Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke

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
Using tissue plasminogen activator (tPA) in the treatment of patients with acute stroke.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
Patients with acute ischemic stroke.

Setting
Hospital. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data were extracted from NINDS rt-PA Stroke Trial conducted between January 1991 and October 1994, the results of which were published in 1995. Clinical probabilities relating to the epidemiological course of events were obtained from studies published between 1982 and 1997. The utility values related to different discharge states were based on studies published in 1994 and 1995. The cost data were extracted from studies published between 1991 and 1996. The fiscal year was 1996.

Source of effectiveness data
Effectiveness data were derived from a single study and a review of the literature.

Link between effectiveness and cost data
Costing was mostly performed on the same patient sample as that used in the effectiveness analysis. It was performed retrospectively.

Study sample
Power calculations were used to determine the sample size in each of the two parts of the study. In part 1 (assessment of changes in neurologic deficits 24 hours after the onset of stroke) a total of 280 patients were required based on a power of 0.90 to identify a 24% difference between the groups, assuming a rate of 16% in outcome in the placebo group and an alpha level of 0.05. In part 2 (assessment of recovery from stroke) 360 patients were required based on a power of 0.95 to detect a difference of 20%. 312 patients were randomly assigned to each study group (total = 624). In part 1 of the study, there were 144 patients in the t-PA group with an average age of 67 (+/- 10) years and 147 in the placebo
group with an average age of 66 (+/- 11) years. The corresponding figures in part 2 of the study were 168 with an average age of 69 (+/- 12) years and 165 with an average age of 66 (+/- 13) years.

Study design
The study was a randomised, placebo-controlled trial. The number of centres involved in the study was not explicitly specified. The duration of the follow-up was 3 months. The effectiveness data for 1 patient in Part 1, and 4 patients in part 2 of the study, were missing. A permuted-block randomisation was used with stratification by clinical centre and time from the onset of stroke to the start of the treatment (0 to 90 or 91 to 180 minutes).

Analysis of effectiveness
The principle used in the analysis of effectiveness was intention to treat. The health outcome measures were early improvement (in part 1 of the study) defined as complete resolution of the neurologic deficit or an improvement from baseline in the score on the National Institute of Health Stroke Scale (NIHSS); the length of initial hospital stay; intracerebral haemorrhage (ICH); discharge disposition from initial hospitalisation; post-stroke disability states (measured by modified Rankin disability scale, Barthel index, and Glasgow scale) and mortality. The study groups were shown to be comparable in terms of all baseline features except for weight in part 1 of the study, and age and aspirin use in part 2. The effects on the global odds ratio of confounding variables (aspirin use, weight, age, clinical centre and time to treatment after the onset of stroke) were investigated.

Effectiveness results
In part 1 of the study, the t-PA group had an improvement rate of 47% (combined results) versus 39% in the placebo group (relative risk, 1.2 (1.0-1.4), p=0.06) at 24 hours after the onset of stroke. The global odds ratio for a favourable outcome in part 2 of the study was 1.7 (95% CI: 1.2 to 2.6) and p=0.008. According to the assessment scales, the patients in the t-PA group were at least 30% more likely to experience minimal or no disability at three months. The mean (standard deviation) length of initial hospital stay was 10.88 (10.04 ) days for the t-PA group versus 12.41 (11.1) days, (p=0.02). The ICH rate was 6.45% in the t-PA group versus 1% in the placebo group, (p<0.001). The t-PA group had a mortality rate (at three months) of 17% versus 21% in the placebo group. Discharge dispositions from initial hospitalisation to home, rehabilitation unit, and nursing home were 48%, 29%, and 7% in the t-PA group versus 36%, 37%, and 13%, respectively, in the placebo group, (p=0.002).

Clinical conclusions
Despite an increased incidence of symptomatic intracerebral haemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months.

Modelling
A Markov model was constructed to estimate the costs and benefits of the intervention relative to the comparator in the long run.

