



*An initiative of NSW Clinical
Pharmacologists & Pharmacists
Funded by the NSW Department of Health*

THROMBOLYSIS FOLLOWING ACUTE MYOCARDIAL INFARCTION

A Position Statement of the NSW Therapeutic Assessment Group Inc.

First published February 1994¹
Updated July 1999²

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EXECUTIVE SUMMARY

Thrombolytic therapy improves survival following acute myocardial infarction. This paper addresses selection of the most appropriate thrombolytic agent, the most effective adjuvant therapy and the patient populations most likely to benefit.

The thrombolytics which are currently available in Australia are streptokinase, urokinase and the tissue plasminogen activators alteplase (tPA) and reteplase (rtPA). Streptokinase, alteplase and reteplase have general marketing approval for thrombolysis following acute myocardial infarction.

The New South Wales Therapeutic Assessment Group recommends that:

1. Thrombolytic therapy should be offered to patients with acute myocardial infarction presenting within 12 hours of the onset of symptoms.
2. Aspirin should be used in all patients following acute myocardial infarction.
3. Tissue Plasminogen Activator (alteplase or reteplase), used in combination with intravenous heparin should be used for those who present less than 12 hours after symptom onset and have had streptokinase previously.
4. Alteplase (tPA) or reteplase (rtPA), used in combination with intravenous heparin may be considered for patients aged <75 years who present within 4 hours of the onset of symptoms and have definite ECG evidence of evolving anterior myocardial infarction or bundle branch block. The mortality advantage (over SK) for this sub-group of patients is up to 2% but at significantly higher cost. The decision to recommend use of alteplase or reteplase in this sub-group, therefore should be made by individual drug and therapeutics committees.
5. Streptokinase should be used in other patients presenting later than 4 hours but within 12 hours of the onset of symptoms.
6. Immediate Coronary Angioplasty may be preferred in patients with a contraindication to thrombolytic therapy, high risk patients with evolving infarction and in patients with cardiogenic shock or sustained hypotension.

1 INTRODUCTION

Thrombolytic therapy has been shown to significantly improve left ventricular function and survival following acute myocardial infarction. Because of questions of which thrombolytic is most effective, the potentially large numbers of patients and the cost differential between individual agents, the

NSW Therapeutic Assessment Group has produced this statement in consultation with clinicians from teaching hospitals in NSW. The paper will address the issues of which thrombolytic agent is preferred, optimal adjuvant therapy and appropriate patient populations.

2 BACKGROUND AND CLINICAL TRIALS

The thrombolytics which are currently available in Australia are streptokinase, urokinase and the tissue plasminogen activators alteplase (tPA) and reteplase (rtPA). Streptokinase, alteplase and reteplase have general marketing approval in Australia for thrombolysis following acute myocardial infarction.

The thrombolytic agents activate plasminogen to plasmin which results in fibrinolysis and depletion of circulating fibrinogen, factor V and factor VIII.

The goals of thrombolytic therapy are to establish and maintain patency of the infarct-related coronary artery. Clinical outcomes may include a reduction in infarct size, preservation of left ventricular function and reduction in mortality following acute myocardial infarction.

2.1 Placebo Controlled Trials

Placebo-controlled trials of thrombolytic agents demonstrated improved survival with streptokinase¹⁻⁴ or tPA⁵ which persisted for up to one year. The relative reduction in mortality was of the order of approximately 20% (in absolute terms, approximately 25 lives saved per 1000 patients treated).

2.2 Streptokinase versus Alteplase

2.2.1 Gissi-2

The first of the large comparative trials of streptokinase and tPA was the second study of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2).⁶ This was a multicentre open trial which randomised 12,490 patients with myocardial infarction, presenting within 6 hours, to receive streptokinase (1.5MU) alone, streptokinase plus heparin (12,500 units sci bd commenced 12 hours after streptokinase), tPA (100mg over 3hours) alone or tPA plus heparin (12,500 units sci bd commenced 12 hours after tPA). The study end-point was a combined estimate of death plus severe left ventricular damage, but no difference was found in any of the four treatment groups. The total percentage of reported endpoint events was 23.1%, 22.5%, 22.7% and

22.9% for the tPA, streptokinase, heparin and no heparin groups, respectively. The incidence of major bleeds was significantly higher in the streptokinase and heparin treated patients but the incidence of stroke was similar in all groups.

