Stroke

CLINICAL AND POPULATION SCIENCES

# Cost-Effectiveness of Tenecteplase Before Thrombectomy for Ischemic Stroke

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**BACKGROUND AND PURPOSE:** Tenecteplase improved functional outcomes and reduced the requirement for endovascular thrombectomy in ischemic stroke patients with large vessel occlusion in the EXTEND-IA TNK randomized trial. We assessed the cost-effectiveness of tenecteplase versus alteplase in this trial.

**METHODS:** Post hoc within-trial economic analysis included costs of index emergency department and inpatient stroke hospitalization, rehabilitation/subacute care, and rehospitalization due to stroke within 90 days. Sources for cost included key study site complemented by published literature and government websites. Quality-adjusted life-years were estimated using utility scores derived from the modified Rankin Scale score at 90 days. Long-term modeled cost-effectiveness analysis used a Markov model with 7 health states corresponding to 7 modified Rankin Scale scores. Probabilistic sensitivity analyses were performed.

**RESULTS:** Within the 202 patients in the randomized controlled trial, total cost was nonsignificantly lower in the tenecteplase-treated patients (40 997 Australian dollars [AUD]) compared with alteplase-treated patients (46 188 AUD) for the first 90 days($P$=0.125). Tenecteplase was the dominant treatment strategy in the short term, with similar cost (5412 AUD [95% CI, −13 348 to 2523]; $P$=0.181) and higher benefits (0.099 quality-adjusted life-years [95% CI, 0.001–0.1967]; $P$=0.048), with a 97.4% probability of being cost-effective. In the long-term, tenecteplase was associated with less additional lifetime cost (96 357 versus 106 304 AUD) and greater benefits (quality-adjusted life-years, 7.77 versus 6.48), and had a 100% probability of being cost-effective. Both deterministic sensitivity analysis and probabilistic sensitivity analyses yielded similar results.

**CONCLUSIONS:** Both within-trial and long-term economic analyses showed that tenecteplase was highly likely to be cost-effective for patients with acute stroke before thrombectomy. Recommending the use of tenecteplase over alteplase could lead to a cost saving to the healthcare system both in the short and long term.

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**Key Words:** cost-benefit analysis ■ infarction ■ stroke ■ tenecteplase ■ thrombectomy



Stroke is a leading cause of disability and death worldwide and, therefore, a major economic burden to society. Reperfusion therapies with thrombolysis and endovascular thrombectomy have transformed patient outcomes by reducing disability and are highly cost-effective.[1,2] Alteplase administered within 4.5 hours of stroke onset reduces disability in a broad range of patients with ischemic stroke,[3] and endovascular thrombectomy (in addition to alteplase in eligible patients) improves functional outcomes in patients with large vessel occlusion.[4] Although the probability of alteplase-induced reperfusion before endovascular thrombectomy was low (<10%),[4] patients who responded rapidly to alteplase were often excluded from thrombectomy trials.

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **AUD** | Australian dollar |
| **IQR** | interquartile range |
| **mRS** | modified Rankin Scale |
| **QALY** | Quality-adjusted life-year |
| **USD** | US dollar |

Furthermore, meta-analysis of observational studies suggested that alteplase pretreated patients had improved recanalization and better outcomes than patients ineligible for alteplase, although the reasons for ineligibility may have confounded the results.[5] Tenecteplase—a genetically modified variant of alteplase with greater fibrin specificity and longer half-life—is established as the first-line intravenous thrombolytic treatment for myocardial infarction.[6] The EXTEND-IA TNK randomized trial (Tenecteplase Versus Alteplase Before Thrombectomy for Ischemic Stroke) demonstrated that thrombolysis with intravenous tenecteplase before endovascular thrombectomy increased reperfusion and improved functional outcomes versus alteplase.[7] Symptomatic intracerebral hemorrhage occurred in 1% of both the tenecteplase and alteplase-treated patients.[7]

Tenecteplase is cost-effective for acute myocardial infarction versus alteplase using simulation over a lifetime horizon, despite increased initial cost due to higher overall patient survival.[8] We assessed the cost-effectiveness of tenecteplase for large vessel ischemic stroke via 2 approaches: (1) within-trial economic analysis of the EXTEND-IA TNK trial; (2) long-term modeling to extrapolate the short-term outcomes observed in the trial over the cohort's lifetime.

