Title: Mechanical thrombectomy in patients with acute ischemic stroke: a cost-utility analysis

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Abstract

Background: The beneficial effects of endovascular treatment with new generation mechanical thrombectomy (MT) devices compared with intravenous thrombolysis (IVT) alone to treat acute large-artery ischemic stroke has been demonstrated in randomized controlled trials (RCTs).

Methods: A Markov decision analytic model was developed to assess the cost-effectiveness of MT+IVT versus IVT alone from the public payer perspective in Canada. Comprehensive literature searches were conducted to populate model inputs. The efficacy of MT+IVT was estimated from a meta-analysis of 5 RCTs, and the long term clinical outcomes (i.e. 91 days or more) of stroke patients were based on the Oxford Vascular Study. Incremental cost-effectiveness ratios (ICER) were calculated using a 5-year time horizon.

Results: The base case analysis showed the cost and effectiveness of MT+IVT of $126,620 (Canadian Dollars) and 1.489 QALYs (2.971 life-years), and $124,419 and 1.273 QALYs (2.861 life-years) for IVT alone. The MT+IVT strategy was associated with an ICER of $10,222 per QALY gained. Including the productivity loss and unpaid care givers' time, MT+IVT strategy dominated the IVT alone with lower costs and greater QALYs. Probabilistic sensitivity analysis showed that the probability of the MT+IVT being cost-effective was 60.7%, 91.5% and 99.8%, at thresholds of $20,000, $50,000, and $100,000 per QALY gained, respectively. The main factors influencing the ICER were the time horizon, the extra cost of MT treatment, age, and the perspective of analysis.

Interpretation: MT as an adjunct therapy to IVT appears to be cost-effective compared with IVT alone for patients with acute large-artery ischemic stroke.

Introduction:

Acute Ischemic Stroke (AIS) is caused by occlusion of a cerebral artery.[1] This condition carries a high burden of disability and death. In Canada, there are 62,000 new strokes per year and more than 300,000 stroke survivors (1.1% of the population).[2] The economic burden of stroke is high due to hospitalization, healthcare for the long term disability, and productivity loss.

Hyper-acute treatment of AIS includes therapies designed to open the occluded blood vessels in order to re-establish blood flow. This can be accomplished through either intravenous thrombolysis (IVT), and/or endovascular treatment via mechanical thrombectomy (MT) with retrievable stents and thrombus aspiration.[3] Prior to 2015, IVT was the standard of care for treating AIS. However, this treatment has several limitations including a narrow therapeutic time-window, applicability to only a subset of stroke patients, and relative ineffectiveness for stroke resulting from proximal large artery occlusion or large clot burden.[4]

Efforts to improve recanalization rates in patients with a large artery occlusion were explored with intra-arterial therapy and endovascular treatment with first-generation MT devices. While these therapies failed to show clinical benefit in randomized controlled trials (RCT),[5-7] new generation MT devices (i.e. stent retriever and thromboaspiration) have shown more promising results. A recent systematic review and meta-analysis based on 5 RCTs [8-12] of new generation MT reported a clinically significant increase in functional independence for patients who were treated with MT employing retrievable stents or thromboaspiration devices (with or without IVT) compared with those treated with IVT and/or best medical therapy. [13] This therapy has now been recommended as the new standard of care for acute ischemic stroke due to large artery occlusion.[14] We conducted cost utility analysis from the public payer perspective to determine the health economic impact of MT for treatment of large artery AIS patients in Canada.

## Methods:

### Overview

We developed a decision analytic model to address the cost-effectiveness of endovascular treatment with new generation MT devices, with or without IVT, for acute large-artery ischemic stroke patients. We modelled treatment with MT+IVT vs IVT alone as the expected treatments. More than 70% of patients in the RCTs received IVT in both study arms, and more than 80% of patients received mechanical thrombectomy in the MT+IVT arm. [8-12] We assumed an age range similar to the five recent RCTs (mean age 65 to 70 years old) and an equal proportion of men and women. [8-12] Patients should have had the occlusion and eligibility for MT confirmed by imaging and established clinical criteria, [12] and were functioning independently prior to the stroke. Clinical outcomes for the first 90 days were based on evidence from a systematic review and meta-analysis.[13] Long-term outcomes (after 3 months) were based on a large cohort of stroke patients in the United Kingdom. [15, 16] A comprehensive literature search was conducted to obtain the most appropriate inputs of health utility and cost for the cost-utility analysis.

### The Markov Decision Analytic Model

A Markov decision analytic model was developed to assess the long term clinical and economic outcomes of MT+IVT versus IVT alone (Figure 1). The model combined a decision tree for the first 90 days post-AIS and Markov model for those at risk after 3 months. The Markov model consists of three mutually exclusive health states, functional independence (modified Rankin Scale (mRS) = 0-2), disability (mRS = 3-5) and death (mRS = 6). Target patients would receive MT+IVT or IVT alone, and they would be either functionally independent, disabled, or dead at 90 days. Survivors at 90 days would join the corresponding health state in the Markov model. Patients could transfer between health states or stay in the same health states at the end of each monthly cycle, with assigned probabilities. In the model, patients could recover from disability to functional independence during the first year following a stroke, but not after the first year.

Principal assumptions

The following assumptions were made for the base-case analysis:

- Compared with IVT alone, MT+IVT can reduce the risk of disability at 90 days, but not mortality [13] as only 1 of the 5 trials showed a mortality reduction.[12]
- Patients' long- term health outcomes (i.e., more than 3 months after a major stroke) would be conditional on their health status at 90 days (i.e. functional independence or disability).
- Disability is associated with increased risk of mortality and reduced health related quality of life.
- The two treatments are associated with a similar risk of symptomatic intracerebral hemorrhage. [13] Thus, we ignored it in the model as it would not impact the incremental cost-effectiveness ratio (ICER).

Model Input Parameters

Data were obtained from the best available evidence (Table 1). When necessary, we contacted authors to clarify questions we had regarding their publications. When we could not obtain the desired estimates, we adapted available data after discussion with clinical experts. We also consulted experts to validate our parameter estimates.

Intervention Summary Estimates (the first 90 days): We conducted a meta-analysis to estimate the proportion of functional independence and mortality in the IVT alone arm at 90 days, and estimated these parameters in MT+IVT arm at the given odds ratio (OR) from meta-analysis. [13] The pooled estimate of the adjusted beta coefficient in the linear regression in 2 RCTs [8, 10] showed that MT+IVT increased health utility by 0.074 (95% confidence interval (CI): 0.014, 0.133) at 90 days, compared with IVT alone. We assumed that the two arms had the same utility at baseline, but the difference in utility linearly increased over time reaching 0.074 at 90 days post stroke. As a result, the MT arm would lead a quality-adjusted life years (QALY) gain of 0.008 in the first 90 days, i.e. (((0+ 0.074)/ 2)* 0.25)* (1-0.1786).

Natural History (3 months post-stroke): The evidence for long term outcomes for AIS is relatively sparse in Canada. For our model inputs, we used evidence from the Oxford Vascular Study, a large cohort study from the United Kingdom. [15, 16] We calibrated the parameters for the Markov model using a seven-step approach introduced by Vanni et al.[29] We summarized the calibration process in Figure 2 (more details in Appendix 1). We defined the parameters for estimating time-dependent transition probabilities and selected the proportions of mortality, functional independence and disability at 6 months, and 1 year, 2 years and 5 years in the moderate stroke group in Oxford Vascular Study as the calibration targets. [15, 16] We used a grid search to obtain plausible ranges for each parameter, and then simulated 1,000,000 parameter sets by sampling values from the plausible ranges. We assessed the goodness of fit (i.e. absolute deviation and sum of squares due to error (SSE)) for the model output produced by each parameter set. The best fitting parameter set (i.e. minimal SEE) was used as the base case, and 1,000 parameter sets were randomly selected from those meeting the acceptance criteria for probabilistic sensitivity analysis (PSA).

