Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs

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
The use of thrombolytic treatment with intravenous recombinant tissue plasminogen activator (rt-PA), in addition to standard care, for acute ischaemic stroke patients.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The model was populated with data from the Lothian Stroke Register (LSR), Scotland (Wardlaw et al. 1998, see 'Other Publications of Related Interest' below for bibliographic details), because patients included in thrombolysis trials were highly selected and largely recruited from non-UK centres. LSR patients represented a "realistic" estimate of the types of patients who might be offered rt-PA within the NHS.

Setting
The setting was secondary care. The study was carried out in the UK, with emphasis on Scottish data.

Dates to which data relate
The effectiveness evidence for rt-PA was drawn from a 1998 review of the literature (Wardlaw et al. 2003, see 'Other Publications of Related Interest' below for bibliographic details). The authors performed literature searches to 2002 and did not identify any new trials to add to the review. Other health outcome data came from 1989 - 2000 (LSR). The resource data were obtained from LSR, a published model (Chambers et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details) and from the authors' hospital (Western General Hospital, Edinburgh; 1998 - 1999). The price year used was 1999/2000; medication costs were dated September 2000.

Source of effectiveness data
The effectiveness data came from a Cochrane systematic review.

Modelling
The authors constructed a decision-analysis model of the pathways followed by acute ischaemic stroke patients upon entering hospital. On entering hospital, patients entered one of five treatment pathways as follows.

Group 1: Patients admitted to hospital more than 6 hours after stroke onset. Patients who had symptoms on waking were included in Group 1.
Group 2: Patients with contraindications to rt-PA. Patients were assumed to have contraindications if they had a pre-stroke Modified Rankin Scale (MRS) of at least 3, or were on long-term anti-coagulants.

Group 3: Patients whose computed tomography (CT) scan was performed later than 6 hours after onset.

Group 4: Patients with intracranial haemorrhage on CT scan.

Group 5: Patients eligible for thrombolysis (all remaining patients).

To predict the health and economic outcomes of rt-PA after the first year, a Markov model was employed. This model used age-specific mortality, risk of recurrent stroke, stroke-specific case fatality and probabilities of functional outcomes to estimate the probabilities of being dead, alive and dependent, or alive and independent each year. The Markov process was run repeatedly in 1-year cycles until the end of the patient cohort lifetime, when the total costs and outcomes were calculated.

**Outcomes assessed in the review**
The health outcomes for the model included:

- treatment pathway probabilities,
- the probabilities of different functional outcome states,
- mortality,
- the risk of stroke recurrence, and
- the efficacy of rt-PA.

**Study designs and other criteria for inclusion in the review**
Not reported in this paper, for details please see the full HTA report (Sandercock et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details).

**Sources searched to identify primary studies**
Not reported in this paper, for details please see the full HTA report.

**Criteria used to ensure the validity of primary studies**
Not reported in this paper, for details please see the full HTA report.

**Methods used to judge relevance and validity, and for extracting data**
Not reported in this paper, for details please see the full HTA report.

**Number of primary studies included**
Not reported in this paper, for details please see the full HTA report.

**Methods of combining primary studies**
Not reported in this paper, for details please see the full HTA report.

**Investigation of differences between primary studies**
Results of the review

Efficacy of rt-PA within 6 hours of stroke onset: the odds ratio was 1.16 (95% confidence interval, CI: 0.94 - 1.44) for death, and 0.79 (95% CI: 0.68 - 0.92) for death or dependency.

The estimated annual risk of stroke recurrence after 1 year was 0.05.

The estimated annual stroke mortality among patients with recurrent stroke was 0.25.

The probabilities of functional outcomes (death, dependence or independence) at 6 and 12 months were calculated for the treatment groups from LSR data and, for patients receiving rt-PA, from the Cochrane Review. These were not reported in this paper, but they were tabulated in the NICE HTA monograph.

Pathway probabilities were estimated from LSR data:

- admission within 6 hours, 0.2981 (range: 0.2981 - 0.7000);
- no contraindications to rt-PA, 0.7424;
- CT performed within 6 hours, 0.2857 (range: 0.2857 - 1.000);
- no haemorrhage on CT scan, 0.8304.

