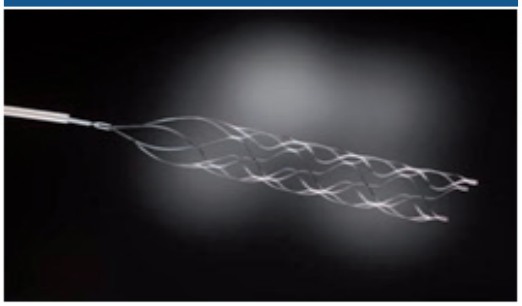
Healthcare Improvement Scotland

evidence note

This evidence note was based on a EUnetHTA rapid review in response to an inquiry from the Centre for Clinical Brain Sciences, University of Edinburgh

Number 61 May 2016

What is the clinical effectiveness, safety and cost effectiveness of endovascular therapy using mechanical thrombectomy devices for patients with acute ischaemic stroke?



Example of stent retriever device

What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in a period of up to 12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produce an Advice Statement to accompany all evidence reviews.

The clinical effectiveness and safety sections of this evidence note are adapted from a review of endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke. Published in December 2015, this was developed using the HTA Core Model® for Rapid Relative Effectiveness Assessment as part of the European Network for Health Technology Assessment (EUnetHTA) WP5 Joint Action 2 programme[1]. Healthcare Improvement Scotland was a dedicated reviewer to the project.

Literature search

EUnetHTA based their review and meta-analysis on studies identified in a systematic search of the published literature undertaken on 11 August 2015 to identify RCTs and prospective observational studies published since 1 January 2005. The databases searched were PubMed, Embase, the Cochrane Register of Controlled Trials, Clinical-Trials.gov, the International Clinical Trials Registry

Key points

- Stroke is a major public health concern resulting in significant levels of disability.
- Around 85% of strokes are ischaemic in origin, resulting from obstruction within a blood vessel supplying the brain.
- Meta-analyses of randomised controlled trials (RCTs) indicate that endovascular therapy with mechanical thrombectomy using stent-based devices, as an addition to standard care, results in improved rates of functional independence at 90 days for selected patients with ischaemic stroke who have confirmed large vessel occlusion.
- Meta-analyses found no statistically significant difference in all-cause mortality at 90 days between patients having mechanical thrombectomy and those receiving standard care.
- Studies were conducted in specialist centres with rapid access to neuro-imaging and interpretation and on-site facilities for neuro-intervention. There are likely to be significant organisational issues in translating study findings to routine care.
- A United Kingdom (UK) cost-utility analysis, Swedish Health Technology Assessment (HTA) and a United States (US) cost-effectiveness study estimated that mechanical thrombectomy was cost-effective with an incremental cost-effectiveness ratio of £7,061.
- The lack of detail presented in the economic analyses regarding the handling of the clinical data used to populate the model was a weakness across studies leading to a need for caution in interpretation of base case results.
- The Swedish HTA and the US study were conducted from a societal perspective which limits the generalisability of the results to NHSScotland.

Platform (ICTRP), the metaRegister of Controlled Trials (mRCT) and the Stroke Trials Registry.

A search of the secondary clinical-effectiveness literature and the cost-effectiveness literature was carried out by Healthcare Improvement Scotland on 25 November 2015.

Search terms included: thrombectomy, mechanical thrombus removal, endovascular intervention, mechanical thrombolysis and clot retrieval.

Introduction

A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either ruptured or is blocked by a thrombus (blood clot). Haemorrhagic stroke relates to the rupture of a weakened blood vessel. Ischaemic stroke results from an obstruction within a blood vessel supplying the brain and accounts for around 85% of all stroke cases[2].

The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, loss of balance or co-ordination; severe headache with no known cause; fainting or unconsciousness. The effects of a stroke depend on which part of the brain is injured and how severely it is affected. A very severe stroke can cause sudden death[3].

Stroke is a significant public health concern and is the main cause of disability in Scotland[4]. Stroke survivors may experience a range of significant physical, mental and emotional consequences[1].

Treatment for stroke depends on the results of brain imaging which differentiates haemorrhagic from ischaemic events and can exclude stroke mimics such as tumours. The 2008 SIGN guideline on management of patients with stroke or transient ischaemic attack (TIA) recommends that: "All patients with suspected stroke should have brain imaging immediately on presentation." For patients with confirmed ischaemic stroke, thrombolysis with recombinant tissue plasminogen activator (rt-PA) is recommended: "Patients admitted with stroke within four and a half hours of definite onset of symptoms, who are considered suitable, should be treated with 0.9 mg/kg (up to maximum 90 mg) intravenous rt-PA"[4].

Two guidelines specifically on mechanical thrombectomy were identified[5,6]. In February 2016, the National Institute for Health and Care Excellence (NICE) interventional procedure guidance (IPG548) stated the following recommendations[5]:

- Current evidence on the safety and efficacy of mechanical clot retrieval for treating acute ischaemic stroke is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.
- Selection of patients for mechanical clot retrieval for treating acute ischaemic stroke should be done by clinicians experienced in the use of thrombolysis for stroke and in interpretation of relevant imaging. The procedure should only be carried out by appropriately trained specialists with regular experience in intracranial endovascular interventions, with appropriate facilities and neuroscience support.

The consensus statements of the European Stroke Organisation (ESO), released in February 2015 in collaboration with the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR), made a number of recommendations on mechanical thrombectomy including the following 'A' grade recommendations based on systematic review of RCTs[6]:

- Intracranial vessel occlusion must be diagnosed with non-invasive imaging whenever possible before considering treatment with mechanical thrombectomy.
- Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset.
- Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy.
- Mechanical thrombectomy should be performed as soon as possible after its indication.

