Thrombolysis in acute myocardial infarction: analysis of studies comparing accelerated t-PA and streptokinase

Brendon J Smith

Abstract
Objectives—To compare outcomes from accelerated alteplase (recombinant tissue plasminogen activator, t-PA) and streptokinase use in acute myocardial infarction.

Methods—Review of available studies identified by Medline and other literature searches that met the criteria of being a prospective, randomised clinical trial enrolling over 1000 patients with acute myocardial infarction. The studies had to contain an intervention arm comprising accelerated infusion t-PA, or an intervention arm comprising streptokinase provided accelerated t-PA that was compared in the same trial. Interventions compared were streptokinase 1.5 million units given over one hour compared with accelerated t-PA infusion, with concomitant use of aspirin and heparin, and main outcome measure of 30 day mortality.

Results—Four studies met prespecified criteria, these being the GUSTO I, GUSTO IIb Angioplasty Substudy, GUSTO III, and COBALT trials. There was a total study population of 64 387 patients of whom 20 251 received streptokinase, 19 474 received t-PA, with others receiving different treatment. Pooled data show that accelerated t-PA produces a marginal 30 day mortality advantage compared with streptokinase (6.6% v 7.3%, p = 0.02, Bonferroni adjusted p = 0.12, that is borderline significance, relative risk 0.918, 95% confidence interval 0.854 to 0.986). Any benefit is attributable entirely to patients recruited in the United States in the GUSTO I study. There is an increased incidence of stroke with t-PA.

Conclusions—The data do not consistently show a 30 day mortality benefit from using t-PA compared with streptokinase in acute myocardial infarction, but do show increased risk of stroke. Streptokinase can be considered the thrombolytic agent of choice.


Keywords: acute myocardial infarct; thrombolysis; streptokinase; t-PA

Thrombolysis is part of standard treatment for acute myocardial infarction, however there is controversy as to the preferred agent to use. The GUSTO I trial1 included an accelerated alteplase (recombinant tissue plasminogen activator, t-PA) infusion arm which showed a 30 day survival benefit compared with streptokinase, achieved at a cost of an excess of strokes. Although there is controversy regarding this conclusion,3 there is the perception that t-PA is better than streptokinase, but that its higher cost precludes more widespread use.4

Subsequent trials5–7 in comparable groups of patients have included identical t-PA treatment arms to that used in GUSTO I.1 The purpose of this study is to incorporate these additional data to compare outcomes from accelerated t-PA and streptokinase use in acute myocardial infarction.

Methods
Articles were identified by a search to June 1998 of Medline, The Cochrane Library database, and Emergency Medicine Abstracts. Search term used were “myocardial infarct and thrombolysis”, “myocardial infarct and streptokinase”, and “myocardial infarct and t-PA”. Articles obtained were further checked to obtain relevant citations, and the index of a number of major publications were searched manually.

The primary data were obtained from trials meeting the following criteria:

(1) Study population of over 1000 patients with acute myocardial infarction defined by electrocardiographic criteria.

(2) One intervention arm comprising accelerated infusion t-PA (given as a 15 mg bolus, followed by 0.75 mg/kg up to 50 mg over 30 minutes, then 0.5 mg/kg up to 35 mg over 60 minutes).

(3) One intervention arm comprising streptokinase 1.5 million units given over one hour, provided accelerated t-PA used in the same trial.

(4) Thirty day mortality as a primary outcome measure.

(5) Concomitant use of aspirin and heparin (intravenous heparin for the t-PA arm).

Treatment arms that were the same or equivalent were combined to provide comparisons. Statistical comparison between groups was made by calculating a p value using the χ2 test to test the null hypothesis that treatment with accelerated t-PA was equivalent to streptokinase as measured by 30 day mortality. Bonferroni adjusted p values were calculated based on six analyses performed overall in this study so as to adjust for the increased likelihood of a significant p value arising by chance due to multiple comparisons being made. Such an adjustment, which multiplies...
Table 1  Data reported from GUSTO I study

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase and subcutaneous heparin</th>
<th>Streptokinase and intravenous heparin</th>
<th>Accelerated t-PA and intravenous heparin</th>
<th>Both thrombolytic agents and intravenous heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>(n=9796)</td>
<td>(n=10 377)</td>
<td>(n=10 344)</td>
<td>(n=10 328)</td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>7.3</td>
<td>7.4</td>
<td>6.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Patients recruited in the United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 90 min</td>
<td>54</td>
<td>60</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>At 180 min</td>
<td>73</td>
<td>74</td>
<td>76</td>
<td>85</td>
</tr>
<tr>
<td>Infarct related artery patency after initiation thrombolytic treatment (%)</td>
<td>(n=10 649, combined figure)</td>
<td>(n=5751)</td>
<td>(n=5635)</td>
<td></td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>7.0</td>
<td>5.8</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>Patients recruited outside the United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct related artery patency at 90 minutes (%)</td>
<td>(n=8655, combined figure)</td>
<td>(n=4429)</td>
<td>(n=4389)</td>
<td></td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>7.6</td>
<td>6.9</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>Infarct related artery patency at 90 minutes (%)</td>
<td>(n=4921)</td>
<td>(n=10 138)</td>
<td>(n=4378)</td>
<td></td>
</tr>
</tbody>
</table>

