cmajOPEN

Research

Cost-effectiveness of endovascular thrombectomy with alteplase versus endovascular thrombectomy alone for acute ischemic stroke secondary to large vessel occlusion

Zhikang Ye PhD, Ting Zhou PhD, Mengmeng Zhang PhD, Junwen Zhou PhD, Feng Xie PhD, Michael D. Hill MD, Eric E. Smith MD MPH, Jason W. Busse DC PhD, Yi Zhang BSc, Ying Liu MSc, Xin Wang MSc, Zhuo Ma MSc, Zhuoling An PhD

Abstract

Background: Recent randomized trials have suggested that endovascular thrombectomy (EVT) alone may provide similar functional outcomes as the current standard of care, EVT combined with intravenous alteplase treatment, for acute ischemic stroke secondary to large vessel occlusion. We conducted an economic evaluation of these 2 therapeutic options.

Methods: We constructed a decision analytic model with a hypothetical cohort of 1000 patients to assess the cost-effectiveness of EVT with intravenous alteplase treatment versus EVT alone for acute ischemic stroke secondary to large vessel occlusion from both the societal and public health care payer perspectives. We used studies and data published in 2009–2021 for model inputs, and acquired cost data for Canada and China, representing high- and middle-income countries, respectively. We calculated incremental cost-effectiveness ratios (ICERs) using a lifetime horizon and accounted for uncertainty using 1-way and probabilistic sensitivity analyses. All costs are reported in 2021 Canadian dollars.

Results: In Canada, the difference in quality-adjusted life-years (QALYs) gained between EVT with alteplase and EVT alone was 0.10 from both the societal and health care payer perspectives. The difference in cost was $2847 from a societal perspective and $2767 from the payer perspective. In China, the difference in QALYs gained was 0.07 from both perspectives, and the difference in cost was $1550 from the societal perspective and $1607 from the payer perspective. One-way sensitivity analyses showed that the distributions of modified Rankin Scale scores at 90 days after stroke were the most influential factor on ICERs. For Canada, compared to EVT alone, the probability that EVT with alteplase would be cost-effective at a willingness-to-pay threshold of $50 000 per QALY gained was 58.7% from a societal perspective and 58.4% from a payer perspective. The corresponding values for at a willingness-to-pay threshold of $47 185 (3 times the Chinese gross domestic product per capita in 2021) were 65.2% and 67.4%.

Interpretation: For patients with acute ischemic stroke due to large vessel occlusion eligible for immediate treatment with both EVT alone and EVT with intravenous alteplase treatment, it is uncertain whether EVT with alteplase is cost-effective compared to EVT alone in Canada and China.

Stroke is one of the leading causes of disability and death globally and is associated with substantial economic burden to patients and society.[1,2] One-fourth of the population will experience a stroke during their lifetime,[1,3] and, in 2016, there were about 13.7 million new stroke cases and 5.5 million deaths due to stroke worldwide.[3] Acute ischemic strokes due to large vessel occlusion account for 10%–30% of all ischemic strokes, and, compared to non–large-vessel occlusion strokes, are associated with higher mortality, worse functional outcomes and longer hospital stays.[4,5] Endovascular thrombectomy (EVT) is a recently established treatment for acute ischemic stroke due to large vessel occlusion in the anterior cerebral circulation, and intravenous administration of alteplase is the standard of care.[6] Current guidelines strongly recommend administration of both EVT and alteplase for patients who are eligible for these treatments.[7,8]

Six recent randomized controlled trials of EVT with alteplase (current standard of care) compared to EVT alone in patients with acute ischemic stroke eligible for immediate treatment with both therapies showed no significant differences in

Competing interests: See the end of the article.

This article has been peer reviewed.

Correspondence to: Zhuoling An, anzhuoling@163.com

***CMAJ Open* 2023 May 16. DOI:10.9778/cmajo.20220096**

functional outcomes between the 2 groups.[9–15] This evidence triggered a rapid clinical practice guideline, developed from the perspective of patients but also considering a societal perspective, in which costs are relevant as a secondary issue.[16] Evidence with respect to the economic efficiency of EVT with alteplase versus EVT alone is needed to generate the guideline recommendations.

In prior economic analyses, investigators have explored EVT with alteplase versus alteplase alone and concluded that combination therapy was more cost-effective.[17–19] There is a lack of evidence on the cost-effectiveness of combination therapy versus EVT alone. To evaluate the cost-effectiveness of EVT with alteplase versus EVT alone and to provide economic evidence for the development of the international guideline, we conducted an economic analysis. We selected Canada and China as the settings of our analysis to represent high- and middle-income countries, respectively.

Methods

Study design

We developed a decision analytic model to estimate the cost and cost-effectiveness of EVT with intravenously administered alteplase (combination therapy) versus EVT alone for acute ischemic stroke secondary to large vessel occlusion. The analysis was conducted from both the societal and the public health care payer perspectives, in Canada and China, over a lifetime horizon. We reported this study following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[20]

Cohort

In this analysis, we simulated a hypothetical cohort of 1000 patients (mean start age 70 yr) with acute ischemic stroke due to large vessel occlusion. We further assumed occlusion of the intracranial internal carotid artery or the first segment of the middle cerebral artery, confirmed by imaging; eligibility for both intravenous alteplase and EVT treatment within 4.5 hours of stroke onset; and functional independence before stroke (i.e., modified Rankin Scale [mRS] score 0–2).

