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Endovascular Thrombectomy in Patients with Large Core Ischemic Stroke: A Cost-Effectiveness Analysis from the SELECT Study

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Endovascular Thrombectomy in Patients with Large Core Ischemic Stroke: A Cost-Effectiveness Analysis from the SELECT Study

Abstract:

Background: Whether endovascular thrombectomy (EVT) is cost-effective in large ischemic core infarcts is unknown.

Methods: In the prospective multicenter cohort study of imaging selection study (SELECT), large core was defined as CT ASPECTS < 6 or CTP ischemic core volume (rCBF<30%) ≥ 50 cc. A Markov model estimated costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) of EVT compared to medical management (MM) over life time. The lower and upper willingness to pay (WTP) per QALY were set at $50,000 and $100,000 and the net monetary benefit (NMB) for EVT were calculated. Probabilistic sensitivity analysis (PSA) and cost-effectiveness acceptability curves (CEAC) were assessed for EVT in SELECT and other pivotal EVT trials.

Results: From a prospective cohort trial of 361 patients, 105 had large core on CT or CTP (EVT 62, MM 43). 19 (31%) EVT patients achieved mRS 0-2 vs 6 (14%) MM patients (aOR: 3.27, 95% CI: 1.11-9.62; P = .03) with a shift towards better mRS (adj cOR: 2.12, 95% CI: 1.05-4.31, P = .04). Over the projected lifetime of stroke patients presenting with large ischemic core, EVT was associated with incremental costs of $33,094 and a gain of 1.34 QALYs per patient, resulting in ICER of $24,665 per QALY. EVT has a higher NMB compared to MM at the lower (EVT: -$42,747 vs MM: -$76,740) and upper (EVT: $155,041 vs MM: $57,134) thresholds of willingness to pay. The PSA confirmed the results and the CEAC showed 77% and 92% cost-effectiveness probability of EVT at the WTP of $100,000, respectively. EVT was associated with an increment of $28,962 in societal costs. The Pivotal EVT trials (HERMES, DAWN and DEFUSE 3) were dominant in a sensitivity analysis at the same inputs, with societal cost savings of $38,072, $86,358 and $22,837, respectively.

Conclusion: EVT may result in better outcomes in large core patients with higher QALYs, NMB and high cost-effectiveness acceptability rates based on current WTP thresholds.

Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT02446587

Introduction

Stroke is a global health problem, with more than 13 million new strokes and 5.5 million deaths every year[1]. In the USA, every year 795,000 individuals suffer from new or recurrent stroke, resulting in 140,000 deaths[2]. Stroke is also the leading cause of serious long-term disability, resulting in 116.5 million quality-adjusted life year (QALY) lost[1] worldwide every year. Moreover, it is an expensive disease to treat and manage with annual direct costs of $28 billion and indirect costs of $17.5 billion on the US economy, with a projected increase in direct costs to $94.3 billion by year 2035[2]. Effective stroke treatments that improve clinical outcomes and reduce disability may help reduce the economic burden of stroke in society and in our health care systems by reducing direct and indirect costs.

Endovascular thrombectomy (EVT) has been established as a transformative treatment for ischemic stroke patients with large vessel occlusion; safety and efficacy have been well documented in patients with small ischemic core infarcts, both in early[3–7] and late[8,9] time windows. While randomized trials for efficacy and safety of EVT in patients with large ischemic stroke are ongoing[10–13], potential evidence of EVT efficacy and safety in these patients was recently presented from a large, multicenter, prospective cohort data[14]. With prevalence of large core strokes estimated to be as high as ~30%[14], these patients are frequently encountered in daily practice. Treating physicians have several considerations while determining the treatment approaches, such as the poor natural history in patients treated with medical management only as compared to the lower likelihood of functional independence and the potential safety concerns with EVT. One of the considerations for the healthcare systems and for society is whether treatment with endovascular thrombectomy is cost-effective. While cost-effectiveness of EVT in patients with small ischemic core has been assessed and deemed favorable[15–21], it remains unknown whether EVT is cost-effective in patients presenting with large ischemic core infarcts. The implications of EVT on societal costs related to large stroke patients have also not been studied in detail.

We sought to assess EVT cost-effectiveness by performing a cost- effectiveness analysis for EVT as compared to medical management only (MM) using outcomes in patients with large ischemic core infarcts on CT (ASPECTS <6), CTP (rCBF <30% volume ≥ 50 cm^3) or both from the SELECT study, a prospective, multicenter cohort study of imaging selection[22].