- For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered.
- If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions.
- High age alone is not a reason to withhold mechanical thrombectomy as an adjunctive treatment.

And the following 'C' grade recommendation on service delivery based on expert opinion:

- The decision to undertake mechanical thrombectomy should be made jointly by a multidisciplinary team comprising at least a stroke physician and a neurointerventionalist and performed in experienced centres providing comprehensive stroke care and expertise in neuroanaesthesiology.

The present evidence note focuses on the effectiveness, safety and cost-effectiveness of mechanical thrombectomy plus standard of care versus standard of care alone, in adults aged 18 years or older with acute ischaemic stroke. The clinical-effectiveness outcomes examined are shown in Table 1.

Epidemiology

In 2014–2015, there were 8,502 new cases of stroke in Scotland (new hospital admissions plus stroke deaths with no hospital admission). Over 75% of cases were in patients aged 65 or over. The European age-sex standardised incidence rate was 192 per 100,000 population for men and 159.2 per 100,000 population for women. There were 2,318 deaths due to stroke in Scotland in 2014. (A. Deas, Principal Information Analyst, ISD Scotland. Personal Communication, 9 February 2016.)

In the Scottish Health Survey 2014, 3.3% of men and 3.1% of women reported that they had experienced a stroke[7].

Table 1 Mechanical thrombectomy clinical-effectiveness outcomes

Primary outcomes	
Mortality due to ischaemic stroke at 90 days	
Disability - Modified Rankin Scale (mRS) at 90 days	The mRS is a global measure of disability. The scale ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death; persons with a score of 0, 1 or 2 are considered to be independent in daily function.
Secondary outcomes	
All-cause mortality at 90 days	
Ability to perform activities of daily living (ADL) - Barthel Index at 90 days	This index ranges from 0 to 100 with higher values indicating good performance of ADL. A score between 95 and 100 indicates no disability that interferes with daily activities.
Neurological deficit - National Institutes for Health Stroke Scale (NIHSS)	This scale ranges from 0 to 42, and quantifies neurological deficits into 11 categories, with higher scores indicating more severe neurological deficit.
Health-related quality of life - The EuroQol Self-Report Questionnaire (EQ-5D)	This examines five dimensions of health status, namely mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. Each dimension has three levels: no problems, slight or moderate problems; and extreme problems. More recently, the EQ-5D-5L has been developed – this contains five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.
Reperfusion at 24 hours and/or revascularisation at final angiography	Reperfusion assessed using computed tomography (CT) or magnetic resonance imaging (MRI). Revascularisation measured by the Thrombolysis in Cerebral Infarction Score (TICI) or by the modified TICI. Range is 0 (no perfusion) to 3 (complete perfusion).

Health technology description

At least 15 CE marked mechanical thrombectomy devices are available (see Table 2). Most are indicated for the restoration of blood flow in patients experiencing acute ischaemic stroke caused by a large intracranial vessel occlusion.

The aim of the technology is to retrieve the thrombus and rapidly restore blood flow to the affected area. Devices may be broadly classified into one of three categories: coil retrievers (first-generation devices) with a mechanism akin to pulling a cork from a bottle, stent retrievers (second-generation devices) which work by enmeshing the clot inside a basket before removal and aspiration/suction devices. All require similar endovascular access and should be used as early as possible after stroke onset, preferably within 6–12 hours of symptom onset. In clinical trials general anaesthesia was used in between 7% and 38% of procedures[1]. Mechanical thrombectomy may be used in conjunction with intravenous and/or intra-arterial thrombolysis or as an alternative to it in patients experiencing an acute ischaemic stroke who are not candidates for thrombolysis or in whom thrombolysis appears to have failed[1].

Around 10–20 mechanical thrombectomy procedures are carried out each year in Scotland. It is estimated that around 500 patients per year could be identified as suitable for the intervention[8].

Clinical effectiveness

The EUnetHTA review and meta-analysis included eight multicentre RCTs with a total of 2,423 patients[1]. Selected study characteristics are outlined in tables 3 and 4. All trials compared standard medical therapy, including intravenous thrombolysis (IV tPA), where appropriate, with standard medical therapy plus on-site endovascular therapy (mechanical thrombectomy with or without intra-arterial (IA) tPA in which tPA is infused directly into the artery close to the occlusion). In two of the trials, less than 40% of patients randomised to the intervention group received mechanical thrombectomy[10,11]. Average (mean or median) age of patients ranged from 64 to 71, and upper age limits for inclusion were 80 (3 trials[9,11,12]), 82 (1 trial[10]) and 85 (1 trial[13]). The proportion of males in studies ranged from 47% to 59%. Six trials provided data on median time from onset of symptoms to commencement of thrombolysis with IV tPA for both their control and intervention arms[9,10,12,14-16]. The median time from onset of symptoms to thrombolysis in the control groups in these trials ranged from 87 to 145 minutes; it ranged from 85 to 127 minutes in the intervention arms. Trials varied as to the maximum time allowed between the first symptoms and the commencement of endovascular therapy. This ranged from 5 to 12 hours (300 to 720 minutes). Median time from symptom onset to the start of the procedure for patients receiving endovascular therapy was reported in five trials and ranged from 210 to 269 minutes[9,11,12,14,15]. Location of stroke was confined to anterior circulation in six trials. Six trials specified pre-stroke functional ability as part of the inclusion criteria. Three stated this as mRS≤2[10,13], two as mRS≤1[9,12] with one study specifying Barthel index pre-stroke as ≥90[16].