Costs: Costs for stroke were based on the Economic Burden of Ischemic Stroke (BURST) study [26] and are expressed in 2015 Canadian Dollars ($CAD).[30] The BURST study was a prospective cohort study of ischemic stroke patients in 12 Canadian stroke centres. Authors stratified the costs for disability status (mRS = 0-2 and mRS = 3-5) measured at discharge. Authors also divided costs into direct costs (such as emergency services, hospitalizations, rehabilitation, physician services, diagnostics, medications, etc.) and indirect costs (such as productivity loss and resource use for unpaid caregivers). We considered direct costs from the BURST study in the base case analysis, and direct plus indirect costs to be the costs from a societal perspective in the sensitivity analysis. Stroke recurrence was not included as a separate event in our model, but the health care costs of recurrence was accounted for in the cost estimates.

It is difficult to make a precise estimate of the additional cost of MT+IVT intervention relative to IVT, as apart from the materials and staffing, MT may also impact the intensive care unit time, angiography suite time, diagnostics, physician time and rehabilitation. According to the published health economic studies of MT (with or without IVT) versus IVT (or best medical therapy), the extra cost of MT treatment versus control in most studies ranged from $10,000 to $20,000. [19-25] (see Appendix 2 for more details). We estimated that the additional cost of MT therapy in Ontario lies somewhere in the middle at $15,000.

Health utilities: Several different factors significantly affect the health utility of stroke patients, including the stroke severity, co-morbidity and age. [16] For simplicity, we used EQ-5D utilities from Dorman et al which only considered the stroke severity of functional independence and disability. [27]



Analysis

Using our Markov decision analytic model, we compared the cost effectiveness of the two treatment strategies. Our main outcome was the ICER, measured as cost per QALY gained. Since there are considerable uncertainties of long term outcomes for both treatment strategies, we selected a 5 year time horizon as the base case scenario. An annual discount rate of 5% was applied to both costs and QALYs.

We conducted a scenario analysis using inputs from the ESCAPE trial. [12] Eleven health centres in Canada participated in this trial. This study included patients with proximal occlusions and contra-indications to intravenous tissue plasminogen activator, representing 25% of the trial subjects and the group of patients who may obtain the most benefit from MT treatment. We also conducted one-way and multi-way sensitivity analyses to assess factors that affect the incremental cost per QALY gained. Additionally, PSA was conducted by assigning probability distributions to model parameters (N iterations: 1,000). Distributions of inputs can be found in Table 1.

Economic analyses and calibration were conducted using SAS 9.4 (SAS, Cary, NC). We also used R 3.1.2 (R Development Core Team, Vienna, Austria) for meta-analysis ("metafor" package[31] in R) and simultaneous confidence interval for multinomial proportion ("MultinomialCI"[32] and "CoinMinD"[33] packages in R).

Results:

Base Case Analysis and Scenario Analysis Using Inputs from ESCAPE Trial

Based on the model proposed in Figure 1 and using the parameter estimates given in Table 1, MT+IVT strategy was associated with an ICER of $10,222 per QALY gained over 5 years compared with IVT alone in the base case (Table 2). Including the productivity loss and unpaid care givers' time, MT+IVT strategy dominated the IVT alone with lower costs and greater QALYs (Table 2). Compared with the base case, inputs from the ESCAPE Trial resulted in greater QALYs gained (0.348 QALYs) with higher incremental cost ($9,324), corresponding to an ICER of $26,815 per QALY gained. Although there is no universally accepted maximum willingness-to-pay threshold in Canada, the MT+IVT strategy is highly likely to be cost-effective if the willingness-to-pay threshold were $50,000/QALY or higher. Details regarding model validity can be found in Appendix 3.

Deterministic Sensitivity Analysis

We examined several factors that could affect the ICER of MT+IVT versus IVT alone (Table 3). When the model inputs were varied, the MT+IVT approach remained cost-effective in most scenarios. The main factors influencing ICER were the time horizon, the additional cost of MT and age. The ICER decreased dramatically with longer follow-up time in the first 4 years (Appendix 4), and was relatively stable at approximately $10,000/QALY gained at a follow up time of five years or longer.

Probabilistic Sensitivity Analysis

The results of the Monte Carlo simulations were consistent with those in the base case (Figure 3). The probability of MT+IVT dominating IVT alone, MT+IVT with lower costs and higher QALYs, was 0.309. The cost-effectiveness acceptability curve (CEAC) showed that the probability of the MT+IVT being cost-effective was 60.7%, 91.5% and 99.8%, at thresholds of $20,000, $50,000, and $100,000 per QALY gained, respectively (Appendix 5).

Interpretation

The results of our economic analysis demonstrate that MT is highly likely to be cost-effective according to commonly discussed cost effectiveness thresholds. This is concordant with the large clinical effect size observed in the randomized trials, and sensitivity analyses suggest that these findings are robust.

Our findings were consistent with the most recent published economic evaluation from the United States, [19] which evaluated new generation devices and used efficacy estimates from a single RCT. [8] In that evaluation, MT (with or without IVT) resulted in an ICER of $14,137 USD per QALY gained. Four earlier studies also investigated the cost-effectiveness of MT, [23-25, 34] but used older-generation devices and the health benefit was based on observational studies as RCT data was not available at that time. Later RCTs failed to demonstrate the benefits of the older-generation MT devices. [5-7] Although the results of these four earlier studies also showed that MT was cost-effective compared to IVT or medical therapy, from dominant to an ICER of $16,000 USD per QALY gained, we cannot compare our results with theirs because the health outcomes in these models contradicted the evidence from RCTs for old generation MT. [5-7] See Appendix 6.

In the Canadian health care context where general tax revenues pay for both acute and long term care, upfront investment in acute stroke thrombectomy services can be recouped by reduced need for long-term care of the neurologically disabled. Indirect costs such as loss of productivity and the cost of unpaid caregiving are partially accounted for in this analysis because of metrics extracted from the BURST study. [26]

The strengths of our study include the use of high level evidence from the meta-analysis of 5 RCTs, [13] the use of monthly compared to yearly cycles in the Markov model which models disease progression more accurately, the transitions from functional independence to disability as well as from disability to functional independence (i.e. recovery), which models the progression of stroke patients more naturally. Furthermore we used a calibration approach to provide relatively reliable parameter estimates for the economic model, and experts validated model assumptions and inputs. Our study also has several limitations. First, the conclusions are limited by the short interval follow-up (90 days) in the 5 RCTs identified and the need to combine results with a cohort study to model longer term outcomes. Second, many of our parameter estimates came from studies conducted outside Ontario, and it may be that parameter estimates would be different if data from Ontario were available. Third, we caution that we did not model specific endovascular devices or patient imaging selection strategies and cost-effectiveness may be influenced by these choices. In addition, future RCTs examining long-term outcomes of stroke patients would help validate several important parameters in our model. Further examination of additional costs due to MT would also help confirm the important model inputs.

Conclusions:

MT as an adjunct therapy to IVT appears to be cost-effective compared with IVT alone for patients with acute large-artery ischemic stroke.



