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Lifetime quality of life and cost consequences of delays in endovascular treatment for acute ischaemic stroke: a cost-effectiveness analysis from a Singapore healthcare perspective

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ABSTRACT

Objectives Endovascular therapy (EVT) significantly improves clinical outcomes in patients with acute ischaemic stroke (AIS), while the time of EVT initiation after stroke onset influences both patient clinical outcomes and healthcare costs. This study determined the impact of EVT treatment delay on cost effectiveness of EVT in the Singapore healthcare setting.

Design A short-term decision tree and long-term Markov health state transition model was constructed. For each time window of symptom onset to EVT, the probability of receiving EVT or non-EVT treatment was varied, thereby varying clinical outcomes (modified Rankin Scale scores), short-term costs and long-term modelled (lifetime) costs; all of which were used in calculating an incremental cost-effectiveness ratio of EVT vs non-EVT treatment. Clinical outcomes and cost data were derived from clinical trials, literature, expert opinion, electronic medical records and community-based surveys from Singapore. Deterministic one-way and probabilistic sensitivity analyses were performed to assess the uncertainty of the model. The willingness to pay for per quality-adjusted life-year (QALY) was set to Singapore $50 000 (US$36 500).

Setting Singapore healthcare perspective.

Participants The model included patients with AIS in Singapore.

Interventions EVT performed within 6 hours of stroke onset.

Outcome measures The model estimated incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMB) for EVT versus non-EVT treatment, varied by time from symptom onset to time of treatment.

Results EVT performed between 61 min and 120 min after the stroke onset was most cost-effective time window to perform EVT in the Singapore population, with an ICER of Singapore $7197 per QALY (US$5254) for performing EVT at 61–120 min versus 121–180 min. The resulting incremental NMB associated with receipt of EVT at the earlier time point is Singapore $39 827 (US$29 074) per patient at the willingness-to-pay threshold of Singapore $50 000. Each hour delay in EVT resulted in an average loss of 0.54 QALYs and 195.35 healthy days, with an average net monetary loss of Singapore $26 255 (US$19 166).

Conclusions From the Singapore healthcare perspective, although EVT is more expensive than alternative treatments in the short term, the lifetime ICER is below the willingness-to-pay threshold. Thus, healthcare policies and procedures should aim to improve efficiency of pre-hospital and in-hospital workflow processes to reduce the onset-to-puncture duration.

Strengths and limitations of this study

- A Markov model estimated lifetime quality-adjusted life-years of endovascular therapy (EVT) treated patients and associated costs based on the duration between stroke onset and initiation of EVT, which provides insights at the national health system level.
- The base case model input parameters of healthcare costs, utilities and hazard ratios for mortality in the present study were specific to the Singapore population, derived directly from the Singapore Ministry of Health's database and community surveys from Singapore Ministry of Health.
- A limitation of this study is the cost inputs used for one-way and probabilistic sensitivity analyses. Given we only had point estimates for costs with no distribution information, cost distributions for sensitivity were partially derived from a global study.

INTRODUCTION

Stroke is one of the leading causes of disability in Singapore,[1] where stroke prevalence is 7.6% and is among top four causes of mortality.[2 3] The majority of stroke cases in Singapore (>80%) are ischaemic, based on a 2016 report by Singapore Stroke Registry.[4] Clinical efficacy of endovascular therapy (EVT) in the treatment of acute ischaemic stroke (AIS) has been demonstrated compared with intravenous thrombolysis (IVT) in improving stroke-related mortality rates and functional outcomes among

patients with AIS caused by proximal anterior circulation occlusions, and further influences post-stroke care in the long term.[5–10] However, the outcomes of EVT are time dependent and decline with increasing delay between stroke onset and initiation of EVT.[11] A study based on the US population demonstrated that every hour of treatment delay in EVT reduced a patient's quality-adjusted life-years (QALY) by 0.77.[12] As such, American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend EVT in AIS patients within 6 hours of symptom onset.[13]

