Mechanical Thrombectomy in Patients with Acute Ischaemic Stroke: a Cost-effectiveness and Value of Implementation Analysis

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Abstract

Objective: To determine the cost-effectiveness, and the value of future research and implementation of mechanical thrombectomy, compared with standard treatment, from the perspective of the UK NHS and PSS.

Design: We estimated the cost-effectiveness of mechanical thrombectomy, compared with standard practice over two time horizons: (i) 90-days – alongside the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial, using UK clinical and cost data, and (ii) lifetime – based on a decision-analytic model, using all available evidence. We performed a meta-analysis of seven clinical trials to estimate treatment effects. We used one-way and probabilistic sensitivity analysis to address uncertainty. Value of implementation analysis was used to estimate the potential value of implementing ~~this~~ endovascular thrombectomy~~treatment~~ into routine clinical practice.

Setting: UK healthcare system.

Participants: Patients with acute ischaemic stroke eligible for mechanical thrombectomy.

Intervention: Mechanical thrombectomy plus standard treatment, compared with standard treatment alone.

Main outcome measure: Costs, quality-adjusted life-years gained (QALYs), cost-effectiveness.

Results: Based on a 90-day time horizon, mechanical thrombectomy was not shown to be cost-effective. However, over a lifetime horizon, this was no longer the case. Mechanical thrombectomy plus IV-tPA, compared to IV-tPA alone, had an incremental cost of £7,649 and 2.207 QALYs and an incremental cost-effectiveness ratio of £3,466 per QALY gained. The net monetary benefit (health benefit in monetary terms) was £36,484 per patient. Based on the assumption of 51,404 eligible patients over a five year period, the value of implementation (at full implementation) was £1.3 billion. We estimate the "break-even" value of implementation activity point at approximately 30% implementation.

Conclusion: Our economic model ~~suggests~~ indicates that mechanical thrombectomy is cost-effective compared with standard care over a patient's lifetime. On the assumption of full implementation being achieved throughout the UK healthcare system, we estimate that the population health benefits obtained from this treatment are greater than the cost of implementation.

Trial registration: NCT01745692

Background

Until recently, thrombolysis, using intravenous tissue plasminogen activator (IV-tPA), has been the standard treatment for patients with ischaemic stroke who can be treated within 4.5 hours (1, 2). However, since 2015, evidence from eight randomised controlled trials (RCTs) ~~have~~ has demonstrated the superiority of mechanical thrombectomy~~, using second-generation devices,~~ in the treatment of acute ischaemic stroke, in terms of the proportion of patients achieving favourable outcomes on the modified Rankin Scale (mRS) (3-10). In 2016, the National Institute for Health and Care Excellence (NICE) in the UK updated their guidelines for the treatment of acute ischaemic stroke to recommend the use of mechanical thrombectomy (2). In the following year, NHS England approved the use of mechanical thrombectomy in routine practice.

Mechanical thrombectomy is ~~an expensive and complicated~~ highly skilled procedure undertaken predominantly in neurosciences centres. Several studies have assessed the cost-effectiveness of thrombectomy in combination with IV-tPA compared with IV-tPA alone, and concluded thrombectomy to be potentially cost-effective (11-18) and cost-saving (19-22). Two model-based cost-utility analyses, from the perspective of the UK NHS have been carried out (14, 21). Based on meta-analysis of five RCTs, compared with IV-tPA, thrombectomy in combination with IV-tPA was associated with an additional £7,061 per quality adjusted life year gained(14). In the other study, based on data from an RCT conducted in the US and Europe (the SWIFT-PRIME trial), thrombectomy in combination with IV-tPA was reported to be associated with cost-savings of £33,190 per patient (21). However, the adoption and implementation of thrombectomy into routine practice will require additional investment in staff and capital equipment, and is also likely to require significant reorganisation of the healthcare system (23). Currently, one study has estimated the budget impact of adopting and implementing mechanical thrombectomy in Ireland (13). Based on treatment being delivered at two centres and treating 268 patients per year, the cost of implementation was estimated to be 7.2 million euros over five years.