The calculated p value by the number of comparisons made, renders an otherwise significant p value between 0.01 and 0.05 of questionable importance. Relative risk values for mortality with use of t-PA were calculated, together with the 95% confidence interval (CI).

Results

Four studies met the specified criteria, these being the GUSTO I, GUSTO IIb Angioplasty Substudy, GUSTO III, and COBALT trials, which contained a combined study population of 64 387 patients. Those in the GUSTO IIb Angioplasty Substudy were also randomised to heparin or hirudin. These subsets were considered equivalent on the basis of the results of the main GUSTO IIb trial comparing heparin and hirudin which showed no difference in outcome. There are minor discrepancies in numbers among different papers reporting GUSTO I data, as has been noted previously.

Thirty day mortality together with 90 and 180 minute coronary artery patency data from GUSTO I are shown in table 1, and 30 day mortality data from the other trials are in table 2. Patency is defined as TIMI grade 2 or 3 flow. It would be expected that treatments where there is a large difference in patency rates would consistently have significantly different 30 day mortality rates (defined as p <0.05 on χ² test), and those with comparable patency rates would have similar mortality rates, however there is an inconsistent correlation.

Pooled data shows that accelerated t-PA produces a marginal 30 day mortality advantage compared with streptokinase (6.6% vs 7.3%, p = 0.02), however this is of questionable significance (Bonferroni adjusted p = 0.12, relative risk 0.918, 95% CI 0.854 to 0.986). The benefit of t-PA over streptokinase demonstrated in GUSTO I (6.3% vs 7.3%, p = 0.0001, Bonferroni adjusted p = 0.006, relative risk 0.862, 95% CI 0.789 to 0.943) was attributed to an improved coronary artery patency at 90 minutes from initiation of thrombolytic treatment, with no differences in patency seen at any other time. However this benefit was found only among patients recruited in the United States (5.8% for t-PA vs 7.0% for streptokinase among United States patients, p = 0.003, Bonferroni adjusted p = 0.018, relative risk 0.828, 95% CI 0.730 to 0.938). Among non-United States patients in GUSTO I, there was no statistically significant difference in mortality between the t-PA and streptokinase treatment groups (6.9% vs 7.6%, p = 0.138, Bonferroni adjusted p = 0.828, relative risk 0.906, 95% CI 0.795 to 1.032). This is despite a 90 minute coronary artery patency difference approaching 30% (82% vs 53%). The same accelerated t-PA infusion regimen used in the GUSTO IIb, GUSTO III, and COBALT trials did not produce 30 day mortality rates that were as favourable as in GUSTO I (7.3% for pooled non-GUSTO I studies vs 6.3% for GUSTO I, p = 0.004, Bonferroni adjusted p = 0.024, relative risk 1.164, 95% CI 1.049 to 1.292). The combined non-GUSTO I t-PA results was the same as for streptokinase (7.3%, p = 0.931, Bonferroni adjusted p = 5.86, relative risk 1.004, 95% CI 0.919 to 1.096).

Table 2  Thirty day mortality (%) in studies of treatment for myocardial infarction: GUSTO IIb, GUSTO III, COBALT

<table>
<thead>
<tr>
<th></th>
<th>GUSTO IIb</th>
<th>GUSTO III</th>
<th>COBALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated t-PA</td>
<td>7.0 (n=573)</td>
<td>7.2 (n=4921)</td>
<td>7.5 (n=3584)</td>
</tr>
<tr>
<td>Double bolus t-PA</td>
<td></td>
<td></td>
<td>8.0 (n=3585)</td>
</tr>
<tr>
<td>Retplace</td>
<td></td>
<td>7.5 (n=10 138)</td>
<td></td>
</tr>
<tr>
<td>Angioplasty*</td>
<td>5.7 (n=535)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Values for treatment comparisons</td>
<td>p=0.37</td>
<td>p=0.54</td>
<td>p=0.53</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.80</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.49 to 1.30</td>
<td>0.91 to 1.18</td>
<td>Odds ratio and CI not reported in study.</td>
</tr>
</tbody>
</table>

