Fibrinolytic Therapy

Is It A Treatment of the Past?

Cindy L. Grines, MD; Patrick Serruys, MD; William W. O’Neill, MD

Fibrinolytic therapy has been an important means of establishing reperfusion for decades. However, limitations to the use of thrombolytic therapy include perceived or definite contraindications, intracranial bleeding, inability to establish Thrombosis In Myocardial Infarction (TIMI-3) flow in many patients, and high rates of recurrent ischemia and reocclusion. Accordingly, primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion strategy.

Nearly all acute myocardial infarction (AMI) patients are eligible for emergency catheterization. Knowledge of the coronary anatomy allows immediate triage to surgery, medical therapy, or primary PCI, when appropriate, and results in earlier hospital discharge compared to thrombolytic therapy.1 Primary PCI establishes TIMI-3 flow in >90% of patients and is associated with reduced rates of recurrent ischemia and reocclusion. With the addition of stenting, reocclusion has been further reduced to 5% at routine 6-month angiography.2–3 Small studies have suggested that pharmacological adjuncts to PCI such as abciximab may improve myocardial perfusion and limit infarct size4,5 without the risk of bleeding observed with thrombolytic therapy.6 Finally, new technologies such as coronary thrombectomy, distal projection, and systemic cooling are easily applied in the catheterization laboratory and may further improve myocardial perfusion and infarct size.

Although primary PCI has been in use for more than 25 years, the first trials randomizing PCI to intravenous thrombolytics therapy were not published until 1993.7 A meta-analysis of the first 10 randomized trials demonstrated a reduction in death, reinfarction, and stroke with primary PCI in all subgroups, but the greatest absolute benefit was observed in high-risk patients.8

On the basis of these early results, many experienced interventionalists were no longer willing to randomize patients to thrombolytic therapy. Therefore, the next decade of research was focused on perfecting the primary PCI technique, with studies randomizing patients to intraaortic balloon pumps, stents, glycoprotein IIb/IIIa inhibitors, and early discharge.2–5,9,10 High rates of TIMI-3 flow and low mortality rates were consistently observed with primary PCI in these trials, confirming the results of the earlier studies. However, some physicians continued to express concern that too few primary PCI studies had been performed, the results may not be reproducible in less experienced centers, and that withholding thrombolytics while awaiting primary percutaneous transluminal coronary angiography (PTCA) could cause harm.

Over the past few years, several additional studies addressed these issues. To date, 23 trials have randomized 7739 patients to receive thrombolytics (76% of whom were randomized in tissue plasminogen activator [tPA] trials) compared with primary PCI.11 In a meta-analysis of these studies, Keeley et al11 reported that primary PCI was associated with improved 30-day outcomes, including death (7% versus 9%, \( P=0.0002 \)), nonfatal reinfarction (2.5% versus 6.8%, \( P<0.0001 \)), and stroke (1% versus 2%, \( P=0.0004 \)), with absolute differences so great that 60 patients would...
benefit for every 1000 patients treated (Figure 1). The beneficial results with primary PCI were sustained at long-term follow-up and were observed in both streptokinase- and tPA-treated patients and in situations where transfer (up to 3 hour delay) was required for performance of primary PCI or PCI was performed in hospitals without on-site surgery. There is no question that primary PCI, when available, is the treatment of choice. The significant improvement in mortality, saving 20 lives for every 1000 patients treated, is likely due to higher patency and reduced reinfarction and stroke. Mortality rates after AMI appear to be inversely related to the ability to achieve TIMI-3 flow. The greatest benefit of primary PCI may be its ability to achieve TIMI-3 flow in more than 90% of patients, even when the patient is treated in the late stages of infarction. By contrast, thrombolytic therapy has a marked decrease in thrombolytic efficacy in patients treated more than a few hours after symptom onset (Figure 2). Although it has been recommended that PCI must be performed within 90 minutes of presentation, in fact, most of the patients enrolled in primary PCI trials achieved their excellent outcomes with median treatment times of 120 minutes.

Randomized studies have consistently shown primary PCI to be superior to thrombolysis at reducing reinfarction. Reinfarction occurs in lesions with slow flow or severe residual stenosis and may also be exacerbated by thrombolytic-induced platelet aggregation. Primary PCI avoids the thrombolytic-induced platelet aggregation, produces a widely patent artery with minimal residual stenosis, and results in virtually no intracranial bleeding. Given these findings, why would physicians continue to recommend thrombolytic therapy?

Advocates of thrombolysis claim that fibrinolysis remains viable given improved pharmacological regimens and the ability to treat patients more quickly. However, attempts to further augment TIMI flow with more potent or higher-dose thrombolytics or more potent anti-thrombotics

![Figure 1. Meta-analysis of 23 randomized trials of primary PCI versus thrombolysis. CVA indicates cerebrovascular accident. Reprinted with permission from Elsevier Science. Lancet. 2003;361:13–20.](image-url)
have all resulted in increased risk of intracranial bleeding. More recently, studies combining low-dose thrombolytic drugs with abciximab have also shown increased rates of intracranial hemorrhage in elderly patients. Although combining low molecular weight heparin with thrombolytics was thought to be safe, a recently reported study also demonstrated a significant increase in intracranial bleeding. It is unwise to believe that any systemically administered pharmacological agent or agents designed to achieve rapid and sustained thrombolysis will confine its action to the coronary arteries.