This study sub-analysis aims were:

1. To assess the overall gain in QALYs
2. To identify the incremental cost-effectiveness ratio (ICER) for EVT
3. To assess the net monetary benefit (NMB) at various thresholds of willingness to pay (WTP)
4. To compare EVT cost-effectiveness in patients with large ischemic core to those with small core infarcts.
5. To assess EVT societal cost benefits in patients with large ischemic core

Methods:

Study population:

"The Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT): a Prospective Multicenter Cohort Study of Imaging Selection"[22] enrolled patients with stroke attributable to large-vessel occlusion who were treated with endovascular thrombectomy plus medical management or medical management alone, based on CT or CTP findings, up to 24 hours from the point that they were last known to be well at 9 comprehensive stroke centers across the United States. The decision to proceed with EVT vs medical management alone was made at the discretion of the local investigators in a nonrandomized fashion. The study initially included patients up to 8 hours after stroke onset, with the enrollment window extended up to 24 hours after the results of the Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trial[8] were announced. Patients with large ischemic cores were defined as having an ASPECTS of 5 or less on non-contrast CT or an ischemic core volume of 50 cm^3 or more on CTP based on the volume of tissue with a relative cerebral blood flow less than 30% at presentation.

Cost-Effectiveness Analysis:

We performed a cost-effectiveness analysis to compare costs and outcomes of endovascular thrombectomy (EVT) in addition to medical management (MM) compared to MM only in patients with large core acute ischemic stroke. The outcome measures were quality-adjusted life years (QALYs). QALYs are assessed using the survival time and the utility associated to the modified Rankin Scale (mRS) score. For each mRS score we used utility values obtained from a recent consensus analysis. The analysis took the health care service provider perspective, including only the costs of direct medical treatment (hospital admissions, ICU, rehabilitation). An analysis from societal perspective was also attempted that accounts for the societal costs (as in productivity losses, informal care and private cost for patients). Costs were calculated in 2017 US$, inflated where necessary[23]. The time horizon was selected to be over lifetime. All costs and outcomes after the first year were discounted at an annual rate of 3%.

Model Structure:

We created a decision analysis model to assess cost-effectiveness of EVT using TreeAge Healthcare Pro version 2020 (TreeAge, Williamstown/MA). The treatment arms include best MM (including the use of IV tPA where applicable) without subsequent EVT vs best MM followed by EVT. The decision model consisted of two different models 1) a short run model to assess the transitions measured at 90 days following stroke and 2) a long run model to assess transitions over the course of lifetime following the initial stroke, beginning at 90-day post stroke. The short run model analyzed the clinical outcomes and costs associated with the treatment at 90-day interval following the index stroke. The long run model was created to estimate the transitions in clinical outcomes and associated post-stroke costs with cycles of 1 year. At the end of each cycle, the patient could remain in the same health state, experience a recurrent stroke and recover to the same state or transition to other states or die from stroke or other causes. Outcomes were based on modified Rankin Scale (mRS) scores measured at 90 days after stroke.[24]

Model Input Parameters

The initial probabilities for short run model to analyze 90 day clinical outcomes were identified from the large core cohort of the SELECT study[14]. The study reported outcomes of 105 patients (62 EVT, 43 MM) with large ischemic stroke on non-contrast CT, CT perfusion or both; demonstrating functional independence rates of 31% and 14% in patients treated with EVT and MM respectively. For comparative models for patients with small core, results provided in HERMES metanalysis[25] were used for short run models in early time window (0-6 hours), DAWN[8] and DEFUSE 3[9] results were used for trials beyond 6 hours of stroke onset. The transitional probabilities beyond 90 days of stroke onset were populated using historical data from multiple prospective cohort studies, identifying probabilities of recurrent stroke, death and changes in functional status over the course of time for patients suffering from index stroke.[26–28] The measures for utilities at different mRS categories were obtained from a prospectively validated cohort evaluating EuroQol in post-stroke patients.[29] Table 1 provides further information regarding the parameters used in the decision analysis model.

Treatment Costs

Data was used from the National Inpatient Sample[30] and data available in the literature[31] to estimate costs and we inflated as necessary using the inflation rate from national sources[24]. The costs are presented in Table 1.

The additional cost of IV thrombolysis was estimated to be $6,961, including the cost of the therapy, the medication and administration from the National Inpatient Sample[30], inflated at the 2017 US $.

The cost of the EVT varied in each trial was estimated to be $14,454. This includes the cost of the devices (stent-retreivers), materials and intervention.

