

CADTH Health Technology Review

Tenecteplase for Acute Ischemic Stroke

Authors: Khai Tran, Melissa Severn

ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AIS	acute ischemic stroke
ALT	alteplase
ICER	incremental cost-effectiveness ratio
mRS	modified Rankin Scale
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
TNK	tenecteplase
WTP	willingness-to-pay

Key Message

- Both included economic evaluation studies (1 from Iran and 1 from Australia) found that tenecteplase was the dominant treatment strategy (i.e., lower costs and higher benefit) compared with alteplase over a lifetime horizon.

Context and Policy Issues

There are approximately 878,000 people who currently live with stroke, and more than 89,000 strokes occur in Canada each year.¹ Stroke is the third leading cause of death in Canada.¹ The annual cost of acute care hospitalization for stroke in Canada is \$146 million.¹ The total cost of stroke to the Canadian economy is approximately \$3.6 billion per year.¹ There are 2 types of strokes: ischemic stroke, the most common form of stroke, which occurs when blood clots block blood vessels to the brain, and hemorrhagic stroke, which occurs when a blood vessel in the brain ruptures causing bleeding in or around the brain.¹ Another subclass of stroke, called a transient ischemic attack (also referred to as mini-stroke), is caused by a small clot that briefly blocks a blood vessel in the brain.¹ A transient ischemic attack is a warning sign that a major stroke may occur.¹ Approximately 1.9 billion brain cells die every minute during a stroke.¹ Therefore, early recognition of the signs of stroke and early stroke treatment and proper care as soon as possible will lead to a better chance of survival and better recovery.¹

Thrombolysis (a process using medications to break down blood clots in blood vessels) is an approved treatment for acute ischemic stroke (AIS), which is a sudden loss of blood flow to part of the brain that results in the loss of neurologic function.² Patients may be eligible for thrombolytic treatment if AIS is diagnosed within 4.5 hours of the onset of stroke symptoms.² Alteplase (ALT), a thrombolytic drug, is approved in Canada and indicated for treatment of AIS within 3 hours after the onset of stroke symptoms and after exclusion of hemorrhagic stroke.³ ALT is a recombinant tissue plasminogen activator that cleaves plasminogen to form plasmin, an enzyme involved in the degradation of fibrin clots.⁴ ALT is given as an IV infusion over a period of 1 hour at a recommended dose of 0.9 mg/kg (maximum of 90 mg).³ Research has identified several limitations of ALT, including that it has a relatively short half life (initial half life of less than 5 minutes⁵), requires a long infusion,⁶ and is associated with low incidence of reperfusion after large-vessel occlusion.⁷

Tenecteplase (TNK), a genetically modified variant of ALT, has a longer half life that allows for bolus administration⁸ and faster reperfusion.⁹ TNK has been indicated for treatment of acute myocardial infarction,¹⁰ but has yet to be approved for treatment of AIS in Canada. An economic evaluation in Greece showed TNK was cost-effective for acute myocardial infarction compared with ALT over a lifetime horizon.¹¹ A study of off-label use of TNK for treatment of AIS suggested that TNK was safe and was potentially associated with improved functional outcomes compared with ALT.¹² Evidence from the EXTEND-IA TNK (Tenecteplase Versus Alteplase Before Thrombectomy for Ischemic Stroke) randomized trial conducted in Australia showed that thrombolytic treatment with TNK at a dose of 0.25 mg/kg increased reperfusion and improved functional outcomes compared with ALT.¹³ A recent randomized trial in Canada (AcT) showed that TNK at a dose of 0.25 mg/kg was noninferior to ALT for treatment of AIS.¹⁴ Both trials^{13,14} included patients with AIS within 4.5 hours after symptom onset who met the standard-of-care criteria for IV thrombolysis. There were no differences in terms of symptomatic intracerebral hemorrhage and death between the TNK and ALT groups

in both trials.^{13,14} Thus, it is necessary to determine the comparative cost-effectiveness of these 2 thrombolytic agents to see if there is a need for change in the guidelines and clinical practice in replacing ALT with TNK for treatment of AIS.

The aim of this report is to summarize the evidence regarding the cost-effectiveness of TNK compared with ALT for AIS.

