Cost-Effectiveness of Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke Assessed by a Model Based on UK NHS Costs

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Background and Purpose—Thrombolytic therapy is licensed for use in highly selected patients with acute ischemic stroke. We aimed to model the health economic impact of limited use of thrombolytic therapy and to assess whether it was likely to be cost-effective when used more widely in the UK National Health Service (NHS).

Methods—The authors formed a discussion panel to develop the decision-analysis model of acute stroke care. It consisted of Markov state-transition processes, with probabilities of different health states determined by certain key variables. The range of estimates of efficacy of recombinant tissue plasminogen activator (rt-PA) was taken from an update to a Cochrane systematic review of randomized trials of thrombolysis. Data on outcome after stroke were taken from our hospital-based stroke register, supplemented by data derived from relevant literature sources.

Results—The model suggested that compared with standard care, if eligible patients were treated with rt-PA up to 6 hours, there was a 78% probability of a gain in quality-adjusted survival during the first year, at a cost of £13,581 per quality-adjusted life-year (QALY) gained. Over a lifetime, rt-PA was associated with cost-savings of £96,565 per QALY. However, the estimates were imprecise and highly susceptible to the assumptions used in the economic model; under several plausible assumptions, rt-PA was much less cost-effective than standard care, and under others, a great deal more cost-effective.

Conclusions—The estimates of effectiveness and cost-effectiveness were imprecise. Although the benefits appeared promising, the data did not support the widespread use of thrombolytic therapy outside the terms of the current restricted license in routine clinical practice in the NHS. There is a case for new large-scale randomized trials comparing thrombolytic therapy with control up to 6 hours to determine more precisely the effects of rt-PA on short-term and long-term survival and its cost-effectiveness when used in a wider range of patients. (Stroke. 2004;35:1490-1498.)

Key Words: thrombolytic therapy • tissue plasminogen activator • cerebral infarction • cost-benefit analysis

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) was first licensed for the treatment of acute ischemic stroke in the USA in 1996, and soon afterward in Canada and Germany. A conditional license has been granted in many European countries. The published economic evaluations of rt-PA for acute ischemic stroke have had significant limitations, because they were based on the North American1 or Australian2 health care systems, or based their efficacy estimates on a limited subset of the randomized trial evidence,1-3 or performed only limited sensitivity analyses or modeled only very limited use within the first 3 hours.1-3 To decide whether UK National Health Service (NHS) should implement thrombolytic treatment, and if so, how widely, we

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undertook an economic analysis constructed from the perspective of the NHS commissioned by the NHS Health Technology Assessment Programme.4 This assessment sought to explore a range of scenarios encompassing limited use under the current restrictive license for patients presenting within 3 hours and wider use up to 6 hours after onset.

Subjects and Methods

Full details of the methods, data sources, assumptions, analytic approach, and results are reported elsewhere (available online at http://www.nchta.org/project.asp?PjId=1127).4

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Please see Appendix I (available online at http://stroke.ahajournals.org) for a complete list of Conflicts of Interest.

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Care pathways and outcomes. C indicates contraindication to rt-PA; HAE, intracranial hemorrhage on CT; ISCH, ischemic stroke confirmed by CT. The groups were defined. Group 1 included patients admitted to hospital >6 hours after stroke onset. Patients who had symptoms on waking were included in Group 1. Group 2 included patients with contraindications to rt-PA. Patients were assumed to have contraindication to rt-PA if they had a prestroke modified Rankin Scale score of ≥3 or were using long-term oral anticoagulants. Group 3 included patients whose CT scan was performed >6 hours after stroke onset. The time from symptom onset to CT scanning was known for a subset of patients and extrapolated to all patients in the data set. Patients known to have undergone CT scan >6 hours from stroke onset were included in group 3. Group 4 included patients with intracranial hemorrhage on CT scan. If an intracranial hemorrhage was seen on the first CT scan after stroke onset, the patient was included in Group 4. Group 5 included patients eligible for thrombolysis, ie, all those who remained after exclusion from Groups 1 to 4. Group 5a was modeled on the assumption that eligible patients received standard care plus rt-PA. The model was then rerun on the assumption that all rt-PA–eligible patients received standard care (Group 5b). For survival after 1 year and recurrence, we assumed that after the first year, deaths occurred at an equal rate in dependent and independent survivors. We used published estimates of all-cause mortality, adjusting for age and history of previous stroke, assuming that the overall death rate after the first year was 2.5 times the age-adjusted mortality of the UK population. Among patients who had a recurrent stroke after the first year, we calculated survival from the rate of recurrent stroke and the case fatality of patients with recurrent stroke in the Lothian Stroke Register, assuming the risks to be equal in dependent and independent patients. We also assumed that patients remaining alive after the recurrent stroke were reallocated equally to the independent and dependent functional outcome category. For example, in a particular model year, the number of independent patients that had a recurrent stroke and remained alive were allocated in equal numbers to the independent and dependent functional outcome category.