2.2.2 Isis-3

The Third International Study of Infarct Survival (ISIS -3)⁷ was designed to directly assess the balance between the benefits and risks of different antithrombotic regimens and different fibrinolytic regimens. A total of 41,299 patients with acute myocardial infarction, presenting within 24 hours of symptom onset, were randomised to receive streptokinase (1.5MU infused over 1 hour), tissue plasminogen activator (alteplase 0.60MU/kg infused over 4 hours) or anisoylated plasminogen-streptokinase activator complex (APSAC, "Eminase", 30 units over 3 minutes). All patients received aspirin, and half of all patients were randomly allocated to receive calcium heparin (12,500 units sc bid, commencing at 4 hours, for 7 days) in addition to aspirin. Streptokinase caused less hypersensitivity (3.6% vs 5.1%, $p < 0.0001$) and cerebral haemorrhage (0.24% vs 0.55%, $p < 0.0001$) than APSAC with no reported differences in the incidence of re-infarction or other clinical events. When compared with tPA, streptokinase showed a higher incidence of allergic reactions (3.6% vs 0.8%, $p < 0.00001$), and hypotension (11.8% vs 7.1%, $p < 0.00001$), but a lower incidence of total stroke (1.04% vs 1.39% $p < 0.01$). Re-infarctions were recorded in hospital significantly less commonly in patients receiving tPA than streptokinase (2.74% vs 3.47%, $p < 0.02$), but no significant difference was reported in mortality or other clinical events for the 2 groups. The addition of heparin was associated with a higher incidence of major bleeds compared with aspirin alone (1% vs 0.8%, $p < 0.01$), but with no effect on 35-day mortality (10.3% vs 10.6%).

2.2.3 Gusto

Both GISSI-2 and ISIS-3 were criticised because intravenous heparin was not routinely administered. The aim of the Global Utilisation of Streptokinase or tPA for Occluded Coronary Arteries (GUSTO) trial⁸⁻¹⁰ was to assess the effect of tPA, streptokinase or a combination of both on survival. GUSTO enrolled 41,021 patients, presenting with acute myocardial infarction within 6 hours of symptom onset, to randomly receive one of four treatments: "accelerated" tPA

(Genentech; 15mg bolus, 0.75mg/kg over 30 minutes not to exceed 50mg, and 0.5mg/kg up to 35mg, over 60 minutes) plus intravenous heparin; tPA-streptokinase (1mg/kg tPA over 60 minutes, not to exceed 90mg, 10% given as a bolus and 1 million units streptokinase over 60 minutes) and intravenous heparin; streptokinase (1.5 million units over 60 minutes) plus subcutaneous heparin, and streptokinase (1.5 million units over 60 minutes) plus intravenous heparin. The 30-day mortality figures were 6.3% for accelerated tPA, 7.0% for tPA-streptokinase combination, 7.2% for streptokinase and subcutaneous heparin and 7.4% for streptokinase and intravenous heparin. The accelerated tPA regimen saved significantly more lives than the comparators, although it was associated with a higher incidence of haemorrhagic stroke than streptokinase (0.72% vs 0.52%). Since approximately half the patients suffering haemorrhagic stroke died and most of the survivors had permanent neurological sequelae, some commentators have proposed a "net clinical benefit" for accelerated tPA of approximately 9 per 1000 patients treated. (Ten fewer deaths, at a cost of one disabling stroke.) This issue is discussed further in a subsequent section.

The differential benefit of accelerated tPA therapy over the other thrombolytic modalities was greatest when treatment was given early, and in fact lost significance beyond 4 hours from the onset of pain^{9,10}. The actual mortality rates for those treated with tPA or streptokinase respectively were 4.3% and 5.4% within 2 hours of symptom onset, 5.5% and 6.7% within 2-4 hours, 8.9% and 9.3% within 4-6 hours and 10.4% and 8.3% if treated more than 6 hours after symptom onset.¹⁰

Further analysis of the GUSTO data shows that the differential benefit for accelerated tPA over the other treatment modalities was greater for anterior than non-anterior infarctions (accelerated tPA vs combined streptokinase groups: mortality for anterior infarcts, 8.6% vs 10.5% and for "other" infarcts 4.7% vs 5.3%), but apart from this, was remarkably consistent across various subgroups.