*Median time from hospital arrival to angioplasty 1.9 hours. CI = confidence interval.
location infarct, and fewer with cardiac dysfunction (Killip class >1) in GUSTO IIb. The proportion of patients with underperfusion angioplasty was substantially higher in the United States arm of the GUSTO I trial.\(^1\)

**Discussion**

Combining 30 day mortality figures from the GUSTO I, GUSTO IIb Angioplasty Substudy, GUSTO III, and COBALT trials using thrombolytic treatment for acute myocardial infarction shows that accelerated t-PA infusion gives a small benefit of borderline significance compared to streptokinase,\(^1\) 5-7 which is attributable entirely to patients recruited in the United States in the GUSTO I study.\(^10\) The same t-PA regimen was used in the GUSTO IIb, GUSTO III, and the COBALT trials and did not reproduce the low mortality rate achieved in GUSTO I and pooled mortality data from those trials for t-PA are the same as for streptokinase.\(^1\) 5-7 The patients given t-PA from the four studies were comparable as regards baseline clinical factors that influence outcome (see table 3).\(^11\) Age is the most significant variable, and was equivalent between studies. The variation in numbers with cardiac dysfunction above Killip class I would predispose to a more favourable outcome in the non-GUSTO I studies, whereas the actual outcome is worse. Infarct location is one of many factors individually having substantially less impact and the variations would not be expected to alter the overall conclusion.

The ISIS-3\(^3\) and GISSI-2\(^2\) trials showed no advantage of t-PA infused over three or four hours compared with streptokinase. It was speculated that the use of subcutaneous rather than intravenous heparin in these trials may have prevented a benefit from t-PA from being demonstrated.\(^14\) Although intravenous heparin gives improved delayed patency,\(^15\) 17 there is no difference between t-PA compared with t-PA plus intravenous heparin in patency at 90 minutes.\(^1\) The better outcome in the accelerated t-PA arm of GUSTO I was attributed to a transient advantage in coronary artery patency at 90 minutes from initiation of thrombolytic treatment which was no longer apparent by 180 minutes or at any later time.\(^1\) It is therefore unlikely that the results of GISSI-2 and ISIS-3 were attributable to heparin which does not influence this variable.

It was claimed that GUSTO I "...resoundingly confirms the open-artery theory", which maintains that establishing early coronary artery patency and reperfusion results in myocardial salvage, improved ventricular function, and improved survival.\(^19\) However, although data for a number of interventions demonstrate a higher rate of coronary artery patency, subsequent clinical trials of sufficient size (n >1000) have not demonstrated a survival benefit. These interventions include a three or four hour t-PA infusion compared with streptokinase\(^12\) 13 20 21; reteplase compared with accelerated t-PA\(^22\) 23; hirudin compared with heparin given together with t-PA\(^24\) 25-28; angioplasty compared with accelerated t-PA;\(^1\) and routine angioplasty compared with conserva-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GUSTO I* ((n=1936))</th>
<th>GUSTO IIb ((n=573))</th>
<th>GUSTO III* ((n=4921))</th>
<th>COBALT(^a) ((n=3584))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years</td>
<td>62 (52, 70)</td>
<td>62 (52, 70)</td>
<td>63 (53, 72)</td>
<td>62 (53, 70)</td>
</tr>
<tr>
<td>Age &gt;75 in years (%)</td>
<td>12.5</td>
<td>13.8</td>
<td>13.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>25</td>
<td>21.5</td>
<td>27.2</td>
<td>24</td>
</tr>
<tr>
<td>Median systolic blood pressure (mm Hg)</td>
<td>130 (113, 144)</td>
<td>130 (116, 148)</td>
<td>134 (119, 150)</td>
<td>140 (120, 160)</td>
</tr>
<tr>
<td>Median heart rate (beats/min)</td>
<td>73 (62, 86)</td>
<td>74 (62, 86)</td>
<td>73 (62, 86)</td>
<td>75 (63, 88)</td>
</tr>
<tr>
<td>Killip class &gt;1 (%)</td>
<td>15*</td>
<td>8.2</td>
<td>14.7</td>
<td>16</td>
</tr>
<tr>
<td>Median interval: symptom onset to treatment (hours)</td>
<td>2.7 (2.0, 3.8)</td>
<td>3.0 (2.0, 4.3)</td>
<td>2.7 (1.9, 3.9)</td>
<td>2.9 (2.0, 4.0)</td>
</tr>
<tr>
<td>Anterior infarction (%)</td>
<td>39*</td>
<td>n/r</td>
<td>47.7</td>
<td>43</td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>6.3</td>
<td>7.0</td>
<td>7.2</td>
<td>6.7</td>
</tr>
<tr>
<td>All strokes (%)</td>
<td>1.5</td>
<td>1.9</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemorrhagic strokes (%)</td>
<td>0.7</td>
<td>1.4</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Angioplasty (% performed)</td>
<td>US</td>
<td>non-US</td>
<td>n/r</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*Pooled data from entire GUSTO I cohort, not reported separately for accelerated t-PA arm.\(^1\)

Calculations made as necessary from source data.\(^1\) 5-7 10

Values in parentheses are the 25th and 75th percentiles.

n/r: not reported.
combination t-PA/streptokinase group (see tables 1 and 2).

