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Treatment of Acute ST-Elevation Myocardial Infarction

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Key Points

- If there is one constant in this still rapidly evolving field, it is the major impact that the time from symptom onset to effective coronary reperfusion has in modulating patient outcome.
- Effective reperfusion therapy initiated within the first hour of symptom onset saves lives. Hence, whereas 65 of 1000 patients so treated are saved, this benefit declines over time, within the second hour, to 37 of 1000 patients treated. Less than half the benefit found in the first hour is achieved, if reperfusion is delayed 4 to 6 hours after symptom onset.
- Effective fibrinolytic therapy and percutaneous coronary intervention (PCI) are administered with antithrombotic therapy (aspirin; an antithrombin, usually unfractionated heparin or low molecular weight heparin).
- When faced with a patient with ST-elevation myocardial infarction (STEMI), the physician should pose the following key questions:
  - What is the time from symptom onset to first medical contact?
  - What is the baseline risk of the myocardial infarction, based on incorporation of the 12-lead electrocardiogram (ECG)?
  - What is the risk of fibrinolysis?
  - What is the time required to transport the patient and achieve PCI by a skilled operator?
- Percutaneous coronary intervention is superior to fibrinolytic therapy in circumstances where there is immediate access to skilled facilities and physician/health care teams. If this is not available, fibrinolytic therapy is an effective alternative, usually consisting of tPA, TNK-tPA, or rPA. Care should be exercised in balancing the risk of the myocardial infarction (MI) with the risk of fibrinolysis, paying particular attention to those with a prior cerebrovascular accident, systemic arterial hypertension, recent major surgery, and known bleeding diathesis.
- Overcoming undertreatment and applying reperfusion therapy promptly is likely more important than the choice of which reperfusion therapy is employed.
- It is essential that community hospitals develop or enhance effective communication strategies with fully equipped tertiary care centers to ensure that timely transfer of high-risk patients as well as those not responding to fibrinolytic therapy can occur.
- Secondary prevention after MI begins on admission and consists of pharmacologic therapy with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, aspirin, and often clopidogrel. This, plus appropriate lifestyle modifications and rehabilitation are important determinants of longer term outcome.

Since this topic was last addressed in the prior edition of *Cardiovascular Medicine,* profound changes have occurred in the management strategies of patients with acute ST-elevation myocardial infarction (STEMI). Even the lexicon associated with this disorder has been transformed. Hence, ST elevation and Q-wave myocardial infarction (MI) are not synonymous; although most ST elevation MIs evolve to produce Q waves on the electrocardiogram (ECG), at least 20% do not.[1] Moreover, among those with non-ST elevation MI, Q waves develop in approximately 18% of such patients; thus, transmurality and Q waves are not synonymous.[2]

Rather, Q waves mark patients with spatially extensive (but not necessarily transmural) infarction that is evident on magnetic resonance imaging (MRI).[3] Although pharmacologic reperfusion therapy is generally considered to have ushered in the "thrombolytic era," more recent understanding of the role of platelets and other elements that congregate within the fibrin-linked foundation of coronary thrombosis have been persuasive in reviving the use of the more venerable and appropriate term *fibrinolysis*.[4] Other key novel developments in the approach to STEMI include the introduction of effective, bolus fibrinolytic agents, enhancement of catheter-based reperfusion strategies, and the introduction of secondary preventative pharmacologic and device strategies that improve long-term outcomes.[5,6] Finally, new guidelines for the management of STEMI have been promulgated by both the European Society of Cardiology and most recently the American College of Cardiology (ACC)/American Heart Association (AHA) 2004 STEMI guidelines to which substantial reference is made in this chapter.[7,8]

The discussion that follows addresses the recognition, early assessment, and management of STEMI as it relates to its symptoms, primary cause, and consequences; secondary prevention; and long-term pharmacologic therapy.

Because some aspects of STEMI are addressed in greater detail in other chapters, specifically tachy- and bradyarrhythmias complicating STEMI, cardiogenic shock, mechanical reperfusion, and the use of electrical devices, they will not be discussed in detail here.

Importance of Time

If there is one constant in this rapidly evolving field, it is the extraordinary impact of the time lapse from symptom onset to effective reperfusion. There remains remarkable homogeneity in median time to treatment across clinical trials of fibrinolysis in STEMI over the past decade, and aggressive public educational programs have failed to modify the behavioral aspects of delay in seeking medical attention (Fig. 40.1).[9] A profile of patients who exhibit delays in presentation after symptom onset has emerged, indicating that those who are elderly, female, diabetic, African American, or of lower socioeconomic status are most likely to delay calling for help.[10,11]

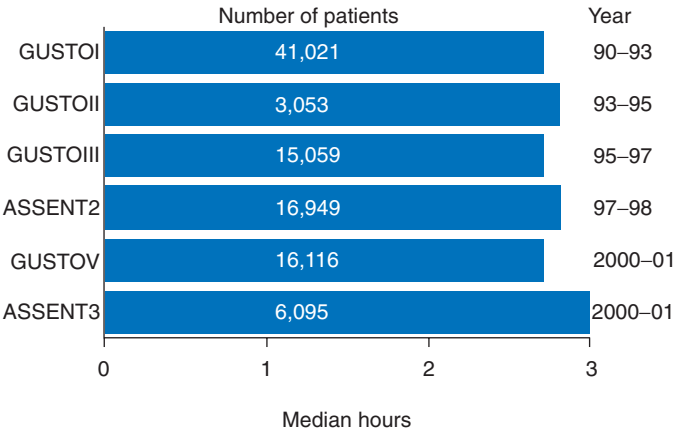


FIGURE 40.1. Time to treatment monotony.

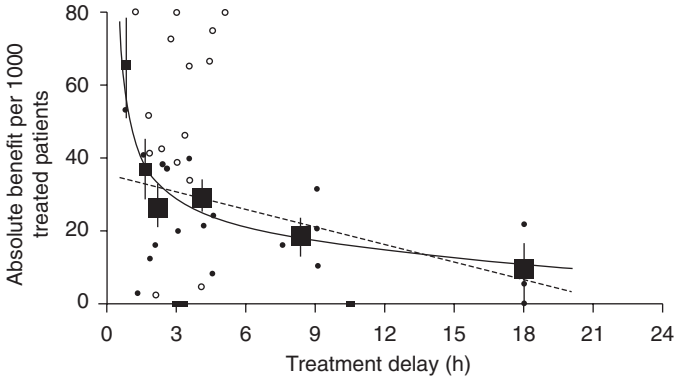


FIGURE 40.2. Absolute 35–day mortality reduction versus treatment delay. Small closed dots: information from trials included in Fibrinolytic Therapy Trialists' (FTT) analysis; open dots: information from additional trials; small squares: data beyond scale of x/y cross. The linear (34.7 – 1.6x) and nonlinear (19.4 – 0.6x + 29.3x – 1) regression lines are fitted within these data, weighted by inverse of the variance of the absolute benefit in each data point.[4] Black squares: average effects in six time-to-treatment groups (areas of squares inversely proportional to variance of absolute benefit described).

An additional public health challenge relates to the choice of transportation to a health care facility. Hence, at least 50% of patients do not employ telephone and the emergency medical services (EMS) system, but rather present as "walk-ins" to the emergency room.[12] Patients who self-present in this way are subject to further delays in diagnostic recognition and therapy. The ongoing initiative of the American Heart Association and the National Heart, Lung, and Blood Institute (NHLBI) "act in time to heart attack signs" (www.nhlbi.nih.org) highlights the heart attack warning signs, encourages calling 911 promptly, and articulates an appropriate planning process for patients and their families.

