

Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke : Experience From Australian Stroke Center

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Cost-Effectiveness of Thrombolysis Within 4.5 Hours of Acute Ischemic Stroke

Experience From Australian Stroke Center

Sharman P. Tan Tanny, BmedSci; Lucy Busija, PhD; Danny Liew, MBBS, PhD, FRACP; Sarah Teo; Stephen M. Davis, MBBS, MD, FRACP; Bernard Yan, MBBS, FRACP

Background and Purpose—Previous economic studies outside Australia have demonstrated that patients treated with tissue-type plasminogen activator (tPA) within 4.5 hours of stroke onset have lower healthcare costs than those not. We aim to perform cost-effectiveness analysis of intravenous tPA in an Australian setting.

Methods—Data on clinical outcomes and costs were derived for 378 patients who received intravenous tPA within 4.5 hours of stroke onset at Royal Melbourne Hospital (Australia) between January 2003 and December 2011. To simulate clinical outcomes and costs for a hypothetical control group assumed not to have received tPA, we applied efficacy data from a meta-analysis of randomized trials to outcomes observed in the tPA group. During a 1-year time-horizon, net costs, years of life lived, and quality-adjusted life-years were compared and incremental cost-effectiveness ratios derived for tPA versus no tPA.

Results—In the study population, mean (SD) age was 68.2 (13.5) years and 206 (54.5%) were men. Median National Institutes of Health Stroke Scale score (interquartile range) at presentation was 12.5 (8–18). Compared with no tPA, we estimated that tPA would result in 0.02 life-years and 0.04 quality-adjusted life-years saved per person >1 year. The net cost of tPA was AUD \$55.61 per patient. The incremental cost-effectiveness ratios were AUD \$2377 per life-year saved and AUD \$1478 per quality-adjusted life-years saved. Because the costs of tPA are incurred only once, the incremental cost-effectiveness ratios would decrease with increasing time-horizon. Uncertainty analyses indicated the results to be robust.

Conclusions—Intravenous tPA within 4.5 hours represents a cost-effective intervention for acute ischemic stroke. (*Stroke*. 2013;44:00-00.)

Key Words: cost-benefit analysis ■ stroke, acute ■ stroke ■ thrombolytic therapy
■ tissue-type plasminogen activator

Acute ischemic stroke imposes significant health and economic burden.¹ It accounts for ≥49 million disability-adjusted life-years annually worldwide.² In Australia, the burden is estimated to be 272 500 disability-adjusted life-years, making it the second leading cause of death and disability (after ischemic heart disease).³ The total annual cost of strokes in Australia in 2011 is estimated to be the equivalent of USD \$2.25 billion.⁴

Intravenous thrombolysis with recombinant tissue-type plasminogen activator (tPA) has been shown to reduce death and disability in ischemic stroke ≤4.5 hours from onset.^{5–9} Randomized controlled studies demonstrated reduction in poor clinical outcomes by 2% to 30% for tPA treatment relative to no tPA treatment.^{10–12} Economic studies conducted in North America and Europe showed tPA to be a cost-effective intervention for stroke.^{13–16} Cost incurred at 1 year for patients treated with tPA within 3 hours of ictal onset was

USD \$29 207, and USD \$29 810 for patients not treated with tPA, resulting in estimated cost savings of USD \$600 per patient treated with tPA in the first year after stroke.^{16,17}

Although effectiveness and cost-effectiveness of tPA administered within 3 hours of symptom onset are well established, recent studies have also demonstrated benefits ≤4.5 hours after onset.^{13,18} In addition, there are inadequate data on the tPA cost-benefits in Australia. Because of differences in healthcare systems, costing methods and demographics, non-Australian data may not be relevant in Australia. One previous study¹⁹ investigated cost-effectiveness of tPA in Australian setting within 3 hours of ictal onset. However, to date, there are no Australian data to validate the cost-effectiveness of tPA when given ≤4.5 hours after onset.

We aimed to assess the cost-effectiveness of tPA treatment ≤4.5 hours after stroke onset in a contemporary Australian

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setting. The results may help inform future resource allocation for stroke treatment in Australia.