Research Question

What is the cost-effectiveness of tenecteplase compared with alteplase for acute ischemic stroke?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tenecteplase and acute ischemic stroke. CADTH-developed search filters were applied to limit retrieval to economic studies. The search was completed on December 21, 2022, and limited to English-language documents published since January 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with acute ischemic stroke
Intervention	Tenecteplase
Comparator	Alteplase
Outcomes	Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, incremental cost-effectiveness ratio)
Study designs	Economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#) or were published before 2018.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Drummond checklist¹⁵ for economic evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 30 citations were identified in the literature search. Following screening of titles and abstracts, 22 citations were excluded and 8 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were found from the grey literature search. Of the 8 potentially relevant articles, 6 publications were excluded for various reasons. Two publications met the inclusion criteria and were included in this report. [Appendix 1](#) presents the PRISMA¹⁶ flow chart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in [Appendix 2](#).

Study Design

In their economic evaluation study, Hajian et al. (2022)¹⁷ conducted a cost-utility analysis using a decision tree model and a Markov model to evaluate the cost-effectiveness of TNK versus ALT in managing AIS. The study was carried out from the payer's perspective in Iran, with a lifetime horizon. The lifetime horizon was assumed to be a maximum of 30 years, given the hypothetical patient age of 60 years at baseline. A decision tree model was constructed to model the disease's natural progression after receiving TNK or ALT for 90 days, during which time patients may or may not have received thrombectomy. Patients could experience 1 of 3 outcomes: no event, recurrent stroke, or death. The probabilities for recurrent stroke were obtained from the published literature; the probabilities of death for patients with stroke in Iran were from the Iran life tables from WHO. The Markov model assigned 1 of 7 poststroke health states to each patient using a modified Rankin Scale (mRS) (scores 0 to 6). It was assumed that the Markov model was irreversible, such that patients with recurrent stroke could stay in the same state or progress to a worse state. The annual transition probabilities between different health states were obtained from the cost-effectiveness study by Gao et al. (2020)¹⁸ that is also included in our report. In the mRS, a score of 0 is no disability, 1 is no significant disability despite symptoms, 2 is mild disability (unable to carry out all previous activities, but able to take care of own affairs without assistance), 3 is moderate disability (requires some help, but able to walk without assistance), 4 is moderately severe disability (unable to walk or unable to attend bodily needs without assistance), 5 is disability requiring constant care

for all needs, and 6 is dead. Each health state was assigned a utility value, which was used to calculate quality-adjusted life-years (QALYs), as described in the study by Gao et al.¹⁸ Costs of hospitalization procedures were obtained from 3 hospital databases. Other nonhospital costs, such as costs associated with laboratory tests, visits, home nursing, rehabilitation, and medications, were also included in the analyses. All costs were expressed in Iran's currency, rial (IRR), and converted to US dollars (US\$1 = IRR42,000 in June 2022). Costs and benefits were discounted at 5% annually.

In their economic evaluation study, Gao et al. (2020)¹⁸ performed a cost-utility analysis of TNK for large-vessel ischemic stroke via 2 approaches: within-trial economic analysis of the EXTEND-IA TNK trial¹³ and long-term modelling to extrapolate the short-term outcomes. A Markov model with 7 health states representing 7 mRS scores was used to evaluate the long-term cost-effectiveness of TNK versus ALT. The initial health status of patients in the model was their initial health state at day 90. From day 91 over the rest of their lifetime, patients in each health state could face 1 of 3 possibilities: no event, recurrent stroke, or death. Patients with recurrent stroke could only transition to a state that was equal or worse than their current state. The study was carried out from the Australian health care system perspective, with the time horizon consistent with the trial follow-up (i.e., 90 days) and a lifetime horizon for long-term modelling. The source of the clinical data was the EXTEND-IA TNK trial.¹³ The source of costs included the key study site for costs related to the acute hospitalization, published literature, and government websites. QALY gains were calculated from the utility (EQ-5D-3L) weight mapped from the mRS at day 90. Costs and benefits were discounted at 3% annually for a lifetime horizon. All costs were expressed in Australian dollars.

Country of Origin

The included economic evaluation studies were conducted by authors in Iran¹⁷ and Australia.¹⁸

Patient Population

Patient characteristics in the study by Hajian et al. (2022)¹⁷ were not reported. The study only mentioned that the target population was a hypothetical cohort of AIS patients aged 60 years at baseline.

Patients in the study by Gao et al. (2020)¹⁸ were those eligible for IV thrombolysis within 4.5 hours after the onset of ischemic stroke with large-vessel occlusion on CT angiography. The median time from stroke onset to hospital arrival was 60 minutes for the TNK group and 72 minutes for the ALT group.

