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# **THROMBOLYSIS FOLLOWING ACUTE MYOCARDIAL INFARCTION**

**A Position Statement of the NSW Therapeutic Assessment Group Inc.**

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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 marketed in Australia are streptokinase, and the tissue plasminogen activators alteplase (tPA), reteplase (rtPA) and tenecteplase (TNK), all of which 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. Alteplase, reteplase or tenecteplase, 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.

Based on data comparing alteplase and streptokinase (SK), the mortality advantage (tPA over SK), for this sub-group of patients is up to 2% (absolute), but at significantly higher cost. The novel plasminogen activators reteplase and tenecteplase have been shown in clinical trials to be equivalent to alteplase and therefore the decision to recommend use of alteplase, reteplase or tenecteplase in this sub-group of patients should be made by individual drug and therapeutics committees.

4. Streptokinase should be the thrombolytic of first choice in other patients presenting later than 4 hours but within 12 hours of the onset of symptoms and who have not previously received SK..
5. Immediate Coronary Angioplasty (where available), may be preferred in patients with a contraindication to thrombolytic therapy, and in high risk patients with evolving infarction. It is the treatment of choice in patients with cardiogenic shock or sustained hypotension due to acute myocardial infarction.

## **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 (SK), and the tissue plasminogen activators alteplase (tPA), reteplase (rtPA) and tenecteplase (TNK), all of which have general marketing approval in Australia for thrombolysis following acute myocardial infarction. Urokinase is no longer marketed in Australia but is available for treatment of individual patients via the Special Access Scheme.

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 streptokinase<sup>1-4</sup> or alteplase<sup>5</sup> 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 alteplase was the second study of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2).<sup>6</sup> 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 sc bd commenced 12 hours after streptokinase), alteplase (100mg over 3hours) alone or alteplase plus

heparin (12,500 units sc bd commenced 12 hours after alteplase). 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 alteplase, 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)<sup>7</sup> 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 bd, 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 tissue plasminogen activator, 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 tissue plasminogen activator 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) trial<sup>8-10</sup> was to assess the effect of alteplase (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<sup>9,10</sup>. 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.<sup>10</sup>

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 alteplase 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 (rt-PA) is a deletion mutant of wild-type tissue plasminogen activator. Its half life allows administration as a bolus injection<sup>11</sup>. Two angiographic studies, the Reteplase Angiographic Phase 2 International Dose-finding study (RAPID I; 606 patients)<sup>12</sup> and the Reteplase vs Alteplase Patency Investigation During Acute Myocardial Infarction study (RAPID II; 324 patients)<sup>13</sup>, 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.<sup>14</sup>

The GUSTO III trial<sup>15</sup> 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.<sup>16</sup>

### **2.4 Tenecteplase**

Tenecteplase (TNK) is a genetically engineered variant of reteplase. Modification of amino acids is believed to be responsible for the increased fibrin specificity compared with alteplase and reteplase<sup>17-19</sup> and also the improved resistance to inactivation by plasminogen activator inhibitor-1 (PAI 1).

Efficacy for clot lysis of single bolus administration of tenecteplase was studied in the TIMI 10A and TIMI 10B (Thrombolysis in Myocardial Infarction) trials<sup>20,21</sup>, and safety assessed in the ASSENT-1<sup>22</sup> study (Assessment of Safety of a New Thrombolytic).

The ASSENT II trial<sup>23</sup> was a phase III randomised double blind trial comparing 30 day mortality rates in approximately 16500 patients with MI confirmed by ECG. Patients were treated within 6 hours of onset of symptoms with either a single bolus dose of tenecteplase (30-50mg according to bodyweight) or an accelerated infusion of alteplase (up to 100mg over 90minutes). The mortality rates at 30 days were 6.18% for tenecteplase and 6.15% for alteplase. Major bleeding was significantly lower in patients receiving tenecteplase compared to alteplase (4.68% vs 5.94%;  $p < 0.01$ ). Thus tenecteplase was shown to be therapeutically equivalent to alteplase in terms of survival benefit, but associated with fewer bleeding complications.

The reduced plasma clearance and longer half life of tenecteplase compared to alteplase allow for more convenient dosing; tenecteplase could be given in the community setting.

## **2.5 Urokinase**

Urokinase is no longer marketed in Australia. However, it is still available for treatment of individual patients via the Special Access Scheme. Small 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%).<sup>24</sup> Combinations of urokinase and alteplase did not improve patency or re-occlusion rates when compared with alteplase alone.<sup>25</sup> In the absence of large scale studies to confirm these results, there is no good reason to recommend the use of urokinase in acute myocardial infarction.

## **2.6 Angioplasty**

Recent studies have shown immediate coronary angioplasty to result in no better myocardial salvage<sup>26</sup> but a higher rate of patency, better left ventricular function<sup>27</sup>, less recurrent myocardial ischaemia and infarction<sup>27,28</sup> and possibly a reduced mortality<sup>28</sup> 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.<sup>29</sup> Where appropriate facilities are available, direct angioplasty should be considered for patients unsuitable for thrombolysis.