# METHODS

## Within-Trial Economic Analysis

The data that support the findings of this study are available from the corresponding author upon reasonable request. Post hoc within-trial economic analysis used data collected during the EXTEND-IA TNK randomized trial comparing tenecteplase (0.25 mg/kg, maximum 25 mg) or alteplase (0.9 mg/kg, maximum 90 mg) 0 to 4.5 hours after symptom onset in ischemic stroke patients with large vessel occlusion for the first 90 days. The trial protocol[9] and results[7] were reported previously. In total, 202 patients recruited at 13 sites in Australia and New Zealand between March 2015 and October 2017 were followed for 90 days with functional outcome assessed used the modified Rankin Scale (mRS). The trial was approved by an institutional ethics committee at each site, and written informed consent was obtained from each patient or a legal representative before enrollment except in jurisdictions that allowed deferral of consent for emergency treatment, in which case consent to continue participation was obtained.

## Perspective and Time Horizon

An Australian healthcare system perspective was taken with the time horizon consistent with the trial follow-up. All costs were expressed in Australian dollars (AUD) for the 2017 reference year. The Consumer Price Index for health goods was applied to inflate the cost,[10] if no recent unit price was available.

## Resource Utilization and Costs

Resources used during the index stroke hospitalization (including emergency department presentation of the index hospitalization, thrombectomy, intensive care unit, etc), inpatient rehabilitation admission, and outpatient rehabilitation were collected prospectively during the trial using a standardized data collection tool. The cost of emergency department visits and acute stroke hospitalizations was extracted directly from the hospital costing databases of Royal Melbourne Hospital; the average cost adjusted by the length of stay was used as a proxy for the other 12 sites. The number of outpatient rehabilitation sessions was sourced from the published literature.[11] The unit costs of outpatient rehabilitation sessions and inpatient rehabilitation hospital admissions (average daily cost) were informed by government reports and hospital costing data from the Royal Melbourne Hospital (Table 1). The cost of thrombolytic therapy using either one 40-mg tenecteplase vial or the most cost-effective combination of 50 and 10 mg alteplase vials was calculated for each patient based on their weight and treatment allocation. The cost for medication (including medications related to stroke secondary prevention and any other comorbidities) within 90 days of the index hospitalization is not included in the current analysis.

## Outcome Measures

### *Quality-Adjusted Life-Year*

Utility (EuroQoL-5D-3L) was mapped from the mRS score at day 90 using a published algorithm.[14–16] Quality-adjusted life-year (QALY) gains for each participant were calculated from the utility weight mapped from the mRS with an assumption that baseline utility weights were comparable between the 2 groups. The average QALY gain over the trial duration for each treatment arm was then computed to allow between-group comparison.

## Cost-Efficacy Analysis

The incremental cost-effectiveness ratio was computed per additional QALY gain at day 90 regardless of the statistical significance of the difference.[17] The often cited willingness-to-pay/QALY of 50 000 AUD was adopted to ascertain the cost-effectiveness of tenecteplase versus alteplase over the trial duration.[18]

## Statistical Analysis

All analyses were performed on an intention-to-treat basis, with an assumption for the main analysis that data were missing at random. Continuous variables were summarized as mean (SD) or median (interquartile range [IQR]), depending on the distribution. Categorical variables were presented as the number and percentage and compared across groups using $\chi^2$

**Table 1. Unit Cost for Rehabilitation Services**

| Unit cost of rehabilitation | Unit | AUD | Sources |
|---|---|---|---|
| Outpatient rehabilitation | Per session | $239 | From AVERT trial economic analysis[11] |
| Fast-stream inpatient rehabilitation | Per day | $815 | Costing data from Royal Melbourne Hospital, Australia |
| Slow-stream inpatient rehabilitation | Per day | $663 | Costing data from Royal Melbourne Hospital, Australia |
| Low-level care (hostel) | Per day | $34 | Productivity commission: caring for older Australians 2011[12] |
| Nursing home/transitional care | Per day | $267 | Costing data from Royal Melbourne Hospital, Australia |
| Palliative care | Per day | $360 | Department of Health, revised residential care subsidies[13] |
| Other | … | $0 | Assumption |

AVERT indicates A Very Early Rehabilitation Trial.

statistics. Generalized linear model with gaussian distribution and log link (other family of distribution was also tested)[19] using treatment group as the factor variable and adjusted for baseline stroke severity and age was utilized to compare the QALY difference at day 90. A generalized linear model with gamma distribution and log link was adopted to compare the difference in costs between treatment groups adjusted for the same covariates. Nonparametric bootstrap simulation with 2000 iterations was used to construct 95% CIs around mean cost and effects regardless of the significance of between-group differences. The cost-efficacy analysis was performed using STATA v15.0 (StataCorp, College Station, TX).