Data from a sub-study of GUSTO in which patients underwent early invasive studies confirm that the accelerated tPA regimen led to faster opening of the infarct related artery than did the other regimens. The potential benefit of this was no doubt enhanced by the fact that patients were treated somewhat earlier in GUSTO than in previous studies such as ISIS-3 and GISSI-2. Twenty five percent had actually started treatment within 2 hours from the onset of pain and 77% within 4 hours. Since the curve relating myocardial cell death to time from coronary artery occlusion in humans is steepest within the first 3 hours and then tends to plateau, earlier treatment time would tend to accentuate any difference in speed of action between thrombolytic regimens. This could therefore in part explain why ISIS-3 and GISSI-2 failed to show a significant difference between tPA and streptokinase. Other possible factors are the universal use of intravenous heparin tending to maximise the advantage gained from tPA and minimise the possibly greater tendency to reocclusion with this short acting agent and the accelerated regimen employed in the administration of tPA in GUSTO compared to earlier trials.

Mention should also be made of the fact that while overall, accelerated tPA was associated with the lowest mortality, sub-group analysis of the approximately 18,000 patients treated outside the United States shows the lowest mortality in the group who receive the combination of tPA and streptokinase. While such retrospective sub-group analysis is not strictly valid, it does give rise to questions, particularly when the sub-group is so large. It may be partially ascribed to chance, but another factor which should be noted is that the early coronary angioplasty rate in the United States was approximately 30%, compared to approximately 10% elsewhere. In other words, an alternative interpretation of the GUSTO data is that a combination of accelerated tPA and, where indicated clinically, aggressive early invasive investigation and angioplasty is superior to other treatment regimens. In either case, one should not lose sight of the fact that in both the patients treated within the US and those treated outside, those given tPA in one regimen or the other did better than those not given tPA.

Consideration also should be given to the most feared complication of thrombolysis, cerebral haemorrhage. Good data are available from GUSTO as 93% of 589 patients who had a stroke had either a CT scan or a postmortem investigation. Primary cerebral haemorrhage occurred in 0.49% of those given streptokinase and subcutaneous heparin, 0.54% given streptokinase and intravenous heparin, 0.72% of those given accelerated tPA and 0.94% of those given tPA plus streptokinase. Of the 589 patients suffering from stroke, 44% died and approximately one-quarter were permanently disabled. The mortality rate in those for whom cerebral haemorrhage was the cause of their stroke was approximately 60%. As expected the rate of stroke increased with age and was also nearly twice

as high in women as in men, suggesting that some dose adjustment for sex as well as for body weight should be considered in the future.

Analysis of stroke incidence in previous large scale trials of thrombolytic therapy has suggested that the excess stroke rate for tPA is exclusively accounted for by patients over 65 years of age. For unknown reasons, the incidence of cerebral haemorrhage associated with tPA therapy appears to rise progressively beyond the age of 65 and particularly beyond the age of 75, but remains essentially constant across the age range for streptokinase.

2.3 Reteplase

Reteplase is a deletion mutant of wild-type tissue plasminogen activator. It's half life allows administration as a bolus injection¹¹. Two angiographic studies, the Reteplase Angiographic Phase 2 International Dose-finding study (RAPID I; 606 patients)¹² and the Reteplase vs Alteplase Patency Investigation During Acute Myocardial Infarction study (RAPID II; 324 patients)¹³, showed that double bolus dosing of reteplase (10units followed by 10units thirty minutes later) produced significantly higher coronary artery patency rates than accelerated alteplase (100mg as a 1.5 hour infusion). In 5,986 patients randomised to either reteplase (10units plus 10units) or streptokinase (1.5MU) in the International Joint Efficacy Comparison of Thrombolytics trial (INJECT), 35 day survival rate was equivalent in the two groups and there was no difference in complications.¹⁴

The GUSTO III trial¹⁵ randomised 15,059 patients presenting within 6 hours after the onset of symptoms in a 2:1 ratio to receive reteplase (10units bolus plus 10units bolus 30 minutes later) or alteplase (100mg over 90 minutes). The mortality rate at 30 days was 7.47% for reteplase and 7.24% for alteplase ($p = 0.54$; odds ratio, 1.03; 95% confidence interval, 0.91 to 1.18). The 95% confidence interval for the absolute difference in mortality rates was -1.1 to 0.66 %. Stroke occurred in 1.64% of patients treated with reteplase and in 1.79% of those treated with alteplase ($p = 0.5$). The rates of combined end point of death or nonfatal disabling stroke were 7.89% for reteplase and 7.91% for alteplase ($p = 0.97$; odds ratio, 1.0; 95% confidence interval, 0.88 to 1.13). There was therefore no survival benefit for reteplase, but also no significant difference between reteplase and alteplase in terms of efficacy or complications.