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Table 1-1: Model inputs for base case

| Description | Mean (95% CI) | Distribution for PSA | References |
|---|---|---|---|
| Efficacy of treatment at 90 days post AIS | | | |
| IVT alone strategy | | | |
| All–Cause Mortality (%) | 17.86 (13.89, 21.82) | Beta (64.03, 294.50) | [8–12] |
| Functional independence (%) | 28.74 (21.80, 35.67) | Beta (46.68, 115.75) | [8–12] |
| MT plus IVT strategy | | | |
| All–Cause Mortality (%) | 17.86 (13.89, 21.82) | Beta (64.03, 294.50) | [8–12] |
| Odds ratio of functional independence, MT+IVT versus IVT alone* | 2.44 (1.92, 3.10) | Log–normal (0.8920, 0.1222) | [8–12] |
| Difference in Health Utility, relative to IVT | 0.0735(0.0137, 0.1333) | Normal (0.0735, 0.0305) | [8, 10] |
| Calibrated monthly transition probabilities of natural history for > 3 months after stroke | The best fitting parameter set | 1000 convergent parameter sets | |
| From functional independence to disability | | | |
| 4–6 months | 0.0321 | –– | [15–18] |
| 7–12 months | 0.0220 | –– | [15–18] |
| 13–24 months | 0.0134 | –– | [15–18] |
| 25–36 months | 0.0111 | –– | [15–18] |
| 37–48 months | 0.0093 | –– | [15–18] |
| 49–60 months | 0.0077 | –– | [15–18] |
| From disability to functional independence | | | |
| 4–6 months | 0.0372 | –– | [17] |
| 7–12 months | 0.0156 | –– | [17] |
| 13–60 months | 0 | –– | Assumption§ |
| From functional independence to death | | | |
| 4–12 months | 0.0080 | –– | [15–18] |
| 13–24 months | 0.0034 | –– | [15–18] |
| 25–36 months | 0.0039 | –– | [15–18] |
| 37–48 months | 0.0043 | –– | [15–18] |
| 49–60 months | 0.0047 | –– | [15–18] |
| From disability to death | | | |
| 4–12 months | 0.0229 | –– | [15–18] |
| 13–24 months | 0.0096 | –– | [15–18] |
| 25–36 months | 0.0108 | –– | [15–18] |
| 37–48 months | 0.0122 | –– | [15–18] |
| 49–60 months | 0.0131 | –– | [15–18] |
| Healthcare costs@ ($CAD, 2015) | | | |
| First 3 months after stroke | | | |
| Extra cost of MT treatment | 15,000 | Gamma (25, 600) | [19–25] |
| Functional independence (mRS of 0–2) | 18,852 | Gamma (25, 754.08) | [26] |
| Disability (mRS of 3–6) | 57,382 | Gamma (25, 2,295.28) | [26] |
| IVT alone, weighted by health status† | 46,308 | –– | [19–26] |
| MT+IVT, weighted by health status‡ | 53,271 | –– | [19–26] |
| More than 3 months after stroke | | | |
| Functional independence (mRS of 0–2) | 1,384 per month | Gamma (25, 55.36) | [26] |
| Disability (mRS of 3–5) | 3,080 per month | Gamma (25, 123.2) | [26] |
| Health utility for > 3 months after stroke | | | |
| Functional independence (mRS of 0–2) | 0.71 (0.68, 0.74) | Beta (623.29, 254.58) | [27] |
| Disability (mRS of 3–5) | 0.31 (0.29, 0.34) | Beta (407.26, 906.49) | [27] |

Abbreviations: $CAD, Canadian dollar in 2015; AIS, acute ischemic stroke; MT, mechanical thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale.

*: Given the odds ratio of 2.44 and pooled proportion of functional independence of 0.2874, we estimated that the proportion of functional independence was 0.4960.

§: Evidence suggests that the chance of patients recover from disable to functional independence after one year post–acute stroke is small. (17)

@: BURST study(26) did not report the 95%CI or standard error (SE) of their cost estimates. We assumed the SE is equal to 20% mean in the PSA.

†: $18,852 × 0.2874 + $57,382 × 0.7126 = $46,308

‡: $15,000 + $18,852 × 0.4960 + $57,382 × 0.5040 = $53,271

Table 1-2: Model inputs for scenario analysis and sensitivity analysis

| Description | Mean | Reference |
|---|---|---|
| Costs from the societal perspective, ($CAD, 2015) | | |
| First 3 months after stroke | | |
| Functional independence (mRS of 0–2) | 21,471 | [26] |
| Disability (mRS of 3–6) | 65,355 | [26] |
| IVT alone, weighted by health status | 52,743 | [19–26] |
| MT+IVT, weighted by health status | 58,589 | [19–26] |
| More than 3 months after stroke | | |
| Functional independence (mRS of 0–2) | 2,647 per month | [26] |
| Disability (mRS of 3–5) | 5,913 per month | [26] |
| | | |
| Inputs from ESCAPE trial, efficacy of treatment at 90 days post AIS | | |
| IVT alone strategy | | |
| All–Cause Mortality (%) | 19.0 | [12] |
| Functional independence (%) | 29.3 | [12] |
| Cost in first 3 months, weighted by health status ($CAD) | 46,093 | [12, 26] |
| MT plus IVT strategy | | |
| All–Cause Mortality (%) | 10.4 | [12] |
| Functional independence (%) | 53.0 | [12] |
| Cost in first 3 months, weighted by health status ($CAD) | 51,961 | [12, 26] |
| | | |
| Odds ratio of functional independence in subgroup patients, MT+IVT versus IVT | | |
| ≤ 70 years old | 3.02 | [8–12] |
| > 70 years old | 1.79 | [8–12] |
| | | |
| Cost of end-of-life care ($CAD) | 50,892 | [28] |

Table 2: Main results (time horizon = 5 years)

| Strategy | Average Total Costs ($CAD) | Incremental Cost ($CAD) | QALYs | QALYs Gained | ICER* ($CAD) |
|---|---|---|---|---|---|
| Base Case | | | | | |
| IVT | 124,419 | | 1.273 | | |
| MT plus IVT | 126,620 | 2,201 | 1.489 | 0.215 | 10,222 |
| From societal perspective | | | | | |
| IVT | 202,584 | | 1.273 | | |
| MT plus IVT | 199,236 | −3,348 | 1.489 | 0.215 | Dominant |
| Efficacy based on ESCAPE trial | | | | | |
| IVT | 122,901 | | 1.265 | | |
| MT plus IVT | 132,224 | 9,323 | 1.613 | 0.348 | 26,815 |

Abbreviations: $CAD, Canadian dollar in 2015; MT, mechanical thrombectomy; ICER, incremental cost effectiveness ratio; IVT, intravenous thrombolysis; QALY, quality adjusted life year.

*: Incremental cost per QALY gained.

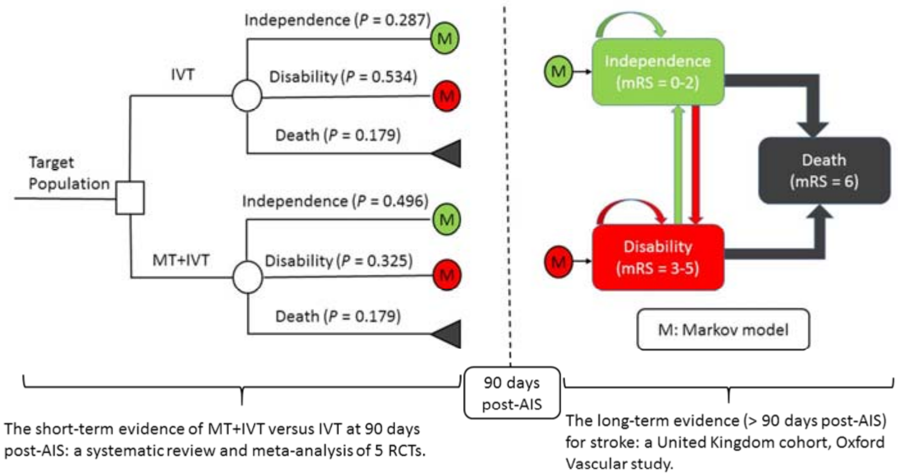
Note: numbers may appear inexact due to rounding.

