Tissue plasminogen activator was cost-effective compared to streptokinase in only selected patients with acute myocardial infarction


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Tissue plasminogen activator (t-PA) was compared with streptokinase in the treatment of acute myocardial infarction (MI).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population was obtained from patients enrolled in the Thrombolytic Predictive Instrument (TPI) clinical trial. The patients were enrolled from a diverse sample of 28 US hospitals from August 1995 to January 1997. A total of 1,032 emergency department patients with confirmed acute MI were treated with thrombolytic therapy. Complete data to support model predictions were available for 921 of these patients.

Setting
The study setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2002. The price year was 1999.

Source of effectiveness data
The analysis was based on the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial and its subsequent analysis. However, data from other trials, such as the TPI trial, were used in the analysis.

Modelling
To predict patient-specific incremental benefits of t-PA therapy, the authors used a model that assumed that the incremental benefits and risks of t-PA (compared with streptokinase) across individuals were proportional to those of thrombolytic therapy generally. The patient-specific benefit of thrombolytics was estimated from the TPI trial. A derived logistic regression model was then used to predict the risk of thrombolytic-related intracranial haemorrhage.

For the benefits predicted by the model to yield results consistent with the incremental benefit of t-PA compared with streptokinase as found in the GUSTO trial, the authors multiplied each patient's TPI-predicted mortality benefit by a constant. This related the model predictions to the actual observed benefit in the GUSTO trial participants. This constant was the ratio of the TPI-predicted benefit of thrombolytics (compared with placebo) and the incremental
observed benefit of t-PA (compared with streptokinase). Similarly, the predicted thrombolytic-related intracranial haemorrhage risk was standardised to reflect the incremental risk from t-PA observed in the GUSTO trial.

To estimate each patient's predicted composite incremental benefit from t-PA, the authors subtracted the patient's incremental risk of intracranial haemorrhage from the patient's incremental mortality benefit.

A life-expectancy function was estimated with a Markov model, using age- and gender-specific mortality from the National Centre for Health Statistics and an excess mortality of 2% to account for disease-specific mortality.

**Outcomes assessed in the review**
The outcomes assessed were:

- the incremental mortality benefit of t-PA relative to predicted mortality benefit from thrombolytic therapy;
- the incremental intracranial haemorrhage risk with t-PA relative to the predicted thrombolytic-related intracranial haemorrhage risk;
- the incremental heart failure benefit with t-PA relative to predicted mortality from thrombolytic therapy;
- the utility of surviving acute MI;
- the disutility of intracranial haemorrhage; and
- the disutility of surviving acute MI with heart failure.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
The analysis was based on the GUSTO trial and its subsequent analysis. However, data from other trials, such as the TPI trial, were used in the analysis.

**Methods of combining primary studies**
Not applicable.

**Investigation of differences between primary studies**
Not applicable.
Results of the review
In the base-case scenario, the incremental mortality benefit of t-PA relative to predicted mortality benefit from thrombolytic therapy was 0.1473.

The incremental intracranial haemorrhage risk with t-PA relative to the predicted thrombolytic-related intracranial haemorrhage risk was 0.1697.

The utility of surviving acute MI was 1.0.

The disutility of intracranial haemorrhage was -1.0.

The disutility of surviving acute MI with heart failure was 0.

Measure of benefits used in the economic analysis
The measure of benefits used was the life-years saved (LYS).

Direct costs
The resource quantities and the costs were not reported separately. The direct costs of the hospital were included in the analysis. The costs were obtained from an economic sub-study of the GUSTO trial (Mark et al. 1995, see 'Other Publications of Related Interest' below for bibliographic details). To estimate the average total cost of t-PA therapy, the authors updated costs to 1999 dollars and added it to the difference in the average wholesale prices of the drugs. Consistent with the prior cost-effectiveness analysis, the authors assumed that the average cost was the same across patients and that there were no differences in cost between the two groups after the first year. Discounting was appropriate, as the costs were incurred over the lifetime of the patient, and the future costs were discounted at 3% per annum. The study reported the incremental costs. The price year was 1999.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
In sensitivity analyses, the authors investigated the effect of increasing the discount rate to 5% and of excluding intracranial haemorrhage from the analysis (i.e. all patients who survived were assigned a utility of 1.0 denoting perfect health, whether or not they sustained thrombolytic-related intracranial haemorrhage).