## Long-Term Modeling

### Model Structure

A Markov model was used to evaluate the long-term cost-effectiveness of tenecteplase versus alteplase in patients with stroke eligible for endovascular thrombectomy.[20,21] Briefly, there were 7 Markov states representing 7 mRS scores (0–6). The initial status of patients in the model was their health state at day 90 as represented by their mRS score. From day 91 over the rest of their lifetime, patients could face recurrent stroke and background mortality. For those who experienced recurrent stroke, it was assumed that they could only transit to a health state that was equal to or worse than their current one and were not able to return to a better health state (eg, moving from mRS score 2–1). The long-term modeling was conducted using TreeAge software (Williamstown, MA). The model structure is shown in Figure I in the Data Supplement.

### Transition Probabilities

The only difference in transition probabilities between the 2 arms was the proportion of patients commencing the long-term simulation at each of the 6 health states (ie, mRS score of 0–5; patients who died in the first 90 days were excluded from the long-term modeling, but the costs were included). The annual probabilities of recurrent stroke were identical for the 2 treatment arms. The transition probabilities for both arms are summarized in Table 2 and Table I in the Data Supplement.

### Costs

Costs associated with each health state were sourced from published literature.[20] To account for the higher probability of recurrent events in the first year post-acute stroke, the costs of managing stroke were separately derived for the first year and subsequent years (Table 2). The cost of adverse events was included within the initial hospitalization cost (the impact of adverse events that prolonged hospital stay was captured). As treatment-related adverse events occur in the first few days, the long-term modeling did not include additional consideration of adverse effects.

### Quality-Adjusted Life-Year

The health-related quality of life (utility weight) representing each of the Markov states was obtained from published literature (Table 2).[14] Disutilities associated with experiencing recurrent stroke were not assigned since there was no evidence indicating they would be different between the 2 arms.

### Cost-Effectiveness Analysis

A lifetime time horizon with yearly cycle (ie, modeled until all patients had died) was chosen to accumulate the costs and benefits associated with tenecteplase and alteplase adjusted by the half-cycle correction. The cost and QALYs by treatment group for the first 90 days post-index stroke were also included in the long-term model. Costs and benefits were discounted at 3% annually.[31] An incremental cost-effectiveness ratio was estimated to determine the long-term cost-effectiveness of tenecteplase versus alteplase.

### Sensitivity Analyses

The Markov cohort model utilized parameters that do not have uncertainty measured at the group level, thus no *P* can be reported for the long-term modeling. However, both deterministic and probabilistic sensitivity analyses were undertaken to test the robustness of base case results. For deterministic sensitivity analysis, a series of 1-way sensitivity analyses were undertaken. The results from the 1-way sensitivity analyses were shown as Tornado diagrams, graphing sequentially the variable with the largest impact on the cost-utility results. Probabilistic sensitivity analysis was performed to assess the overall impact of uncertainty in the model by defining distributions for the key parameters (ie, variability in key transition probabilities, utilities and costs identified from deterministic sensitivity analysis). Additionally, the mRS outcome at 90 days was tested with a Dirichlet distribution. A total of 5000 iterations (ie, second-order Monte Carlo simulation) were run to obtain a mean and 95% CI for the corresponding cost and benefit. Results were plotted on a cost-effectiveness plane.

### Estimation of National Implications

To quantify the implications of administering tenecteplase at a national level, the annual numbers of patients with stroke eligible for both thrombolysis and thrombectomy were estimated