The overwhelming evidence from the Fibrinolytic Trialists' overview that therapy initiated within the first hour of symptom onset saves lives (65/1000 treated) and that the benefit declines sharply thereafter (37/1000 in the second hour), such that less than half of the early benefit is seen between 4 and 6 hours after symptom onset provides cogent testimony to the value of early therapy (Fig. 40.2).[13,14] Although an overall 18% relative risk reduction for fibrinolysis over placebo is evident, no benefit was evident beyond 12 hours after symptom onset. Further insight into the anticipated margin of benefit among specific subgroups according to the assessment of baseline risk is also feasible from this analysis.[13]

An emphasis on enhanced patient awareness in the 2004 ACC/AHA guidelines has been coupled with specific recommendations concerning the emergency medicine response.[8] As is evident in Figure 40.3, dispatch of EMS should occur within 1 minute of a 911 call with the expectation that it should be on the scene within 8 minutes of dispatch. The 911 system in the United States is dominated by non–medical-related calls, and this, coupled with challenges in evaluating some emergency calls from contemporary cell phones, further contributes to potential delays. The new ACC/AHA guidelines strongly encourage the performance of 12-lead electrocardiograms and consideration of prehospital

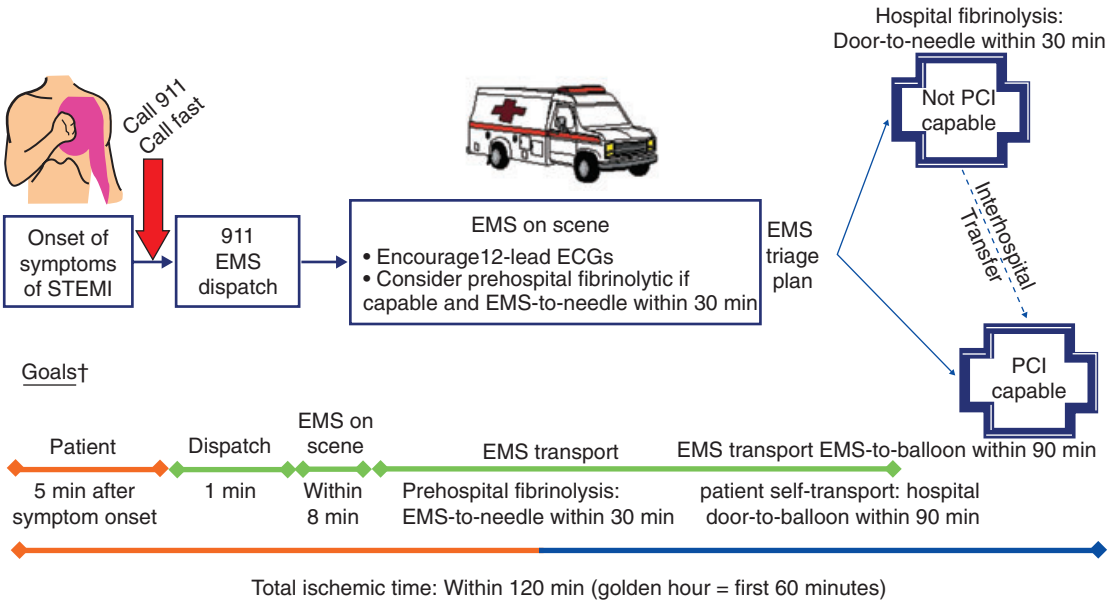


FIGURE 40.3. Options for transportation of STEMI patients and initial reperfusion treatment. Patient transported by emergency medical services (EMS) after calling 911. Reperfusion in patients with STEMI can be accomplished by the pharmacologic (fibrinolysis) or catheter-based (primary percutaneous coronary intervention, PCI) approaches. Implementation of these strategies varies based on the mode of transportation of the patient and capabilities at the receiving hospital. Transport time to the hospital is variable from case to case, but the goal is to keep total ischemic time within 120 minutes. There are three possibilities: (1) If EMS has fibrinolytic capability and the patient qualifies for therapy, prehospital fibrinolysis should be started within 30 minutes of EMS arrival on the scene. (2) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a non–PCI-capable hospital, the hospital door-to-needle time should be within 30 minutes for patients in whom fibrinolysis is indicated. (3) If EMS is not capable of administering prehospital fibrinolysis and the patient is transported to a PCI-capable hospital, the hospital door-to-balloon time should be within 90 minutes.

Interhospital transfer: It is also appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization if (1) there is a contraindication to fibrinolysis; (2) PCI can be initiated promptly (within 90 minutes after the patient presented to the initial receiving hospital or within 60 minutes compared to when fibrinolysis within a fibrin-specific agent could be initiated at the initial receiving hospital); (3) fibrinolysis is administered and is unsuccessful (i.e., "rescue PCI"). Secondary nonemergency interhospital transfer can be considered for recurrent ischemia.

Patient self-transport: Patient self-transportation is discouraged. If the patient arrives at a non–PCI-capable hospital, the door-to-needle time should be within 30 minutes. If the patient arrives at PCI-capable hospital, the door-to-balloon time should be within 90 minutes. The treatment options and time recommendations after first hospital arrival are the same.

fibrinolysis if appropriate personnel and oversight are positioned to deliver it promptly. This capacity is of additional value in identifying patients better suited to percutaneous coronary intervention (PCI) and thus triaged directly from the field to a PCI-capable institution (Fig. 40.3).

Because at least one third of the deaths from MI occur prior to hospital presentation, out-of-hospital cardiac arrest remains a major public health challenge. The "chain of survival" program introduced by the AHA emphasizes early recognition and bystander activation of EMS as well as prompt bystander cardiopulmonary resuscitation (CPR) and defibrillation prior to the provision of advanced cardiac life support.[8] Cardiopulmonary resuscitation training of family members of patients at high risk and ready accessibility to automated external defibrillators (AEDs) have been shown to enhance clinically meaningful survival.[15]

Pharmacologic Reperfusion Therapy

No intervention has had a greater impact on the global management of acute STEMI than fibrinolytic therapy. The objectives of reperfusion therapy are (1) the achievement of rapid, high-quality coronary flow; (2) the maintenance of high-quality coronary patency so as to prevent recurrent ischemia and reinfarction; and (3) the enhancement of patient survival and quality of life.[4] The three core components of pharmacologic reperfusion consist of a fibrinolytic agent and concomitant antithrombotic and antiplatelet conjunctive agents. A variety of factors influence the success of fibrinolytic therapy, including the depth, complexity, and contents of the ruptured plaque; the age of the coronary thrombus; the role of distal microembolization and small vessel occlusion; coexistent vasospasm; and endothelial dysfunction.[4]

A convenient classification of currently available fibrinolytic agents begins with streptokinase, the most venerable fibrinolytic agent employed as a short-term infusion (30 to 60 minutes) in doses of 1.5×10^6 U (Table 40.1). Tissue plasminogen activator (tPA) until recently was the fibrin specific prototype and has increasingly given way to tPA congeners, tenecteplase (TNK-tPA) and reteplase (rPA). These latter agents are characterized by longer plasma half-lives than tPA, thereby permitting bolus injection that not only simplifies the administration of these agents but also reduces the potential for medication errors. Although they do not provide

TABLE 40.1. Pharmacology and pharmacokinetics of fibrinolytic agents for treatment of acute myocardial infarction

Property	*Streptokinase*	*Alteplase*	*Reteplase*	*TNK-tPA*
Molecular weight, kd		70	39	70
Dose	1.5×10^6 U	100 mg/90 min	2×10 IU bolus 30-min apart	0.5 mg/kg bolus
Plasma $t_{1/2\alpha}$ (min)	20	4–8	15	20
Fibrin-specificity	–	++	+	+++
Antigenicity	+	–	–	–
90-min patency	++	+++	++++	+++(+?)
Mortality reduction	+	++	++	++
Hemorrhagic stroke	+	++	++	++
Clinical development	Approved for general use	Established standard	Approved for general use	Approved for general use; likely to replace Alteplase.

additional mortality reduction over that provided by front-loaded, accelerated tPA, the increased fibrin specificity afforded by TNK-tPA does confer a significant decrease in major systemic bleeding.[4]

In Table 40.1, the pharmacology and pharmacokinetics of the four commercially available fibrinolytic agents are summarized. As systemic fibrinolytic therapy is administered, so too (and somewhat paradoxically) procoagulant counterbalancing forces emerge. These relate, in part, to fibrinolytic-induced exposure of surface-bound thrombin, as well as activation of platelets, which, on their surface, provide a rich source of factor Xa. A host of procoagulant factors contained in the alpha granules of platelets is also engaged. These include plasminogen activator inhibitor-1, α_2-antiplasmin, platelet factor IV, and vasoconstrictor substances, such as serotonin and thromboxane A_2. Table 40.2 provides an overview of the contraindications and cautions in using fibrinolytic therapy.