### Study Question
From the perspective of the UK NHS, is thrombolytic treatment for acute ischemic stroke (compared with standard care) cost-effective as judged by the incremental cost per quality-adjusted life-year (QALY) gained?

### Perspective
The perspective was a broad health care and personal social services perspective. We included the direct costs of hospital stay, rehabilitation, and long-term care. We did not include assessments of any indirect economic costs, such as loss of work-related earnings, or of the capital and revenue costs of developing services for patients with acute stroke to the point at which acute stroke care was delivered across the whole NHS to the standard required.

### Assessment of Alternatives to Thrombolytic Treatment
It is difficult to define, in economic terms, a standard package of general care for patients with acute stroke (even more so to define one for patients treated with thrombolysis). We have therefore assumed that the alternative treatments being compared are "standard care" and "standard care plus thrombolysis."

### Form of Evaluation
We have adopted a cost-utility approach, assessing health gains in QALYs. We have modeled costs and effectiveness over the short-term (1 year) and the long-term (lifetime).

### Steps to Improve Generalizability of Results
The patients included in the trials of thrombolysis were highly selected and were largely recruited from non-UK centers. So, to produce results that were more relevant to the NHS, we undertook a modeling approach, applying data on efficacy from the trials to a population of stroke patients treated within the NHS (or similar publicly funded health service).

### Choice of Measure of Benefit
The use of QALYs as the measure of benefit enabled us to encompass the utility values that stroke patients assign to the different health states after stroke (ie, death, survival in a dependent state, or survival in an independent state).

### Decision-Analysis Model
The authors formed a discussion panel to construct a decision-analysis model of the pathways that acute stroke patients follow after being admitted to hospital. The model was constructed by discussion among the reviewers, analysis of our own stroke registry (Lothian Stroke Register) data, and review of the literature. The model was entered into a software package (Data 3.5 software; TreeAge Software Inc) and is shown in Figure 1. We defined 5 groups of patients (see Figure 1 legend for definitions). Table 1 lists all of the base-case values (with plausible ranges) used in the model and the sources of the estimates. These include estimates of treatment effect for rt-PA to those that formed the basis for its current approval for use in clinical practice within 3
To predict the health and economic outcomes of rt-PA after the first year, we used a Markov modeling approach. The Markov model used age-specific mortality, risk of recurrent stroke, and stroke-specific case-fatality to estimate the probabilities of being dead, dependent, and independent at the beginning of each year. The Markov process was run repeatedly in 1-year cycles until the end of the cohort lifetime, and totals were computed for the accumulated health outcomes and costs.