In adopting non-drug interventions into clinical practice, challenges to implementation may have an impact on cost-effectiveness. We conducted an economic evaluation to determine the cost-effectiveness of mechanical thrombectomy (using stent retrievers) in combination with IV-tPA compared with IV-tPA alone, in patients with acute ischaemic stroke. In addition, we also estimated the monetary value of future research and the value of enhancing implementation of thrombectomy, using UK clinical and cost data.

Methods

We estimated the cost-effectiveness of mechanical thrombectomy with IVT-tPA, compared with IV-tPA alone over two time horizons: (i) 90-days – alongside the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial (9) and (ii) lifetime – based on a decision-analytic model. The lifetime model was used to conduct one-way and probabilistic sensitivity analysis. We also estimated the potential value of future research and the value of implementation initiatives to support the introduction of thrombectomy in routine practice. The analysis was carried out from the perspective of the National Health Service (NHS) and Personal and Social Services (PSS). Costs and health benefits were discounted at 3.5% in line with national guidelines (24).

Within-trial analysis

The PISTE trial was a multicentre, randomised controlled clinical trial comparing mechanical thrombectomy plus IV-tPA with IV-tPA alone, in patients who had acute ischaemic stroke with large artery occlusive anterior circulation stroke. Eligible patients were administered IV-tPA within 4.5 hours of stroke. Patients receiving additional mechanical thrombectomy were treated within a target time of <90 mins from IV-tPA start to arterial puncture. The primary outcome was the proportion of patients achieving functional independence (mRS ~~state~~ 0-2) at 90 days.

We conducted an economic evaluation ~~alongside~~ using data from the PISTE trial. Clinical outcome at 90 days was measured by the modified Rankin Scale (mRS). The mRS scores were converted into health utilities using a conversion algorithm (25). Health utilities were used to calculate quality-adjusted life-years (QALYs) over 90 days. Resource use estimates collected during the trial included hospital bed days and costs of treatment~~s~~ with IV-tPA and mechanical thrombectomy. Unit costs were obtained from the literature (14, 26, 27)and applied to resource use.

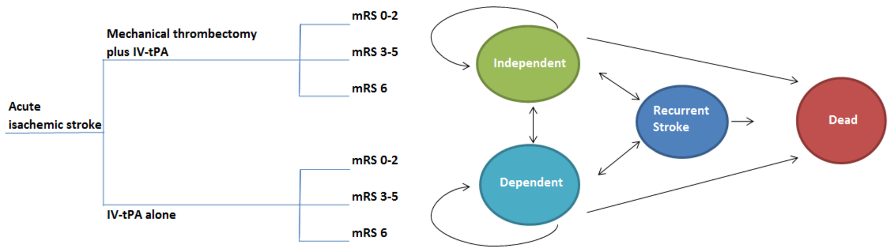
Mean patient costs and QALYs were estimated by using a generalised linear model (GLM) and adjusting for potential confounding (28). We adjusted for the following covariates: age group, National Institutes of Health Stroke Scale (NIHSS) group, and baseline health utility (QALY estimates only). The appropriate family for the GLM was selected based on the results of the modified Park's test. Our final cost model was based on the log link and gamma family. Our final QALY model was based on the identity link and Gauss family. All analyses were conducted in Stata 12. Based on the estimation of the final statistical model, the total cost and QALY difference between groups is based on the marginal prediction.

Cost-effectiveness was expressed as the incremental cost-effectiveness ratio (ICER). We employed the use of nonparametric bootstrapping to calculate 95% confidence intervals for our estimate of the difference in mean cost and QALYs between treatment groups.

Lifetime economic model

The economic model was based on a previously published model (14) and is in line with the clinical pathway described for patients with acute ischaemic stroke who are eligible for treatment with both IV-tPA and mechanical thrombectomy, according to the guidance set out by NICE (National Institute for Clinical Excellence 2016) (figure 1).

Figure 1: Lifetime economic model (decision tree and Markov model)



The first three months following stroke is represented by a decision tree. Following treatment, patients may result in one of three possible mutually exclusive health states state (mRS ≤2: functional independence; mRS 3-5: functional dependence; mRS 6: death). Subsequently, a four-state Markov model is used to estimate costs and outcomes beyond three months. The model runs for 80 cycles of three months (20 years).