Methods

Participants

Our study was based on data from 378 patients with acute ischemic stroke who received intravenous tPA at Royal Melbourne Hospital Comprehensive Stroke Center between January 2003 and December 2011. Information was collected on age, sex, preadmission residence, discharge destination, 30-day mortality, incidence of intracranial hemorrhage, National Institutes of Health Stroke Scale score on admission and 24 hours after onset of stroke, and modified Rankin Scale (mRS) scores on admission, at discharge, and at 3-month follow-up. The mRS scores at 3 months follow-up were scored by the patients' consultant neurologists.

Efficacy of tPA

Data on efficacy of tPA versus placebo at 3 to 4.5 hours after stroke onset were drawn from the recent meta-analysis of 4 randomized trials by Lansberg et al.⁸ This analysis found that compared with placebo, the odds ratio for attaining mRS of 0 or 1 at day 90 was 1.31 (95% confidence interval, 1.07–1.59). This odds ratio was used instead of an odds ratio for the time window of 0–4.5 hours because the cost-effectiveness of tPA given within 3 hours is already well studied. Moreover, our assumption would have led to an under-estimation of the true cost-effectiveness of tPA.

Cost-Effectiveness Analysis

Decision analysis²⁰ was used to compare downstream consequences of tPA treatment (tPA group) with absence of tPA treatment (control group) and is conceptualized in Figure 1. The clinical outcome of interest was attainment of mRS of 0 or 1 at 90 days, as per the Lansberg meta-analysis.⁸ The time-horizon of the evaluation was 1 year after tPA treatment, with the assumption that patients' clinical and functional status would remain stable between 90 days and 1 year.

Outcomes in the tPA group ≤ 90 days were based on observed data drawn from the 378 tPA-treated patients at Royal Melbourne Hospital. Outcomes in the control group were derived by applying the odds ratio reported in the Lansberg meta-analysis⁸ to the observed data. Specifically (in the base-case analysis), it was assumed that in the control group, there would be 1.31-fold less patients categorized to mRS 0 or 1 at 90 days. Therefore, there would be, overall, more patients in mRS categories 2 to 6, so that the total number of patients remained the same (378). Among patients assumed to reside in categories 2 to 6, the proportional distribution across these 5 categories was assumed to be the same as in the tPA group.

The main outputs of economic analyses were as follows: (1) net costs, (2) net health effects in terms of years of life saved and quality-adjusted life-years (QALYs) saved, and (3) incremental cost-effectiveness ratio (ICER) in terms of net costs per year of life and QALYs

saved. Net costs were calculated as costs of tPA minus costs saved from the reduction in downstream healthcare utilization.

Cost and Utilities

Cost and utility inputs used for the decision analysis are summarized in Table 1. In-hospital costs were based on actual expenditure for each of the 378 patients included in our study. These data were sourced from the Clinical Costing Unit of Royal Melbourne Hospital, which assigns detailed, itemized costs to every patient encounter. Out-of-hospital costs were based on discharge destinations of patients included in the study and estimated from the North East Melbourne Stroke Incidence Study.¹ Inflation rates were not factored in. The cost of tPA was assumed to be USD \$3465, on the basis of the cost of 2 vials of tPA administered per patient (\$1640.29 per 50-mg vial) and personnel cost based on a neurology advance trainee pay grade (USD \$63 per hour).

We assumed that patients who survived to 90 days after stroke would survive ≤ 1 year. Hence, total years of life lived by each cohort simply equated to number of survivors at 3 months. QALYs were derived by multiplying total number of patient-years lived during the first 12 months after tPA by utilities commensurate with their mRS scores. The utilities associated with different mRS scores after stroke were derived from Samsa and are summarized in Table 1.²¹ For example, mRS score 1 was assigned a utility of 0.8. Therefore, each 90-day survivor (also assumed to survive 1 full year) with an mRS of 1 was assumed to have lived $1 \times 0.8 = 0.8$ QALYs. In this calculation, we assumed that mRS stayed constant between 90 days and 12 months from the acute event.