**Table 2. Model Inputs for the Long-Term Modeled Cost-Effectiveness Analysis**

| Model parameters | Base case value | Range | Distribution* | References |
|---|---|---|---|---|
| Probability of recurrent stroke | | | | |
| ≤1 y | 6.49% | … | … | Mohan et al[22] |
| >1 y | 2.01% | 0%–6% | β (α=97.97; β=4776.15) | Pennlert et al[23] |
| Probability of death with recurrent stroke | 17.83% | 10%–30% | … | Fagan et al[24] |
| | | | | Campbell et al[7] |
| Death hazard ratios | | | | Samsa et al[25] |
| mRS 0 | 1 | 1.0–1.2 | … | |
| mRS 1 | 1 | 1.0–1.2 | … | |
| mRS 2 | 1.11 | 1.0–1.2 | … | |
| mRS 3 | 1.27 | 1.2–1.4 | … | |
| mRS 4 | 1.71 | 1.3–2.0 | γ (α=99.99; λ=58.48) | |
| mRS 5 | 2.37 | 1.5–4.0 | … | |
| Utility (QALY) | | | | |
| mRS 0 | 1 | 0.76–1 | … | |
| mRS 1 | 0.91 | 0.869–0.952 | β (α=8.09; β=0.80) | |
| mRS 2 | 0.76 | 0.723–0.797 | β (α=23.24; β=7.34) | |
| mRS 3 | 0.65 | 0.610–0.689 | β (α=34.35; β=18.50) | |
| mRS 4 | 0.33 | 0.299–0.359 | … | |
| mRS 5 | 0 | 0–0.071 | … | |
| Cost of care in Australia (AUD) | | | | |
| Recurrent stroke hospitalization | $23 426 | $4025–$30 000 | γ (α=100; λ=0.0043) | AR-DRG, version 8.0 round 20 (2015–2016)[26] |
| Stroke management cost (mRS 0)† | | | | |
| ≤1 y | $10 499 | $8399–$12 599 | … | Arora et al[20]; Gloede et al[27]; Baeten et al[28] |
| >1 y | $1431 | $1145–$1717 | … | |
| Stroke management cost (mRS 1)† | | | | |
| ≤1 y | $13 230 | $10 584–$15 876 | … | |
| >1 y | $1431 | $1145–$1717 | … | |
| Stroke management cost (mRS 2)† | | | | |
| ≤1 y | $15 943 | $12 754–$19 132 | … | |
| >1 y | $1814 | $1451–$2177 | … | |
| Stroke management cost (mRS 3)† | | | | |
| ≤1 y | $17 540 | $14 032–$21 048 | … | |
| >1 y | $1814 | $1451–$2177 | … | |
| Stroke management cost (mRS 4)† | | | | |
| ≤1 y | $20 722 | $16 618–$24 926 | … | |
| >1 y | $14 027 | $11 222–$16 832 | … | |
| Stroke management cost (mRS 5)† | | | | |
| ≤1 y | $24 169 | $19 335–$29 003 | … | |
| >1 y | $17 943 | $14 354–$21 532 | γ (α=100; λ=0.0071) | |
| Cost of care in US (USD) | First 90 d (USD) | Long-term (USD) | | |
| Stroke management cost (mRS 0) | $7996 | $11 245 | | Dawson et al[29] |
| Stroke management cost (mRS 1) | $11 038 | $11 579 | | Shireman et al[1] |
| Stroke management cost (mRS 2) | $17 336 | $13 395 | | |
| Stroke management cost (mRS 3) | $21 440 | $23 009 | | |
| Stroke management cost (mRS 4) | $28 729 | $46 553 | | |
| Stroke management cost (mRS 5) | $34 319 | $68 441 | | |
| Stroke management cost (mRS 6) | $8067 | … | | |
| Rehospitalization for stroke | $23 032 | | | Chambers et al[30] |
| Additional cost of thrombectomy | $14 554 | | | Shireman et al[1] |

Stroke management cost includes costs related to medications of stroke secondary prevention, outpatient consultation, rehabilitation service, and aged care facilities in the source study.[27] AR-DRG indicates Australian Refined Diagnosis Related Groups; AUD, Australian dollar; mRS, modified Rankin Scale; QALY, quality-adjusted life-year; US, the United States; and USD, US dollar.

*Distributions are tested in the probabilities sensitivity analyses.

†The range was constructed by varying the base case value for 20%.

for Australia[32] and, for broader interest, the United States.[33–36] For the United States, the country-specific cost of care for stroke was derived to estimate the cost implications both in the short and long term. The details of cost of care corresponding to the index stroke severity (ie, defined by mRS score) for the United States are summarized in Table 2.

# RESULTS

## Within-Trial Economic Analysis

### Resource Utilization and Cost

There were 202 patients randomized, 101 to tenecteplase and 101 to alteplase. The median pretreatment National Institutes of Health Stroke Scale score was 17 (IQR, 12–22) in both treatment groups. The planned thrombectomy was performed in 75 (74.5%) of the tenecteplase-treated patients and 85 (84.2%) of the alteplase-treated patients. The main reason for not performing thrombectomy was that there was no longer any retrievable thrombus (ie, successful thrombolysis in n=22 versus n=10) or the occluded vessel could not be accessed. The median (IQR) length of stay for the acute hospitalization was 6 (3–11) and 6 (3–10) days for the tenecteplase and alteplase groups. There was a trend for patients randomized to tenecteplase to spend more time at home within the first 90 days compared with those assigned to the alteplase group: 74 days (IQR, 36–86) versus 65 days (IQR, 0–85); *P*=0.052 (Table 3). Overall, patients treated with tenecteplase were likely to incur less total cost than those treated by alteplase (40 997 versus 46 188 AUD), although this between-group difference was nonsignificant (*P*=0.125, from generalized linear model analysis).

