EUnetHTA WP5 Joint Action 2 (2012-2015)
Rapid assessment of other technologies

**Pilot rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke

Pilot ID: WP5-SB-16

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Final Version Update

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Disclaimer

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Consultation of the draft Pilot Rapid Assessment

The following WP5 Strand B members have provided comments during WP5 consultation [V 1.1]	Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland Institute for Quality and Efficiency in Health Care (IQWIG), Germany Ludwig Boltzmann Institute for HTA (LBI HTA), Austria National Institute of Pharmacy and Nutrition, Department of Health Technology Assessment (OGYÉI), Hungary
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Conflict of interest

All authors and reviewers, except one external reviewer, involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of Interest and Confidentiality Undertaking of Interest (DOICU) statement form.

One external reviewer, Professor Martin Scott Dennis, has declared *a financial or another relationship with a Developing and/or Producing and/or Distributing Organisation (DPDO) for the technology or comparators undergoing assessment*, and thus has a conflict of interest according to the EUnetHTA guidelines for handling conflict of interest. Professor Dennis acted in an unpaid and informal advisory capacity for a DPDO responsible for the health technology under assessment (Medtronic). In addition, Professor Dennis declared to have carried out clinical studies in relation to the development of a medical device other than the one included in this assessment for a DPDO as investigator (Covidien, now Medtronic); for these studies, the DPDO provided equipment free of charge, but did not pay him an honorarium. According to the EUnetHTA guidelines for handling conflict of interest, the involvement of Professor Dennis as external expert is acceptable for commenting on the draft assessment without having access to any potentially confidential material.

Erratum

Subsequent to the original publication, a number of errata were identified and corrected in February 2016. Four studies had an inclusion criterion that required patients to have been eligible for, or have commenced, infusion of IV tPA within 4.5 hours of symptom onset. The original report stated there were six studies. The original report had incorrectly extracted the data for the number of patients achieving a modified Rankin scale of 0-2 at 90 days for the SYNTHESIS EXPANSION trial. This changed the estimated risk ratio from 1.36 (95% CI: 1.03 to 1.80) to 1.37 (95% CI: 1.09 to 1.73). The changes to the report do not affect the findings or the interpretation of the findings.

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LIST OF ABBREVIATIONS

ACA	anterior cerebral artery
ADL	activities of daily living
AHA/ASA	American Heart Association/American Stroke Association
ASPECTS	Alberta Stroke Programme Early Computed Tomography Score
CI	confidence interval
CT	computed tomography
CTA	computed tomographic angiography
CRP	C-reactive protein
DALYs	disability-adjusted life years
DRG	Diagnosis Related Groups
DSA	digital subtraction angiography
DWI-MRI	diffusion-weighted magnetic resonance imaging
ECASS	European Cooperative Acute Stroke Study
ECG	electrocardiogram
ED	Emergency Department
EMS	Emergency Medical Services
EQ-5D	EuroQol Group – 5 Dimension Self-Report Questionnaire
ESMINT	European Society of Minimally Invasive Neurological Therapy
ESNR	European Society of Neuroradiology
ESO	European Stroke Organisation – Karolinska Stroke Update
ESPro	Erlangen Stroke Registry
EU	European Union
FAST	Face–Arms–Speech–Time
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
IA tPA	intra-arterial tissue plasminogen activator
ICA	internal carotid artery
ICTRP	International Clinical Trials Registry Platform
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
INR	international normalised ratio
IQR	interquartile range
IV tPA	intravenous tissue plasminogen activator
KSU	Karolinska Stroke Update
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRCT	metaRegister of Controlled Trials
mRS	Modified Rankin Scale

NIHSS	National Institutes of Health Stroke Scale
MCA	middle cerebral artery
MeSH	Medical Subject Headings
mTICI	modified thrombolysis in cerebral infarction
PISTE	Pragmatic Ischaemic Stroke Thrombectomy Evaluation
PT	prothrombin time
PTT	partial thromboplastin time
r-tPA	recombinant tissue plasminogen activator
RCT	randomised controlled trial
SAE	serious adverse events
SD	standard deviation
SICH	symptomatic intracerebral haemorrhage
SITS	Safe Implementation of Treatments in Stroke
SITS TBY	SITS Mechanical Thrombectomy
TICI	thrombolysis in cerebral infarction
TGA	Therapeutic Goods Administration
tPA	tissue plasminogen activator
WHO	World Health Organization

SUMMARY OF RELATIVE EFFECTIVENESS OF MECHANICAL THROMBECTOMY DEVICES FOR ACUTE ISCHAEMIC STROKE

Scope

The aim of this project was to examine the effectiveness and safety of mechanical thrombectomy plus standard of care versus standard of care alone, in adults aged 18 years or older with acute ischaemic stroke in the anterior and/or posterior region. CE-marked aspiration/suction devices, and stent and coil retrievers, were included in the analysis. The assessment of effectiveness includes evidence from a systematic review of randomised controlled trials (RCTs); the assessment of safety includes evidence from RCTs, prospective clinical studies, medical device adverse event registers and postmarketing surveillance data on device-related adverse events. Outcome measures of effectiveness considered in this analysis include the modified Rankin Scale (mRS) and all-cause mortality at 90 days (primary outcomes). The National Institutes for Health Stroke Scale (NIHSS), the Barthel Index, and reperfusion and/or revascularisation at final angiography were also considered (secondary outcomes). Outcome measures of safety that were considered included symptomatic intracerebral haemorrhage (SICH), any cerebral haemorrhage, recurrent ischaemic stroke at 90 days, and device-related adverse events (see Scope).

Introduction

Description of technology

Mechanical thrombectomy is used in patients with acute ischaemic stroke due to occlusion of a proximal cerebral artery. Several endovascular techniques and products have been used over the years to re-canalise blocked vessels. Techniques and devices used have included the injection of saline or pharmacological agents into the clot and the use of various types of devices to try to disrupt, catch or aspirate the clot from the patient's bloodstream [1]. Intravenous thrombolysis with tissue plasminogen activator (tPA) remains the standard medical treatment for acute stroke as a comparator to mechanical thrombectomy under the conditions given by the guideline from the European Stroke Organisation – Karolinska Stroke Update (ESO) [2] (**B0001**).

Although tPA remains the standard medical treatment for acute stroke today, it has been shown to have modest clinical efficacy in severely affected patients [3]. This is because, in order for the administration of tPA to be effective and provide maximum benefit, it must be administered within 4.5 hours after the onset of stroke symptoms [4]. In the setting of large-vessel occlusions (or proximal artery occlusions), it is limited in its ability to revascularise the occlusion. Furthermore, intravenous tPA (IV tPA) has multiple constraints, including unresponsiveness of large thrombi to rapid enzymatic digestion and the risk of cerebral and systemic haemorrhage [4]. Endovascular treatment with mechanical thrombectomy administered within 6–12 hours of stroke onset has been suggested as an effective and safe adjunct to usual care, such as tPA alone [5]. The efficacy and safety of mechanical thrombectomy is discussed in detail below [4, 6-9] (**B0002**).

Health problem

Ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. The blockage results in an insufficient amount of blood being delivered to that portion of the brain. This can lead to deterioration in function which, if not addressed in a timely manner, will be irreversible [10]. Delays in recanalisation have been demonstrated to reduce the odds of a good outcome (**A0002**).

The target population for mechanical thrombectomy in this assessment is patients experiencing an acute ischaemic stroke due to a proximal or large neurovascular vessel occlusion. Patients with an occlusion of a major intracranial artery, such as the internal carotid artery (ICA), middle cerebral artery (MCA), or basilar artery, have a very poor prognosis if the occlusion is not opened [11] (**A0007**).

According to the World Health Organization (WHO) in 2002, 15 million people worldwide suffer a stroke each year. The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking. However, the absolute number of strokes continues to increase because of the ageing population [12]. Stroke was the second most frequent cause of death worldwide in 2012 accounting for 6.7 million deaths (~12% of the total); it was the third most common cause of death in developed countries and the most common cause in upper-middle-income countries [13] (**A0023**).

Methods

A preliminary working version of the HTA Core Model® for Rapid Relative Effectiveness Assessment, based on the 'HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0', was used as the primary source for selecting the assessment elements. Additionally, assessment elements from other EUnetHTA Core Model Applications were screened and included, if believed relevant to the present assessment.

A systematic literature search was used in compiling the 'Clinical effectiveness' and 'Safety' domains. This included RCTs published between 1 January 2005 and August 2015, inclusive. The databases searched were PubMed, Embase, the Cochrane Register of Controlled Trials, ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), the metaRegister of Controlled Trials (mRCT) and the Stroke Trials Registry. Data were also requested from manufacturers (seven manufacturers provided information via submission files) and the Health Products Regulatory Authority of Ireland.

Selection of relevant documents was performed by two independent researchers. Only RCTs were included in the assessment of 'Clinical effectiveness'. For the 'Safety' domain, other relevant prospective studies which contained information on device-related adverse events were included. These were identified in the review of clinical effectiveness or through published systematic reviews.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence for 'Clinical effectiveness' and 'Safety'. The methodological quality of the studies was assessed using the Cochrane risk of bias tool for RCTs.

A manual search and basic search were performed for 'Health problem and current use' and 'Description and technical characteristics'.

Results

Available evidence

Eight RCTs with a total of 2,423 patients were included in the assessment of 'Clinical effectiveness'; 1,110 controls and 1,313 patients who were randomised to endovascular treatment. All trials compared standard medical therapy, including IV tPA, where appropriate, with standard medical therapy plus endovascular therapy (mechanical thrombectomy with or without intra-arterial tPA [IA tPA]). The average duration of the included trials was 33 months (range 24–80 months). The earliest trial began enroling in 2004 and the latest in 2013, with all eight publishing their main results between 2013 and 2015. Four trials noted that included patients must have been eligible for, or commenced infusion of, IV tPA within 4.5 hours of symptom onset. The maximum time allowed between onset of symptoms and commencement of the endovascular intervention ranged from 5 to 12 hours across the trials. A subgroup analysis was undertaken of the five most recent trials on the basis that they were methodologically different (e.g. device generation and patient selection criteria) from the first three trials.

While the overall risk of bias for each of the RCTs was generally rated as low, a number of issues that could potentially have affected the outcome data were identified – one trial performed a per protocol analysis [14] while the other seven were analysed on an intention-to-treat basis; one trial did not report on all outcomes as planned in the study protocol [15]; and five of the eight trials were stopped early. The quality of the evidence was rated as low for the mRS and moderate for other outcomes of effectiveness.

The same eight RCTs also formed the basis for the assessment of 'Safety'. With the exception of mortality at 90 days and SICH, there was inconsistency in how these eight trials reported their safety outcomes, making comparability and interpretation difficult. Data on device-related events from six additional studies (two RCTs and four prospective studies) were also extracted and analysed. All six studies were performed between 2010 and 2012 and all were published in 2012 or 2013.

No additional data on clinical effectiveness or safety were obtained from review of manufacturer submissions nor from the Health Products Regulatory Authority of Ireland.

Clinical effectiveness

The evidence suggests that the intervention is not associated with a lower all-cause mortality at 90 days (risk ratio = 0.89; 95% confidence interval (CI): 0.73 to 1.09; p = 0.27) when compared with standard medical care alone (**D0003**). This outcome did not change when analysis was limited to results from the five most recent trials.