Table 3: One-way or two-way sensitivity analysis results

| Scenarios | Incremental cost per QALY gained ($CAD) |
|---|---|
| Base case analysis (reference) | 10,222 |
| Time horizon | |
| 1 year | 84,715 |
| 3 years | 17,997 |
| 10 years | 10,290 |
| 15 years* | 11,826 |
| MT with reduced mortality risk (odds ratio of mortality, MT+IVT vs. IVT alone, 0.80) | 21,156 |
| Extra cost of MT treatment | |
| $10,000 | Dominant |
| $20,000 | 33,439 |
| Costs from a societal perspective | Dominant |
| Age groups | |
| ≤ 70 years old | 3,684 |
| > 70 years old | 22,745 |
| Health utility in functional independence and disability states | |
| Lower limits of 95%CI | 10,542 |
| Upper limits of 95%CI | 10,067 |
| No discounting for both cost and utility | 8,401 |
| Including cost for end-of-life care for those who survive at 90 days after an acute ischemic stroke | 2,437 |

Abbreviations: $CAD, Canadian dollar in 2015; MT, mechanical thrombectomy; IVT, intravenous thrombolysis; QALY, quality-adjusted life-year.
*: About 5.4% and 6.9% patients survive in the IVT alone and IVT+MT arms, respectively, at 15 years follow up in our model.

Figure 1: Decision analytic model of MT + IVT versus IVT alone for AIS




Abbreviations: AIS, acute ischemic stroke; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; RCT, randomized controlled trial.

Figure 2: Flowchart of Calibration for Time-dependent Transition Probabilities

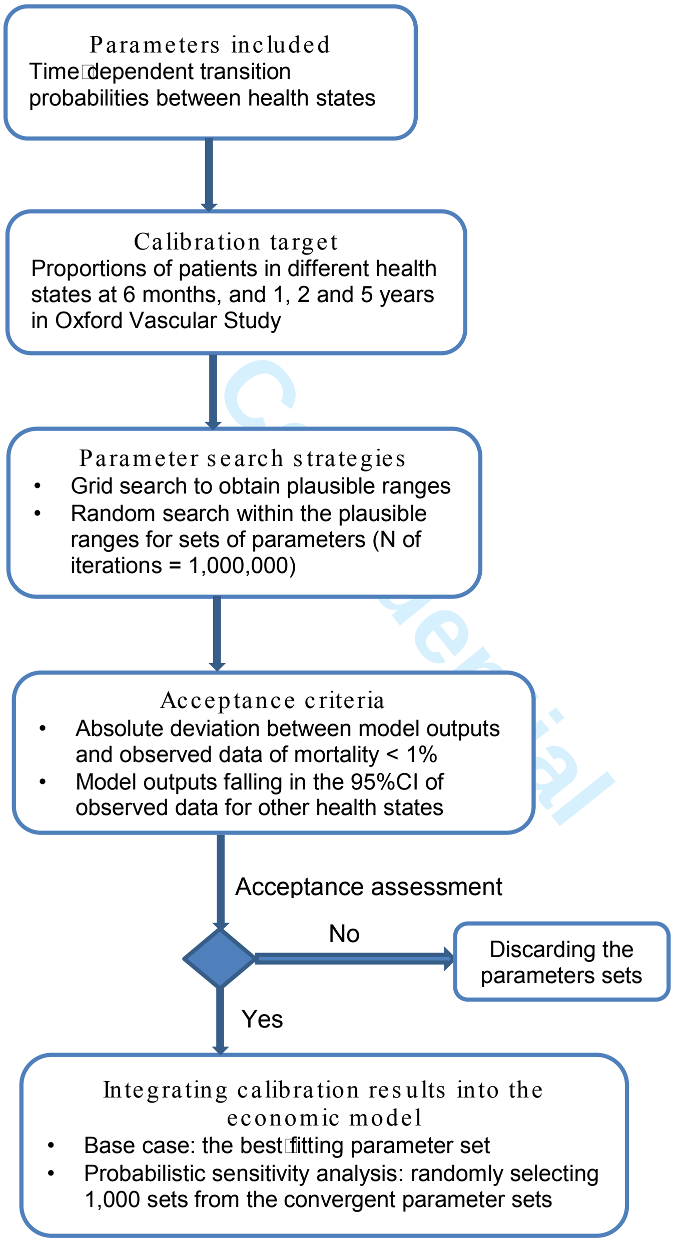
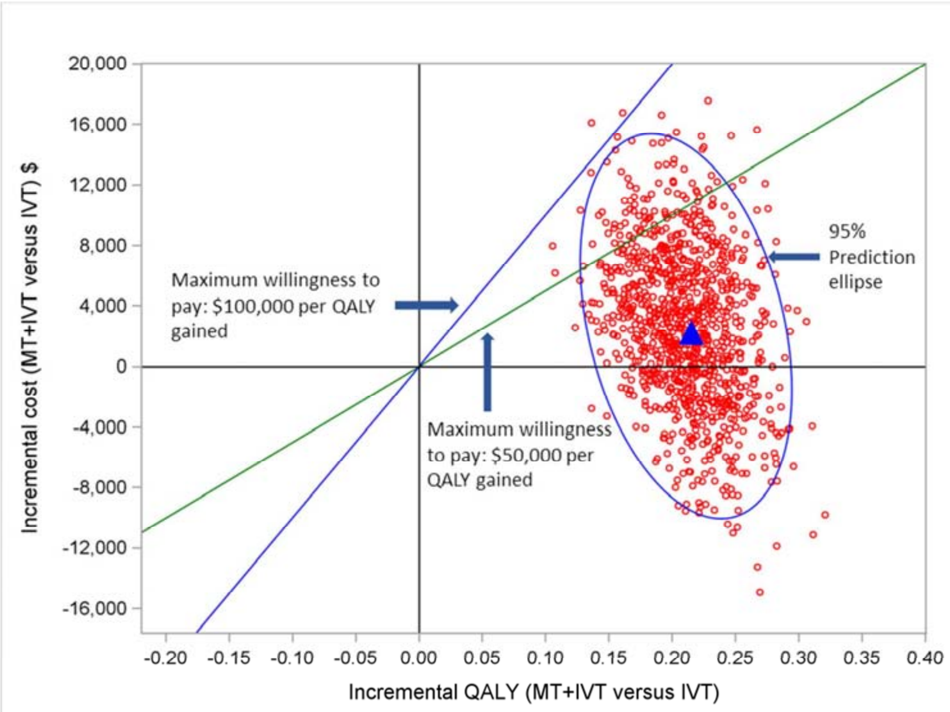


Figure 3: Cost-effectiveness plane: the incremental cost and QALY gained of MT+IVT versus IVT alone. The blue triangle in the centre of the circle indicates the base case scenario. Each red circle surrounding the blue triangle represents a single result from the simulation, presenting the incremental effects and incremental costs of MT+IVT relative to IVT alone.




Abbreviations: IVT, intravenous thrombosis, MT, mechanical thrombectomy; QALY, quality adjusted life year.

# APPENDICES

Appendix 1: Calibration of Natural History, Post-stroke Patients

Appendix 2: Cost of Mechanical Thrombectomy treatment

Appendix 3: Validation of Economic Model

Appendix 4: Incremental cost effectiveness ratio (ICER) by Follow-up Time

Appendix 5: Cost-Effectiveness Acceptability Curve

Appendix 6: Economic Literature Review

## Appendix 1: Calibration of Natural History, Post-stroke Patients

Using data from the Oxford Vascular Study, we were able to estimate the proportion of acute ischemic stroke patients who were functionally independent (modified Rankin Scale (mRS) = 0–2), disabled (mRS = 3–5), and dead (mRS = 6) at different follow-up points, (1, 2) but we could not obtain transition probabilities between two states, since more than one transition contributes to a change in the proportion of patients in the three health states. For example, we know the proportion increase of death in a given time interval, but we do not know for certain whether patients died when they were in functional independence or disability. For this reason, we calibrated the parameters for the Markov model using a seven-step approach introduced by Vanni et al. (3) The calibration was performed with SAS, version 9.4 (SAS Institute, Cary, North Carolina).