For all of the included studies, overall risk of bias as assessed by the Cochrane risk of bias tool for RCTs was generally rated as low. Despite this overall rating, quality assessment identified some methodological issues which could have influenced study outcomes. One trial used a per protocol rather than intention-to-treat analysis[13] and five of the eight trials were stopped early, see Table 4[9,10,12,15,16].

The quality of the body of evidence was rated as low for the outcome of mRS at 90 days due to inconsistency between findings of earlier and later trials. If analysis was confined to studies which commenced after 2010, the evidence would be deemed moderate. Evidence for the mortality outcome was rated as moderate due to the potential for bias arising from trials stopping early.

Table 2 Mechanical thrombectomy technologies[1]

Coil retrievers	Merci Retrieval System
Stent retrievers	Acandis Aperio® Thrombectomy Device BONnet Catch EmboTrap ERIC® MindFrame Capture™ LP System REVIVE™ SE Thrombectomy Device Solitaire™ 2 Revascularization Device/ Solitaire™ FR Trevo® ProVue™ Retrieval System Trevo® XP ProVue™ Retrieval System pREset, pREset® LITE
Aspiration/suction devices	Penumbra System®/ACE™ (Penumbra 3D Separator) SOFIA™ Distal Access Catheter Vasco+35ASPI

Table 3 Mechanical thrombectomy RCT characteristics

Author/Year Trial name/ Location	Products used	Number of patients intervention/ control	% of intervention group treated with a mechanical thrombectomy device[17]	Imaging based patient selection	Year of first enrolment
Kidwell 2013[13] MR RESCUE North America	Merci Retriever, Penumbra System®	64/54	95%	No	2004
Broderick 2013[10] IMS III USA, Canada, Australia, Europe	Merci Retriever, Penumbra System®, Solitaire™FR	434/222	39%	Yes following protocol alteration	2006
Ciccone 2013[11] SYNTHESIS Expansion Italy	Including; Solitaire™, Penumbra System®, Trevo®, Merci	181/181	31%	No	2008
Berkhemer 2015[14] MR CLEAN The Netherlands	Retrievable stents used in 81.5% cases	233/267	82%	Yes	2010
Campbell 2015[15] EXTEND IA Australia, New Zealand	Solitaire™FR	35/35	77%	Yes	2012
Jovin 2015[9] REVASCAT Spain	Solitaire™FR	103/103	95%	Yes	2012
Saver 2015[12] SWIFT PRIME USA, Europe	Solitaire™FR Solitaire™2	98/98	89%	Yes	2012
Goyal 2015[16] ESCAPE Canada, USA, UK, South Korea, Ireland	Solitaire™FR + unspecified others	165/150	79%	Yes	2013

Table 4 Mechanical thrombectomy RCT characteristics

Author/Year Trial name/Location	Study sponsor	Study stopped early/reason
Kidwell 2013[13] MR RESCUE North America	National Institute of Neurological Disorders and Stroke. Concentric Medical provided study devices until August 2007; after which costs were covered by study funds or third-party payers.	No
Broderick 2013[10] IMS III USA, Canada, Australia, Europe	National Institutes of Health, National Institute of Neurological Disorders and Stroke, Genentech, and industry (Genentech, EKOS, Concentric Medical, Cordis Neurovascular, Boehringer)	Study stopped early because of futility, according to the pre-specified rule.
Ciccone 2013[11] SYNTHESIS Expansion Italy	Italian Medicines Agency	No
Berkhemer 2015[14] MR CLEAN The Netherlands	Dutch Heart Foundation and others	No
Campbell 2015[15] EXTEND IA Australia, New Zealand	Covidien	Trial stopped early because of efficacy.
Jovin 2015[9] REVASCAT Spain	Covidien	Trial stopped early due to loss of equipoise.
Saver 2015[12] SWIFT PRIME USA, Europe	Covidien	Trial stopped early because of efficacy.
Goyal 2015[16] ESCAPE Canada, USA, UK, South Korea, Ireland	Covidien and others	Trial stopped early because of efficacy.

Results of meta-analysis for the clinical-effectiveness outcomes are shown in Table 5. Data from the analysis of all RCTs, and from subgroup analysis based on the most recently conducted trials which used mainly second generation stent-based devices, are displayed on the basis that these five trials are most relevant to the intervention as it is currently practised[1].

Mortality

No studies in the analysis reported data on mortality from ischaemic stroke. There was no evidence of a difference in all-cause mortality at 90 days between patients receiving mechanical thrombectomy plus usual care when compared with patients in the control group. This finding was consistent for analysis of all eight RCTs and for the five most recent studies (Table 5).

Disability

The proportion of patients with an mRS of 0–2 at 90 days was higher for the mechanical thrombectomy intervention group (42.8%) when compared with the control group (32.0%) and this benefit was statistically significant. When all eight studies were combined there was substantial heterogeneity for this outcome which was completely eliminated when the three older studies were excluded from the analysis (Table 5). The analysis suggests that patients randomised to mechanical thrombectomy are more likely to be functionally independent at 90 days when compared with patients randomised to standard care.

Neurological deficit

Although six studies[9,11,12,14-16] provided information on neurological deficit, it was not possible to combine data due to variation in outcome reporting. Measures included: change in median NIHSS score at 24 hours, mean change in NIHSS score at 27 hours, proportion of patients achieving a reduction of ≥8 NIHSS points or a score of 0 or 1 at 3 days. Five of the six studies reported better scores in the intervention compared with the control group. The EUnetHTA review does not indicate if the beneficial effects were statistically significant.