## **2.7 Aspirin**

The beneficial effects of aspirin in combination with thrombolytic therapy in acute myocardial infarction were demonstrated in ISIS-2<sup>4</sup>. 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.

## **2.8 Heparin**

The additional use of subcutaneous heparin was found to have no overall effect on survival in ISIS-3<sup>7</sup> and GISSI-2<sup>6</sup> and to be associated with a slightly higher incidence of haemorrhage. Angiographic studies do not support the widespread use of intravenous heparin with streptokinase.<sup>30</sup> 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 alteplase was given without intravenous heparin and since the alteplase 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 alteplase is unresolved. Nonetheless, the best data that we have, combined with theoretical considerations, suggest that if alteplase is administered, intravenous heparin should also be administered. This situation also applies to reteplase and tenecteplase.

Recent data suggest lower initial doses of heparin may be more appropriate. The ACC/AHA guidelines<sup>31</sup> recommend an initial bolus of unfractionated heparin of 60 U/ kg to a maximum of 4,000 U and an initial infusion of 12U/ kg per hour (to a maximum of 1000 U). An APTT of 50 to 70 seconds should be obtained by regular monitoring and appropriate adjustment of heparin infusion.

There is little data for the use of low molecular weight heparins (LMWH), with fibrinolytic therapy. The HART II study<sup>32</sup> showed that enoxaparin with alteplase produced equal patency rates and lower reocclusion rates than standard unfractionated heparin, with no adverse safety profile.

## **3 ADVERSE EFFECTS**

A study which compared the frequency and severity of side effects caused by streptokinase and alteplase<sup>33</sup> reported an overall incidence of side effects of 41.7% with streptokinase and 13.3% for alteplase. 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 alteplase.

### **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.<sup>4</sup> 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 a thrombolytic other than streptokinase in all patients who have previously received it .

### **3.2 Risk of Haemorrhage**

The risk of intracranial haemorrhage (ICH) 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 alteplase than streptokinase. The use of heparin further increases the risk of intracranial haemorrhage. Patients over 65 are thought to be at increased risk.

In the ASSENT II study<sup>23</sup>, the rate of ICH with tenecteplase was 0.4% in patients less than 65 years, 1.6% for those 65-74 years and 1.7% for patients over 75 years. Overall rates of ICH were similar for tenecteplase (0.93%) and alteplase (0.94%). In the GUSTO III trial, intracranial haemorrhage rates were 0.91% for reteplase and 0.87% for alteplase .

## **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 Adjunctive therapy**

#### **4.1.1 Aspirin**

Aspirin is recommended in all patients with acute myocardial infarction.

#### **4.1.2 Heparin**

In Australia, unfractionated heparin by infusion is currently advised for use with alteplase, tenecteplase and reteplase (but not for streptokinase - see 4.2). The National Heart Foundation (Aust) guidelines<sup>34</sup> recommend an initial bolus of unfractionated heparin of 60 U/ kg (maximum 4,000 U) and an initial infusion of 12U/ kg per hour (maximum 1000U). An APTT of 50-70 seconds should be obtained by regular monitoring and appropriate adjustment of heparin infusion.

### **4.2 Fibrinolytic agents**

The choice of fibrinolytic agent will depend on patient characteristics, particularly age, infarct size, convenience and cost. The new bolus fibrinolytic agents offer great convenience and widen the potential sites of fibrinolytic delivery eg home, ambulance, and smaller hospitals.

Streptokinase is recommended in patients with acute myocardial infarction presenting between four and 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 1.5 million units over 60 minutes, with subcutaneous heparin 12,500 units bd.

In the interest of cost containment the recommendations given below limit the use of the tissue plasminogen activators- alteplase, reteplase and tenecteplase- to those subgroups of patients most likely to benefit and least likely to suffer cerebral haemorrhage from these agents. As the absolute advantage of using the tissue plasminogen activators is small and the cost relatively high, Drug and Therapeutics Committees may wish to contract or extend recommendations for use of these agents in their institution.

Alteplase (in the "accelerated" regimen employed in the GUSTO study), reteplase (10 units by intravenous bolus, followed by 10 units 30 minutes later) or tenecteplase (6000–10,000 IU depending on bodyweight<sup>35</sup>) in combination with intravenous heparin can be supported for patients who:

- Are of any age, present within 12 hours of the onset of symptoms and have received streptokinase previously.
- 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 beyond age 75).

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

- Some Drug and Therapeutic Committees may wish to consider the use of tissue plasminogen activators in one or more of the following groups where the absolute mortality advantage over streptokinase (as reported by GUSTO) is  $<$  or  $=$  to 1%:
  - Patients with large inferior infarcts.
  - Patients presenting between 4 and 6 hours after the onset of symptoms.

### **4.3 Immediate Coronary Angioplasty**

This is only a practical option in situations where it is available on an urgent basis. It is 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.<sup>36-39</sup> A cost-utility study of anistreplase (APSAC)<sup>37</sup> 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.<sup>40</sup> This was considered to be a cost-effective therapy.

The cost of treatment of one patient with alteplase (\$1863) and reteplase (\$1921) and tenecteplase (\$1998 for 50mg) 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.<sup>28</sup> 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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