### Table 1. Base-Case Values and Range of Plausible Values

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Base-Case Value</th>
<th>Plausible Range</th>
<th>Source/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathway probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission within 6 h</td>
<td>0.2981</td>
<td>0.2981–0.7</td>
<td>LSR (1/3 of pts with symptoms present on waking)²⁰</td>
</tr>
<tr>
<td>No contraindications to rt-PA</td>
<td>0.7424</td>
<td></td>
<td>LSR²¹</td>
</tr>
<tr>
<td>CT performed within 6 h</td>
<td>0.2857</td>
<td>0.2857–1.0</td>
<td>LSR²¹</td>
</tr>
<tr>
<td>No hemorrhage on CT</td>
<td>0.8304</td>
<td></td>
<td>LSR²¹</td>
</tr>
<tr>
<td><strong>Probabilities of different functional outcome states at 6 &amp; 12 mo in Groups 1–5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients dying &lt; 6 mo</td>
<td>21 d</td>
<td></td>
<td>LSR²¹</td>
</tr>
<tr>
<td>Patients dying 6–12 mo</td>
<td>300 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median survival within the first year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual age-specific mortality rates</td>
<td></td>
<td></td>
<td>LSR²¹; National Statistics (average cohort starting age: 69 years)¹⁹</td>
</tr>
<tr>
<td>Multiplier for age-specific mortality among stroke patients</td>
<td>2.5</td>
<td></td>
<td>Perth Community Stroke Study²¹</td>
</tr>
<tr>
<td>Survival after the first year among patients who have had a recurrent stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual risk of stroke recurrence after 1 year</td>
<td>0.05</td>
<td></td>
<td>LSR²¹</td>
</tr>
<tr>
<td>Annual stroke mortality among patients with recurrent stroke</td>
<td>0.25</td>
<td></td>
<td>LSR²¹</td>
</tr>
<tr>
<td><strong>Efficacy of rt-PA within 6 h</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR for death</td>
<td>1.16</td>
<td>0.94–1.44</td>
<td>Cochrane systematic review of trials of rt-PA updated to 2002²²</td>
</tr>
<tr>
<td>OR for death or dependency</td>
<td>0.79</td>
<td>0.68–0.92</td>
<td>Cochrane systematic review of trials of rt-PA updated to 2002²²</td>
</tr>
<tr>
<td><strong>Utility values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independence</td>
<td>0.74</td>
<td>0.69–0.79</td>
<td>LSR⁵</td>
</tr>
<tr>
<td>Dependence</td>
<td>0.38</td>
<td>0.29–0.47</td>
<td>LSR⁵</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td></td>
<td>LSR⁵</td>
</tr>
<tr>
<td>Mean unit cost per inpatient day</td>
<td>£200</td>
<td>£150–500</td>
<td>Scottish Health Service Costs 1998–1999 for Western General Hospital, Edinburgh; Range for Scotland²³</td>
</tr>
<tr>
<td>Mean length of stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent survivor</td>
<td>14 d</td>
<td>14–31 days</td>
<td>LSR²³,²⁴</td>
</tr>
<tr>
<td>Dependent survivor</td>
<td>51 d</td>
<td>51–78 days</td>
<td>LSR²³,²⁴</td>
</tr>
<tr>
<td>Nonsurvivor</td>
<td>33 d</td>
<td>33–34 days</td>
<td>LSR²³,²⁴</td>
</tr>
<tr>
<td>Cost of rt-PA treatment</td>
<td>£480</td>
<td>£480–1000</td>
<td>Base case assumes drug costs only²⁵</td>
</tr>
<tr>
<td>Cost of (ambulatory) rehabilitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent survivor</td>
<td>£40</td>
<td></td>
<td>MEDTAP model²⁶,²⁷</td>
</tr>
<tr>
<td>Dependent survivor</td>
<td>£763</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annual cost of long-term care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent survivor</td>
<td>£876</td>
<td></td>
<td>MEDTAP model²⁶,²⁷</td>
</tr>
<tr>
<td>Dependent survivor</td>
<td>£11 292</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rate for (future) costs and outcomes (QALYs)</td>
<td>0.06</td>
<td>0.03</td>
<td>National rate</td>
</tr>
</tbody>
</table>

LSR indicates Lothian Stroke Register; QALY, quality-adjusted life-year; rt-PA, recombinant tissue plasminogen activator; OR, odds ratio.

