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OBJECTIVES:

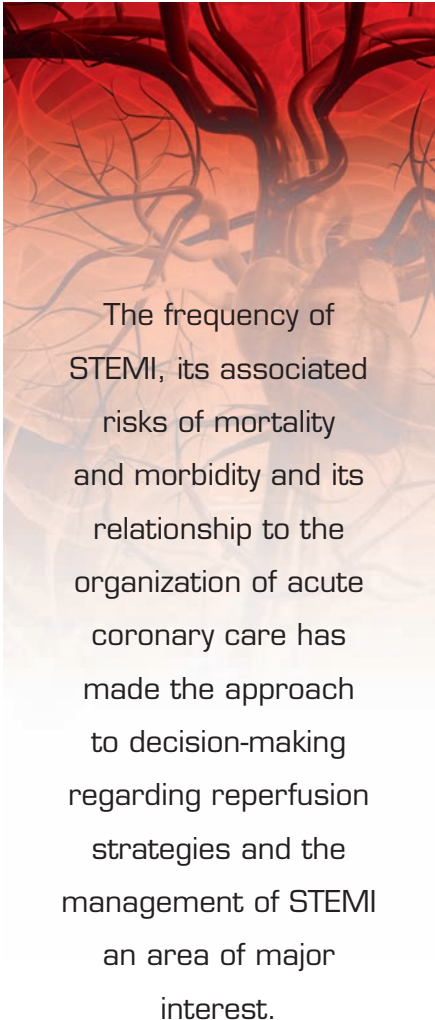
1. Discuss clinical decision making in the determination of a reperfusion strategy for STEMI with a review of the current ACC/AHA guidelines and other literature.
2. Discuss the impact of time of reperfusion on outcome.
3. Review the potential role of prehospital care in reperfusion strategies.

INTRODUCTION

Since the recognition of the role of an acute atherothrombotic coronary occlusion in acute ST-segment elevation myocardial infarction (STEMI), the major therapeutic goal has been re-opening the occluded coronary artery. American, Canadian and European guidelines for the management of patients with STEMI emphasize the restoration of blood flow through reperfusion therapy as rapidly as possible.¹⁻³ In the 1980's multiple large clinical trials evaluated pharmacologic reperfusion strategies with fibrinolytics and demonstrated reduction of infarct size, improved left ventricular function, and enhanced short, and long-term survival.⁴ Percutaneous coronary intervention (PCI) with balloon angioplasty was used initially for patients with contraindications to fibrinolysis or in cases of failed fibrinolysis, with the subsequent addition of intra-coronary stent placement.⁵ The effectiveness of primary PCI in restoring myocardial perfusion in STEMI has been demonstrated in multiple clinical trials, and it has taken the primary role for

reperfusion in STEMI. The emergency physician has an integral role in the diagnosis and management of STEMI including the timely initiation of a reperfusion strategy, so a comprehensive understanding of the management of this disease process is critical.

The frequency of STEMI, its associated risks of mortality and morbidity, and its relationship to the organization of acute coronary care has made the approach to decision-making regarding reperfusion strategies and the management of STEMI an area of major interest.⁶ With the direct relationship between patient outcome and timing of reperfusion, a significant emphasis has been placed on the rapid evaluation, diagnosis and timely initiation of a reperfusion strategy. Many factors influence the determination of a reperfusion approach, including the individual patient characteristics, presence of contraindications, time elapsed since onset of myocardial ischemia, ED and institutional capabilities, and the immediate accessibility to cardiac catheterization facilities.⁷



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This monograph will briefly review selected aspects of the American College of Cardiology/American Heart Association (AHA/ACC) Guidelines² for the management of patients with STEMI as related to the determination of reperfusion strategies and will briefly review risks and benefits of PCI and fibrinolytics as well as evidence supporting their time sensitive nature. The impact of prehospital care on these strategies will be highlighted. Adjunctive therapies, including antiplatelet and antithrombin agents are integral to the management of STEMI. Several recent papers provide a comprehensive review of contemporary issues in management of myocardial infarction including reperfusion therapies and adjunctive therapies.⁷⁻⁹

The ACC/AHA guidelines for the management of patients with STEMI and Canadian Cardiovascular Society Working Group perspective on the guidelines, set time frames of a door/first medical contact to balloon time of less than or equal to 90 minutes for primary PCI and door/first medical contact to needle time less than 30 minutes if reperfusion is carried out with fibrinolytic agents.¹⁻³ If the estimated first medical contact/door to balloon time is 90 minutes or less from patient presentation, PCI is recommended as the optimal therapy. However, if the delay in providing reperfusion with PCI is greater than one hour in excess of the 30 minute time period required for the delivery of fibrinolytics, fibrinolysis is considered the preferred reperfusion strategy. In STEMI patients presenting within three hours of the onset of symptoms, the ACC/AHA guidelines express no specific preference between fibrinolytics and PCI.^{2,5} If the STEMI presentation is greater than three hours after the onset of symptoms, PCI is the preferred strategy.²