The health care costs in the 3 months following a stroke include the acute management (length of stay in the acute stroke unit, in the acute high dependency unit, and in the rehabilitation ward, as well as the supported discharge cost and community care costs) and rehabilitation costs.[32] The ongoing costs in the following years include rehabilitation costs and follow-up costs.[31] Both acute and ongoing costs were applied based on the disability observed at 90-day on modified Rankin Scale score in 7 different categories. The cost of a recurrent stroke was estimated as the mean expected cost to treat an average stroke that does not need MM or EVT.[33]

Initial and Transitional Probabilities

The initial probabilities were defined based on modified Rankin Scale score at 90 days and were assessed using results from the SELECT study for patients presenting with large ischemic core for the main results. The initial probabilities for comparison models with the trials were assessed from the results published from the DAWN[8] and DEFUSE 3 trials[9] and HERMES meta-analysis[25]. The transitional probabilities were defined as the probability to move from one health state to another after 90 days results and were implemented in annual cycle for the long run model for a horizon of lifetime. The age specific annual death rates were obtained from United States Life Tables.[27] Excess deaths because of stroke were incorporated as additional hazard ratios identified from the contemporary cohort studies.[28] The other transitional probabilities were also obtained from various large prospective cohorts.[26]

Cost-Utility Measures and Outcomes:

The cost-effectiveness of EVT was expressed in terms of its incremental cost-effectiveness ratio (ICER), defined as the ratio of the difference in the costs between EVT and MM and gain in Qality Adjusted Life Years between the treatments demonstrated by the model.

$$ICER = \frac{Average\ Cost\ of\ EVT - Average\ Cost\ of\ MM}{Average\ QALYs\ of\ EVT - Average\ QALYs\ of\ MM}$$

Results are also expressed in terms of net monetary benefits (NMB), calculated as the mean QALYs per patient accruing to that treatment multiplied by the willingness to pay (WTP) for a QALY (the cost-effectiveness threshold) minus the mean cost per patient for the treatment.

$$Net\ Monetary\ Benefit = [Average\ QALYs\ with\ EVT\ X\ Willingness\ to\ Pay] - Mean\ Difference\ in\ the\ Cost\ of\ EVT$$

The lower and upper willingness to pay for NMB calculations were set to $50,000 and $100,000 per QALY.

Analysis from Societal Perspective:

To assess the impact of index stroke on overall societal productivity, we used human captial approach to calculate costs associated with lost productivity as well as costs of informal care provided by the family. Lost societal productivity due to premature deaths and post stroke morbidity were calculated separately. Using US Census Bureau[34] gross wages and age-based employment rates provided by US Bureau of Labor Statistics[35], lost productivity due to premature mortality was calculated. Furthermore, we assumed complete retirement at age 80. Non-stroke related premature deaths were not considered for these evaluations.

To obtain the lost productivity due to stroke-related morbidity, the aforementioned productivity measures were multiplied by relative earnings of stroke survivors (82.5%) and probabilities of return to work (RTW) based on 90-day functional status. The cost of informal care provided by the family members were stratified based on 90-day functional status and calculated using hourly wages for home health aides for year 2017.[34]

Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was performed to establish the impact of the uncertainty characterising the input parameters and assess the robustness of the results, using

10,000 runs for the second order Monte Carlo simulation. A distribution was assigned to each parameter value and a random value from the corresponding distribution was selected to be used as an input for the Markov model. The mean (median) cost, QALYs and NMB for each treatment were calculated from the 10,000 simulations; and the probability that the interventions are cost-effective is summarised in the cost-effectiveness acceptability curves (CEACs). We also conducted the same analysis, using the data from randomized trials that proved EVT efficacy and safety in patients with small ischemic core: HERMES[25], DEFUSE 3[9] and DAWN[8].

Results

Functional Outcomes in Patients with Large Ischemic Core Infarcts:

Of 361 patients enrolled in SELECT, 105 (29%) had a large ischemic core on CT or CTP or both (EVT 62, MM 43). Functional independence (modified Rankin Scale score of 0-2) at 90 days was achieved in 19 (31%) EVT patients vs 6 (14%) MM (OR: 3.27, 95% CI: 1.11-9.62; $P = .03$) with a shift towards better mRS (cOR: 2.12, 95% CI: 1.05-4.31, $P = .04$)[14]. Mortality was observed in 29% (18/62) of EVT and 42% (18/43) of MM patients, p=0.17. Neurological worsening (EVT: 13/62 (21%) vs MM: 8/43 (20%), p=0.87) and symptomatic ICH (EVT: 8/62 (13%) vs 3/43 (7%), p=0.51).

Base Case Analysis:

Using base case values, EVT following MM performed in patients with large ischemic core infarcts was associated with an incremental cost of $33,094 per patient over projected lifetime(Table 2). EVT-treated patients could gain 1.34 incremental QALYs.

The ICER of EVT compared to MM was $24,665 per QALY. The EVT has a higher NMB compared to MM alone at the lower (EVT: -$42,747 vs MM: -$76,740) and upper (EVT: $155,041 vs MM: $57,134) thresholds of WTP, indicating that EVT is cost-effective. EVT was also associated with incremental costs of $28,962 in an analysis from the societal perspective.

