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Cost-utility analysis of mechanical thrombectomy between 6 and 24 hours in acute ischemic stroke

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Abstract

Background

Recently, two randomized controlled trials demonstrated the benefit of mechanical thrombectomy performed between 6 and 24 hours in acute ischemic stroke. The current economic evidence is supporting the intervention only within 6 hours, but extended thrombectomy treatment times may result in better long-term outcomes for a larger cohort of patients.

Aims

We compared the cost-utility of mechanical thrombectomy in addition to medical treatment versus medical treatment alone performed beyond 6 hours from stroke onset in the UK National Health Service (NHS).

Methods

A cost-utility analysis of mechanical thrombectomy compared to medical treatment was performed using a Markov model that estimates expected costs and quality-adjusted life years (QALYs) over a twenty-year time horizon. We present the results of 3 models using the data from the DEFUSE 3 and DAWN trials and evidence from published sources.

Results

Over a 20 year period, the incremental cost per QALY of mechanical thrombectomy was \$1,564 (£1,219) when performed after 12 hours from onset, \$5,253 (£4,096) after 16 hours and \$3,712 (£2,894) after 24 hours. The probabilistic sensitivity analysis demonstrated that thrombectomy had a 99.9% probability of being cost-effective at the minimum willingness to pay for a QALY commonly used in the UK.

Conclusions

The results of this study demonstrate that performing mechanical thrombectomy up to 24 hours from acute ischemic stroke symptom onset is still cost-effective, suggesting that this intervention should be implemented by the NHS on the basis of improvement in quality of life as well as economic grounds.

Introduction

Stroke is a global health issue and continues to be a leading cause of mortality and disability worldwide.^{1, 2} A number of prospective randomized trials published in 2015 showed mechanical thrombectomy is safe and effective in the management of ischemic stroke within 6 hours of symptom onset.³⁻⁷ Published evidence has shown it is also cost-effective.⁸⁻¹³ The precedent to transform stroke management was therefore set. Some of the 2015 endovascular therapy studies suggested further benefits beyond this time window. Specifically, REVASCAT and ESCAPE actively recruited beyond the 6-hour window with encouraging, but not definitive safety and efficacy outcomes.^{5, 6} This suggestion is now more certain with two prospective randomized controlled trials recently demonstrating that thrombectomy plus standard medical therapy for ischemic stroke at 6 to 16 hours (DEFUSE 3) and 6 to 24 hours (DAWN) results in a better functional outcomes at 90 days than standard medical therapy alone.^{14, 15}

Previous economic evaluations of thrombectomy undertaken in the UK, have been based on the evidence supporting endovascular intervention only within 6 hours.^{8, 9} Clinical encounters do not always conform to these time-frames and the recent evidence shows extending thrombectomy treatment times may result in better long term outcomes for this cohort.

Aims

We investigated the cost-utility of mechanical thrombectomy in the acute management of stroke with symptom onset between 6 and 24 hours in the UK, using the results of the DAWN and DEFUSE 3 trials.

Methods

We undertook a cost-utility analysis to compare costs and outcomes of mechanical thrombectomy (MT) following standard medical therapy (SMT) compared to SMT alone in patients with acute ischemic stroke. We used the data from the DEFUSE 3 trial to estimate the cost-utility of MT at 16 hours, and the data from the DAWN trial to estimate the cost-utility of MT at 12 and 24 hours. The outcome measure was quality-adjusted life years (QALYs), which combine length of life and quality of life, based on National Institute for Health and Care Excellence (NICE) recommendations.¹⁶ The number of deaths averted was also reported as an additional outcome measure. The cost-effectiveness of mechanical thrombectomy was expressed in terms of its Incremental Cost Effectiveness Ratio (ICER), compared to the current medical therapy. The analysis took a UK National Health Service (NHS) and personal social services (PSS) perspective. Costs were calculated in 2017 UK£, inflated where necessary and presented in US\$ using an exchange rate of £1= US\$1.28.¹⁷⁻¹⁹ The time horizon was 20 years, reflecting the average life expectancy of the patients treated in both trials. All costs and outcomes after the first year were discounted at an annual rate of 3.5%.¹⁶

