Cost-Effectiveness of Tissue-Type Plasminogen Activator in the 3- to 4.5-Hour Time Window for Acute Ischemic Stroke

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Background and Purpose—The aim of this study was to determine the cost-effectiveness of tissue-type plasminogen activator (tPA) treatment in the 3- to 4.5-hour time window after ischemic stroke.

Methods—Decision-analytic and Markov state-transition models were created to determine the cost-effectiveness of treatment of ischemic stroke patients with intravenous tPA administered in the 3- to 4.5-hour time window compared with medical therapy without tPA. Health benefits were measured in quality-adjusted life-years (QALYs). The economic outcome measure of the model was the difference in estimated healthcare costs between the 2 treatment alternatives. The incremental cost-effectiveness ratio was calculated by dividing the cost difference by the difference in QALYs. One-way sensitivity and probabilistic analyses were performed to test the robustness of the model.

Results—The administration of tPA compared with standard medical therapy resulted in a lifetime gain of 0.28 QALYs for an additional cost of $6050, yielding an incremental cost-effectiveness ratio of $21 978 per QALY. One-way sensitivity analyses demonstrated that the incremental cost-effectiveness ratio was most sensitive to the cost of hospitalization for patients who received tPA. Based on probabilistic analysis, there is an 88% probability that tPA is the preferred treatment at a willingness-to-pay threshold of $50 000 per QALY.

Conclusions—The balance of costs and benefits favors treatment with intravenous tPA in the 3- to 4.5-hour time window.

Key Words: stroke ■ tissue-type plasminogen activator ■ cost-effectiveness ■ quality-adjusted life-year

Stroke is one of the most costly health problems affecting Americans and is a leading cause of serious, long-term disability in the United States.1 Multiple analyses have shown that treatment with tissue-type plasminogen activator (tPA) is cost-effective when administered within the first 3 hours after symptom onset.2 It is estimated that tPA treatment within 3 hours of symptom onset adds 0.75 quality-adjusted life-years (QALYs) and saves $6000 per patient treated.3 These data, however, do not apply to treatment with tPA in the 3- to 4.5-hour window, because the effect of tPA decreases with longer symptom-onset-to-treatment times. The goal of this study was to determine the cost-effectiveness of tPA in this later treatment time window.

Methods

A decision-analytic model was created (TreeAge Software, Inc) to determine the cost-effectiveness of treatment of ischemic stroke patients with intravenous tPA administered in the 3- to 4.5-hour time window compared with treatment without tPA. We developed a Markov state-transition model to account for the possible health states an individual may enter after presenting with acute ischemic stroke (Figure 1). In the analysis, we estimated average healthcare costs and benefits of each alternative from the time of stroke until death.

Input Parameters

Model input parameters were drawn from the published literature (Table).2,4–9 The base case is a man who is 65 years old at the time of his index stroke. This is the mean age of the patients who were enrolled in the ECASS-3 stroke trial.4 The death rates and the distribution of functional outcomes of patients treated with tPA and of patients treated without tPA were also based on results from this trial. Quality-of-life estimates for stroke survivors were based on published utility values stratified by modified Rankin score (mRS) category.9 All costs reflect published estimates inflated to 2010 dollars according to the medical care component of the Consumer Price Index. Hospitalization costs for the index event were based on nationwide US estimates of Medicare costs.10 The additional cost incurred by patients with symptomatic intracranial hemorrhage (sICH) was estimated on the basis of the difference in cost per hospital day for ICH patients compared with ischemic stroke patients and multiplied by the average length of stay for ischemic stroke patients.6 This additional cost was applied to the base hospitalization cost for the proportion of patients who experienced an sICH. Annual posthospitalization costs were determined from lifetime costs for

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patients with minor and major stroke. Death (by stroke or other causes) is the only absorbing state after which the patient is excluded from the model. No further costs or benefits incurred by the absorbing state are included in the analysis. Subsequent hospital costs for recurrent stroke were obtained from an economic study that assessed these costs at 5 major academic centers. All costs and utilities were discounted by 3% per year, which has been suggested as the optimal discount rate for cost-effectiveness analyses.

Health States
In the model, patients could undergo transitions between 7 poststroke disability states based on the mRS disability scale: no symptoms (mRS = 0), no significant disability (mRS = 1), minimal disability (mRS = 2), moderate disability (mRS = 3), moderate to severe disability (mRS = 4), severe disability (mRS = 5), and death (mRS = 6). The model cycle length was 1 year with a time horizon of 30 years. At the end of each annual cycle, patients could remain in their current health state, transition to a lower health state due to recurrent stroke, or die due to a recurrent stroke or an age-related cause (see Figure 1).