Antithrombotic Therapy

A variety of antithrombotic agents have been developed to combat the coagulation cascade and thereby sustain the benefits of fibrinolytic therapy. A summary of potential antithrombotic partners to the four generally available fibrinolytic agents is provided in Table 40.3.[15] The reference antithrombotic standard remains unfractionated heparin, even though the nonspecific binding of heparin to plasma proteins contributes to substantial variation in anticoagulant effect, and the dose-response relationships make it difficult to maintain patients in an optimal therapeutic range for a sustained

TABLE 40.2. Contraindications and cautions for fibrinolysis use in STEMI*

Absolute contraindications
Any prior intracranial hemorrhage (ICH)
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed head or facial trauma within 3 months
Relative contraindications
History of chronic severe poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP greater than 180 or DBP greater than 110 mm Hg)†
History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications
Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks)
Recent (within 2–4 weeks) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

INR, international normalized ratio; CPR, cardiopulmonary resuscitation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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

†Could be an absolute contraindication in low-risk patients with myocardial infarction (see Section 6.3.1.6.3.2 of ACC/AHA guidelines).

TABLE 40.3. Clinical advances in reperfusion therapy

Fibrinolytic (superscripts are references)	*Antithrombotic*
Streptokinase[10] 1,500,000 units IV in 30–60 min	Heparin SQ 7,500–12,500 b.i.d. or Heparin 5,000-IU bolus and 1,000 IU/h (PTT 60–90) or Bivalirudin 0.1-mg/kg bolus and 0.25 mg/kg/h*
Tissue plasminogen activator (tPA)[7,10] 15 mg bolus + 0.75 mg/kg in 30 min (max. 50 mg) + 0.5 mg/kg in 60 min (max. 35 mg)	Heparin 5,000-IU bolus and 1,000 IU/h (PTT 60–90)**
Reteplase (rPA)[29,30] 10 mg + 10 mg double bolus (q 30 minutes)	Heparin 5,000-IU bolus and 1,000 IU/h (PTT 60–90)**
Tenecteplase (TNK-tPA)[8,9,12,13]	Heparin 5,000-U bolus and 1,000 U/h (PTT 60–90) or
Weight adjusted (30–50 mg) single bolus	Heparin 60-U/kg bolus (max. 4,000 U) and 12 U/kg/h (max. 1,000 U/h) targeting a PTT of 50 to 70** or Enoxaparin 30-mg bolus and 1 mg/kg SQ b.i.d. (caution for patients >75 years of age)

Note: All combinations include acetylsalicylic acid (ASA) 160–325 mg chew and swallow ASAP.

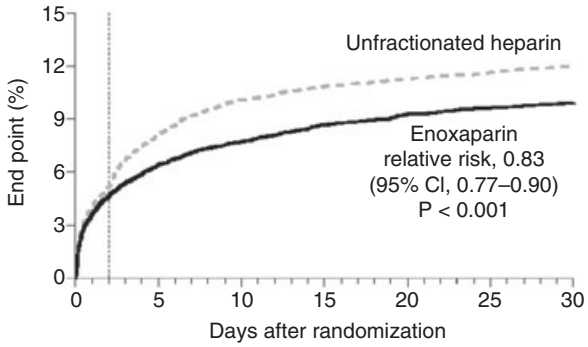
PTT, partial thromboplastin time.

* Recommended only when heparin is contraindicated.

** AHA/ACC guidelines recommend reduced dose heparin, i.e., 60 U/kg (max. 4,000 U) and 12 U/kg/h (max. 1,000 U/h) targeting a PTT of 50 to 70 minutes.

period. Confirmation of the safety and efficacy of this form of conjunctive therapy for both tPA and TNK has recently been provided and it supports a bolus of unfractionated heparin of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U/h) with a partial thromboplastin time (PTT) target of 50 to 70 seconds during the initial 48 hours.[16] Provision for down-titration of the heparin dose 3 hours after its initiation is also encouraged if the PTT is greater than 70 seconds. The evidence supporting the use of intravenous unfractionated heparin with fibrin-specific agents is not strong, yet it has a class I recommendation, largely based on angiographic findings of improved infarct-related patency.[8] Continuation beyond 48 hours should be individualized, based on risk of pulmonary and systemic embolization and other factors. Since recurrent ischemia has been noted after sudden cessation of unfractionated heparin, it is prudent to be vigilant during this time frame and consider more gradual cessation of therapy.[17] During therapy, the platelet count should be monitored daily to assess the occurrence of heparin-induced thrombocytopenia. Support for the use of intravenous unfractionated heparin with streptokinase is less certain, and there appears to be no obvious advantage over that provided by subcutaneous heparin.[8]

Considerable interest and promise relates to the use of low molecular weight heparin in conjunction with fibrinolytic therapy, given its ease of administration, relative stability of anticoagulant effect, greater factor Xa inhibition, and avoidance of the need for laboratory monitoring. Consistent reduction in the frequency of reinfarction and refractory ischemia afforded with enoxaparin is evident in clinical trials. To date, this benefit comes at a cost of a modest but significant increase in systemic bleeding.[16] However, in the prehospital ASSENT III PLUS experience, an excess of intracranial hemorrhage in low body weight women over age 75 has signaled caution regarding enoxaparin in this setting.[18] This issue has now been clarified by the *E*noxaparin and *T*hrombolysis *R*eperfusion for *A*cute Myocardial Infar*c*tion *T*reatment (ExTRACT) trial, which studied over 20,000 patients receiving a variety of fibrinolytic agents for treatment of STEMI. Patients were randomized to unfractionated heparin (ACC/AHA guideline dosing) or enoxaparin dosed according to the patient's age and renal function; hence, those with a creatinine clearance less than 30 mL/minute had their subcutaneous dose adjusted to a 24-hour versus a 12-hour repeat dosing regimen. Additionally, patients over age 75 did not receive an intravenous bolus of enoxaparin, and their subcutaneous dose was reduced to 0.75 mg/kg q12h. Those treated with enoxaparin showed a significant reduction in the primary efficacy end point of death or nonfatal MI (Fig. 40.4). Although there was some excess in systemic bleeding with enoxaparin, the rates of intracranial hemorrhage were modest and not different from unfractionated heparin (UH) (0.8 vs. 0.7%).[16,18,19] The promise of direct thrombin inhibitors emerged from phase II trials, suggesting that the outcome of STEMI patients treated with streptokinase and bivalirudin as compared with UH was associated with enhanced



No. at risk							
Unfractionated heparin	10,223	9385	9188	9109	9064	9027	8994
Enoxaparin	10,256	9595	9460	9362	9301	9263	9234

FIGURE 40.4. ExTRACT-TIMI 25 study: cumulative incidence of primary end point.

coronary reperfusion and no excess in systemic bleeding.[20] Since these agents are capable of inactivating both circulating and bound thrombin, the phase III Hirulog and Early Reperfusion or Occlusion (HERO) II study compared bivalirudin and unfractionated heparin in patients receiving streptokinase for STEMI within 6 hours of symptom onset was undertaken.[21] Although a clear reduction in the rate of reinfarction was evident in patients treated with bivalirudin, there was a tendency toward excess systemic and intracranial bleeding and no reduction in mortality. Hence, bivalirudin's current role in STEMI appears to be as an alternative when unfractionated heparin is contraindicated.