Model structure

Figure 1 illustrates the model structure. The model combined a decision tree for the first 90 days after acute ischemic stroke and a Markov model for survivors after 90 days over a lifetime horizon incorporating each population's life expectancy at the age of 70 years (Canada: 17 yr, China: 13 yr).[21,22] The decision tree and Markov model consisted of 7 health states represented by mRS scores of 0–6, with 0 indicating no symptoms; 1, symptoms without clinical disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death. Target patients who received EVT alone or with alteplase achieved 1 of the 7 health states at 90 days after stroke, which was the patients' terminal status in the decision tree and the survivors' initial status in the Markov model. For the Markov model, we assumed that patients' health outcomes beyond 90 days of the index stroke would be independent of earlier treatments but conditional on their health status at 90 days (i.e., mRS score 0–5) after stroke.[23] We further assumed that, at the end of each annual cycle, patients could transfer between any health states except mRS 6 (death) or stay in the same health state.

Model parameters

Model parameters related to efficacy of treatment at 90 days after stroke,[9–15] health utilities[24–26] and costs of care[18,27–35] are summarized in Appendix 1, Supplementary Table S1 (available

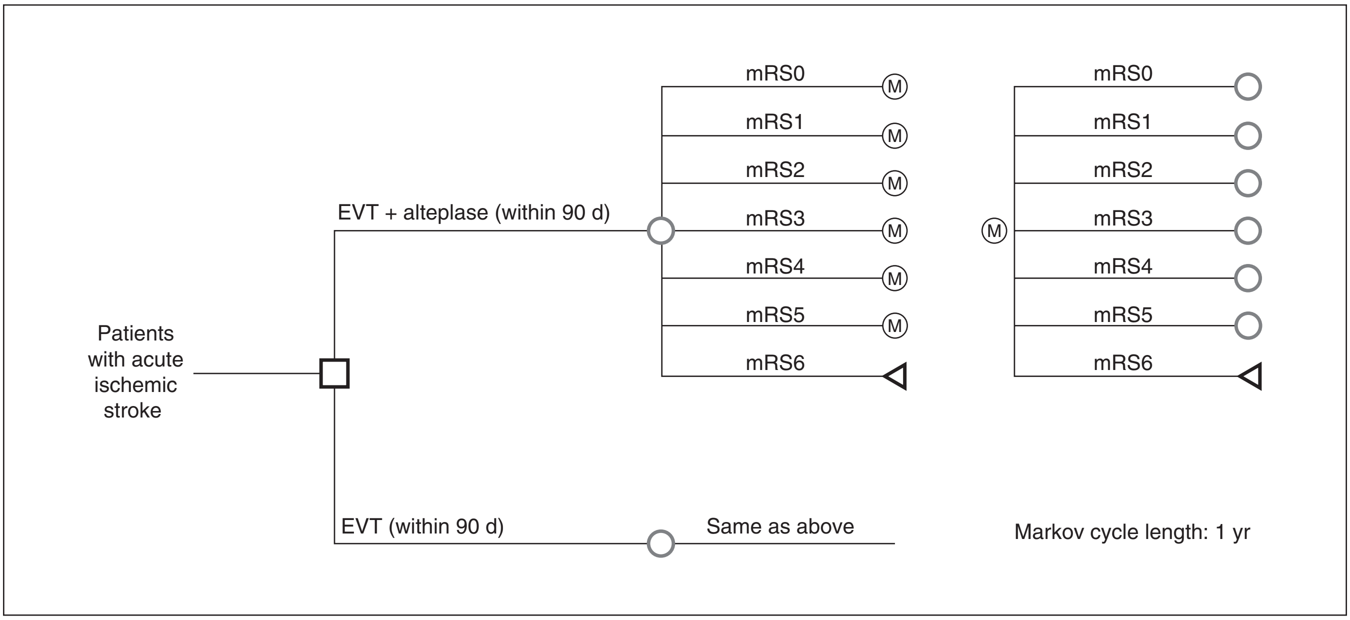

Figure 1: Decision analytic model of endovascular thrombectomy with alteplase versus endovascular thrombectomy alone. Note: EVT = endovascular thrombectomy, M = Markov, mRS = modified Rankin Scale.

at www.cmajopen.ca/content/11/3/E443/suppl/DC1). The descriptions, sources and assumptions for the parameters are also provided in Appendix 1. Patients with ischemic stroke who receive EVT with alteplase or EVT alone are similar in demographic characteristics and the use of other medical resources.[15] Accordingly, we assumed that the difference in direct costs within 90 days after stroke between the 2 arms was the price of alteplase, and that direct costs beyond 90 days after stroke and indirect costs in all phases for each mRS were the same between the 2 arms. All costs in our study were presented in 2021 Canadian dollars. We applied a currency exchange rate of 0.19 from the Chinese yuan to the Canadian dollar as well as the Consumer Price Index to convert and inflate costs.[36,37]