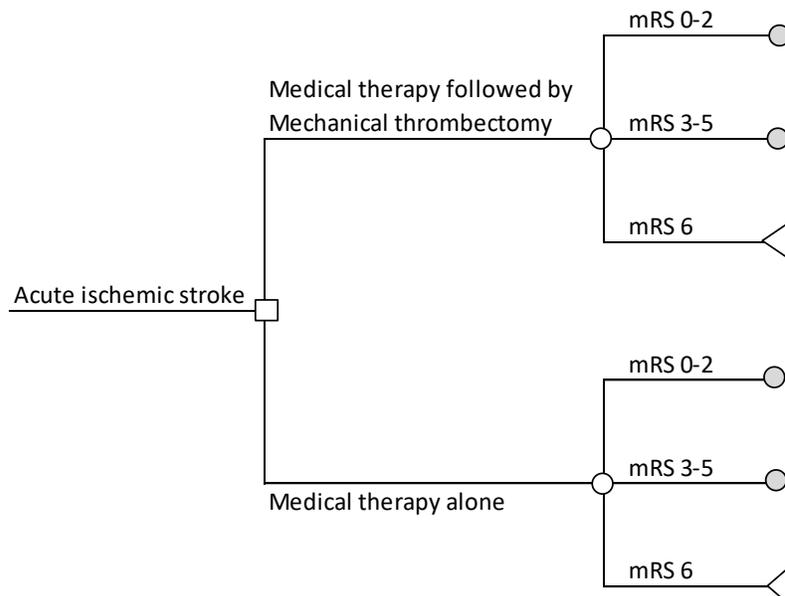
Model structure

We considered two treatment options: SMT alone (which includes intravenous tissue plasminogen activator (IV-tPA)) versus SMT followed by MT. Outcomes in both options were based on modified-Rankin-Scale (mRS) scores measured at 90 days after stroke, which were assumed to be affected by recanalization rates.

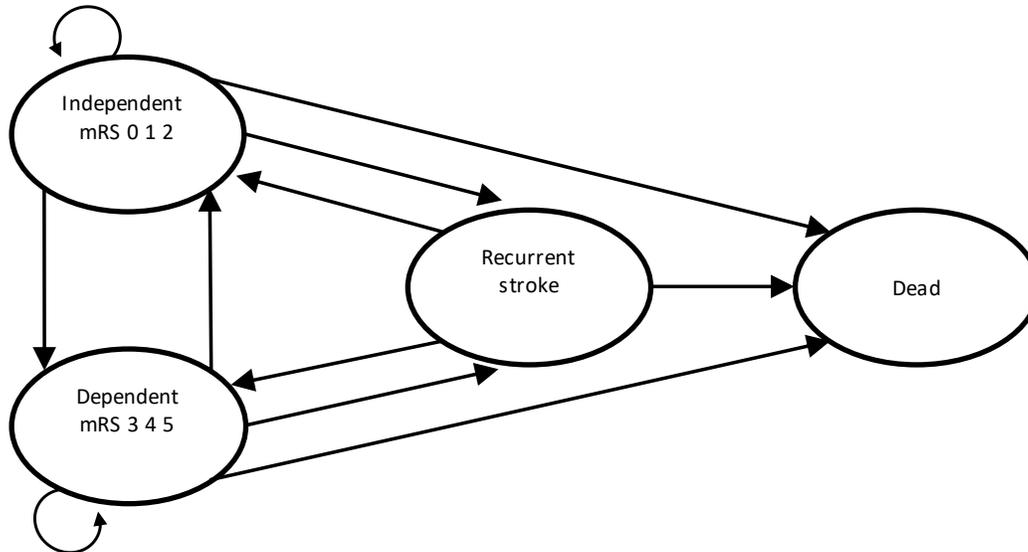
A short-run decision analytical model (Figure 1A) was created to assess costs and clinical outcomes within 3 months from stroke and subsequently was utilised to distribute a theoretical cohort of patients into one of three possible health states. A long-run Markov state-transition model was then used to estimate the expected costs and outcomes over a lifetime horizon of 20 years using cycles of 3 months (Figure 1B).

Figure 1. Decision model.

A. Short-run analytical model (first 3 months after stroke).



B. Long-run Markov model.



We populated the model with data from the DEFUSE 3 trial to estimate the cost-utility at 16 hours and from the DAWN trial to estimate the cost-effectiveness at 12 and 24 hours (Supplementary Table I). In doing so, we took into account the different treatments provided and the different type of devices used for the thrombectomy and outcomes.

Costs

A micro-costing approach was used to calculate the cost of the two treatment options pathways.

The cost of medical therapy was estimated to be \$2,346 (£1,819), including the cost of the IV-tPA medication and administration (Supplementary Table II and III).^{20, 21} Staff time costs were estimated using the data on the average cost per hour.¹⁷

The cost of the thrombectomy varied in each trial: it was estimated to be \$8,320 (£6,486) for the DEFUSE 3 trial (where a stentriever was used in 80% of cases), and \$6,339 (£4,942) in the DAWN trial (where a Trevo® stentriever was used for all the MT interventions). This includes the cost of the devices, materials and intervention (Supplementary Table III). The health care costs in the first 3 months after stroke and the ongoing costs in the following years differ according to disability (mRS score). The acute management costs include length of stay in the Hyper 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.^{8, 17, 21} We estimated the cost of a recurrent stroke as the mean expected cost to treat an average stroke that does not need SMT or MT.