The data on cost effectiveness of EVT in South Asian countries, including Singapore, are lacking. Moreover, the results of cost-effectiveness studies are region specific due to different QALY, medical costs and willingness-to-pay thresholds for the same disease among different regions. The cost effectiveness and the long-term cost savings associated with EVT have been assessed only in few healthcare settings, such as the USA, Europe and Australia.[5 14–19] Recently, Pan *et al* found that EVT performed within 6 hours of stroke onset is cost effective in China, with a cost of US$9690 per QALY gained at a willingness-to-pay threshold of US$19 300 per QALY.[20] The average annual cost for treating ischaemic stroke in Singapore has been estimated over Singapore dollar (S$) 8000, of which 90% are inpatient costs.[21] A cost-effectiveness analysis may help rationalise the long-term clinical and economic benefits of EVT in the Singapore healthcare system. The purpose of the present study was to analyse the impact of delay in EVT on healthcare costs and QALYs on the population in Singapore and determine its cost effectiveness within different time windows (up to 6 hours) of symptom onset.

METHODS

Model overview

A Markov health state transition model was constructed using decision-analytic software (TreeAge Pro 2018, TreeAge, Williamstown, Massachusetts, USA) to compare five times to treatment windows among a base case cohort of patients with AIS aged 67 years. Outcomes within treatment initiation time windows of 61–120 min, 121–180 min, 181–240 min, 241–300 min and 301–360 min from onset were simulated over a lifetime horizon. Incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) were calculated to evaluate cost effectiveness. We used a willingness-to-pay threshold of S$50 000 per QALY (US$36 500 per QALY).[14 22]

Model structure and inputs

A short-term decision tree model was created to analyse costs and patient outcomes following the index AIS stroke within the first 3 months after stroke onset. Figure 1A–1D details the structure of the model chronologically. We assigned patients to receive either EVT or no EVT based on the probability of eligibility for treatment at different treatment initiation time windows. Treatment eligibility probabilities for the overall study population and patient subgroups were extracted from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials collaboration's meta-analysis of patient-level data from the five major randomized controlled trials (RCTs) (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA).[5] EVT eligibility was 100% for patients presenting within 2 hours of symptom onset, and decreased by 3% with every 30-minute delay in treatment for patients presenting later than 2 hours; this was a conservative assumption based on expert consensus review of the existing literature (table 1).[5] To account for patients who received IVT, the acute treatment costs implied in both EVT and non-EVT strategies were adjusted by the percentage of patients receiving IVT.[11] After treatment assignment, patients entered one of the seven possible health states according to the degree of disability as assessed by the modified Rankin Scale (mRS)