Given that there is sparse evidence for long-term (after 90 d) stroke outcomes in Canada and China, we estimated the long-term outcomes using data from the Oxford Vascular Study, a prospective cohort study involving all registered patients with acute vascular events in Oxfordshire, United Kingdom, that began in 2002.[38] We consulted stroke experts (M.D.H. and E.E.S.) on our team and achieved consensus that the transition probabilities beyond 90 days after stroke are very similar between the UK, Canada and China. Transition probabilities are directly related to prognosis after an incident stroke. Stroke prognosis is grossly dependent on 3 factors: mobility, swallowing and cognitive status. Broadly, these 3 factors are based on physiology, which does not differ by country, race or ethnicity. In contrast, care delivery and availability of care is a sociopolitical construct that does vary by country and political organization. On balance, physiology plays a stronger role,[15] which means that transition probabilities are more similar than they are different in different countries. The final transition probabilities[38–44] used in the Markov model and their sources and assumptions are summarized in Table 1.

Outcomes

Our primary outcome was incremental cost-effectiveness ratio (ICER), and our secondary outcomes were incremental costs, incremental life-years and incremental quality-adjusted life-years (QALYs). We calculated the ICER by dividing the difference in costs by the difference in QALYs gained between the 2 study arms (EVT with alteplase and EVT alone).

Statistical analysis

Base-case analyses

Using the decision analytic model, we conducted a cost-effectiveness analysis from both the societal and the public health care payer perspectives to compare the cost-effectiveness of EVT with alteplase versus EVT alone in Canada and China. We applied an annual discounting rate of 1.5% and 5% for Canada and China, respectively.[45,46] Following the Canadian Agency for Drugs and Technologies in Health guideline, we used the distributions of model parameter inputs as listed in Table 1 and Appendix 1, Supplementary Tables S1–S3, in the probabilistic analysis and ran the model through 1000 Monte Carlo simulations. We estimated the expected mean values of costs and QALYs over the 1000 simulations and calculated the expected ICERs. We also adopted the deterministic technique for the base-case analyses.

Sensitivity analyses

To account for the uncertainty in our model, we conducted one-way and probabilistic sensitivity analysis. We assessed the impact of all factors in the model on ICER, QALYs gained and costs in a one-way sensitivity analysis. We also assessed the probabilities that EVT with alteplase would be cost-effective compared to EVT alone when using different willingness-to-pay thresholds for 1 unit of QALY gain. Specifically, we assessed the probabilities that EVT with alteplase would be a cost-effective strategy under often-used willingness-to-pay thresholds of $50 000 in Canada and $47 185 (3 times the gross domestic product per capita in China in 2021) in China, respectively.[45–48] Given that alteplase has 2 different dosages (50 mg/vial and 20 mg/vial) with different unit prices in China, we also explored the impact of different scenarios in which patients might share the drug or use the 20-mg vial only, 50-mg vial only, or a combination of 20-mg and 50-mg vial(s). We also explored the impact of different time horizons (e.g., 5 yr, 10 yr) and mean ages of the target patient (e.g., 55 yr, 60 yr) on our results.

We performed our economic analysis using Microsoft Excel and estimated the transition probability using R version 4.0.5 (R Foundation for Statistical Computing).

Ethics approval

Ethics approval was not required for this cost-effectiveness analysis, as our study used publicly available aggregate data only.

Results

Base-case analyses

The results of deterministic base-case analyses in the setting of Canada and China from the societal and health care payer perspectives are presented in Table 2. Compared to EVT alone, EVT with alteplase incurred more costs and gained more QALYs. The base-case ICERs per QALY gained in Canada were $27 270 and $26 511 from the societal and public payer perspectives, respectively; the corresponding values for China were $22 057 and $22 864.

The results of probabilistic base-case analyses in the setting of Canada and China from the societal and health care payer perspectives are presented in Appendix 1, Supplementary Table S4. Compared to EVT alone, EVT with alteplase incurred more expected costs and gained more expected QALYs. The expected ICERs per QALY in Canada were $31 707 and $30 035 from the societal and payer perspectives, respectively; the corresponding values for China were $22 846 and $22 713.

Sensitivity analyses

One-way sensitivity analyses suggested that the most influential variable in our economic model for Canada was the