Antiplatelet Therapy

The International Study of Infarct Survival II (ISIS-2) defined the important role of aspirin in doses of 162 to 325 mg as enhancing survival, both as solo therapy and incrementally when added to streptokinase.[22] Chewable aspirin, or buccal or oral administration of nonenteric coated aspirin is advisable to ensure rapid initial effect. Subsequently, lifelong therapy with lower dose aspirin (i.e., at least 81 mg enteric coated), is a mandatory component of long-term secondary prevention.

The recognition that myocardial perfusion mediated both by microcirculatory flow as well as epicardial perfusion is a key mediator of infarct size and clinical outcome has focused attention on the use of antiplatelet therapy that provides incremental antiplatelet efficacy over that afforded by aspirin alone.[23,24]

The current STEMI ACC/AHA guidelines support the use of the adenosine diphosphate (ADP) antagonist clopidogrel in patients allergic to aspirin.[8] New data on the use of clopidogrel has emerged from the CLARITY and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trials as it relates to the use of clopidogrel in patients with STEMI treated with fibrinolysis and aspirin within 12 hours.[25,26] In the CLARITY study, a 300-mg loading dose followed by 75 mg once daily reduced a composite end point of death, recurrent MI or infarct artery occlusion, a median of 3.5 days after presentation by approximately one third (odds ratio 0.53–0.76, $p < .001$).[25] Importantly, this end point was heavily influenced by clopidogrel's impact on angiographic patency; hence, mortality was 2.2% and recurrent MI 3.6% in the placebo group and 2.6% and 2.5%, respectively, in clopidogrel-treated patients. Furthermore, this study was restricted to patients younger than 75, constraining the general applicability of these findings to the broad cross section of fibrinolytic-treated patients with MI. By contrast, the COMMIT study, conducted in 46,000 patients in China within 24 hours of the onset of STEMI using 75 mg of clopidogrel without a loading dose, revealed a 9% relative risk reduction in the composite of death, reinfarction, or stroke at hospital discharge (10.1% vs. 9.3%, $p = .002$).[26] Approximately half the patients received fibrinolysis (mainly urokinase) and no age or weight limit was applied. Taken together with CLARITY, the COMMIT study indicates that the major contribution of clopidogrel in the setting of an acute STEMI is a benefit on reinfarction and culprit artery patency, and potentially on overall mortality.[26]

The emergence of the platelet glycoprotein IIb/IIIa receptor blockers and their efficacy in patients with non–ST-elevation acute coronary syndromes led to substantial enthusiasm about their potential role as part of the pharmacologic armamentarium in patients with STEMI.[27] In particular, it was suggested that combining them with reduced dose fibrinolytic might not only enhance the potential for both macro- and microcirculatory reperfusion but also reduce the propensity for intracranial hemorrhage and systemic bleeding.[28] Extensive phase II studies of this approach[29–31] provided evidence of reduced reocclusion and more rapid and effective reperfusion. However, when this concept was first tested in a large-scale phase III study (GUSTO V) using a combination of half-dose reteplase and full-dose abciximab as compared with full-dose reteplase, no benefit on mortality occurred, although there was less reinfarction with combination therapy.[32] Subsequently, half-dose tenecteplase with abciximab was evaluated in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT 3) study, and a similar benefit on reinfarction and recurrent ischemia was evident as compared with monotherapy with tenecteplase, although again, there was no subsequent improvement in mortality.[16] In both studies, however, there was an excess of severe bleeding, and a trend toward excess intracranial hemorrhage in patients above the age of 75 with combination glycoprotein IIb/IIIa inhibition and fibrinolysis. Percutaneous coronary intervention followed by full-dose fibrinolysis with unfractionated heparin has recently been compared to direct PCI in over 1600 patients in the ASSENT-4 PCI study. This investigation was concluded before its target enrollment because of an excess in mortality presumed to be related to recurrent thrombosis in the fibrinolytic arm, in which most patients received intracoronary stents in association with their PCI.[33] Hence, at this juncture, facilitated coronary intervention remains largely experimental, but ongoing investigation continues.[34] Further investigation of this approach in the context of facilitation prior to intended percutaneous coronary intervention is ongoing.

Standard Initial Therapy

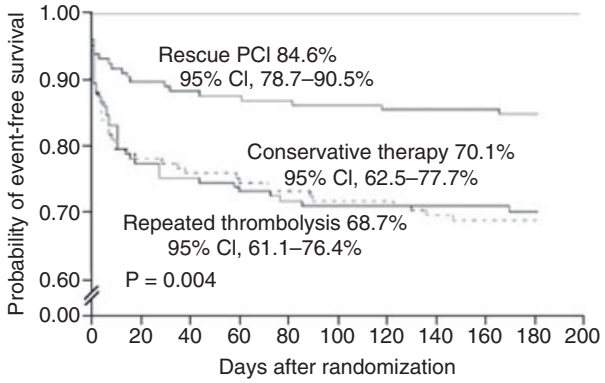
Supplemental oxygen therapy aimed at limiting the extent of ischemic myocardial injury remains a standard component of the therapeutic armamentarium in the initial hours after the onset of STEMI. Maintenance of an oxygen saturation of at least 90% until clinical stability occurs, and more aggressive oxygen administration in the setting of congestive heart failure or with major hemodynamic or electroinstability is indicated. In uncomplicated STEMI cases, reevaluation of oxygen use beyond 6 hours is reasonable.

Because a component of myocardial ischemia and coronary occlusion may be mediated by coronary vasoconstriction, judicious use of sublingual nitroglycerin, employing two to three doses separated by 5 to 7 minutes, may be helpful. In instances where persisting ischemic pain, hypertension, or concomitant congestive heart failure are present, intravenous nitroglycerin beginning at an infusion rate of approximately 5 to 10 μg/min and titrating upward to achieve desired response is useful. Caution concerning the use of

nitrates, especially given by any route other than intravenously, in acute MI is warranted if hypotension, bradycardia, or right ventricular infarction is present. It is also prudent to inquire about the patient's prior use of phosphodiesterase inhibitors for erectile dysfunction, since these agents potentiate the blood pressure lowering effect of nitrates, and their combination could unnecessarily exacerbate the clinical course.

Interestingly, in the most recent ACC/AHA guidelines, patients are encouraged to call 911 in 5 minutes or less from the onset of chest pain and after taking only one sublingual nitroglycerin.[8] For patients with established stable angina that is severe and recurrent, two to three nitroglycerin tablets are sometimes necessary and 5 to 10 minutes often required to alleviate their usual ischemic pain. Hence, in such a circumstance, it is our view that this advice should be tempered with room for individualized therapy.[35]

At the first point of medical contact, nonenteric aspirin, 162 to 325 mg should be administered in a manner that achieves rapid absorption: chewing, sucking, or swallowing a crushed preparation.



No. of event-free patients									
Repeated thrombolysis	110	106	105	101	99	99	96	95	93
Conservative therapy	109	104	102	99	98	97	96	95	93
Rescue PCI	129	127	124	122	120	118	117	116	115

FIGURE 40.5. REACT trial Kaplan-Meier estimates of cumulative rate of the composite primary end point (death, recurrent myocardial infarction, severe heart failure, or cerebrovascular event) within 6 months.