All eight trials reported data for mRS at 90 days, with data available on 2,387 patients in total. A total of 42.8% (553/1,293) of patients in the intervention arm were reported to have achieved an mRS of 0–2 (indicative of independent daily function) at 90 days; this compared with 32.0% (350/1,094) of patients who were assigned to the control arms of the studies. The risk ratio for achieving an mRS of 0–2 at 90 days was 1.37 (95% CI: 1.09 to 1.73; p = 0.008) in favour of the intervention; when subgroup analysis was performed on the five trials commenced in 2010 or later, the risk ratio for achieving an mRS of 0–2 at 90 days was 1.72 (95% CI: 1.48 to 1.99; p<0.0001). The evidence presented suggests that the intervention is associated with a higher likelihood of patients being independent, as assessed using the mRS, at 90 days post acute ischaemic stroke. A high degree of heterogeneity was observed between the eight RCTs; this heterogeneity is completely eliminated by restricting the analysis to the five studies which began enroling from 2010 onwards. As noted, greater effect is observed for the intervention when the analysis is limited to these five trials (**D0005**, **D0006**, **D0011**, **D0016**).

Three trials provided data which were amenable to comparison in relation to the Barthel Index. All three reported the proportion of patients in the control and intervention groups (total = 938 patients) who achieved a score of ≥95 at 90 days; 52.2% (240/460) of patients achieved this score in the intervention groups with 30.3% (145/478) achieving it in the control arms. The risk ratio for achieving a Barthel Index of 95 or higher at 90 days was 1.70 (95% CI: 1.45 to 2.01; p<0.0001) in favour of the intervention. This evidence suggests that the intervention is associated with better outcomes in relation to activities of daily living (ADL), as measured using the Barthel Index, at 90 days, with all three studies individually demonstrating better outcomes associated with the intervention (**D0005**, **D0006**, **D0011**, **D0016**).

While six trials reported on NIHSS in different ways and at different time points, all appeared to demonstrate relatively better outcomes in the intervention groups – the significance of this is difficult to assess, however, given the heterogeneity in reporting. For example, the time of measurement of NIHSS varied between 24 hours and 7 days post procedure. Similarly, while just two trials reported on reperfusion at 24 hours, and again did so in different ways, both reported markedly improved rates of reperfusion in the intervention versus the control groups (**D0005**, **D0006**, **D0011**, **D0016**).

Restoration of cerebral blood flow on final angiography, as assessed using the modified thrombolysis in cerebral infarction (mTICI) score, was only reported in the intervention groups as catheter angiography is not standard of care for patients administered IV tPA alone. Scores varied markedly across the seven trials for which data were presented and, while there are valid reasons for this variability, it is difficult to arrive at any firm conclusions in relation to this outcome measure (**D0006**).

Three trials reported health-related quality of life, as measured using the EuroQol Group – 5 Dimension Self-Report Questionnaire (EQ-5D); the results from all three are consistent in suggesting that mechanical thrombectomy has a positive effect on this outcome measure (**D0012**). No data were presented on disease-specific quality of life (**D0013**).

Safety

All eight RCTs reported data on SICH across a total cohort of 2,422 patients. In all, 5% (66/1,313) of patients in the intervention arm and 4.8% (53/1,109) of patients in the control arm suffered a SICH. There was no statistically significant difference between the groups (risk ratio = 1.07; 95% CI: 0.74 to 1.53; p = 0.73) suggesting that the intervention is not associated with a higher overall rate of SICH when compared with the control (**C0008**). This outcome did not change when analysis was limited to results from the five trials commenced in 2010 or later.

Seven of the eight studies reported comparable data on any cerebral haemorrhage at between 24 and 30 hours: 39.8% (450/1,132) patients in the intervention arm and 23.1% (214/928) patients in the control arm suffered a cerebral haemorrhage. The risk ratio for any cerebral haemorrhage was 1.45 (95% CI: 1.26 to 1.66; p<0.0001). The evidence suggests that the intervention is associated with a higher overall rate of any cerebral haemorrhage when compared with the control (**C0008**). This outcome did not change when analysis was limited to results from the five trials commenced in 2010 or later. However, it should be noted that the events included in the overall and subgroup analyses included types of cerebral haemorrhage which may not be clinically significant.

The proportion of the intervention group suffering a recurrent ischaemic stroke within 90 days ranged from 3.9% to 5.6% across the four trials which reported on this outcome. Three of the four trials individually reported higher rates of recurrent stroke within the intervention group, one of which was statistically significant (MR CLEAN). The pooled data from these four trials do not suggest that the intervention is associated with a higher overall rate of recurrent stroke within 90 days, when

compared with standard medical care (risk ratio = 1.97; 95% CI: 0.64 to 6.03; p = 0.24) (**C0008**). When the analysis was limited to trials which commenced in 2010 or later, there was weak evidence of mechanical thrombectomy being associated with a higher rate of recurrent stroke.

Just one of the eight RCTs specifically reported device-related events (5.1% of intervention group) [4]. Relevant data on device-related adverse events were identified in six additional studies – these reported a range from 2.8% to 13.5% of patients affected (**C0008**).

A number of questions related to 'Safety', as outlined in the final project plan, could not be addressed. In particular, the included trials did not present evidence regarding the variables which may be associated with the use of mechanical thrombectomy devices and which may impact the frequency and/or severity of harms associated with this technology (**C0008**). In addition, there were insufficient data to perform subgroup analysis which could identify patient groups more likely to be harmed by the use of mechanical thrombectomy devices, and relevant contraindications or interactions with other technologies were not identified (**C0005**). Finally, none of the trials identified potential harms that can be caused by those that undertake mechanical thrombectomy, nor were issues of potential intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns with respect to mechanical thrombectomy addressed (**C0007**).

Upcoming evidence

A number of trials were in progress or had stopped following the publication of results from trials included in this pilot assessment (Appendix 1, Table 15). We are aware of two trials which are in the process of preparing results for publication – the Endovascular Acute Stroke Intervention (EASI) trial and the Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE) trial. The Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) trial in the UK is one of 12 ongoing or suspended trials that were identified at the time of publication of this pilot assessment.

Reimbursement

Information on the reimbursement of mechanical thrombectomy devices was obtained from 13 countries which indicated inconsistent reimbursement policies ranging from no (formal) reimbursement, ad hoc reimbursement, conditional reimbursement to routine reimbursement of selected devices.

Summary table of the relative effectiveness of mechanical thrombectomy

Acute ischaemic stroke						
	Health benefit			Harm		
Outcomes	**All-cause mortality**	**mRS 0–2 at 90 days**	**Barthel Index ≥95 at 90 days**	**SICH**	**Any cerebral haemorrhage**	**Recurrent stroke at 90 days**
Mechanical thrombectomy **Standard of care**	Risk ratio = 0.89 (95% CI: 0.73 to 1.09) Risk difference = −0.02 (95% CI: −0.05 to 0.01) (**D0001**, **D0003**) *[4, 6-9, 14-16]*	Risk ratio = 1.37 (95% CI: 1.09 to 1.73) Risk difference = 0.11 (95% CI: 0.03 to 0.20) (**D0005**, **D0006**, **D0011**, **D0016**) *[4, 6-9, 14-16]*	Risk ratio = 1.70 (95% CI: 1.45 to 2.01) Risk difference = 0.22 (95% CI: 0.14 to 0.30) (**D0005**, **D0006**, **D0011**, **D0016**) *[6, 8, 9]*	Risk ratio = 1.07 (95% CI: 0.74 to 1.53) Risk difference = −0.002 (95% CI: −0.018 to 0.014) (**C0008**) *[4, 6-9, 14-16]*	Risk ratio = 1.45 (95% CI: 1.26 to 1.66) Risk difference = 0.10 (95% CI: 0.01 to 0.19) (**C0008**) *[4, 6-9, 14, 15]*	Risk ratio = 1.97 (95% CI: 0.64 to 6.03) Risk difference = 0.02 (−95% CI: 0.01 to 0.05) (**C0008**) *[6, 8, 9, 15]*
Quality of body of evidence*	*Moderate*	*Low*‡	*Moderate*	*Moderate*	*Low*	*Low*

Abbreviations: CI, confidence interval' mRS, Modified Rankin scale; SICH, symptomatic intracerebral haemorrhage.

*GRADE System used to assess the quality of the pooled evidence. High = we are very confident that the true effect lies close to that of the estimate of the effect; Moderate = we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low = our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

‡ If analysis was confined to studies that commenced after 2010, the evidence would be deemed moderate.

Discussion

The results of this pilot assessment suggest that, compared with standard medical care, mechanical thrombectomy is associated with improvements in mRS at 90 days and other endpoints linked to morbidity, function and generic quality of life. The intervention is not associated with an increased risk of all-cause mortality at 90 days or SICH when compared with standard medical therapy alone. Based on a subgroup analysis of three of the four trials reporting data for recurrent ischaemic stroke, there is weak evidence that mechanical thrombectomy is associated with a higher overall rate of recurrent ischaemic stroke within 90 days.

These results must be interpreted in light of a range of important factors associated with the eight trials from which they came. Variability was seen across the studies with respect to the types of devices used (second-generation stent retriever technology versus first-generation devices), the use or non-use of non-invasive arterial imaging in patient selection, the proportion of patients assigned to the intervention who had already received IV tPA, and the proportion of patients assigned to the intervention who actually received mechanical thrombectomy. In particular, concern has been raised about combining results from the earliest three trials (MR RESCUE, IMS III, SYNTHESIS Expansion) with the five later trials in meta-analysis, as it is widely acknowledged that there were major methodological differences between these trials, not least of which is that different types of devices were employed. This concern has been taken into account in this assessment, with subgroup analysis of the five trials (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE) that commenced from 2010 onwards performed. When limited to a subgroup analysis of these five trials, an enhanced effect in favour of the intervention was observed with respect to the primary outcome, mRS at 90 days.

Time to treatment is regularly highlighted as a key factor in determining outcomes post intervention for acute ischaemic stroke. The results presented here must also be considered with respect to the centres in which these trials took place, and it remains to be seen whether the stroke management systems in place in these institutions can be replicated in other units.

The final project plan for this assessment identified 15 CE-marked devices which were potentially evaluable within the scope of the assessment. While two of the trials included a number of 'other' non-named devices, it can be surmised that the majority of the evidence presented here relates to just five devices (Merci Retriever; Penumbra System®; Solitaire™ FR; Solitaire™ 2; Trevo®) and the applicability of the results to other devices is uncertain. It is noted that stent retriever technology was used in all, or the majority of cases, in the five latest trials; again, the applicability of the results presented to other devices is uncertain. In addition, the mean or median time to endovascular intervention in seven of the eight trials was less than 6 hours; the applicability of the results to patients who receive the intervention beyond this time frame is uncertain.

Five of the eight trials included in this analysis were stopped early. While the reasons for this are explained in each instance, it does affect the overall interpretation of the data presented, and it is possible that the estimated effects of mechanical thrombectomy are at risk of bias as a result. A number of other trials are ongoing, and the results of these trials could impact on the estimated relative effectiveness of mechanical thrombectomy.

Mechanical thrombectomy is not associated with an increased risk of overall mortality at 90 days, SICH or with recurrent ischaemic stroke at 90 days, when compared with standard medical therapy alone. These findings were similar, both for the analysis as a whole, and also for the subgroup analysis, which concentrated on the five most recently completed studies. This pilot analysis suggests, however, that the intervention may by associated with a higher rate of any cerebral haemorrhage. The significance of this is difficult to evaluate, however, because at least some of these

cases will not have been clinically significant. In addition, differences in reporting of device and/or procedural-related adverse events make comparability across the trials and the additional included studies difficult.

The applicability of the evidence presented will partly depend on the type of occlusion, local conditions and the ability to commence treatment within the time frames observed in the clinical trials.

Conclusion

The evidence presented in this pilot assessment suggests that mechanical thrombectomy is of benefit, in terms of morbidity and function and, perhaps, generic quality of life, in selected patients with anterior circulation acute ischaemic stroke, treated with second-generation (stent retriever) thrombectomy devices after having first received IV tPA, where appropriate. There is currently insufficient evidence to determine the applicability of this evidence to the much larger, heterogeneous cohort of patients with ischaemic stroke who are treated in the real-world setting and who may be ineligible for IV tPA, who arrive outside the time window for treatment and/or who are managed in non-specialised institutions or units.