Interventions and Comparators

Both the included economic evaluation studies^{17,18} assessed the cost-effectiveness of TNK versus ALT. In the study by Hajian et al. (2022),¹⁷ TNK was assumed to be administered at a dose of 0.40 mg/kg and ALT at 0.9 mg/kg. In the study by Gao et al. (2020),¹⁸ TNK was administered at 0.25 mg/kg (maximum 25 mg) and ALT at 0.9 mg/kg (maximum 90 mg).

Outcomes

The main outcome in both economic studies^{17,18} was the incremental cost-effectiveness ratio (ICER) expressed as incremental cost per additional QALY gain. In the study by Hajian et al. (2022),¹⁷ a willingness-to-pay (WTP) threshold of US\$2,756.70 (equivalent to the Islamic Republic of Iran's gross domestic product per capita) was used to assess the sustainability of the ICER. In the study by Gao et al. (2020),¹⁸ the WTP per QALY was set at AU\$50,000.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included economic evaluation studies^{17,18} are provided in [Appendix 3](#).

Both included economic evaluation studies,^{17,18} clearly stated the objective, the economic importance of the research question, the rationale for choosing the alternative comparators (i.e., TNK versus ALT), and the type of economic evaluation (i.e., cost-utility analysis) that was conducted. The analyses in both studies^{17,18} were carried out with a clear perspective and time horizon. For data collection, the source of the clinical effectiveness data in the study by Hajian et al. (2022)¹⁷ comparing TNK and ALT was not reported, whereas the source of the clinical effectiveness data in the study by Gao et al. (2020)¹⁸ was clearly stated. The study by Gao et al. (2020),¹⁸ a post hoc within-trial economic analysis, used data collected during the EXTEND-IA TNK trial which was open-label but blinded to outcome assessors.¹³ A limitation of the EXTEND trial was that its results applied to patients with ischemic stroke and large-vessel occlusion who were eligible to undergo thrombectomy,¹³ which represents approximately 13% of all patients with ischemic stroke.¹⁹ Both economic evaluation studies^{17,18} clearly reported the source of cost data and resource utilization. The estimations of utilities and QALYs were described in both studies.^{17,18} Both studies^{17,18} used a Markov model for economic evaluation of the long-term consequences of AIS. However, it was unclear whether the results of a follow-up of 90 days after treatment were long enough to be extrapolated to a lifetime horizon in the model. For the analysis and interpretation of results, both studies^{17,18} clearly stated the time horizon of costs and benefits, statistical tests and confidence intervals, justification for the choice of variables for sensitivity analysis, and the ranges over which the variables were varied. In both studies, costs and benefits were discounted at 5%¹⁷ and 3%¹⁸ annually for a lifetime horizon. However, the reason for the choice of discount rate was not stated. Both studies reported incremental analyses and presented major outcomes in a disaggregated and aggregated form. The economic evaluation studies^{17,18} used both deterministic (1-way) and probabilistic sensitivity analyses (PSA) to test the robustness of the base-case results. The conclusion in both studies^{17,18} was based on the data reported. With respect to data collection, the study by Hajian et al. (2022)¹⁷ was of moderate methodological quality (due to the use of a hypothetical AIS population and unclear source of clinical effectiveness data), whereas the study by Gao et al. (2020)¹⁸ was of good methodological quality. Both studies^{17,18} were of good methodological quality with respect to analysis and interpretation of results.

Summary of Findings

[Appendix 4](#) presents the main study findings and authors' conclusions.

Cost-Effectiveness of Tenecteplase for Acute Ischemic Stroke

The cost-utility analysis over a lifetime horizon in the study by Hajian et al. (2022)¹⁷ showed that TNK was associated with lower cost compared to ALT, with an incremental cost (US\$) of -4,444.81, whereas TNK had a higher benefit than ALT, with an incremental QALY of 0.25. The calculated ICER (US\$ per QALY) was -17,450.29, showing that TNK was the dominant strategy for managing AIS. The cost-effectiveness acceptability curve in PSA showed that TNK was dominant compared with ALT regardless of the selected threshold values.

In the study by Gao et al. (2020),¹⁸ the within-trial economic analysis (i.e., 90-day follow-up) showed TNK had a lower cost with an incremental cost (AU\$) of -5,412, and had higher benefit (i.e., incremental QALY of 0.10) compared with ALT, indicating that TNK was the dominant treatment strategy in the short-term. PSA, using a WTP threshold of AU\$50,000

per QALY, showed TNK had a 97.4% probability of being cost-effective compared with ALT within 90 days, and TNK had a 91.0% probability of being dominant over ALT. In the long-term modelling, TNK was also associated with lower lifetime cost than ALT (AU\$96,350 versus AU\$106,311) and greater benefit (QALY: 7.77 versus 6.48). Both the base-case analysis and PSA showed that TNK had a 100% probability of being cost-effective (i.e., dominant strategy).