### Methods

Step 1: Parameters Included
We divided the follow-up time (> 3 months) into three phases: 4 to 6 months, 7 to 12 months, and 13 months or more. Parameters used in each phase were addressed separately. The potential parameters included in months 4 and 6 post-stroke are shown in Table A1-1.

Table A1-1: Parameters for Months 4 to 6 Post-stroke

| Parameter | Definition |
|---|---|
| $R_{ab4\text{-}6}$ | Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke) |
| $R_{ba4\text{-}6}$ | Annual recovery rate from disability to functional independence: 0.455 per patient!year |
| $RR_{ac4\text{-}6}$ | Relative risk of mortality versus the age!specific general population for patients in functional independence |
| $RR_{bc4\text{-}6}$ | Relative risk of mortality versus the age!specific general population for patients in disability |

If $R_{ab4\text{-}6}$ and $R_{ba4\text{-}6}$ changed simultaneously, their values would be balanced (at least partially), but the exact value of each parameter was unobservable from the summarized data. Thus, we fixed $R_{ba4\text{-}6}$ using an estimated annual recovery rate of 0.455 from months 4 to 6 in the mRS 4 group, as reported by Hankey et al. (4) According the Kaplan-Meier curve of time to recovery, we approximated patient-years and number of patients recovered in a given time interval by assuming no censoring, and then we calculated the recovery rate. (4) We used the formula below to translate the rate into transition probability.

$P = 1 - \exp(-\text{rate} * t)$

P: transition probability.
t: time interval, 1 month in this study.

For example, the monthly transition probability from disability to functional independence from months 4 to 6 was $1 - \exp(-0.455/12) = 0.037$.

In addition, the risk of mortality per month was assumed to be equal to the risk of age-specific mortality for the general population, multiplied by the relative risk for a given health state. The age-specific monthly risk of mortality was based on the United Kingdom population in 2004 (Table A1-2), because our calibration target was based on a cohort study from the United Kingdom (adults 75 years old recruited between 2002 and 2007). (5) Sex was not a significant predictor of long-term mortality for stroke patients, so we did not consider it in this analysis. (1, 6)

Table A1-2: Life Tables, United Kingdom, 2004

| Age | Monthly Probability of Mortality[a] (Both Sexes, 2004) |
|---|---|
| 75 | 0.003027 |
| 76 | 0.003328 |
| 77 | 0.003724 |
| 78 | 0.004202 |
| 79 | 0.004532 |
| 80 | 0.005064 |
| 81 | 0.005607 |
| 82 | 0.006284 |
| 83 | 0.006774 |
| 84 | 0.008258 |
| 85 | 0.008288 |
| 86 | 0.009484 |
| 87 | 0.010762 |
| 88 | 0.011789 |
| 89 | 0.013033 |

[a]The monthly probability of mortality for 75! to 79!year!olds was used in the model calibration, and the probability for 80! to 89!year!olds was used to project long!term outcomes.

The parameters for months 7 to 12 post-stroke were similar as those for months 4 to 6 (Table A1-3). The recovery rate ($R_{ba7-12}$) was 0.188 per patient-year, and the corresponding monthly transition probability was 0.0156. (4)

Table A1-3: Parameters for Months 7 to 12 Post-stroke

| Parameter | Definition |
|---|---|
| $R_{ab7-12}$ | Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke) |
| $R_{ba7-12}$ | Annual recovery rate from disability to functional independence: 0.188 per patient!year |
| $RR_{ac7-12}$ | Relative risk of mortality versus the age!specific general population for patients in functional independence |
| $RR_{bc7-12}$ | Relative risk of mortality versus the age!specific general population for patients in disability |

The parameters for months 13 to 60 are presented in Table A1-4. We assumed that patients in the disability state could not recover to functional independence after 1 year post-stroke ($R_{ba13\text{-}60} = 0$), while patients in functional independence could still transition to disability over time (risk related to age). $OR_{ab\_age}$ denoted the odds ratio of age for risk of disability (an increment of 12 cycles was equivalent to 1 year in the model) and $P_{ab13\text{-}24}$ (derived from $R_{ab13\text{-}24}$) denoted the risk of disability at age 76 years or the second year post-stroke. We could then calculate the risk of disability at different follow-up times.

Table A1-4: Parameters for Months 13 to 60 Post-stroke

| Parameter | Definition |
|---|---|
| $R_{ab13\text{-}24}$ | Annual disability rate from functional independence to disability (e.g., disability following recurrent ischemic stroke) |
| $OR_{ab\_age}$ | Odds ratio of age for risk of disability |
| $RR_{ac13\text{-}60}$ | Relative risk of mortality versus the age!specific general population for patients in functional independence |
| $RR_{bc13\text{-}60}$ | Relative risk of mortality versus the age!specific general population for patients in disability |



In summary, excluding two fixed parameters, $R_{ba4\text{-}6}$ and $R_{ba7\text{-}12}$, we calibrated 10 parameters in total.

Step 2: Calibration Target

Good-quality Canadian data should provide the best calibration targets. Ideally, patients in local data should have the same indications and similar age to the target population (i.e. those reported in the five recent RCTs (7-11)). As well, the data should have a substantial sample size, sufficient length of follow-up, and lack of bias. However, the evidence for long-term outcomes in acute ischemic stroke is relatively sparse in Canada, and for this reason we selected the Oxford Vascular Study to use for our target population. (1, 2) This study had a large sample size and was well conducted; the United Kingdom population is similar to the Canadian population; and the evidence from this study was more recent than some others, because the stroke patients' long-term outcomes substantially improved over the previous two decades. (12)

The United Kingdom cohort (about 83% were ischemic stroke) had three subgroups: minor stroke (National Institutes of Health Stroke Scale [NIHSS] 0–3), moderate stroke (NIHSS 4–10), and major stroke (NIHSS > 10). (1, 2) Ideally, our target population would be similar to the major stroke group, but in this subgroup, the 3-month mortality rate was as high as 56.5%, and about 95% of survivors were disabled at 1 month and 6 months post-stroke. We determined that this subgroup had much more severe stroke than our target population. In contrast, the moderate stroke group had a 3-month mortality rate of about 22%, and about 60% of survivors were disabled. Outcomes were similar to those of the control arms in the five RCTs (mortality rate of 18% and disability rate of about 60% for survivors). (7-11) As a result, we used the moderate subgroup (n = 169 patients) for our calibration targets (Table A1-5).

Table A1-5: Expected Percentage of Patients in Three Health States

| Time Post-stroke | Functional Independence, % (mRS 0–2) | Disability, % (mRS 3–5) | Death, % (mRS 6) |
|---|---|---|---|
| 3 months[a] | 30.3 | 47.5 | 22.2 |
| 6 months | 31.7 | 42.0 | 26.3 |
| 1 year | 29.9 | 36.5 | 33.6 |
| 2 years | 23.6 | 38.4 | 38.0 |
| 5 years | 15.4 | 28.6 | 56.0 |

Abbreviation: mRS, modified Rankin Scale.
[a]We started with month 4 in calibration, so the targets were observations in month 6 or later. A total of 68% and 57% of survivors were in the disability state at the end of months 1 and 6, respectively, but the authors did not report the percentage who were disabled at 3 months. (1) We assumed that the proportion of patients in disability at month 3 should be between the values in months 1 and 6, but closer to that of month 6, so we estimated that 61% of survivors were disabled at 3 months.



Mortality at different follow-up time points was the primary calibration target, since the mortality data were accurate, and there were considerable missing mRS data for survivors at years 2 and year 5. Mortality was estimated using the Kaplan-Meier curve in Luengo-Fernandez et al. (2) Secondary calibration targets were the percentages of patients from the entire cohort in functional independence and disability at different follow-up times; this was estimated by multiplying the percentage of disabled patients by the percentage of survival. (1, 2)

Step 3: Measure of Goodness-of-Fit
We set multiplex calibration targets in step 2. For the primary target of mortality, we used absolute deviations to assess goodness of fit.

$$D = \left| y - f(x) \right|$$

D: absolute deviation.
y: observed mortality at a given time point.
f(x): the output of mortality from the model given a set of parameters.

