Evolution of Reperfusion Therapies for Acute Brain and Acute Myocardial Ischemia
A Systematic, Comparative Analysis

Richa D. Patel, BS; Jeffrey L. Saver, MD

Background and Purpose—Early reperfusion is the most effective therapy for both acute brain and cardiac ischemia. However, the cervicocephalic circulatory bed offers more challenges to recanalization interventions. The historical development of reperfusion interventions has not previously been systematically compared.

Methods—Medline search identified all multi-arm, controlled trials of coronary revascularization for acute myocardial infarction and multicenter trials of cerebral revascularization for acute ischemic stroke reporting angiographic reperfusion rates.

Results—Thirty-seven trials of coronary reperfusion enrolled 10908 patients from 1983 to 2009, and 10 trials of cerebral reperfusion enrolled 1064 patients from 1992 to 2009. Coronary reperfusion trials included 10 of intravenous fibrinolysis alone, 8 combined intravenous fibrinolysis and percutaneous transluminal coronary angioplasty with or without stenting, 3 intra-arterial fibrinolysis, and 16 percutaneous transluminal coronary angioplasty with or without stenting. Cerebral reperfusion trials included 1 of intravenous fibrinolysis alone, 3 intra-arterial fibrinolysis, 3 endovascular device alone, and 3 of endovascular treatment ± intravenous fibrinolysis. In both circulatory beds, endovascular treatments were more efficacious at achieving reperfusion than peripherally administered fibrinolitics. In the coronary bed, rates of achieved reperfusion began at high levels in the 1980s and improved modestly over the subsequent 3 decades. In the cerebral bed, reperfusion rates began at modest levels in the early 1990s and increased more slowly. Most recently, in 2005 to 2009, cardiac reperfusion rates substantially exceeded cerebral, partial reperfusion 86.1% versus 61.1%, complete reperfusion 78.6% versus 23.4%.

Conclusions—Reperfusion therapies developed more slowly and remain less effective for cerebral than cardiac ischemia. Further, cerebral circulation–specific technical advances are required for physicians to become as capable at safely restoring blood flow to the ischemic brain as the ischemic heart. (Stroke. 2012;44:94-98.)

Key Words: brain ischemia ■ myocardial infarction ■ reperfusion ■ stroke

Beginning in the early 1980s, clinical trials have tested iteratively improving acute reperfusion interventions for both myocardial infarction and ischemic stroke. In both circulatory beds, treatments have evolved in a similar pattern, beginning with intravenous fibrinolitics, followed by intra-arterial fibrinolitics, then mechanical endovascular therapies, and finally exploration of combined intravenous and catheter treatments.

However, in important ways, therapies in the different vascular beds have evolved distinctively. For example, primary stenting has become a mainstay of acute coronary reperfusion, reflecting its efficacy in treating target atherosclerotic plaques with supervening thrombi, whereas mechanical retrieval and aspiration techniques are the leading endovascular therapies for cerebral ischemia, because of their appropriateness for target embolic thrombi residing in relatively normal recipient vessels.

Even more importantly, the technical efficacy of lytic and mechanical treatments in achieving reperfusion has evolved at different rates in the cerebral and cardiac circulatory beds. However, the difference in success rates of reperfusion treatments for brain and heart have not been previously systematically characterized and quantified. We therefore undertook a formal systematic analysis of reperfusion efficacy over the past 30 years of cerebral and cardiac revascularization strategies.

Methods

Search and Inclusion Criteria

A systematic search was performed to identify all multi-arm trials of coronary revascularization for acute myocardial infarction and multicenter trials of cerebral revascularization for acute ischemic stroke (AIS) with reperfusion assessed by catheter angiography. Medline was searched from 1950 to 2010: (1) crossing the terms...
thrombolysis or recanalization or reperfusion or Thrombolysis in Myocardial Infarction (TIMI) with myocardial infarction (MI) or acute coronary ischemia; (2) crossing the terms thrombolysis or recanalization or reperfusion or TIMI with cerebral infarction or acute cerebral ischemia. We also reviewed salient Cochrane Database meta-analyses and cited references in retrieved trials and related meta-analyses to identify additional trials. The search was limited to trials published in English from 1950 to 2010.

