and are pivotal in the pathogenesis of ACS. The integrin GP IIb/IIIa receptor is considered the final common pathway for platelet aggregation, leading to binding of circulating adhesive macromolecules such as fibrinogen and von Willebrand factor, which cross-link on adjacent platelets, allowing platelet aggregation. Administration of a GP IIb/IIIa receptor antagonist (inhibitor) is one method of reducing acute ischemic complications after plaque fissure or rupture.

More than 30 000 patients with ACS without ST-segment elevation have been studied in clinical trials evaluating multiple therapeutic agents to block the GP IIb/IIIa receptor.204 Although GP IIb/IIIa inhibitors have an impressive ability to reduce adverse cardiac events such as MI and death (see Figure 11), another class of drugs, LMWH, has also been shown to reduce death and nonfatal MI in patients with unstable angina or non–ST-segment elevation AMI (see LMWH later in this section).

The PURSUIT trial enrolled 10 948 patients in a multicenter, randomized, placebo-controlled trial of GP IIb/IIIa inhibition.205 The primary end point was death from any cause or nonfatal MI at 30 days. Patients were enrolled a median of 11 hours after onset of symptoms, and epifibatide was infused for a median of 72 hours. Treatment with epifibatide for 72 hours or until discharge significantly reduced the incidence of death and MI at each time point. There was a 1.5% absolute reduction in the frequency of the combined end point by 96 hours; this reduction was maintained for 30 days. The early divergence of the Kaplan-Meier curves was maintained throughout the study. PCI was used in 23.3% of patients in the epifibatide group and 24.8% of patients in the placebo group.

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trials both used tirofiban (another GP IIb/IIIa inhibitor) to manage unstable angina and non–ST-segment elevation MI.206 In the PRISM trial, researchers hypothesized that inhibition of the final common pathway for platelet aggregation with tirofiban, a nonpeptide GP IIb/IIIa receptor antagonist, would improve clinical outcome in patients with unstable angina or non–ST-segment elevation MI. A total of 3232 patients were randomly assigned to receive tirofiban, aspirin, and placebo heparin, or aspirin and heparin. The primary end point was death, MI, or refractory ischemia at 7 days. The rate of death, MI, or refractory ischemia at 7 days was 10.3% in the tirofiban group and 11.2% in the heparin group; the difference between the groups was nonsignificant. Although the difference was nonsignificant at 7 days, Kaplan-Meier curves showed an early divergence of and a significant difference in mortality at 30 days. A reduction in the combined end point was observed during early (48-hour) administration of tirofiban. This reduction was not maintained at 7 or 30 days.

The PRISM-PLUS trial continued to evaluate tirofiban, generally in the treatment of higher-risk patients with unstable angina or non–Q-wave MI. A total of 1915 patients were enrolled to evaluate tirofiban, heparin, or the combination of tirofiban and heparin. The primary end point was death due to any cause, new MI, or refractory ischemia within 7 days after randomization. The study of tirofiban without heparin was discontinued early because of excess mortality at 7 days. Tirofiban provided additional benefit when added to standard therapy (heparin and aspirin) at 7 days. Kaplan-Meier curves showed early divergence at 48 hours before PCI in many patients.

A meta-analysis of clinical trials evaluating GP IIb/IIIa receptor antagonists included 32 134 patients.204 The meta-analysis reviewed death, MI, and revascularization in 16 controlled trials of GP IIb/IIIa inhibitors in which a Bayesian random-effects model was used to describe combined outcomes. For the combined end point of death or nonfatal MI, there was a highly significant benefit of use of GP IIb/IIIa inhibitors at every time point (48 to 96 hours, 30 days, and 6 months). Use of GP IIb/IIIa inhibitors in the ACS trials resulted in no significant differences in mortality at any end point, but a significant benefit of GP IIb/IIIa inhibitors was observed for the combined end point early and at 30 days. For the combined end point of death, MI, or revascularization in the ACS trials, a highly significant benefit favoring GP IIb/IIIa inhibitors was noted at all time points (48 to 96 hours, 30 days, and 6 months).
Inclusion criteria and end point definitions in the GP IIb/IIIa inhibitor trials vary widely. For example, there are differences in definitions of high-risk unstable angina, ECG inclusion criteria, definitions of abnormal cardiac marker results, timing of randomization from 12 to 24 hours after the index event, and definitions of recurrent and new MI and refractory ischemia. Aspirin was administered during all trials, but administration of heparin, heparin dosing, and activated partial thromboplastin times (aPTTs) varied among trials. None of these trials used troponin as a predictor of high risk during risk stratification. Risk stratification of patients with unstable angina also varied among trials.