When the absolute deviations of mortality were within the acceptable range for all four follow-up times (6 months, 1 year, 2 years, and 5 years), we evaluated goodness of fit using the sum of squares due to error for the proportion of the three health states at the four observation times. A smaller sum of squares due to error indicates a better-fitting parameter set.

$$SSE = \sum_{i=1}^{n} W_i * (y_i - f(x_i))^2$$

SSE: sum of squares due to error.
n: the number of calibration targets; 12 in total.
yi: observed data, proportion of patients in a given health states at a given follow!up time.
f(xi): output from the model given a set of parameters.
Wi: weight for each data point; 1 in this study.

Step 4: Parameter Search Strategy

We started with calibrations for parameters from the 4 to 6 months post-stroke ($R_{ab4\text{-}6}$, $RR_{ac4\text{-}6}$ and $RR_{bc4\text{-}6}$), because these values were not affected by the parameters used in the > 6 months model. Initially, we set wide ranges and used a grid-search method to gradually narrow the possible parameter space. When this range of parameters was fairly stable, we moved on to the calibrations for 7 to 12 months post-stroke, and then the parameters for 13 to 60 months post-stroke. After obtaining plausible ranges for all, we used a random-search method to generate numerous sets of parameters with sampling values from the plausible ranges.

Step 5: Acceptance Criteria

There is no consensus on the most appropriate convergence or acceptance criteria. We set the minimum acceptable level of accuracy as follows: a) the absolute deviation of mortality between observed data and the model output was < 1% at 6 months, and 1, 2 and 5 years; and b) the model outputs falling in the 95% confidence intervals of observed data for the proportion of patients in functional independence and disability states at each follow-up point. Parameter sets that met these convergence criteria were considered to be good-fitting.

Based on Table A1-5, and assuming no censoring of the 169 patients, we calculated the expected number of patients in each health state at each time point. Then we estimated 95% simultaneous confidence intervals for the multinomial distribution of the three classes (functional independence, disability, and death) using the method by Sison and Glaz in 1995. (13) (Table A1-6).

Table A1-6: 95% Simultaneous Confidence Intervals for Patients in Three Health States

| Time Post-stroke | Functional Independence, % (mRS 0–2) | Disability, % (mRS 3–5) | Death, % (mRS 6) |
|---|---|---|---|
| 3 months | 22.5–38.5 | 40.0–55.6 | 14.8–30.8 |
| 6 months | 24.3–40.5 | 34.3–50.5 | 18.3–34.6 |
| 1 year | 21.9–38.2 | 29.0–45.3 | 26.0–42.3 |
| 2 years | 16.0–32.2 | 30.8–47.0 | 30.2–46.4 |
| 5 years | 8.3–23.6 | 21.3–36.6 | 49.1–64.4 |

Abbreviation: mRS, modified Rankin Scale.

Step 6: Stopping Rule

We generated 1,000,000 unique parameter sets using a random search strategy. The search strategy and number of iterations in simulation could be changed, in the event that we obtained no adequate sets of convergent parameters.

Step 7: Integrating Calibration Results Into the Economic Model

We used the best-fitting parameter set as the base case in the economic model, and randomly selected 1,000 convergent parameter sets for the probabilistic sensitivity analysis.

## Results

The values for the best-fitting parameter set are shown in Table A1-7. The corresponding monthly transition probabilities can be found in Table 1 of the main text.

Table A1-7: Values of the Best-Fitting Parameter Set

| Parameter | Value |
|---|---|
| $R_{ab4!6}$ | 0.392 per patient!year |
| $R_{ab7!12}$ | 0.267 per patient!year |
| $R_{ab13!24}$ | 0.164 per patient!year |
| $OR_{ab\_age}$ | 0.830 |
| $RR_{ac4!12}$[a] | 2.65 |
| $RR_{bc4!12}$[a] | 7.57 |
| $RR_{ac13!60}$ | 1.035 |
| $RR_{bc13!60}$ | 2.899 |

[a]Since the values of the time-dependent parameters in the 4-6 months and 7-12 months were fairly close, we combined them.



Table A1-8 presented the percentage of patients in different health states at various follow-up times using the best-fitting parameter set.

Table A1-8: Percentage of Patients in Three Health States, Best-Fitting Model

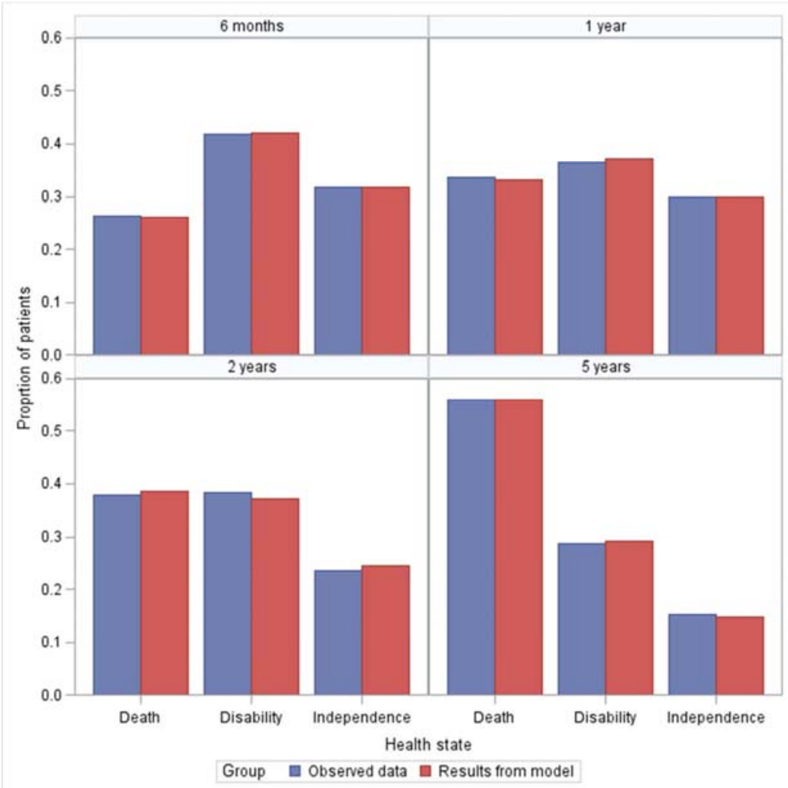
| Time Post-stroke | Functional Independence, % (mRS 0–2) | Disability, % (mRS 3–5) | Death, % (mRS 6) |
|---|---|---|---|
| 3 months | 30.3 | 47.5 | 22.2 |
| 6 months | 31.7 | 42.2 | 26.1 |
| 1 year | 29.9 | 37.1 | 33.1 |
| 2 years | 24.4 | 37.1 | 38.5 |
| 5 years | 14.9 | 29.1 | 56.0 |

Abbreviation: mRS, modified Rankin Scale.

We plotted the modelled and observed proportions of the populations in the three health states from 6 months to 5 years (Figure A1). The calibrated results were very close to the observed data. In addition, to represent post-calibration uncertainty, we randomly selected 1,000 good-fitting parameter sets for probabilistic sensitivity analysis.