We performed a meta-analysis to estimate the probabilities of patients resulting in the three mRS states using data from five RCT studies published in 2015 (3-7) and two recent trials – THRACE and PISTE trials (9, 10). Transition probabilities for the Markov model were sourced from the literature. Table 1 presents a list of parameters used in the lifetime model.

Table 1: Parameter used in the lifetime economic model

Parameter	Point estimate	Probability distribution	Source
Decision tree			
mRS 0-2 (IV-tPA + Mech Throm)	0.57	Conditional beta distribution	Meta-analysis
mRS 3-5 (IV-tPA + Mech Throm)	0.27	Conditional beta distribution	Meta-analysis
mRS 6 (IV-tPA + Mech Throm)	0.16	Conditional beta distribution	Meta-analysis
mRS 0-2 (IV-tPA only)	0.26	Conditional beta distribution	Meta-analysis
mRS 3-5 (IV-tPA only)	0.55	Conditional beta distribution	Meta-analysis
mRS 6 (IV-tPA only)	0.19	Conditional beta distribution	Meta-analysis
Markov model			
Year 1			
From independent (mRS 0-2) to:			
mRS 0-2	0.955	Conditional beta distribution	Davis (2012)
mRS 3-5	0.024	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.008	Conditional beta distribution	Davis (2012)
From dependent (mRS 3-5) to:		Conditional beta distribution	Davis (2012)
mRS 0-2	0.029	Conditional beta distribution	Davis (2012)
mRS 3-5	0.919	Conditional beta distribution	Davis (2012)

recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.039	Conditional beta distribution	Davis (2012)
After year 1			Davis (2012)
From independent (mRS 0-2) to:			Davis (2012)
mRS 0-2	0.979	Conditional beta distribution	Davis (2012)
mRS 3-5	0	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.008	Conditional beta distribution	Davis (2012)
From dependent (mRS 3-5) to:		Conditional beta distribution	Davis (2012)
mRS 0-2	0	Conditional beta distribution	Davis (2012)
mRS 3-5	0.948	Conditional beta distribution	Davis (2012)
recurrent stroke	0.013	Conditional beta distribution	Davis (2012)
dead	0.039	Conditional beta distribution	Davis (2012)
Recurrent stroke		Conditional beta distribution	Davis (2012)
(IV-tPA + Throm) mRS 0-2	0.867	Conditional beta distribution	Davis (2012)
(IV-tPA + Throm) mRS 3-5	0.104	Conditional beta distribution	Davis (2012)
(IV-tPA + Throm) recurrent stroke	0	Conditional beta distribution	Davis (2012)
(IV-tPA + Throm) dead	0.029	Conditional beta distribution	Davis (2012)
(IV-tPA alone) mrs 0-2	0.834	Conditional beta distribution	Davis (2012)

(IV-tPA alone) mrs 3-5	0.137	Conditional beta distribution	Davis (2012)
(IV-tPA alone) recurrent stroke	0	Conditional beta distribution	Davis (2012)
(IV-tPA alone) dead	0.029	Conditional beta distribution	Davis (2012)
Health utilities			
Independent	0.74	Beta distribution	Dorman (2000)
Dependent	0.38	Beta distribution	Dorman (2000)
Recurrent	0.34	Beta distribution	Dorman (2000)
Costs			
IV-TPA	£1,919	Gamma distribution	British National Formulary
Thrombectomy	£8,912	Gamma distribution	Ganesalinham (2015), Davis (2012)
first 3 months:		Gamma distribution	
Independent	£7,302.83	Gamma distribution	Ganesalinham (2015)
Dependent	£15,627.49	Gamma distribution	Ganesalinham (2015)

Cost-effectiveness was expressed as ICER and the incremental Net Monetary Benefit (NMB). The NMB is a measure of the health benefit, expressed in monetary terms, which incorporates the cost of the new strategy, the health gain obtained, and the societal willingness to pay for health gains. The NMB is calculated using the following formula:

Incremental Net Monetary Benefit (NMB) = $(\Delta E * WTP) - \Delta C$

E = effectiveness; WTP = willingness-to-pay threshold (£20,000 in the UK); C = cost

Uncertainty

Uncertainty around the parameter estimates used in our model was fully characterised and propagated through to the model results by conducting probabilistic sensitivity analysis (PSA). This was done by defining parameter values using distributions rather than point estimates. The model was then run 5,000 times with a value randomly drawn from the assigned probability distribution. This produced a distribution of model outputs which was represented visually on the cost-effectiveness plane. A cost-effectiveness acceptability curve (CEAC) was used to represent the probability that an intervention would be cost-effective compared to the control group at a range of willingness-to-pay thresholds (λ).

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. We tested: the cost of the mechanical thrombectomy procedure; the health utility associated with functional independence, dependence and death; the proportion of patients achieving functional independence, dependence and death, following treatment with mechanical thrombectomy or IV-tPA alone. We tested the impact on the model's estimate of cost-effectiveness (i.e. the ICER) of varying each of these parameters individually by +/- 20% Further details are given in the appendix.

Value of information

Value of information analysis on the expected value of perfect information (EVPI) was carried out to quantify the potential value of further research based on the difference between the expected health benefits (NMB) with perfect information and with existing information. The EVPI represents the amount a decision maker should be willing to pay to eliminate uncertainty regarding which intervention is the best option. This uncertainty is characterised in the model in terms of parameter uncertainty and is addressed through the use of PSA which produces a distribution of outcomes, in terms of costs and QALYs, for each treatment. The difference between the NMB, based on a decision made with perfect information (i.e. no uncertainty) and with current information, represents the EVPI.

It has been estimated that approximately 11,000 patients with acute ischaemic stroke are eligible for mechanical thrombectomy per year in the UK (29-31). For the analysis, we assumed the effective population (discounted population) which stands to benefit from this treatment to be 51,404 patients over a five year period, and that the lifetime of the new technology to be five years.

Value of implementation

We calculated the value of implementation as the value of perfect implementation minus the cost of implementation (32), measured over a five year time horizon. We estimate the maximum potential value of implementation as the net monetary benefit of achieving 100% implementation across the UK (51,404 patients over five years). We then subtracted from this the cost of 29 comprehensive stroke centres across the UK necessary to perform this procedure. We included costs of ongoing staff salaries and initial set-up costs - such as training and equipment (full details are given in the appendix). We also estimate the "break-even" point at which the NMB obtained from the proportion of eligible patients treated is equal to the cost of implementation.

Results

Within-trial analysis

The results of the within-trial analysis found that mechanical thrombectomy plus IV-tPA, compared to IV-tPA alone, had a total cost of £17,156 compared with £11,949. Over the course of the trial (90 days), the QALYs gained in the intervention group were 0.142, compared with 0.117 in the control group. This equates to an incremental cost of £5,207 and 0.025 QALYs associated with the addition of mechanical thrombectomy to standard treatment and an ICER of £205,279 per QALY gained. The bootstrapped mean cost difference between groups was £5,207 (95% CI: -£1,458, £11,873) and the mean QALY difference was 0.026 (95% CI: -0.008, 0.059).

Lifetime economic model

The results of the economic model found that mechanical thrombectomy plus IV-tPA, compared to IV-tPA alone, had a total cost of £46,684 compared with £39,035 (table 2). Over a lifetime horizon, the QALYs gained in the intervention group were 7.614, compared with 5.408 in the control group. This equates to an incremental cost of £7,649 and 2.207 QALYs associated with the addition of mechanical thrombectomy to standard treatment and an incremental cost-effectiveness ratio of £3,466 per QALY gained and an incremental NMB of £36,484 per patient.