Sensitivity Analysis:

Figure 2 demonstrates the probabilistic sensitivity analysis based on 10,000 simulations. A significantly higher proportion of results are in the quadrant where an increment in costs is associated with a QALY gain and most of the result are under the $100,000/QALY threshold line, therefore there is a high probability that EVT is cost-effective. The cost-effectiveness acceptability curves (CEAC) demonstrates the probability that each treatment is cost-effective at different values of the willingness to pay for a QALY (Figure 3). EVT has 77% & 92% probability of being cost-effective compared to MM when the willigness to pay is $50,000 and $ 100,000 per QALY, respectively.

Comparison of EVT Cost-Effectiveness in Large Core Infarcts to Patients with Small Core Infarcts:

Overall, data from HERMES meta-analysis in early time window and DAWN and DEFUSE 3 in late time window demonstrated overall higher lifetime costs associated with MM as compared to EVT. Cost-effectiveness analysis based on data from HERMES meta-analysis demonstrated average overall cost savings of $29,964 over lifetime in patients treated with EVT, with a gain of 1.62 QALY (i.e. dominant over MM) and almost 100% probability of EVT being cost-effective in probabilistic sensitivity analysis at lower and upper thresholds of WTP. EVT also decreased the societal costs by $38,072. Similar results are obtained based on outcomes from DAWN trial (dominant) and DEFUSE 3 trial (dominant) with both the trials demonstrating almost 100% of being cost-effective at the willingness to pay thresholds of $50,000 and $100,000. EVT was also associated with a reduction in societal costs by $86,358 in DAWN and $22,837 in DEFUSE 3 trial. Table 3 demonstrates the comparison of incremental EVT costs, QALYs, ICER and societal cost benefits in SELECT large ischemic core patients as compared to previously published RCTs over the horizon of lifetime.

Discussion:

We found that EVT may result in more lives saved and improved quality of life in large core patients from the SELECT prospective cohort study. This treatment strategy had an acceptable ICER, a higher NMB and high probabilities of being cost-effective at even the lowest bounds of current willingness-to-pay thresholds for the United States healthcare system.

Our analysis suggests that in patients with large ischemic core on CT or CTP, EVT was associated with 1.34 QALY gained and ICER of $24,665 for each QALY gained. While it resulted in initial $33,094 incremental cost per patient, EVT was associated with more lives saved and improved likelihood of being functionally independent (mRS 0-2), increasing the QALYs.

Our results showed an incremental lifetime cost associated with EVT as compared to prior RCTs that enrolled patients with small core.[8,9,25] This is to a large part likely due to the high mortality rate in SELECT large core subpopulation that received MM only; 42% as compared to 19% in HERMES[25], in 26% in DEFUSE 3[9] and 18% in DAWN[8]. Such a high mortality rate paradoxically largely reduces the cost in the MM group. For example, healthcare policy makers recognize that life-saving interventions may increase long-term expenditures, creating counter-intuitive results. Prominent examples include the effect of smoking cessation or of several preventive measures, which may increase costs in the long run due to a higher life expectancy of the population.[36,37]

Within the same lines, the social cost was higher in our large group cohort due to the reduced mortality with EVT primarily with similar rates of severe and profound disability (mRS) 4-5 between EVT and MM as compared to a difference within the same mRS grades in prior EVT RCTs. Additionally, the median age for our cohort was higher than prior RCTs which may have resulted in an underestimation of the potential savings attributable to EVT and overall savings including productivity losses and higher societal costs.

Previous studies demonstrated the cost-effectiveness of EVT compared to MM up to 24 hours of stroke in small core infarcts[15–21] with ICER significantly below the current willingness to pay thresholds in patients included in randomized controlled trials (put references only from RCTs). Since most of these trials excluded patients with large ischemic core, involvement of these patients in such analyses is limited. Prior report[18] demonstrated cost-effectiveness of EVT in patients with ASPECTS of 0-5 at a higher ICER, however concluded that the estimates may be uncertain because of systemic exclusion of such patients from the trials.

With several ongoing clinical trials assessing the efficacy and safety of EVT in stroke patients with large ischemic core on different imaging modalities (SELECT 2[13], IN EXTREMIS[12], TESLA[11], TENSION[10]), the randomized evidence is forthcoming in this important sub population, which represents more than 20% of the patients encountered in daily practice.

Meanwhile, our cost-effectiveness analysis from the SELECT prospective cohort[14] suggests that EVT may be cost-effective. These results, while still need to be confirmed based on data from the upcoming RCTs, represent further evidence from economical, societal and quality of life assessment to justify these randomized trials to evaluate intervening in patients with more extensive areas of infarct.