Assessment of Reperfusion After Fibrinolytic Therapy

Having decided to administer fibrinolytic therapy, the clinician has a cardinal responsibility to systematically assess the patient's response over the subsequent minutes to hours. Resolution of ischemic chest pain, restoration of hemodynamic stability, and resolution of the initial ST-segment elevation by at least 50% of its original height are helpful signs of reperfusion.[36] Indeed, ST resolution is a good indicator of both macro- and micromyocardial perfusion and is aligned with better recovery of ventricular function, a lesser infarct size, and enhanced clinical outcome.[36]

Emergence of an accelerated idioventricular rhythm is uncommon but has also been correlated with the achievement of infarct vessel patency. Although a variety of investigative techniques, including contrast echocardiography and magnetic resonance imaging, are under investigation, no single technique that is clinically applicable at the bedside has emerged. Hence, the clinician is left with a collage of clinical and electrocardiographic parameters: the latter can be more refined by continuous ST segment monitoring, or at least by a systematic algorithm that requires repeat 12-lead electrocardiography at 60 and 90 minutes.[8] Failure to achieve reperfusion may signal the need to proceed with an invasive catheter based strategy; the Rescue Angioplasty Versus Conservative Therapy or Repeat Thrombolysis (REACT) trial investigators have demonstrated that this approach is superior to conservative therapy or repeat fibrinolysis (Fig. 40.5).[37,38] This judgment should take into account the risk of the initial infarct, other comorbidities, and the patient's wishes.

Similarly, observation for recurrent ischemic symptoms, if associated with objective evidence of further ST segment shift or reinfarction, especially in the first 48 hours after the administration of fibrinolytic therapy, is often an indication for co-intervention with catheterization and mechanical intervention.

Percutaneous Coronary Intervention

The choice of the optimal reperfusion strategy for STEMI[39,40] has been the subject of major controversy, spirited debate, and ongoing research. It seems clear that for patients with absolute contraindications for fibrinolysis and those in Killip class III and IV, primary PCI is the preferred option, provided it can be accessed in a timely fashion, by a skilled operator, in an experienced facility. Although a systematic review of primary PCI as opposed to fibrinolysis has suggested that the former is a superior option, even in patients requiring interhospital transfer, there are several methodologic concerns associated with this report that, in the minds of the authors, position it as hypothesis generating.[41,42] In brief, these concerns are related to the patient characteristics, bias toward patient entry within the usual working hours, the failure to apply conventional catheter-based co-intervention in fibrinolytic-treated patients, and uncertainty as to whether the technical expertise of within-trial operators is transferable to a much wider group of individuals and locations.[39]

In our view, rather than engage in an unnecessary protracted debate that leaves the front-line physician charged with the responsibility of STEMI care uncertain: hence the current algorithm that embraces an integrated approach to management (Fig. 40.6) is preferred.[43] Within this algorithm, now adapted from the ACC/AHA guidelines by the Canadian Cardiovascular Society, the following key questions are posed[8,35]:

1. What is the time from symptom onset to first medical contact?
2. What is the baseline risk of the myocardial infarction, based on incorporation of the 12-lead ECG?
3. What is the risk of fibrinolysis?
4. What is the time required to transport the patient and achieve PCI by a skilled operator?

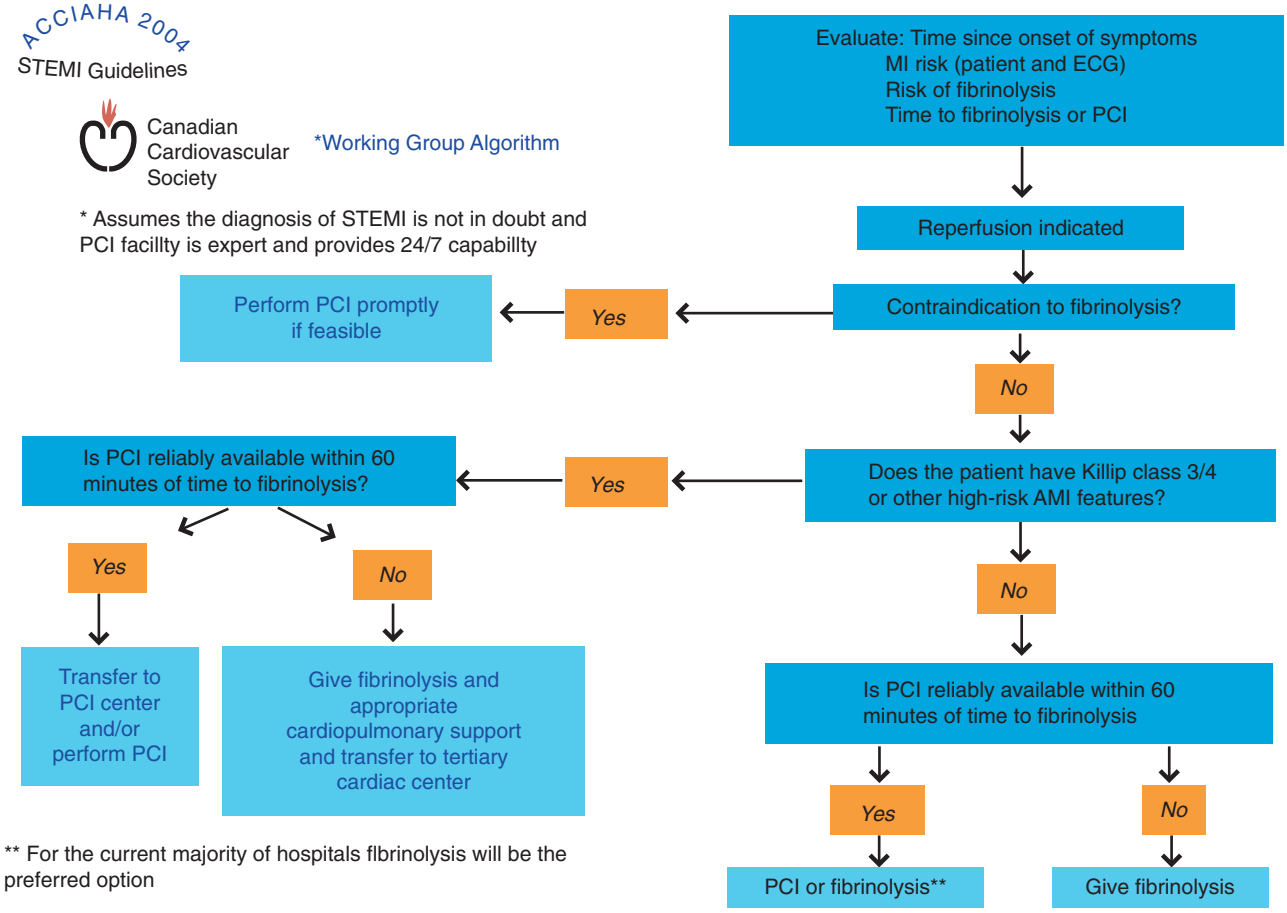


FIGURE 40.6. STEMI guidelines.