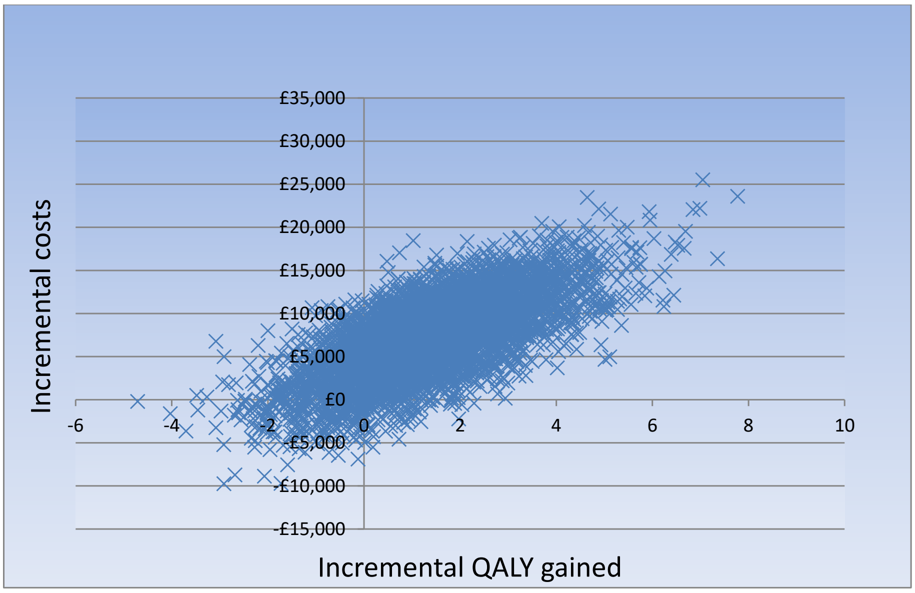
Table 2: Results of lifetime economic model

Treatment	Cost (£)	QALYs gained	Incremental cost (£)	Incremental QALYs gained	Incremental cost/QALY gained (ICER)	Incremental NMB
IV-tPA	£39,035	5.408				
IV-tPA + Mechanical thrombectomy	£46,684	7.614	£7,649	2.207	£3,466	£36,484

Probabilistic sensitivity analysis

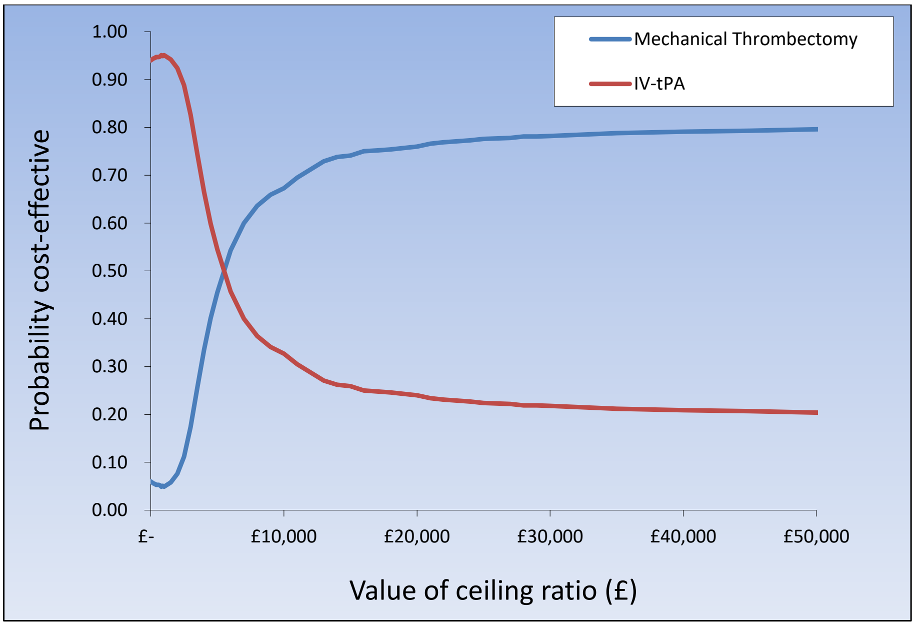
The cost-effectiveness plane shows the results of running the model 5,000 times and recording the difference in cost and effectiveness between the mechanical thrombectomy and IV-tPA (figure 2). Although most data points are observed in the upper right quadrant of the plane (representing the scenario of 'more costly and more effective'), there is considerable uncertainty surrounding the extent and existence of the additional expected costs and the existence and extent of the additional expected QALYs.