Limitations

Both included economic evaluation studies^{17,18} had some limitations, including the assumptions of some parameters used in the model. For example, it was unclear what key assumptions were made in the analyses. Due to lack of information for the Iranian setting in the study by Hajian et al. (2022),¹⁷ some parameters, such as utility values and QALYs, relied on international evidence, which might not be applicable to the Iranian setting. The sources of clinical data and population characteristics were not clearly presented in the Iranian study, which makes it difficult to appraise the internal and external validity of the analysis.¹⁷ The study by Hajian et al. (2022)¹⁷ was carried out from the payer's perspective in Iran, which is not applicable to the Canadian context. The study by Gao et al. (2020)¹⁸ made multiple assumptions for the parameters (e.g., the probabilities of recurrent stroke, probability of background mortality, health-related quality of life, and cost of managing stroke were assumed to be identical between groups) in the analyses, which may not reflect the real situation. However, deterministic sensitivity analysis and PSA were used to test the robustness of the results, and the results were consistent with the base-case analysis. Because this study¹⁸ was a post hoc economic analysis using clinical data derived from the EXTEND-IA TNK trial,¹³ the health-related quality of life used in the analysis were not measured during the study. Therefore, a mapping algorithm from published literature was used to estimate the utility at day 90 for each patient.¹⁸ Although treatment with TNK was associated with nominally lower costs than ALT, the difference did not reach statistical significance.¹⁸ Given the lower drug cost and reduced frequency of endovascular thrombectomy procedures with the TNK treatment, a larger sample size would be needed to demonstrate a significant difference in total costs. No relevant Canadian economic evaluations were identified; however, the study by Gao et al. (2020)¹⁸ was carried out from the Australian health care system perspective, which could be generalized to the Canadian health care system. Both economic evaluation studies^{17,18} did not consider the indirect costs (i.e., societal perspective) in their models.

Conclusions and Implications for Decision- or Policy-Making

This report identified 2 economic evaluation studies^{17,18} that used a cost-utility approach to compare the cost-effectiveness of TNK versus ALT in patients with AIS. Both studies^{17,18} found TNK was the dominant treatment strategy (i.e., lower cost and higher benefit) compared with ALT over a lifetime horizon. The Australian study¹⁸ estimated a total cost savings for the Australian health care system of AU\$28 million in the short-term and another AU\$19 million in the long-term. Because the clinical effectiveness data from the AcT trial¹⁴ in Canada were