To assess external consistency, we compared the calibrated relative risks of mortality (post-stroke patients versus the age-specific general population) with that of the Perth Community Stroke Study in Australia. (6) The weighted relative risk by the proportion of patients with functional independence or disability from our model was close to that of post-stroke patients in Australia. Also, the trend of risk of mortality over time in our calibrated results was same as that in a study of the Swedish population. (14)

Figure A1: Modelled and Observed Proportions of Health States



## Appendix 2: Cost of Mechanical Thrombectomy

Table A2: Literature Review of Costs for Mechanical Thrombectomy—Summary

| Author, Year | Mean Hospitalization Cost for Mechanical Thrombectomy | Mean Hospitalization Cost for Control | Currency, Cost Year | Extra Cost due to Mechanical Thrombectomy treatment[a] ($CAD 2015) |
|---|---|---|---|---|
| Leppert et al, 2015 (15) | $14,405 (additional cost of MT, relative to IVT) | NA | USD, 2012 | $14,572 |
| Rai et al, 2015 (16) | $23,698 (favourable outcome)<br>$31,500 (poor outcome) | $13,688 (favourable outcome)<br>$20,934 (poor outcome) | USD, cost year unclear | $12,359 (favourable outcome)<br>$13,046 (poor outcome) |
| Simpson et al, 2014 (17) | $35,130 | $25,630 | USD, 2012 | $9,610 |
| Bouvy et al, 2013 (18) | €4,171 (additional costs at 6 months IVT relative to conservative treatment, 50% patients used retrievable stent) | €971 (additional costs at 6 months IVT relative to conservative treatment) | Euro, 2010 | $4,558 |
| Chen, 2012 (19) | At least $10,000 more per patient (estimate) | Not report explicitly | USD, 2012 | ≥$10,116 |
| Nguyen!Huynh et al, 2011 (20) | $19,210 (without SICH)<br>$28,087 (with SICH) | $4,686 (without SICH)<br>$10,245 (with SICH) | USD, 2009 | $17,681 (without SICH)<br>$21,720 (with SICH) |
| Kim et al, 2011 (21) | $20,657 (without SICH)<br>$29,534 (with SICH) | $8,408 (without SICH)<br>$15,945 (with SICH) | USD, 2009 | $14,910 (without SICH)<br>$16,543 (with SICH) |
| Patil et al, 2009 (22) | $24,154 | $6,749 | USD, 2008 | $20,349 |
| University Health Network (UHN), 2015 | $41,941 (entire episode of care, excluding physician fee)<br>$16,965 (device) | NA | CAD, 2015 | NA |
| Ottawa Hospital, 2015 | $10,473 (assuming 1.3 devices per patient) | NA | CAD, 2015 | NA |
| Turk et al, 2014 (23) | Traditional Penumbra aspiration system with separator: $33,611 (total); $7,421 (device)<br>Stent retriever with local aspiration: $51,599 (total); $10,263 (device)<br>direct aspiration first!pass technique: $54,700 (total); $15,798 | NA | USD, 2013 | NA |
| Bing et al, 2013 (24) | €5,018 (cost of materials, wires, catheters, femoral introducers, carotid stents, et al) or CAD $6,936 | NA | Euro, 2010<br>CAD, 2010 | NA |
| Brinjikji et al, 2011 (25) | $36,999 (median, with good outcomes)<br>$50,628 (median, with severe disability)<br>$35,109 (median, with mortality) | NA | USD, 2008 | NA |

Abbreviations: MT, mechanical thrombectomy; IVT, intravenous thrombolysis; SICH, symptomatic intracerebral hemorrhage.
[a]We used historical exchange rates to convert US dollars or Euros to Canadian dollars in the corresponding year. (26) Then, we used the Consumer Price Index to adjust costs to 2015 Canadian dollars. (27)

Appendix 3: Validation of Economic Model

The plots of the health state probabilities (i.e. the probabilities of functional independence, disability and mortality over time) following MT+IVT and IVT alone based on our Markov model are shown in Figures A3-1 and A3-2. These plots reflect our model inputs and assumptions, and assume that the model captures the different health state probabilities appropriately.

Figure A3-1: Health State Probabilities Following MT+IVT

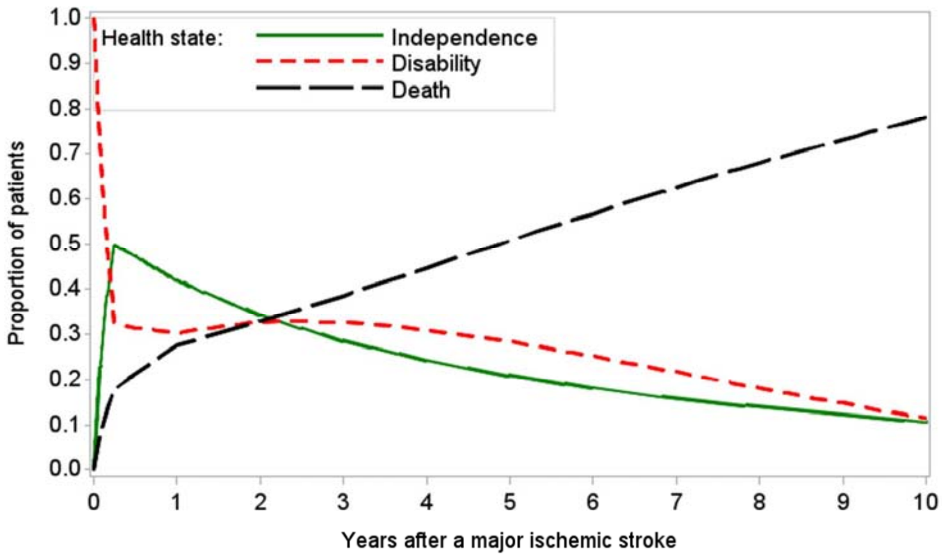
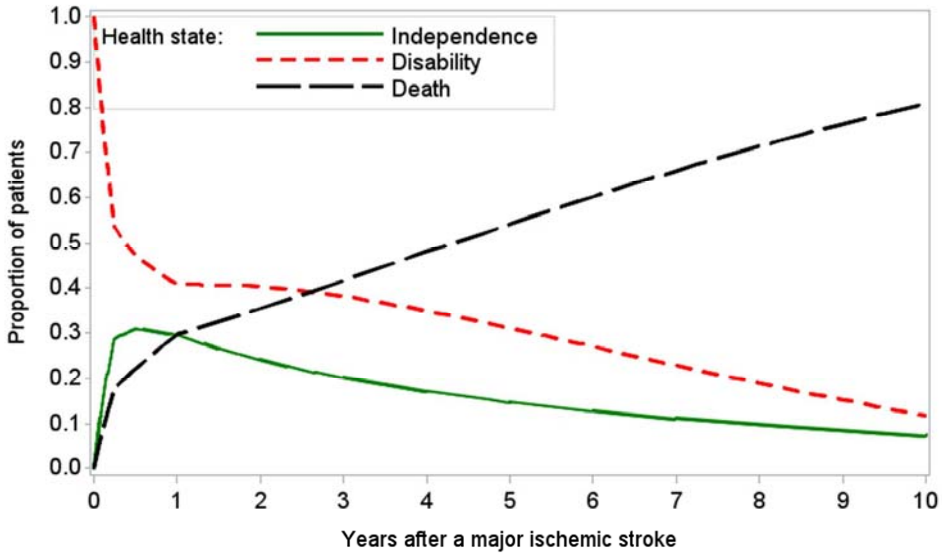
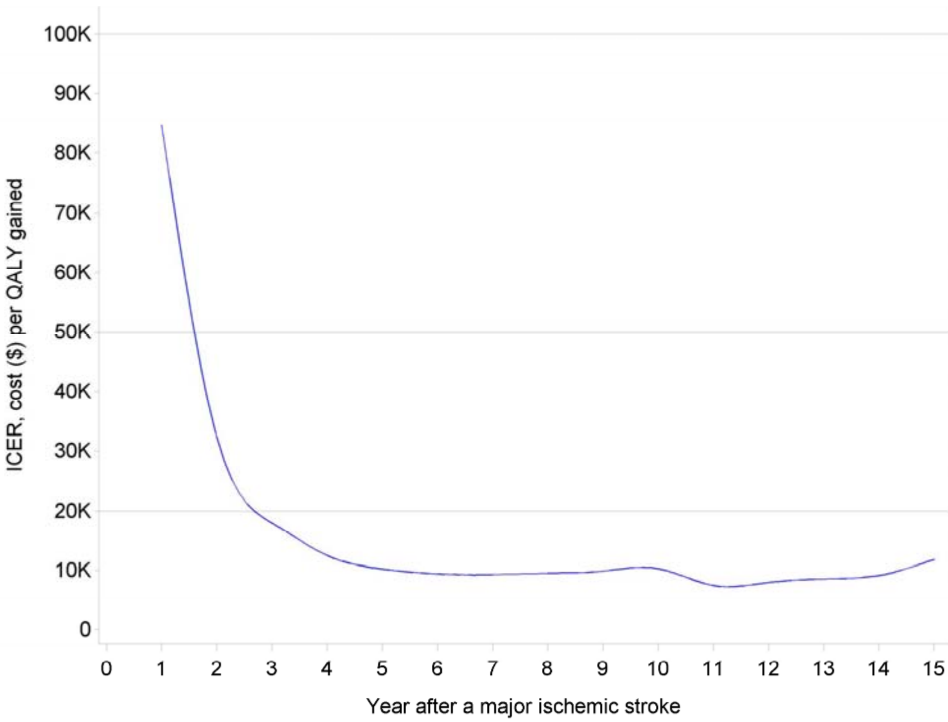