The evidence suggests that mechanical thrombectomy is safe – with regard to all-cause mortality at 90 days, SICH and recurrent ischaemic stroke – when compared with standard medical care alone, in selected patients. There remains insufficient evidence, however, to determine the significance or otherwise of device- and/or procedure-related complications which may be associated with this intervention.

It appears that the results of the five trials published most recently have acted as a ‘watershed’ for mechanical thrombectomy, with a number of other trials having halted and an apparent sea change in attitude when compared with that which followed publication of the first three trials in 2013. Stent retriever technology was used in all, or the majority of cases, in these trials and hence the evidence presented here should not be interpreted as evidence of effect for other types of thrombectomy device. Similarly, all of these trials incorporated non-invasive arterial imaging in patient selection and, again, the evidence presented here should not be interpreted as evidence of effect outside of settings where this imaging forms part of the treatment planning process. Future studies will be helpful in better delineating subpopulations and techniques that will further enhance the delivery of optimal care for patients who experience anterior circulation acute ischaemic stroke. In the interim, careful patient selection, optimisation of time to intervention and the use of stent retriever technologies should help to ensure maximum benefit is derived for these patients.

1 SCOPE

Description	Project scope
Population	Adults aged 18 years or older with acute ischaemic stroke in the anterior and/or posterior region. ICD-10: I63 Medical Subject Headings (MeSH) term: Stroke
Intervention	Mechanical thrombectomy plus standard of care. (Mechanical thrombectomy may be used in combination 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.) Fifteen CE-marked devices will be considered in this assessment: Aspiration/suction devices • Penumbra System®/ACE™ (Penumbra 3D Separator) • SOFIA™ Distal Access Catheter • Vasco+35ASPI Stent retrievers • Acandis Aperio® Thrombectomy Device • BONnet • Catch • EmboTrap • ERIC® • MindFrame Capture™ LP System • REVIVE™ SE Thrombectomy Device • Solitaire™ 2 Revascularization Device • Trevo® ProVue™ Retrieval System • Trevo® XP ProVue™ Retrieval System • pREset, pREset® LITE Coil retrievers • Merci Retrieval System MeSH terms: Endovascular procedures; Stents; Tissue plasminogen activator; Angioplasty, Balloon; Thrombectomy
Comparison	Standard of care (which may include intravenous and/or intra-arterial thrombolysis where appropriate). Comparators have been chosen based on CE-mark-specific indications, information in published clinical guidelines for treatment of acute ischaemic stroke and EUnetHTA guidelines [17-19].
Outcomes	Effectiveness: • Primary outcomes: o mRS at 90 days o Mortality from ischaemic stroke • Secondary outcomes: o NIHSS score change at 24 hours o Barthel Index at 90 days o Reperfusion at 24 hours o Revascularisation at final angiography (mTICI score) o Health-related quality of life (EQ-5D) o All-cause mortality

Description	Project scope
	Safety: • Cerebral haemorrhage (symptomatic and asymptomatic) consistent with the European Cooperative Acute Stroke Study (ECASS) III trial definition) (symptomatic being an intracranial bleed associated with a clinical deterioration) • Perforation/dissection • Other haemorrhage • New ischaemic stroke in a different vascular territory • New ischaemic stroke in the same vascular territory • Any device-related adverse events • Any procedure-related adverse events Outcomes have been selected based on the recommendations from the clinical guidelines (ESO guidelines) and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety [19, 20].
Study design	Effectiveness: • Primary studies o RCTs Safety: • RCTs • Prospective clinical studies • Medical device adverse event registers • Postmarketing surveillance data on device-related adverse events

1.1 Deviations from project plan

The following deviations from the final version of the project plan were made:

1. In contrast to the project plan, the primary effectiveness outcome 'NIHSS score change at 24 hours' was amended to 'NIHSS score at 24 hours' because studies provided mean or median scores for the cohorts as a whole, rather than supplying individual patient information regarding how NIHSS scores changed between pre- and post-procedure.
2. Reperfusion at 24 hours and revascularisation at final angiography were assessed under the one heading – 'Reperfusion at 24 hours and/or revascularisation at final angiography'.
3. 'Cerebral haemorrhage (symptomatic and asymptomatic) consistent with the ECASS III trial definition (symptomatic being an intracranial bleed associated with a clinical deterioration)' was separated out into 'SICH (consistent with the ECASS III trial definition) (symptomatic being an intracranial bleed associated with a clinical deterioration)' and 'Any intracerebral haemorrhage (symptomatic or asymptomatic) (consistent with the ECASS III trial definition)'.
4. 'New ischaemic stroke in a different vascular territory' and 'New ischaemic stroke in the same vascular territory' were replaced by 'Recurrent stroke within 90 days'.
5. 'Any device-related adverse events' and 'Any procedure-related adverse events' were combined into 'Any device- or procedure-related adverse events'.

2 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

2.1 Research questions

Element ID	Research question
B0001	What are mechanical thrombectomy devices and what are the comparators?
B0002	What are the claimed benefits of mechanical thrombectomy devices in relation to the comparators?
B0004	Who undertakes mechanical thrombectomy and its comparator technologies and in what context and level of care are these technologies provided?
B0008	What kind of special premises are needed to provide percutaneous mechanical thrombectomy and its comparator(s)?
B0009	What supplies are needed to undertake mechanical thrombectomy and the comparators?
B0010	What kind of data and/or registry is/are needed to monitor the use of mechanical thrombectomy devices?

2.2 Results

B0001 – What are mechanical thrombectomy devices and what are the comparators?

Endovascular treatment with mechanical thrombectomy administered within 6–12 hours of stroke onset has been suggested as an effective and safe adjunct to usual care in patients with acute ischaemic stroke caused by a proximal intracranial arterial occlusion. The efficacy and safety of mechanical thrombectomy are discussed in detail in Sections 4 and 5 of this report [4, 6-9].

Several endovascular techniques and products have been used over the years to re-canalise blocked vessels. Techniques and devices used have included the injection of saline or pharmacological agents into the clot and the use of various types of devices to try to disrupt, catch or aspirate the clot from the patient's bloodstream. The earlier techniques and the first generation of mechanical thrombectomy devices failed to show significant efficacy. The appearance of second-generation devices (e.g. 'stent retrievers') appears to have been associated with significantly improved outcomes.The clinical impact was illustrated in several trials comparing first-generation and second-generation devices and showing a higher efficacy in the latter, in terms of both recanalisation and clinical outcome [1].

Table 1 provides an overview of the different types of mechanical thrombectomy devices, including their similarities and differences. The three types of mechanical thrombectomy devices use the same endovascular access for the procedure. The different mechanisms of action of these three types of devices are also shown in Table 1.

Table 2 provides the basic features of the mechanical thrombectomy devices and the information listed is that which was collected from manufacturers in the assessment process.

Table 1: Overview of thrombectomy devices

Device type	Mechanism of action	Similarities	Differences
Aspiration devices	Suction thrombectomy devices employ vacuum aspiration to remove occlusive clots. These are effectively like access catheters but are developed to be flexible enough to navigate to the site of the clot while having a sufficiently large inner diameter to aspirate the clot within.	Same endovascular access for the procedure	Device is like a distal access or intermediate access catheter, sucks the clot inside
Stent retrievers (second-generation mechanical thrombectomy devices)	The stent retrievers are self-expanding stents that are deployed in the occluded vessel within the thrombus, pushing it aside and entangling it within the stent struts. The stent and thrombus are then withdrawn back into the delivery catheter.		Device works by enmeshing the clot inside the basket
Coil retrievers (first-generation mechanical thrombectomy devices)	The coil retrievers are composed of Nitinol shape-memory wire and delivered through a microcatheter across the target clot. As the device is extruded from the delivery catheter, it immediately reassumes its native coil form. The neurointerventionist deploys the loops of the coil through the clot to engage the thrombus, and then pulls both coil and clot back into the catheter.		Device works like pulling a cork from a bottle

Source: [21]

Focusing on the European context and according to the consensus statements of the ESO, in collaboration with the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) [18]:

- 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 (Grade A, Level 1a, Karolinska Stroke Update [KSU] Grade A).
- Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A).
- Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A).
- For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A).
- Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C).
- If intravenous thrombolysis is contraindicated (e.g. warfarin-treated with therapeutic international normalised ratio [INR]), mechanical thrombectomy is recommended as first-line treatment in large-vessel occlusions (Grade A, Level 1a, KSU Grade A).
- Patients with acute basilar artery occlusion should be evaluated in centres with multimodal imaging and treated with mechanical thrombectomy in addition to intravenous thrombolysis when indicated (Grade B, Level 2a, KSU Grade C); alternatively they may be treated within an RCT for thrombectomy approved by the local ethical committee.

The comparator is standard of care as defined in clinical guidelines; this may include intravenous and/ or intra-arterial thrombolysis where appropriate. In order for the administration of tPA to be effective and most beneficial, it must be administered within 4.5 hours after onset of stroke symptoms [2].

B0002 – What are the claimed benefits of mechanical thrombectomy devices in relation to the comparators?

The aim of this technology is to retrieve thombi and rapidly restore blood flow in patients with acute ischaemic stroke secondary to intracranial occlusive vessel disease. It may be used with aspiration and with the injection or infusion of contrast media and other fluids [1].

Although tPA remains the standard medical treatment for acute stroke today under the conditions given by the guidelines, it has been shown, however, to have modest clinical efficacy in patients with who suffer severe strokes [3]. Compared with tPA, mechanical thrombectomy has the following claimed benefits:

- The window of treatment for the neurothrombectomy devices is much longer than tPA treatment, extending up to 12 hours after the onset of stroke symptoms [8]. In contrast, in order to provide most effect and benefit, tPA should be administered within 4.5 hours of symptom onset [4].
- In addition, IV tPA has multiple constraints, including unresponsiveness of large thrombi to rapid enzymatic digestion, a narrow time window for administration, and the risk of cerebral and systemic haemorrhage.

Among patients with occlusions of the intracranial ICA or the first segment of the MCA (or both), IV tPA resulted in early reperfusion in only 13–50% of patients [4]. Endovascular treatment vis-a-vis mechanical thrombectomy has therefore emerged over the past decade as a potential primary treatment option for patients with acute ischaemic stroke.

B0004 – Who undertakes mechanical thrombectomy and its comparator technologies and in what context and level of care are these technologies provided?

While there are no specific recommendations in the guidelines, the decision to undertake mechanical thrombectomy, and so to initiate the use of the technology, should be made jointly by a multidisciplinary team comprising at least a stroke physician and a neurointerventionalist. It should be performed in experienced centres providing comprehensive stroke care and expertise in neuroanaesthesiology [22].

For the comparators, in order to increase the use of IV tPA, acute stroke care has to integrate Emergency Medical Services (EMS), Emergency Department (ED) staff and stroke care specialists. Communication and collaboration between EMS, ED staff, radiologists, clinical laboratories and neurologists are important for rapid delivery of treatment [20].

B0008 – What kind of special premises are needed to provide percutaneous mechanical thrombectomy and its comparator(s)?

According to ESO recommendations, imaging techniques for determining infarct and penumbra sizes can be used for patient selection and correlate with functional outcome after mechanical thrombectomy (Grade B, Level 1b, KSU Grade B) – new [18], intracerebral vessel occlusion must be diagnosed with non-invasive imaging whenever possible before considering treatment with mechanical thrombectomy .

During the procedure, continuous imaging is needed to perform the procedure and to assess re-canalisation .

The availability of appropriate facilities for postoperative care should be ensured. However, this should not delay the start of intervention. If necessary, alternative facilities can be sought whilst the procedure is performed. Patients who have received general anaesthesia should be managed postoperatively in a neurointensive care unit or high-dependency care/stroke unit to continue invasive monitoring and neurological monitoring [22].