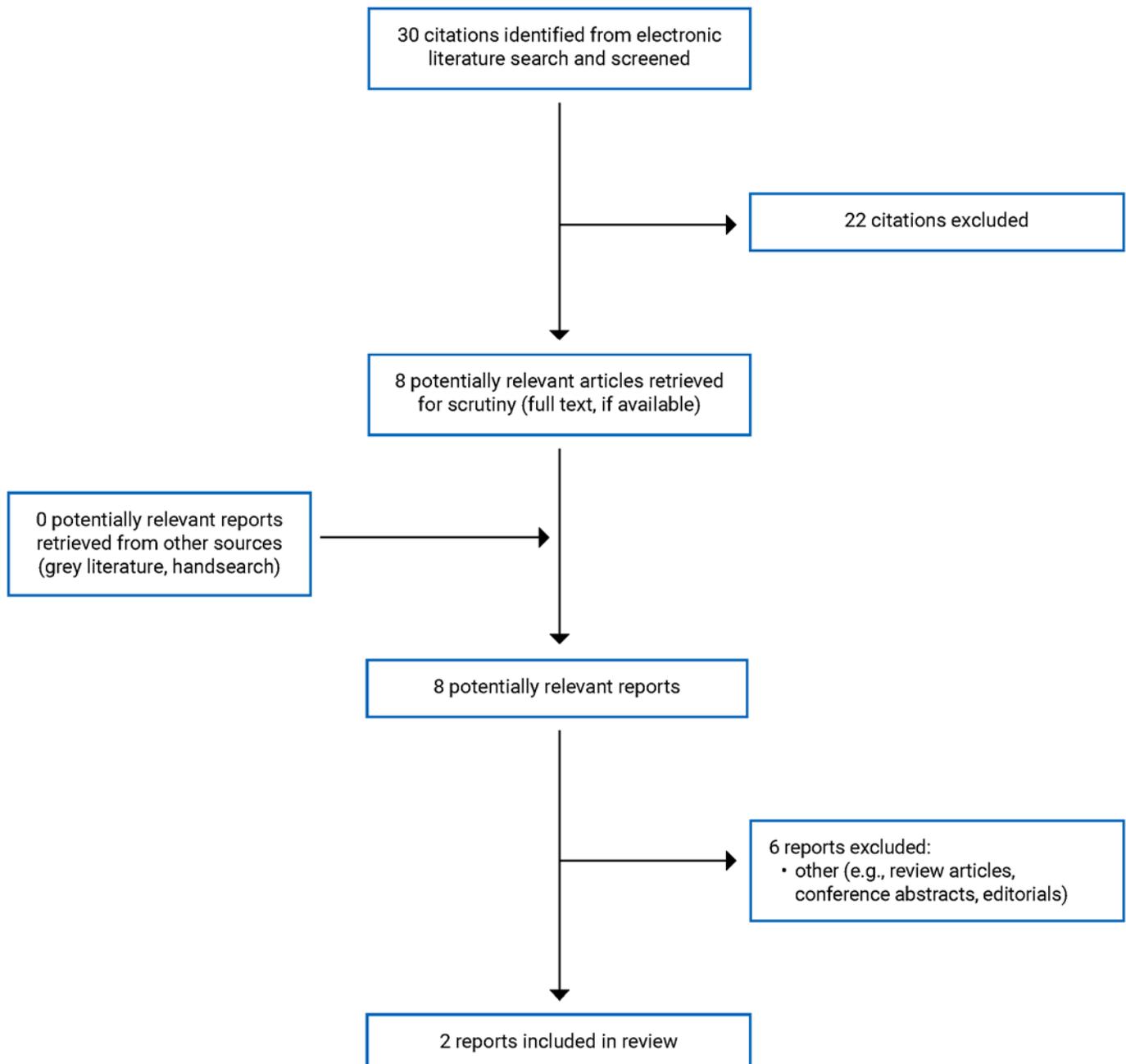
consistent with data from the EXTEND-IA trial,¹³ the cost-effectiveness of TNK treatment in the Australian study¹⁸ is likely to generalize to the Canadian health care system, providing TNK is less expensive than ALT in the Canadian market. Therefore, an economic evaluation from the Canadian health care perspective or from the Canadian societal perspective, with a lifetime horizon, would be useful to assess the cost-effectiveness of TNK in patients with AIS in Canada.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Economic Evaluations

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Hajian et al. (2022) ¹⁷ Iran Funding source: Tehran University of Medical Sciences	Analysis: Cost-utility analysis Time horizon: Lifetime Perspective: Payer's perspective in Iran	A hypothetical cohort of patients with AIS aged 60 at baseline. Patient characteristics were not reported.	Intervention: TNK (0.40 mg/kg; assuming a 70 kg patient) Comparator: ALT (0.9 mg/kg; assuming a 70 kg patient)	A decision tree model and a Markov model were used for economic evaluation of the long-term consequences of AIS. ICER was calculated as US dollars per QALY. A cost-effectiveness threshold of US\$2,756.7 (equivalent to the Islamic Republic of Iran's GDP per capita) was used to assess the sustainability of the ICER. Both deterministic (1-way) and probabilistic sensitivity analyses were used to test the robustness of the base-case results.	Source of clinical effectiveness data was not reported. The annual transition probabilities between different health states was from the cost-effectiveness study by Gao et al. (2020). ¹⁸ Cost data were obtained from 3 hospital databases. The analysis included the costs of hospitalization for stroke, radiology, electrocardiography, laboratory testing, visits, home nursing, rehabilitation, and medications. Each health state of the 7 poststroke disability states using the mRS was assigned a utility value, which was used to calculate QALY. Cost data were expressed in the Iran's currency (IRR) and converted to US dollars (US\$1 = 42,000 IRR in June 2022). Costs and benefits were discounted at 5% annually for a lifetime horizon.	The Markov model was assumed to be irreversible that patients could stay in the same health state or progress to a worse one.