Outcomes

Outcomes were expressed in quality-adjusted life years (QALYs), which combine length of life and quality of life.¹⁶ These were measured starting from the mRS score in which are categorized the patients affected by stroke: independent (mRS score ≤ 2), dependent (mRS score 3-5) or dead (mRS=6).²² For each mRS score we used the most updated and

reliable values available in the literature that take into account the EuroQol elicitation method (Supplementary Table II).^{21, 23-25} Other sources were used for the sensitivity analyses.^{26, 27}

Probabilities

We used the data provided in the two trials to calculate the probability of being independent, dependent or dead at 90 days in each treatment arm.^{14, 15} For the following months we applied the transition probabilities in Supplementary Table II, transformed for cycles of 3 months. We assumed that the probability of having a recurrent stroke was the same for a patient coming from an independent or a dependent state. Patients could move between a dependent and independent state only in the first year, but thereafter they were assumed to remain in that state, have a recurrent stroke or die. Patients who survived another stroke could either die or move into a dependent state, or remain independent.^{23, 28}

Measuring cost-effectiveness

Cost-effectiveness of MT plus SMT compared to SMT alone was measured in terms of the incremental cost per QALY gained (ICER). We also report the Net Monetary Benefits (NMB), calculated as the mean QALYs per patient accruing to that treatment multiplied by the maximum willingness to pay (WTP) for a QALY (the cost-effectiveness threshold) minus the mean cost per patient for the treatment. The lower and upper limit of the maximum willingness to pay for a QALY are \$33,000 (£20,000) and \$49,500 (£30,000) respectively in the UK.¹⁶

Sensitivity analysis

Extensive sensitivity analyses were performed, including a probabilistic sensitivity analysis (PSA) to determine the impact of the uncertainty surrounding the model input parameters.¹⁶ The distributions assigned to each parameter value are described in Supplementary Table II. A random value from the corresponding distribution was selected. This generated an estimate of the mean cost and mean QALY and the NMB associated with each treatment. This was repeated 10,000 times and the results for each simulation were noted. The proportion of times either treatment had the highest NMB was calculated for a range of values of the WTP for a QALY. The results are summarized using cost-effectiveness acceptability curves (CEACs). The mean cost, QALYs and NMB for each treatment were calculated from the 10,000 simulations; these are probabilistic results (Figure 3 and Supplementary Table IV).

Results

Using base case values, the thrombectomy following SMT performed within 12, 16 and 24 hours from an acute ischemic stroke was associated with incremental costs per patient of \$2,545 (£1,984), \$8,818 (£6,875), and \$8,289 (£6,463), respectively. Over 20 years, patients treated with MT at 12, 16 and 24 hours could gain 1.62, 1.68, and 2.23 QALYs respectively (Table 1). The higher cost of thrombectomy is represented by the cost of the

devices, materials and intervention. Thrombectomy saves more lives and those patients who survive are more likely to be independent (mRS 0-2), therefore the higher QALYs. Over 20 years, thrombectomy performed up to 24 hours after symptom onset could avert 143 deaths over a theoretical cohort of 1000 patients (875 deaths in patients treated with SMT alone versus 732 deaths in patients treated with MT).

The ICER of thrombectomy compared to SMT was \$1,564 (£1,219) per QALY if performed within 12 hours, \$5,253 (£4,095) per QALY if performed within 16 hours and \$3,712 (£2,894) per QALY gained if performed within 24 hours (Table 1). The NMB of thrombectomy plus SMT was higher than the NMB of SMT alone at both the lower and upper limits of the maximum WTP for a QALY, indicating that this option was preferred on cost-effectiveness ground.

The PSA confirms the main results (Supplementary Table IV).

The cost-effectiveness acceptability curves for the two interventions show that mechanical thrombectomy had 99.9% probability of being cost-effective at the lower and upper values of the maximum willingness to pay for QALY commonly used in UK (Figure 2 and 3).

The results of the one-way sensitivity analysis showed that the cost of thrombectomy must exceed \$42,563 (£33,185) using the DEFUSE 3 trial data at 16 hours for the intervention to become borderline cost-effective for the lower value of the maximum willingness to pay for QALY. Similarly, it must exceed \$45,555 (£35,518) and \$55,331 (£43,140) using the DAWN trial data at 12 and 24 hours respectively to no longer be cost-effective.

Table 1. Base-case results: Expected values per 1,000 patients (deterministic results).