Table 1: Transition probabilities according to modified Rankin Scale score*

Time after stroke; mRS score†	mRS score; 9-mo transition probabilities between different mRS states from 90 d to 1 yr after stroke‡						
90 d	0	1	2	3	4	5	6
Canada							
0	0.450	0.427	0.089	0.014	0.002	0.000§	0.017
1	0.159	0.575	0.196	0.045	0.008	0.000§	0.017
2	0.057	0.333	0.371	0.174	0.046	0.002	0.017
3	0.007	0.064	0.147	0.467	0.210	0.015	0.090
4	0.001	0.012	0.039	0.212	0.336	0.052	0.349
5	0.000§	0.001	0.004	0.035	0.115	0.444	0.401
China							
0	0.445	0.422	0.088	0.014	0.002	0.000	0.029
1	0.157	0.568	0.193	0.044	0.008	0.000	0.029
2	0.056	0.328	0.367	0.172	0.045	0.002	0.029
3	0.007	0.063	0.145	0.461	0.207	0.015	0.102
4	0.001	0.011	0.038	0.208	0.329	0.051	0.362
5	0.000	0.001	0.004	0.034	0.113	0.435	0.413
	mRS score; annual transition probabilities between different mRS states beyond 1 yr after stroke						
1 yr	0	1	2	3	4	5	6
Canada							
0	0.782	0.188	0.013	0.000§	0.000§	0.000§	0.017
1	0.046	0.819	0.108	0.005	0.005	0.000§	0.017
2	0.002	0.082	0.746	0.073	0.070	0.002	0.024
3	0.000§	0.001	0.021	0.367	0.351	0.021	0.239
4	0.000§	0.001	0.021	0.367	0.351	0.021	0.239
5	0.000§	0.000§	0.000§	0.000§	0.000§	0.733	0.267
China							
0	0.772	0.185	0.013	0.000§	0.000§	0.000§	0.029
1	0.045	0.808	0.106	0.005	0.005	0.000§	0.029
2	0.002	0.080	0.737	0.072	0.069	0.002	0.036
3	0.000§	0.001	0.020	0.361	0.346	0.021	0.251
4	0.000§	0.001	0.020	0.361	0.346	0.021	0.251
5	0.000§	0.000§	0.000§	0.000§	0.000§	0.721	0.279

Note: mRS = modified Rankin Scale.
*All the transition probabilities in the table were used for the base-case analysis. All probabilities in the table follow a Dirichlet distribution. We constructed the ranges of all transition probabilities by increasing and decreasing the base-case value by 20%.
†0 = no symptoms, 1 = symptoms without clinical disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6 = death.
‡Sources and assumptions: we initially estimated the transition probabilities for both arms, within 1 year and beyond 1 year, by fitting the data from the Oxford Vascular Study[38] into a multistate model (Appendix 2, available at www.cmajopen.ca/content/11/3/E443/suppl/DC1).[23,39] We further adjusted the probabilities to account for the differences in background mortality between populations from different countries by substituting mortality data for the UK population in the Oxford Vascular Study with mortality rates for Canada and China and proportionally adjusting the other transition probabilities.[40–44] We assumed that the transition probabilities within 1 year and beyond 1 year were the same in the 2 treatment arms.
§The value is not 0 but, rather, smaller than 0.0005.

Table 2: Results of deterministic base-case analyses

Perspective	Intervention	Cost, $	IncCost, $	QALYs	IncQALYs	ICER
Canada						
Societal	EVT with alteplase	143 411	2847	4.68	0.10	27 270
	EVT	140 564	–	4.58	–	–
Payer	EVT with alteplase	102 644	2767	4.68	0.10	26 511
	EVT	99 876	–	4.58	–	–
China						
Societal	EVT with alteplase	39 000	1550	3.12	0.07	22 057
	EVT	37 450	–	3.05	–	–
Payer	EVT with alteplase	25 712	1607	3.12	0.07	22 864
	EVT	24 105	–	3.05	–	–

Note: EVT = endovascular thrombectomy, ICER = incremental cost-effectiveness ratio, incCost = incremental cost, incQALY = incremental quality-adjusted life-year, QALY = quality-adjusted life-year.

distribution of mRS scores at 90 days after stroke, from both the societal and the payer perspectives. We found similar results for China. Scenario analyses results for EVT alone versus EVT with alteplase are presented in Appendix 1, Supplementary Table S5.

The cost-effectiveness acceptability curves for Canada suggested that, at a willingness-to-pay threshold of $50 000 per QALY gained, the probability that EVT with alteplase would be cost-effective compared to EVT alone was 58.7% from the societal perspective and 58.4% from the payer perspective (Figure 2A and 2B). For China, at a willingness-to-pay threshold of $47 185, the probability that EVT with alteplase would be cost-effective was 65.2% from the societal perspective and 67.4% from the payer perspective (Figure 2C and 2B). Incremental cost-effectiveness planes are presented in Appendix 1, Supplementary Figures S1–S4.

Interpretation

The results of our analysis of the cost-effectiveness of EVT with intravenous alteplase treatment versus EVT alone were uncertain. In Canada, the difference in QALY between EVT with alteplase and EVT alone was 0.10 from both the societal and the health care payer perspectives; the corresponding differences in cost were $2847 and $2767. In China, the difference in QALY was 0.07 from both the societal and health care payer perspectives, and the corresponding differences in cost were $1550 and $1607. The probability that EVT with alteplase would be cost-effective was about 60% for both countries.