Uncertainty Analysis

To account for uncertainty in key model inputs, uncertainty (probabilistic sensitivity) analyses were undertaken via Monte Carlo simulation,²² using @Risk for Microsoft Excel (Palisade Corporation; Ithaca, NY). In terms of the odds ratio for attaining mRS score of 0 or 1, the point estimate and limits of the 95% confidence interval reported by Lansberg et al.⁸ were applied to a triangular probability distribution, with the limits of the 95% confidence interval cutting off 2.5% of the distribution at each end. A uniform probability distribution was applied to the uncertainty range of the utilities reported by Samsa²¹ (Table 1), and a $\pm 20\%$ uniform probability distribution applied to the assumed costs. The Monte Carlo simulation involved 10 000 model simulations. With each iterative evaluation, values for the key data inputs were sampled according to their probability distributions. Multiple model outputs were thus generated and probability distributions around these generated to describe uncertainty.

Results

Participants

Patient characteristics at presentation are summarized in Table 2. The mean (SD) age was 68.2 (13.5) years and 54.5% were men.

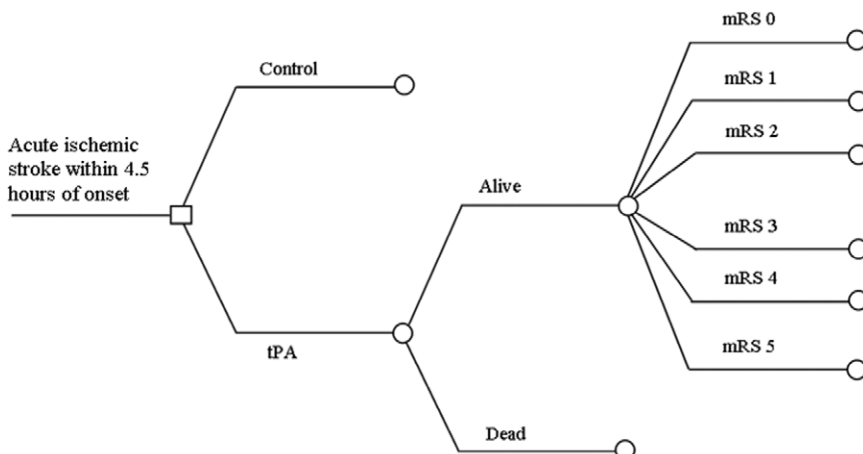


Figure 1. Decision analytic model used to model cost-effectiveness analysis of tissue-type plasminogen activator within 4.5 hours of acute ischemic stroke. Note: The decision analytic model was constructed by analysis of the Royal Melbourne Hospital stroke registry data and literature review. The 2 main branches are the tPA group and the hypothetical control group. The square node represents a decision node. The circular nodes represent chance nodes. The branches of the decision tree represent the treatment nodes. The branches of the decision tree represent the treatment. mRS indicates modified Rankin Scale.

Table 1. Cost and Utility Estimates Used in Decision Analysis Modeling of Cost-Effectiveness of tPA Within 4.5 hours of Acute Ischemic Stroke

Modified Rankin Scale	Poststroke Utilities*		Median Costs (USD)†		
	Base-Case Value	Uncertainty Range	Inpatient Cost	Out-of-Hospital Cost	Total Cost
0: No symptoms at all	0.80	0.80–1.00	\$20650	\$9203	\$29406
1: No significant disability, despite symptoms	0.80	0.80–0.95	\$20895	\$11 597	\$32214
2: Slight disability	0.65	0.68–0.90	\$22503	\$13975	\$36205
3: Moderate disability	0.50	0.45–0.65	\$22503	\$15375	\$37878
4: Moderately severe disability	0.35	0.10–0.40	\$20107	\$18208	\$39522
5: Severe disability	0.20	0.00–0.32	\$20107	\$21 186	\$41780
6: Death	0.00	0.00–0.00	—	\$14572	\$16727

*Data source: Samsa et al.²²

†Inpatient cost sourced from the Clinical Costing Unit of Royal Melbourne Hospital. Out-of-hospital cost based on discharge destination of patients in our study and estimated from North East Melbourne Stroke Incidence Study.

Information on preadmission residence was available for 355 (94%) patients. Before admission, the majority (69.8%) lived at home with relatives, 18.8% had been independent at home, and 5.0% lived at home with community support. One patient (0.3%) was an inpatient at Royal Melbourne Hospital at stroke onset.