GP IIb/IIIa inhibitors provide additional benefit in reducing adverse events over aspirin and heparin. There has been a slight increase in bleeding when GP IIb/IIIa inhibitors have been used. Most bleeding has been at vascular access sites, and attention to early vascular sheath withdrawal and heparin dosing had reduced this observation in early clinical trials with these agents. There has been no increase in ICH, as seen with fibrinolytic therapies. Kaplan-Meier curves showed early divergence of the GP IIb/IIIa groups in the PRISM, PURSUIT, and PRISM-PLUS trials. These results suggest an additional benefit of early treatment with GP IIb/IIIa inhibitors in the high-risk ACS population. Direct comparisons among GP IIb/IIIa inhibitors are unavailable, and the specific choice of agent remains speculative. The TARGET trial (Tirofiban and Abciximab for Revascularization Give Equivalent Outcomes) is currently comparing the efficacy of abciximab and tirofishan in several subsets of patients.

On the basis of this new evidence, we recommend the use of GP IIb/IIIa inhibitors for patients with non–ST-segment elevation MI or high-risk unstable angina (Class IIa). GP IIb/IIIa inhibitors have incremental benefit in addition to conventional therapy with UFH and aspirin (Class IIa). LMWH is an equivalent alternative for UFH in patients with non–ST-segment elevation MI or unstable angina. However, GP IIb/IIIa inhibitor therapy should be used with UFH until the results of safety and efficacy trials with LMWH are reported. The combination of GP IIb/IIIa inhibitor with LMWH appears promising.

Low-Molecular-Weight Heparin

In addition to platelet activation, plaque disruption activates the extrinsic coagulation system by exposing tissue factor to plasma proteins. Heparin, an indirect inhibitor of thrombin, has been widely used as adjunctive therapy for fibrin-specific lytic and, in combination with aspirin, for the treatment of unstable angina. New antithrombins have been studied, including LMWH. UFH is a heterogeneous mixture of sulfated glycosaminoglycans with varying chain lengths. UFH has several disadvantages, including an unpredictable anticoagulant response in individual patients, the need for intravenous administration, and the requirement for frequent monitoring of aPTT. Also, heparin can stimulate platelet activation, be inhibited by platelet factor 4, and cause thrombocytopenia, which can be serious or fatal in a small percentage of patients.

Three LMWHs have been compared with heparin: enoxaparin (Lovenox, Clexane), dalteparin (Fragmin), and nadroparin (Fraxiparin, Fraxaparine). The TIMI-11B trial studied enoxaparin in 3910 patients with high-risk unstable angina or non–Q-wave MI. After 1800 patients were enrolled, inclusion criteria were modified to focus on higher-risk patients; the new criteria required either ST-segment deviation or positive cardiac markers. The primary end point was all-cause mortality, recurrent MI, or urgent revascularization at 8 days (43 days for those receiving tPA therapy). At 8 days the primary end point was observed in 14.5% of patients receiving UFH and in 12.4% of patients receiving enoxaparin (OR 0.83; 95% CI 0.69 to 1.00; P = 0.048). Death or MI was reduced from 5.9% in the UFH group and 4.6% in the enoxaparin group (P = NS). Kaplan-Meier plots remained parallel, suggesting no further relative benefit of an additional 35 days of enoxaparin therapy.

The ESSENCE study (see Figure 12) was a prospective, randomized, double-blind, parallel-group, multicenter trial. A total of 3171 patients were enrolled in this study, which included recent-onset angina occurring within 24 hours before randomization. The primary end point was death, MI, or recurrent angina at 14 days. The risk of death, MI, or recurrent angina was significantly lower in the enoxaparin group than in the UFH group (16.6% versus 19.8%, OR 0.83; 95% CI 0.67 to 0.96, P = 0.019). This benefit was maintained over 30 days.

The Fragmin and Fast Revascularization during InStability In Coronary disease (FRISC II) trial evaluated >2000 patients with unstable coronary disease and administered subcutaneous dalteparin twice daily for 3 months. At 30 days and at 3 months there was a significant reduction in the primary end points of death and nonfatal MI, but this advantage was lost at the 6-month follow-up. This study also compared an invasive strategy with conservative medical management. Patients in the invasive arm underwent coronary angiography before 7 days and revascularization before 10 days. Patients who underwent early angiography with indicated revascularization had a significantly decreased incidence of MI. There was also a nonsignificant trend toward reduction in mortality. Angina and recurrent admissions were halved by the invasive strategy.

Nondiagnostic ECG

Screening of patients with nondiagnostic ECGs and ischemic or atypical chest pain in the ED is an area of clinical, legal,
Figure 13. The Acute Pulmonary Edema, Hypotension, and Shock Algorithm.
and economic significance. Special protocols, rapid determination of cardiac markers, 2D echocardiographic screening for regional wall motion abnormalities, myocardial perfusion imaging, and computer-based diagnostic aids are of greatest importance in these patients. Use of new cardiac markers, echocardiography, and perfusion imaging continues to be evaluated.