### Outcome Measures

#### Quality-Adjusted Life-Years

As reported previously, there was a significant shift in ordinal analysis of the day 90 mRS in favor of the tenecteplase-treated patients, and a nonsignificantly higher proportion of tenecteplase patients achieved functional independence (mRS score 0–2: 63 of 101 [62.4%] with tenecteplase versus 50 of 101 [49.5%] with alteplase, *P*=0.06).[7] This translated to a mean utility at day 90 of 0.618 (SD, 0.336) for tenecteplase-treated patients versus 0.512 (0.367) for alteplase-treated patients (*P*=0.045; Table 3).

### Cost-Efficacy Analysis

Treatment with tenecteplase was associated with nominally lower costs (5412 AUD [95% CI, −13 348 to 2523]; *P*=0.181, from bootstrapping) and significantly improved quality of life (0.100 [95% CI, 0.002–0.2004]; *P*=0.048, from bootstrapping) within the 90-day trial follow-up. Using the 50 000 AUD/QALY willingness-to-pay threshold,[18] tenecteplase had a 97.4% probability of being cost-effective compared with alteplase within 90 days, including a 91.0% probability of being dominant (Figure 1). The cost-effectiveness acceptability curve is shown in Figure II in the Data Supplement.

**Table 3. Resource Utilization, Cost, and Outcomes Over the First 90 Days Poststroke**

| | Tenecteplase (n=101) | Alteplase (n=101) | *P* value |
|---|---|---|---|
| Received thrombectomy procedure | 75 (74.5%) | 85 (84.2%) | 0.083 |
| Duration of acute hospitalization, d; median (IQR) | 6 (3–11) | 6 (3–10) | 0.790 |
| Discharge destination | | | 0.567 |
| Home | 38 (37.6%) | 32 (31.7%) | |
| Fast-stream inpatient rehabilitation | 9 (8.9%) | 8 (7.9%) | |
| Slow-stream inpatient rehabilitation | 37 (36.6%) | 32 (31.7%) | |
| Low-level care (hostel) | 6 (5.9%) | 10 (9.9%) | |
| Nursing home/transitional care | 2 (2.0%) | 2 (2.0%) | |
| Palliative care | 2 (2.0%) | 6(5.9%) | |
| Other* | 7 (6.9%) | 11 (10.9%) | |
| Location at month 3 | | | 0.241 |
| Home | 75 (74.3%) | 66 (65.3%) | |
| Fast-stream inpatient rehabilitation | 1 (1.0%) | 3 (3.0%) | |
| Slow-stream inpatient rehabilitation | 4 (4.0%) | 2 (2.0%) | |
| Low-level care (hostel) | 2 (2.0%) | 0 (0%) | |
| Nursing home/transitional care | 8 (7.9%) | 12 (11.9%) | |
| Palliative care | 0 (0%) | 0 (0%) | |
| Death | 11 (10.9%) | 18 (17.8%) | |
| Home time,* d; median (IQR) | 74 (36–86) | 65 (0–85) | 0.052 |
| Cost of thrombolysis | $1637 | $3342 | <0.001 |
| Cost of thrombectomy | $13 240 | $14 331 | 0.071 |
| Cost of acute stroke unit | $13 342 | $15 654 | 0.286 |
| Cost of rehabilitation | $10 394 | $9917 | 0.915 |
| Other costs† | $2339 | $3374 | 0.121 |
| Total cost | $40 997 | $46 188 | 0.125 |
| EQ-5D utility | | | |
| Premorbid, mean (SD) | 0.884 (0.106) | 0.878 (0.126) | 0.868 |
| 90 d, mean (SD) | 0.618 (0.336) | 0.512 (0.367) | 0.045 |

Currency is expressed in AUD. AUD indicates Australian dollar; EQ-5D, EuroQol-5D; and IQR, interquartile range.

*Number of days spent at home in the first 90 d poststroke.

†Costs relating to intensive care unit, imaging at emergency department, pharmacy, administration, transport, etc.

## Long-Term Modeling

### Cost-Effectiveness Analysis

Over the lifetime time horizon, treatment with tenecteplase was associated with lower costs (96 357 AUD) and greater benefit (7.77 QALY and 10.30 life-years), compared with treatment with alteplase (106 304 AUD; 6.48 QALY and 9.27 life-years; Table 4).