Table 5 Results of random effects meta-analysis for the clinical-effectiveness outcomes

Outcome	Meta-analysis of all RCTs reporting outcome	Meta-analysis restricted to the five most recent RCTs[9,12,14-16]
Primary outcomes		
Mortality due to ischaemic stroke at 90 days	Data not available from studies	
Functional independence - Achieving an mRS of 0-2 at 90 days	8 studies RR=1.37* 95% CI 1.09 to 1.73 p = 0.008, I^2=76%	5 studies RR=1.72 95% CI 1.48 to 1.99 p<0.0001, I^2=0%
Secondary outcomes		
All-cause mortality at 90 days	8 studies RR=0.89 95% CI 0.73 to 1.09 p = 0.27, I^2=16.8%	5 studies RR=0.82 95% CI 0.60 to 1.11 p = 0.20, I^2=24.1%
Neurological deficit - National Institutes for Health Stroke Scale (NIHSS)	Variously reported in 6 studies, meta-analysis not possible	
Health-related quality of life - The EuroQol Self-Report Questionnaire (EQ-5D)	Variously reported in 3 studies meta-analysis not possible	
Reperfusion at 24 hours and/or revascularisation at final angiography.	Variously reported in 7 studies meta-analysis not possible	
Activities of daily living. Achieving Barthel Index score of ≥95 at 90 days	3 studies RR=1.70 95% CI 1.45 to 2.01 p<0.0001, I^2=2.5%	

RR=risk ratio

*Data from Kidwell 2013[13] for this outcome was from an age-adjusted analysis

Health related quality of life

Three trials reported on health related quality of life[9,14,16]. Data from all three suggested that mechanical thrombectomy had a positive effect on this outcome measure. The EUnetHTA review does not indicate if the beneficial effects were clinically or statistically significant.

Reperfusion/revascularisation

One trial provided data on reperfusion at 24 hours reporting that the proportion of patients who achieved >90% reperfusion at 24 hours without symptomatic intracerebral haemorrhage (SICH) was 89% for the mechanical thrombectomy group compared with 34% in the control group. The difference was statistically significant, p<0.001[15].

Angiography is not part of standard care so revascularisation at final angiography was only reported for the intervention arm of studies. For the five most recent trials, the proportion of patients in modified TICI class 2b-3 ranged from 58.7%[14] to 88%[12].

Activities of daily living

Meta-analysis of data from three studies was possible[9,14,16]. The proportion of patients with a score of ≥95 on the Barthel Index at 90 days was higher in the intervention group compared with controls (Table 5). This difference was statistically significant suggesting that mechanical thrombectomy results in improved outcomes in relation to ADL when compared with standard care.

Additional meta-analyses

Table 6 highlights primary outcome data from published meta-analyses contemporaneous with the EUnetHTA review and notes selected findings from subgroup analyses. Since the analyses used largely the same evidence base, findings were consistent across the analyses in reporting statistically significant benefit for endovascular therapy with mechanical thrombectomy in terms of functional independence at 90 days. There was no evidence of any statistically significant difference between study groups on all-cause mortality at 90 days. Subgroup analyses suggest that imaging-based patient selection/

confirmation of large vessel occlusion may be important factors in clinical effectiveness[17-26].

Two individual patient data meta-analyses investigated the efficacy and safety of stent-based mechanical thrombectomy based on the five most recent RCTs identified in the EunetHTA report[27,28]. The larger of the two analyses (n=1,287) confirmed benefit for the intervention in relation to reduced post-stroke disability in subgroups of interest, including: patients older than 80 years; patients randomised after 300 minutes from symptom onset; and patients for whom IV tPA is contraindicated[28].

Safety

The safety outcomes most consistently reported in RCTs were mortality at 90 days and SICH defined as an intracranial bleed associated with a clinical deterioration. As shown in Table 4 of the clinical effectiveness section, there was no evidence of impact of endovascular therapy with mechanical thrombectomy on mortality at 90 days when compared with control. On meta-analysis of the eight RCTs identified there was no evidence that the intervention led to higher overall rate of SICH, which was around 5% in both study groups (RR 1.07, 95% CI 0.74 to 1.53, p=0.73, I^2=0%). This finding was unchanged when meta-analysis was restricted to the five most recent RCTs, (RR 1.08, 95% CI 0.64 to 1.83, p=0.78, I^2=0%)[1]. Seven studies provided information on the rate of any intracranial haemorrhage at between 24 and 30 hours. Meta-analysis indicated that a greater proportion of the patients in the intervention groups (39.8%) experienced an event when compared with patients in the control groups (23.1%), RR=1.45, 95% CI 1.26 to 1.66, P<0.0001, I^2=7.5%)[1]. Recently published individual patient data meta-analyses focusing on stent retriever devices suggest that overall risk of intracranial haemorrhage does not differ between study groups[27,28].

Four trials provided data on the number of patients experiencing a recurrent ischaemic stroke within 90 days[9,10,14,16]. Across all patient groups, event rates ranged from 0.4% to 6.3%. There was substantial statistical heterogeneity across the studies for this outcome (I^2=67.8%). There was no evidence from random effects meta-analysis that the intervention led to a statistically significant difference in the rate of recurrent stroke when compared with control (RR=1.97, 95% CI 0.64 to 6.03, p=0.24)[1].

Data on adverse events such as vessel perforation, vessel dissection, groin haematoma and vasospasm requiring treatment, were both classified differently across trials and reported differently across trials making comparison problematic. Table 7 outlines data from the trials relating to serious adverse events and to device/procedure-related adverse events. There was a lack of clarity in studies as to what constituted a serious adverse event so interpretation of this outcome is limited and meta-analysis of data was not possible. Most of the trials did not distinguish between device and procedure-related adverse events but rather combined these. Rates ranged from 10.9% to 29.12%, although it was unclear if data related to unique patients so caution is required in interpretation. In addition to the eight RCTs identified for the clinical-effectiveness assessment, the EUnetHTA review identified six additional studies (four prospective observational studies and two RCTs) which provided information on the proportion of patients experiencing a device-related adverse event[29-33]. This ranged from 2.8%[29] to 13.5%[30].