Figure 2: Cost effectiveness plane



The cost-effectiveness acceptability curve (CEAC) shows the probability of mechanical thrombectomy being cost-effective for different levels of willingness-to-pay thresholds, compared with IV-tPA alone (figure 3). The CEAC shows that, at a willingness-to-pay threshold of £20,000 per QALY gained, mechanical thrombectomy has a 76% probability of being cost-effective, compared with IV-tPA alone.

Figure 3: Cost-effectiveness acceptability curve



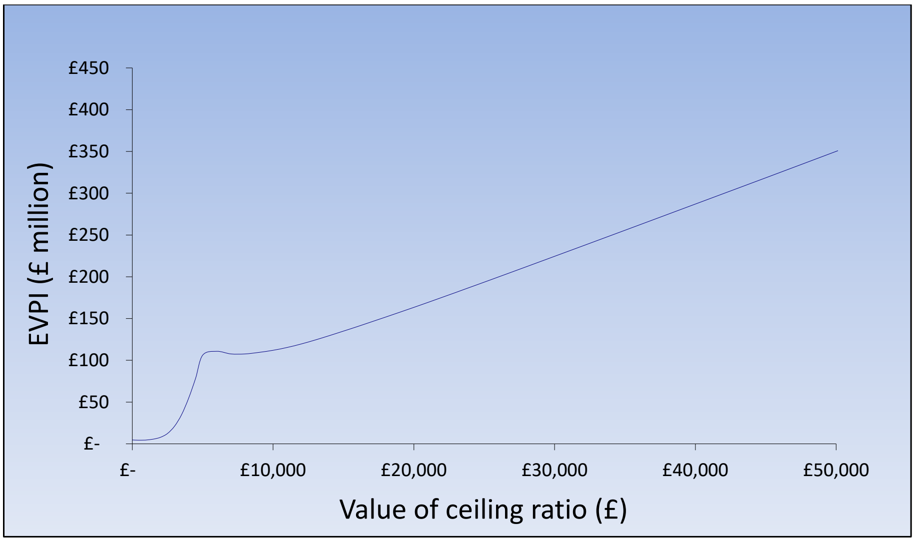
One-way sensitivity analysis

We conducted one-way sensitivity analysis on the key parameters driving the cost-effectiveness estimate of mechanical thrombectomy in our model. Our results showed that varying all of these key parameters within our model had no impact on the decision problem, i.e. all ICER estimates remain below £20,000 per QALY. The parameter which had the greatest negative impact on cost-effectiveness (i.e. increased the ICER) was the proportion of patients achieving functional independence (mRS 0-2) after receiving mechanical thrombectomy.

Value of information

The expected value of perfect information per patient affected by the decision is estimated at £3,178 per person. Based on our assumptions of 11,000 eligible patients per year over a five-year lifetime of this technology, at a willingness-to-pay of £20,000 per QALY gained, this equates to an expected value of perfect information of £163 million over a five year period for the UK population (figure 5).

Figure 5: The expected value of perfect information (population level)



Value of implementation

We estimate the value of perfect implementation as the net monetary benefit from mechanical thrombectomy (£36,484 per person) multiplied by the effective population (51,404). This implies that the expected value of perfect implementation in UK would be £1.7 billion. We estimate a cost of £413 million to implement this procedure across the UK (a full breakdown of the cost calculation is given in the appendix). This suggests an expected value of implementation of £1.3 billion over five years. We estimate the "break-even" value of implementation activity point at approximately 30% implementation (approx. 3,084 patients per year). Below this point, the cost of implementing mechanical thrombectomy into routine practice is expected to be greater than the benefit, in NMB terms.

Conclusion

Based on a lifetime horizon, our economic model suggests that mechanical thrombectomy is cost-effective compared with standard care. Further research costing more than £163 million would not be considered a cost-effective use of resources. This is because the return of the investment from further research, in terms of the costs and/or health benefits gained from choosing an alternative strategy based on the new evidence, is expected to be no higher than the figure of £163 million.

On the assumption of full implementation being achieved throughout the UK healthcare system, we estimate that the value of implementation is greater than the cost of implementation. We find that this result holds for any level of implementation greater than approximately 30%.