Inclusion criteria for acute MI studies to be included in this analysis were as follows: (1) multi-arm trial; (2) qualifying event was acute coronary ischemia; (3) intervention was any combination, singly or together, of intravenous fibrinolysis, intra coronary fibrinolysis or endovascular mechanical (eg, angioplasty, stenting, aspiration, or retrieval); (4) baseline angiogram demonstrated occluded target coronary artery; (5) angiographic reperfusion within 90 minutes of treatment start was systematically assessed as an end point among all patients in at least 1 study arm. Inclusion criteria for the AIS studies were as follows: (1) prospective, multicenter trial; (2) qualifying event was acute cerebral ischemia; (3) intervention was intravenous or intra-arterial fibrinolysis or endovascular mechanical recanalization therapy (eg, angioplasty, stenting, aspiration, or retrieval); (4) baseline angiogram demonstrated occluded target cerebral artery; (5) angiographic reperfusion within 120 minutes of treatment start was systematically assessed as an end point among all patients in at least 1 study arm. Exclusion criteria for both acute MI and AIS studies were as follows: study presented in a non-English language.

In 1 stroke trial of bridging fibrinolysis and endovascular therapy, patients without a prelytic angiogram were considered to have had a prelytic treatment large artery occlusion if the pretreatment National Institutes of Health Stroke Scale score ≥ 10. Patients in this trial with pretreatment National Institutes of Health Stroke Scale score <10 were excluded from the analysis because the presence of a large vessel occlusion before treatment was less certain.

Data Collection

Study arms in each trial were categorized as active or control following the characterization of study authors. Over time, as therapies moved from experimental to standard of care, they migrated from the active category to the control category. For acute ischemic stroke trial, intravenous fibrinolytics were the active treatment and placebo was the control. In later MI trials, stenting was the active treatment and intravenous fibrinolysis was the control. Accordingly, our control category analyses reflect standard of care practice throughout the study period, and our treatment category analyses reflect emerging and experimental care throughout the study period.

For each study, we extracted year of publication, treatment and control arm sample size, and treatment and control arm partial and complete reperfusion rates. For reperfusion rates, when available, Thrombolysis in Myocardial Infarction (TIMI) Scale scores were used, with scores ≥2 counted as at least partial reperfusion and scores of 3 as complete reperfusion. For MI trials, TIMI scores were not stated in some studies reported before 1988. For these studies, partial and complete reperfusion rates directly stated by the authors were extracted. Data extraction was performed by one investigator (R.D.P.), with assistance from a second investigator (J.L.S.) whenever abstraction was not straightforward.

Some trials had multiple active treatment arms testing several doses of the same novel fibrinolytic agent. For these trials, very low dose tiers, generally targeting safety rather than efficacy, were not analyzed. A single active treatment recanalization rate was obtained by using a sample size-weighted average of the reperfusion rates in the 2 highest dose tiers.

In acute MI studies testing fibrinolytics, recanalization measurement was performed at differing intervals after drug treatment across and within the analyzed trials. For our analysis, reperfusion at 90 minutes was used, if available; if not, reperfusion at 60 minutes was used. In the 1 acute ischemic stroke trial with multiple time points of reperfusion ascertainment after intra-arterial lytic infusion, the assessment immediately on end of lytic infusion (120 minutes after lytic start) was used.

Numerator and denominators for reperfusion rates were based on intention to treat analysis. Accordingly, patients were included in the denominator if they were enrolled but later excluded from treatment by complications, and patients were included in both the numerator and denominator if they had spontaneous recanalization before treatment (considered a complete reperfusion outcome). Similarly, in studies of combined therapy strategies of both intravenous fibrinolysis (IVF) followed by intra-arterial fibrinolysis or mechanical treatment, patients were included in both the numerator and denominator if they had recanalization after IVF and therefore did not undergo endovascular intervention, and were classified according to the reperfusion grade of the post-IVF angiogram.