These translated to a probability of 0.053 that patients would enter Group 5 (i.e. eligible for rt-PA treatment).

The probability of dying after the first year was calculated using a multiplier of 2.5 on national age-specific mortality rates.

Measure of benefits used in the economic analysis

The outcome measure used was the quality-adjusted life-years (QALYs). Patient utility values for the dependent and independent states were derived from EQ-5D categorical scores measured in a sample of 157 LSR patients. The utilities were generated from these responses using the preferences of the general public.

Direct costs

Direct costs of rt-PA medication, hospital stay, rehabilitation and long-term care were included. Discounting at a rate of 6% per annum was applied. The quantities and the costs were reported separately for hospital admissions, with days of admission calculated from LRS. The average annual costs for rehabilitation and long-term care were estimated from a published model in which resource use had been estimated by an expert panel of clinicians and costs from standard national sources. The list price of rt-PA was taken as the base-case estimate of rt-PA treatment. Inpatient stay costs were taken from the Western General Hospital, Edinburgh.

Statistical analysis of costs

The costs were treated deterministically.

Indirect Costs

The authors stated that indirect economic costs, such as loss of work-related earnings or the capital and revenue costs of developing services for patients with acute stroke, were not included.
Currency
UK pounds sterling (). 

Sensitivity analysis
The authors performed several one-way sensitivity analyses and threshold analyses. The parameters investigated were rt-PA efficacy (upper and lower 95% CIs), system efficiency, utility values, the costs of rt-PA treatment, the length of hospital stay, and the unit cost per inpatient day.

The authors also performed a multi-way first-order Monte Carlo simulation to determine how likely certain levels of cost-effectiveness were when all ranges of values for all parameter inputs were simultaneously incorporated.

Estimated benefits used in the economic analysis
The estimated QALYs gained at 12 months per 100 patients were 40.24 for standard care and 41.05 for standard care plus rt-PA. This equated to a QALY gain of 0.81 per 100 patients treated (5th and 95th percentiles: -0.4202, 1.8259).

The estimated QALYs gained over the cohort lifetime per 100 patients were 223.38 for standard care and 227.01 for standard care plus rt-PA. This equated to a QALY gain of 3.63 per 100 patients treated (5th and 95th percentiles: -3.32, 8.48).

Cost results
The estimated total costs at 12 months per 100 patients were 614,964 for standard care and 625,965 for standard care plus rt-PA. This equated to an incremental cost of 11,001 per 100 patients treated (5th and 95th percentiles: -44,065, 47,095).

The estimated total costs over the cohort lifetime per 100 patients were 2,971,394 for standard care and 2,620,862 for standard care plus rt-PA. This equated to a cost-saving of 350,532 per 100 patients treated (5th and 95th percentiles: -443,596, -306,685).

Synthesis of costs and benefits
The estimated benefits and costs were used to calculate the incremental cost per QALY ratios. The incremental cost per QALY of rt-PA treatment at 12 months was 13,581. The analysis also showed that there was an 85.5% probability of an increase in QALYs with rt-PA treatment. Under the assumption that rt-PA increased QALYs, the incremental cost per QALY ratio was 142,205 at the 95th percentile, and showed rt-PA dominant at the 5th percentile.

The incremental cost per QALY of rt-PA treatment over the cohort lifetime showed rt-PA treatment was dominant (lower costs and QALY gains). The Monte Carlo simulation also showed that there was a 76.6% probability of an increase in QALYs with rt-PA treatment. Under the assumption that rt-PA increased QALYs, the incremental cost per QALY ratio showed rt-PA dominant at both the 5th and 95th percentiles.

The impact of assuming highest rt-PA efficacy was to increase the number of QALYs gained over a lifetime from 3.63 to 19.41 QALYs, to reduce the cost-savings from 350,532 to 267,713, and to change the marginal cost-effectiveness ratio from 95,565 to 13,793 saved per QALY gained. The impact of assuming worst rt-PA efficacy was a loss of 13.21 QALYs, so the marginal ratio could not be calculated. The cost-effectiveness estimates were sensitive to rt-PA efficacy and rt-PA costs. Other parameters thought to be important, such as system efficiency and patient values, did not have any significant impact on the marginal cost-effectiveness ratio.