Unlike previous authors of economic analyses assessing the cost-effectiveness of management strategies for ischemic stroke, we did not use health states based on recurrent stroke only in the long-term progression of stroke or dichotomize mRS 0–5 into independence (mRS 0–2) and disability (mRS 3–5) in our models.[17–19,34] One reason is that stroke survivors can develop multiple events other than recurrent stroke in the long term. The incidence of nonvascular (e.g., seizures) and other, vascular events (e.g., cognitive impairment) in stroke survivors is high, and complex relations exist among these clinical events. A review of studies examining the long-term prognosis of stroke survivors showed that the incidence of cognitive impairment was as high as 35%; incident stroke is associated with accelerated cognitive impairment, and post-stroke dementia is associated with higher stroke occurrence rates.[49] Thus, it is important to incorporate multiple clinical events other than recurrent stroke in the model to capture the clinical complexity of poststroke recovery. Another reason is the loss of information in dichotomized models; there is a stronger relation between individual mRS categories and long-term outcomes and costs for stroke survivors than between dichotomized mRS scores and stroke survivors' long-term outcomes and costs.[50] Using recurrent stroke as the only long-term event or dichotomizing mRS 0–5 to capture the prognosis of stroke survivors may not be accurate.

For both Canada and China, the difference in costs and QALY gains (although the absolute difference is small) over lifetime between EVT with alteplase and EVT alone was due mainly to the cost of alteplase and to different patient distributions across mRS scores 0–6 at 90 days after stroke, which we derived from a meta-analysis of 6 randomized controlled trials using a randomized effect model.[15] In the setting of China, the utility values for mRS 0–1 were higher than the values applied in Canada, whereas the utility values for mRS 2–4 were lower than those used in Canada. In addition, the life expectancy for the 70-year-old population is 13 years in China and 17 years in Canada. These differences in utility values and life expectancies were associated with a slightly lower QALY gain in China than in Canada, from both the societal and health care payer perspectives.

Limitations

Some model inputs were from studies conducted outside Canada or China. Our long-term clinical outcomes for this analysis