Statistical Methods

This systematic analysis was a study-level review, where each study, not each patient, was treated as a unit. Both quantitative and qualitative analyses were undertaken. As data on reperfusion rates in control arms were missing from multiple studies, analyses for changes over time focused on data from the active treatment arms.

In the quantitative analysis, trends over time in reperfusion rates were analyzed by using a fixed effects weighted logistic regression model. Separate regressions were carried out for partial or better reperfusion rate and complete reperfusion rate for each disease (acute MI and AIS). For each meta-regression, event rates were inversely weighted to their variance estimates by assuming the numbers of events corresponded to Poisson distributions. Year was considered a fixed effect. To compute 1 summary rate of change per year, it was assumed that, on the log odds (logit) scale, the relation with year was linear.

The weighted, quantitative analysis analyzed changes in reperfusion rates beginning from the achieved rates in the active arms of the first recanalization intervention studies. However, additional perspective is provided, including spontaneous reperfusion rates that occurred under supportive care in the prerereperfusion treatment era. An unweighted, graphic analysis was therefore undertaken, in which an anchor prerereperfusion era year of 1980 was added, with spontaneous complete reperfusion rate values derived from untreated control arms of early reperfusion treatment trials (rate of complete reperfusion for acute MI of 1.2%3,4 and for AIS of 1.4%5,6). In this figure, each study was treated as of equal weight, and curves were fitted as second order polynomials.

Results

The systematic search identified 37 studies of coronary reperfusion enrolling 3972 patients in active reperfusion treatment control arms and 6936 patients in novel reperfusion treatment arms patients, with the first study published in 1983 and the last in 2009. For cerebral reperfusion, the search identified 10 studies enrolling 149 patients in active reperfusion treatment control arms and 915 patients in novel reperfusion treatment arms, with the first study published in 1992 and the last in 2009. Characteristics of individual studies are shown in Supplemental Tables 1 and 2.

Coronary reperfusion trials included 10 of IVF alone from 1984 to 1998; 8 of combined IVF and percutaneous transluminal coronary angioplasty with or without stenting from 1988 to 2007; 3 of intracoronary fibrinolysis (ICF) in 1983; and 18 of percutaneous transluminal coronary angioplasty with or without stenting from 1993 to 2005. Rates of reperfusion were higher for trials using percutaneous transluminal coronary angioplasty with or without stenting than IV or IC fibrinolysis alone (Figure 1). Cerebral reperfusion trials included 1 of IVF alone in 1992; 3 of endovascular fibrinolysis alone from 1998 to 2007; 3 of device alone from 2005 to 2009; and 3 of endovascular ± IVF from 1999 to 2007. Rates of reperfusion
were higher for studies using endovascular cerebral reperfusion techniques than for intravenous fibrinolysis alone (Figure 1).

In the weighted logistic regression analysis (Figure 2), achieved coronary reperfusion rates began at high levels in the 1980s and improved modestly over the subsequent 3 decades. In different time epochs, rates of coronary reperfusion were as follows: pre-1995, partial reperfusion (PR) – 70.2%, complete reperfusion (CR) – 63.5%; 1995 to 2004, PR – 81.6%, CR – 73.1%; 2005 to 2010, PR – 86.1%, CR – 78.2%. In contrast, for the cerebral bed, achieved reperfusion rates began at modest levels in the early 1990s and increased slowly over the next 2 decades. Rates of cerebral reperfusion in different calendar epochs were as follows: pre-1995, PR – 32.0%, CR – 5.3%; 1995 to 2004, PR – 45.2%, CR – 14.2%; 2005 to 2010, PR – 61.1%, CR – 23.4%.

With an anchor added for spontaneous reperfusion rates in the prerEPERUSION therapy era, analysis of complete reperfusion rates showed a rapid rise to a peak rate near 80 to 90% for coronary reperfusion versus a slow rise to plateau of 20 to 25% for cerebral reperfusion (Figure 3).