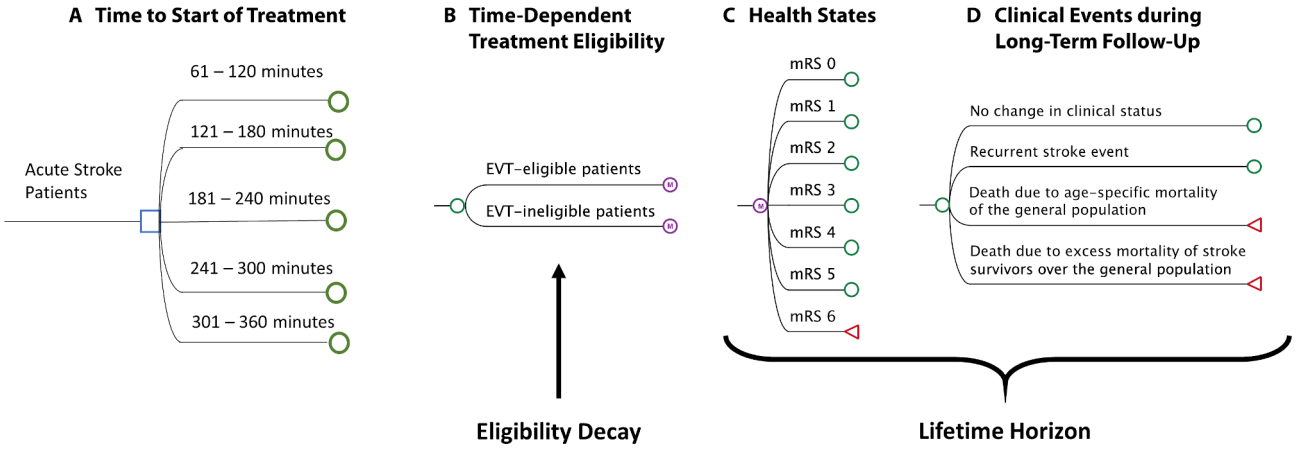

Figure 1 Model structure. A–C respresent the short-term decision model. D represents the long-term Markov model. Patients with acute ischaemic stroke in Singapore entered the model-based analysis, received either EVT or no EVT based on the eligibility rate at different treatment initiation time windows, and entered a health state based on the modified Rankin Scale (mRS) score at 90 days. During each 1-year cycle of Markov model, patients remained in the same health state, experienced a recurrent stroke or died from either age-specific mortality or excess mortality due to stroke.

Table 1 Clinical input parameters

Model input	Base-case value	Range for sensitivity analysis	Reference
Initial probabilities			
For each health state, mRS 0–6 among EVT-treated patients	90-day mRS distribution for different times to EVT	Adjusted by distribution according to sample size	HERMES data[5 11]
For each health state, mRS 0–6 among EVT-ineligible patients	90-day mRS distribution of ASPECTS 0–5 control arm	Adjusted by distribution according to sample size	HERMES data[5 11]
EVT eligibility by time			
61–120 min	1	0.90–1.00	HERMES data and expert consensus[5]
121–180 min	0.94	0.84–1.00	
181–240 min	0.88	0.78–0.98	
241–300 min	0.82	0.72–0.92	
301–360 min	0.76	0.66–0.86	
IVT eligibility by time			
61–120 min	0.86	0.81–0.91	HERMES data[11]
121–240 min	0.89	0.87–0.91	
241–300 min	0.87	0.83–0.91	
Transition probabilities			
Recurrent stroke rate	Time-dependent values	0.044–0.082	Pennlert *et al*[23]
Annual death rate of population	Age-dependent values	N/A	Singapore Life Table[25]
Death HR by mRS, relative to general age-matched population			
mRS 0	1.53	1.21–1.84	Administrative data from Singapore Ministry of Health's database
mRS 1	1.53	1.21–1.84	
mRS 2	1.64	1.58–1.69	
mRS 3	1.64	1.58–1.69	
mRS 4	2.7	2.37–3.03	
mRS 5	5.13	3.83–6.44	
mRS distribution			
mRS after recurrent stroke	90-day mRS distribution of HERMES control arm	Adjusted by distribution according to sample size	HERMES data[5 11]

ASPECTS, Alberta Stroke Programme Early CT Score; EVT, endovascular therapy; HERMES, Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials; IVT, intravenous thrombolysis; mRS, modified Rankin Scale.

score of 0 to 6. The mRS score was further used to calculate healthcare costs.

After health state assignment based on 90-day mRS in the short-term model, patients entered the long-term Markov model to estimate the expected costs and outcomes over a lifetime horizon, using a 1-year cycle length. The combination of a short-term model with a long-term model enabled us to combine the data from the short-term outcomes derived from recent RCTs with additional data from long-term observational studies.[12]

During each cycle of the Markov model, patients could remain in the same health state, experience a recurrent stroke or die from either age-specific mortality or excess mortality due to history of stroke. Given that the rate of recurrent stroke rate is age dependent, and the frequency of recurrent strokes increases in the first few years following the index stroke, we implemented yearly recurrent stroke rates following the index stroke based on the data from a stroke registry.[23] The total healthcare costs for each patient were the sum of the 90-day short-term healthcare costs after initial AIS and lifetime healthcare costs. Recurrent stroke rates with corresponding mRS scores were obtained from the study by Hong and Saver.[23 24] The age-specific death rate was drawn from the Singapore Life Table (online supplemental table 1).[25] Excess mortality risk due to stroke was incorporated in the model as the hazard rate ratio for each mRS health state obtained from electronic medical records (EMRs), relative to age-matched controls without AIS in the general population (table 1).