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Fibrinolysis

Intravenous fibrinolytic therapy is indicated for patients with myocardial infarction presenting within 12 hours of symptom onset, if the patient has ST-segment elevation, a new left bundle branch block, or ST-segment depression in leads V₁ to V₃ consistent with a true posterior MI, provided there are no contraindications.^{2,9} In 1994, the Fibrinolytic Therapy Trialists group did an analysis of placebo controlled clinical trials with greater than 1,000 STEMI patients, and demonstrated a 2.6% absolute reduction in mortality for patients with STEMI treated within the first 12 hours of onset of symptoms.⁴ This meta-analysis demonstrated a very significant relationship between outcome and time of administration of fibrinolysis, with the greatest mortality benefit being seen in the first hour. For patients treated within one hour of symptom onset an absolute mortality benefit of 39 lives saved per 1,000 patients was observed. If fibrinolysis was carried out between two and three hours after symptom onset, 30 lives were saved per 1,000 patients, and if the therapy occurred between seven and twelve hours following symptom onset, 21 lives per 1,000 patients were saved. With each additional hour of delay, the trial demonstrated an absolute benefit reduction of 1.6 lives per 1,000 patients.⁴ The reperfusion of patients with STEMI by fibrinolysis was been demonstrated to reduce 35 day mortality of patients of STEMI by 18%.⁴

Contraindications for fibrinolytic therapy are defined as absolute and relative and primarily relate to the risk of bleeding. The contraindications for fibrinolysis are listed in [Table 1](#).^{2,10}

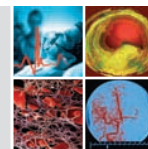


Table 1. Absolute and Relative Contraindications for Thrombolytic Therapy in Patients with ST-Segment Elevation Myocardial Infarction

Absolute contraindications

- Any previous intracranial hemorrhage
- Known structural cerebral vascular lesion
- Known malignant intracranial neoplasm
- Ischemic stroke within the past 3 months (except for acute 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, or poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
- History of ischemic stroke more than 3 months previously, dementia, or known intracranial disorders not covered in absolute contraindications
- Traumatic or prolonged cardiopulmonary resuscitation (>10 minutes) or major surgery (within past 3 weeks)
- Recent internal bleeding (within past 2 to 4 weeks)
- Noncompressible vascular punctures
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulant agents: the higher the international normalized ratio, the higher the risk for bleeding
- Previous exposure (>5 days earlier) to or previous allergic reaction to streptokinase or anistreplase

The major complications of fibrinolysis are also related to hemorrhage with the most significant being that of intracranial hemorrhage (ICH), occurring in an average of 1% of patients receiving fibrinolysis.⁹ If ICH occurs, it is potentially fatal in one-half to two-thirds of patients. Other risk factors for ICH include: increased age, female sex, black race, previous CVA, systolic blood pressure greater or equal to 160 mm Hg on admission, lower body weight, and excessive anticoagulation in addition to the characteristics of the specific fibrinolytic agent used.^{2,7} An estimate of an individual patient's risk of ICH can be approximated using a risk score incorporating parameters including age, gender, body size, history of prior cerebrovascular accident, and hypertension.¹¹

A meta-analysis of randomized fibrinolysis trials between 1983 and 1993, a total of 22 trials with 50,246 patients, demonstrated treatment within the first hour of symptom onset had a benefit of nearly twice compared to treatment started between one and two hours of symptom onset. This translated to 65 vs. 37 lives saved per 1000 treated patients.¹² There is evidence supporting the significant

impact of fibrinolytic therapy on mortality and infarct size if administered within one - two hours of symptom onset.¹³ In the ASSENT 3 trial, it was noted that 25% of patients treated in the first hour after symptom onset had an "aborted MI", defined as maximal CK $\leq 2 \times$ the upper limit of normal combined with typical evolutionary ECG changes.^{14, 15}

There is a risk of subsequent re-occlusion of the coronary artery with fibrinolysis.¹⁶ If fibrinolysis is unsuccessful or only partially successful, rescue PCI should be considered. The REACT trial demonstrated survival after failed fibrinolysis was significantly higher with rescue PCI than with either repeated fibrinolysis or conservative management.¹⁷ If a patient has persistent chest pain and prolonged ST-segment elevation following administration of fibrinolytic, he or she should be referred for urgent angiography and PCI.^{2,5} ST-segment resolution has been described as the best indicator of reperfusion.¹⁸ The extent of ST-segment resolution predicting reperfusion, however, 50% vs. 70%, and the time interval following fibrinolysis when its' efficacy should be assessed (45, 60 or 90 minutes), are still the subject of debate.¹⁸