Stone et al demonstrated that the presence of spontaneous (not thrombolytic-induced) reperfusion before primary PCI is beneficial. Accordingly, there has been great interest in the use of full or half-dose thrombolytics to “facilitate” the angioplasty. Although this is an interesting concept, studies conducted to date suggest no benefit and potential harm with the use of thrombolytics before PCI (Table). Even in the situation where primary PCI was delayed because of the need to transfer to a PCI facility, increased bleeding and worse outcomes were observed in

Studies Comparing Thrombolytic Pretreatment With PCI Alone

<table>
<thead>
<tr>
<th>Randomized Study</th>
<th>Drug</th>
<th>Result With Lytic</th>
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<tbody>
<tr>
<td>Williams et al</td>
<td>tPA</td>
<td>↑ MACE</td>
</tr>
<tr>
<td>Ambrose et al</td>
<td>IC-UK</td>
<td>↑ Abrupt closure, ↑ MACE</td>
</tr>
<tr>
<td>O’Neill et al</td>
<td>SK</td>
<td>↑ Bleeding, ↑ Em CABG</td>
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<td>Vermeer et al</td>
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</tr>
<tr>
<td>Ross et al</td>
<td>tPA 50 mg</td>
<td>↑ Early TIMI 3 flow, Clinical events, EF similar</td>
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</tbody>
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MACE indicates major adverse cardiac events; CABG, coronary artery bypass grafting; and IC-UK, intracoronary urokinase.
patients randomized to thrombolysis before transfer compared with withholding thrombolysis.\textsuperscript{12,11} There are several ongoing and planned trials which will further evaluate the role of facilitated PCI. However, these trials are designed to exclude patients who benefit the most from primary PCI (those near an available catheterization lab, elderly patients, and those with chest pain lasting more than 6 hours). Furthermore, despite the known beneficial effects of clopidogrel when administered at least a few hours before stenting, its use is “prohibited” before PCI in the ASsessment of the Safety and Efficacy of New Treatment strategy for AMI (ASSENT-4) trial. Thus, the facilitated PCI trials may be designed to put primary PCI in an unfavorable light.

The recently published Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial Infarction (CAPTIM) trial\textsuperscript{22} compared prehospital thrombolysis to primary PCI and found no statistically significant benefit to primary PCI. However, it should be pointed out that this trial did not enroll the necessary sample size and was prematurely stopped because of poor recruitment. Secondly, 26\% of thrombolytic patients required rescue angioplasty for failed thrombolysis, which represents 10 times higher utilization than other trials.\textsuperscript{11} Finally, even though CAPTIM enrolled a very low-risk population, a 24\% improvement in the primary endpoint of combined death, reinfarction, or disabling stroke was observed in the primary PTCA arm.

A meta-analysis of 6 trials comparing prehospital to in-hospital thrombolysis demonstrated a 1\% improvement in survival.\textsuperscript{23} However, several issues need to be pointed out. First, primary PCI has a greater (2\%) absolute improvement in survival compared with in-hospital thrombolysis.\textsuperscript{11} Secondly, all prehospital trials excluded AMI patients with chest pain >6 hours, and half of the trials excluded patients with pain >4 hours. Therefore, patients were highly selected to have the best chance of reperfusion (Figure 2). Moreover, given the facts that 50\% of AMI patients do not call 911 but rather drive themselves to the hospital, only 4\% of all chest pain calls to emergency medical systems (EMS) are eligible for thrombolytic therapy, and a physician does not cover EMS run, prehospital thrombolysis has not been embraced in the United States. A more practical approach to improving the time to PCI-mediated reperfusion is to have EMS technicians obtain an ECG in the field.\textsuperscript{24} If ST-segment elevation is observed, the nearest angioplasty center should be notified to prepare the catheterization laboratory and the patient should be transferred directly to that facility.

However, not all angioplasty operators are proficient at performing PCI. To date, the randomized trials were conducted by relatively high-volume operators who either had years of primary PCI experience or who underwent extensive training and scrutiny before study participation. There may be a substantial learning curve when initiating a primary PCI program.\textsuperscript{25} Moreover, registry data demonstrated that in high-volume centers, primary PCI outcomes were superior, but in low-volume centers, primary PCI outcomes were similar to thrombolytic therapy.\textsuperscript{26} This raises the question whether small hospitals should spend the time, effort, and money to initiate primary PCI programs. Because time to reperfusion is less critical with PCI than with thrombolytic therapy, efforts may be better directed at providing prehospital ECGs and efficient transport systems for regional performance of primary PCI.

In conclusion, the available data demonstrate that primary PCI is superior to thrombolysis in reducing death, reinfarction, intracranial bleeding, recurrent ischemia, and infarct vessel reocclusion. Primary PCI without thrombolysis to facilitate reperfusion is the treatment of choice if it can be performed within 3 hours by a competent operator. We should work toward a goal of obtaining ECGs in the field, and transferring patients with ST elevation from home directly to a “heart attack center.”

References


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