Study citation, country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
<p>Gao et al. (2020)¹⁸ Australia</p> <p>Funding source: Medtronic, NHMRC of Australia, RACP, RMHF, NHSF of Australia, and the state government of Victoria</p>	<p>Analysis: Cost-utility analysis</p> <p>Time horizon: 90 days and lifetime</p> <p>Perspective: Australian health care perspective</p>	<p>Adult patients, from the EXTEND-IA TNK trial,¹³ undergoing IV thrombolysis within 4.5 hours after the onset of ischemic stroke and having cerebral vascular occlusion on CT angiography.</p> <p>Mean age, years:</p> <p>TNK: 70.4 ALT: 71.9</p> <p>% Male:</p> <p>TNK: 57 ALT: 51</p> <p>Median NIHSS score (IQR):</p> <p>TNK: 17 (12 to 22) ALT: 17 (12 to 22)</p> <p>Median time from stroke onset to hospital arrival (IQR), minutes:</p> <p>TNK: 60 (44 to 89) ALT: 72 (53 to 104)</p>	<p>Intervention: TNK (0.25 mg/kg, maximum 25 mg); N = 101</p> <p>Comparator: ALT (0.9 mg/kg, maximum 90 mg); N = 101</p>	<p>Cost-effectiveness was evaluated using both within-trial economic analysis and long-term modelling.</p> <p>For within-trial economic analysis, ICER was computed per additional QALY gained at day 90. WTP per QALY was set at AU\$50,000.</p> <p>Long-term cost-effectiveness was estimated using Markov model with 7 states representing 7 mRS^a scores (0 to 6).</p> <p>Both deterministic (1-way) and probabilistic sensitivity analyses were used to test the robustness of the base-case results.</p>	<p>Clinical data were from the EXTEND-IA TNK trial.¹³</p> <p>The cost of thrombolytic therapy using either tenecteplase or alteplase was calculated for each patient based on weight and treatment allocation.</p> <p>Resource utilization including hospitalization, inpatient rehabilitation, and outpatient rehabilitation were collected during the trial.</p> <p>The costs of ED visits and acute stroke hospitalizations were extracted from the hospital databases. The unit costs of outpatient and inpatient rehabilitation were from government reports.</p> <p>QALY gains were calculated from the utility (EQ-5D-3L) weight mapped from the mRS at Day 90.</p> <p>Costs and benefits were discounted at 3% annually for a lifetime horizon. All costs were expressed in Australian dollars.</p>	<p>It was assumed that the baseline utility weights were comparable between the 2 groups.</p> <p>It was assumed that the risk of recurrent stroke to be the same for both groups.</p> <p>All analyses were performed on an ITT basis, with an assumption for the main analysis that data were missing at random.</p> <p>In the modelled study, a series of assumptions about the model parameters were made. However, the robustness of the base-case results was tested with sensitivity analyses.</p>

AIS = acute ischemic stroke; ALT = alteplase; ED = emergency department; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; IRR = Iranian rial; ITT = intention-to-treat; IQR = interquartile range; QALY = quality-adjusted life-year; mRS = modified Rankin Scale; NHMRC = National Health and Medical Research Council; NIHSS = National Institutes of Health Stroke Scale; NHSF = National Heart and Stroke Foundation; RACP = Royal

Australasian College of Physicians; RMHF = Royal Melbourne Hospital Foundation; TNK = tenecteplase; WTP = willingness-to-pay.

*Modified Rankin Scale having scores of 0 to 6 is used to assess disability in patients who have had a stroke and is followed over time to check for recovery. A score of 0 is no disability, 5 is disability requiring constant care for all needs, and 6 is dead.

Note that this table has not been copy-edited.

Appendix 3: Critical Appraisal of Included Publications

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Table 3: Strengths and Limitations of Economic Evaluations Using the Drummond Checklist¹⁵

Strengths	Limitations
Hajian et al. (2022)¹⁷	
Study design	
<p>The authors of the study evaluated the cost-effectiveness of TNK vs. ALT in patients with AIS.</p> <p>The economic importance of the research question was stated that the cost-effectiveness of those thrombolytic strategies has not been adequately investigated.</p> <p>The analysis was performed from the payer’s perspective in Iran.</p> <p>The study used a cost-utility approach to compare the cost-effectiveness of tenecteplase vs. alteplase.</p>	—
Data collection	
<p>The primary end point for the economic evaluation was ICER, which was computed per additional QALY gained.</p> <p>Benefits were expressed as QALY gains, which were calculated from the utility value assigned from the mRS.</p> <p>Cost data were expressed in the Iran’s currency (IRR) and converted to US dollars.</p> <p>Resource utilization and costs were clearly described.</p> <p>A Markov model used to evaluate the long-term modelling was clearly described.</p>	<p>Clinical data were not clearly reported, although it appears that they were sourced from the previous economic study by Gao et al. (2020).¹⁸</p> <p>Details of the population characteristics were not reported.</p> <p>Key parameters such as utility values, QALYs, transition probabilities were obtained elsewhere, which may not be applicable to the study population.</p> <p>The assumptions that the probabilities of recurrent stroke, the probability of background mortality, the health-related quality of life, and the cost of managing stroke were identical between groups, might not be appropriate.</p>
Analysis and interpretation of results	
<p>A lifetime horizon was incorporated into the model.</p> <p>Costs and benefits were discounted at 5% annually.</p> <p>The study was explicit in terms of details of statistical tests and confidence intervals, approach to sensitivity analysis, choice of variables for sensitivity analysis, ranges over which the variables were varied, and incremental analysis.</p> <p>Major outcomes are presented in a disaggregated as well as aggregated form.</p> <p>Both deterministic (1-way) and probabilistic sensitivity analyses were undertaken, with WTP threshold being US\$2,756.7 (equivalent to the Islamic Republic of Iran’s GDP per capita).</p> <p>The results of the study answered the research question.</p> <p>The conclusion was made based on reported data that tenecteplase is the dominant strategy compared to alteplase for the management of AIS patients.</p>	<p>The reason for the choice of discount rate was not stated.</p>