1. The upper 95% CI were used as the best-case estimates for the effects of rt-PA, and the lower limit for the worst-case (see Table 4). Readers should note that the best case scenario corresponds closely with the estimate of effect seen in the NINDS trial, which forms the main basis for the current approval for the use of rt-PA within 3 hours.
2. These estimates of the length of stay for the acute admission for patients with different outcomes at 6 months were obtained from a hospital-based cohort of stroke patients (LSR). See http://www.ncchta.org/project.asp?PjtId=1127 for details.
Assumptions About Cost of Implementing rt-PA

We sought to assess the typical additional costs of implementing rt-PA treatment in a “typical” district general hospital. However, we were unable to define a nationally agreed level of resource use required to deliver thrombolysis for acute stroke or to obtain reliable measures of the variation in the current level (and cost) of acute stroke care in UK hospitals. We therefore sought to identify, in a qualitative way, the specific extra resources we considered necessary to deliver thrombolysis (in the context of a randomized controlled trial) in our own hospital (Table 2). However, the resources currently allocated to acute stroke care vary greatly between centers across the UK, so any quantitative estimates of the extra implementation costs derived from these local data could not be reliably extrapolated to other hospitals in the UK.

Adjustment for Timing of Costs and Benefits

We accounted for the longer time horizon over which costs and health benefits may accrue by discounting outcomes and cost at an annual rate of 6%.

Scenarios Modeled

We performed a number of 1-way sensitivity analyses and threshold analyses to explore the impact of varying key parameters in the model: rt-PA efficacy (we used a range that encompassed larger benefits expected when used in a highly selected population within 3 hours and expected smaller benefits when used in a wider variety up to 6 hours); system efficiency (this ranged from the small proportion currently treated to a scenario where rt-PA was available at all hospitals); utility values; costs of rt-PA treatment; length of hospital stay; and unit cost per inpatient day. We also performed a multiway first-order Monte Carlo simulation to determine how likely certain levels of cost-effectiveness were when we simultaneously incorporated all ranges of values for variables listed in Table 1.

Results

Cost-Effectiveness at 12 Months

Table 3 presents the costs and outcomes at 12 months per 100 patients treated with rt-PA. The base-case analysis assumed that only 5.3% of the patients admitted to hospital were eligible for rt-PA treatment, showed that treatment with rt-PA costs an additional £11 001, and resulted in a QALY gain of 0.81 per 100 patients treated. This gives a marginal cost-effectiveness ratio for rt-PA treatment of £13 581 per QALY gained. The multiway Monte Carlo simulation showed that the 5th and 95th percentiles for the increase in costs at 12 months were £44 065 and £47 095, respectively, and that the corresponding percentiles for the impact on health outcomes were −0.4020 and 1.8259 QALYs, respectively. The analysis also showed that there was 85.5% probability of an increase in QALYs with rt-PA treatment. If we assumed that rt-PA increased QALYs, the 5th and 95th percentiles for the incremental cost-effectiveness ratio for this group were £81 680 (cost-savings) and £142 505 (additional costs) per QALY gained. The lower sections of the Tables summarize the sensitivity analyses.

Cost-Effectiveness at End of the Cohort Lifetime

Costs accrue in the short-term (eg, initial acute care), whereas survival gains accumulate over a far longer period, and analyses performed at 12 months therefore underestimate expected yield (eg, in terms of QALYs gained) relative to costs. Nursing home/long-term care is higher for a stroke survivor with high levels of disability, and hence the cost-savings associated with reduced disability, are large and only
TABLE 3. Costs (£), Health Outcomes (QALYs), and Costs per QALY Gained at 12 Months per 100 Patients Eligible for rt-PA