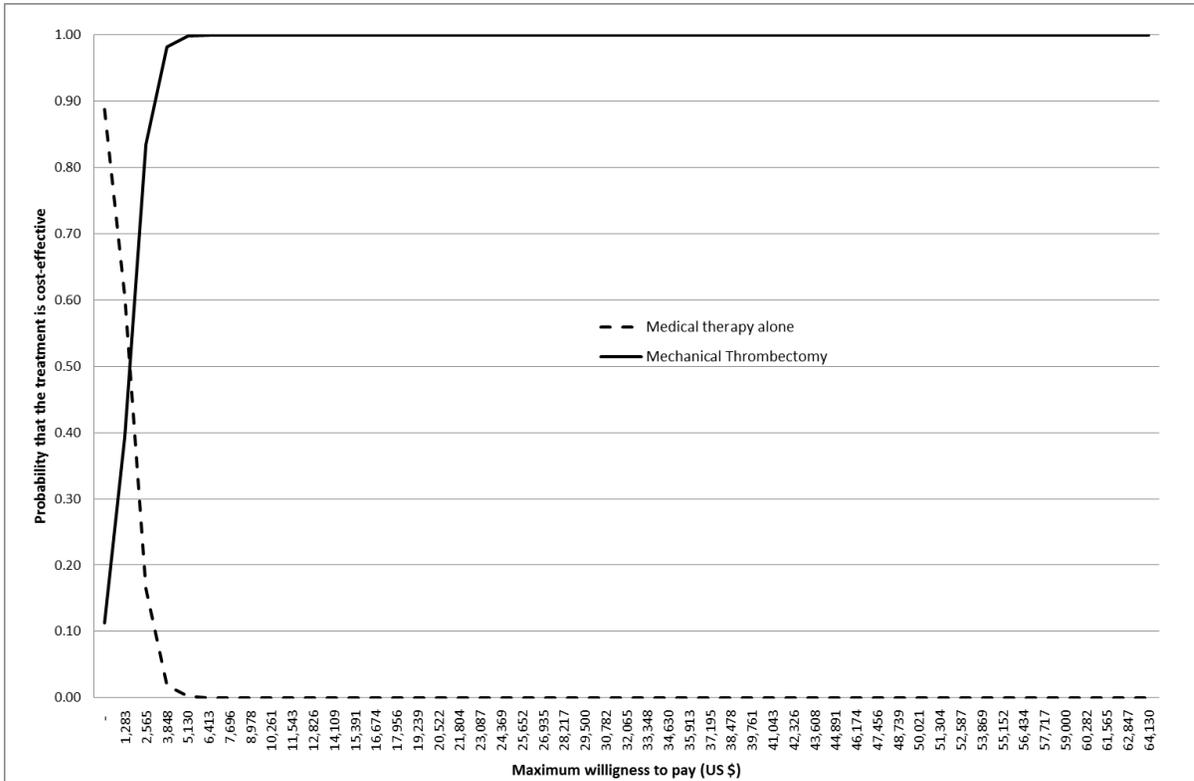
Cost-utility of Mechanical Thrombectomy performed within 12 hours			
	Medical Therapy alone	Mechanical Thrombectomy	Difference
Costs	\$35,397,797	\$37,943,267	\$2,545,470
QALYs	3,071	4,698	1,628
ICER			\$1,564
Net Monetary Benefit			
Lower	\$43,367,050	\$82,582,131	
Upper	\$82,749,474	\$142,844,829	

Cost-utility of Mechanical Thrombectomy performed within 16 hours			
	Medical Therapy alone	Mechanical Thrombectomy	Difference
Costs	\$40,601,040	\$49,419,626	\$8,818,586
QALYs	3,123	4,802	1,679
ICER			\$5,253
Net Monetary Benefit			
Lower	\$39,516,181	\$73,758,367	
Upper	\$79,574,792	\$135,347,364	