Patients with stroke were assumed to have an all-cause mortality rate higher than that of the average population. Life tables for stroke patients were generated by adjusting life tables from the US National Vital Statistics Reports according to mRS-specific death hazard ratios, referring to death from causes other than stroke.

Patients with recurrent stroke were assumed to have a mortality of 0.19. Patients remaining alive after recurrent stroke events were reallocated equally among Rankin categories of greater disability. For example, patients in Rankin category 3 who had a recurrent stroke and lived were allocated equally among Rankin 4 and 5 categories (see Figure 1).

Outcome Assessment
Health outcomes were measured in quality-adjusted life-years (QALYs), which capture the effects of treatment on rates of morbidity and mortality. The economic outcome measure of the model was the difference in estimated health care costs between the 2 treatment alternatives. The economic costs included the cost of hospitalization for acute ischemic stroke, the cost of sICH, and the cost of posthospitalization long-term care (such as inpatient and outpatient rehabilitation and ambulatory care costs) associated with each health state.

The differences in the costs and benefits between treatment with tPA and treatment without tPA were assessed. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the cost difference by the difference in QALYs. The intervention was considered cost-effective if the ICER was <$50 000 per QALY gained and borderline cost-effective if the ICER was between $50 000 and $100 000 per QALY gained. Cost per death prevented at 90 days after stroke was also calculated. The analysis was conducted from the societal perspective. Indirect economic costs such as lost work productivity were not included.

Sensitivity Analysis
Deterministic one-way sensitivity analyses were performed to test the robustness of the model. Parameters varied and included hospitalization costs for each treatment, annual posthospitalization costs, recurrent stroke cost, sICH costs, probability and mortality of recurrent stroke, utilities, hazard ratios, and discount rates (Figure 2). Plausible ranges were obtained from the literature or by varying estimates up to 20% in each direction (see Table).

Because parameters are unlikely to change in isolation, all parameters were also varied simultaneously in a probabilistic sensitivity analysis (Monte Carlo simulation). Costs were varied after assuming a normal distribution. Probabilities were varied after assuming a beta distribution. Utilities were varied according to a gamma distribution. The analysis was run 10 000 times to capture stability in the results. Uncertainty was represented on a scatterplot (Figure 3). Probabilities that tPA therapy is cost-effective were determined over a wide range of willingness-to-pay (WTP) thresholds (Figure 4).

Results
Base Case Analysis
For the base case scenario, medical therapy without tPA was associated with 6.08 residual poststroke QALYs at a cost of $95 603. Treatment with intravenous tPA in the 3- to 4.5-hour time window was associated with 6.35 QALYs at a cost of $101 653. Therefore, the administration of tPA resulted in a
lifetime gain of 0.28 QALYs at an additional cost of $6050,
yielding an ICER of $21 978 per QALY. At 90 days after
stroke, the additional cost associated with tPA treatment to
prevent 1 death was $629 073.

### Sensitivity Analysis

One-way sensitivity analyses indicated that the study results
were robust. The effects of varying input parameters on the
ICER are illustrated in the tornado diagram in Figure 2.
Changes in parameters led to small changes in the ICER that were well within the limits of cost-effectiveness for all parameters tested. The ICER was most sensitive to the cost of hospitalization for patients who received tPA. At the upper bound of the hospitalization cost for patients who received tPA ($22,088), the ICER increased to a maximum of $35,349 per QALY. The ICER was relatively insensitive to varying parameters of recurrent stroke cost, sICH costs, probability of recurrent stroke, probability of death from recurrent stroke, utilities, hazard ratios, and discount rates.

Results of the probabilistic sensitivity analysis are shown in Figure 3. In 7.7% of simulation runs, tPA was less costly and more effective than standard medical therapy and was thus recommended. In 80.7% of simulation runs, tPA was more costly and more effective than standard medical therapy and was recommended because the ICER did not exceed the WTP threshold of $50,000 per QALY. In 11.6% of simulation runs, tPA was more costly and more effective and was not recommended because the ICER exceeded $50,000 per QALY. Overall, there was an 88% probability that tPA was the preferred treatment at a WTP threshold of $50,000 and a 98.2% probability at a WTP threshold of $100,000. A cost-effectiveness acceptability curve shows the probability of cost-effectiveness of tPA as a function of the WTP threshold (Figure 4).