Authors' conclusions
The authors conclude that their analysis, based on an up-to-date and valid estimate of recombinant tissue plasminogen activator (rt-PA) effectiveness and modelled on the National Health Service (NHS), suggests that rt-PA treatment could be cost-effective. However, while the long-term cost-savings were impressive, they noted that both the long-term and
short-term cost-effectiveness estimates were very imprecise. Therefore, the cost-effectiveness of rt-PA in acute stroke could not be assessed reliably until large-scale randomised trials provide sufficiently precise estimates of rt-PA efficacy.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was explicitly justified as incorporating current practice in the UK (i.e. usual care versus usual care plus rt-PA therapy), in NHS hospitals, for acute ischaemic stroke. You should decide whether this represents an appropriate comparator in your setting.

Validity of estimate of measure of effectiveness
The authors stated that a systematic review of the literature had been undertaken. The methods and conduct of the review were fully reported in the HTA report, but were not provided in this paper. To fully evaluate the credibility of the effectiveness estimates the reader is referred to the full report. The authors also applied data from a Scottish stroke registry and a Scottish general hospital, which may not have been appropriate for an analysis seeking to draw conclusions for the NHS throughout the UK. It was stated that the stroke registry study sample was representative of stroke patients in the UK (the target population), although evidence of this was not provided. A statistical analysis of the data was not reported.

Validity of estimate of measure of benefit
The estimate of benefits (QALYs gained) was modelled. The model used to derive a measure of health benefit and the instrument (EQ-5D) used to derive a value for the health benefits were appropriate and valid.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted were included in the analysis. It also appears that all the relevant costs for each cost category have been included, though quantities of resources used following hospital discharge were not presented and could not be evaluated for omissions. In addition, in the base-case analysis, the costs of administering rt-PA treatment were not included, though they were estimated for the sensitivity analysis using a Scottish general hospital. Although the perspective adopted did not demand their inclusion, the analysis may have been enhanced by expanding the perspective to include indirect costs. The costs and the quantities were reported separately for hospital stays only. The sensitivity analysis of the quantities was limited to changing the length of hospital stay, the inclusion of rehabilitation or long-term care costs, and the inclusion of rt-PA-associated treatment costs. Clinical experts estimated post-discharge care costs; it would be useful to accumulate accurate patient-level data. A sensitivity analysis of the prices was not performed. It was unclear whether prices were appropriately inflated to the price year (1999/2000).

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability was addressed, with the authors noting the effect of their efforts to customise the evaluation to the NHS setting. The authors did not present their results selectively. The authors’ conclusions reflected the scope of the analysis, which was to examine the cost-effectiveness of implementing rt-PA therapy widely in the NHS for acute ischaemic stroke. The authors reported limitations to their study. For example, the imprecision of the cost-effectiveness estimates generated (arising from uncertainty in many influential parameters). Also, rt-PA treatment administration costs were excluded from the model, owing to the lack of data on a nationally agreed level of resource use necessary for rt-PA, together with the lack of reliable measures of current variation in the level and costs of resources for standard care.

The economic evaluation described here and the systematic review upon which it draws were reported in greater detail in the HTA monograph (Sandercock et al. 2002).

Implications of the study
The authors acknowledged that the primary analyses suggest cost-effectiveness or even cost-savings over the longer term. However, citing the imprecision and sensitivity of the estimates, and lack of data on the costs of implementing rt-PA treatment nationwide, they were unable to model the costs of widespread use of rt-PA for acute stroke in the UK. Therefore, no change in current policy of treating to the limited licence was recommended. The authors highlighted the need for further research into rt-PA efficacy, the costs of implementing treatment in the NHS, and resource and health effect consequences of treatment. Further research into the effect of post-stroke disability on subsequent survival, recurrence and eligibility for re-treatment with rt-PA, is also required.

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