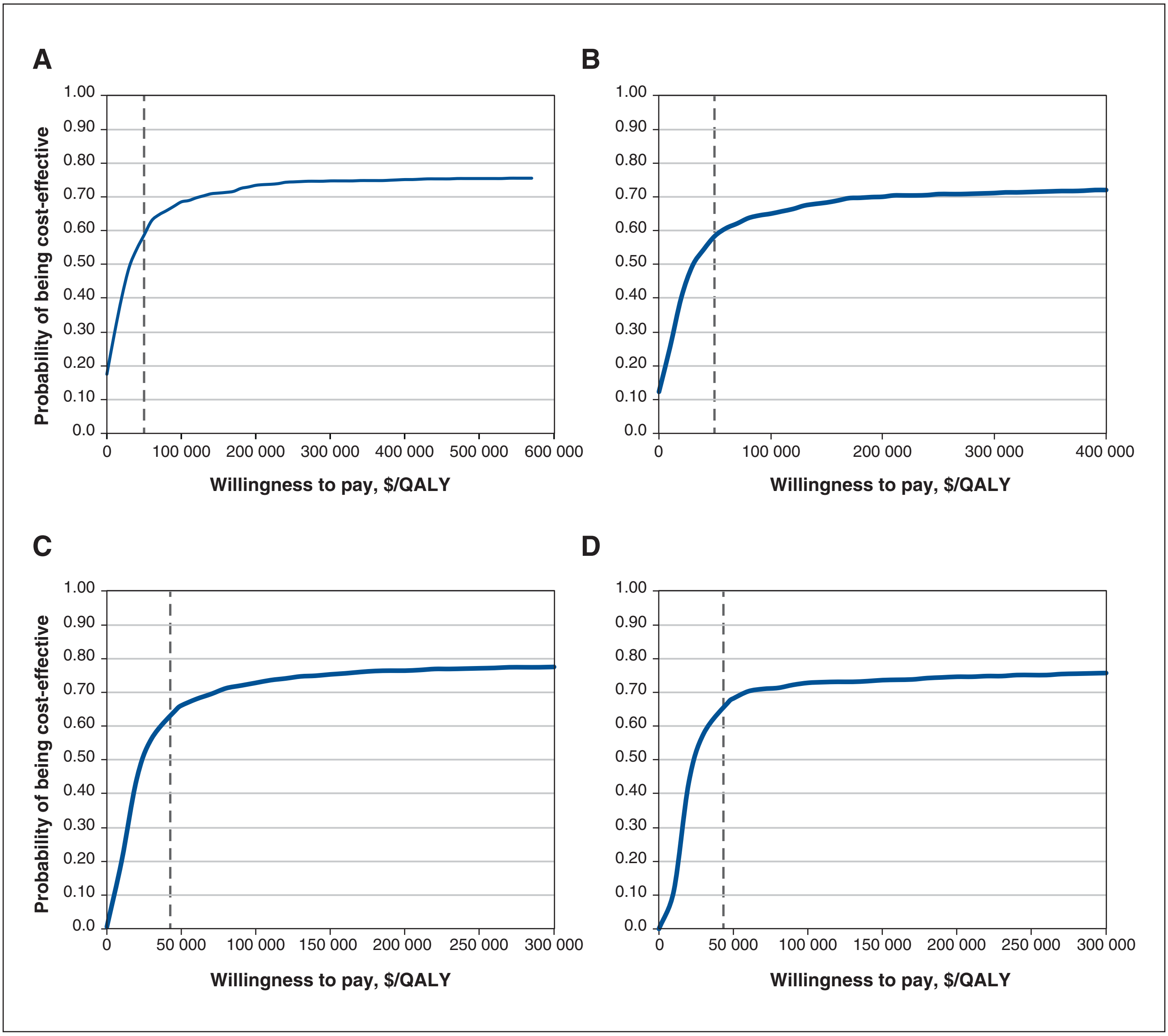

Figure 2: Cost-effectiveness acceptability curves of being cost-effective for endovascular thrombectomy (EVT) with alteplase versus EVT alone. (A) Canada, societal perspective, (B) Canada, health care payer perspective, (C) China, societal perspective, (D) China, health care payer perspective. Dashed vertical lines indicate threshold of $50 000 for Canada and $47 185 for China. Note: QALY = quality-adjusted life-year.

were acquired from the UK Oxford Vascular Study,[38] and we estimated costs beyond 1 year in Canada using ratios reported in Australian studies.[31,32] However, we adjusted model inputs using local background mortality and costs data, and performed sensitivity analysis. Our results were robust in all sensitivity and scenario analyses. We assumed that the difference in direct costs between EVT with alteplase and EVT alone within 90 days after stroke in the model was the price of alteplase. Alteplase-related costs (e.g., nursing time, intravenous pumps and tubing) were not considered in the model because they are much lower than the cost of alteplase; however, we explored the impact of varying alteplase cost on ICERs and found similar results in all scenarios. Finally, we estimated the indirect costs in China by conducting a survey among 11 selected neurologists working in 6 provinces of China, and the results might not be representative outside of these provinces.

Conclusion

For patients in Canada and China with acute ischemic stroke due to large vessel occlusion eligible for immediate treatment with both EVT alone and EVT with alteplase, the cost-effectiveness of EVT with alteplase versus EVT alone was uncertain. Our analysis provides insight into the economic efficiency of taking alteplase out of the currently recommended regimen of EVT with alteplase for the management of ischemic stroke.

