

Fibrinolytic Therapy for STEMI

The role of this treatment in the era of primary percutaneous intervention.

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The role of fibrinolytic therapy as a sole means of reperfusion in ST-elevation myocardial infarction (STEMI) is becoming increasingly limited, whereas the roles played by primary and facilitated percutaneous coronary intervention (PCI), especially the role of prehospital or pretransfer fibrinolytic administration, are continuing to grow. For most STEMI patients, the safety and efficacy of PCI is superior compared to treatment with fibrinolysis. Furthermore, the availability of qualified interventional cardiologists and the number of primary PCI-capable hospitals continues to grow, expanding access to primary PCI. In addition, contemporary methods of mechanical reperfusion, including thrombectomy, drug-eluting stents, and improved adjuvant pharmacotherapy, have led to a reduced bleeding risk and improved patient outcomes with primary PCI. Taken together, these factors limit the role of primary fibrinolytic-based therapy in STEMI and expand the roles of primary PCI and, as we will discuss, facilitated PCI.

BLEEDING RISK AND EFFICACY

Issues of safety and efficacy limit the role of primary fibrinolysis as a sole means of reperfusion in STEMI. In carefully selected patients, full-dose fibrinolysis does have an acceptable risk-benefit ratio. In large randomized trials, the overall risk of major bleeding with third-generation fibrinolytics varies according to bleeding definition; however, the risk of the most serious bleeding (intracranial hemorrhage [ICH]) is relatively uniform at approximately 0.9%.^{1,2} The list of absolute and relative contraindications to fibrinolytic therapy is substantial (Table 1).³ Although the risk of ICH may seem acceptably low, the consequences of ICH are dramatic and often deadly, and thus, extra vigilance is necessary to avoid this complication. Making matters worse,

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essential historical data are often unobtainable at the time of STEMI treatment. In a 2006 review of the National Registry of Myocardial Infarction database, Pinto et al found that nearly 20% of STEMI patients who were eligible for reperfusion therapy did not undergo either PCI or fibrinolysis.⁴ The inability to accurately assess the bleeding risk of a patient, along with the seriousness of a potential adverse outcome, may lead to treatment delays or failure to provide appropriate therapy in some cases.

Although the issue of fibrinolytic safety is fundamental, there are also very real concerns regarding efficacy and durability. Ninety-minute patency rates for tenecteplase and reteplase vary between 60% and 75%, and TIMI grade 3 flow is only 60% to 65% (Table 2).⁵ This means nearly one-third of fibrinolytic-treated patients will have suboptimal results after therapy. In addition, the 30-day rate of recurrent angina is 19% to 28% with third-generation fibrinolytics. One-quarter of lytic-treated patients will require mechanical intervention after having failed fibrinolysis.^{1,2} In our experience, and in multiple randomized and nonrandomized studies, the procedural success rate with drug-eluting stents in STEMI is greater than 93%, and the 12-month target lesion revascularization rate is less than 7%. Therefore, both angiographic results and efficacy endpoints are superior with mechanical intervention. With an aging population, the risks associated with primary fibrinolytic-

TABLE 1. ABSOLUTE AND RELATIVE CONTRAINDICATIONS FOR FIBRINOLYSIS IN STEMI**Absolute Contraindications**

- Any previous ICH
- Known structural cerebral vascular lesion (eg, 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 (systolic greater than 180 mm Hg or diastolic greater than 110 mm Hg)
- History of 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 (within less than 3 weeks)
- Recent (within 2–4 weeks) internal bleeding
- Noncompressible vascular punctures
- For streptokinase/anistreplase: previous exposure (more than 5 days earlier) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the international normalized ratio, the higher the risk of bleeding

Adapted from Antman EM et al. 2007 focused update of the ACC/AHA 2004

Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). J Am Coll Cardiol. 2008;51:210–473.³

ic therapy are considerable. When this is coupled with the relative uncertainty of success, mechanical reperfusion is frequently a more attractive option.