Table 6 Findings from meta-analyses contemporaneous with the EUnetHTA rapid technology assessment^

Study	N studies	mRS 0-2 at 90 Days	All cause mortality at 90 days	Notes/Subgroup findings
Badhiwala I 2015[18] Canada	8	OR=1.71 95% CI 1.18 to 2.49 p=0.005, I^2=75.4%	OR=0.87 95% CI 0.68 to 1.12 p=0.27, I^2=17.7%	Analysis of data from four studies identified benefit in favour of thrombectomy for angiographic revascularisation at 24 hours, OR=6.49 95% CI 4.79 to 8.79 P<0.001
Balami I 2015[17] United Kingdom	8	OR=1.71 95% CI 1.18 to 2.48 P=0.005, I^2=75%	OR=0.84 95% CI 0.67 to 1.05 p=0.12, I^2=0%	This review formed basis of NICE IPG 548[5] Subgroup analysis of trials where >50% of patients received thrombectomy in treatment group found OR=2.23 95%CI 1.77 to 2.81 for mRS 0-2 at 90 days
Chen 2015[19] United States	8	OR=1.71 95% CI 1.18 to 2.49 p=0.005, I^2=75%	OR=0.87 95% CI 0.67 to 1.12 p=0.27, I^2=19%	On subgroup analysis of two studies without confirmation of large vessel occlusion, there was no evidence of a difference in functional independence between study groups OR=0.99 95%CI 0.76 to 1.30 p=0.94
Elgendy I 2015[22] United States	9	RR=1.45 95% CI 1.22 to 1.72 p=0.021, I^2=54%	RR=0.86 95% CI 0.72 to 1.02 p=0.608, I^2=0%	Trials which prohibited IV thrombolysis before thrombectomy were excluded. Analysis included two unpublished studies THERAPY and THRACE (see Table 8)
Grech 2015[23] Malta	5	OR 2.40 95% CI 1.89 to 3.05 p=0.000	OR 0.81 p=0.15	Included trials of stent-based devices only
Hong 2015[24] Korea	13	OR=1.79 95% CI 1.34 to 2.40 p=0.0001, I^2=62%	OR=0.87 95% CI 0.71 to 1.05 p=0.15, I^2=0%	Included trials from 1999 to 2015
Sardar 2015[25] United States	8	OR=1.73 95% CI 1.18 to 2.53 p=0.005, I^2=77%	OR=0.89 95% CI 0.68 to 1.15 p=0.36, I^2=21%	Sensitivity analysis indicated that use of stent retrievers and rate of successful reperfusion were significantly related to the rate of functional independence.
Touma 2016[26] Canada	5	RR=1.72 95% CI 1.48 to1.99 I^2=0%	RR=0.82 95% CI 0.60 to 1.11 p=0.26, I^2=23.9%	Stent-based devices only
Yarbrough 2015[20] United States	8	OR=1.75 95% CI 1.20 to 2.54 p=0.001, I^2=71.8%	OR=0.78 95% CI 0.57 to 1.08 p=0.117, I^2=39.3%	Subgroup analysis noted that benefit to functional independence was found in both 'younger' and 'older' patients as variously defined in four studies
Zheng 2015[21] China	4	RR=1.75 95% CI 1.48 to 2.06 I^2=0%	RR=0.78 95% CI 0.60 to 1.01 I^2=21.4%	Computed tomographic angiography (CAT)-based patient selection was associated with greater functional benefit and the difference was statistically significant

OR = odds ratio

^note: critical appraisal of methodology not conducted

Table 7 Adverse event data from mechanical thrombectomy RCTs

Author/Year Trial name/ Location	Products used	Number of patients Intervention/control	Serious adverse events	Device and or procedure related adverse events
Kidwell 2013[13] MR RESCUE North America	Merci Retriever Penumbra System®	64/54	79/127*	10/64∞
Broderick 2013[10] IMS III USA, Canada, Australia, Europe	Merci Retriever Penumbra System® Solitaire™FR	434/222	I:256/434 C:126/222	70/434
Ciccone 2013[11] SYNTHESIS Expansion Italy	Including; Solitaire™ Penumbra System® Trevo®, Merci	181/181	I: 10/181≡ C:5/181	Not reported
Berkhemer 2015[14] MR CLEAN The Netherlands	Retrievable stents used in 81.5% cases	233/267	I: 110/233 C:113/267	26/333
Campbell 2015[15] EXTEND IA Australia, New Zealand	Solitaire™FR	35/35	I:7/35 ▲ C:10/35	4/35∞
Jovin 2015[9] REVASCAT Spain	Solitaire™FR	103/103	Unable to interpret	30/103∞
Saver 2015[12] SWIFT PRIME USA, Europe	Solitaire™FR Solitaire™2	98/98	I:30/97 C:35/98	7/98∞^
Goyal 2015[16] ESCAPE Canada, USA, UK, South Korea, Ireland	Solitaire™FR + unspecified others	165/150	I:35/165 C:27/150	18/165