References

1. Campbell BCV, Khatri P. Stroke. *Lancet* 2020;396:129-42.
2. Rochmah TN, Rahmawati IT, Dahlui M, et al. Economic burden of stroke disease: a systematic review. *Int J Environ Res Public Health* 2021;18:7552.
3. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:439-58.
4. Al Khathaami AM, Aldriweesh MA, Al Bdah BA, et al. Anterior circulation large vessel occlusion stroke in Saudi Arabia: prevalence, predictors, and outcome. *J Stroke Cerebrovasc Dis* 2020;29:105080.
5. Tsang ACO, You J, Li LF, et al. Burden of large vessel occlusion stroke and the service gap of thrombectomy: a population-based study using a territory-wide public hospital system registry. *Int J Stroke* 2020;15:69-74.
6. Goyal M, Menon BK, van Zwam WH, et al.; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723-31.
7. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:I-LXII.
8. 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:e344-418.
9. Yang P, Zhang Y, Zhang L, et al.; DIRECT-MT Investigators. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981-93.
10. Zi W, Qiu Z, Li F, et al.; DEVT Trial Investigators. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234-43.
11. Suzuki K, Matsumaru Y, Takeuchi M, et al.; SKIP Study Investigators. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244-53.
12. LeCouffe NE, Kappelhof M, Treurniet KM, et al.; MR CLEAN–NO IV Investigators. A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;385:1833-44.
13. Fischer U, Kaesmacher J, Strbian D, et al.; SWIFT DIRECT Collaborators. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022;400:104-15.
14. Mitchell PJ, Yan B, Churilov L, et al.; DIRECT-SAFE Investigators. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4.5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022;400:116-25.
15. Wang X, Ye Z, Busse JW, et al. Endovascular thrombectomy with or without intravenous alteplase for acute ischemic stroke due to large vessel occlusion: a systematic review and meta-analysis of randomized trials. *Stroke Vasc Neurol* 2022 June 20 [Epub ahead of print]. doi: 10.1136/svn-2022-001547.
16. Ye Z, Busse JW, Hill MD, et al. Endovascular thrombectomy and intravenous alteplase in patients with acute ischemic stroke due to large vessel occlusion: a clinical practice guideline. *J Evid Based Med* 2022;15:263-71.
17. Barral M, Armoiry X, Boudour S, et al. Cost-effectiveness of stent-retriever thrombectomy in large vessel occlusion strokes of the anterior circulation: analysis from the French societal perspective. *Rev Neurol (Paris)* 2020;176:180-8.
18. Pan Y, Cai X, Huo X, et al. Cost-effectiveness of mechanical thrombectomy within 6 hours of acute ischaemic stroke in China. *BMJ Open* 2018;8:e018951.
19. Xie X, Lambrinos A, Chan B, et al. Mechanical thrombectomy in patients with acute ischemic stroke: a cost–utility analysis. *CMAJ Open* 2016;4:E316-25.
20. Husereau D, Drummond M, Petrou S, et al.; ISPOR Health Economic Evaluation Publication Guidelines – CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) — explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* 2013;16:e1-5.
21. *Table 13-10-0114-01: Life expectancy and other elements of the complete life table, three-year estimates, Canada, all provinces except Prince Edward Island*. Ottawa: Statistics Canada; 2022. Available: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401 (accessed 2021 July 18).
22. The Global Health Observatory: China. Geneva: World Health Organization. Available: https://www.who.int/data/gho/data/countries/country-details/GHO/china?countryProfileId=adf73789-9c42-4bc5-a39b-b4d7ba337beb (accessed 2021 June 29).
23. Ganesh A, Luengo-Fernandez R, Wharton RM, et al.; Oxford Vascular Study. Time 9. *J Am Heart Assoc* 2017;6:e005788.
24. Rebchuk AD, O'Neill ZR, Szefer EK, et al. Health utility weighting of the modified Rankin Scale: a systematic review and meta-analysis. *JAMA Netw Open* 2020;3:e203767.
25. Szende A, Janssen B, Cabases J, editors. Self-reported population health: an international perspective based on EQ-5D. Dordrecht (Netherlands): Springer; 2014. Available: https://pubmed.ncbi.nlm.nih.gov/29787044/ (accessed 2021 July 19).
26. Wang YL, Pan YS, Zhao XQ, et al.; CHANCE investigators. Recurrent stroke was associated with poor quality of life in patients with transient ischemic attack or minor stroke: finding from the CHANCE trial. *CNS Neurosci Ther* 2014;20:1029-35.
27. Mittmann N, Seung SJ, Hill MD, et al. Impact of disability status on ischemic stroke costs in Canada in the first year. *Can J Neurol Sci* 2012;39:793-800.
28. Data search. National Medical Products Administration. Available: https://www.nmpa.gov.cn/datasearch/home-index.html?79QlcAyHig6m=1669206996841#category=ylqx (accessed 2021 June 29).
29. Sevick LK, Demchuk AM, Shuaib A, et al.; ESCAPE Trialists. A prospective economic evaluation of rapid endovascular therapy for acute ischemic stroke. *Can J Neurol Sci* 2021;48:791-8.
30. Goyal M, Demchuk AM, Menon BK, et al.; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019-30.
31. Gao L, Moodie M, Mitchell PJ, et al.; EXTEND-IA TNK Investigators. Cost-effectiveness of tenecteplase before thrombectomy for ischemic stroke. *Stroke* 2020;51:3681-9.
32. Gloede TD, Halbach SM, Thrift AG, et al. Long-term costs of stroke using 10-year longitudinal data from the North East Melbourne Stroke Incidence Study. *Stroke* 2014;45:3389-94.
33. Wang Y, Li Z, Zhao X, et al.; GOLDEN BRIDGE–AIS Investigators. Effect of a multifaceted quality improvement intervention on hospital personnel adherence to performance measures in patients with acute ischemic stroke in China: a randomized clinical trial. *JAMA* 2018;320:245-54.
34. Meng Canwen, deputy director of the Population and Employment Statistics Department of the National Bureau of Statistics, interprets the average wage data of urban employees in 2020. Beijing: National Bureau of Statistics; 2021. Available: http://www.stats.gov.cn/tjsj/sjjd/202105/t20210519_1817670.html (accessed 2021 July 19).
35. Ministry of Human Resources and Social Security. China's average retirement age is less than 55 years old, the earliest in the world and will be gradually postponed. *People's Daily Online* (Beijing) 2015 Oct. 15. Available: http://politics.people.com.cn/n/2015/1015/c1001-27699956.html (accessed 2021 July 18).
36. Consumer Price Index: 2000 to present. Ottawa: Bank of Canada. Available: https://www.bankofcanada.ca/rates/price-indexes/cpi/ (accessed 2021 July 18).
37. SDDS real sector: time series data. Beijing: National Bureau of Statistics of China; 2022. Available: http://www.stats.gov.cn/english/nbs/200703/t20070329_59238.html (accessed 2022 May 19).
38. Rothwell PM, Coull AJ, Silver LE, et al.; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005;366:1773-83.
39. Cassarly C, Martin RH, Chimowitz M, et al. Treatment effect on ordinal functional outcome using piecewise multistate Markov model with unobservable baseline: an application to the modified Rankin scale. *J Biopharm Stat* 2019;29:82-97.
40. Buxton J. Mortality rates by single year of age [data set]. Newport (UK): Office for National Statistics; 2021. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/mortalityratesqxbysingleyearofage (accessed 2021 July 18).
41. Park N. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. Newport (UK): Office for National Statistics; 2020. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates#population-estimates-data (accessed 2021 July 18).
42. Storey A. Mid-year population estimates of the very old, including centenarians: UK [data set]. Newport (UK): Office for National Statistics; 2021. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/datasets/midyearpopulationestimatesoftheveryoldincludingcentenariansunitedkingdom (accessed 2021 July 18).
43. *Table 13-10-017001: Mortality rates, by age group*. Ottawa: Statistics Canada. Available: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310071001 (accessed 2021 July 18).
44. China. Beijing: WHO Country Office. Available: https://www.who.int/countries/chn (accessed 2021 July18).
45. Guidelines for the economic evaluation of health technologies: Canada. Ottawa: Canadian Agency for Drugs and Technologies in Health; updated 2021 May 13. Available: https://cadth.ca/guidelines-economic-evaluation-health-technologies-canada-0 (accessed 2021 July 18).
46. Announcement of the Chinese Pharmaceutical Association on the release of group standards for the "Guidelines for the Evaluation of Chinese Pharmacoeconomics 2020." Beijing: Chinese Pharmaceutical Association; 2020. Available: https://www.cpa.org.cn/index.php?do=info&cid=75553 (accessed 2021 July 18).
47. Hailey D, Jacobs P, Stickland M, et al. *Pulmonary rehabilitation for chronic obstructive pulmonary disease: clinical, economic, and budget impact analysis*. Technology report no. 126. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010.