Before stroke, the majority of patients (73.8%) were fully functioning with no symptoms (mRS, 0), and only a small proportion (6.9%) had moderately severe disability (mRS, 4). At stroke onset, median National Institutes of Health Stroke Scale score (interquartile range) was 12 (8–18).

Outcomes of patients treated with tPA are summarized in Table 3. By 24 hours, median National Institutes of Health

Stroke Scale score decreased to 8 (3–16). A substantial proportion of patients (7.1%) experienced hemorrhage (symptomatic intracranial hemorrhage or parenchymal hematoma type 2) after tPA. The majority of patients (31.5%) were discharged to inpatient rehabilitation, followed by geriatric evaluation and management unit (18.3%), home with relatives (15.9%), home with community support (11.6%), independent to home (4.2%), and palliative care (2.3%). In-hospital mortality was 12.4%, and 30-day mortality was 13.4%. At discharge, the majority of patients had moderately severe (26.2%) or severe (13.8%) disability (mRS, 4 and 5, respectively), and only a small proportion had no symptoms (mRS, 0; 8.2%) or no significant disability despite symptoms (mRS, 1; 8.2%).

The distribution of mRS scores among the hypothetical control group is also summarized in Table 3. Compared with the tPA group, the numbers of patients in each of mRS categories 0 and 1 were reduced by a factor of 1.31 (76%). Consequently, the numbers of patients in each of the other mRS categories increased by 12% (such that overall number of patients was maintained at 378).

Table 2. Clinical and Demographic Characteristics of Patients Treated With tPA at the Royal Melbourne Hospital Between January 2003 and December 2011 (N=378)

Characteristic	
Age, mean (SD)	68.2 (13.5)
Male, n (%)	206 (54.4)
Premorbid function (preadmission modified Rankin Scale), n (%)	
0: No symptoms at all	279 (73.8)
1: No significant disability despite symptoms	11 (2.9)
2: Slight disability	25 (6.6)
3: Moderate disability	37 (9.8)
4: Moderately severe disability	26 (6.9)
5: Severe disability	0 (0.0)
NIH Stroke Scale score at admission, median (IQR)	12 (8–18)
Residence before admission, n (%)	
Independent at home	71 (18.8)
Home with relatives	264 (69.8)
Home with community support	19 (5.0)
Geriatric evaluation and management unit	1 (0.3)
Unknown	23 (6.1)

IQR indicates interquartile range; tPA, tissue-type plasminogen activator; and NIH, National Institutes of Health.

Cost-Effectiveness of tPA

In the base-case analysis, the total number of years lived by the end of the 12-month study period was 305 among the tPA group, compared with 296 in the control group. Quality of life among stroke survivors treated with tPA was also better compared with the untreated cohort, with 185 and 171 QALYs lived, respectively. These equated to 0.02 and 0.04 years of life and QALYs saved per person. The total costs ≤1 year incurred by the tPA group was AUD \$11 241 869 compared with AUD \$11 220 849 for the control group, meaning tPA was associated with a net cost of AUD \$55.61 per patient. The ICERs were, therefore, AUD \$2377 per life-year saved and AUD \$1478 per QALY saved, during a 1-year time-horizon. Because the costs of tPA are incurred only once, the ICERs would decrease with an increasing time-horizon.

Of the 10000 results generated from the uncertainty analyses (Monte Carlo simulation), the 2.5th and 97.5th percentiles

Table 3. Outcomes for Patients Treated With tPA and a Hypothetical Cohort of Control Patients