Patients with a nondiagnostic ECG who have an indeterminate or a low risk of MI should receive aspirin and other therapy as clinically indicated while undergoing serial cardiac studies to assess ongoing cardiac necrosis or unstable coronary syndromes. It is important to examine serial ECG tracings during evaluation in the ED, chest pain unit, or CCU for the development of ST-segment deviation or dynamic T-wave changes with pain, events that may also be detected by systems with continuous ST-segment monitoring capabilities. Patients in whom myocardial necrosis is excluded should then undergo a functional study based on clinical assessment, facility capabilities, and physician expertise.

**Complicated AMI**

**Cardiogenic Shock, LV Power Failure, and CHF**

Infarction of 40% of the LV myocardium usually results in cardiogenic shock and death. Despite recent advances in therapy, from 1975 to 1988 the incidence of cardiogenic shock remained relatively constant (approximately 7.5%).

Although the incidence of cardiogenic shock has decreased in recent trials, mortality is still high, averaging 50% to 70%. There also are differences between patients with ST-segment elevation and ST-segment depression. Of those who developed shock, patients without ST-segment elevation developed shock significantly later than patients with ST-segment elevation. Patients without ST-segment elevation are older, more frequently have diabetes mellitus, and have more 3-vessel disease. Mortality was high for both groups: 63% among patients with ST-segment elevation and 73% in those without ST-segment elevation. Nondiagnostic ECGs are more common in the elderly and patients with previous MI.

Severe but lesser degrees of infarction may result in hemodynamic instability and CHF. The ejection fraction of the heart falls when the amount of blood pumped with each heart beat (stroke volume) decreases. The ventricle dilates with an increase in end-diastolic volume. These changes may increase myocardial oxygen consumption, increase ischemia in viable or distant myocardium, and extend infarction. Progressive dysfunction may be manifested by increasing heart rate (sinus tachycardia) as the failing ventricle attempts to compensate for decreased stroke volume. Patients then develop pulmonary congestion and edema as LV filling pressures rise, and they develop hypotension as cardiac output falls. The combination of hypotension and pulmonary edema constitutes clinical cardiogenic shock. Hemodynamically the patient with LV dysfunction often has a cardiac index (cardiac output corrected for body weight) <2.5 L min⁻¹ m⁻², an elevated pulmonary capillary wedge pressure >18 to 20 mm Hg, and SBP <100 mm Hg. When the cardiac index falls to 2.2 L min⁻¹ m⁻² and SBP falls to 90 mm Hg, frank signs of poor peripheral perfusion are usually present.

Initial therapy for LV dysfunction includes intravenous diuresis and preload and afterload reduction with intravenous administration of nitrates (see Figure 13). Use an initial low nitrate dose (approximately 5 μg/kg) and gradually increase the dose until mean SBP falls by 10% to 15%, being careful to avoid hypotension (SBP <90 mm Hg). If the patient becomes markedly hypotensive, administer norepinephrine intravenously until SBP is 80 mm Hg, and then try dopamine. When SBP reaches 90 mm Hg, add dobutamine to reduce the requirement for dopamine (see “Part 6, Section 6: Agents to Optimize Cardiac Output and Blood Pressure”). Consider using intra-aortic balloon counterpulsation if available, or transfer the patient to a cardiac interventional facility. Results from the GUSTO-I trial and SHOCK trial suggest that an aggressive, invasive approach increases survival and that use of these resources reduces mortality.

Fibrinolytic therapy has not been shown to consistently improve outcome in patients with cardiogenic shock, and it may have several limitations. The small number of patients in clinical trials has limited outcome data and recommendations. In early clinical trials hospital survival rates of 20% to 50% were reported after treatment with fibrinolytic therapy. The only placebo-controlled trial of fibrinolitics compared streptokinase without adjunctive aspirin. A mortality rate of 70% was found for both treated and control patients. The FIT trial did not specifically identify patients with shock but found that patients with sinus tachycardia and low blood pressure benefited from reperfusion therapy. This finding implies inclusion of a group with cardiogenic shock. In the GUSTO trial, fewer deaths occurred in patients who presented with shock and were treated with streptokinase, and shock developed in fewer patients treated with IPA. Primary PCI has been advocated for patients in shock. In nonrandomized trials, survival rates as high as 70% have been reported, but in 1 trial the mortality rate was 80% in patients in whom patency was not achieved. Current randomized trials are further defining the role of PCI in patients with shock. In the GUSTO trial the mortality rate at 30 days and 1 year was lower in patients treated with aggressive medical therapy and with PCI. Early revascularization benefited patients in shock who were <75 years of age (see above).