### Sensitivity Analyses

The deterministic sensitivity analysis showed that the incremental cost-effectiveness ratio was sensitive to

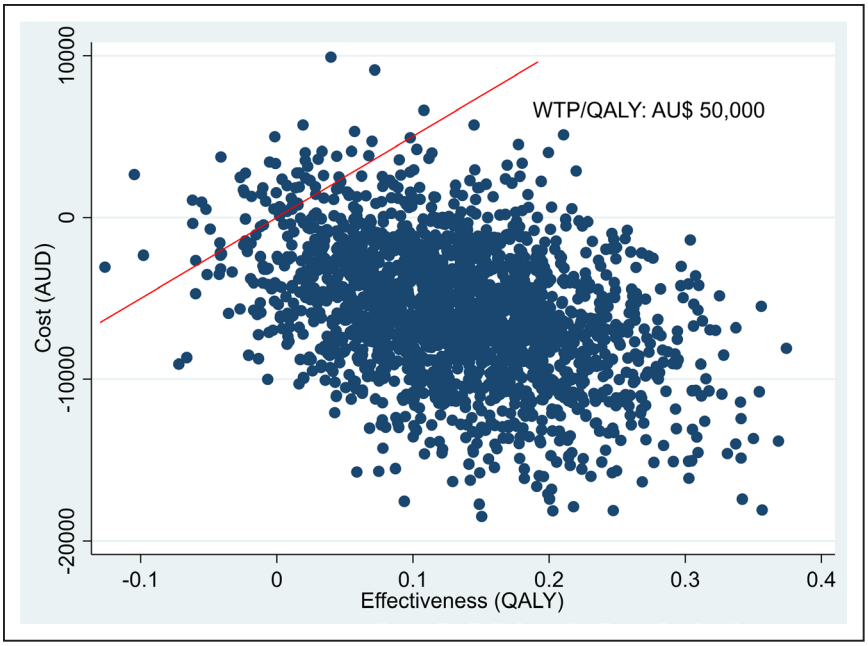


**Figure 1. Incremental cost-effectiveness plane for the within-trial economic analysis.**
AUD indicates Australian dollar; QALY, quality-adjusted life-year; and WTP, willingness to pay.

probability of background mortality and, time horizon modeled, cost of managing stroke (mRS score of 4) and utility weight with mRS score of zero. The other model parameters including probability of recurrent stroke, hazard ratio of mortality poststroke, cost of managing stroke (mRS scores of 0 and 5), and age of the index stroke impact on the base case incremental cost-effectiveness ratio to a lesser extent (Figure III in the Data Supplement).

The probabilistic sensitivity analyses showed that by incorporating the uncertainty of key model parameters, the results in terms of costs and effects (QALY and life-years) were slightly different from the base case, with both lower cost and benefits (in terms of QALY; Table 4). However, the conclusion of the cost-effectiveness analysis remained unchanged, with tenecteplase being the dominant treatment option (ie, lower cost and greater benefit; Figure 2).

### *Estimation of National Implications*

In the United States, stroke occurs in >795 000 people per annum, 87% are ischemic,[33] and 10% of these may be eligible for thrombolysis and thrombectomy.[34–36] Care costs differ in the United States (see unit costs in Table 2), but treatment with tenecteplase before the endovascular procedure in ≈69 165 patients per annum (10% of all ischemic strokes) could lead to a total saving of 366 million US dollars (USD) within the first 3 months and an additional 435 million USD over the cohort's life time (Table II in the Data Supplement). In Australia, over 48 720 people have ischemic stroke every year.[32] It is estimated that administering tenecteplase before the scheduled endovascular intervention would potentially save a total of 28 million AUD in the short term and another 19 million AUD in the long term (purchasing power parity: 1 USD=1.11 AUD, Organization for Economic Co-operation and Development [OECD] 2018).[37]

## DISCUSSION

This study has demonstrated short-term and long-term economic dominance of tenecteplase over alteplase in patients with ischemic stroke caused by large vessel occlusion in whom endovascular thrombectomy was planned. This resulted from reduced medication costs, reduced requirements for endovascular thrombectomy, and reduced long-term care costs flowing from the reduction in disability and improved quality of life.