There are limitations to our study that should be considered when interpreting the findings. This includes the lack of randomization and potential selection biases associated with prospective, cohort data. Additionally, we did not have direct economic data from the prospective cohort and thus relied upon the overall payments based on current diagnosis-related group (DRG) for EVT. Another limitation is represented by the variability in the methodology adopted in the different trials of EVT effectiveness in patients with small core infarcts, including the use of different devices and medical treatment to treat stroke. However, we conducted an extensive sensitivity analysis that confirms the results.

The strengths of the presented study include data from a multicentre, prospective cohort study, use of prior validated methods, inclusion of probabilistic sensitivity analysis and comparative analysis with prior RCTs using the same parameters that allows for the direct comparison of cost-effectiveness.

Conclusion:

EVT may result in better outcomes and more lives saved in large core patients with higher QALYs, NMB and an acceptable ICER. This further justifies a randomized trial for EVT efficacy and safety in patients with large core.

Declaration of conflicting interests

The authors declare no conflict of interest.

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Model Input	Base-case value	Distribution	Source
Initial probabilities for achieving mRS 0/1/2/3/4/5/6			
SELECT Large Core		Dirichlet	Sarraj et al.
EVT	0.0806/0.0645/0.1613/0.0968/0.2419/0.0645/0.2903		
MM Only	0.0233/0.0233/0.0930/0.1628/0.1628/0.1163/0.4186		
HERMES		Dirichlet	Goyal et al.
EVT	0.1000/0.1690/0.1910/0.1690/0.1560/0.0620/0.1530		
MM Only	0.0500/0.0790/0.1360/0.1640/0.2470/0.1350/0.1890		
DAWN		Dirichlet	Nogueira et al.
EVT	0.0900/0.2200/0.1700/0.1300/0.1300/0.0900/0.1600		
MM Only	0.0400/0.0500/0.0400/0.1800/0.1600/0.1800/0.1800		
DEFUSE 3		Dirichlet	Albers et al.
EVT	0.1000/0.1600/0.1800/0.1500/0.1800/0.0800/0.1400		
MM Only	0.0800/0.0400/0.0400/0.1600/0.2700/0.1600/0.2600		
Transition probabilities			
Recurrent stroke rate	0.059 (for 1st y)	Beta	Pennlert et al.
Annual death rate	0.013 (for 65 y)	Beta	Arias et al.
Annual death hazard rates for survivors mRS 0/1/2/3/4/5	1.53/1.52/2.17/3.18/4.55/6.55	Log normal	Hong et al
After recurrent stroke	control arm from HERMES meta-analysis	Dirichlet	Goyal et al.
Health care costs			
Costs within first 90 days after stroke for mRS 0/1/2/3/4/5/6 (excluding IVT and EVT)	$7.996/$11.038/$17.336/$21.440/$28.729/$34,319/$8,067	Gamma	Dawson et al.
Additional cost of IVT treatment	$6,961	Gamma	NIS 2014
Additional cost of EVT treatment	$14,454	Gamma	Shireman et al.
Long-term annual costs after stroke for mRS 0/1/2/3/4/5	$11,245/$11,579/$13,395/$23,009/ $46,553/$68,441	Gamma	Shireman et al.
Recurrent stroke hospitalization	$23,032	Gamma	Chambers et al.
Utilities			
mRS 0/1/2/3/4/5/6	1.00/0.91/0.76/0.65/0.33/0.00/0.00	Beta	Chaisinanunkul et al.
Societal costs			
Paid workforce productivity			
Average annual earnings of employed population	$33 000 (for 65 y)	Gamma	US Census Bureau 2017

Population employment rate	0.312 (for 65 y)	Beta	US Bureau of Labor Statistics 2017
Relative earnings of stroke survivors	0.825	Beta	Vyas et al.
Return-to-work after stroke mRS 0/1/2/3/4/5	0.63/0.72/0.49/0.19/0.14/0.00	Beta	Tanaka et al.
Unpaid domestic productivity			
Informal annual caregiving costs	mRS 0–1: $1503 mRS 2–5: $7518	Gamma	Hickenbottom et al.

Table 1 represents the model parameters and range of values used for sensitivity analysis. short term transition probabilities were used from SELECT[14], HERMES, DAWN[8] and DEFUSE 3[9] population. Long term transition probabilities were based on multiple large prospective cohort studies[25, 27-29]. Acute costs in the first 3 months include baseline medical management including adminstration of IV tPA. Utilities were derived from a validation cohort for EuroQol[23].