Table 2 Healthcare costs and utilities

	Costs/utility	Lower boundary	Upper boundary	Reference
Acute 90-day healthcare costs by 90-day mRS				
mRS 0	$4117	$2785	$5449	EMR data from Singapore healthcare system
mRS 1	$4314	$3911	$4717	
mRS 2	$6553	$5190	$7916	
mRS 3	$10517	$8758	$12276	
mRS 4	$12683	$11332	$14034	
mRS 5	$25395	$13186	$37604	
mRS 6	$5969	$5295	$6700	
Long-term annual healthcare costs by 90-day mRS				
mRS 0	$1798	$1259	$2337	Community-based surveys in Singapore
mRS 1	$1798	$1259	$2337	
mRS 2	$7709	$5397	$10022	
mRS 3	$7709	$5397	$10022	
mRS 4	$8948	$6264	$11632	
mRS 5	$22465	$15726	$29204	
Additional cost of IVT	$13500	$8829	$18171	Experts' opinion
Additional cost of EVT	$3000	$2100	$3900	Experts' opinion
Recurrent stroke cost	$9706	$8841	$10572	EMR data from Singapore healthcare system
Utilities by 90-day mRS				
mRS 0	0.88	0.84	0.92	Ali *et al*[28]
mRS 1	0.74	0.71	0.77	
mRS 2	0.51	0.49	0.53	
mRS 3	0.23	0.22	0.24	
mRS 4	−0.16*	−0.14	−0.17	
mRS 5	−0.48*	−0.43	−0.52	

All costs are in Singapore dollars.
*Utilities are represented on a scale, with 0 indicating equivalence with death, 1 representing perfect health and negative values indicating health states considered worse than death.
$, Singapore dollar; EMR, electronic medical record; EVT, endovascular therapy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale.

Costs

All costs are reported in 2018 Singapore dollar. The short-term 90-day healthcare costs by mRS score were based on administrative records from the Singapore Ministry of Health's database. Long-term annual stroke-related healthcare costs by mRS score at 90 days were obtained from community surveys by the Singapore Ministry of Health. The costs of EVT and IVT were estimated by a stroke physician in Singapore based on expert experience, as no national cost data for each treatment are available for the Singapore population. Given only point values were available for Singapore estimated cost data, the ratio of upper and lower bounds (relative to the mean) of stroke-related healthcare costs used in a prior model was used to derive the lower and upper boundaries of cost inputs for our present model's sensitivity analyses.[26] All costs were discounted by 3% each year (table 2).[27]

Utilities

Therapy effectiveness was measured by QALYs. Utility weights were derived from a study by Ali *et al*, including stroke patients from Asian countries.[28] Utility values ranged from −0.48 for patients with an mRS of 5 to 0.88 for those with an mRS of 0 (table 2). All QALYs were discounted by 3% each year.[27]

Cost-effectiveness analysis

Cost effectiveness was compared in terms of ICERs and incremental NMBs (INMBs). The ICER was calculated as incremental costs divided by incremental QALYs. INMB rearranges the ICER and incorporates a health system's willingness to pay for a particular outcome into one measure as follows: INMB=(incremental QALYs×willingness to pay)−incremental costs. The willingness to pay was set to S$50 000 per QALY.[14 22] Generally, if the INMB is a positive value, it suggests that the intervention should

be adopted per the health system's willingness-to-pay threshold.