Strengths	Limitations
Gao et al. (2020)¹⁸	
Study design	
<p>The authors of the study assessed the cost-effectiveness of TNK vs. ALT for large-vessel ischemic stroke based on data from the EXTEND-IA TNK trial.¹³</p> <p>The economic importance of the research question was stated that thrombolysis with IV tenecteplase increased reperfusion and improved functional outcomes compared to alteplase, and economic evaluation of these 2 strategies has not been available.</p> <p>The analysis was performed from the Australian health care system perspective.</p> <p>The study used a cost-utility approach to compare the cost-effectiveness of tenecteplase vs. alteplase.</p>	—
Data collection	
<p>Clinical data were from the results of the EXTEND-IA TNK trial.¹³ Details of the EXTEND-IA TNK trial¹³ were given. The clinical trial and the economic evaluation were conducted by the same investigator group.</p> <p>The primary end point for the economic evaluation was ICER, which was computed per additional QALY gain at day 90 and over the cohort's lifetime.</p> <p>Benefits were expressed as QALY gains, which were calculated from the utility (EuroQoL-5D-3L) weight mapped from the mRS.</p> <p>All cost data were listed in Australian dollars.</p> <p>Resource utilization and costs were clearly described.</p> <p>A Markov model used to evaluate the long-term modelling was clearly described.</p>	<p>The health-related quality of life was not collected during the EXTEND trial.</p> <p>A series of assumptions were made about the model parameters such as the probabilities of recurrent stroke, the probability of background mortality, the health-related quality of life, and the cost of managing stroke, which were assumed to be identical between groups.</p>
Analysis and interpretation of results	
<p>For short-term, the time horizon consistent with the trial follow-up (90 days) was used. For long-term modelling, a lifetime horizon was incorporated into the model.</p> <p>Costs and benefits were discounted at 3% annually.</p> <p>The study was explicit in terms of details of statistical tests and confidence intervals, approach to sensitivity analysis, choice of variables for sensitivity analysis, ranges over which the variables were varied, and incremental analysis.</p> <p>Major outcomes are presented in a disaggregated as well as aggregated form.</p> <p>Both deterministic (1-way) and probabilistic sensitivity analyses were undertaken, with WTP threshold being AU\$50,000.</p> <p>The results of the study answered the research question.</p> <p>The conclusion was made based on reported data that TNK</p>	<p>The reason for the choice of discount rate was not stated.</p>

Strengths	Limitations
dominates ALT in patients with AIS in both short-term and long-term economic evaluation.	

AIS = acute ischemic stroke; ALT = alteplase; GDP = gross domestic product; IRR = Iranian rial; mRS = modified Rankin Scale; QALY = quality-adjusted life-year; TNK = tenecteplase; WTP = willingness-to-pay.

Appendix 4: Main Study Findings

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Table 4: Summary of Findings of Included Economic Evaluations