<table>
<thead>
<tr>
<th>Costs per 100 Patients</th>
<th>QALYs</th>
<th>Incremental Costs (5th and 95th Percentiles)*</th>
<th>Incremental QALYs (5th and 95th Percentiles)*</th>
<th>Incremental Costs Per QALY Gained (5th and 95th Percentiles)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base-case analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rt-PA</td>
<td>625 965</td>
<td>614 964</td>
<td>41.05</td>
<td>40.24</td>
</tr>
<tr>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variation of parameter values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rt-PA efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best-case efficacy</td>
<td>616 083</td>
<td>614 964</td>
<td>43.92</td>
<td>40.24</td>
</tr>
<tr>
<td>Worst-case efficacy</td>
<td>634 755</td>
<td>614 964</td>
<td>37.99</td>
<td>40.24</td>
</tr>
<tr>
<td>System efficiency‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% admitted within 6 h (12% of pts eligible) for rt-PA</td>
<td>629 608</td>
<td>618 250</td>
<td>43.12</td>
<td>42.27</td>
</tr>
<tr>
<td>No delay to CT (18% of pts eligible)</td>
<td>637 793</td>
<td>625 994</td>
<td>41.42</td>
<td>40.74</td>
</tr>
<tr>
<td>50% admitted within 6 h and no delay to CT (31% of pts eligible)</td>
<td>635 579</td>
<td>623 850</td>
<td>42.73</td>
<td>41.96</td>
</tr>
<tr>
<td>70% admitted within 6 h and no delay to CT (43% of pts eligible)</td>
<td>634 644</td>
<td>622 946</td>
<td>43.29</td>
<td>42.48</td>
</tr>
<tr>
<td>Utility values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent state: decreased to 0.29</td>
<td>625 965</td>
<td>614 964</td>
<td>39</td>
<td>37.52</td>
</tr>
<tr>
<td>Dependent state: increased to 0.47</td>
<td>625 965</td>
<td>614 964</td>
<td>43.1</td>
<td>42.96</td>
</tr>
<tr>
<td>Independent state: decreased to 0.69</td>
<td>625 965</td>
<td>614 964</td>
<td>38.66</td>
<td>38.29</td>
</tr>
<tr>
<td>Independent state: increased to 0.79</td>
<td>625 965</td>
<td>614 964</td>
<td>43.23</td>
<td>42.18</td>
</tr>
<tr>
<td>Cost of rt-PA treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubled (to £1000)</td>
<td>673 965</td>
<td>614 964</td>
<td>41.05</td>
<td>40.24</td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent survivor increased to 78 d</td>
<td>743 799</td>
<td>765 212</td>
<td>41.05</td>
<td>40.24</td>
</tr>
<tr>
<td>Independent survivor increased to 31 d</td>
<td>769 651</td>
<td>744 880</td>
<td>41.05</td>
<td>40.24</td>
</tr>
<tr>
<td>Unit cost per inpatient day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced to £150</td>
<td>481 474</td>
<td>461 223</td>
<td>41.05</td>
<td>40.24</td>
</tr>
<tr>
<td>Increased to £500</td>
<td>1 492 912</td>
<td>1 537 411</td>
<td>41.05</td>
<td>40.24</td>
</tr>
</tbody>
</table>

*5th and 95th percentiles for the frequency distribution of incremental costs, incremental QALYs, and incremental cost-effectiveness ratios, based on ranges of possible values and assumptions given in Tables 1 and 2 (Monte Carlo 1-way, 2-way (system efficiency), and 3-way (rt-PA efficacy) sensitivity analysis with 10 000 iterations). It does not represent the confidence interval (reflecting random error) surrounding the point estimates in the table.
†The Monte Carlo simulations were consistent with a (small) risk of loss of QALYs, in which case the costs per QALY gained is not applicable. The 5th and 95th percentiles for the incremental cost-effectiveness ratios, given that there is a gain in QALYs, are provided in the text.
‡Analyses include patients who were excluded in the base case analysis because of delayed admission, delayed CT scan, or both.

partly offset by the costs associated with increased survival.

The base-case analysis showed that over the cohort lifetime, giving rt-PA then became the dominant strategy (Table 4). Treatment with rt-PA was more effective (gain in QALYs of 3.63 per 100 patients treated), less expensive than standard treatment (cost savings of £350 532), and resulted in a reduced cost of £96 565 per QALY gained. The multiway Monte Carlo simulation showed that there was a 76.6% probability of increased QALYs. If we assume that rt-PA increases QALYs, the 5th and 95th percentiles for the incremental cost-effectiveness ratios for this group were −£908 153 (net savings) and −£96 565 to £13 793 saved per QALY gained. When we assumed the least favorable estimate of rt-PA effectiveness, rt-PA resulted in a loss of 13.21 QALYs, and the incremental cost-effectiveness ratio could not be calculated. Detailed sensitivity analyses are presented in the full report.4