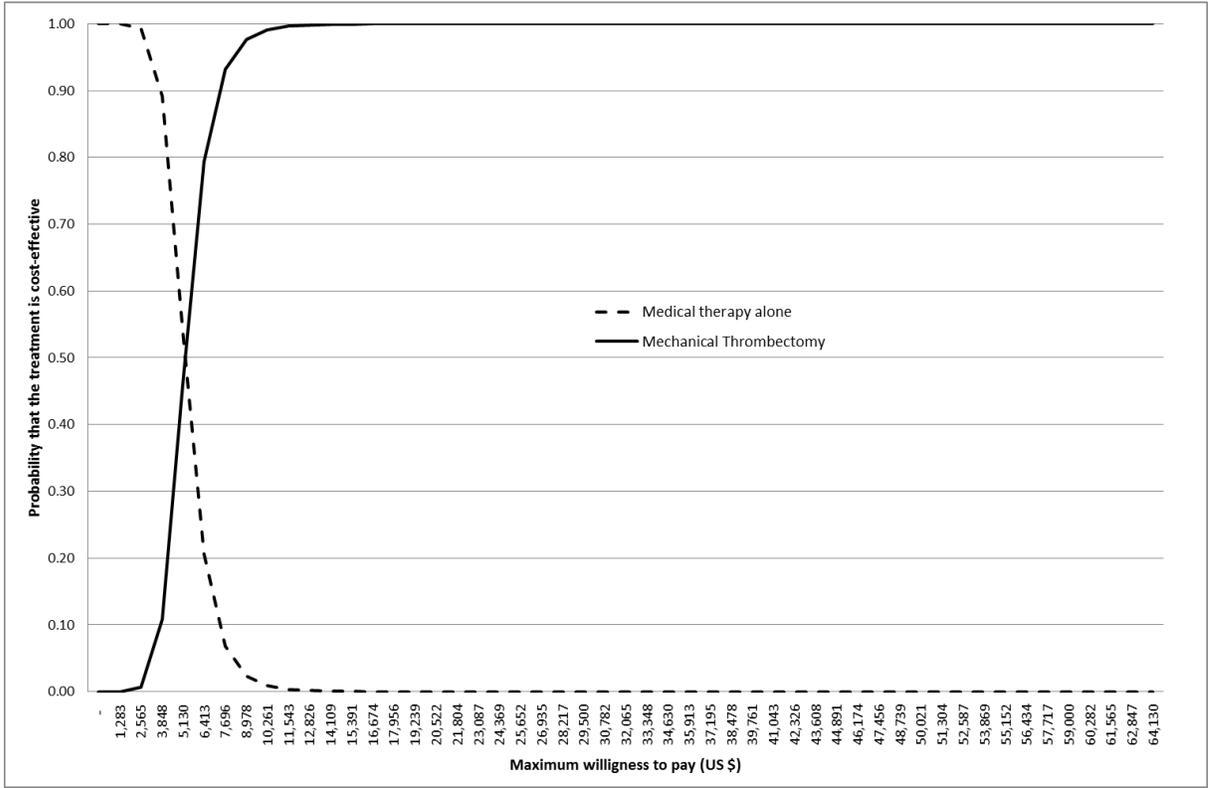
Cost-utility of Mechanical Thrombectomy performed within 24 hours			
	Medical Therapy alone	Mechanical Thrombectomy	Difference
Costs	\$34,363,561	\$42,653,404	\$8,289,843
QALYs	2,322	4,555	2,233
ICER			\$3,712
Net Monetary Benefit			
Lower	\$25,208,427	\$74,198,857	
Upper	\$54,994,422	\$132,624,987	

Figure 2. Cost-effectiveness acceptability curves showing the probability that each option is cost-effective at different values of the WTP for a QALY.

A) Thrombectomy performed within 12 hours (DAWN trial).



B) Thrombectomy performed within 16 hours (DEFUSE 3 trial).



C) Thrombectomy performed within 24 hours (DAWN trial).