Figure 2. One-way sensitivity analyses: effect of parameter variation on the incremental cost-effectiveness ratio. All model parameters were varied, and those with the highest relative effect on incremental cost-effectiveness ratio are displayed. Dark-shaded bars represent the lower bound of the variable range. Light-shaded bars represent the upper bound. The first number listed after the variable name is the base case value. Numbers listed in parentheses indicate the range over which the value was varied in the sensitivity analysis. Incremental cost per quality-adjusted life-year (QALY) is ~$22 000 for the base-case scenario. IV tPA indicates intravenous tissue-type plasminogen activator; mRS, modified Rankin score.

Figure 3. Results of probabilistic sensitivity analysis: incremental cost-effectiveness scatterplot. Incremental effectiveness is measured in quality-adjusted life-years (QALYs). The dotted diagonal line represents the willingness-to-pay (WTP) threshold of $50,000 per QALY. All points to the right of the WTP line are considered cost-effective. Each point represents a simulation run. Treatment with tPA was the preferred option at a WTP threshold of $50,000 in 88% of the simulation runs. The dark square represents the base case result (0.28 QALYs gained at an incremental cost of $6050).
nearly equivalent between groups, we assumed higher hospitalization costs to be only partially offset by a reduction in long-term care costs for patients treated with tPA. This 3- to 4.5-hour time window leads to an increase in costs. This increase results from higher initial hospitalization costs that are associated with better outcomes and higher costs. The incremental cost-effectiveness of intravenous tPA given within 3 to 4.5 hours, compared with treatment without tPA, is $22 000 per QALY gained.

The robustness of our study results are supported by the probabilistic sensitivity analysis. At the commonly used WTP threshold of $50 000 per QALY, there was a > 85% probability that tPA is the preferred treatment option. Although $50 000 per QALY is a commonly used threshold, it is not a universally accepted norm, and some experts have recommended against using any kind of preset threshold. We have therefore presented a full range of thresholds in a cost-effectiveness acceptability curve (Figure 4). This curve shows that tPA treatment remains the preferred option with at least a 50% probability at WTP thresholds down to $25 000 per QALY.

Multiple prior studies support the cost-effectiveness of treating acute stroke patients with tPA within 3 hours of symptom onset. An early study based on the NINDS Stroke Trial results showed that intravenous tPA therapy reduced health expenditures by $8000 per QALY (1996 US dollars). A subsequent study based on a meta-analysis of 6 trials (NINDS parts 1 and 2, ATLANTIS A and B, and ECASS-1 and -2) also found that tPA was economically dominant within the 3-hour time window. In this study, tPA therapy was associated with a gain of 0.43 QALYs and $16 000 in cost savings compared with standard treatment. In contrast, our study shows that, though cost-effective, tPA treatment in the 3- to 4.5-hour time window leads to an increase in costs. This increase results from higher initial hospitalization costs that are only partially offset by a reduction in long-term care costs for patients treated with tPA.

The difference in cost-effectiveness between this study and prior studies is the result of two key factors. First, whereas prior studies assumed the initial hospitalization costs to be nearly equivalent between groups, we assumed higher hospitalization costs for patients treated with tPA. This is based on recent cost-analysis studies showing that in-hospital costs of acute ischemic stroke are higher for patients treated with tPA compared with patients not treated with tPA. This is also reflected in higher Medicare reimbursement for patients treated with tPA (MS-DRG 61-63 = $14 806 2010 US dollars) compared with patients not treated with tPA (MS-DRG 64-66 = $8968). The relatively small increase in QALYs (0.28 over a lifetime) associated with tPA treatment is also comparable to cancer therapy. For example, radiation therapy after conservative surgery for breast cancer, compared with surgery alone, resulted in 0.09 QALYs gained and an ICER of $52 200 per QALY gained (2010 US dollars).

Our study has some limitations. First, we used best estimates from previously published data for our input parameters. By using high-quality cost data from the literature and inflating the costs to 2010 dollars, we have attempted to closely approximate current actual costs. It is, however, possible that these best estimates over- or underestimate the true value of any of the model parameters. Studies that reassess current actual costs of tPA use, stroke hospitalization, and long-term care would provide valuable data for future cost-effectiveness studies of tPA and stroke. It is unlikely that the conclusions of our study would have changed based on data derived from such studies because our findings were robust against reasonable variations in all model inputs. Second, in the Markov model, we captured future changes in health status as a result of recurrent stroke and all causes of death, but changes in functional status from causes other than stroke were not modeled. Although this is a limitation of the study, it is unlikely that tPA treatment has a significant differential effect on such changes. This limitation is therefore also unlikely to have affected the overall results of the study.

In conclusion, the balance of costs and benefits favors treatment with intravenous tPA in the 3- to 4.5-hour time window over standard nonthrombolytic therapy. From a societal perspective, this supports the use of tPA therapy in this time window for patients with acute ischemic stroke.

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**Disclosures**

None.
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