When possible, triage high-risk patients with cardiogenic shock or refer them to cardiovascular facilities with interventional specialists. Consider triage or transfer for patients with a large anterior wall infarct and for patients with CHF or pulmonary edema. Cardiogenic shock is not a contraindication to fibrinolysis, but defer fibrinolytic therapy when interventional procedures are rapidly available as an alternative (balloon inflation time of 60 minutes). In hospitals without such facilities, rapidly administer a fibrinolytic agent and transfer the patient to a tertiary care facility in which adjunct PCI can be performed if low-output syndromes or ischemia continues.

**RV Infarction**

RV ischemia or infarction (ST-segment elevation in lead V₄₅) may occur in up to 50% of patients with inferior wall
MI. RV infarction is clinically manifested by jugular venous distention, Kussmaul’s sign, and various degrees of hypotension. These clinical findings develop in 10% to 15% of patients with inferior MI.220,221 Suspect RV infarction in patients with inferior wall infarction, hypotension, and clear jugular fields. In patients with inferior wall infarction, obtain an ECG of the right side of the heart by using precordial leads. ST-segment elevation in lead V₁,R is sensitive (90%) and a strong predictor of in-hospital complications and mortality.222 A right atrial pressure ≥ 10 mm Hg or 80% of the pulmonary capillary wedge pressure indicates RV dysfunction. The in-hospital mortality rate of patients with RV dysfunction is 25% to 30%. Routinely consider reperfusion therapy for these patients. Fibrinolytic therapy reduces the incidence of RV dysfunction.223 PCI is indicated for patients in shock.

It is important to recognize that patients with RV dysfunction and acute infarction are very dependent on maintenance of RV filling pressures to maintain cardiac output.224 Avoid use of agents that reduce preload, such as nitrates and diuretics, because severe hypotension may develop. If hypotension develops in patients with inferior wall infarction who were treated with sublingual nitrates, evaluate for RV infarction. Initial therapy consists of volume loading with a 500-mL intravenous bolus of normal saline, up to 1 to 2 L. Perform serial assessments for pulmonary congestion. Depending on the coronary anatomy, various degrees of LV infarction and dysfunction may develop, and pulmonary edema may be a complication, particularly in patients with previous MI. If blood pressure does not improve after fluid loading, give dobutamine for inotropic support of the right ventricle. For refractory hypotension, consider augmentation of the systemic pressure by means of an IABP to allow reduction of RV afterload and combination therapy with arterial vasodilators.

**Adjunctive Therapy for ACS**

**Heparin**

The Fifth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommended administration of heparin to all patients with diagnosed AMI.225 Use of heparin in patients receiving fibrinolytic therapy is controversial, and some issues have yet to be resolved. Randomized trials performed before the reperfusion era documented a 17% reduction in mortality and a 22% reduction in the risk of reinfarction with heparin therapy. A recent meta-analysis of anticoagulant therapy for patients with suspected MI found only a 6% reduction in mortality when heparin was used in the presence of aspirin.226 There is little data to suggest an additional benefit of heparin administration when patients are treated with aspirin, β-blockers, nitrates, and ACEIs. Use of heparin with nonselective fibrinolytic agents has been equivocal at best, and subcutaneous heparin appeared to be as beneficial as intravenous heparin when benefit was shown.

In angiographic trials heparin has been shown to increase patency of the infarcted artery when tPA is used.155,227 but the effects of heparin on overall clinical outcomes have not been as impressive. Heparin is currently recommended in patients receiving selective fibrinolytic agents (tPA/retaplaste/tentaplaste) (Class IIa).13

To reduce the incidence of ICH, the 1999 update to the ACC/AHA Guidelines for the Management of Myocardial Infarction recommends a lower dose of heparin than was previously recommended. The current recommendations now call for a bolus dose of 60 U/kg followed by infusion at a rate of 12 U/kg per hour (a maximum bolus of 4000 U/kg and infusion of 1000 U/h for patients weighing <70 kg).13 An aPTT of 50 to 70 seconds is considered optimal. Increased rates of bleeding and ICH have been related to more intensive heparin therapy and higher aPTTs (>70 seconds). The incidence of stroke is increased in patients with a large anterior wall infarction and thrombus,228 significant LV dysfunction,229 atrial fibrillation, and a previous embolic event. Treat these high-risk patients with heparin for an extended period; warfarin therapy may be initiated in some.

The indications for heparin use in some clinical situations remain controversial. The following recommendations, however, are consistent with data from randomized trials and expert consensus opinion for use in ST-segment elevation acute MI (Table 5) and non–Q-wave MI/unstable angina (Table 6).

**β-Adrenergic Receptor Blockers**

β-Blockers reduce the size of the infarct in patients who do not receive fibrinolytic therapy.55,230,231 They also reduce the incidence of ventricular ectopy and fibrillation.232,233 In patients who receive fibrinolytic agents, β-blockers decrease postinfarction ischemia and nonfatal MI. A small but significant decrease in death and nonfatal infarction has been shown.