48. Tan-Torres Edejer T, Baltussen R, Adam T, et al., editors. *Making choices in health: WHO guide to cost-effectiveness analysis*. Geneva: World Health Organization; 2003.
49. Singh RJ, Chen S, Ganesh A, et al. Long-term neurological, vascular, and mortality outcomes after stroke. *Int J Stroke* 2018;13:787-96.
50. Ganesh A, Luengo-Fernandez R, Wharton RM, et al.; Oxford Vascular Study. Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology* 2018;91:e1951-60.

Competing interests: Michael Hill reports grants to the University of Calgary: for the TEMPO-2 trial from Boehringer-Ingelheim; from Biogen, outside the submitted work; for the ESCAPE-NA1 trial and ESCAPE-NEXT trial from NoNO and the Canadian Institutes of Health Research; and for the HERMES collaboration from Medtronic. He also reports an Alberta Innovates grant to the University of Calgary for the QuICR Alberta Stroke Program (some of the funds were used for the ESCAPE-NA1 trial). He has received fees for adjudication of clinical trial outcomes from Sun Pharma and Brainsgate. He holds US Patents 62/086,077 and 10,916,346 (licensed to Circle Neurovascular Imaging). He was chair of the data safety monitoring committee for the RACECAT trial (ended in 2020), and is chair of the data safety monitoring committee for the Oncovir Hiltonol trial, chair of the data safety monitoring committee for the DUMAS trial, a member of the data safety monitoring board for the ARTESiA trial and a member of the data safety monitoring board for the BRAIN-AF trial. He is president of the Canadian Neurological Sciences Federation and a board member of the Canadian Stroke Consortium. He holds stock in Circle and PureWeb. No other competing interests were declared.

Affiliations: Department of Pharmacy (Ye, Y. Zhang, Liu, Wang, Ma, An), Beijing Chaoyang Hospital, Capital Medical University, Beijing, China; School of International Pharmaceutical Business (T. Zhou), China Pharmaceutical University, Nanjing, China; The Michael G. DeGroote National Pain Centre (Ye, Busse), McMaster University, Hamilton, Ont.; Department of Health Research Methods, Evidence, and Impact (M. Zhang, Xie, Busse), McMaster University, Hamilton, Ont.; Health Economics Research Centre (J. Zhou), Nuffield Department of Population Health, University of Oxford, Oxford, UK; Department of Clinical Neurosciences and Hotchkiss Brain Institute (Hill), Departments of Medicine, Community Health Sciences and Radiology, Cumming School of Medicine, and Department of Clinical Neurosciences and Calgary Stroke Program (Smith), University of Calgary, Calgary, Alta.; Department of Anesthesia (Busse), McMaster University; The Chronic Pain Centre of Excellence for Canadian Veterans (Busse), Hamilton, Ont.

Contributors: Zhikang Ye, Michael Hill, Eric Smith, Jason Busse and Zhuoling An contributed to the conception of the work. Zhikang Ye, Ting Zhou, Mengmeng Zhang, Junwen Zhou, Feng Xie, Michael Hill, Eric Smith, Jason Busse and Zhuoling An contributed to the design of the work. Zhikang Ye, Ting Zhou, Mengmeng Zhang, Junwen Zhou, Feng Xie, Ying Liu, Xin Wang, Zhuo Ma, Michael Hill, Eric Smith, Jason Busse, Ying Liu and Zhuoling An contributed to data acquisition, analysis and interpretation. Zhikang Ye, Ting Zhou and Mengmeng Zhang drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Zhikang Ye, Ting Zhou and Mengmeng Zhang are joint primary (first) authors.

Data sharing: All data included in the analyses were derived from published studies and open access databases.

Acknowledgements: The authors thank Bram Rochwerg for reaching out to his pharmacist colleagues for the price of alteplase, and Christine Wynne, Candice Cameron and Manraj K.S. Heran for providing the price of 50-mg/vial and 100-mg/vial alteplase for intravenous use at the Hamilton Juravinski Hospital, Foothills Medical Centre and Vancouver General Hospital, respectively.

Disclaimer: The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/11/3/E443/suppl/DC.