For the comparators, in order for the administration of tPA to be effective and most beneficial, it must be administered within 4.5 hours after the onset of stroke symptoms [2]. Imaging of the brain and supplying vessels is crucial in the assessment of patients with stroke and transient ischaemic attack. Brain imaging distinguishes ischaemic stroke from intracranial haemorrhage and other conditions, and is used to identify those patients who are suitable for the administration of tPA [20].

B0009 – What supplies are needed to undertake mechanical thrombectomy and the comparators?

For this procedure, different access catheter combinations are needed [23], such as balloon guide catheters, regular guide catheters, or a combination of a long-sheath or guide catheter plus a flexible distal access catheter, sometimes also called intermediate catheter. In addition, there is a requirement for a microcatheter through which the stent retriever is delivered. Additional supplies include contrast media, saline and syringes and an infusion line.

IV tPA is administered as an intravenous bolus followed by a short intravenous infusion. Other than saline, syringes and an infusion line, there are no specific supplies required.

B0010 – What kind of data and/or registry is/are needed to monitor the use of mechanical thrombectomy devices?

Long-term monitoring in registries is required to assess patient data for benefits and harms related to the use of mechanical thrombectomy devices. Population-based registries (stroke registry) to monitor thrombectomy in an unbiased way generate real-life, long-term data on clinical outcomes as well as costs.

An example of such a registry is the Safe Implementation of Treatments in Stroke (SITS)-Global Stroke Network . SITS is an academic-driven, non-profit international collaboration in Sweden, which was initiated by the medical profession to accelerate clinical trials and to certify excellence in acute and secondary prevention stroke treatment . The positive outcomes of ESCAPE, EXTEND IA and SWIFT PRIME, in addition to the earlier results from MR CLEAN, seem to inspire accelerated recruitment to SITS Open and the registry SITS TBY (SITS Mechanical Thrombectomy). Several centres, previously participating in one of these trials, have now contacted SITS to join SITS Open, a direct comparison between mechanical thrombectomy and a concurrent control of medical management alone. Since SITS Open is not randomised, with blinded and central outcome evaluation and with final propensity score matching between active and control, it will be possible to increase the numbers in trials without ethical concerns [25] .

Other examples for established stroke registries are the South London Stroke Register [26], the Erlangen Stroke Registry (ESPro) [27, 28] and the Dijon Stroke Registry [29].

Table 2: Features of the intervention

	Technology				
Device type	Aspiration catheter	Stent retriever	Stent retriever	Stent retriever	Stent retriever
Proprietary name	SOFIA™ Aspiration Catheter, SOFIA™ PLUS	Trevo® (XP) ProVue™ Retriever	EmboTrap® Revascularization Device	ERIC® Retrieval Device	REVIVE™ Self Expanding (SE) Thrombectomy Device
Manufacturer	MicroVention Europe	Concentric Medical, Inc., USA	Neuravi Ltd.	MicroVention Europe	Medos International SÀRL
Reference codes	DA5115ST, DA5125ST, DA6115ST, DA6125ST, DA6131ST, DA6135ST	Trevo® ProVue™: 90184; Trevo® XP ProVue™ Retriever 6x25mm: 90186; Trevo® XP ProVue™ Retriever 4x20mm: 90182; Trevo® XP ProVue™ Retriever 3x20mm: 90183.	ET-007	ER173015, ER173020, ER174024, ER174030, ER176044	FRS 214522-99
Class/GMDN code	CT1582 – Vascular infusion/aspiration catheters	Class EU = III GMDN code : 58173	58173, Embolectomy/ thrombectomy suction catheter	CT2141 – Embolectomy/ thrombectomy systems	EU class III/ GMDN code 58173
	Technology				
Device type	Stent retriever	Stent retriever	Stent retriever	Stent retriever	
Proprietary name	Solitaire™ 2 Revascularization Device	MindFrame Capture™ LP	pREset, pREset LT	Aperio® Thrombectomy Device	
Manufacturer	Medtronic	Medtronic	Phenox GmbH	Acandis GmbH. & Co. KG	
Reference codes	SRD2-4-15 SRD2-4-20 SRD2-6-20 SRD2-6-30	300010, 10 Capture 3 LP 300011, 10 Capture 3 LP Short 300012, 10 Capture 4 LP 300013, 10 Capture 4 LP Short 300014, 10 Capture 5 LP	pREset: PRE-4-20, PRE-6-30 pREset® LITE: PRE-LT-3-20 PRE-LT-4-20	01-000700, 01-000701, 01-000702, 01-000703	
Class/GMDN code	58'173, Embolectomy/ thrombectomy suction catheter Class lll, Rule 7	58'173, Embolectomy/ thrombectomy suction catheter Class lll, Rule 7	N/A	III/10714	

Source: [30-36]

2.3 Discussion

Endovascular therapy using mechanical thrombectomy devices is indicated for the treatment of acute ischaemic stroke caused by a proximal intracranial arterial 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), stent retrievers (second-generation devices) 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. Mechanical thrombectomy is used in conjunction with intravenous and or intra-arterial thrombolysis (where appropriate) and as an alternative to standard care (including intravenous and or intra-arterial thrombolysis, where appropriate). Proposed benefits of mechanical thrombectomy include extension of the treatment window (from 4.5 hours up to 6–12 hours) and improved revascularisation compared with standard of care alone [4, 6-9].

Of 15 CE-marked mechanical thrombectomy devices, five have also been approved by the Food and Drug Administration (FDA), including MindFrame Capture™ LP System, Solitaire™ 2 Revascularization Device, Trevo® Retrieval System AND Merci Retrieval System, SOFIA™ Aspiration Catheter, SOFIA™ PLUS.

The results of five recent RCTs focusing on endovascular therapy using mechanical thrombectomy devices are highly promising, but methodological heterogeneity (e.g. patient populations, imaging-selection strategies, and treatment alacrity) of these studies affects the comparability of efficacy and safety results. Long-term monitoring in registries is required to assess patient data for benefits and harms related to the use of mechanical thrombectomy devices. Population-based registries (stroke registries) have the potential to monitor the use of mechanical thrombectomy in an unbiased way, and may provide additional information regarding appropriate selection of participants and data reporting, while also generating real-life, long-term data on clinical outcomes and costs.

3 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

3.1 Research questions

Element ID	Research question
A0002	What is the health condition in the scope of this assessment?
A0003	What are the known risk factors for developing an acute ischaemic stroke?
A0004	What is the natural course of acute ischaemic stroke?
A0005	What are the symptoms and the burden of acute ischaemic stroke for the patient?
A0006	What are the consequences of acute ischaemic stroke for society?
A0007	What is the target population in this assessment?
A0011	To what extent is mechanical thrombectomy currently used?
A0020	For which indications have the mechanical thrombectomy devices received marketing authorisation or CE marking?
A0021	What is the reimbursement status of mechanical thrombectomy devices?
A0023	How many people belong to the target population?
A0024	How is acute ischaemic stroke currently diagnosed according to published guidelines?
A0025	How is acute ischaemic stroke currently managed according to published guidelines?

3.2 Results

A0002 – What is the health condition in the scope of this assessment?

Ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. The blockage results in an insufficient amount of blood being delivered to that portion of the brain. This can lead to deterioration in function which, if not addressed in a timely manner, will be irreversible [10].

The underlying condition resulting in this type of obstruction is the development of fatty deposits lining the vessel walls. These fatty deposits can cause two types of obstruction [10]:

- **Cerebral thrombosis** refers to a thrombus (blood clot) that develops at the clogged part of the vessel. Cerebral thrombosis can be divided into an additional two categories that correlate with the location of the blockage within the brain:
    - Large-vessel thrombosis is the term used when the blockage is in one of the brain's larger blood-supplying arteries, such as the carotid or middle cerebral artery.
    - Small-vessel thrombosis involves one (or more) of the brain's smaller, and deeper, penetrating arteries.

- **Cerebral embolism** generally refers to a blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck. A portion of the blood clot breaks loose, enters the bloodstream and travels through the brain's blood vessels until it reaches vessels too small to let it pass. A second important cause of embolism is an irregular heartbeat, known as atrial fibrillation; it creates conditions in which clots can form in the heart, dislodge and travel to the brain.

Acute stroke is the one of the leading causes of morbidity and mortality worldwide [37]. After cardiovascular disease and cancer, stroke ranks as the third most common cause of death in industrialised countries. For the relevant International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes, see Appendix 3: ICD-10-CM Diagnosis Codes.

A0003 – What are the known risk factors for developing an acute ischaemic stroke?

A large case-control study of stroke has identified 10 risk factors that explain approximately 90% of the population-attributable risk, with hypertension being the most important risk factor [38]. Other significant risk factors which contribute to the risk of stroke include lipid levels, physical inactivity, smoking, and diet. In addition, larger waist-to-hip ratios, a history of diabetes, increased alcohol intake, psychosocial stress and/or depression, and cardiac morbidity all contribute to stroke [11].

A0004 – What is the natural course of acute ischaemic stroke?

Stroke can affect people physically, mentally, emotionally, socially or a combination of the four. The consequences of stroke vary widely depending on size and location of the lesion [39]. Dysfunctions correspond to areas in the brain that have been damaged. Disability affects 75% of stroke survivors enough to decrease their employability [40].

Some of the physical disabilities that can result from stroke include muscle weakness, numbness, pressure sores, pneumonia, incontinence, apraxia (inability to perform learned movements), difficulties carrying out ADL, appetite loss, speech loss, vision loss and pain. If the stroke is severe enough, or in a certain location, such as parts of the brainstem, coma or death can result [24].

Emotional problems following a stroke can be due to direct damage to emotional centres in the brain or from frustration and difficulty adapting to the new limitations. Post-stroke emotional difficulties include anxiety, panic attacks, depression, flat affect (failure to express emotions), mania, apathy and psychosis. Other difficulties may include a decreased ability to communicate emotions through facial expression, body language and voice [41].

Cognitive deficits resulting from stroke include perceptual disorders, aphasia [42], dementia [43], and problems with attention [44], and memory [45]. A stroke sufferer may be unaware of his or her own disabilities, a condition called anosognosia. In a condition called hemispatial neglect, the affected person is unable to attend to anything on the side opposite to the brain hemisphere that is damaged. Cognitive and psychological outcome after a stroke can be affected by the age at which the stroke occurs, prestroke baseline intellectual functioning, psychiatric history and whether there is pre-existing brain pathology [46]. Up to 10% of people following a stroke develop seizures, most commonly in the week subsequent to the event; the severity of the stroke is linked to the likelihood of seizure, with more severe strokes associated with an increased incidence of seizure [47-49].

A0005 – What are the symptoms and the burden of acute ischaemic stroke for the patient?

Symptoms

The main stroke symptoms can be summarised with the word FAST: Face–Arms–Speech–Time [50, 51].

- **Face** – the face may have dropped on one side, the person may not be able to smile or their mouth or eye may have drooped.
- **Arms** – the person with suspected stroke may not be able to lift both arms and keep them there because of arm weakness or numbness in one arm.
- **Speech** – the speech may be slurred or garbled, or the person may not be able to talk at all despite appearing to be awake.
- **Time** – it is time to dial emergency number immediately.

Symptoms in the FAST test identify most strokes, but a stroke can also cause different symptoms. Other symptoms and signs may include:

- Complete paralysis of one side of the body
- Sudden loss or blurring of vision
- Dizziness
- Confusion
- Difficulty understanding what others are saying
- Problems with balance and co-ordination
- Difficulty swallowing (dysphagia)
- A sudden and very severe headache resulting in a blinding pain unlike anything experienced before
- Loss of consciousness.