*Not characterised according to whether intervention or control group.
∞Not clear if these were unique patients.
≡These events were characterised as non-cerebral events and were subdivided into fatal (I:3/181, C: 1/181) and non-fatal (I: 7/181, C: 4/181) rather than severe and non-severe adverse events. They included severe extracranial bleeding, pulmonary embolism, myocardial infarction, sepsis, deep vein thrombosis and pulmonary oedema. One additional event in each group ie 11/181 and 6/181.
▲ Not characterised as serious or non-serious.
^Procedure-related events not reported

Organisational aspects

Use of the technology presents substantial implications for organisation of services. EUnetHTA states[1]:

"Endovascular stroke therapy has major implications for stroke services and for triaging decisions by emergency medical services. Ideally, this procedure should be undertaken as soon as possible following stroke onset in comprehensive stroke centres by consultant specialists trained in interventional neuroradiological techniques. Trial data also suggest a requirement for rapid access to neuroimaging to identify eligible patients with large-vessel occlusion. These criteria require substantial stroke-workflow efficiencies and organisation of specialist stroke services that may not be readily available in many regions."

UK standards for providing safe acute ischaemic stroke thrombectomy services have been published[34].

Ongoing studies

The EUnetHTA review identified several ongoingand unpublished studies as outlined in Table 8[1].

Cost effectiveness

In 2015, a UK *de novo* cost-effectiveness model was developed to determine the cost effectiveness of thrombolysis and mechanical thrombectomy compared with thrombolysis alone in patients with acute ischaemic stroke[35]. The analysis was undertaken from a UK NHS perspective.

A short-term decision tree model was developed to analyse the respective costs and clinical outcomes within 3 months from stroke for each treatment arm. This was then used to inform a long-run model, which took the form of a three state Markov model to analyse the expected long-term costs and outcomes over a 20-year lifetime time horizon. For both treatment arms, outcomes were based on mRS scores at 90 days after stroke, which were assumed to be affected by recanalisation rates and symptomatic haemorrhage rates. On completion of the short-term model, patients were categorised into one of the three Markov states based upon their predicted mRS score: independent (mRS≤2), dependent (mRS=3-5) or dead (mRS=6).
In the model, the independent health state means patients recover from the stroke, and the dependent health state means patients are reliant on carers and require assistance for daily functions to varying degrees. Upon entering the Markov model, patients were assumed to remain in the state they entered for the first 3 months. Movements through the model were based on transition probabilities generated from a meta-analysis of five RCTs. The trials included in the meta-analysis were MR CLEAN, ESCAPE, EXTEND 1A, SWIFT-PRIME and REVASCAT, all of which are described within the clinical effectiveness section. The model makes a simplified assumption around stroke severity whereby the probability of having a recurrent stroke is the same regardless of whether the person is in the independent stroke health state or the dependent stroke health state. Patients in the dependent state after 12 months were assumed to be unable to transition to the independent state. Patients who remained in the independent state after 12 months were assumed to remain in that state unless they experienced a stroke and would therefore either move to the dependent state or die.

Utility values for the health states were taken from the published literature and were applied as follows: independent 0.74, dependent 0.38 and recurrent stroke 0.34. Costs included in the model are the cost of the medication and also its administration. The sources of these costs were: British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and NICE Technology Appraisal Guidance 122 on alteplase for the treatment of acute ischaemic stroke. The cost of mechanical thrombectomy included the costs associated with stent, materials and surgery. These costs were taken from PSSRU and the manufacturer's price list. Resource use post stroke was also accounted for in the model and varied by mRS score and the corresponding health state, with the costs including: acute and ongoing management, inpatient and high dependency hospital stay, discharge and community care costs. The costs applied in the model for recurrent stroke were assumed to be the same for each arm and were based on the cost of a stroke not requiring thrombolysis or thrombectomy. The source of these costs in the model was taken from the review (conducted by University of Sheffield) of NICE TA122[36]. Both costs and outcomes were discounted at an annual rate of 3.5%.