Outcomes	tPA (N=378)	Control Group—Predicted (n=378)
NIH Stroke Scale score at 24 h, median (IQR)	8 (3–16)	...
Hemorrhage (symptomatic ICH and PH-2), %	7.1	...
Function at discharge (modified Rankin Scale), n (%)		
0: No symptoms at all	31 (8.2)	...
1: No significant disability despite symptoms	31 (8.2)	...
2: Slight disability	39 (10.3)	...
3: Moderate disability	45 (11.9)	...
4: Moderately severe disability	99 (26.2)	...
5: Severe disability	52 (13.8)	...
6: Death	47 (12.4)	...
Unknown	34 (9.0)	...
Function at 3 mo (modified Rankin Scale), n (%)		
0: No symptoms at all	60 (15.9)	46 (12.1)
1: No significant disability despite symptoms	68 (18.0)	52 (13.7)
2: Slight disability	58 (15.3)	65 (17.2)
3: Moderate disability	51 (13.5)	57 (15.1)
4: Moderately severe disability	39 (10.3)	44 (11.6)
5: Severe disability	29 (7.3)	33 (8.6)
6: Death	73 (19.3)	82 (21.7)
Discharge destination, n (%)		
Independent at home	16 (4.2)	...
Home with relatives	60 (15.9)	...
Home with community support	44 (11.6)	...
Inpatient rehabilitation	119 (31.5)	...
Geriatric evaluation and management unit	69 (18.3)	...
Palliative	9 (2.3)	...
Death	51 (13.4)	...
Other	8 (2.1)	...
Unknown	2 (0.5)	...
30-Day mortality, %	13.4	...

ICH indicates intracranial hemorrhage; IQR, interquartile range; tPA, tissue-type plasminogen activator; NIH, National Institutes of Health; and PH-2, parenchymal hematoma type 2.

for the ICERs were USD \$1298 and USD \$9222 per life-year saved, and USD \$696 and USD \$5017 per QALY saved, respectively. The results for the USD per life-year saved are summarized in Figure 2 as cost-effectiveness acceptability curves, which plot the probability of tPA being cost-effective, depending on what threshold is used to determine cost-effectiveness. At the commonly used cost-effectiveness threshold of USD \$50 000 to USD \$100 000 per QALY saved²³, our analysis suggests that tPA is close to 100% probability of cost-effectiveness.

Discussion

In this study, we showed that tPA administration for acute ischemic stroke ≤ 4.5 hours would be highly cost-effective in an Australian stroke population. The threshold for cost-effectiveness criteria is generally in the range of USD \$50 000 to USD \$100 000 per QALY.²³ For comparison, the ICER of renal dialysis relative to the next least costly alternative is on average USD \$129 090 per QALY.²⁴ Also, note that these ICER thresholds also apply to lifetime horizons, although our study was limited to a short 1-year time-horizon. Cost-effectiveness of interventions, especially those for which costs are only incurred once, improves with longer model time-horizons. We elected not to simulate a lifetime time-horizon for 2 reasons. First, our evaluation >1 year already showed cost-effectiveness, and second, we did not have access to data inputs that would have allowed for accurate simulation of events over longer periods.

To our knowledge, this study is the first Australian study of its kind because other studies previously investigated cost-effectiveness of tPA within the 3-hour time window,^{15,17,19,25} and those that have investigated cost-effectiveness within the 4.5-hour window were conducted in non-Australian settings.^{13,18}

Within the 3-hour time window, studies have estimated a decrease in health expenditure by AUD \$2669 during 1-year time-horizon¹⁹ to AUD \$3654 during a 30-year time-horizon.²⁶ Because tPA administration was also associated with health gain, it was considered a dominant strategy (less costly and more effective), and hence, ICERs were not calculated. These included 1 Australian study by Mihalopoulos et al,¹⁹ but because this had been based on 1994 data, results may no longer be applicable.

Because the results of the second European Cooperative Acute Stroke Study III showed the efficacy and safety of tPA administration between 3 and 4.5 hours after the onset of acute ischemic stroke, treatment practice has changed accordingly.⁵ Hence, there is a need to study the cost-effectiveness within the 4.5-hour time window. This has been performed in Europe and United States but not in Australia. Findings include ICERs ranging from EUR \$2432 to EUR \$37 462 per QALY saved in a European study on a hypothetical cohort by Boudrea et al¹⁸ and an ICER of USD \$21 978 per QALY over a lifetime time-horizon in the US study by Tung et al.¹³

In non-Australian settings, cost-effectiveness within the 6-hour time window has been studied. In United States, Johnston²⁷ found a cost saving of USD \$8099 per QALY >10 years; and in the United Kingdom, Sandercock et al^{25,28} found an ICER of GBP \$13 581 per QALY saved >1 -year lifetime time-horizon. The findings of these individual studies were supported by Jung et al¹⁴ in a systematic review of 8 studies across 6 countries with a 1-year to lifetime time-horizon. This study found that tPA administration led to a net long-term cost saving of USD \$21 938 to USD \$207 253 from a societal perspective and USD \$4662 to USD \$41 137 from a healthcare system perspective.