Reteplase does, however, offer a simpler administration schedule than alteplase which may permit earlier initiation of thrombolysis with fewer dosing errors.¹⁶

2.4 Urokinase

Smaller studies have compared urokinase with streptokinase. Intracoronary urokinase compared with streptokinase achieved similar coronary reperfusion rates (60% vs 57%) but had a lower incidence of bleeding complications (11% vs 29%).¹⁷ Combinations of urokinase and tPA did not improve patency or re-occlusion rates when compared with tPA alone.¹⁸ In the absence of large scale studies such as those discussed above for tPA and streptokinase, there seems no good reason to recommend the routine use of urokinase in acute myocardial infarction.

2.5 Angioplasty

Recent studies have shown immediate coronary angioplasty to result in no better myocardial salvage¹⁹ but a higher rate of patency, better left ventricular function²¹, less recurrent myocardial ischaemia and infarction^{20,21} and possibly a reduced mortality²¹ compared to thrombolytic therapy. The strategy of primary angioplasty will always be limited by restricted access to this procedure, and it will not be a practical option for the majority of patients with acute myocardial infarction in New South Wales.²² Where appropriate facilities are available, direct angioplasty should be considered for patients unsuitable for thrombolysis.

2.6 Aspirin

The beneficial effects of aspirin in combination with thrombolytic therapy in acute myocardial infarction were demonstrated in ISIS-2⁴. When compared with placebo, the aspirin group had a decrease in mortality (8% vs 13.2%), re-infarctions (1.8% vs 2.9%) and strokes (0.6% vs 1.1%) at 5 weeks. This difference remained significant at 15 months. Aspirin was used as part of the routine management in all arms of the GUSTO study and should certainly form part of any routine myocardial infarction protocol in New South Wales.

2.7 Heparin

The additional use of subcutaneous heparin was found to have no overall effect on survival in ISIS-3⁷ and GISSI-2⁶ and to be associated with a slightly higher incidence of haemorrhage. Angiographic studies do not support the widespread use of intravenous heparin with streptokinase.²³ GUSTO provides very little further insight into this issue. There appear to be no differences between patients given streptokinase with either intravenous or subcutaneous heparin and there was no arm of the study in which streptokinase was given without heparin. In the absence of data to the contrary, it is probably reasonable to continue using subcutaneous heparin 12,500 units bd when administering streptokinase, although it should be borne in mind that the evidence supporting this is fairly slim. Since GUSTO contained no treatment arm where tPA was given without intravenous heparin and since the tPA regimen was different from that used with subcutaneous heparin in earlier trials, it is still possible to argue that the issue of adjuvant therapy with heparin in patients given tPA is unresolved. Nonetheless, the best data that we have, combined with theoretical considerations, suggest that if tPA is administered intravenous heparin should also be administered.

3 SIDE EFFECTS

A study which compared the frequency and severity of side effects caused by streptokinase and tPA²⁴ reported an overall incidence of side effects of 41.7% with streptokinase and 13.3% for tPA. Minor bleeding (13.9% vs 7.8%), hypotension (22.2% vs 5.6%), and allergic reactions (5-6% vs 0) were all more common in the streptokinase group than in patients treated with tPA.

3.1 Antibody Formation

Streptokinase causes the formation of antibodies which are responsible for the allergic reactions reported in 4-5% of patients. Prophylactic steroids do not appear to be beneficial.⁴ Raised IgG levels may persist for at least 4 years. It is common practice at present not to repeat streptokinase administration within 12 months of an earlier administration. This purely arbitrary time limit was largely derived from earlier studies suggesting persistent antibody levels at 1 year. Since subsequent studies from the same and other groups have suggested that the antibody levels remain relatively constant for another 3-4 years at least, one could argue quite reasonably that streptokinase administration should not be repeated for at least 4-5 years and possibly beyond. The main problem from a clinical point of view is not allergy but the possibility of inefficacy due to neutralisation by the antibodies. Since the effect on efficacy of any circulating antibodies is impossible to ascertain reliably in an individual patient, there is a very strong case to be made for using tPA in all patients who have previously received streptokinase.