Figure A3-2: Health State Probabilities Following IVT Alone



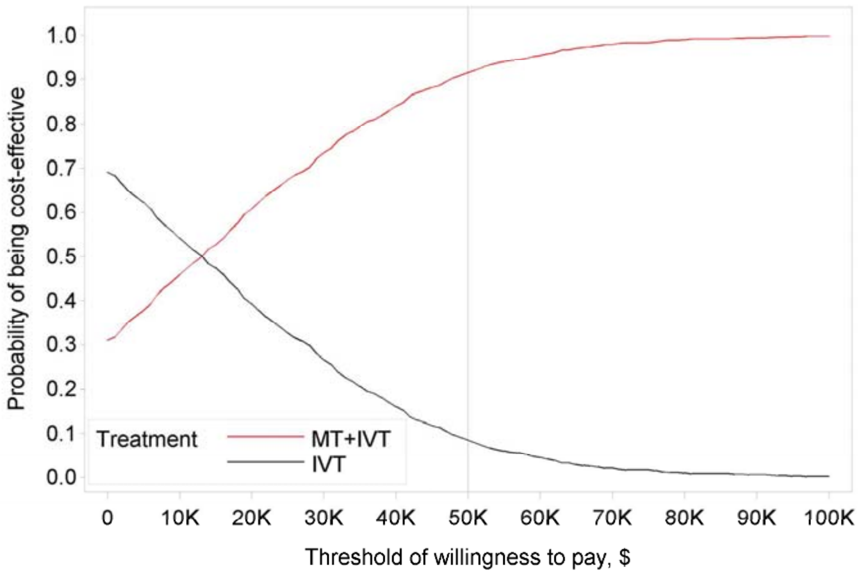
Appendix 4: Incremental cost effectiveness ratio (CER) by Follow-up Time

Figure A4: Sensitivity Analysis Examining ICER by Follow-up Time, MT+IVT versus IVT alone



Appendix 5: Cost-Effectiveness Acceptability Curve

Figure A5: Cost-Effectiveness Acceptability Curve: MT+IVT Versus IVT alone



## Appendix 6: Economic Literature Review

### Table A6: Results of Economic Literature Review—Summary

| Name, Year | Study Design and Perspective | Population | Interventions Comparators | Results | | |
|---|---|---|---|---|---|---|
| | | | | Health Outcomes | Costs | Cost-Effectiveness |
| Leppert et al, 2015 (15) | Type of analysis: CUA<br>Study design: decision!analytic model<br>Perspective: payer, United States<br>Time horizon: lifetime | Adults with an acute large!vessel ischemic stroke; see MR CLEAN study for details (7) | IV tPA<br>IV tPA plus MT | QALY gained: 0.70<br>Total QALYs: 3.10 (IV tPA); 3.80 (IV tPA plus MT)<br>Annual discount rate: 3% | Cost year: 2012<br>Incremental cost: $9,911 USD<br>Total costs: $130,144 USD (IV tPA); $140,055 USD (IV tPA plus MT)<br>Annual discount rate: 3% | ICER: $14,137 per QALY gained |
| Bouvy et al, 2013 (18) | Type of analysis: CUA<br>Study design: decision!analytic model<br>Perspective: health sector, Netherlands<br>Time horizon: lifetime | Patients with a clinical diagnosis of ischemic stroke, and no contraindications for IVT or MT | Medical therapy<br>IVT<br>IA thrombolysis[a]<br>IV!IA thrombolysis | QALY gained: 0.28 (IA vs. medical therapy); 0.11 (IV!IA vs. IVT)<br>Total QALYs: 3.39 (medical therapy); 3.61 (IVT); 3.67 (IA thrombolysis); 3.72 (IV!IA thrombolysis)<br>Annual discount rate: 3% | Cost year: 2010<br>Incremental cost: –€1,983 (IA vs. medical therapy); €222 (IV!IA vs. IVT)<br>Total costs: €34,182 (medical therapy); €32,113 (IVT); €32,199 (IA thrombolysis); €32,335 (IV!IA thrombolysis)<br>Annual discount rate: 3% | ICER: dominant (IA thrombolysis vs. medical therapy); €1,922 per QALY gained (IV!IA thrombolysis vs. IVT) |
| Nguyen! Huynh et al, 2011 (20) | Type of analysis: CUA<br>Study design: decision!analytic model<br>Perspective: society, United States<br>Time horizon: lifetime | 65!year!old men or women with acute ischemic stroke and an occlusion of a major intracranial artery, but not eligible for IV tPA | Best medical therapy<br>Neurointerventional radiology, typically MT | QALY gained: 0.82<br>Total QALYs: NA<br>Annual discount rate: 3% | Cost year: 2009<br>Incremental cost: $7,718 USD<br>Total costs: NA<br>Annual discount rate: 3% | ICER: $9,386 per QALY gained |
| Kim et al, 2011 (21) | Type of analysis: CUA<br>Study design: decision!analytic model<br>Perspective: payer, United States<br>Time horizon: lifetime | 68!year!old patient with an acute large! vessel ischemic stroke who was eligible for IV tPA | IV tPA<br>IV tPA plus MT | QALY gained: 0.68<br>Total QALYs: NA<br>Annual discount rate: 3% | Cost year: 2009<br>Incremental cost: $10,840 USD<br>Total costs: NA<br>Annual discount rate: 3% | ICER: $16,001 per QALY gained |
| Patil et al, 2009 (22) | Type of analysis: CUA<br>Study design: decision!analytic model<br>Perspective: payer, United States<br>Time horizon: 20 years | 67!year!old patient with a large!vessel ischemic stroke but ineligible for IV tPA | Best medical therapy<br>MT | QALY gained: 0.54<br>Total QALYs: 1.83 (best medical therapy); 2.37 (MT)<br>Annual discount rate: 3% | Cost year: 2008<br>Incremental cost: $6,600 USD<br>Total costs: $142,000 USD (best medical therapy); $148,600 USD (MT)<br>Annual discount rate: 3% | ICER: $12,120 per QALY gained |

Abbreviations: CUA, cost!utility analysis; IA, intra!arterial; ICER, incremental cost!effectiveness ratio; IVT, intravenous thrombolysis; IV tPA, intravenous tissue plasminogen activator; NA, not applicable; QALY, quality!adjusted life!year.
[a]50% of patients underwent treatment using a retrievable stent.

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(1) Luengo-Fernandez R, Paul NL, Gray AM, et al. Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford Vascular Study. Stroke. 2013;44:2854-61.

(2) Luengo-Fernandez R, Gray AM, Bull L, et al. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology. 2013;81:1588-95.

(3) Vanni T, Karnon J, Madan J, et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconomics. 2011;29:35-49.

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