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Facilitated PCI refers to the administration of a pharmacologic reperfusion regimen prior to the patient undergoing primary PCI in a cardiac catheterization laboratory.⁹ The evidence to date has not supported fibrinolytic therapy facilitated PCI having advantages over primary PCI.^{2, 13, 19} The results of the Facilitated Intervention with Enhanced reperfusion Speed to Stop Events, (FINESSE), trial are pending and should provide additional information regarding the role of facilitated PCI in the management of STEMI.

Primary PCI

Primary PCI, if performed in a timely fashion and at an experienced center, is the preferred approach to reperfusion in STEMI.^{2, 5} Keeley undertook a meta-analysis of 23 randomized clinical trials comparing primary angioplasty and intravenous fibrinolytic therapy in the management of STEMI.²⁰ The analysis included a total of 7,739 patients and demonstrated primary angioplasty resulted in a significant improvement in reducing overall short-term mortality over fibrinolytic therapy, (7% versus 9%: $P = 0.0002$), non-fatal reinfarction, (3% versus 7%: P less than 0.0001), and stroke, (1% versus 2%: $P = 0.0004$).²⁰ These benefits appear to be maintained at 6 months.²¹

When compared with fibrinolysis, management of myocardial infarction by PCI has a number of advantages⁷ including 1) fewer patient exclusions and contraindications; 2) significantly higher TIMI-3 reperfusion flow rates (70 – 90%); 3) lower risks of intracranial hemorrhage;²⁰ 4) definitive characterization of coronary artery anatomy, left ventricular function

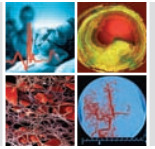
and mechanical complications;¹⁰ and 5) risk stratification of patients.^{2,7} Specific clinical scenarios in which PCI is preferred reperfusion strategy include⁷ 1) elderly patients defined as age greater than 75 years, 2) patients presenting with cardiogenic shock, congestive heart failure, ventricular arrhythmias, and 3) patients with an uncertain diagnosis of STEMI.

Analysis of data from the DANAMI-2 trial demonstrates that primary PCI has a significant mortality advantage over fibrinolysis in high-risk patients as defined by the TIMI risk score.²² Patients presenting in cardiogenic shock should undergo reperfusion with PCI.^{2, 5}

The major limitation of primary PCI is its availability, with estimates of only 20 - 25% of hospitals in the USA having primary PCI capabilities²³. In the absence of access to an immediately available cardiac catheterization laboratory, the clinician caring for a patient with an acute STEMI is faced with the choice of transferring the patient to a PCI-capable facility for primary PCI or administering a fibrinolytic agent. The 2004 ACC/AHA guidelines for the management of patients with STEMI advise first medical contact to balloon time should be ≤ 90 minutes, making estimates for time to PCI with transfer very important.² A recent paper demonstrated that the superiority of PCI over fibrinolysis was maintained up to 110 minutes.²⁴

As PCI is a technical procedure, the skill and experience of the cardiac catheterization team involved is also a significant factor. The ACC/AHA guidelines support treatment for STEMI when the overall median door to balloon

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time was 180 minutes.²³ Factors noted to be related to prolonged the door to balloon time in patients that were transferred for PCI included, comorbid conditions, absence of chest pain, delayed presentation after symptom onset, less specific ECG findings, and off-hours hospital presentation.²³ With every 10 minute delay in reperfusion with PCI, there is a 1% loss of the mortality advantage of PCI over fibrinolysis.²⁴⁻²⁷

A study evaluating the difference between door to balloon and door to needle times in relationship to mortality was carried out by Pinto on patients in the NRMI database. The relationship between PCI related delay, patient risk factors, and in-hospital mortality was evaluated. With increased door to balloon – door to needle times, the mortality advantage of PCI over fibrinolysis declines, and the advantage was noted to have considerable variation depending on patient characteristics of age and location of infarct.²⁸

The current guidelines do not have recommendations for reperfusion strategies in patients with STEMI presenting greater than 12 hours after symptom onset.^{2,5} The Beyond twelve 12 hours Reperfusion AlternatiVe Evaluation (BRAVE-2) trial demonstrated that primary PCI reduced left ventricular infarct size in patients with STEMI treated between 12 and 48 hours after symptom onset.^{29,30} It is not clear how this will impact future guidelines.