The main strength of our study lies in the use of contemporary, representative data inputs, and the adoption of a micro-simulation approach to modeling. Compared with the more commonly used cohort analysis model, which is limited by an unrealistic assumption that every subject in the modeled

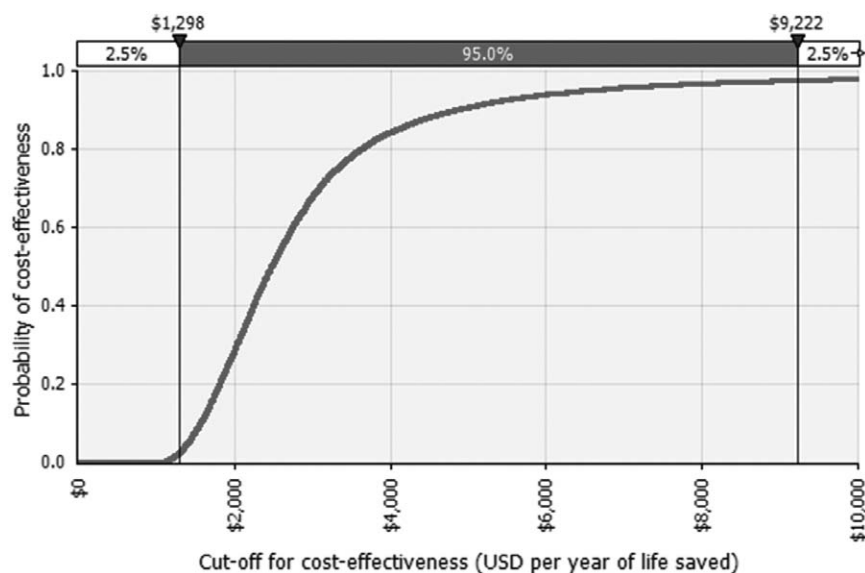


Figure 2. Results of the uncertainty analyses: cost-effectiveness acceptability curves. The probabilities of achieving cost-effectiveness (y axis) are plotted against threshold for incremental cost-effectiveness ratios (ICERs) (x axis). QALYs indicates quality-adjusted life-years.

cohort shares the same characteristics, a microsimulation model uses individual-level data and simulates the unique health experiences of every subject.²⁹ If the modeled subjects are representative of the population to whom results are to be applied, uncertainty surrounding the results of the model is reduced, and its generalizability improved.²² Our study population, derived from a major stroke unit that services patients whose demographic profile resembles that of all Australians, is likely to be representative of Australian patients with stroke eligible for tPA. To further reduce uncertainty, cost data were based on actual care expenditure for these patients. Finally, uncertainty was limited by restriction of the time-horizon of our model to 1 year, which obviated the need for assumptions on long-term events and costs. However, as mentioned, having a short time-horizon meant a significant underestimation of the lifetime cost-effectiveness of tPA.

The main limitation of our study pertained to the assumption that survival and quality of life among our study subjects would not change between 90 days and 12 months after stroke. However, given that patients with worse outcomes (as for the control group versus the tPA group) are more likely to experience deterioration and death, our assumption served to further underestimate the cost-effectiveness of tPA.

Furthermore, although our analysis was concerned with using tPA in the time window of 0 to 4.5 hours, efficacy data were drawn from analyses of studies of tPA being given between 3 and 4.5 hours.⁸ As discussed, this OR was used instead of an OR in the time window of 0 to 4.5 hours because the cost-effectiveness of tPA given within 3 hours is already well studied. Moreover, our assumption would have led to an under-estimation of the true cost-effectiveness of tPA.

Conclusions

Our study suggests that intravenous tPA given within a 4.5-hour window to patients with acute ischemic stroke is likely to be highly cost-effective. Given that the delivery of acute stroke treatment requires an integrated hospital systems approach, this finding has implications for healthcare resource allocation.

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Disclosures

None.

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