**Discussion**

This study-level systematic review demonstrates a substantial historical divergence in reperfusion rates between cerebral and coronary acute reperfusion interventions. Reperfusion rates for occluded vessels in acute myocardial ischemia increased above the natural history rate earlier, escalated more quickly, and currently are at a markedly higher level in comparison with those for occluded vessels in acute cerebral ischemia. In evaluating 37 trials of coronary reperfusion and 10 trials of cerebral reperfusion, coronary reperfusion therapies first showed higher rates than control 9 years earlier (1983 versus 1992). Coronary complete reperfusion rates improved 3 times more quickly, 3.0% versus 0.9% per year. At the end of the study period, complete reperfusion was being achieved 3 times more often for coronary than cerebral interventions (78.2% versus 23.4%).

Several factors likely contribute to the later and slower progress in reperfusion rates in the cerebrovascular compared with cardiovascular circulation. Occlusions in the cerebrovascular bed are more heterogeneous in composition than in the coronary bed, including embolic thrombi of arterial and cardiac origin in addition to in situ atherosclerosis with supervening thrombosis, requiring a greater range of treatment strategies.11,12 Proximal cerebral arteries are longer and wider than coronary arteries, so that cerebral occlusive thrombi frequently present much larger burdens of thrombus to be chemically digested or mechanically dislodged. Recanalization rates with intravenous fibrinolitics in smaller brain arteries, such as M3 and M4 middle cerebral artery branches, are likely more comparable with those achieved in coronary arteries. Differences in clot burden and exposed thrombus surface also likely account for the differences in recanalization efficacy of intravenous and intra-arterial routes of fibrinolytic administration in the 2 vascular beds. In smaller coronary arteries, intravenous and intra-arterial administration yielded similar rates of recanalization, whereas in the larger, proximal cerebral arteries, the higher concentration of lytic delivered to a large clot volume and surface achievable with intravenous versus intra-arterial therapy appeared to produce more recanalization success.

In addition, cerebral vessels are more fragile compared with coronary arteries, making the brain a more bleeding-prone end organ than the heart, constraining fibrinolytic doses, use of concomitant antiplatelet and anticoagulant medications, and the mechanical energies exerted by recanalization devices. In contrast to the cardiac vasculature, the brain has more tortuous feeding arteries, making endovascular navigation to the target occlusion more difficult. Also, the cerebral vascular tree has a more complex, highly ordered arborization, sometimes requiring treatment of multiple vessel branches, rather than a single linear target.

Although there have been no directly comparable studies evaluating recanalization rate changes over time, our findings for the coronary circulation are consistent with studies that have shown improvements in clinical outcomes among patients during the analyzed time period. For acute coronary ischemia, from 1990 to 2002, clinical trials comparing pharmacologic thrombolysis with primary angioplasty found a reduction
in the combined end point of death, nonfatal reinfarction, and stroke, from 14% to 8% with percutaneous coronary intervention, leading to its increasing clinical use, reaching about one-half of ST-elevation myocardial infarction and one-quarter of all myocardial infarction patients.13,14 Between 1995 and 2006, 30 day risk-standardized case-fatality rates for acute MI declined by 16% in US hospitals.15 From 2007 to 2009, primary percutaneous coronary intervention increased in frequency in acute MI patients from 75.3 to 83.0% and in-hospital mortality for ST-elevation myocardial infarction declined.16 For acute cerebral ischemia, from 2001 to 2009 rates of intravenous thrombolysis use in the US tripled,17 and from 2006 to 2008 rates of endovascular embolectomy rose.18 However, analyses of changes in outcomes for AIS patients in clinical care during these time periods have not focused on recanalization-eligible patients (moderate to severe ischemic stroke), but on the broader stroke population, among whom the observed improvement in acute in-hospital case-fatality is likely multifactorial in origin.19