United States recruitment was a significant predictor of improved survival yet combined TIMI grade 2 or 3 patency rates were similar between United States and non-United States patients in GUSTO I (see table 1). Despite improved early patency with t-PA in GUSTO I, there was no improvement in global ejection fraction at 90 minutes nor at 5–7 days. The survival curves began to diverge at 6–8 hours, well after the observed transient improvement in coronary artery patency.

The GUSTO I trial was not blinded as to treatment given. There were substantial protocol violations as to whether heparin was given at all and by which route, and large variations in other non-protocol medical treatments given.3 10 The survival advantage attributable to United States recruitment is apparent only in the t-PA arm and not the other three treatment groups. This intragroup survival advantage for t-PA approximates the overall t-PA versus streptokinase advantage.2 It is plausible that factors unrelated to the choice of thrombolytic agent produced a superior result that has been attributed to use of accelerated t-PA.

The use of angioplasty and bypass surgery was similar between the four treatment groups in GUSTO I, however the rate among United States patients was 31% and 13%, respectively, compared with 10% and 3% for non-United States patients.9 10 Although it has been speculated that this excess of intervention did not contribute to the survival difference among United States patients, the variables were not controlled for. The possibility that more frequent revascularisation procedures, together with other unmeasured differences in care provided to United States patients, resulted in improved survival cannot be excluded.10 Among those in cardiogenic shock there was also a greater rate of revascularisation and surgical intervention in the group from the United States which did result in a significantly lower 30 day mortality.30 Conversely, the COBALT trial authors speculated that the lower rate of revascularisation procedures was a reason why the same t-PA treatment regimen used in the COBALT trial gave a less favourable outcome.7

A limitation of this analysis is that streptokinase data are available from only one trial. It is not appropriate to pool data from previous trials using streptokinase without an accelerated t-PA arm. In contrast, the studies using t-PA were either done by the same group (GUSTO)5 9 10 or used an identical protocol (COBALT).7 It is notable that although there have been extensive efforts by the pharmaceutical industry to sponsor and promote trials using t-PA, there has been little comparable effort with streptokinase despite evidence indicating that accelerated infusions are also superior to standard administration.9 37

Finally, there is the question of what survival benefit can be expected from hastening early reperfusion with t-PA. The Fibrinolytic Therapy Trials’ Collaborative Group concluded that each hour of delay is associated with an increase in 30 day mortality of 1.6 +/- 0.6 per 1000 patients.38 Accelerated t-PA achieves patency up to one hour earlier than streptokinase, yet GUSTO I suggested a benefit of 10 per 1000 patients, which is inconsistent and somewhat implausible.1 It is not disputed that there are more strokes with t-PA use compared with streptokinase, with an excess of 3:1000 among patients treated in GUSTO I.1 A study of 71 073 patients in the national registry of t-PA use for myocardial infarction in the United States sponsored by Genentech Inc, manufacturer of t-PA, documents a higher rate of intracranial haemorrhage in community practice (0.9%) compared with that reported in GUSTO I (0.7%).69 Cost considerations would further establish streptokinase as the preferred agent (A$201.68 v A$2245.04 for t-PA as listed in the Australian Schedule of Pharmaceutical Benefits, February 1999).

In conclusion, existing data do not convincingly demonstrate a benefit from using t-PA compared with streptokinase in acute myocardial infarction. No advantage was shown by the ISIS-312 and GISSI-213 trials that used a three or four hour t-PA infusion. In subsequent trials using an accelerated infusion regimen, only one of five arms showed a benefit from t-PA.5 7 10 Streptokinase can be considered the thrombolytic agent of choice for use in acute myocardial infarction based on available evidence as to efficacy and risk.

I am grateful for the expert statistical advice given, and calculations performed, by Ms Sue Middleton, Department of Statistics, School of Mathematics, University of New South Wales.

Conflict of interest: none.

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12 ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anis-
t-PA versus streptokinase in myocardial infarction


Marber MS, Brown DL, Kloner RA. The open artery hypothesis: to open, or not to open, that is the question. Eur Heart J 1996;17:505-9.