Global burden of stroke

The WHO predicts that disability-adjusted life years (DALYs, a measure of the burden of disease) lost to stroke will rise from 38 million in 1990 to 61 million in 2020 [12].

Overall, in 2010, there were an estimated 16.9 million cases of stroke worldwide (69% in low- and middle-income countries, 31% in high-income countries); there was an estimated prevalence of 33.0 million stroke cases (52% in low- and middle-income countries, 48% in high-income countries), an estimated 5.9 million stroke deaths (71% in low- and middle-income countries, 29% in high-income countries), and 102.2 million DALYs lost (78% in low- and middle-income countries, 22% in high-income countries) [52].

A0006 – What are the consequences of acute ischaemic stroke for society?

Stroke is a significant public health concern because of its high morbidity and the disability it causes. Although associated mortality has decreased, stroke remains important because of demographic change. It is the most important cause of morbidity and long-term disability in Europe and imposes an enormous economic burden. More patients survive stroke today than in the past, but a large proportion of them will be disabled for the rest of their lives [25].

Comprehensive estimates for 30 European countries indicate total annual costs of stroke at EUR 64.1 billion for 2010 [53].

A German lifetime cost of ischaemic stroke study showed that the number of stroke patients and the healthcare costs of strokes in Germany will rise continuously until the year 2025 [28, 54]. National projections for the period from 2006 to 2025 showed 1.5 million and 1.9 million new cases of ischaemic stroke in men and women, respectively, at a present cost of EUR 51.5 and 57.1 billion, respectively. It is estimated that there will be 200 patients in every 100,000 population until 2025. Rehabilitation has been estimated to account for 37% of overall cost per first-year survivor, and in subsequent years outpatient care is the major cost driver.

A0007 – What is the target population in this assessment?

As Table 3 shows, most CE-marked mechanical thrombectomy devices are designed to restore blood flow in patients experiencing acute ischaemic stroke due to large intracranial vessel occlusion. Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment. Devices approved by the FDA are indicated for use within 8 hours of symptom onset in patients experiencing acute ischaemic stroke.

Common contraindications are for patients with a known hypersensitivity or allergy, and where the vessel diameter is not within the recommended vessel diameter range. This information was collected from manufacturers via submission files.

A0011 – To what extent is mechanical thrombectomy currently used?

Several manufacturers have provided information regarding the number of mechanical thrombectomy devices that have been released for use in clinical procedures in the European Union (EU) to date via the submission files, but have asked for this information to be treated as confidential.

A0020 – For which indications have the mechanical thrombectomy devices received marketing authorisation or CE marking?

Table 3: Description of indications and contraindications of each authorised mechanical thrombectomy device

Proprietary name	Institution issuing approval	Indications	Contraindications
Aperio® Thrombectomy Device	DQS Medizin-produkte GmbH	The Aperio® Thrombectomy Device is intended for restoration of the arterial flow in patients diagnosed with ischaemic stroke due to large intracranial vascular occlusion (i.e. in the ICA, M1 and M2 segments of the MCA). Patients who fail intravenous thrombolytic therapy or who are ineligible for thrombolysis may be suitable for treatment with the Aperio® Thrombectomy Device.	• For occlusions in vessels with a diameter not within the recommended vessel diameter range (see label). • For patients with anatomic conditions or vessel pathologies (i.e. stenosis proximal to the occlusion to be treated) that may preclude a safe thrombus removal. • For calcified lesions which cannot be removed by percutaneous transluminal angioplasty. • In cases of recent, non-lysed, non-organized thrombotic or embolic material.
EmboTrap® Revascularization Device	BSI (Federal Office for Information Security)	The EmboTrap® Revascularization Device (the Device) is intended to be used to restore blood flow in patients experiencing an acute ischaemic stroke due to a large-vessel neurovascular occlusion. The Device is designed for use in the anterior and posterior neurovasculature in vessels of diameter 1.5–5 mm, such as the ICA, the M1 and M2 segments of the MCA, the A1 and A2 segments of the anterior cerebral artery, the basilar, the posterior cerebral and the vertebral arteries. The Device should only be used by physicians trained in neurointerventional catheterisation and the treatment of ischaemic stroke.	• Allergy or hypersensitivity to nickel–titanium. • Excessive vessel tortuosity that may prevent device delivery.
ERIC® Retrieval Device	DQS Medizin-produkte GmbH	The ERIC® Retrieval Device is intended for use in the revascularization of acute ischaemic stroke caused by the intracranial occlusive vessels of patients who are not eligible for IV tPA or who fail IV tPA therapy.	• Patients with known hypersensitivity to nickel–titanium. • Patients with stenosis proximal to the thrombus site that may prevent safe recovery of the ERIC® Retrieval Device. • Patients with angiographic evidence of carotid dissection.
MindFrame Capture™ LP Revascularization Device	FDA	The Capture™ LP Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischaemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment.	• Patients with known sensitivity to nickel–titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the MindFrame Capture™ Device • Patients with angiographic evidence of carotid dissection.
	DQS Medizin-produkte GmbH	The MindFrame Capture™ LP is indicated for temporary use to restore blood flow in the cerebral vasculature of patients suffering from an acute ischaemic stroke. The MindFrame Capture™ LP is positioned across the embolus or blood clot and is used to facilitate the restoration of blood flow and removal of the clot obstruction.	• Delivery of pharmacological agents not routinely used to treat ischaemic stroke. • Patient presents with nickel allergy. • Patients with suspected or known allergies to contrast media. • Pregnancy. • Glucose <50 mg/dL. • Excessive vessel tortuosity that prevents the placement of the device. • Known haemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy with INR >3.0.

Proprietary name	Institution issuing approval	Indications	Contraindications
		The MindFrame Capture™ LP is indicated for: • Endovascular temporary use in patients with acute ischaemic stroke. • Endovascular temporary use to restore blood flow in patients who are experiencing symptoms of an acute ischaemic stroke caused by an embolus in a cerebral vessel.	• Patient received heparin within 48 hours with a PTT greater than 2 times the lab normal. • Patient has baseline platelets <30,000. • Evidence of rapidly improving neurological signs of stroke. • Coma. • Pre-existing neurological or psychiatric disease. • Patient has severe sustained hypertension. • CT/MRI scan reveals significant mass effect with midline shift. • Patient's angiogram shows an arterial stenosis >50% proximal to the embolus.
pREset LT Device	DQS Medizin-produkte GmbH	The pREset (LT) Thrombectomy Stent is designed for mechanical clot retrieval from intracranial arteries as acute ischaemic stroke treatment • For patients who are ineligible for intravenous thrombolysis or • For patients who failed thrombolysis therapy and • As a supplement treatment of initiated thrombolysis therapy.	There are no known contraindications.
REVIVE™ Self Expanding (SE) Thrombectomy Device	BSI (Federal Office for Information Security)	The REVIVE™ SE Thrombectomy Device is intended to restore blood flow in patients with acute ischaemic stroke secondary to intracranial occlusive vessel disease by providing temporary bypass across the occlusion and/or by the non-surgical removal of emboli and thrombi. It may be used with aspiration and with the injection or infusion of contrast media and other fluids.	• Blood vessel with extreme tortuosity or other conditions preventing the access of the device. • Patients with a known hypersensitivity or allergy to nitinol. • Reference vessel diameter less than 1.5 mm.
SOFIA™ Aspiration Catheter, SOFIA™ PLUS	DQS Medizin-produkte GmbH	The SOFIA™ Catheter is indicated for general intravascular use, including the neuro- and peripheral vasculature. The SOFIA™ Catheter can be used to facil-itate introduction of diagnostic or therapeutic agents. The SOFIA™ Catheter is not intended for use in coronary arteries. Moreover, the SOFIA™ Catheter is intended for use in removal/aspiration of emboli and thrombi from selected blood vessels in the arterial system, including the peripheral and neurovasculatures.	There are no known contraindications.

Proprietary name	Institution issuing approval	Indications	Contraindications
Solitaire™ 2 Revascularization Device	TGA (Therapeutic Goods Administration)	The Solitaire™ 2 Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischaemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment.	• Patients with known sensitivity to nickel–titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the Solitaire™ 2 Revascularization Device • Patients with angiographic evidence of carotid dissection.
	DQS Medizinprodukte GmbH	The Solitaire™ 2 Revascularization Device is designed for use in the flow restoration of patients with ischemic stroke due to large intracranial vessel occlusion. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The Solitaire™ 2 Revascularization Device should only be used by physicians trained in interventional neuroradiology and treatment of ischemic stroke.	The same as above.
	Ministry of Health, Labour and Welfare (MHLW) Japan	The Solitaire™ 2 Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischaemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment.	• Patients with known sensitivity to nickel–titanium, radiographic contrast agents or nickel–chromium. • Arterial tortuosity that would prevent the Solitaire™ 2 Revascularization Device from reaching the target vessel. • Patients with angiographic evidence of carotid dissection, occlusion or vasculitis of whole carotid artery. • Patient with highly suspected cerebral bleeding as follows: 1. CT or MRI evidence of haemorrhage on presentation. 2. CT or MRI showing marked compression observation such as median-line excursion. 3. CT showing hypodensity or MRI showing hyperintensity involving more than one-third of the MCA territory (or in other territories, >100 mL of tissue) on presentation. 4. Uncontrolled hypertension defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg. 5. Bleeding diathesis, such as cranial tumour. 6. Anticoagulated patient with PT/INR >3.0 or APTT elevated. 7. Platelet count <30,000/mm^3.
	FDA	The same as above.	The same as that described for TGA.

Proprietary name	Institution issuing approval	Indications	Contraindications
Trevo® ProVue™ Retrieval System; Trevo® XP ProVue™ Retrieval System	LNE (Laboratoire national de métrologie et d'essais), FDA, TGA	The Trevo® Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischaemic stroke within 8 hours of symptom onset. Patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment.	There are no known contraindications.
	MHLW Japan	The same as above.	• Known serious allergy for nickel–titanium alloy, platinum-iridium alloy and stainless Steel. • Known haemorrhagic diathesis. • Known coagulation factor deficiency. • Oral anticoagulant therapy with INR >3.0. • Platelets <30,000 mm^3. • Uncontrolled and sustained severe hypertension (systolic blood pressure >185 mmHg or diastolic blood pressure > 110 mmHg). • CT or MRI shows significant mass effect with midline shift. • History of severe allergy (more than a rash) to contrast media. • Patients who have arterial tortuosity to prevent device delivery to target vessel. • Following patients who will have highly possible intracranial haemorrhage. 1. CT/MRI evidence of haemorrhage 2. CT showing hypodensity or MRI showing hyperintensity involving more than one-third of MCA territory. For non-MCA territory, CT showing hypodensity or MRI showing hyperintensity involving >100 mL of tissue.

APTT, activated partial thromboplastin time; CT, computed tomography; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time.

Source: [30-36]

For more details see Appendix, Table 6.

A0021 – What is the reimbursement status of mechanical thrombectomy devices?

The reimbursement information of mechanical thrombectomy devices has been provided by EUnetHTA JA2 WP5 Strand B members for some European countries, and can be found in Table 4.