Sensitivity analysis

We used deterministic sensitivity analyses to test the robustness of the model results. Deterministic one-way sensitivity analysis was performed to identify variables that significantly influence the modelled outcomes. Input ranges for deterministic sensitivity analysis were determined by the 95% CI of the initial probabilities, utilities and costs (tables 1 and 2). As base-case utilities associated with mRS 4 and 5 were negative as reported by Ali *et al*,[28] we performed two additional sensitivity analyses: first, by setting negative utilities to 0 and second, by using utilities from a global study.[29] A probabilistic sensitivity analysis was also undertaken to evaluate uncertainty due to the simultaneous variability of the input variables. We assumed that the costs followed a gamma distribution, death HR followed a log-normal distribution and probabilities and eligibility rates followed a beta distribution. The simulation was run 10 000 times.

This study did not require institutional review board approval as the input parameters for this modelling study were obtained from published literature, expert opinion or generated from databases in which patient-identifiable information was not available.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to interpret the results. Patients were not invited to contribute to the writing or editing of this document.

RESULTS

Base-case analysis

Based on our model, EVT after 4 hours from stroke onset resulted in higher lifetime healthcare costs and lower QALY relative to initiating EVT treatment within 3–4 hours of stroke onset (table 3, treatment time windows 301–366 min and 241–300 min). Initiation of EVT between 61 min and 120 min improved quality of life but increased lifetime healthcare costs compared with EVT initiated between 121 min and 180 min, resulting in an ICER of S$7197 per QALY (US$5254). Using S$50 000 (US$36 500) as willingness-to-pay threshold, the incremental NMB associated with receipt of EVT at the earlier time point is S$39 827 (US$29 074) per patient (table 3). Each hour delay in initiating EVT resulted in an average loss of 0.54 QALYs and 195.35 healthy days (online supplemental table 2). Consequently, the average net monetary loss per hour due to delay in EVT treatment was estimated at S$26 255 (US$19 166). Therefore, EVT within 4 hours of onset is cost effective when compared with initiating EVT at a later time window, which is associated with increased costs but decreased QALYs.

Sensitivity analysis

The results of the deterministic one-way sensitivity analysis are presented in figure 2. The clinical outcome and costs for the two most cost-effective treatment time subgroups, 61–120 min and 121–180 min, were compared when the input parameters were varied within pre-specified ranges. The ICER comparison between the 61–120 min and 121–180 min time windows ranged from approximately S$5000 to S$9500 (US$3650–US$ 6935) for all one-way sensitivity results (horizontal bars in figure 2). Based on the willingness-to-pay threshold of S$50 000 (US$36 500), treatment initiated within 61–120 min of stroke onset was determined as more cost effective than that initiated within 121–180 min. Moreover, the outcomes demonstrated that ICER is most sensitive to long-term annual healthcare cost inputs.

Two additional sensitivity analyses using two sets of utilities associated with different mRS levels were performed. Results from each one-way utility sensitivity analysis were consistent with the base-case results, showing that the treatment window of 61–120 min was most cost effective among all treatment initiation times (online supplemental tables 3 and 4). The probabilistic sensitivity analysis

Table 3 Cost-effectiveness analyses of time delays in EVT treatment

Time window of EVT initiation (min)	Cost	Incremental cost	QALY	Incremental QALY	ICER	INMB*
181–240 min	$96 121		2.98			
121–180 min (vs 181–240 min)	$97 870	$1749	3.76	0.78	$2249	$37 139
301–360 min (vs 121–180 min)	$100 982	$3112	1.95	–1.81	Dominated	
241–300 min (vs 121–180 min)	$102 545	$4675	2.55	–1.21	Dominated	
61–120 min (vs 121–180 min)	$104 567	$6697	4.69	0.93	$7197	$39 827

*INMB rearranges the ICER and incorporates a health system's willingness to pay for a particular outcome into one measure as follows: INMB=(incremental QALYs×willingness to pay)–incremental costs. The willingness to pay was set to $50 000 per QALY. Generally, if the NMB is positive, it suggests an intervention should be adopted per the health system's willingness-to-pay threshold. All costs are in Singapore dollars.

$, Singapore dollar; EVT, endovascular therapy; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; NMB, net monetary benefit; QALYs, quality-adjusted life-years.