**TABLE 5. Heparin and ST-Segment Elevation MI**

| Class I (supported by definitive evidence): all patients undergoing PCI |
| Class IIa (evidence strongly supports use): IV heparin in patients receiving selective fibrinolytic agents (alteplase, reteplase, tenectaplaste); heparin in patients treated with nonselective fibrinolytic agents (streptokinase, APSAC) who are at increased risk for systemic emboli (large anterior MI, atrial fibrillation, known LV thrombus, or previous embolic event) |
| Class IIb (supported by less definitive evidence): subcutaneously (7500 U twice daily) for pulmonary embolism prophylaxis until fully ambulatory, particularly in the presence of CHF |
| Class III (not beneficial, possibly harmful): routine IV heparin within 6 hours to patients receiving a nonselective fibrinolytic agent (streptokinase, APSAC) who are not at high risk for systemic emboli |

AP SAC indicates anisoylated plasminogen streptokinase activator complex.

**TABLE 6. Heparin and ST-Segment Depression and Non–Q-Wave MI/Unstable Angina**

- IV heparin therapy for 3 to 5 days is standard for high-risk and some intermediate-risk patients. The ACC/AHA Practice Guidelines recommend treatment for 48 hours, then individualized therapy.
- LMWH is an acceptable alternative to IV UFH (see above). Enoxaparin is preferable to UFH.
- UFH is recommended for use with GP IIb/IIIa inhibitors until data on safety and efficacy regarding combination with LMWH is available.
- All unstable angina patients should receive 325 mg of aspirin per day.
Nitroglycerin (or Glyceryl Trinitrate)

In trials conducted before the era of fibrinolytics, intravenous nitrate therapy (nitroglycerin; glyceryl trinitrate in Europe) was shown to reduce the size of infarcts. An analysis of subgroup results in the largest of these studies showed that most of this benefit occurred in patients with large anterior wall infarcts, and a meta-analysis concluded that nitroglycerin-in-effectively reduced mortality. Evidence from ISIS-4 andGISSI-3 was insufficiently conclusive to recommend routine administration in AMI.117,235

The totality of evidence does not support routine administration of nitroglycerin. Nitroglycerin is indicated for the initial management of pain and ischemia in patients with AMI, except in those with RV infarction, and nitrates are indicated during the first 24 to 48 hours in patients with recurrent ischemia. They may be useful in patients with hypertension, CHF, and large anterior wall MI. Use nitrates if these indications are present, but discontinue nitrates if low blood pressure precludes use of other agents known to be harmful. It is the consensus of the ACC/AHA AMI Guidelines Committee that these agents are still used too frequently.

Nitrate therapy (nitroglycerin; glyceryl trinitrate in Europe) was shown to reduce mortality after acute MI, and in certain patients with cardiovascular disease there is data to suggest that they are harmful. It is the consensus of the ACC/AHA AMI Guidelines Committee that these agents are still used too frequently.

ACEI Therapy

Inhibition of ACE has improved survival in patients with AMI.117,241–244 The reduction in mortality is seen early after onset of AMI. Proposed mechanisms include an early effect on limitation of infarct expansion, attenuation of the remodeling process, reduction of the neurohumoral impact on the heart, and increases in collateral flow to the peri-infarct ischemic area.

The larger trials have consistently demonstrated a survival advantage for ACEI therapy started early during the acute phase of MI. An overview of 4 trials with nearly 100 000 patients evaluated data on patients who received ACEI (Figure 14). Overall, a reduction of 5 deaths per 1000 patients treated was observed, and most of this benefit occurred early in the first week. Selection of higher-risk patients amplified the treatment effect.
the modest 7% proportional reduction in mortality; patients with evidence of LV dysfunction and anterior wall MI benefited most.245 The Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) trial was terminated early—a controversial decision—when it was thought that a high probability of a beneficial effect would be lacking. Concern was also raised because of an early hypotensive effect observed in the elderly treated with ACEI. The study used an intravenous preparation of enalaprilat, enalaprilat.246 Largely based on this trial, IV ACEI therapy is not recommended. Oral ACEI therapy is initiated after 6 hours when the patient is stable and other initial treatments have been started (lytics, β-blockers, nitrates).

The data supports the 2 strategies currently used: ACEI administration to a general group of AMI patients with subsequent reassessment of the need for continued treatment (eg, LV ejection fraction <0.35) at 4 to 6 weeks (Class IIa) or selective administration to higher-risk patients with clinical heart failure or large AMI (Class I). Give ACEI therapy early within the first day after MI when the patient is stable and after reperfusion, initial measures, and other therapies have been started. Avoid its use in the presence of hypotension (SBP <100 mm Hg), clinically relevant renal failure, bilateral renal artery stenosis, or documented allergy.