3.2 Risk of Haemorrhage

The risk of intracranial haemorrhage is increased with thrombolytic therapy. As noted above, both GISSI-2 and ISIS-3 showed that total stroke and suspected intracranial haemorrhage were more common with r-tPA than streptokinase. The use of heparin further increases the risk of intracranial haemorrhage. Patients over 65 are thought to be at increased risk.

4 RECOMMENDATIONS FOR USE

The NSW Therapeutic Assessment Group recommends that thrombolytic therapy be offered for patients with acute myocardial infarction presenting within 12 hours of the onset of symptoms. A minority of patients will be more appropriately treated by immediate coronary angioplasty if available (see 4.5 below).

4.1 Aspirin

Aspirin is recommended in all patients with acute myocardial infarction.

4.2 Alteplase

In the interest of cost containment the recommendations given below limit the use of tPA to those subgroups of patients most likely to benefit and least likely to suffer cerebral haemorrhage from this agent. As the absolute advantage of using tPA is small and the cost relatively high, Drug and

Therapeutics Committees may wish to contract or extend recommendations for tPA use in their institution.

Tissue plasminogen activator in the "accelerated" regimen employed in the GUSTO study in combination with intravenous heparin can be supported for patients who:

4.2.1 Are of any age, present within 12 hours of the onset of symptoms and have received streptokinase previously.

4.2.2 Are under the age of 75, present within 4 hours of the onset of symptoms and have definite ECG evidence of evolving anterior myocardial infarction or bundle branch block. (Extension beyond age 75 is not recommended as available data suggest a prohibitive level of cerebral haemorrhage with tPA beyond age 75).

In such subjects, the GUSTO data suggest an absolute benefit of tPA over streptokinase of approximately 20 lives saved per thousand patients treated.

4.2.3 Some Drug and Therapeutic Committees may wish to consider the use of tPA in one or more of the following groups where the absolute mortality advantage over streptokinase (as reported by GUSTO) is $\leq 1\%$:

- Patients with large inferior infarcts.
- Patients presenting between 4 and 6 hours after the onset of symptoms.

4.3 Reteplase

Reteplase may be used as an alternative to alteplase in the indications described in 4.2. The recommended dose is 10 units by intravenous bolus, followed by 10 units 30 minutes later.

4.4 Streptokinase

Streptokinase is recommended in patients with acute myocardial infarction presenting less than 12 hours after the onset of symptoms, who have not received streptokinase previously.

Patients presenting between 12 and 24 hours should be considered for streptokinase therapy, but available evidence suggests that this should only be administered if there is good reason to believe that ischaemia and myocardial necrosis are ongoing, for example continuing pain and ST segment elevation.

The recommended dose is 1.5Mu over 60 minutes, with subcutaneous heparin 12,500 units bd.

4.5 Immediate Coronary Angioplasty

This is only a practical option where available on an urgent basis. It is probably the preferred form of therapy for patients presenting with cardiogenic shock. If the patient cannot be taken immediately to the catheterisation laboratory, thrombolytic therapy should normally be given in any case.

Consideration may then be given to "rescue" angioplasty if the clinical situation persists or continues to deteriorate.

5 FINANCIAL CONSIDERATIONS

Several economic analyses of thrombolytic therapy have been published.²⁶⁻²⁹ A cost-utility study of anistreplase (APSAC)²⁷ found that the cost per quality-adjusted life year (QALY) was \$3000 - \$4000 and this cost was not significantly affected by early or late treatment of acute myocardial infarction. A cost effectiveness study of streptokinase in elderly patients (>75 years) found that the cost per life year saved was approximately \$20,000 - \$50,000.²⁵ This was considered to be a cost-effective therapy.

The cost of treatment of one patient with alteplase (\$1893) and reteplase (\$1921) is considerably higher than with streptokinase (\$167). An economic analysis of the potential incremental benefits of alteplase versus streptokinase for treatment of acute myocardial infarction found that if alteplase achieves a 1% short term mortality advantage, the cost per life year gained would be \$58,600.²⁸ The overall mortality advantage found in the GUSTO trial for patients who presented early was approximately 1% after adverse events were considered.

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Acknowledgments: Members of NSW Therapeutic Assessment Group; Dr Nelson, Royal North Shore Hospital; Dr Charles Pawsey, Concord Hospital; Dr Ben Freedman, Royal Prince Alfred Hospital; Ms Anne Steffensen, Prince of Wales Hospital.