**Table 4. Results of Long-Term Modeled Cost-Effectiveness Analysis**

| | Cost | QALY | LY | ICER |
|---|---|---|---|---|
| Base case analysis | | | | |
| Tenecteplase | $96 357 | 7.77 | 10.30 | Dominant |
| Alteplase | $106 304 | 6.48 | 9.27 | … |
| Probabilistic sensitivity analysis | | | | |
| Tenecteplase | $96 350 (92 267–100 673) | 7.77 (7.09–8.27) | 10.30 (10.06–10.51) | Dominant |
| Alteplase | $106 311 (102 286–110 569) | 6.48 (5.82–6.86) | 9.27 (9.22–9.32) | … |

Dominant means tenecteplase is associated with less costs and greater benefits than alteplase. Currency is expressed in Australian dollars. ICER indicates incremental cost-effectiveness ratio; LY, life-year; and QALY, quality-adjusted life-year.

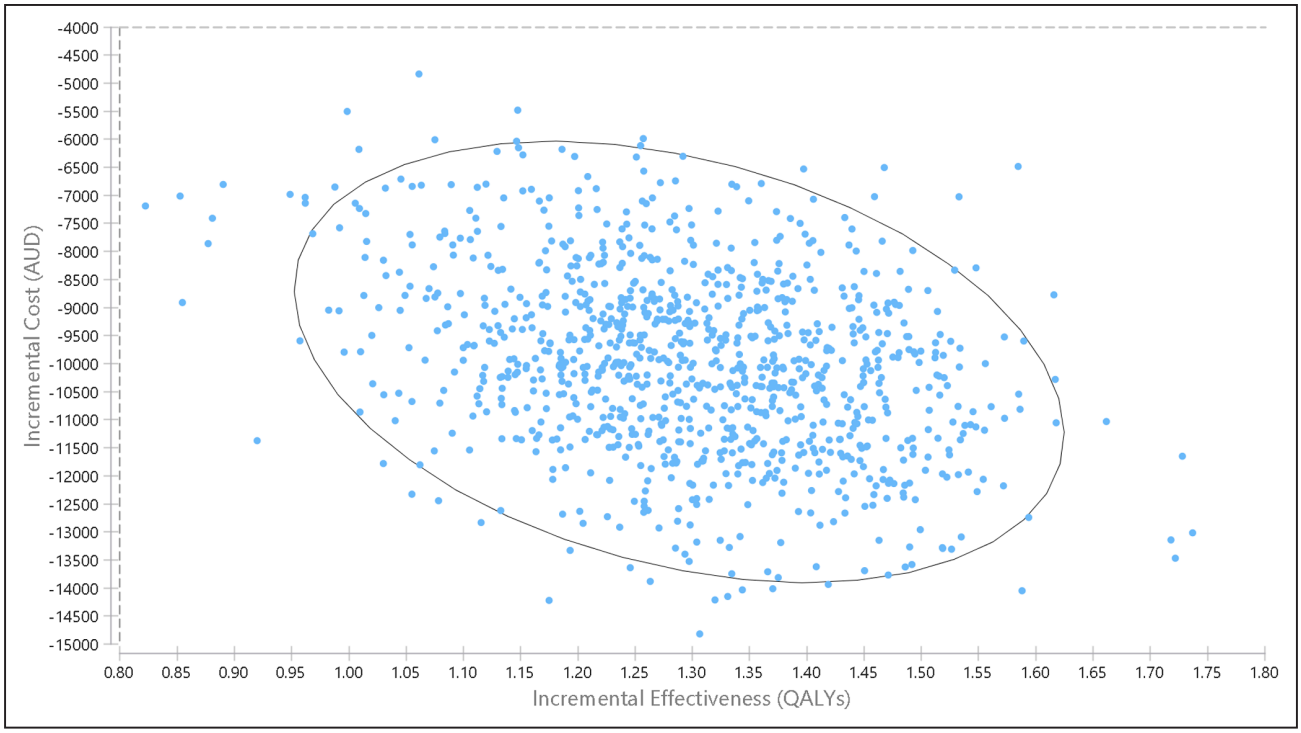


**Figure 2. Incremental cost-effectiveness plane for the long-term modeling.**
AUD indicates Australian dollar; and QALY, quality-adjusted life-year.

Although the EXTEND-IA TNK trial was conducted in Australia and New Zealand, the cost savings are likely to generalize to other health systems. Tenecteplase at stroke dosage is also less expensive than alteplase in the US market (by ≈3000 USD), but in other countries, for example, Canada, there is little cost differential. The reduction in the requirement for thrombectomy procedure in 1 in 10 patients treated with tenecteplase rather than alteplase does, however, reduce costs substantially in all health systems.[1] Differential costs related to reduced disability in the tenecteplase group are also consistently beneficial across health systems. We estimate that the use of tenecteplase rather than alteplase across the United States for eligible large vessel ischemic stroke patients (69 165 patients per annum) would save 366 million USD in acute hospital costs (including avoided thrombolysis and thrombectomy for the first 3 months) with an additional 435 million USD in savings over the lifetime. In Australia, over 48 720 people have an ischemic stroke every year. Tenecteplase before the endovascular intervention for 4872 large vessel occlusion patients would potentially save a total of 28 million AUD in the short term and another 19 million AUD in the long term.