Magnesium

The routine use of magnesium in AMI was proposed after a meta-analysis of 7 small randomized trials found an impressive reduction in mortality of 55% associated with administration of magnesium.247 The mechanism of effect was thought to be a reduction in ventricular arrhythmias and VF. The Second Leicester Intravenous Magnesium Interventional Trial (LIMIT-2) subsequently reported a 24% reduction in mortality, but this reduction was not due to a reduction in arrhythmia.248 Post hoc analyses suggested that the reduction in mortality was associated with a reduction in CHF. This finding led to a reconsideration of the importance of the cellular protective effects that magnesium had against calcium ion influx in ischemia.248

No reduction in mortality was found in the large ISIS-4 trial,117 and a possibility of slight harm was noted in association with magnesium administration. Relatively late administration of magnesium, after administration of the fibrinolytic, was suggested as one possible reason for the negative outcome.249 A small randomized trial conducted in patients ineligible for fibrinolytic therapy found a significant reduction in mortality due to a decreased incidence of CHF and cardiogenic shock. ISIS investigators performed a retrospective review and compared patients treated early and late with magnesium but still found no benefit or difference in mortality.

To further address this issue, the Magnesium in Coronary Disease (MAGIC) trial will evaluate the role of magnesium in AMI, particularly early administration before fibrinolytic therapy in high-risk patients, including the elderly and patients not eligible for fibrinolytic therapy.250 Currently there is no routine indication for administration of magnesium to patients with MI.

Metabolic Manipulation of the Infarct: Glucose-Insulin-Potassium

Metabolic modulation of the acute myocardial infarct was first proposed by Sodi-Pallares et al in 1962 and brought to clinical trial in 1969.251 Early experimental and clinical studies were promising and demonstrated a reduction in infarct size, heart failure, and mortality.252–255 Initial enthusiasm fell dormant until a meta-analysis revived interest in this simple and inexpensive therapy256 after the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study group reported favorable results in diabetic patients with AMI.257 The trials and meta-analysis provided the impetus for a prospective randomized clinical trial.258 Two clinical trials recently reported conflicting results, and a large clinical trial is essential to determine the magnitude of benefit and subgroups who may particularly benefit.259,260

Glucose-insulin-potassium (GIK) therapy may reduce mortality during AMI by several mechanisms. GIK has anti–free fatty acid (FFA) activity. FFAs are toxic to the ischemic myocardium, and GIK reduces circulating FFAs and myocardial uptake. GIK also antagonizes the effects of catecholamines and heparin on increased FFAs. A relatively small increase in ischemic glycolytic adenosine triphosphate may be beneficial in the low-flow myocardium.

A meta-analysis performed in patients before the era of fibrinolytic therapy found a reduction in mortality of 28% to 48% associated with GIK therapy, depending on the dose and timing of administration.256 Researchers in the DIGAMI trial also found an impressive 29% to 58% decrease in relative mortality, depending on the subgroup evaluated.261 The Estudios Cardiologicos Latinoamerica (ECLA) Collaborative Group, which conducted a large prospective randomized trial during the era of fibrinolytic therapy, reported an impressive 66% relative reduction (15.2% to 5.2% absolute reduction) in mortality.259 Only the recently reported Pol-GIK trial failed to find a reduction in mortality with a nonsignificant hazard in treated patients.260 The difference between these 2 trials may be attributable to patient selection, because patients in the ECLA trial were sicker than those in the Pol-GIK trial and were treated with higher doses of GIK.

In summary, GIK therapy for patients with AMI may be helpful; it is easily administered and associated with few adverse effects. Administration through a peripheral vein is associated with a 2% incidence of significant phlebitis but no serious metabolic consequences, even in diabetic patients. Before GIK is widely recommended, larger clinical trials are needed to further evaluate its efficacy in a broad patient group with AMI and to identify patient subgroups for which it may be particularly beneficial (Class Indeterminate).

Arrhythmias Associated With Ischemia, Infarction, and Reperfusion

Cardiac rhythm abnormalities and the clinical pharmacology of agents used to treat them are discussed in “Part 6: Advanced Cardiovascular Life Support.” This section discusses management of these arrhythmias during acute ischemia and infarction.
Ventricular Rhythm Disturbances

Treatment of ventricular arrhythmias after MI has been a controversial topic for 2 decades. Similarly, management of ventricular arrhythmias during the acute phase of MI continues to evolve as treatment strategies are reviewed in the context of new information and changing epidemiological data during the era of adjunctive medical and reperfusion therapy.