Discussion

Our results suggest indicate that mechanical thrombectomy, in addition to IV-tPA, compared with IV-tPA alone, is likelymeets standard criteria -to be considered a cost-effective use of resources in a UK health service setting. The results of our study are consistent with other UK economic evaluations which suggest the cost-effectiveness of mechanical thrombectomy over a patient's lifetime perspective (14, 21). One UK study found mechanical thrombectomy to be cost-saving. This is primarily driven by the assumption of higher long-term care costs associated with disability after stroke patients and the savings resulting from greater the avoidance of disability due to treatment with mechanical thrombectomy.

Our results suggest that the use of mechanical thrombectomy is unlikely to be cost-effective over a 90-day time horizon, based on data from the UK-based (PISTE trial). This is due to a very small difference in health benefits between the two treatments, the incremental QALY gain was 0.025. The incremental cost of mechanical thrombectomy over a 90-day period was £5,207, compared with £7,649 over a lifetime horizon. However, the QALY gain over a 90-day horizon was 0.025 QALYs, compared with 2.207 QALYs over a lifetime horizon. This implies that, over a lifetime horizon, there is a proportionally greater increase in QALYs than costs.

Our lifetime cost-effectiveness model used clinical evidence from seven RCTs of mechanical thrombectomy (using second generation stent retrievers), but did not consider subsequent trials indicating benefit from mechanical thrombectomy in patients presenting in later time windows (6-24 hours) based on additional imaging selection criteria (30, 31). In order to estimate the cost of routinely providing mechanical thrombectomy across the UK, it was necessary to make some assumptions (see appendix). In terms of staffing costs, our results are likely to be an overestimate. This is because we have chosen to provide the cost of a full-time equivalent for some staff (interventional neuroradiology, anaesthetist) to reflect the need to have these staff available on demand over a 24 hour service. In practice it is likely that a proportion of these staff will spend their time on activities unrelated to thrombectomy. In addition, we have included the full cost of an angiography suite required to undertake the procedure to reflect the initial set-up costs required, however, in practice this equipment will be available for other activities and hence not all costs associated with the suite will be attributable to thrombectomy.

The ability to identify patients mostly likely to benefit from mechanical thrombectomy and to triage these patients from stroke onset to initiation of treatment within the required time period presents a challenge. To meet this challenge, significant system reorganisation will be required (23). The clinical trial evidence relates to patients ~~which~~ who were predominantly able to receive treatment within 6 ~~8~~ hours from stroke onset, a small minority being treated beyond 6 hours in the two trials with longer time windows (ESCAPE 12 hours and REVASCAT 8 hours). Patient level meta-analysis confirms steeply declining benefit with later treatment even within the first 6 hours.(33) As such, strategies aimed at minimising door-to-needle times are recommended. The role of imag~~in~~ing in the ~~early identification~~selection of patients ~~mostly likely to benefit from~~for mechanical thrombectomy, ~~or to benefit from treatment~~as undertaken in ~~-~~both trials of thrombectomy beyond the ~~currently recommended~~ 6 hour time window,(34, 35) ~~is a topic of ongoing research~~remains uncertain for those treated within the first 6 hours, since only two trials mandated similar selection criteria.(36, 37) ~~(PRACTICE)~~ (38). The role of regional hospitals ("primary stroke centres"), unable to deliver mechanical thrombectomy, in the early administration of IV-tPA prior to transfer to a comprehensive stroke centre - the so called "drip and ship" model vs. the "mothership" model - ~~remains unresolved~~is likely to require local planning dependent on service characteristics and transport networks (39). The need to maintain a minimum institutional and individual workload to maintain skills would likely pose a challenge to regional hospitals. Further research in these areas will contribute to the discussion around optimal system organisation and will impact on the cost-effectiveness of mechanical thrombectomy that will ~~should expect to~~be observed in routine practice. ~~However, t~~The results of our implementation analysis suggest~~s~~ that the cost-effectiveness of mechanical thrombectomy in practice is not contingent on achieving full implementation. Indeed, our results suggest that any level of implementation greater than 30% is likely to be a cost-effective use of resources.

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