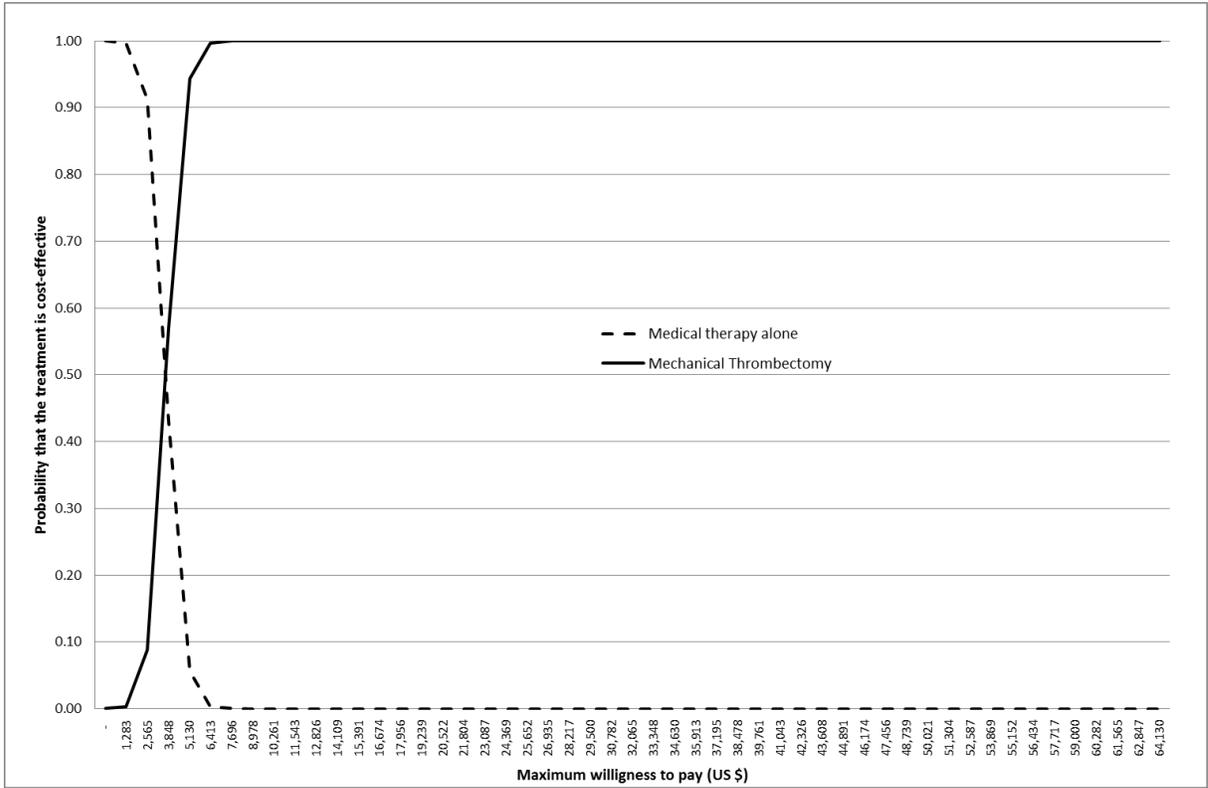
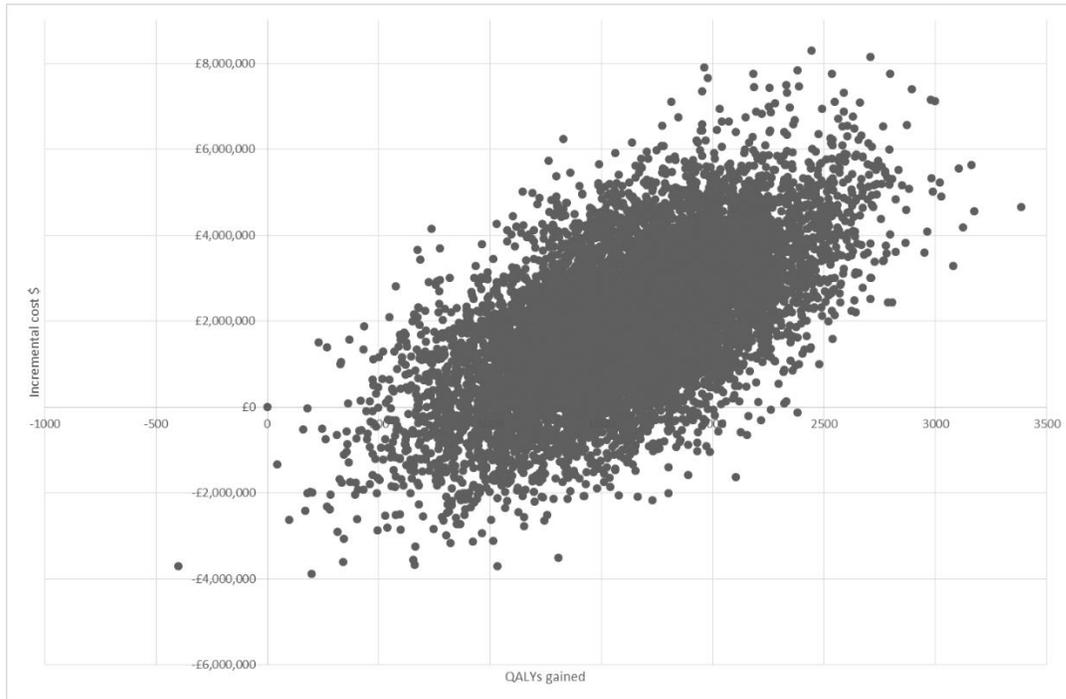
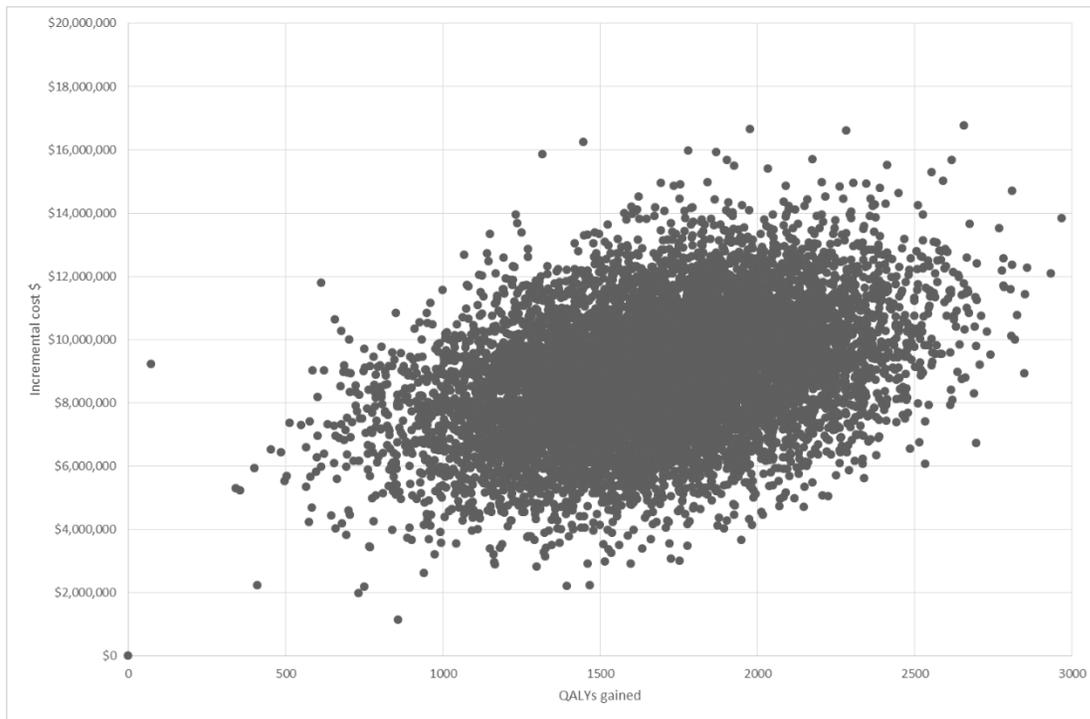