Primary VF accounts for the majority of early deaths during AMI. The incidence of primary VF is highest (3% to 5%) during the first 4 hours after coronary occlusion and then declines markedly. VF is an important contributor to mortality during the first 24 hours. Primary VF should be distinguished from secondary VF occurring in the setting of CHF or cardiogenic shock. Epidemiological data suggests that the incidence of primary VF may be decreasing. Although prophylaxis with lidocaine reduced the incidence of VF by approximately one third, a meta-analysis of randomized trials suggests that this decrease was offset by an increased incidence of total mortality by the same degree. However, too few events and limited follow-up precluded any conclusion regarding harm or efficacy. Thus, the practice of routine prophylactic administration of lidocaine has been largely abandoned.

Routine intravenous administration of β-blockers to patients without hemodynamic or electrical contraindications, however, is associated with a reduced incidence of primary VF. Low serum levels of potassium but not magnesium have been associated with ventricular arrhythmia. It is prudent clinical practice to maintain serum potassium levels >4.0 mEq/L and magnesium levels >2.0 mEq/L. Routine administration of magnesium to patients with MI has no significant clinical mortality benefit, particularly in patients receiving fibrinolytic therapy. As noted above, a mortality benefit may be seen in high-risk patients, provided that magnesium is administered soon after the onset of symptoms. Continuing trials will evaluate use of magnesium in these patients.

Ventricular rhythm abnormalities observed during acute ischemia and infarction include premature ventricular complexes, VT, and VF. The use of the external defibrillator and the proliferation of CCUs reduced hospital mortality by half after the introduction of defibrillation by trained staff. Lidocaine was then shown to be effective in reducing the incidence of VF and complex ventricular rhythm disturbances. It was logical to propose prophylactic use of lidocaine to prevent VF and treat “warning arrhythmias.” Neither of these tenets has withstood the tests of multiple clinical studies. Serious ventricular arrhythmias are absent in almost 50% of patients who experience early VF. Also, the incidence of VF has declined and is low in the fibrinolytic era, in which adjunctive therapy with β-blockers is common. An analysis of data from ISIS-3 showed a reduction in VF in patients treated with lidocaine but a trend toward increased mortality, possibly and inferentially because of an increased incidence of asystole. A subsequent meta-analysis and recent clinical data supported this trend toward increased mortality and increased incidence of asystole, negating the benefit of reduction in primary VF. At present we do not recommend prophylactic treatment of arrhythmias or treatment of asymptomatic warning arrhythmias. Current ACLS protocols recommend lidocaine for the treatment of hemodynamically stable VT and prevention of recurrent VF.

There is no conclusive data to support the use of lidocaine or any particular strategy for preventing recurrent VF. If lidocaine is used, continue it for a short time after MI but no more than 24 hours unless symptomatic VT persists. Identify and correct exacerbating or modulating factors. Hypokalemia is a risk factor for ventricular ectopy and VF. Correct hypoxemia and treat heart failure aggressively. The evidence for magnesium is less clear. Nevertheless, we recommend maintaining serum potassium levels >4.0 mEq/L and magnesium levels >2.0 mEq/L.

Management of ventricular rhythm disturbances is discussed in “Part 6: Advanced Cardiovascular Life Support.”

Bradyarrhythmias and Heart Block: Indications for Pacing During AMI

Approximately one third of patients with AMI develop sinus bradycardia. Because of increased vagal tone, it is often seen in patients with inferior wall infarcts secondary to occlusion of the right coronary artery when that artery supplies the sinus or atrioventricular (AV) nodes. Sinus bradycardia may also occur with reperfusion of the right coronary artery. Atropine-resistant bradycardia and heart block may occur; accumulation of adenosine in ischemic nodal tissue may be responsible. Initial treatment with atropine is indicated only when serious signs and symptoms are related to the decreased rate.

Second- or third-degree AV block complicates approximately 20% of myocardial infarcts. Heart block is present on admission in 42% of patients and within the first 24 hours in two thirds. Heart block is present in 12% of patients who receive fibrinolytic therapy and is associated with increased hospital mortality in these patients. This mortality is usually due to extensive MI with cardiac dysfunction. Only rarely will a patient die of heart block. Heart block is not an independent predictor of mortality, and it is a poor predictor of mortality in patients who survive to discharge. Prognosis is related to the site of infarction (anterior or inferior), level of block in the AV node (infranodal or intranodal), escape rhythm, and degree of hemodynamic compromise.

In general, treatment of first- or second-degree AV block with atropine is not required. When serious rate-related signs and symptoms occur, administer 0.5 to 1.0 mg of atropine every 3 minutes up to a total dose of 0.03 to 0.04 mg/kg. Treatment of patients with symptomatic type I second-degree AV block is occasionally required.