PRIMARY PCI AVAILABILITY

In regions where primary PCI resources are limited, fibrinolytic therapy may remain relatively popular; however, training programs in the United States are graduating an increasing number of qualified operators to staff a growing number of primary PCI-capable hospitals. This increase in operators and facilities expands the availability of primary PCI for STEMI treatment. From 2008 to 2009, there were 134 Accreditation Council for Graduate Medical Education-accredited interventional cardiology training programs, and these programs trained nearly 300 new interventional cardiologists. This total nearly doubles the number of interventional cardiologists trained in the academic year of 2001 to 2002. Commensurate with this increase in the number of interventional cardiologists, the number of primary PCI laboratories has increased. Approximately 25% of acute-care hospitals in the United States have primary PCI capability. From 2005 to 2009, the number of these hospitals in the United States increased from nearly 5,000 to more than 5,800, which means a potential additional 200 primary PCI-capable facilities. Further expanding the availability of primary PCI, recent data suggest that primary PCI for STEMI without on-site surgical backup in well-staffed facilities with quality-control programs achieves similar outcomes when compared to primary PCI performed at sites with on-site surgical backup.⁶ Given that primary PCI is generally preferred over fibrinolysis and recognizing an overall increase in the availability of primary PCI resources, the role of primary fibrinolysis for STEMI is likely to diminish even further.

PHARMACOLYTIC THERAPY

Primary fibrinolytic therapy for STEMI is far from optimal and may not be appropriate for some individuals. Additionally, although the availability of primary PCI continues to grow, many patients living outside major population centers still do not have access to primary PCI within the American College of Cardiology/American Heart Association (ACC/AHA) recommended 90-minute window. So, how do we offer safe and timely reperfusion to all patients, especially in high-risk patients and when transfer times may be longer than desired? The natural choice is facilitated PCI. However, the data on facilitated PCI are equivocal and may suggest harm. Or do they?

Historically, facilitated PCI trials are small, and study design varies considerably, making it difficult to draw

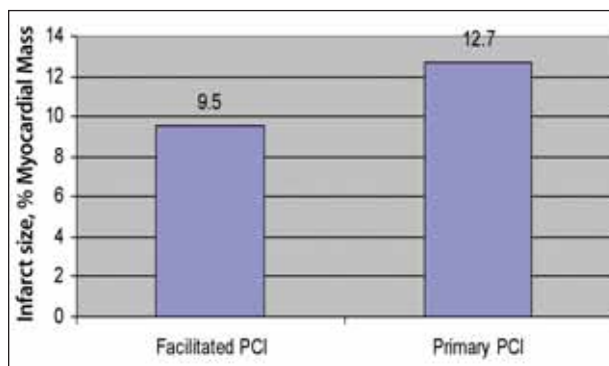


Figure 1. Average MI size measured by magnetic resonance imaging in 124 STEMI patients (facilitated PCI, $n = 75$; primary PCI, $n = 49$). Infarct size is expressed as a percent of myocardial mass. Note that the average size of MI is 25% smaller with facilitated PCI compared to primary PCI ($P = .04$).

sound conclusions from these trials. For the basis of this article, facilitated PCI is considered to be any combination of pharmacological reperfusion therapy followed by planned early revascularization. Theoretically, facilitated PCI is very attractive, combining the speed and accessibility of fibrinolysis with the efficacy and durability of mechanical intervention. Multiple combinations of drugs and devices have previously been explored. Early pharmacological strategies have included regimens with full-dose and half-dose fibrinolytics, combinations of fibrinolytics and IIb/IIIa inhibitors, and programs with IIb/IIIa antagonists alone. The timing and method of revascularization also varies among trials, with planned revascularization taking place as soon as possible in most studies to as late as 24 hours after

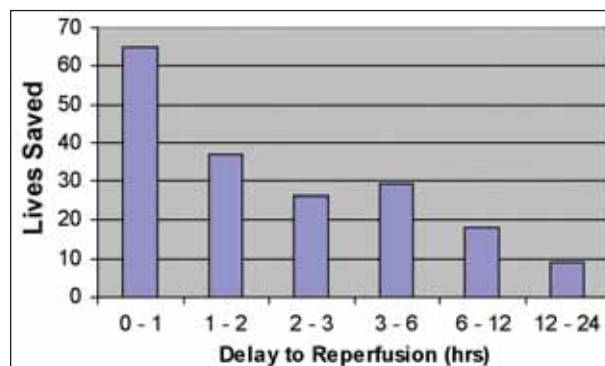


Figure 2. Number of lives saved per 1,000 patients treated with thrombolytic therapy during the first 24 hours after ischemic symptom onset. Note that the number of patients benefiting from treatment during the first hour after symptom onset (65) far exceeds the number spared by treatment during hours 12 to 24.⁹ Adapted from Boersma et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348:1312–1313.¹⁰

hospital admission. Similarly, the means of revascularization differs between older and more recent trials, with earlier programs employing balloon angioplasty as opposed to the more modern use of drug-eluting stents. In an excellent review of facilitated PCI that included both recent and older data, Keely et al determined that facilitated PCI offered no additional advantage over primary PCI.⁷ However, their conclusions were heavily influenced by the ASSENT-4 trial results, which comprised more than one-third of the patients in the 13 trials they analyzed. Furthermore, therapeutic options were not well balanced in this meta-analysis.