Table 4: Reimbursement status

Country	Reimbursement status	Other relevant information
Austria	Ongoing	The products and related intervention are partially covered by the LKF (Leistungsorientierte Krankenanstaltenfinanzierung) reimbursement system. As they are innovative products/an innovative benefit, they are treated similar to a comparable *previous* intervention and are, therefore, temporarily represented in the MEL (Medizinische Einzelleistung) catalogue of benefits (the related code begins with an XN, indicating the preliminary nature; the relevant code would be XN070 'Percutaneous transluminal thrombectomy of intracranial vessels'). As soon as better evidence is available, the intervention/benefit is transferred to a normal code and the reimbursement is newly calculated.
Czech Republic	Yes	• Penumbra System®/ACE™ (Penumbra 3D Separator) • Acandis Aperio® Thrombectomy Device • BONnet • Catch • ERIC® • REVIVE™ SE Thrombectomy Device • Trevo® ProVue™ Retrieval System • Trevo® XP ProVue™ Retrieval System • pREset, pREset® LITE • Merci Retrieval System
	No	• SOFIA™ Distal Access Catheter • Vasco+35ASPI • EmboTrap • MindFrame Capture™ LP System • Solitaire™ 2 Revascularization Device
Germany	Yes	For the 'Percutaneous transluminal removal of foreign bodies and thrombectomy in intracranial vessels using a microwire retriever system', Germany has provided an additional reimbursement since 2010 (amount of money additional to the *usual* stroke treatment reimbursement). Currently, this additional amount is EUR 1,750.27 per system (it doubles when two systems are used); see e.g.: http://www.ukaachen.de/fileadmin/files/global/vorstand/4675038.pdf) Since 2015, there are two different 'Zusatzentgelte (ZE)' for mechanical thrombectomy using microcatheter (ZE133) (aspiration) or stent retrievers (ZE152)
Hungary	No	The HTA Department of the National Institute of Pharmacy and Nutrition (OGYEI) did not receive reimbursement submission in relation to the mentioned products assessed in the 6th pilot assessment.
Ireland	Yes	No formal assessment has taken place as yet to inform decisions concerning a national policy on the use of this technology. Mechanical thrombectomy is, however, currently being provided on a limited basis in a number of centres.
Italy	No	In Italy, there is a regional healthcare system, so each Italian region has its own rules of reimbursement. In particular, all regions adopt the Diagnosis Related Groups (DRG) System, but each region could consider a different fee and could consider an extra fee for a particular procedure in order to reimburse a high-cost device, for example. In the Lazio region, the DRG is '479 Other vascular procedures without complication' and the fee is EUR 4,742. To our knowledge, no regions foresee an ad hoc reimbursement for the device.
Malta	Yes	The Solitaire™ 2 Revascularization Device is currently reimbursed in Malta, which is assessed in the 6th pilot assessment ('Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke').
Netherlands	No	In the Netherlands, each individual device/retriever/etc. is not assessed, so only more general information can be provided. Intra-arterial thrombolysis is conditionally reimbursed for acute ischaemic stroke.

Country	Reimbursement status	Other relevant information
Poland	Yes	Mechanical thrombectomy devices are available in Polish specialist hospital units. Hospitals buy devices with their own funds, but the National Health Fund refunds the procedure on the basis of a positive list of procedures guaranteed in the healthcare system (thrombectomy]inter alia in acute ischaemic stroke] – procedure without specifying the device type to be used).
Scotland	No	A small number of thrombectomy procedures are currently provided on an ad hoc basis in a limited number of centres in Scotland. Reimbursement decisions as such are not made in Scotland – it is up to individual health boards to decide what to fund.
Slovenia	No	The Health Insurance Institute of Slovenia does not reimburse medical devices which are built-in to the body. They are included in regular medical services.
Spain	Yes	Mechanical thrombectomy devices are included in common services porfolio of the National Healthcare System and publicly funded.
Switzerland	Yes	In general, there is no positive list for reimbursement of devices applied in medical procedures (implants, catheters, etc.); reimbursement is regulated on the level of the procedures. Only medical products which are applied by patients themselves (such as glucose-monitoring devices) are listed in the 'Mittel- und Gegenständeliste'. Mechanical thrombectomy is occasionally performed in stroke units. As the efficacy or cost effectiveness of this procedure has never been contested, it has not been evaluated in view of an exclusion from or restriction of reimbursement. So the procedure is reimbursed under the Swiss DRG system. Hospitals are free to choose the products they use as long as they are CE marked. They choose the products based on the recommendations of the clinicians who use the products and on the prices and conditions they can negotiate with the producers.

A0023 – How many people belong to the target population?

Annually, 15 million people worldwide suffer a stroke. The incidence of stroke is declining in many developed countries, largely as a result of better control of high blood pressure, and reduced levels of smoking. However, the absolute number of strokes continues to increase because of the ageing population [12]. Stroke was the second most frequent cause of death worldwide in 2012, accounting for 6.7 million deaths (~12% of the total), the third most common cause of death in developed countries and the most common cause in upper-middle-income countries [13].

According to estimates from the WHO, the number of stroke events in EU countries, Iceland, Norway, and Switzerland is likely to increase from 1.1 million per year in 2000 to more than 1.5 million per year in 2025, solely because of the demographic changes [55].

In Europe, the incidence of stroke varies from 101.1 to 239.3 per 100,000 in men and 63.0 to 158.7 per 100,000 in women [56].

Among patients with occlusions of the intracranial ICA or the first segment of the MCA (or both), IV tPA has been demonstrated to result in early reperfusion in just 13–50% of patients [4]. It has been suggested, meanwhile, that with clear evidence supporting the procedure and improved systems, endovascular thrombectomy will be applicable in up to 10% of all patients with ischaemic stroke [57].

A0024 – How is acute ischaemic stroke currently diagnosed according to published guidelines?

The care pathway requires immediate recognition of the stroke symptoms by the patient or those in his/her environment, rapid and well-organised prehospital support and competent in-hospital treatment at the ED. According to the 2008 ESO Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack [20], emergency care of the acute stroke victims depends on a four-step chain:

1. Rapid recognition and reaction to stroke signs.
2. Immediate EMS contact and priority EMS dispatch.
3. Priority transport with prenotification to the receiving hospital.
4. Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis and administration of appropriate treatments at the receiving hospital.

The 2008 ESO Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack recommend the following emergency diagnostic tests in all acute stroke patients [20]:

1. Brain imaging: computed tomography (CT) or magnetic resonance imaging (MRI)
2. Electrocardiogram (ECG)
3. Laboratory tests:
    - Complete blood count and platelet count, prothrombin time (PT) or INR, partial thromboblastin time (PTT)
    - Serum electrolytes, blood glucose
    - C-reactive protein (CRP) or sedimentation rate
    - Hepatic and renal chemical analysis.

Additional diagnostic tests may be required as indicated and are covered by the guidelines.

However, acute stroke treatment protocols vary by hospital centre. Each EMS or hospital centre should have a validated algorithm for the diagnosis and treatment of ischaemic stroke.

The ESO/ESMINT/ESNR consensus statement [18] recommends diagnosis of intracranial vessel occlusion with non-invasive imaging before considering treatment with mechanical thrombectomy.

A0025 – How is acute ischaemic stroke currently managed according to published guidelines?

Two major societies issued guidelines on stroke management: the consensus statement issued by the ESO, the ESMINT and the ESNR in February 2015 and the guideline from American Heart Association/American Stroke Association (AHA/ASA) in June 2015 [17, 18].

A summary of the AHA/ASA guideline recommendations is also provided in Appendix 1, Table 7 [17]. The 2008 ESO Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack recommend a specific treatment algorithm. The guidelines were updated in 2009 to extend the time window for thrombolytic therapy with tPA (0.9 mg/kg body weight, maximum dose 90 mg) to within 4.5 hours after stroke onset [2]. The consensus statement issued by the ESO/ESMINT/ESNR on mechanical thrombectomy in acute ischaemic stroke [18] provides treatment recommendations, which are summarised in Appendix 1, Table 7.

3.3 Discussion

Stroke was the second most frequent cause of death worldwide in 2012, accounting for 6.7 million deaths (~12% of the total), the third most common cause of death in developed countries and the first cause in upper-middle-income countries [13]. However, among patients with occlusions of the intracranial ICA or the first segment of the MCA (or both), IV tPA results in early reperfusion in just13–50% of patients [4]. It has been suggested, meanwhile, that with clear evidence supporting the procedure and improved systems, endovascular thrombectomy will be applicable in up to 10% of all patients with ischaemic stroke [57]. In large referral centres, about 5–10% of all acute ischaemic strokes and 20–30% of recombinant tissue plasminogen activator (r-tPA)-eligible patients may be candidates for mechanical thrombectomy [8].

One of the most important challenges is focused on system reorganisation that enables thrombectomy treatment to be available to all eligible patients, irrespective of geographical location or time of day [57]. Currently, stroke centres are able to offer the optimal conditions for the use of mechanical thrombectomy devices, because they are well-equipped and have highly-trained medical staff. However, the situation is heterogeneous across Europe, because the various countries are differently organised concerning stroke care [58]. In many European countries, health systems are limited by a restricted neurointerventional workforce without round-the-clock services. There are considerable logistical challenges concerning small, scattered population centres with limitations centred on insufficient procedural volume to support an interventionist [57]. For people living in rural and sparsely populated areas, there is a need to deliver thrombectomy and a relevant interventionist. In addition, some centres cannot provide 24/7 services to ensure each individual carries out enough procedures to maintain expertise, and this should be taken into consideration in the future.

According to Tatlisumak, regional and national plans for covering whole populations with 24/7 adequate acute stroke care need to be developed, in close cooperation with professionals and decision-makers. In addition, there is a strong need for Europe-wide new training programmes for expert physicians in stroke care [58].

4 CLINICAL EFFECTIVENESS

4.1 *Domain framing*

While all of the effectiveness outcomes specified in the final project plan were considered, the initial wording of one ('NIHSS score at 24 hours') was modified in this pilot assessment (see Section 1, Scope).

4.2 Research questions and methods

Research questions

Element ID	Research question	Outcomes
D0001	What is the expected beneficial effect of mechanical thrombectomy on mortality?	Mortality
D0003	What is the effect of mechanical thrombectomy on mortality due to causes other than the target disease?	Mortality
D0005	How does mechanical thrombectomy impact the symptoms and severity of acute ischaemic stroke?	Morbidity
D0006	How does mechanical thrombectomy affect progression (or recurrence) of acute ischaemic stroke?	Morbidity
D0011	What is the effect of mechanical thrombectomy on patients' body functions?	Function
D0016	How does the use of mechanical thrombectomy affect activities of daily living?	Function
D0012	What is the effect of mechanical thrombectomy on generic health-related quality of life?	Health-related quality of life
D0013	What is the effect of mechanical thrombectomy on disease-specific quality of life?	Health-related quality of life
D0017	Was the use of mechanical thrombectomy worthwhile?	Patient satisfaction

In terms of 'mortality', we considered the following outcomes:

- Mortality due to ischaemic stroke at 90 days
- Overall mortality at 90 days.

In terms of 'morbidity and function', we considered the following outcomes:

- mRS at 90 days
- NIHSS score at 24 hours
- Barthel Index at 90 days
- Reperfusion at 24 hours and/or revascularisation at final angiography.

In terms of 'health-related quality of life', we considered the following outcomes:

- Health-related quality of life (EQ-5D).

In terms of 'patient satisfaction', we considered the following outcomes:

- Not assessed.

Sources

The following sources were used to obtain information:

- PubMed (Medline)
- Embase
- Cochrane Register of Controlled Trials
- ClinicalTrials.gov
- ICTRP
  - ISRCTN
  - EU Clinical Trials Registry
- mRCT
- Stroke Trials Registry
- Request to the manufacturer
- Health Products Regulatory Authority, Ireland

We selected relevant articles or documents according to the Population Intervention Control Outcomes Study (PICOS) design scheme described in the project plan. For the 'Clinical effectiveness' domain, only RCTs were included. A detailed description of the search strategy and selection process is given in Appendix 1, page 66.

Analysis

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.

0 No symptoms.

1 No clinically significant disability (able to carry out all usual activities, despite no symptoms).

2 Slight disability (able to look after own affairs without assistance but unable to carry out all previous activities).

3 Moderate disability (requires some help but able to walk unassisted).

4 Moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted).

5 Severe disability (requires constant nursing care and attention, bedridden, and incontinent).

6 Death.

Although inter-rater reliability has been demonstrated to vary with the use of the mRS, it remains the most prevalent functional outcome measure in contemporary stroke research [59].