This systematic review has limitations. Because there are fewer cerebrovascular than cardiovascular studies, the characterization of recanalization success frequencies is less statistically robust for the cerebrovascular bed. Reperfusion status was characterized based on the TIMI scale when available. The TIMI scale was developed for the cardiac circulation. Applying the TIMI scale to the cerebral circulation requires adoption of additional operational rules that are known to have varied between different cerebrovascular studies.20 For this meta-analysis we extracted the TIMI results as stated in each study report. Also, in several very early cardiac and cerebral trials, generally those performed before the development of the TIMI scale, TIMI scores were not reported. For these, reperfusion rates were abstracted based on the trial’s description of partial or complete reperfusion. The time point after treatment at which reperfusion status was assessed varied

Figure 2. Quantitative trends over time in reperfusion rates in active arms of recanalization trials. Left column is coronary, right column cerebral. Top row is partial or better, bottom row complete. The size of each circle on the graphs indicates the sample size of each cohort. Circle colors indicate treatment type: red, intravenous fibrinolysis; blue, percutaneous transluminal coronary angioplasty with or without stenting; green, intravenous fibrinolysis + percutaneous transluminal coronary angioplasty with or without stenting; brown, intraarterial fibrinolysis.

Figure 3. Trends over time in complete reperfusion rates in active arms of coronary (diamond) and cerebral (square) reperfusion trials, without sample size weighting and with spontaneous reperfusion rates placed in 1980 as anchor, prereperfusion therapy era, values.
somewhat across studies. Our analyses of reperfusion rates in active treatment arms of the studies analyzed reflect clinical trial results, not general clinical practice. However, successful treatments identified in these trials generally disseminated rapidly into subsequent clinical practice. The time period of our analysis predates the first reports of multicenter trials of stent retriever in the cerebral circulation, but does provide a useful delineation of reperfusion evolution and status prior to the stent retriever era.

We conclude that, from 1980 to 2010, technical efficacy in achieving acute reperfusion by intravenous and endovascular techniques developed more slowly and plateaued at a much lower level for the cerebral than for the cardiac circulation. These findings suggest that cerebral circulation-specific technical advances that further increase reperfusion rates may be able to substantially further improve patient outcomes from acute ischemic stroke.

Acknowledgments
We thank Jeffrey Gornbein, DrPH, for expert statistical consultation.

Sources of Funding
This work was supported in part by National Institutes of Health–National Institute of Neurological Disorders and Stroke awards P50 NS044378 and U01 NS 44364 (to Dr Saver).

Disclosures
The University of California Regents receive funding for Dr Saver’s services as a scientific consultant regarding trial design and conduct to Covidien and Talecris. Dr Saver is an investigator in the National Institutes of Health Medical Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke—Enhanced Regimen (CLEAR-ER), and Interventional Management of Stroke III (IMS 3) multicenter clinical trials for which the University of California Regents receive payments based clinical trial performance; has served as an unpaid site investigator in a multicenter trials run by Lundbeck and Covidien for which the University of California Regents received payments based on the clinical trial contracts for the number of subjects enrolled; and is an employee of the University of California, which holds a patent on retriever devices for stroke.

REFERENCES
Evolution of Reperfusion Therapies for Acute Brain and Acute Myocardial Ischemia: A Systematic, Comparative Analysis
Richa D. Patel and Jeffrey L. Saver

Stroke. 2013;44:94-98; originally published online November 27, 2012;
doi: 10.1161/STROKEAHA.112.666925
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/1/94

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/11/27/STROKEAHA.112.666925.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Evolution of Reperfusion Therapies for Acute Brain and Acute Myocardial Ischemia: A Systematic, Comparative Analysis