**Discussion**

Main Results

Our analyses, based on an up-to-date estimate of the effectiveness of rt-PA and modeled on the NHS, suggests that rt-PA might well be cost-effective. In the base-case analysis, treatment with rt-PA was associated with an additional cost of £13 581 per QALY gained during the first 12 months after treatment. This estimate was considerably higher than the published estimates for treatment with rt-PA for myocardial infarction,10,11 but it was still well within the range of cost-effectiveness for health care interventions offered within the NHS.12 Donaldson has recently highlighted a limitation of such cost-effectiveness analyses; that is, if a new treatment requires more resources, misuse of cost-effectiveness ratios may lead to inefficient treatments being adopted.13 When the model was run to the end of the cohort lifetime, there appeared to be a substantial cost savings of £96 565 per QALY gained. The short-term and long-term cost-effectiveness estimates were very imprecise. At 12 months,
the 5th and 95th percentiles for the impact on costs ranged from a cost saving of £44 065 to an extra cost of £47 095. There was therefore considerable uncertainty about the exact size of the incremental cost-effectiveness ratio for rt-PA in acute stroke. The cost-effectiveness estimates were sensitive to rt-PA efficacy and costs of rt-PA. Other parameters thought to be important, such as “system efficiency” and patient values, did not have any significant impact on the incremental cost-effectiveness ratio.

Summary of Previous Work
Our results are not as optimistic as earlier estimates. From the perspective of the North American health care system (which included nursing home costs), for every 1000 patients treated, rt-PA increased hospitalization costs by $1.7 million but decreased rehabilitation costs by $1.4 million and nursing home costs by $4.8 million. Multiway sensitivity analyses indicated a >90% probability of cost-savings. The study had some limitations for current health care planning outside the USA: the estimate of efficacy was based on a single trial;14 costs were based on the US health care system; the possibility that treatment might increase case fatality was not modeled; and the estimate of the gain in QALYs was very imprecise (and included the possibility of almost no benefit). A further study, commissioned by a pharmaceutical company (but conducted by an independent economist), concluded that the savings related to disability and long-term care considerably outweighed any potential extra costs of acute therapy, given a broad cost perspective and a time horizon of ≥2 years.1 However, the authors also pointed out that the fixed costs of developing and maintaining a capability to diagnose acute stroke and provide early thrombolysis would need to be taken into account in a more comprehensive analysis.
Furthermore, any downstream savings attributed to the avoidance of social care costs associated with disability are unlikely to be very convincing to budget holders focused on hospital and drug cost alone.  

**Why Might Our Results Be Different?**

As expected, the cost-effectiveness estimate at 12 months was heavily influenced by the source of the data in the model.  

This may invalidate the comparison between our study and previous studies of cost-effectiveness of rt-PA in stroke and may explain the different short-term results. In contrast to earlier studies, we found that the cost-savings were not realized within the first 1 to 2 years after treatment. One likely explanation is that the other studies were based on more optimistic estimates of rt-PA effectiveness, from the NINDS trial alone, in which treatment was given within 3 hours or just 3 of the major rt-PA trials; however, our sensitivity analyses did include a value for the effectiveness of rt-PA comparable to that seen in NINDS. Earlier studies also used more favorable values for patients’ preferences.

We based our estimates of the effectiveness of rt-PA on the results of a systematic review of all the available evidence from randomized controlled trials of rt-PA to date. Furthermore, we used a more conservative estimate of the patient valuation of the dependent state, which, as it turned out, was close to the estimate derived from a recent systematic review of patient utilities after stroke.