	Endovascular Thrombectomy	**Medical Management**	**Difference**
Cumulative Lifetime Costs	$207,866	$ 240,959	$ 33,094
Cumulative Lifetime QALYs gained	3.96	2.62	1.34
Incremental Cost per QALY gained			$ 24,665

Table 2 demonstrates the Costs, QALYs, ICER and NMB of EVT versus Medical treatment (MM) Based on results from patients with large core in SELECT trial. All costs are calculated in 2017 US dollars.

	SELECT Large Core	HERMES	DAWN	DEFUSE 3
Incremental Costs	$33,094	-$29,964	-$69,887	-$12,723
Incremental QALYs	1.34	1.62	2.36	2.21
ICER	$24,665	Dominant	Dominant	Dominant
Societal Costs	$28,962	-$38,072	-$86,358	-$22,837

Table 3 describes the incremental costs, incremental QALY and ICERs of EVT versus MM in USD in SELECT patients with large ischemic core over horizon of lifetime, as compared to the previously published RCTs of patients with small core infarcts in both early and late time window.

The high cost of EVT was in part owing to the high mortality in MM patients in SELECT Large Core cohort, as compared to HERMES, DAWN and DEFUSE 3 cohorts. Similarly, the social cost of EVT in SELECT large core cohort was due to the reduced mortality with EVT primarily with similar rates of severe and profound disability (mRS) 4-5 between EVT and MM as compared to a difference within the same mRS grades in prior EVT RCTs.

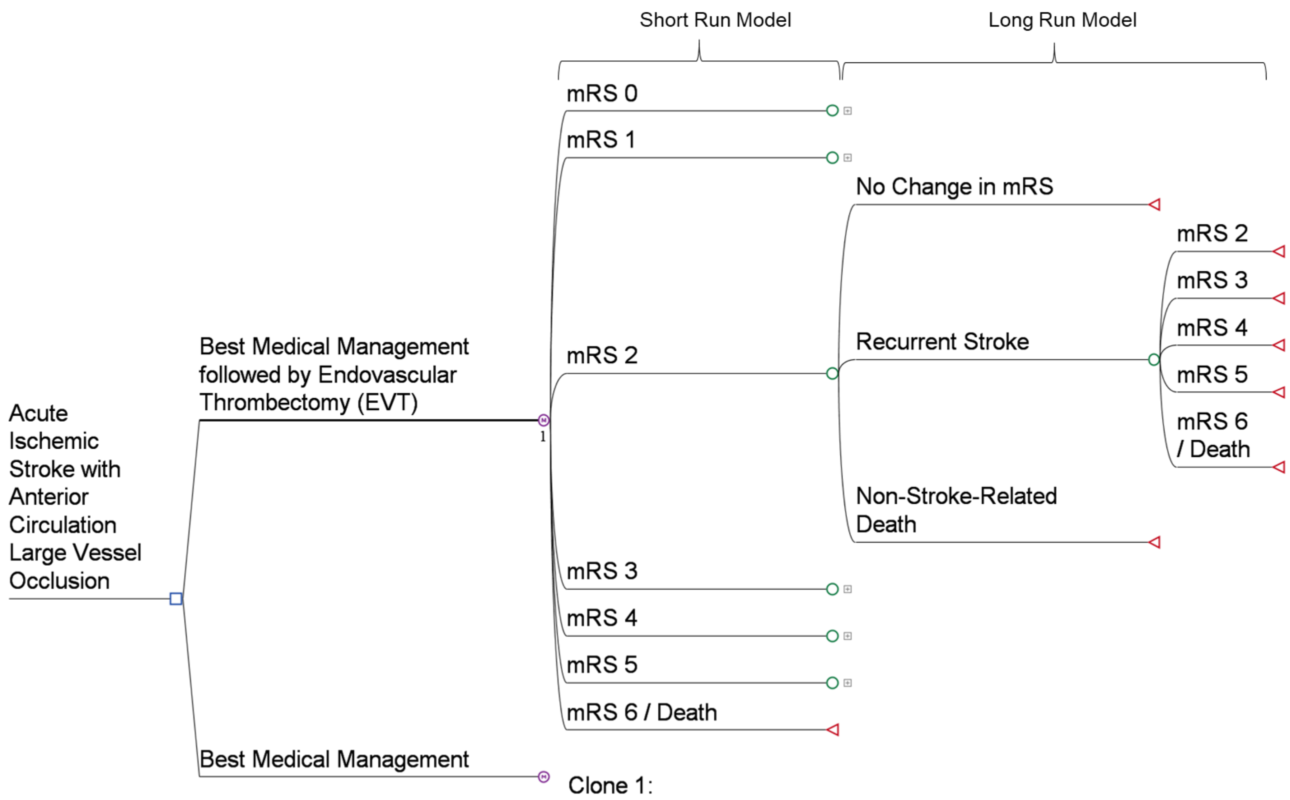

Figure 1. Decision model. A Short run analytical model is used to estimate costs within first 3 months of stroke. A long run Markov model is used to estimate transitions between states and costs beyond first 3 months of stroke.