Richa D. Patel, BS
Jeffrey L. Saver, MD

Stroke Center and Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles
<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Novel/Standard Arms</th>
<th>Reperfusion Treatment Class</th>
<th>No. of Enrolled Patients (Novel/Standard)</th>
<th>Partial or Better Recanalization Rate (Novel/Standard)</th>
<th>Complete Recanalization Rate (Novel/Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khaja et al¹</td>
<td>1983</td>
<td>Streptokinase / placebo</td>
<td>ICF / none</td>
<td>20 / 20</td>
<td>60.0% / 10.0%</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Anderson et al²</td>
<td>1983</td>
<td>Streptokinase / standard therapy</td>
<td>ICF / none</td>
<td>24 / 26</td>
<td>79.2% / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Kennedy et al³</td>
<td>1983</td>
<td>Streptokinase / standard therapy</td>
<td>ICF / none</td>
<td>134 / 116</td>
<td>68.0% / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Leiboff et al⁴</td>
<td>1984</td>
<td>Streptokinase / standard therapy</td>
<td>IVF / none</td>
<td>22 / 18</td>
<td>68.2% / 16.7%</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Mueller et al⁵</td>
<td>1987</td>
<td>IV-rtPA 70mg or 100mg / IV-rtPA 50mg</td>
<td>IVF / IVF</td>
<td>192 / 113</td>
<td>66.3% / 62.0%</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Topol et al⁶</td>
<td>1988</td>
<td>IV-rtPA 2 dose tiers/No non-active control</td>
<td>IVF / NA</td>
<td>384 / NA</td>
<td>71.9% / NA</td>
<td>NR / NA</td>
</tr>
<tr>
<td>GAUS⁷</td>
<td>1988</td>
<td>Single chain IV-rtPA / urokinase</td>
<td>IVF / IVF</td>
<td>125 / 121</td>
<td>67.2% / 63.6%</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Simoons et al⁸</td>
<td>1988</td>
<td>rtPA + immediate PTCA / rtPA</td>
<td>IVF + PTCA±S / IVF</td>
<td>183 / 184</td>
<td>87.4% / NR</td>
<td>76.0% / NR</td>
</tr>
<tr>
<td>TAPS⁹</td>
<td>1991</td>
<td>rtPA / APSAC</td>
<td>IVF / IVF</td>
<td>217 / 218</td>
<td>77.4% / 65.1%</td>
<td>66.4% / 50.0%</td>
</tr>
<tr>
<td>Zijlstra et al¹⁰</td>
<td>1993</td>
<td>Immediate PTCA / streptokinase</td>
<td>PTCA±S / IVF</td>
<td>70 / 72</td>
<td>78.0% / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Ribeiro et al¹¹</td>
<td>1993</td>
<td>Retepase / alteplase</td>
<td>PTCA±S / IVF</td>
<td>50 / 50</td>
<td>80.0% / NR</td>
<td>NR / NR</td>
</tr>
<tr>
<td>Bode et al¹²</td>
<td>1996</td>
<td>Lanoteplase (60 or 120 kU/kg) / alteplase</td>
<td>IVF / IVF</td>
<td>169 / 155</td>
<td>77.5% / 69.0%</td>
<td>56.6% / 42.6%</td>
</tr>
<tr>
<td>Heijer et al¹³</td>
<td>1998</td>
<td>TNK-tPA (40 or 50 mg) / front-loaded tPA</td>
<td>IVF / IVF</td>
<td>478 / 124</td>
<td>59.1% / 61.6%</td>
<td>57.1% / 46.4%</td>
</tr>
<tr>
<td>Cannon et al¹⁴</td>
<td>1998</td>
<td>rtPA / placebo</td>
<td>PTCA±S / IVF</td>
<td>526 / 311</td>
<td>79.1% / 81.7%</td>
<td>58.4% / 62.7%</td>
</tr>
<tr>
<td>Ribichini et al¹⁵</td>
<td>1998</td>
<td>Angioplasty / rtPA</td>
<td>IVF + PTCA±S / IVF</td>
<td>302 / 304</td>
<td>83.1% / 85.9%</td>
<td>77.2% / 83.1%</td>
</tr>
<tr>
<td>PACT¹⁶</td>
<td>1999</td>
<td>Primary angioplasty / systemic tPA</td>
<td>PTCA±S / IVF</td>
<td>111 / 109</td>
<td>92.6% / NR</td>
<td>66.9% / NR</td>
</tr>
<tr>
<td>Garcia et al¹⁷</td>
<td>1999</td>
<td>PTCA (rescue or primary) + alteplase / alteplase</td>