Figure 3. Monte Carlo simulations of incremental cost per QALY gained of mechanical thrombectomy on a cohort of 1000 patients.

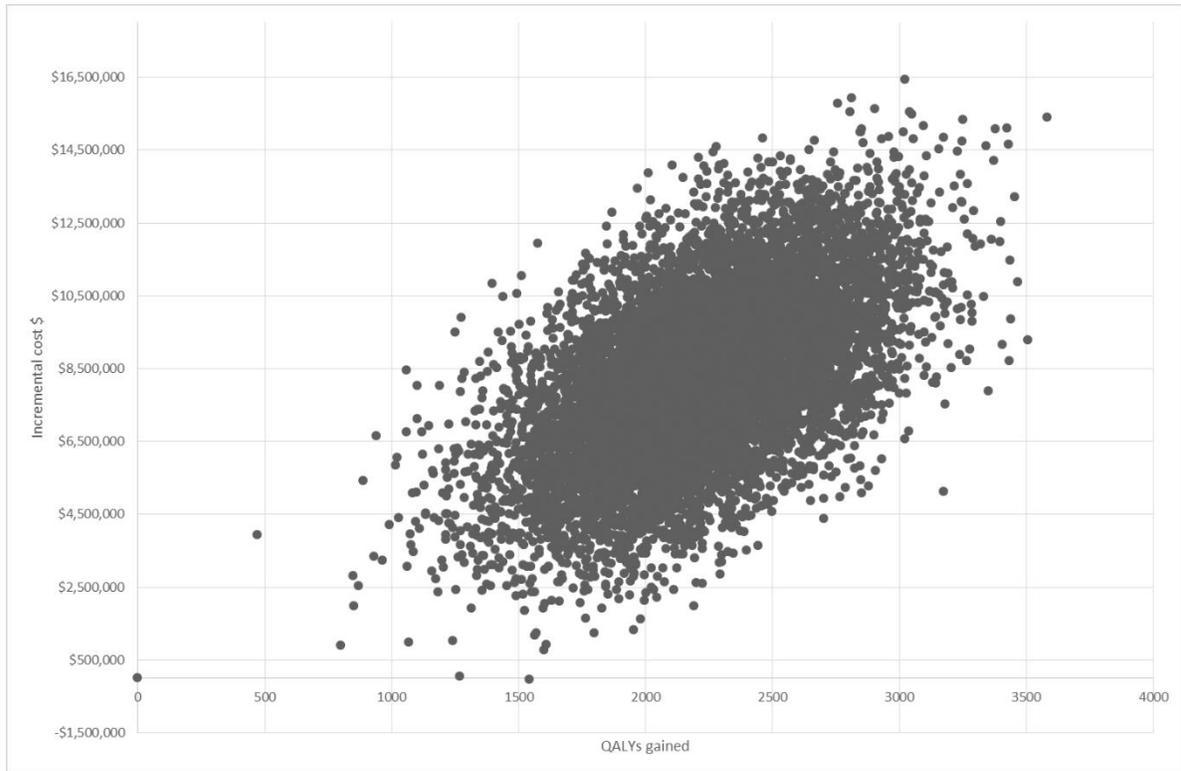
A) Thrombectomy performed within 12 hours (DAWN trial).