Such an approach places a strong priority on rapid EMS response, prehospital ECG, and the capacity for fibrinolysis, appropriate triage of patients in whom primary PCI is preferred, and enhanced state of readiness in the institution that will receive the patient. The sensitivity to time is especially key, given the knowledge that coronary thrombus within the first 2 to 3 hours is especially sensitive to fibrinolysis, and the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial infarction (CAPTIM), Prague-2 and Which Early ST-Elevation Myocardial Infarction Therapy (WEST) studies demonstrate that fibrinolysis is at least as good, if not superior, to primary PCI in that window.[44–46] It is essential that community hospitals develop or enhance effective communication strategies, with fully equipped tertiary care centers, to ensure that timely transfer of high-risk patients and those not responding to fibrinolytic therapy can occur. Since fewer than 20% of U.S. hospitals have facilities for cardiac catheterization, and even fewer the capacity for primary PCI, widespread primary PCI therapy for STEMI is not feasible. Despite calls for regionalization of care in specialized centers, the potential negative effects on patient care associated with transfer and cardiac care in non–acute coronary syndrome (ACS) centers, as well as the economic implications, provide reasons for caution.[47,48]

We agree with the following conclusion of the ACC/AHA STEMI Writing Committee on this subject:

Given the current literature, it is not possible to say definitively that a particular reperfusion approach is superior for all patients, in all clinical settings, at all times of the day. The main point is that some type of reperfusion therapy should be selected for all appropriate patients with suspected STEMI. The appropriate and timely use of some reperfusion therapy is likely more important than the choice of therapy, given the current literature and the expanding array of options.[8]

Ancillary Medical Therapy

The evidence supporting the use of intravenous beta-blockers in patients with acute MI is slim and has been mainly acquired in the pre-reperfusion era and thought to merit a class IIa (level of evidence B) recommendation,[49] whereas intravenous beta-blockers may be useful in the setting of hypertension, tachycardia, atrial and ventricular arrhythmias, and in patients with ongoing ischemic pain. The COMMIT study results indicate that routine intravenous beta-blockers should be avoided, especially in patients with advanced Killip class and hypotension; in these instances an excess of cardiogenic shock was evident.[50] Oral beta-blockade, when started early and when the patient is stable, and most especially with timolol, metoprolol, or propranolol, merits a class Ia recommendation, which is further supported by COMMIT.[51]

TABLE 40.4. STEMI medical therapy: first 24 hours

Agent	*Comment*	*Alternative*	*Level of Recommended Evidence*	
Aspirin 162–325 mg	Chew nonenteric coated for most rapid/predictable absorption	Clopidogrel for ASA intolerance	I	A
Fibrinolytic within 12 hours unless contraindicated	Consider PCI for patients at increased risk and presenting >3 hours	PCI	I	A
Unfractionated heparin (IV)	Clearest evidence is with fibrin specific lytic agents	Bivalirudin for known heparin-induced thrombocytopenia	I	C
Low molecular weight heparin (for dosing, see Table 40.2)	Suitable alternative for patients younger than 75 years without renal dysfunction		IIb	B
Beta-blockers	IV beta-blockers if tachyarrhythmia or hypertension and no contraindication		IIa	B
	Oral agents (other than above)		I	A
ACE inhibitors	Commence for anterior MI, pulmonary congestion, LVEF <40% without hypotension	Angiotensin receptor blockers (ARBs)	I	A
	Uncomplicated acute MI		IIa	B
Nitroglycerin IV for persisting ischemia, congestive heart failure, or hypertension	Avoid with bradycardia and hypotension and use caution with inferior STEMI with right ventricle infarction		I	B
Insulin infusion to normalize blood glucose	During first 24–48 hours to normalize blood glucose		Uncomplicated course IIa Complicated course I	 B B

LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention. Commencement of aldosterone blockers and statins should be considered promptly during hospitalization and at discharge, along with aspirin, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors.

Inhibition of the renin angiotensin aldosterone system with angiotensin-converting enzyme (ACE) inhibitors, has been extensively studied in STEMI and consistently revealed a modest but significant short-term mortality (i.e., less than 1%).[52] This effect, however, is greater in patients with anterior infarction, pulmonary congestion, and diminished left ventricular ejection fraction where early administration of captopril, lisinopril, or enalapril is useful.[53] Care should be taken, as is the case with beta-blockers, in commencing with a low initial dose so as to avoid hypotension. Preference should be given to the commencement of ACE inhibitors in advance of beta-blockers if relative hypotension is of concern, especially in the setting of pulmonary congestion and a large MI. If genuine intolerance to ACE inhibitors exists, angiotensin receptor blockers are an appropriate alternative.

Table 40.4 summarizes the pharmacotherapeutic approach to STEMI in the first 24 hours after symptom onset.

Additional benefit relating to aldosterone blockade has been demonstrated using the selected aldosterone blocker eplerenone in patients with left ventricular dysfunction and heart failure complicating MI.[54] At a mean of 16 months after therapy, begun 3 to 14 days after MI, eplerenone significantly reduced each of the two primary end points (death 16.7% and cardiovascular death and hospitalization 30.0% with placebo to 14.4 and 26.7%, respectively, with eplerenone). Patients with elevated creatinine were excluded from this study, and special care should be used in monitoring both serum potassium and creatinine if this therapy is employed, and most particularly with concomitant use of ACE inhibitors. Although eplerenone received a class Ia recommendation and clearly may be beneficial during the convalescence of STEMI patients, less than half of the patients entered into the EPHESUS study received reperfusion therapy, and the actual proportion with ST elevation on admission is unclear.[8]

Hemodynamic Complications

The development of low-output pulmonary edema and shock are key perturbations in STEMI patients that require careful diagnostic evaluation in order to guide appropriate management (Fig. 40.7). A first priority requires a systematic screen for correctable causes, such as brady- or tachyarrhythmias, hypovolemia, and adverse responses to pharmacotherapy, such as beta-blockers or ACE inhibitors. An especially familiar context for low output in acute inferior MI is vagotonia associated with ischemic cholinergic stimulation that prompts both bradycardia and hypotension; these phenomena may be exacerbated by overzealous use of routine nitrates and intravenous diuretics. Patients with a right ventricular infarction, which occurs in approximately one third of inferior STEMI patients, present a particular therapeutic challenge.[55] Such individuals commonly respond, however, to aggressive volume loading, supplemented with intravenous dobutamine.[56] Hemodynamic monitoring with Swan-Ganz catheterization is useful in documenting right- and left-sided filling pressures and guiding appropriate therapy.