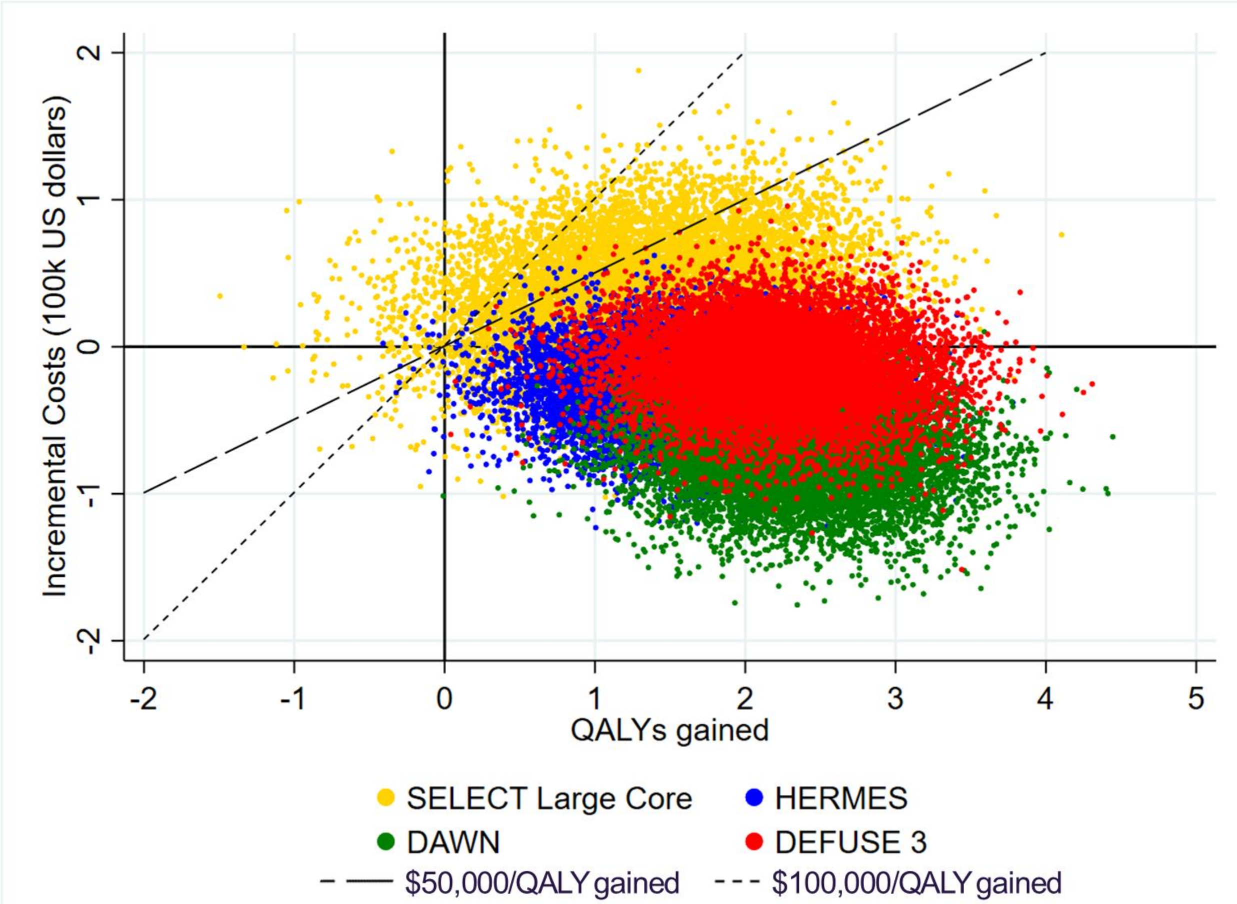

Figure 2. Results of the Probabilistic Sensitivity Analysis (PSA). The figure demonstrates 10000 simulated iterations of the incremental cost per QALY gained of EVT in patients with large core in the SELECT study (yellow), DAWN[8] (green), DEFUSE3[9] (red) and HERMES[25] (blue). The results show that the ***higher proportion of results are in the quadrant where an increment in costs is associated with a QALY gain and most of the result are under the $50000/QALY threshold line***, therefore there is a high probability that the EVT is cost-effective. The long dashed line represents an ICER of $50,000/QALY gained and short dashed line represents an ICER of $100,000/QALY gained. **The high cost of EVT was in part owing to the high mortality in MM patients in SELECT Large Core cohort, as compared to HERMES, DAWN and DEFUSE 3 cohorts.**