Neurological deficit was measured using the NIHSS. This scale ranges from 0 to 42, and quantifies neurological deficits into 11 categories, with higher scores indicating more severe neurological deficit. The NIHSS is the most widely used scale for the assessment of neurological impairment in persons who have experienced a stroke, and has shown excellent reproducibility and inter-rater reliability [60].

The Barthel Index is used to measure the ability to perform ADL. 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. The Barthel Index has demonstrated excellent intra-observer reliability as a measure of outcome after stroke, although this has not been adequately tested in large multi-centre trials [61].

The extent of reperfusion was assessed in three studies based on comparison of pre- and post-treatment perfusion-lesion volume as measured using perfusion imaging (CT or MRI).

The EuroQol Group – 5 Dimension Self-Report Questionnaire (EQ-5D, EQ-5D-3L) examines five dimensions of health status, namely mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. Each dimension has 3 levels: no problems, slight or moderate problems; and extreme problems. More recently, the EQ-5D-5L has been developed – this contains 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The modified Treatment in Cerebral Ischaemia (also termed the modified Thrombolysis in Cerebral Infarction [mTICI]) classification is a measure of reperfusion based on CT angiography (CTA) or magnetic resonance angiography (MRA). Scores range from 0 (no flow) to 3 (normal flow)*:

Grade 0	No perfusion.
Grade 1	Antegrade perfusion beyond the occlusion, but limited distal branch filling with slow distal perfusion.
Grade 2a	Antegrade perfusion of less than half of the occluded artery ischaemic territory.
Grade 2b	Antegrade perfusion of more than half of the target artery ischaemic territory.
Grade 3	Complete antegrade perfusion of the occluded artery ischaemic territory.

* It is noted that the description of the outcome which the mTICI score is taken to represent varied across the included studies. It was variably described as being a measure of reperfusion (i.e. ESCAPE, MR CLEAN) or revascularisation (i.e. MR RESCUE, REVASCAT) or recanalisation (i.e. EXTEND-IA), with the terms often used interchangeably.

Two of the studies included in this analysis, ESCAPE and MR RESCUE, used the Thrombolysis in Cerebral Infarction Score (TICI) (as opposed to the mTICI). Scores in this also range from 0 (no perfusion) to 3 (complete perfusion):

0	No perfusion.
1	Penetration with minimal perfusion. The contrast material fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
2a	Only partial filling (less than two-thirds) of the entire vascular territory is visualised.
2b	Complete filling of all of the expected vascular territory is visualised, but the filling is slower than normal.
3	Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

The GRADE methodology was used to assess the quality of the evidence. The risk of bias was assessed using the Cochrane risk of bias tool for RCTs.

Synthesis

The research questions were answered with reference to the evidence tables included in Appendix 1, page 70. Due to the expected heterogeneity across studies in terms of devices used and time to procedure, random effects meta-analysis was used. Binary outcomes were pooled as risk ratios. Heterogeneity was assessed on the basis of I^2 values. Values in excess of 75% were interpreted as considerable heterogeneity, and values between 50% and 90% were interpreted as potentially substantial heterogeneity. If sufficient studies were available (n ≥10), assessment of small study bias using funnel plots and Egger's test was planned. Meta-analysis was performed for three outcomes: mortality at 90 days; mRS at 90 days; and Barthel Index at 90 days. A meta-analysis was not performed for mTICI at final angiography as results for this outcome were provided for the intervention group only; this and the other remaining outcomes of interest are hence presented in narrative format.

A number of important methodological differences were identified between the first three trials included in this assessment (MR RESCUE, IMS III, SYNTHESIS Expansion) and the other five as discussed in detail in Sections 4.3 (Study characteristics) and 4.4 (Discussion). In particular, these trials used older generation devices and did not use imaging in patient selection which, it has been argued, makes them less relevant to current clinical practice [62]. Therefore, a subgroup analysis including the latter five trials only, in which the majority, or all, of the devices used were stent retrievers, and in which non-invasive arterial imaging was used to guide patient selection, was performed for mortality at 90 days and mRS at 90 days.

4.3 Results

Included studies

Study characteristics

Eight RCTs with a total of 2,423 patients were included for assessment of effectiveness; a total of 1,110 patients were randomised to the control groups and 1,313 were randomised to the intervention groups (endovascular treatment) (Table 5). Please also see additional tables in Appendix 1, page 70 (Tables 6–12).

Table 5: Eight randomised controlled trials included for assessment of effectiveness

Author Year published	Trial name	Country	No. centres	Products used	Study duration
Kidwell 2013 [14]	MR RESCUE	North America	22	Merci Retriever; Penumbra System®;	2004–2011*
Broderick 2013 [15]	IMS III	USA, Canada, Australia, Europe	58	Merci Retriever; Penumbra System®; Solitaire™ FR	2006–2012
Ciccone 2013 [16]	SYNTHESIS Expansion	Italy	24	Including: Solitaire™, Penumbra System® Trevo®, Merci	2008–2012
Berkhemer 2015 [6]	MR CLEAN	Netherlands	16	Retrievable stents used in 81.5% cases	2010–2014
Campbell 2015 [7]	EXTEND IA	Australia, New Zealand	10	Solitaire™ FR	2012–2014

Author Year published	Trial name	Country	No. centres	Products used	Study duration
Jovin 2015 [9]	REVASCAT	Spain	4	Solitaire™ FR	2012–2014
Saver 2015 [4]	SWIFT PRIME	USA, Europe	39	Solitaire™ FR; Solitaire™ 2	2012–2014
Goyal 2015 [8]	ESCAPE	Canada, USA, UK, South Korea, Ireland	22	Solitaire™ FR + unspecified others	2013–2014

* The MR RESCUE trial began enrolment in June 2004. It finished enrolling in 2011 but the exact month is not clear. The duration of 80 months is based on the trial having completed enrolment in January 2011.

All eight trials followed up their cohorts for a minimum of 90 days. The median number of participating centres was 22 (range 4–58). The average duration of the included trials was 33 months (range 24–80 months*). The earliest trial began enrolling in 2004 and the latest in 2013, with all publishing their main results between 2013 and 2015.

Six of the eight trials used non-invasive arterial imaging to guide patient selection; MR RESCUE and SYNTHESIS Expansion did not. One additional study (IMS III) altered its protocol after 284 participants had undergone randomisation; this change permitted the use of CTA in determining trial eligibility for patients with an NIHSS score of 8 or 9. MR RESCUE substratified their cohort by penumbral pattern, such that those assigned to undergo mechanical thrombectomy and those assigned to receive standard care were further subcategorised into those with favourable (substantial salvageable tissue and small infarct core) and unfavourable (large core or small or absent penumbra) penumbral patterns, as assessed using pretreatment CT or MRI.

All trials compared standard medical therapy, including IV tPA where appropriate, with endovascular therapy (mechanical thrombectomy with or without IA tPA). A median of 79.9% (range 0–100%) of patients in the intervention group received IV tPA. As noted above, MR RESCUE substratified their cohort by penumbral pattern, using pretreatment CT or MRI; a median of 85.1% (range 16.1–100%) of those assigned to the intervention group underwent mechanical thrombectomy.

Five trials were stopped early. IMS III was stopped early because of futility after 656 participants had undergone randomisation. The release of data from MR CLEAN led to interim analyses being performed in SWIFT PRIME, ESCAPE and EXTEND IA, and all were stopped early. REVASCAT was stopped early because of a claimed loss of equipoise as a result of the release of data from MR CLEAN, EXTEND IA and ESCAPE. MR CLEAN, SYNTHESIS Expansion and MR RESCUE were not stopped early.

Patient characteristics

Patients had to be aged 18 years and over to be eligible for inclusion in all eight studies. Five studies had an upper age limit for inclusion – three excluded patients aged >80 years (SYNTHESIS Expansion, REVASCAT, SWIFT PRIME), one excluded those aged >82 years (IMS III), and one excluded those aged >85 years (MR RESCUE). Five studies reported mean ages for their intervention and control groups, while the other three reported median ages; only one trial reported a difference in ages between groups of greater than 1 year (MR RESCUE, intervention group mean age 64 years; control group mean age 67 years). All trials reported mean or median ages for their control and intervention groups between 64 and 71 years.

The location of the stroke was confined to the anterior circulation (intracranial ICA, MCA [M1 and/or M2] and/or anterior cerebral artery [A1 and/or A2]) only in six of the eight trials; both IMS III (4/434) and SYNTHESIS Expansion (25/362) included patients with occlusions in the posterior circulation.

Six of the eight trials specified a prestroke functional ability as part of their inclusion criteria; two trials required patients to have had a prestroke mRS of ≤1 (REVASCAT, SWIFT PRIME); three trials required a prestroke mRS of ≤2 (IMS III, MR RESCUE, EXTEND IA); and one trial required a prestroke score on the Barthel Index of ≥90 (ESCAPE).

Four trials (IMS III, MR CLEAN, REVASCAT, SWIFT PRIME) reported prestroke mRS scores for their intervention and control arms; the proportion of patients with mRS scores of 0 (intervention group range 81.5–87.3%; control group range 80.1–88.7%) or ≤1 (SWIFT PRIME, intervention group 99%, control group 98%) were similar in both arms of each of these trials.

Five trials required a minimum baseline level of clinical severity for inclusion, as measured using the NIHSS; one required a baseline NIHSS of ≥2 (MR CLEAN), two required a baseline NIHSS ≥6 (MR RESCUE, REVASCAT), one a baseline NIHSS of ≥8 (SWIFT PRIME), and one specified that in order to be eligible for inclusion, patients had to have a baseline NIHSS of ≥10 at the time that IV tPA was begun or an NIHSS of >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA (IMS III.

The median baseline NIHSS scores in the control and intervention arms of MR RESCUE were both 16 for those with favourable penumbral patterns, and 20.5 and 19 for those with non-favourable patterns, respectively. The median baseline NIHSS scores in the control arms of the other trials ranged from 13 to 18. The median baseline NIHSS scores in the intervention arms of these trials ranged from 13 to 17. Just one trial had a difference of greater than one point in the median baseline NIHSS scores of control and intervention arms (EXTEND IA; control median baseline NIHSS, 13; intervention, 17).

Four trials noted that included patients must have been eligible for, or have commenced infusion of IV tPA within 4.5 hours of symptom onset (see Appendix 1, Table 9). One further trial (IMS III) required that IV tPA had commenced in all patients within 3 hours of symptom onset.

The maximum time allowed between onset of symptoms and commencement of endovascular intervention ranged from 5 to 12 hours (ESCAPE) across the trials (See Appendix 1, Table 9).

Three trials specified an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) as part of their inclusion and exclusion criteria. REVASCAT excluded patients who had an ASPECTS score of <7 on non-contrast CT or <6 on diffusion-weighted imaging-MRI (DWI-MRI). SWIFT PRIME excluded patients with an ASPECTS score of <6 on non-contrast CT or DWI-MRI. ESCAPE, meanwhile, excluded patients with an ASPECTS score of <6 on non-contrast CT or CTA.

The proportion of men in the control groups ranged between 47% and 59%; the proportion of men in the intervention groups ranged between 47% and 59%.

Timing characteristics

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. 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. In four of these trials (MR CLEAN, EXTEND IA, SWIFT PRIME and ESCAPE) the median time to thrombolysis was shorter in the intervention group than in the control group; in the other two trials (IMS III and REVASCAT) the median time to throm-

bolysis was longer in the intervention group (Appendix 1, Table 9). The difference in the median time from symptom onset to thrombolysis between these arms ranged from 2 minutes (MR CLEAN) to 18 minutes (EXTEND IA). In the SYNTHESIS Expansion trial, only those in the control arm received IV tPA; the median time from onset of symptoms to thrombolysis in this group was 165 minutes.