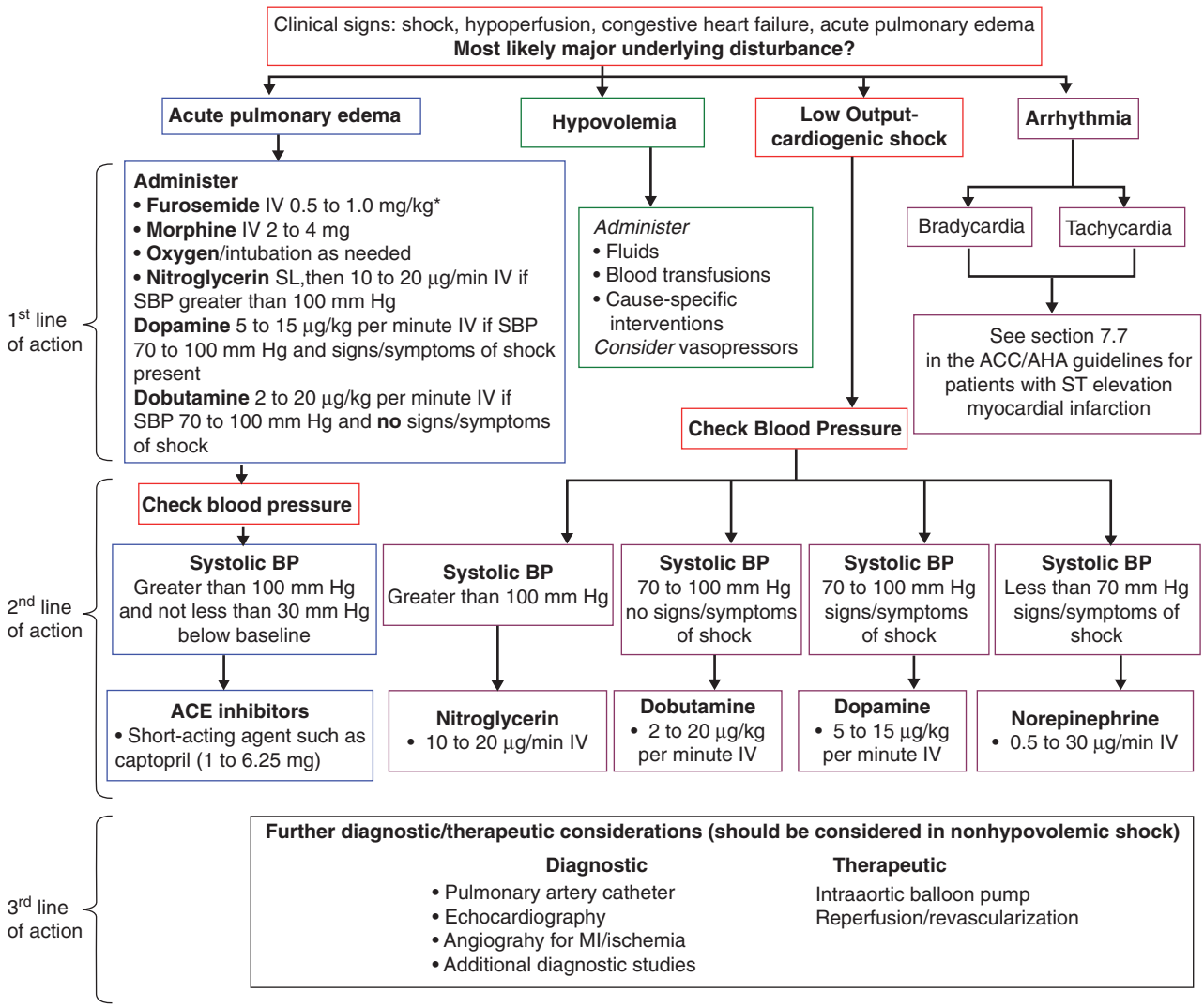


FIGURE 40.7. Emergency management of complicated STEMI.

The appearance of a new systolic cardiac murmur in association with low output or congestive heart failure raises the specter of either a ruptured intraventricular septum or acute mitral regurgitation secondary to papillary muscle dysfunction or dehiscence. Echocardiography is especially useful in delineating evidence of a left to right shunt or mitral regurgitation and invasive hemodynamic monitoring may also assist in the diagnosis but in guiding subsequent management. Since both of these lesions are afterload dependent, unloading the ventricle with intravenous nitroprusside, nitroglycerin, or intraaortic balloon pumping may provide the necessary bridge to stabilize such patients. However, prompt intervention with coronary angiography to define potentially correctable lesions and surgical repair in appropriate cases is required.[8]

Free wall cardiac rupture with rapid hemodynamic collapse associated with electrical mechanical dissociation is a particularly devastating early complication.[57] Emergency pericardiocentesis for concomitant pericardial tamponade may, on occasion, salvage the patients, but surgical intervention is required. It carries a high mortality but is the only alternative. Occasionally, minor free wall perforations may actually self-seal and give rise to pseudoaneurysm formation.

For patients with cardiogenic shock, without demonstrable mechanical defects, and who are younger than 75 years of age with STEMI, compelling data from the SHOCK study support proceeding with early angiography and revascularization as appropriate.[58] Aggressive pharmacologic therapy and the insertion of an intraaortic balloon are usual preambles to angiography, and the evidence suggests that this strategy is applicable to patients who develop shock within 36 hours of MI and for whom revascularization can be undertaken within 18 hours of the onset of shock. Such an approach may also be appropriate for selected patients over the age of 75, recognizing that the biologic and chronologic ascertainments of age may differ.[59]

Figure 40.7 is a management algorithm for the hemodynamic complications of MI.

Ventricular Aneurysm

Left ventricular aneurysm formation is an important mechanical complication of MI. It occurs in association with transmural necrosis, is associated with infarct thinning and the potential for expansion, and is most common in the anterior wall when the infarct artery is occluded and there are no intercoronary collaterals.[60] Although suggested by persisting ST elevation in the setting of a Q wave, the diagnosis is best made from echocardiography or left ventricular angiography. In addition to left ventricular dysfunction and failure, aneurysms may serve as a nidus for mural thrombosis and systemic embolization as well as the substrate for major ventricular arrhythmias. Interrogation of the left ventricular apex for thrombus formation in the early days after a large anterior MI is an important investigation. Warfarin therapy is indicated in the presence of left ventricular thrombosis.[8]

Recurrent Symptoms

Chest pain after STEMI is a common symptom and major focus of clinicians caring for such patients. Indeed, the frequent interrogation of patients in the early hours after presentation may provoke undue anxiety in patients, given that some residual precordial discomfort may persist for hours despite successful reperfusion. Concomitant gastrointestinal distress and anxiety may lead to the reporting of previously ignored discomfort and confound the inexperienced diagnostician. Recurrent ischemia and infarction in the first few days after presentation of STEMI portend a worsened prognosis and require careful assessment.[61,62] Recurrent ST elevation in the distribution of the same infarct location as at presentation versus a different region (so-called ischemia at a distance) are usually indications for early angiography, unless there are obvious secondary causes or suboptimal medical therapy.[63] If the discomfort is sustained and associated with recurrent ST elevation and urgent PCI cannot be undertaken in a timely fashion, then repeat fibrinolytic therapy may be appropriate (using a fibrin specific agent).

Recurrent ischemic pain must be differentiated from that of pericarditis, which is most common in patients with major full-thickness myocardial necrosis and extensive infarctions.[64] The more distinctive characteristics of pericardial pain, exacerbated by respiration and relieved by the upright position, as well as the physical findings of a pericardial friction rub may be useful differential points.[65] More diffuse ST elevation with an upward concavity as well as PR depression are typical electrocardiographic findings. The appreciation of the potential for harm with nonsteroidal antiinflammatory agents and corticosteroids, based on their negative impact on healing, as well as ibuprofen's block of the antiplatelet effect of aspirin have modified prior treatment recommendations.[66,67] Aspirin remains the first line of therapy, with colchicine 0.6 mg orally every 12 hours and acetaminophen as suggested alternatives. Antithrombotic therapy should be discontinued and careful surveillance for pericardial tamponade undertaken clinically and as required with the aid of echocardiography.

Convalescent Care

In asymptomatic patients, the focal points of subsequent management involve thorough risk stratification, appropriate co-intervention, and the application of secondary prevention through evidence-based medication and lifestyle modification. Fundamental to the risk profile of such patients is an objective evaluation of left ventricular function undertaken by echo, nuclear cardiography, or MRI (Fig. 40.8). Patients with depressed ejection fraction have an increased long-term morbidity and mortality, and should be considered for revascularization if appropriate. The role of electrophysiologic consultation, testing and device implantation is addressed in another chapter. A symptom-limited exercise test is valuable in further triaging patients without high risk features. For those in whom the ECG is uninterpretable, or physical disability precludes adequate exercise, pharmacologic stress using dobutamine, echocardiography, or adenosine/dipyridamole nuclear studies is key to detecting reversible ischemia and the desirability of proceeding with invasive study. Exercise testing may play additional useful roles in the post-STEMI patient: (1) to help evaluate the current medical pharmacotherapy, (2) to establish an exercise prescription and reassurance guide regarding functional capacity, and (3) as a baseline for subsequent cardiac rehabilitation. The ability to perform at least 5 metabolic equivalents of task (METs) of exercise without early ST depression and with an appropriate rise in systolic blood pressure is a useful sign of lower risk.