B) Thrombectomy performed within 16 hours (DEFUSE 3 trial).



C) Thrombectomy performed within 24 hours (DAWN trial).



Discussion

Previous evidence demonstrated the cost-effectiveness of mechanical thrombectomy compared to standard medical therapy alone within a 6 hour time-frame from symptom onset. This study not only validates those results, but also suggests that performing thrombectomy beyond this time frame and up to 24 hours after stroke symptom onset remains cost-effective.

The 2015 publications of concordant evidence supporting the use of thrombectomy up to 6 hours after symptom onset resulted in a paradigm shift in the modern management of acute stroke. Subsequently, mechanical thrombectomy is being performed more frequently, with decreasing costs due to economies of scale (discounts in devices purchased and more efficient interventions). Two of the initial seminal trials, REVASCAT and ESCAPE, recruited up to 8 and 12 hours respectively.^{5 6} This additional data was indicative that the 6 hour mark was likely to be a conservative estimate. By combining data from the 5 big trials, the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaborative confirmed that thrombectomy was effective up to 7.3 hours after symptoms onset.²⁹ DAWN and DEFUSE 3 have further added to this evidence

demonstrating significant benefit with thrombectomy beyond 6 hours, which was contributed to by the higher recanalization rate.

An important point to note is the methodology was variable between trials, which makes the formulation of consistent inclusion criteria challenging. However, extrapolating trial parameters to actual population cohorts is necessary when assessing the likely impact any change in practice will deliver. Vanacker et al.³⁰ showed the sub-6 hour endovascular intervention would benefit 10% of people presenting with acute ischemic stroke symptoms. Subsequently, Jadhav et al.³¹ applied DAWN and DEFUSE 3 criteria to a similar cohort and 1.7-2.7% of patients would be eligible for >6 hour MT based on these criteria. This suggests that despite variation in methods, an applicable inclusion model could be formulated.

Between April 2015 and March 2016, health and social care costs related to stroke exceeded £1.7 billion in England, Wales and Northern Ireland.³² Despite mechanical thrombectomy having an initial higher cost, it leads to savings downstream in the stroke care pathway due to better outcomes. Between April 2016 and March 2017, 85,122 new cases of stroke were registered in the UK; of these 74,585 (87.6%) were ischemic strokes and 9,898 had thrombolysis.³³ Despite 11,188 patients meeting the <6-hours eligibility for thrombectomy, only 580 patients (5%) were treated.³³ It is not known how many of those remaining patients could have been treated with thrombectomy between 6 and 24 hours, but assuming this figure is also 5%, we estimate around 3,287 additional patients could have thrombectomy for an incremental budgetary impact of \$8.4 million (£6.5 million) if performed within 12 hours, \$37 million (£29 million) if performed within 16 hours, \$27.2 million (£21.2 million) if performed within 24 hours.

To the best of our knowledge, this is the first study in the UK that assesses the cost-utility of mechanical thrombectomy performed beyond 6 hours from symptom onset. The advantage of this study is that we have used data from randomized controlled trials using thrombectomy specifically looking at the 6 to 24 hour treatment window. These studies focused on anterior circulation events. There remains a paucity of randomized controlled trial evidence looking at posterior circulation events.

The analysis has some limitations. In the DEFUSE 3 trial, patients were treated with different devices. For this analysis, we assumed all used the SolitaireTM device, being the most widely accessed stentriever³⁴ and coincidentally the most expensive device option. This assumption, therefore, may actually overestimate the costs of thrombectomy. We also assumed all patients underwent perfusion imaging in both arms. We did not include in the calculations the etiological main reasons of stroke (e.g. presence of hypertension, diabetes, atrial fibrillation or prior stroke), despite they could add to the costs, because these conditions were reasonably similar in both cohorts of patients. In the DAWN trial, 5% of patients in the intervention arm had IV-tPA compared to 13% in the control arm, therefore the cost has been weighted accordingly. Finally, we assumed dependent and independent patients have the same probability of having a recurrent stroke, although one may expect this probability to be higher among the more disabled. The results of our sensitivity analysis showed that our conclusions were not sensitive to these assumptions.

This study was undertaken from the perspective of the UK NHS and did not include societal costs. Given that the incidence of stroke in patients under 60 years of age has increased by more than 4% in the last three years³³, it is likely that the cost savings attributable to mechanical thrombectomy would be greater than demonstrated if we could take into account productivity losses and societal costs.

We have demonstrated that thrombectomy performed between 6 and 24 hours after symptom onset is cost-effective, based on current data. These results, combined with the recent trial data would make a valuable contribution to reforming acute stroke service models.

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Declaration of conflicting interests

The authors declare no conflict of interest.

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