Table 8 Ongoing and unpublished studies

Study	Study type/comparison	Patient group	Estimated completion date
NCT01745692 (PISTE)	RCT (n=65) Mechanical thrombectomy + IV thrombolysis vs IV thrombolysis	Clinical diagnosis of supratentorial stroke (NIHSS ≥6) and able to commence IV treatment in <4.5 hours and procedure onset possible within 90 minutes	July 2015 (terminated)
NCT01062698 (THRACE)	RCT (n=412) Mechanical thrombectomy + IV thrombolysis vs IV thrombolysis	Symptom onset <4 hours and confirmed occlusion of the proximal cerebral arteries	August 2015 (terminated)
NCT01852201 (POSITIVE)	Multicentre RCT (n=750) Mechanical thrombectomy + IV thrombolysis vs IV thrombolysis	NIHSS ≥ 8 at time of neuroimaging and neuroimaging confirmed large vessel proximal occlusion. Patients are within 6 to 12 hours of symptom onset and have received IV tPA without improvement in symptoms	May 2016
NCT01983644 (REDIRECT)	Multicentre RCT (n=130) RECO Flow Restoration Device Versus Solitaire FR	Acute anterior circulation stroke and CTA/ MRA confirmed large vessel occlusion, and presenting within 4.5 hours of symptom onset with NIHSS 8-24	November 2016
NCT01584609	Multicentre RCT (n=230) Mechanical thrombectomy with Penumbra System with Separator 3D vs Penumbra System	NIHSS ≥ 8 and evidence of large vessel occlusion in the cerebral circulation. Patients are within 8 hours of symptom onset and are refractory to or not eligible for IV tPA	December 2016
NCT01429350 (THERAPY)	Multicentre RCT (n=692) Endovascular therapy plus tPA vs IV tPA	Symptoms consistent with acute ischaemic stroke and evidence of large clot occlusion (clot length >8mm) in the anterior circulation, NIHSS ≥ 25 or aphasic at presentation, and eligible for IV tPA	December 2016
NCT02216565 (EASYTRAL)	Multicentre RCT (n=270) Endovascular treatment plus conventional medical treatment vs conventional medical treatment	Radiologically proven acute proximal occlusion of the middle cerebral artery, NIHSS ≥ 5 and either tandem internal carotid/middle cerebral artery occlusion OR IV tPA contraindicated OR IV tPA not possible because of delay >4.5 hours	March 2017
NCT02419781 (RESCUE-Japan)	RCT (n=200) tPA + endovascular therapy vs tPA	CT confirmed persistent large vessel occlusion not responsive to tPA, NIHSS 8-29, where endovascular treatment delivered within 8 hours of stroke onset	July 2017
NCT02142283 (DAWN)	Multicentre RCT (n=500) Trevo + medical management vs medical management alone	Wake up and late presenting acute ischaemic stroke (NIHSS≥10)	July 2017
NCT02135926 (THRILL)	Multicentre RCT (n=600) Thrombectomy with stent retriever device in patients ineligible for tPA vs best medical care (no tPA)	Ineligible for tPA with symptoms consistent with acute ischaemic stroke and a new focal occlusion confirmed by imaging to be accessible to the thrombectomy device, 7<NIHSS<25 and within 7 hours of stroke onset	March 2018 (suspended)
NCT02157532 (EASI)	RCT (n=480) Mechanical thrombectomy + best standard treatment vs best standard treatment	Occlusion of proximal cerebral arteries following moderate to severe stroke (NIHSS ≥8) within 5 hours of symptoms onset or symptom/imaging mismatch	January 2020
NCT02586415 (DEFUSE 3)	RCT (n=476) FDA cleared thrombectomy devices plus medical management compared to medical management	Target mismatch profile and an MCA (M1 segment) or ICA occlusion who can be randomized and have endovascular treatment initiated between 6-16 hours after last seen well.	January 2020

CTA- computed tomographic angiography
MRA- magnetic resonance angiography

The results presented in the paper found that mechanical thrombectomy was cost effective with an estimated incremental cost-effectiveness ratio (ICER) of £7,061 per quality adjusted life year (QALY); this was based on an incremental cost associated with mechanical thrombectomy and thrombolysis of £7,431 and an additional QALY of 1.05. The key driver of the incremental costs was the device costs and additional resource use, and the key driver for the QALY gain was morbidity and reduced mortality assumed to be associated with lower mRS scores within the long term model. It is worth noting that although 90-day mortality was not included as an outcome in the model, there were no statistically significant differences in this reported in the clinical effectiveness section above. In the model, the QALY gain is being driven by the transition probabilities. For the mechanical thrombectomy arm, a greater proportion of patients are in lower mRS health states, thus are more independent and have reduced morbidity. However, the relationship the model is predicting between the mRS score and improved mortality was not supported by the clinical evidence. The evidence did not show that lower mRS score would translate into improved mortality.

The paper notes the results of the parameters of the one-way sensitivity analysis were only sensitive to increasing the cost of thrombectomy by 130% and reducing the utility value in the independent state from 0.74 to 0.34. Based on these sensitivity analyses, results were borderline cost-effective at a willingness to pay threshold of £20,000. However, no other results are presented in the paper. The probabilistic sensitivity analysis estimates mechanical thrombectomy and thrombolysis has 100% probability of being cost-effective at the lower threshold of the commonly accepted UK cost-effectiveness thresholds.

The key weakness of the analysis is the lack of explanation surrounding the clinical inputs into the short-term decision tree model. No detailed explanation is given regarding the clinical outcomes used to inform the probabilities of the decision tree model, and there appear to be a number of issues with the meta-analysis which underpins the economic model. The paper states that the transition probabilities are derived from a meta-analysis of five recent (completed in 2015) RCTs, but no clinical data are presented in the paper. Upon inspection of the supplementary material accompanying the paper, there is a table detailing, from the five clinical trials mentioned above, the proportion of patients in each of the three health states, then what appears to be a crude analysis of simple addition and division to estimate the pooled proportion of patients in each health state in the model. For example, pooling the results across the studies estimates 46% of patients are in the mRS score 0-2 health state for thrombolysis plus mechanical thrombectomy arm and 26% are in the mRS score 0-2 health state for thrombolysis alone. Following on from the above, there is no accounting for within trial differences or differences across the patients' characteristics of each trial. Thus heterogeneity could have been introduced and does not seem to be accounted for. These estimates underpin the economic evaluation and their uncertainty calls into question the robustness of the analysis.

A further weakness is that the model assumes that patients have the same probability of transitioning through the model irrespective of the results of recent strokes. That is to assume that the risk of a recurrent stroke is the same regardless of the outcome of previous strokes. This could be biasing the QALY gain in favour of mechanical thrombectomy, as it may be more accurate to expect that there would be an increased risk of a recurrent stoke if a patient has had a recent stroke. This assumption is varied in the probabilistic sensitivity analysis, thus the individual effect this is having on the model is not known.

In summary, the analysis has found that mechanical thrombectomy is likely to be cost effective based upon recently publish clinical data. However, there is a lack of clarity surrounding the handling of the clinical data, which brings into question the reliability of the base case results.

In 2015, The Swedish Dental and Pharmaceutical Benefit Agency (TLV) performed an economic analysis of thrombectomy, as an addition to thrombolysis in newly detected cases of acute ischaemic stroke[37]. The report refers only to 'the model' – which is presented over a lifetime time horizon – but no further information is provided.