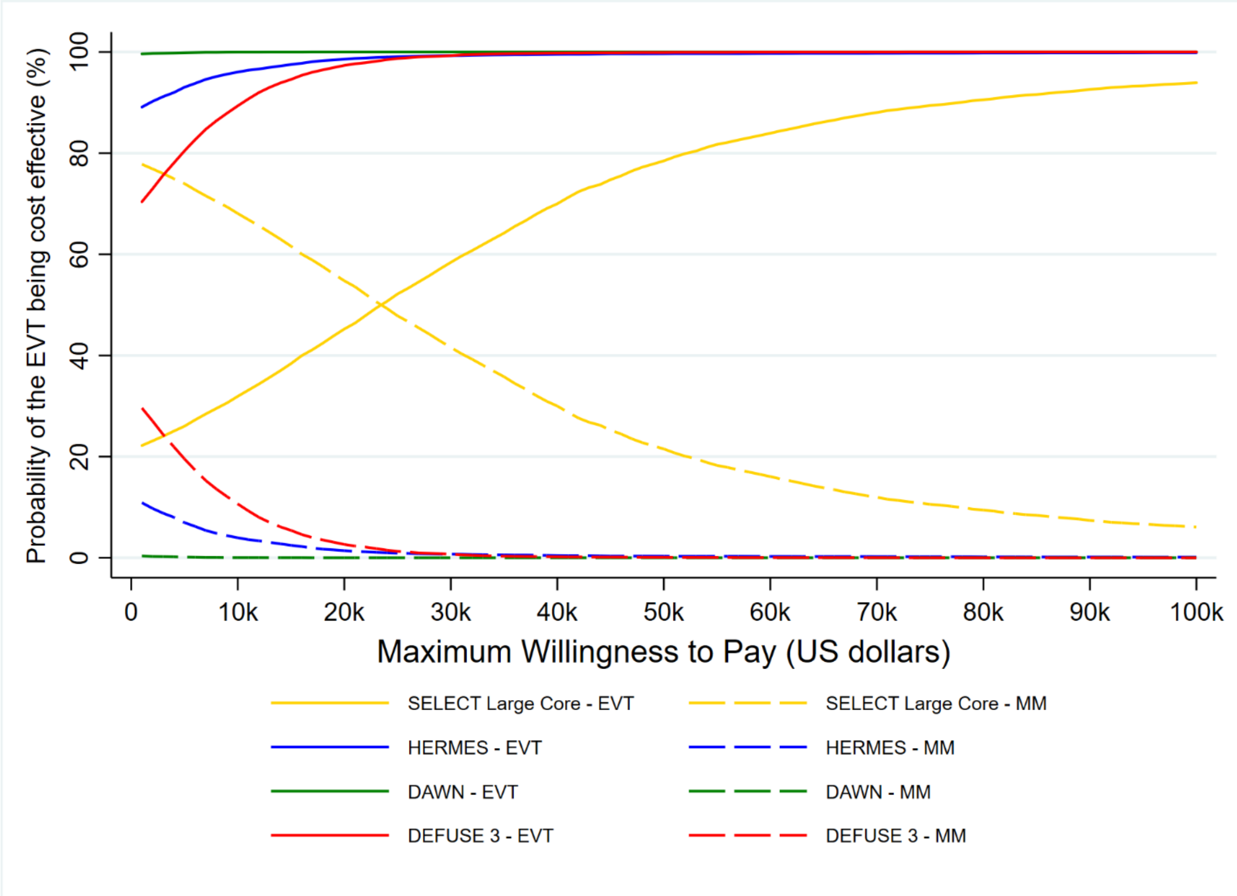

Figure 3. Cost-Effectiveness Acceptability Curves (CEAC) of EVT versus MM in the data from large core patients in SELECT trial[14] (yellow), HERMES[25] trial (blue), DAWN[8] trial (green)and DEFUSE 3[9] trial (red). The CEAC show the probability that each option is cost-effective at different values of the willingness to pay for a QALY. Using SELECT data ***EVT has 77% probability of being cost-effective*** compared to MM when the willigness to pay is ***$50000*** per QALY, and ***92% probability of being cost-effective*** when the ***WTP is $100000*** per QALY. Conversly, ***MM has 23% and 8% probability of being cost-effective*** when the WTP is $50000 and $100000 per QALY respectively. EVT has a probability of being cost-effective of almost 100% in all other trials with a WTP of $50,000 and $100,000 per QALY. The high cost of EVT

was in part owing to the high mortality in MM patients in SELECT Large Core cohort, as compared to HERMES, DAWN and DEFUSE 3 cohorts.