The controlled environment in the early days after a transforming event such as STEMI, provides the clinician with a unique window of opportunity to engage patient and family in aggressive secondary prevention. Appropriate dietary modification to reduce weight and an exercise program developed during rehabilitation are first steps. Smoking cessation, not only for the patient but also those who live in the same household is especially key, and may be coupled with pharmacologic adjuncts, such as nicotine replacement therapy. Appropriate hypoglycemic therapy, beginning acutely with an insulin infusion to normalize blood glucose and subsequently with oral hypoglycemic therapy to control hemoglobin A_{1C} (HbA_{1C}) to less than 7% is desirable.[8] Intense lipid therapy with the early introduction of statins can achieve a low-density lipoprotein (LDL) cholesterol of less than or equal to 100 mg/dL. Recent evidence from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study shows that intensive lipid lowering therapy initiated within 10 days after hospital admission of acute coronary syndromes with 80 mg of atorvastatin to achieve an LDL cholesterol of less than 70 mg/dL achieved a 16% reduction (from 26.3% to 22.4% in a composite end point of death, MI, unstable angina, requiring rehospitalization and coronary revascularization and stroke).[68]

Daily walking should be strongly encouraged with a progressive increase in the pace and distance as tolerated. Sexual activity with the usual partner may be resumed within 2 weeks and is roughly metabolically equivalent to the ability to climb two flights of stairs. Commencement of driving after STEMI is subject to regional jurisdictions, but a waiting period of between 1 week to 1 month for private driving and 3 months for commercial driving is often recommended. However, if revascularization has been undertaken, no

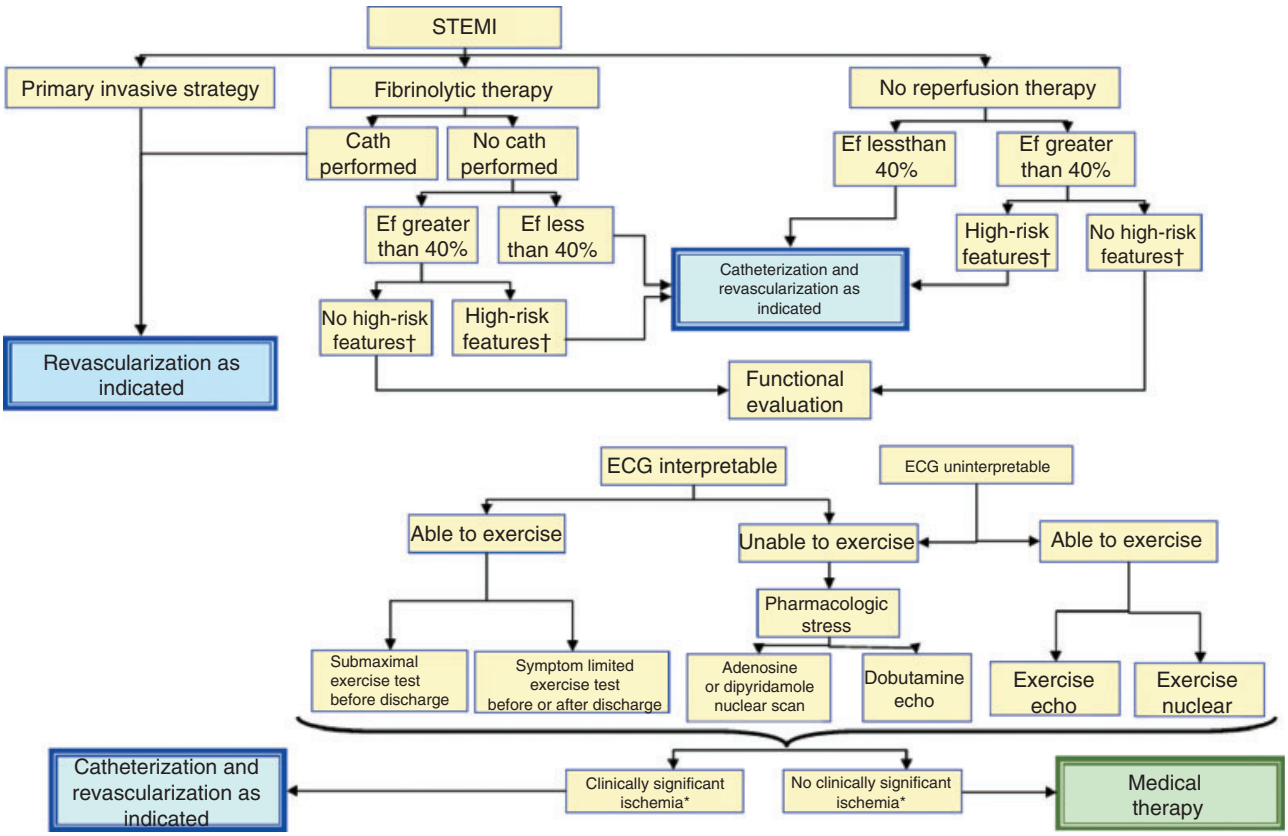


FIGURE 40.8. Evidence-based approach to need for catheterization and revascularization following STEMI: algorithm for catheterization and revascularization after STEMI. The algorithm shows the treatment paths for patients who initially undergo a primary invasive strategy, receive fibrinolytic therapy, or do not undergo reperfusion therapy for STEMI. Patients who have not undergone a primary invasive strategy and have no high-risk features should undergo functional evaluation using one of the noninvasive tests shown. When clinically significant ischemia is detected, patients should undergo catheterization and revascularization as indicated; if no clinically significant ischemia is detected, medical therapy is prescribed post-STEMI. EF, ejection fraction. *See the ACC/AHA Guidelines for the Management of Chronic Stable Angina (Table 23 of that Guideline) for further definition. †See Table 3, Section 6.3.1.6.2., and Section 7.3. in the full-text STEMI guideline for further discussion.

reversible ischemia is evident, and a good functional status demonstrated, a shorter period of time is reasonable.

Prescription of an appropriate medical program at the time of hospital discharge and reevaluation after appropriate up-titration of medical therapy at approximately 1 month thereafter, is a key component of secondary prevention. Aspirin, statin therapy, and an ACE inhibitor are recommended for all patients in the absence of contraindications. For patients with LV dysfunction, beta-blockers are strongly recommended, but uncertainty exists about their role in a successfully reperfused patient at low risk. If ACE inhibitors cannot be tolerated, angiotensin receptor blockers should be substituted and long-term aldosterone blockade added for patients with left ventricular dysfunction and an ejection fraction (EF) less than 40%.

Future Issues

Several lines of investigation hold promise for the future of STEMI patients. These include ongoing investigation into the role of early pharmacologic therapy coupled with rapid transfer for invasive study incorporating the so-called pharmacoinvasive approach. Additional lines of investigation are exploring more proximal antithrombotic and antiplatelet therapies that are more effective and safer, especially in high-risk elderly and female patients, when used in combination with catheter-based or fibrinolytic strategies. Intense investigation to explore the inflammatory hypothesis associated with both the consequences of ischemia and reperfusion injury are under way and show promise in their potential of limiting infarct size, attenuating left ventricular remodeling, and apoptosis after STEMI. Finally, the potential for modulating injury and providing repair and replacement through gene and stem cell therapy is an exciting new frontier in early development.

Notwithstanding these frontiers of research, the more fundamental issues associated with the recognition of patients at risk and overcoming undertreatment remain an essential priority of health care providers and systems. Preparing the convalescent STEMI patient for hospital discharge, and providing a coherent treatment strategy that incorporates the multiplicity of evidence-based medications is a new and still uncharted direction. The promise of the poly-

pill with differing combinations of recommended medications that minimize risk and are cogent players in secondary prevention is of interest.

Summary

The care of patients with ST elevation myocardial infarction has been dramatically transformed in the past decade with a commensurate and profound reduction in both mortality and morbidity. Perhaps more than in any other acute cardiovascular condition, optimizing therapy highlights the critical dependence on the intersection between the content of evidence-based care and the process and timeliness whereby it is delivered. The appreciation of the importance of early assessment of risk, the continuously updating and changing profile of risk, and the application of contemporary invasive and noninvasive approaches to optimize diagnosis and therapy are key components of comprehensive care. Enhanced patient education, early emergency response of appropriately trained and equipped paramedical personnel, streamlined triage and treatment in the field, and the application of the best reperfusion strategy for the right patient at the right time in the right place are key components of enhancing the care of STEMI patients. Application of evidence-based therapy to promote and sustain high-quality reperfusion, limit myocardial damage, and prevent unfavorable left ventricular remodeling and the consequences of myocardial infarction are a key responsibility.

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