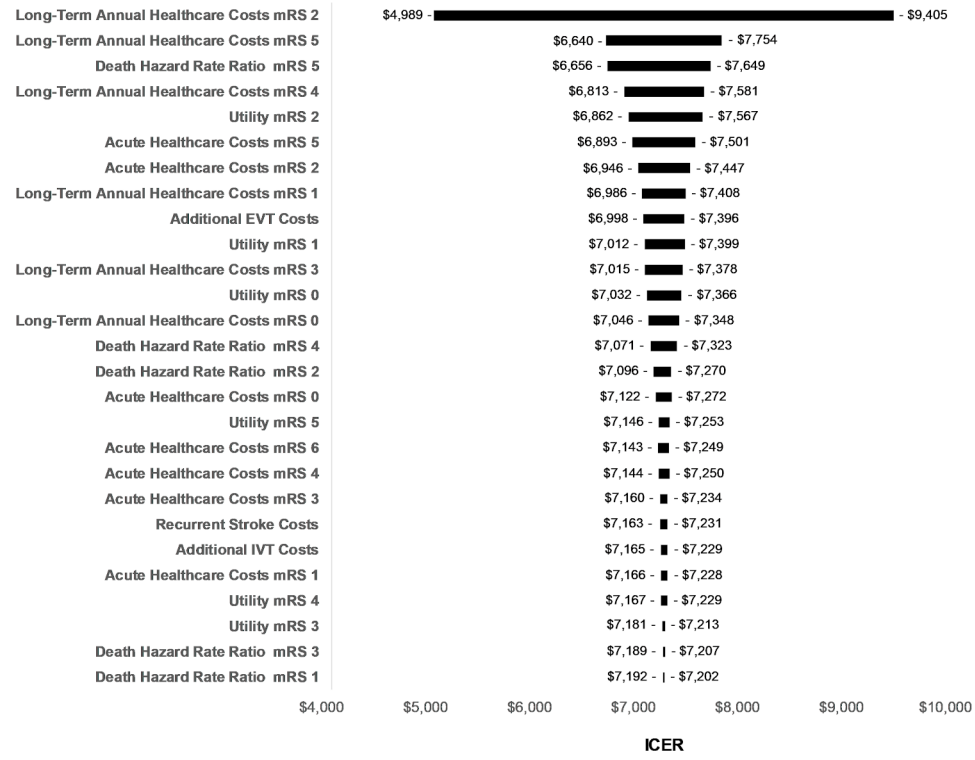

Figure 2 One-way sensitivity analysis: 61–120 min subgroup vs 121–180 min subgroup. The tornado graph indicates changes in the ICER as a result of one-way sensitivity analysis of the indicated model input parameters. EVT, endovascular therapy; mRS, modified Rankin Scale; IVT, intravenous thrombolysis. All costs are in Singapore dollars.

also illustrated that EVT treatment within 61–120 min after the stroke onset was most cost effective in 82.2% of simulation runs at a willingness-to-pay threshold of S$50 000 (US$36 500) (online supplemental figure 1). This increased to 86% at a willingness-to-pay threshold of S$100 000 (US$73 000).

DISCUSSION

This study investigated the lifetime consequences of delayed initiation of EVT after stroke onset in terms of patient quality of life and cost of EVT from the Singapore healthcare perspective. Initiating EVT within 4 hours of symptom onset was shown to be cost effective, while treatment initiation after 4 hours was associated with higher cost and lower QALYs, where each hour of delay in EVT increased the lifetime healthcare costs and reduced patient's quality of life. We applied input parameters specific to the Singapore population, with both short-term and long-term costs as well as utilities derived directly from the administrative data and community surveys in Singapore. The evidence of clinical benefit of EVT does not necessarily warrant its cost effectiveness without considering its impact on healthcare costs, and it is essential for policy-makers to determine whether the benefits of EVT outweighs the higher cost of EVT compared with medical treatment. The current study demonstrates that despite the higher short-term healthcare costs of EVT than alternative treatments, EVT brings in sufficient benefits on patients' QALY, and is most cost effective at earlier time windows after symptom onset.