TABLE 2. FIBRINOLYTIC AGENTS

Agent	Generation	Half-Life (min)	Dosing Instructions	TIMI Grade 3 Flow
Streptokinase	First	18–23	Single infusion: 1.5 mm units IV infused over 30–60 min	32%
Alteplase	Second	5	Bolus plus infusion: 15 mg IV infusion, then 0.75 mg/kg over 30 min, then 0.50 mg/kg over 60 min	54%
Reteplase	Third	13–16	Double bolus: 10 units IV over 2 min, then second bolus, 10 unit IV separated by 30 min	60%
Tenecteplase	Third	20–24	Single bolus, weight based: < 60 kg: 30 mg; 60–69 kg: 35 mg; 70–79 kg: 40 mg; 80–89 kg: 45 mg; > 90 kg: 50 mg	63%

Abbreviations: IV, intravenous; TIMI, thrombolysis in myocardial infarction.

Table adapted from Hilleman et al. Fibrinolytic agents for the management of ST-segment elevation myocardial infarction.

Pharmacotherapy. 2007;27:1558–1570.⁵

The third-generation fibrinolytic, reteplase, was used in only 4.3% of fibrinolytic-treated patients and in only 3.2% of the total population.

Although previous pharmacoinvasive trials have been equivocal, recent data support a much more substantial role for facilitated PCI. In a multicenter collaborative effort, the AMICO registry trialists demonstrated a significant reduction in death, and in the combined end-point of death, reinfarction, and stroke when patients are treated with a facilitated approach. The AMICO registry was composed of 2,869 STEMI patients treated at five high-volume centers in the United States and Europe. Of these, 1,200 patients were treated with facilitated PCI. Thirty-day mortality in the facilitated PCI group was 3.8% versus 6.4% in the primary PCI group ($P = .002$).⁸ Complementing these findings, in a subset of patients at our center undergoing cardiac magnetic resonance imaging after STEMI, we found that patients treated with prehospital, reduced-dose fibrinolytics prior to urgent PCI developed smaller infarcts when compared to patients treated with primary PCI (9.5% vs 12.7%; $P = .04$) (Figure 1). Similarly, a recent subgroup analysis from the FINESSE trial showed improved outcomes when high-risk STEMI patients presenting to non-PCI hospitals were treated with a combination of abciximab and half-dose reteplase before transfer to a tertiary care center.⁹

Although primary fibrinolysis may not be the optimal means of reperfusion in many situations, time to any reperfusion is critical in limiting infarct size and improving outcomes, especially in the precious first hours after symptom onset (Figure 2).¹⁰ A pharmacoinvasive approach combines the speed of primary fibrinolysis with the durability of mechanical intervention. Perhaps in recognition of these issues, the 2007 ACC/AHA STEMI guidelines revised the 2004 class III indication for facilitated PCI to a class IIb recommendation.³ However, the writers limit this recommendation to programs using other than full-dose thrombolytics, and only if patients are high risk, primary PCI is not immediately available, and patient bleeding risk is acceptable. Additional research into which patients will benefit most from a facilitated approach is warranted, and further investigation into the best combination of drugs and devices is also needed.

CONCLUSIONS

In general, there is a strong preference for primary PCI over fibrinolytic therapy in STEMI treatment. This preference is largely due to the superior safety and efficacy of primary PCI compared to fibrinolysis. Improved access to skilled interventionists and the growing avail-

ability of primary PCI facilities will further add to the popularity of primary PCI. Additionally, enhanced methods of mechanical reperfusion and improved adjunct pharmacotherapy further reduce bleeding risk and improve patient outcomes with primary PCI. Finally, emerging data from facilitated PCI programs demonstrate improved outcomes in high-risk STEMI patients. Thus, in an era of primary PCI, the role of fibrinolysis alone for STEMI treatment is decreasing, whereas the role of primary PCI is firmly established, and the role of facilitated PCI continues to take shape. ■

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