<td>IVF + PTCA±S / IVF</td>
<td>149 / 75</td>
<td>89.3% / NR</td>
<td>83.2% / NR</td>
</tr>
<tr>
<td>Vermeer et al¹⁸</td>
<td>1999</td>
<td>PTCA ± streptokinase / streptokinase</td>
<td>IVF / IVF</td>
<td>201 / 99</td>
<td>95.5% / NR</td>
<td>91.5% / NR</td>
</tr>
<tr>
<td>Schomig et al²⁰</td>
<td>2000</td>
<td>PTCA / alteplase</td>
<td>PTCA±S / IVF</td>
<td>71 / 69</td>
<td>95.8% / NR</td>
<td>95.8% / NR</td>
</tr>
<tr>
<td>STAT²¹</td>
<td>2001</td>
<td>Primary stenting / accelerated tPA</td>
<td>PTCA±S / IVF</td>
<td>62 / 61</td>
<td>80.2% / NR</td>
<td>74.2% / NR</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Interventions</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Boer et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2002</td>
<td>PTCA / streptokinase Abciximab after angiography, before angioplasty or immediately / no abciximab</td>
<td>PTCA±S / IVF 46 / 41 NR / NR 80.4% / NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zorman et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2002</td>
<td>Stenting + abciximab / fibrinolysis + abciximab</td>
<td>PTCA±S / PTCA±S 112 / 57 97.0% / 98.0% 90.5% / 92.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kastrati et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>2002</td>
<td>Primary PCI / accelerated tPA Tirofiban in ER / tirofiban in catheterization lab</td>
<td>PTCA±S / IVF 81 / 81 NR / NR 93.0% / NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aversano et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2002</td>
<td>Stenting + abciximab / fibrinolysis + abciximab</td>
<td>PTCA±S / IVF 225 / 226 NR / NR 72.1% / NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIGER-PA&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2003</td>
<td>PCI / primary intervention</td>
<td>PTCA±S / PTCA±S 50 / 50 NR / NR 92.0% / 92.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERAMI&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2003</td>
<td>PCI / streptokinase</td>
<td>PTCA±S / IVF 429 / 421 87.9% / NR 82.6% / NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widimsky et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2003</td>
<td>Open-lab tirofiban ER / GP IIb-IIIa inhibitor after angiography</td>
<td>PTCA±S / PTCA±S 28 / 30 96.0% / 92.0% 84.0% / 85.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutlip et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2003</td>
<td>Pre-hospital tirofiban / tirofiban in catheterization lab</td>
<td>PTCA±S / PTCA±S 251 / 256 NR / NR 78.1% / 81.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-TIME&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2004</td>
<td>Abciximab before angiography, after randomization / abciximab after angiography</td>
<td>PTCA±S / IVF 28 / 27 93.0% / 89.0% 89.0% / 74.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reo-PRO BRIDGING&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2004</td>
<td>Reteplase + abciximab / abciximab Early epitifibatide in ER + during PCI / Late epitifibatide in PCI (or none at all)</td>
<td>PTCA±S / IVF 125 / 81 95.2% / NR 87.2% / NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kastrati et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>2004</td>
<td>Abciximab in ER / abciximab in catheterization lab</td>