Main study findings	Authors' conclusion
Hajian et al. (2022)¹⁷	
<p>Cost-effectiveness analysis over a lifetime horizon</p> <ul style="list-style-type: none"> • Costs (US\$) of TNK vs. ALT: 97,906.06 vs. 102,239.87 • Incremental cost (US\$): -4,444.81 • Effectiveness (QALY) of TNK vs. ALT: 6.78 vs. 6.54 • Incremental QALYs: 0.25 • ICER (US\$ per QALY): -17,450.29 • TNK was the dominant strategy <p>One-way sensitivity analysis:</p> <ul style="list-style-type: none"> • ICER was sensitive to variations in discount rates for costs and QALYs. • ICER was less impacted by probability of thrombectomy and death. • However, changes in any of the factors did not affect the study's overall results. <p>Probabilistic sensitivity analysis:</p> <ul style="list-style-type: none"> • The cost-effectiveness acceptability curve showed that TNK was dominant compared to ALT regardless of the selected WTP threshold values. 	<p>"This study's findings which is one of the first to compare TNK and ALT in AIS patients from the payer's perspective in Iran and throughout a lifetime horizon, showed that TNK strongly dominates ALT. Additionally, Sensitivity analysis demonstrated robustness of the results."¹⁷ (p. 8)</p>
Gao et al. (2020)¹⁸	
<p>Within-Trial Economic Analysis (90 days follow-up)</p> <p>Resource utilization and cost of TNK vs. ALT</p> <ul style="list-style-type: none"> • Thrombectomy: 74.5% vs. 84.2%; P = 0.083 • Median (IQR) of length of stay for acute hospitalization, days: 6 (3 to 11) vs. 6 (3 to 10); P = 0.790 • Median (IQR) of time spent at home within the first 90 days, days: 74 (36 to 86) vs. 65 (0 to 85); P = 0.052 • Total cost, AU\$: 40,997 vs. 46,118; P = 0.125 <p>Outcome measures of TNK vs. ALT</p> <ul style="list-style-type: none"> • Mean (SD) of QALY at 90 days: 0.618 (0.336) vs. 0.512 (0.367); P = 0.045 <p>Cost-effectiveness analysis</p> <ul style="list-style-type: none"> • Difference in costs (95% CI) between TNK and ALT, AU\$: -5,412 (-13,348 to 2,523); P = 0.181 • Difference in QALY (95% CI) between TNK and ALT: 0.100 (0.002 to 0.2004); P = 0.048 • PSA using 50,000 AU\$/QALY WTP threshold: TNK had a 97.4% 	<p>"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."¹⁸ (p. 3688)</p>

Main study findings	Authors' conclusion
<p>probability of being cost-effective compared with ALT within 90 days. TNK had a 91.0% probability of being dominant over ALT.</p> <p>Long-Term Modelling (over lifetime horizon)</p> <p>Base case</p> <ul style="list-style-type: none"> • Cost of TNK vs. ALT, AU\$: 96,357 vs. 106,304 • QALY of TNK vs. ALT: 7.77 vs. 6.48 • ICER: TNK being the dominant treatment option (i.e., lower costs and greater benefit) compared to ALT. <p>One-way sensitivity analysis</p> <p>Model parameters affecting ICER included:</p> <ul style="list-style-type: none"> • Probability of background mortality • Time horizon • Cost of managing stroke • Utility weight with mRS score of 0 • Probability of recurrent stroke • Hazard ratio of mortality poststroke • Age of the index stroke <p>However, TNK remained dominant in 1-way sensitivity analyses</p> <p>Probabilistic sensitivity analysis</p> <ul style="list-style-type: none"> • Costs (95% CI) of TNK vs. ALT, AU\$: 96,350 (92,267 to 100,673) vs. 106,311 (102,286 to 110,569) • QALY (95% CI) of TNK vs. ALT: 7.77 (7.09 to 8.27) vs. 6.48 (5.82 to 6.86) • ICER: TNK had 100% probability of being cost-effective (dominant). 	

ALT = alteplase; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IQR = interquartile range; mRS = modified Rankin Scale; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SD = standard deviation; TNK = tenecteplase; vs. = versus; WTP = willingness-to-pay.

Appendix 5: References of Potential Interest

Conference Abstract

Dasari D, Deshmukh AA. Cost-Effectiveness Analysis of Tenecteplase Vs Alteplase for Treatment of Acute Ischemic Stroke. *Value in Health*. 2020;23(Supplement 1):S268.

Systematic Reviews

Thelengana A, Radhakrishnan DM, Prasad M, Kumar A, Prasad K. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. *Acta Neurol Belg*. 2019;119(3):359-367. [PubMed](#)

Oliveira M, Fidalgo M, Fontao L, et al. Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis. *Am J Emerg Med*. 2021;42:31-37. [PubMed](#)

Randomized Controlled Trials

Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. *N Engl J Med*. 2018;378(17):1573-1582. [PubMed](#)

Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet*. 2022;400(10347):161-169. [PubMed](#)

Guidelines and Recommendations

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. [PubMed](#)

Review Articles

Warach SJ, Dula AN, Milling TJ, Jr. Tenecteplase Thrombolysis for Acute Ischemic Stroke. *Stroke*. 2020;51(11):3440-3451. [PubMed](#)