Outcomes assessed in the review
A literature review was carried out to identify the following outcomes: Stroke recurrence rate per year, recurrent stroke mortality, multiplier for age-specific mortality, discharge to nursing home from rehabilitation for patients aged 65 to 75 years and aged over 75 years. The review also assessed utility values for post-stroke disability states (measured by modified Rankin disability scale) including the states of no symptoms (Rankin 0), no significant disability (Rankin 1), minimal disability (Rankin 2), moderate disability (Rankin 3), moderate to severe disability (Rankin 4), severe disability (Rankin 5), and dead.

Study designs and other criteria for inclusion in the review
Not reported.
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
12 studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Stroke recurrence rate per year (low and high values in parentheses) was 0.052 (0.03, 0.08);
recurrent stroke mortality, 0.19 (0.1, 0.3);
multiplier for age-specific mortality, 2.67 (1.25, 4);
discharge to nursing home from rehab. for patients aged 65 to 75 years, 0.18 (0.13, 0.21);
discharge to nursing home from rehab for patients aged over 75 years, 0.32 (0.24, 0.34);
utility values for the states of no symptoms (Rankin 0), 0.90 (0.85, 0.95);
no significant disability (Rankin 1), 0.80 (0.70, 0.90);
minimal disability (Rankin 2), 0.46 (0.35, 0.65);
moderate disability (Rankin 3), 0.34 (0.2, 0.5);
moderate to severe disability (Rankin 4), 0.30 (0.12, 0.45);
severe disability (Rankin 5), -0.02 (-0.2, 0.2);
and dead, 0.00 (0.00, 0.00).

Based on an unpublished study it was assumed that the recurrent stroke rates were equal across all six disability states.

Measure of benefits used in the economic analysis
The benefit measures were the number of patients discharged to home, and the number of quality adjusted life years (QALYs) saved. The utility values were based on a patient preference survey.
**Direct costs**
Costs were discounted. Quantities were not systematically reported in detail separately from the costs. The cost items were reported separately. The cost analysis covered the costs of t-PA acquisition, physician for t-PA administration, initial hospitalisation, future hospitalization for stroke, nursing home, and rehabilitation. The perspective adopted in the cost analysis was that of a comprehensive health care system including acute through to long-term care facilities. The sources of cost data were a local survey and a literature review. The date of the price data was 1996. The cost analysis did not cover the costs of development of acute stroke teams and improving prehospital care, as these facilities were believed to belong, not specifically to t-PA, but to all acute treatments for both ischemic and haemorrhagic stroke.

**Indirect Costs**
Not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analysis and multiway stochastic sensitivity analysis using Monte Carlo simulations were performed on all parameters of the model. The results of threshold analyses were also reported.

**Estimated benefits used in the economic analysis**
151 patients were discharged to home in the t-PA group versus 112 in the placebo group, (p=0.002). The number of quality adjusted life years (QALYs) saved per 1,000 patients was 564 (3 to 850) over the 30 year time frame of the model.

**Cost results**
The discount rate was 5%. The total cost (acute plus long-term care) per 1,000 patients was $62,716,000 for the placebo approach versus $58,461 for the tPA approach, culminating in $4,255,000 saving (5th and 95th percentiles, $-13,022,000 to $531,000).

**Synthesis of costs and benefits**
Hospitalization cost per additional patient discharged home and cost per QALY gained were used as the measures of synthesis of costs and benefits. The value for the first measure amounted to $15,000 ($1,900 to $80,000) and a saving of $8,000 per QALY gained. The probabilistic sensitivity analysis demonstrated that the probability of a decrease in costs and increase in QALYs due to the use of t-PA was 0.93 and 0.94, respectively. One-way sensitivity analysis established the robustness of the results.

**Authors’ conclusions**
Treating acute ischemic stroke patients with t-PA within 3 hours of symptom onset improves functional outcome at 3 months and is likely to result in a net cost saving to the health care system.

**CRD COMMENTARY - Selection of comparators**
The reason for the choice of the comparator is clear.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness results is reasonably assured given the use of a randomised design.
Validity of estimate of costs
Quantities were not reported separately from the costs. However, adequate details of methods of cost estimation were given.

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Other publications of related interest

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