<td>PTCA±S / PTCA±S 55 / 51 87.3% / 90.2% 81.8% / 76.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTAMI&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2005</td>
<td>Abciximab in ER / abciximab in catheterization lab</td>
<td>PTCA±S / PTCA±S 27 / 28 100.0% / 100.0% 96.3% / 85.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bellandi et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>2005</td>
<td>PCI + TNK / PCI Rescue PCI + TNK or primary PCI / TNK</td>
<td>PTCA±S / IVF 829 / 838 82.8% / 88.9% 76.1% / 80.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assent 4 PCI&lt;sup&gt;35&lt;/sup&gt;</td>
<td>2006</td>
<td>PTCA±S / IVF 204 / 100 81.5% / NR 73.5% / NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEST&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2006</td>
<td>TNK + stenting / primary stenting</td>
<td>PTCA±S / IVF 104 / 108 89.4% / 85.2% 78.8% / 74.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported; NA = No non-active control group; IVF = intravenous fibrinolysis; ICF = intra-coronary fibrinolysis; PTCA±S = percutaneous transluminal coronary angioplasty with or without stenting;
Table S2: Characteristics of Included Cerebral Reperfusion Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication</th>
<th>Year</th>
<th>Novel/Standard Arms</th>
<th>Reperfusion Treatment Class</th>
<th>No. of Enrolled Patients (Novel/Standard)</th>
<th>Partial or Better Recanalization Rate (Novel/Standard)</th>
<th>Complete Recanalization Rate (Novel/Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoppo38</td>
<td>1992</td>
<td></td>
<td>IV rtPA/ NC</td>
<td>IVF / NC</td>
<td>75/ NC</td>
<td>32.0% / NC</td>
<td>5.3% / NC</td>
</tr>
<tr>
<td>PROACT39</td>
<td>1998</td>
<td></td>
<td>IA Pro-urokinase / placebo</td>
<td>IAF / none</td>
<td>31 / 15</td>
<td>48.4% / 13.3%</td>
<td>16.1% / 0.0%</td>
</tr>
<tr>
<td>PROACT II40</td>
<td>1999</td>
<td></td>
<td>IA Pro-urokinase / IV heparin</td>
<td>IAF / none</td>
<td>121 / 59</td>
<td>58.9% / 15.3%</td>
<td>17.0% / 1.7%</td>
</tr>
<tr>
<td>EMS41</td>
<td>1999</td>
<td></td>
<td>rtPA / placebo</td>
<td>IAF</td>
<td>17 / 18</td>
<td>64.7% / 44.4%</td>
<td>47.0% / 22.2%</td>
</tr>
<tr>
<td>EMS42</td>
<td>2004</td>
<td></td>
<td>IV + IA rtPA / NC</td>
<td>IVF + IAF /</td>
<td>80 / NC</td>
<td>47.5% / NC</td>
<td>12.5% / NC</td>
</tr>
<tr>
<td>MERCI43</td>
<td>2005</td>
<td></td>
<td>Retrieval ± adjuvant / NC</td>
<td>MT / NC</td>
<td>151 / NC</td>
<td>45.7% / NC</td>
<td>22.5% / NC</td>
</tr>
<tr>
<td>IMS II44</td>
<td>2007</td>
<td></td>
<td>IV + IA rtPA with US / NC</td>
<td>NC</td>
<td>81 / NC</td>
<td>69.1% / NC</td>
<td>32.1% / NC</td>
</tr>
<tr>
<td>MELT45</td>
<td>2007</td>
<td></td>
<td>IA Urokinase / NR</td>
<td>IAF / none</td>
<td>57 / 57</td>
<td>73.7% / NR</td>
<td>5.3% / NR</td>
</tr>
<tr>
<td>Multi-MERCI46</td>
<td>2008</td>
<td></td>
<td>Retrieval ± adjuvant / NC</td>
<td>MT / NC</td>
<td>177 / NC</td>
<td>52.0% / NR</td>
<td>NR / NC</td>
</tr>
<tr>
<td>Bose et al47</td>
<td>2009</td>
<td></td>
<td>Aspiration ± adjuvant / NC</td>
<td>MT / NC</td>
<td>125 / NC</td>
<td>81.6% / NC</td>
<td>27.2% / NC</td>
</tr>
</tbody>
</table>

NR = Not reported; NA = No control group; IVF = intravenous fibrinolysis; IAF = intra-arterial fibrinolysis; MT = mechanical thrombectomy.
Source Citations for Analyzed Trials