Our findings are similar to those reported in a previous cost-effectiveness analysis of EVT in the US setting.[12] In the USA, EVT initiated between 60 min and 239 min was more cost effective relative to treatment initiated at a later time. Each hour of delay in EVT resulted in an average loss of 0.77 QALYs and increased the healthcare cost by US$6173 per QALY. Earlier treatment with EVT and IVT was associated with lower disability at 90 days after stroke compared with IVT alone,[11] with every of hour of delay in EVT reducing the absolute risk difference for good outcome by 6%.[30] However, recent cost-effectiveness studies in the USA and China suggest that EVT is still cost effective when performed as late as 5–6 hours after stroke onset compared with IVT alone.[19 20] Based on these results and that of the present study, EVT treatment within 4–6 hours of stroke onset is considered a cost-effective treatment option.

In our study, total healthcare costs associated with the 61–120 min subgroup were slightly higher versus patients treated at later time points. This was driven by the greater proportion of patients eligible for EVT at this earlier time window and thereby a greater proportion of patients incurring costs related to EVT relative to the less expensive standard of care. Patients with EVT have higher probability of improved functional outcome (lower mRS score) and reduced morbidity, which is likely to reduce long-term costs associated with nursing home or home

help relative to standard care based on a long-term cost-effectiveness study of thrombectomy.[18] Similar to our findings, Pan *et al* also reported that EVT was associated with higher lifetime costs compared with IVT alone.[20] In spite of the greater initial treatment-related costs, EVT was found to be cost effective in Singapore population, a finding similar to those of previous cost-effectiveness studies performed in both western and eastern countries.[14–20 22] Although the findings from this study might not be directly applied to other countries or regions, the model described here can be adopted to other countries or regions by inputting localised parameters. Most importantly, the overall results will be similar in other healthcare settings, yet the absolute magnitude will be different.

The current study has several limitations. First, long-term annual healthcare costs were collected from Singapore survey data limited to the first 2 years following a stroke. It is possible that the first 2 years of healthcare costs incurred post-stroke could be greater versus later years of follow-up. However, this time-related cost trend is not reflected in the current input parameters, with average long-term annual costs fixed in each year of follow-up. To partially address this limitation, we performed one-way sensitivity analysis on annual healthcare costs to test the robustness of the base-case inputs. Second, the short-term 90-day acute costs were collected from an EMR database. Since lower and upper boundaries are not available, we used ranges from a global study to derive the lower and upper boundaries for sensitivity analysis. The current model is from a Singapore national direct healthcare cost perspective, which does not account for indirect costs related to potential productivity loss. However, given the majority of stroke population consisted of patients with advanced age, indirect costs likely would contribute far less than the direct healthcare costs included in the present study. Moreover, the current study analysed treatment initiated within 6 hours after the onset of stroke due to the availability of eligibility rates of EVT in existing clinical trials. As a recent guideline from the ASA recommended a treatment window up to 12 hours, the model may need to be updated once the relevant eligibility data between 6 hours and 12 hours are available. Finally, modelling results are region specific and typically are only directionally applicable to other regions given specific medical costs, health utility preferences and willingness-to-pay thresholds vary, resulting in different specific ICER estimates. However, the general conclusion on cost effectiveness of treatment at earlier time windows should hold. Future local country adaptations using the structure of our model presented herein would provide more specifics on local ICER values and a more precise local time window in which treatment with EVT is no longer considered cost effective.

CONCLUSIONS

This study indicates that, from the Singapore healthcare perspective, performing EVT at earlier time windows is more cost effective compared with initiating treatment at a later time after stroke onset. Thus, healthcare policies and procedures should aim to improve efficiency of pre-hospital and in-hospital workflow processes to reduce the onset-to-puncture duration.

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Competing interests WN is a full-time employee of Medtronic with stock. MG is a consultant of Medtronic, Stryker, Microvention, entice and GE Healthcare.

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Patient consent for publication Not required.

Ethics approval The study was performed in compliance with the World Medical Association's Declaration of Helsinki.

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