Atropine may be particularly inappropriate for treatment of bradycardia in some patients. For example, patients who have had a heart transplant have denervated hearts and will not respond to atropine. Atropine should not be used to treat some forms of heart block. Avoid administering atropine in type II second-degree AV block. Atropine usually has no effect on AV conduction (infranodal block), and a resulting increase in sinus rate may actually enhance the block or precipitate third-degree AV block. Atropine may be helpful for treating third-degree AV block occurring at the AV node (narrow-complex QRS), because it may improve AV block or accel-
erate the escape rhythm. However, do not use atropine for third-degree AV block with a new wide-QRS complex presumed to be due to AMI. Administration of lidocaine to these patients may also have the effect of suppressing a slow escape rhythm and in this setting may result in ventricular standstill.

The availability of transcutaneous pacing and the need to avoid venipuncture in noncompressible vessels in patients who may receive or have received fibrinolytic therapy have significantly changed the approach to emergency pacing. Transcutaneous pacing should be used as an emergency bridge to temporary transvenous pacing performed by experts, preferably under fluoroscopic guidance, for appropriate indications (Table 8).

Consider placement of transcutaneous patches with provision for immediate pacing for stable bradycardia, new or age-indeterminate right bundle-branch block, and new or age-indeterminate first-degree AV block.

### Atrial Fibrillation Complicating AMI

New-onset atrial fibrillation complicating MI occurs in 10% to 15% of patients. It is usually transient and often self-limited, requiring no therapy. It is associated with increasing age, large infarcts, LV hypertrophy, and CHF. Atrial fibrillation may also be a result of atrial infarction, which occurs with occlusion of the right coronary artery before the sinus node branch or with occlusion of the circumflex coronary artery before the left atrial circumflex branch. Later in the hospital course, pericarditis may precipitate atrial fibrillation.

Fibrinolytic therapy with tPA or streptokinase reduces the incidence of atrial fibrillation. Episodes of atrial fibrillation that are brief and transient or have ventricular response rates <110 bpm require no immediate therapy. Attempt to identify and treat any underlying causes or aggravating conditions (hypoxia, CHF, or an electrolyte abnormality).

When atrial fibrillation produces a rapid ventricular rate resulting in ischemic symptoms or hemodynamic compromise, immediate cardioversion is indicated. In stable patients, β-adrenergic receptor blocking agents may be used to effectively slow the ventricular rate if severe CHF, asthma, and other contraindications are absent. Intravenous administration of diltiazem is often used if β-blockers are contraindicated. Verapamil should be used with caution—if at all—in patients with clinical heart failure or depressed ejection fraction. Calcium channel blockers are not recommended as first-line therapy because of their negative inotropic effect and recent concerns about their use in AMI.

Rapid digitalization may occasionally be effective, but rate control is achieved more slowly, and toxicity is a significant concern, particularly in the setting of acute ischemia.

Mortality is increased when atrial fibrillation develops in the setting of AMI. The risk of stroke is increased with atrial fibrillation. Systemic embolization is 3 times more common in patients with atrial fibrillation, with 50% of episodes occurring within the first 24 hours after onset of the arrhythmia. Echocardiography is recommended to assess the possibility of LV mural thrombi with large anterior wall and apical MIs. If atrial fibrillation develops, administer heparin and maintain aPTT between 50 and 70 seconds.

### ACS at the Dawn of a New Millennium

Significant progress has been made in the identification, urgent treatment, and long-term care of patients with ACS. The reperfusion era ushered in a period of rapid progress in our understanding of coronary artery disease, plaque instability, and the myriad of clinical symptoms and scenarios that are possible. The next decade will certainly focus on the role of the platelet and optimal management in different stages of the ACS spectrum. Intense investigation of the role of inflammation and its prognostic and treatment potential is now unfolding. The focus on the epicardial artery and patency will continue as new treatment strategies are developed and tested to initiate and maintain patency with ACS. A new focus on the microvasculature as an important contributor to myocardial salvage and preservation is beginning, and the target of microvascular dysfunction will add another perspective to our understanding and therapeutic options in the near future.

### References


### Table 8: Indications for Transcutaneous Patches/Pacing

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamically unstable bradycardia (&lt;50 bpm)</td>
</tr>
<tr>
<td>Mobitz type II second-degree AV block</td>
</tr>
<tr>
<td>Third-degree heart block</td>
</tr>
<tr>
<td>Bilateral BBB (alternating BBB or RBBB and alternating LBBB)</td>
</tr>
<tr>
<td>Left anterior fascicular block</td>
</tr>
<tr>
<td>Newly acquired or age-indeterminate LBBB</td>
</tr>
<tr>
<td>RBBB or LBBB and first-degree AV block</td>
</tr>
</tbody>
</table>

RBBB, LBBB indicate right and left bundle-branch block, respectively.


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Part 7: The Era of Reperfusion: Section 1: Acute Coronary Syndromes (Acute Myocardial Infarction)

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