The authors also investigated the effect of including the potential benefits of t-PA on the prevention of heart failure. They also explored the distribution of the effectiveness and cost-effectiveness at a hypothetical upper-limit of t-PA efficacy, by assuming the average benefit found in the GUSTO trial, applied to this population, regardless of differences in the baseline characteristics.

The incremental long-term costs of therapy were also estimated in the sensitivity analysis, by including estimates of the long-term costs for intracranial haemorrhage and heart failure.
Estimated benefits used in the economic analysis
The average incremental expected mortality benefit from t-PA over streptokinase was 0.73 percentage points (i.e. 7.3 in 1,000 patients). Compared with the mean, most of the patients had substantially less predicted benefit; the median mortality benefit of 0.48% points was only two thirds of the mean. Further, 61% of t-PA's incremental mortality benefit accrued to the top 25% patients. Only 4% of the mortality benefit accrued to patients in the lowest quartile.

Cost results
The incremental cost for t-PA over streptokinase was $2,208.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the extra costs required for every LYS). The incremental cost-effectiveness ratio was $40,140 per LYS when t-PA was used over streptokinase. However, only 44% of patients obtained sufficient benefit to have a marginal cost-effectiveness of less than $50,000, while only 62% of them had a cost-effectiveness ratio of less than $100,000.

When the study sample was assumed to achieve an overall benefit to that found in the GUSTO trial, the average incremental cost-effectiveness of t-PA was $28,755 per LYS.

Under all conditions in the sensitivity analyses, the incremental cost-effectiveness fell between $33,000 and $47,000 per LYS. The model was insensitive to changes, such as including heart failure and haemorrhage into the model, as roughly half of all patients remained below the $50,000 threshold, and two thirds were below $100,000.

Authors' conclusions
For many patients meeting clinical criteria for thrombolytics, tissue plasminogen activator (t-PA) is clearly not cost-effective and some patients are more likely to be harmed than to benefit. However, t-PA was so effective and cost-effective in selected patients that the use of streptokinase in such patients was difficult to justify.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for using streptokinase as the comparator, it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
Based on a multivariate model, the authors compared t-PA with streptokinase on 921 consecutive patients from the TPI clinical trial. The model was then populated using data from the GUSTO trial, a randomised controlled trial. The authors provided very few details of these two trials and their own model, making the interpretation of the model difficult to understand.

Validity of estimate of measure of benefit
Even though the authors derived utility values, the benefits used in the economic analysis were the LYS. It was unclear why the authors used disutility decrements, or what these values represented in the model.

Validity of estimate of costs
The authors updated the costs used in the cost-effectiveness analysis of the GUSTO trial. They provided very few details on the costs included in the analysis. Hence it is not possible to state whether all the relevant costs were included, which also limits the generalisability of the authors' results. A limited sensitivity analysis of the costs was undertaken, with the authors including further costs. As the costs were incurred over a long time, the future costs were appropriately discounted. The price year was reported, which will aid any future inflation exercises.
Other issues
The authors did not compare their findings with those from other studies, although they did mention in the introduction of the paper that the GUSTO trial found t-PA to compare favourably with other accepted therapies with a cost-effectiveness ratio of $33,000 per LYS. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors do not appear to have reported their results selectively, although a more detailed explanation of their model would have been desirable. The authors reported a number of further limitations to their study. First, there was no attempt to model patient-specific costs. Second, the study population was not nationally representative. Hence, extrapolations of clinical and economic benefits to the national level should be interpreted with caution. Third, the study provided no evidence that rational targeting would be feasible in actual practice.

Implications of the study
The authors reported that, relative to current practice, tailoring thrombolytic therapy could potentially save both money and lives.

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Other publications of related interest


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