Data to inform the first year of the model were taken from the same five recently published RCTs described above in the clinical effectiveness

section. As with the UK model, the main clinical outcome used in the model is the mRS score. It appears that the 3 months mRS score data have been taken straight from the five RCTs and the proportions of each category (mRS score 0-5) applied in the model. As such, the model assumes that a greater proportion of the thrombectomy patients are in the less severe health states, compared to the comparator arm. The model has then extrapolated associated outcomes over the lifetime.

To estimate QALY gains, the report states that higher mRS scores are associated with greater reductions in quality of life. These reductions in quality of life were combined with quality of life reductions associated with age to determine the overall utility value. The quality of life decrements were taken from the published literature. In terms of the impact on thrombectomy of length of life, while the five RCTs do not report a statistically significant difference in survival after 3 months post stroke, the model assumes the RCTs estimate that 4% more patients survive with thrombectomy after 3 months. It is subsequently expected that as more patients treated with thrombectomy achieve lower mRS scores, these patients have a lower mortality associated with stroke and thus more life years.

The model is built from a societal perspective, thus health and social care costs are included. Extensive costs associated with the first year are included in the analysis which includes the intervention costs, staff costs, and social care costs associated with patients with specific mRS scores from 0-5. Lower long-term health and social costs are associated with patients with lower mRS scores. The sources of the costs were taken from the published literature.

The base case results estimate an ICER of 45,000 SEK per QALY (£3,805 - all conversions based on the exchange rate of £1 = 11.74 SEK as of 15 March 2016), this is based on an incremental cost of 54,600 SEK (£4,633) and a QALY gain of 1.21 for thrombectomy as an additional treatment to intravenous thrombolysis. The report provides details of various one-way sensitivity analyses performed. The results are most sensitive to assuming that 10% of patients within each mRS score move to the next more severe mRS score. This results in the ICER increasing to the upper bounds of the commonly accepted UK cost-effectiveness thresholds of 351,000 SEK (£29,679). The average age in the model is 67 years; this is based on the average age of the patients in the five RCTs. When this is increased to 82 years of age, the ICER increases to nearly 141,900 SEK (£12,000). The results are not sensitive to other parameters that were varied in the model.

The limitations with the TLV evaluation are the following: there is a lack of detail surrounding the type of model developed. There is no reference to the model structure, thus it is not clear if it is a decision tree model or a Markov model for example. There is a lack of detail surrounding how the mRS scores have been pooled to inform the proportion of patients associated with each score in the model, how the data from the RCTs are extrapolated and how patients transition through the model. The quality of life decrement associated with mRS score 6 is 1.00, thus if the patient was in perfect health (value of 1) the associated utility value of mRS score 6 would be 0 - assuming that patients are in a state equal to death. This is unlikely to be appropriate and thus biasing the results in favour of the intervention, as more patients are assumed to be in the higher mRS states with the comparator.

The Swedish study estimates that mechanical thrombectomy was cost-effective. However, the lack of detail surrounding the model and model inputs limits the robustness of the base case analysis. Furthermore, the analysis was conducted from a societal perspective, further limiting the generalisability of the results to NHSScotland.

In addition to the above studies, it is worth noting a US cost-effectiveness analysis published in 2015 aimed to estimate the cost effectiveness of mechanical thrombectomy as an adjunct to thrombolysis for acute ischaemic stroke, by comparing mechanical thrombectomy after thrombolysis with thrombolysis alone[38]. The model used in the analysis is very similar in structure to the UK paper described above. The clinical outcomes within the model were incorporated in the same way as the UK model, with the key difference between this model and the UK model being the cost analysis. Costs were taken from US medical databases of resource use. The base case results estimate an ICER for mechanical thrombectomy as an adjunct to thrombolysis of $14,137 (£9,641) (all conversions

based on the exchange rate of $1 = £0.68 as of 4 February 2016), this is based on an incremental cost of $9,911 (£6,759) and a QALY gain of 0.7. The main limitation of the paper from an NHS point of view is that this is a US analysis based on a societal perspective, and therefore takes into account the wider aspects of the treatment, for example loss of working days and impact on carers. This is not part of an NHS assessment, and thus with this perspective removed, the results are likely to be less cost effective than the base case. No sensitivity analyses have been presented with the societal perspective removed.

In summary, a UK study, Swedish HTA and a US study estimated that mechanical thrombectomy was cost-effective. The lack of detail presented in the economic analyses regarding the handling of the clinical data used to populate the model was a weakness across all studies leading to a need for caution in interpretation of base case results. The Swedish HTA and the US study were conducted from a societal perspective which limits the generalisability of the results to NHSScotland.

Conclusion

Meta-analysis of RCTs indicates that for highly selected patient groups with confirmed large vessel occlusion, rapidly delivered mechanical thrombectomy with stent-based devices, results in a greater proportion of patients achieving functional independence (defined as mRS 0-2 at 90 days) when compared with standard care in ischaemic stroke. This benefit is gained without evidence of an increase in all-cause mortality at 90 days. The overall rate of intracerebral haemorrhage is increased in patients receiving mechanical thrombectomy but there is no evidence of a statistically significant effect on the rate of symptomatic intracerebral haemorrhage or recurrent stroke at 90 days. The external validity of the trials to the Scottish context may be limited by organisational and geographic factors. Although there are some concerns around the method of aggregation of clinical data to populate the economic model, a UK analysis suggests that mechanical thrombectomy following thrombolysis is cost effective at commonly accepted thresholds.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see http://www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

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- Lorna Thompson, Lead Author/Health Services Researcher
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NICE has accredited the process used by Healthcare Improvement Scotland to produce its evidence review products. Accreditation is valid for 5 years from January 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation

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