**Generalizability of These Results**

Another uncertainty relates to the generalizability of the findings. It is likely that both resource use (eg, length of stay) and the valuation of resources (eg, mean unit cost per inpatient day) will vary considerably within the NHS. Hence, we used national official figures to “average out” local differences in unit costs, and we believe that the resources used by patients registered in the Lothian Stroke Register are reasonably representative of the resources used by stroke patients admitted to other UK hospitals. Our analysis did not include the costs of implementing rt-PA in NHS hospitals. We assumed that there were no capacity constraints in the health care system and that there were no extra costs associated with giving rt-PA to more patients. For example, we assumed that all admissions were “equal,” regardless of when they occur; that CT scanning equipment was always readily available, and that the correct number and mix of health care professionals and hospital beds were always in place. We sought to assess the additional costs of developing stroke services to deliver rt-PA treatment by identifying the specific service components we considered likely to be required to deliver thrombolysis in our hospital, over and above those required for “standard” acute stroke care. However, we were unable to find a nationally agreed level of resource use required to deliver thrombolysis for acute stroke and no reliable measures of the variation in the current level (and cost) of acute stroke care in the NHS.

**Conclusions**

**Implications for Practice**

Our economic model, constructed from the perspective of the NHS, suggests that thrombolysis for acute stroke holds the promise, under favorable assumptions, of being cost-effective in terms of QALYs gained, particularly when the longer-term cost and health outcomes were considered.

However, the range of possible incremental cost-effectiveness ratios was considerable, and the conclusions from the economic modeling were very sensitive to the economic assumptions made and a number of parameters, including the effectiveness of rt-PA (detailed in Table 1). The less favorable estimates indicated that rt-PA could be either marginally cost-effective or harmful (ie, standard therapy was the preferred option).

The primary analyses suggested cost-effectiveness or even cost-savings. However, in view of the lack of precision of the estimates and lack of data on the cost of “rolling out” the treatment to the many centers that do not currently have the resources to give rt-PA, we were unable to model the cost of widespread use of rt-PA for stroke in the UK. However, these data do not preclude the use of rt-PA for the treatment of patients who meet the stringent conditions of the present product license (in the small number of appropriately staffed and equipped centers).

**Implications for Research**

The cost-effectiveness of rt-PA could not be assessed reliably because of the imprecise estimates of its efficacy. Large-scale randomized trials would be needed to provide sufficiently precise estimates.

If trials established reliably that thrombolysis was effective, then better estimates of the costs of implementing thrombolysis for acute stroke in the NHS will be needed. A more “dynamic system approach” to explore the relationships between different system components and their impact on patient treatment strategies would be informative.

Because the cost-effectiveness estimates were very sensitive to a relatively small set of parameters, future research could focus on the relationship between thrombolytic therapy, resource consequences, and health effects. More data are needed on the effect of the level of disability at 6 months after stroke on subsequent survival, recurrence, and eligibility for re-treatment with thrombolysis.

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Editorial Comment

What Can Models Teach Us About Stroke Treatment?

Sorting Out the Missing Bits

The report in this issue of *Stroke* on the cost-effectiveness of recombinant tissue plasminogen activator (rt-PA) suggests – with notable uncertainty – that, when compared with standard acute stroke care, thrombolytic therapy provides, on average, greater health benefits (in terms of average quality adjusted life years [QALYs]) at a reasonable average medical cost. This is not itself a unique finding; other similar efforts suggest – with notably greater certainty – that rt-PA is a good value for money. What have we learned from these modeling exercises? Is it true, as the authors propose, that we need another trial of rt-PA? Before considering the answer, it is useful to briefly review a few basics of disease models – what they are and what they can teach us.

Disease models are mathematical representations of a clinical condition, its development, and its outcome, and models are often used to evaluate the impact of potential diagnostic or therapeutic strategies. These models are usually implemented in computer code, ranging from something as simple as a spreadsheet formula to sophisticated clinical event simulations. Sandercock and colleagues frame the question of rt-PA use as a decision tree, with a Markov model as a “calculation engine.” The inputs to this model are epidemiological, clinical trial, and health economic data (specifically applicable to the context of the UK National Health Service [NHS]); the outputs are the month-to-month proportion of individuals in various stroke-relevant health states and their health costs.