Decision Making in Reperfusion Strategy

In the process of determining a strategy for reperfusion in a patient with STEMI, the clinician must consider the time from

symptom onset, the patient's clinical status, the risk of ICH, the presence of STEMI high risk factors, and time to availability of PCI. If there is no PCI facility in the hospital, transfer for PCI should be considered. The time to PCI inclusive of transfer delays must be carefully considered in the determination of whether transfer for PCI or is preferred over fibrinolysis. Availability of a skilled PCI center, defined in the guidelines as having an operator with experience of greater than 75 PCI procedures in a year and a laboratory performing greater than 200 PCI procedures, at least 36 of which are primary PCI for STEMI, should be considered in the decision making process.² Specific complications related to primary PCI include 1) adverse reactions to contrast media, 2) volume loading due to contrast media and additional intravenous fluid, 3) issues related to vascular access, typically the femoral artery and 4) technical complications of the procedure.^{2,7} Re-occlusion of the coronary artery may occur in patients after PCI, however the rate is reduced to less than 5% with intracoronary stent placement.^{7,25}

Impact of Time to Reperfusion

The guidelines for STEMI management recommend PCI in 90 minutes or less from first medical contact. Door to balloon times in routine practice have been demonstrated to be longer than in randomized controlled trials. With many patients requiring transfer for PCI, further delays may be incurred. McNamara reviewed the National Registry of Myocardial Infarction (NRMI) database for patients with myocardial infarction between 1999 and 2002, and demonstrated only 37% of the

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patients met the recommendation of medical contact to balloon time within 90 minutes.²⁶ Nallamothu reviewed the NRM1 3 and 4 databases between 1999 – 2002, and noted only 4.2% of patients transferred for PCI were treated within 90 minutes and immediate fibrinolysis would offer the patient the best potential outcome.²⁷ The presence of a contraindication, to fibrinolysis would necessitate consideration of transfer to another hospital for PCI. In STEMI patients with high risk features treated with fibrinolytics, early transfer should be considered to minimize delay in reperfusion is not successful and rescue PCI is necessary.¹⁸

Roles of Prehospital Care in STEMI Reperfusion

The role of pre-hospital care for improving time to reperfusion has been increasingly apparent. A meta-analysis of pre-hospital fibrinolysis for STEMI demonstrated the interval from onset of symptoms to treatment was reduced by an average of 58 minutes with pre-hospital administration of thrombolysis.³¹ Increasing evidence demonstrated that the use of pre-hospital electrocardiography can provide earlier recognition of STEMI and reduce treatment delays.³²

The CAPTIM randomized trial comparing pre-hospital fibrinolysis and systematic transfer to a PCI center to primary PCI, did not show significant differences in the strategies.^{33,34} The difference in time to treatment between prehospital thrombolysis and primary PCI was 1 hour in this study. A post-hoc analysis of the CAPTIM trial demonstrated patients managed within the first two hours following onset of symptoms did similarly with thrombolysis or primary PCI.³⁴

The Which Early ST-elevation MI therapy (WEST), randomized feasibility study, evaluated STEMI patients presenting within six hours of symptom onset and compared routine fibrinolysis, fibrinolysis with a mandatory invasive study at 24 hours, and primary PCI. This strategy of pre-hospital randomization and treatment shortened ED time from symptom onset to fibrinolysis and reduced the time to PCI by greater than one hour by ensuring enhanced readiness at receiving PCI facilities.³⁵ Opportunities to significantly impact the care of the

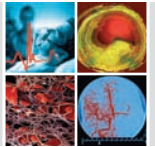
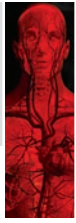
STEMI patient in the pre-hospital environment include earlier recognition of STEMI, pre-hospital initiation of therapy, and potential transport of a patient to an appropriate facility.³⁶

System Level Interventions

Significant efforts have been undertaken to systematically reduce delays in reperfusion therapy. The D2B™ alliance is a program launched by the American College of Cardiology, (ACC), with the goal of reducing door to balloon times in primary PCI systematic organizational change.^{37,38} The importance of an organized system to optimize care patients with STEMI has been recognized as integral to their optimal management.³⁹ Emergency physicians should be actively involved in these planning activities. An integral component of a system for STEMI care is an active improvement process of data collection, analysis, and feedback to improve the system.

SUMMARY

The emergency physician performs a critical role in the recognition and the management of the patients with STEMI. A rapid assessment of the patient's clinical status, time of presentation as related to symptom onset, determination of contraindications, and time frame to availability of PCI must be rapidly made to determine optimal management for these patients. Emergency physicians must be actively involved in the prospective development of systems, with cardiologists, for the management of patients with STEMI to minimize delays in achieving reperfusion.



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