The majority (75%) of EXTEND-IA TNK patients were treated at endovascular thrombectomy-capable hospitals, and the median time from thrombolysis to commencement of endovascular thrombectomy was 43 minutes. The clinical and economic benefits may be further increased in drip-and-ship models of care where the longer time between thrombolysis and thrombectomy increases the probability of pre-endovascular reperfusion. In addition to further reductions in the requirement for thrombectomy, earlier reperfusion consistently translates to reduced disability and, therefore, lower long-term care costs.[38] Tenecteplase, therefore, has great potential to improve stroke outcomes in the geographically dispersed populations common in Australia and North America. The EXTEND-IA TNK part 2 trial specifically included patients in rural and regional centers and found 34% of tenecteplase-treated patients had reperfused by the time of arrival at a thrombectomy-capable hospital.[39] The practical benefits of bolus administration of tenecteplase are also valuable in the context of interhospital transfers to avoid departure delays related to the 60 minute alteplase infusion and remove the need for medical escort in some systems, further reducing costs.

EXTEND-IA TNK did not evaluate tenecteplase as a stand-alone treatment for large vessel occlusion without thrombectomy. However, an individual patient data meta-analysis of 2 earlier trials found that tenecteplase was significantly more effective in achieving reperfusion and improved clinical outcomes versus alteplase in patients with large vessel occlusion who did not receive any endovascular thrombectomy (before the positive trials of endovascular thrombectomy).[40] In many parts of the world, hospitals are capable of delivering intravenous thrombolysis but do not have access to endovascular thrombectomy. It is likely that tenecteplase would also have clinical and economic benefits in these hospitals.

The within-trial economic evaluation was built on the prospectively collected data with optimum internal validity. All the major cost components except for the resource use related to outpatient care were captured in the within-trial economic evaluation. The long-term modeling beyond the trial was informed by the trial data and other published literature.

Limitations include that health-related quality of life was not collected during the trial. A validated mapping algorithm was, therefore, used to estimate day 90 utility for each participant. The reduction in cost of care within the first 90 days did not reach significance within the trial. However, the fixed-cost nature of the differences in thrombolytic drug and reduced endovascular thrombectomy requirement mean that a larger sample would demonstrate a significant difference. For the modeled study, a series of assumptions about the model parameters were required. To test the robustness of the base case results, extensive sensitivity analyses were undertaken. The base case result was robust to the variation in key assumptions, and the cost-effectiveness acceptability curve showed that tenecteplase was cost-effective regardless of the willingness-to-pay per QALY threshold. It was assumed that the treatment effect of tenecteplase did not exist after 90 days of index stroke (same probability of recurrent stroke in both treatment groups); however, this is considered conservative and not favoring tenecteplase in the cost-effectiveness analysis. In addition, given the cost related to the acute hospitalization was sourced from one single hospital, it might reduce the generalizability of the results. However, even applying the identical costs for the first 90 days regardless of treatment groups, tenecteplase remained a cost-saving treatment. Then, the available data on risk of death by day 90 mRS score are historical. However, tenecteplase remained dominant in 1-way deterministic sensitivity analyses when assuming no increased hazard ratio for mortality by mRS score (Figure IV in the Data Supplement). Lastly, it was a post hoc economic analysis, some of the resource uses poststroke were not collected over the course of the trial. Since the 90-day outcome poststroke is the key determinant of the long-term cost-effectiveness, it is believed that the incomplete collection of resource utilization has minimal impact on the conclusion of positive cost-effectiveness of tenecteplase.

In conclusion, tenecteplase reduced short-term costs within 90 days of stroke versus alteplase with a high probability of cost-effectiveness. Long-term economic analysis showed that tenecteplase before thrombectomy was cost saving versus alteplase. The reduction in disability with tenecteplase resulted in reduced cost of long-term care, and there was also a reduction in thrombectomy-related costs given the higher proportion of patients who did not require the procedure. These cost savings are likely to apply across a range of different health systems.

## ARTICLE INFORMATION

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### Supplemental Materials

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