When properly constructed, outputs of disease models can be used in a cost-effectiveness analysis. Cost-effectiveness analysis is a well accepted approach to formulating public resource allocation decisions. The incremental cost-effectiveness ratio, ie, the extra
resource inputs required divided by the extra benefits achieved, is a standard metric that policy makers use to quantify value for money. Under specific assumptions, a society that allocates resources based on incremental cost-effectiveness ratios will optimize “social welfare.” Whether one accepts the theory or, more to the point, accepts the applicability of the theory to the real world, incremental cost-effectiveness ratios have an intuitive appeal. When calculated using standard methods, they provide a compact way of assessing value and making allocation decisions in the face of limited resources.

The current report represents an application of modeling in clinical medicine that is unique to a limited number of countries—a guide to public policy making. The UK is notable for having a formal organizational structure, the NHS Health Technology Assessment Programme, that is responsible for analyses intended to inform the NHS’s funding decisions. Other applications of models include providing insights into disease/treatment dynamics and assisting in clinical research design.

With this information, let us turn to the question presented in the current paper: Is it cost-effective to use rt-PA in the context of the UK NHS? Available effectiveness data has not been collected in the UK setting, the limited trial-based information about resource use is not UK-based, and long-term outcomes (in the UK or elsewhere) have not been studied. The latter point is vital because both health benefits and costs accrue over a lifetime; failure to account for these long-term effects leads to a skewed assessment of the potential costs and benefits of an acute stroke treatment. While a single data source cannot provide a satisfactory answer, a model can offer guidance. Assuming that effectiveness data can be extrapolated to the UK, and given UK-specific cost estimates, one can turn the crank of the calculation engine and estimate the incremental cost-effectiveness of rt-PA for the NHS. Moreover, one can account for uncertainty in the input estimates by performing a so-called Monte Carlo analysis, ie, repeating the analysis many times, each time randomly drawing from likelihood functions of relative risk reduction for poor outcomes, derived from empirical source data. The uncertainty in inputs (in this case, treatment efficacy) is reflected in variations in the outputs.

Based on trial evidence, the NHS model indicates that there is approximately a 3 out of 4 chance that tPA will provide a net benefit over one year, or over a lifetime. For the lifetime outcome, ie, the outcome relevant to policy analysis, rt-PA is likely to not merely be “cost-effective” but actually cost-saving. While one may quibble with some assumptions, input values, or details of the analysis, the results are relatively robust, and are consistent with prior analyses. So, why do the authors suggest that the solution is another trial of rt-PA? And while we are on that point, why, nearly a decade after the NINDS trial of rt-PA, is there continued controversy about whether clinicians should use this therapy and whether policy makers should make systematic efforts to facilitate its use?

If the model were a perfect representation of reality, then, as theory indicates, rt-PA is probably a good use of public resources and — the authors’ claims of inadequate certainty notwithstanding — a society that selects this and similar therapies will tend to optimize the health of its population in light of available resources. However, the current model, like all models, is of necessity an imperfect representation of reality. The NHS model illustrates that even a relatively sophisticated mathematical simulation may not capture the full range of decisional issues with complete fidelity. It is acknowledged that the current model does not capture the full array of resource costs associated with modifying the health care system to accommodate universal use of rt-PA. Another notably missing feature is an accounting of the “disutilities” such as regret following a treatment-associated complication. These missing bits may be key to what makes treatment acceptable or not.

This is not an indictment of modeling. On the contrary, the discord between a model and current opinion and behavior provides insight, and, in turn, grist for further discussion and — yes — research. But the crucial research agenda is not a more precise estimate of rt-PA efficacy. Rather, it is a better understanding of the economic costs (from the perspective of the various payers) and the decisional conflict engendered by this treatment. Moreover, since the case for rt-PA rests largely with the long-term implications of observed short-term improvements, it is essential to determine whether the benefits of rt-PA persist; are patients who improve following rt-PA more likely to subsequently deteriorate than patients with comparable levels of poststroke disability?

When it comes to decision-making, no analysis (and, for that matter, no clinical trial) can provide an answer reflexively. Evidence and analysis is never entirely definitive. Models will never replace human judgment. However, they can, with proper formulation and interpretation, be extremely useful guides to the complex decisions we face in clinical practice and policy.

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