Five trials provided information on the median time from onset of symptoms to randomisation for both their control and intervention arms (Appendix 1, Table 9). The median time from onset of symptoms to randomisation in the control groups in these trials ranged from 145 to 226 minutes; it ranged from 148 to 223 minutes in the intervention arms. The difference in the median time from symptom onset to randomisation between these arms ranged from 2 minutes (SWIFT PRIME) to 8 minutes (MR CLEAN). The MR RESCUE trial reported a mean time from onset of symptoms to randomisation of 315 (standard deviation [SD] 90) and 346 (SD 70) minutes for their control and intervention arms, respectively (these are estimates of the mean and standard deviation for the control and intervention arms, derived from pooling mean times for those with favourable and non-favourable penumbral patterns in each of these arms). The IMS III trial authors noted that all patients were randomised within 40 minutes of thrombolysis while the EXTEND IA authors reported that the median time from thrombolysis to randomisation in the control and intervention arms was 29 and 36 minutes, respectively.

All trials provided information regarding the time from onset of symptoms to the start of the procedure for those randomised to the intervention arms. Five provided median times; these ranged from 210 (EXTEND IA) to 269 minutes (REVASCAT). MR RESCUE reported a mean time from onset of symptoms to the start of the procedure for those randomised to the intervention arm of 381 (SD 74) minutes, while IMS III reported a mean time of 208 (SD 46.7) minutes. The ESCAPE trial authors did not report this information directly; they did, however, note that the median time from stroke onset to study CT was 134 minutes, while the median time from study CT to groin puncture was 51 minutes.

Two trials reported the median duration of the procedure; EXTEND IA (43 [interquartile range (IQR) 24–53] minutes), REVASCAT (75 [IQR 50–114] minutes).

Quality assessment

While the risk of bias overall for each of the RCTs was rated as low (see Appendix 1, page 95), a number of issues which could potentially have affected the outcome data were identified. The quality of the evidence was rated as low for mRS (moderate when confined to studies commenced from 2010 onwards) and moderate for other outcomes of effectiveness (see Appendix 1, page 95).

One of the eight trials (MR RESCUE) carried out a per-protocol analysis, while the other seven were analysed on an intention-to-treat basis. In MR RESCUE, 9/127 subjects were excluded from the final analysis and this may have affected the effectiveness outcomes under review.

While the majority of the studies reported all or the majority of primary and secondary outcomes, IMS III had planned, but did not report, outcomes for EQ-5D, the trail making test and the Barthel Index.

A further concern is the number of trials which were stopped early (five) (see Section 4.3 [Study characteristics] above). Early stopping rules are integral to RCT design, both to allow for loss of equipoise, and to prevent harm and unacceptable adverse events. However, it must also be acknowledged that trials which stop early for benefit may under- or over-estimate the treatment ef-

fect of the intervention; truncated RCTs have previously been demonstrated to be associated with greater effect sizes than RCTs not stopped early [63].

Mortality

D0001 – What is the expected beneficial effect of mechanical thrombectomy on mortality?

D0003 – What is the effect of mechanical thrombectomy on mortality due to causes other than the target disease?

Mortality from ischaemic stroke

Data on mortality from ischaemic stroke were not reported by the studies.

All-cause mortality at 90 days

All eight trials reported all-cause mortality at 90 days, with data reported on 2,418 patients in total. There were 218 deaths out of 1,312 patients in the intervention arm (16.6%), with 201 deaths in 1,106 patients in the control arm (18.2%) (Appendix 1, Table 12). One study found a statistically significant reduction in mortality associated with the intervention (ESCAPE). The pooled risk ratio for mortality was 0.89 (95% CI: 0.73 to 1.09; p = 0.27) (Figure 1). This evidence suggests that the intervention is not associated with lower all-cause mortality, when compared with the control, at 90 days.

A subgroup analysis was performed using data from the five trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE). In these trials, there were 97 deaths out of 633 patients in the intervention arm (15.3%) and 122 deaths out of 649 patients in the control arm (18.8%) (Appendix 1, Table 12). The pooled risk ratio for mortality was 0.82 (95% CI: 0.60 to 1.11; p = 0.20) (Figure 2). When limited to these five trials, the evidence suggests that the intervention is not associated with lower all-cause mortality, when compared with the control, at 90 days.

Figure 1: Random effects meta-analysis of all-cause mortality at 90 days

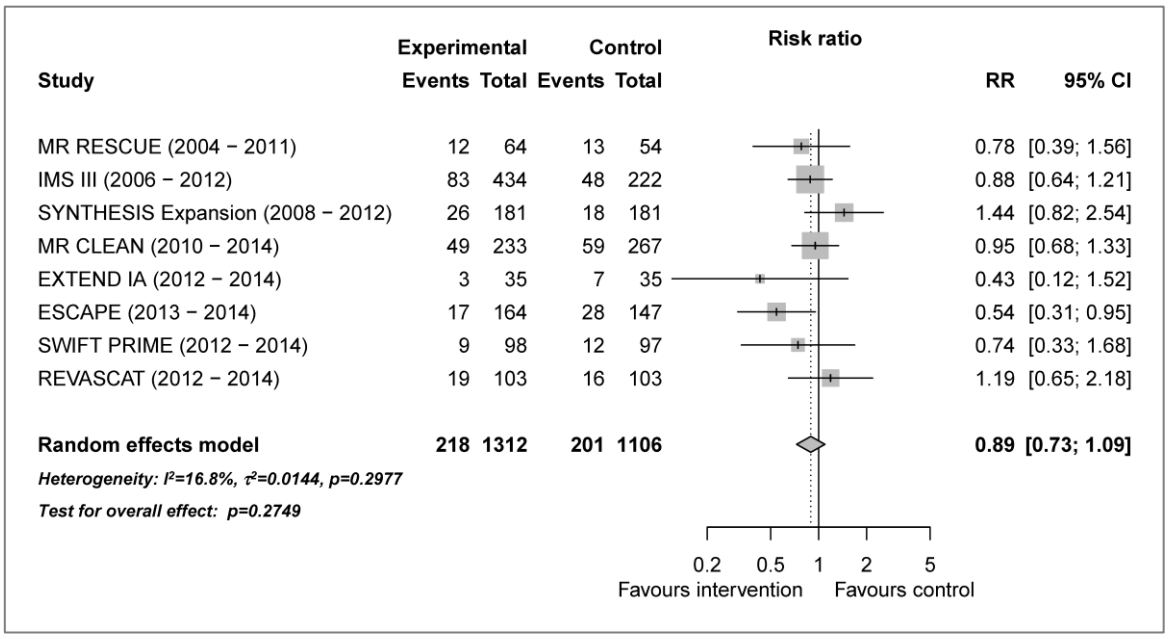
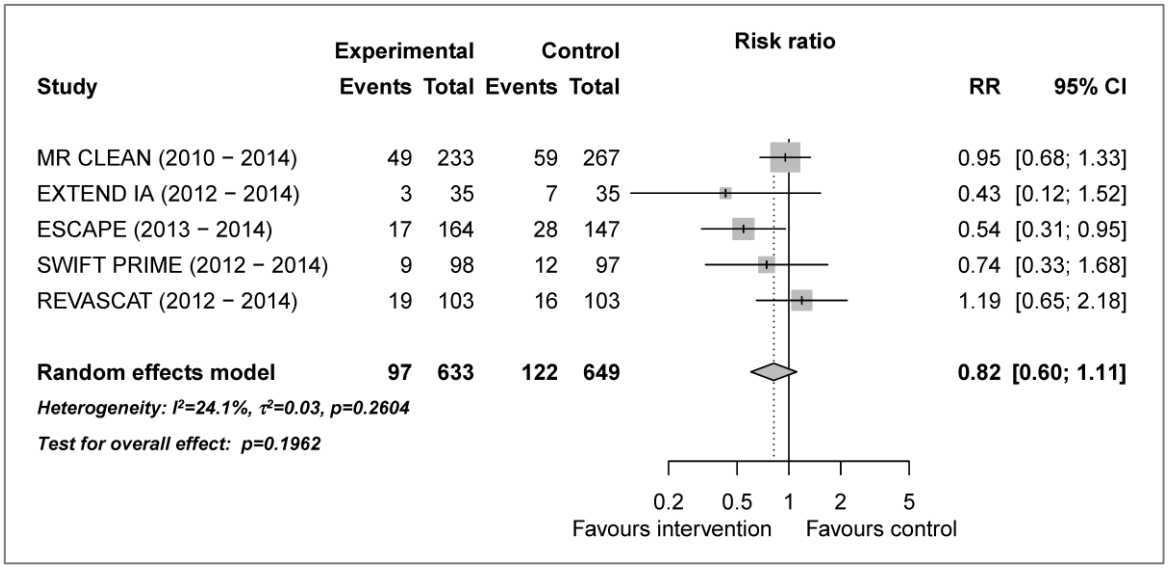


Figure 2: Subgroup random effects meta-analysis of all-cause mortality at 90 days



Morbidity and function

D0005 – How does mechanical thrombectomy impact the symptoms and severity of acute ischaemic stroke?

D0006 – How does mechanical thrombectomy affect progression (or recurrence) of acute ischaemic stroke?

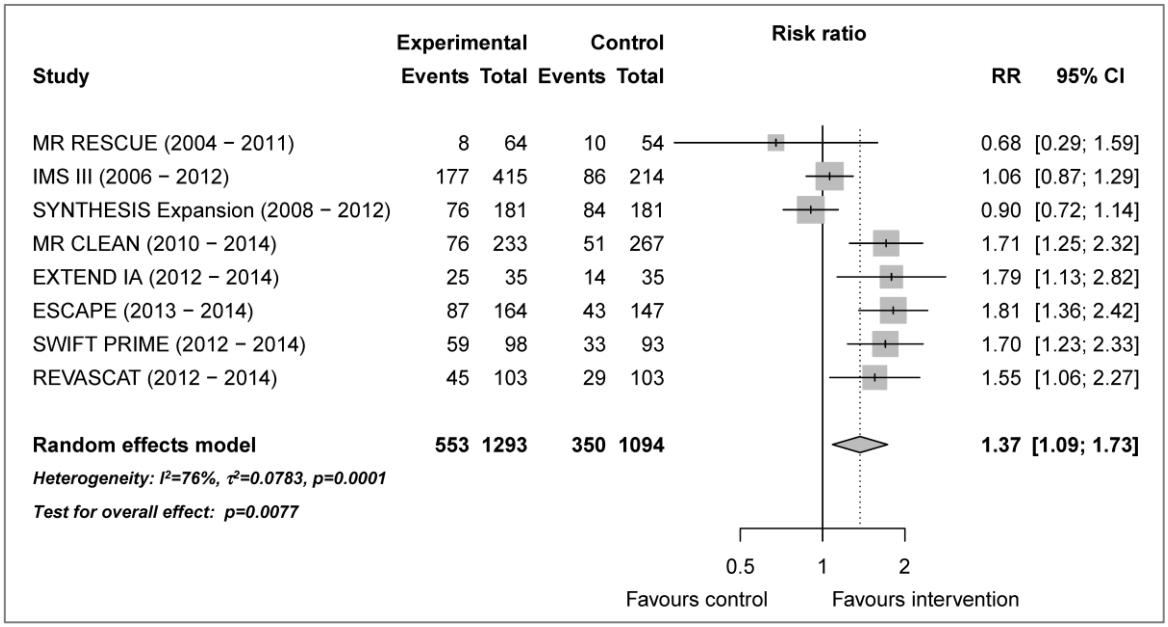
D0011 – What is the effect of mechanical thrombectomy on patients' body functions?

D0016 – How does the use of mechanical thrombectomy affect activities of daily living?

mRS at 90 days

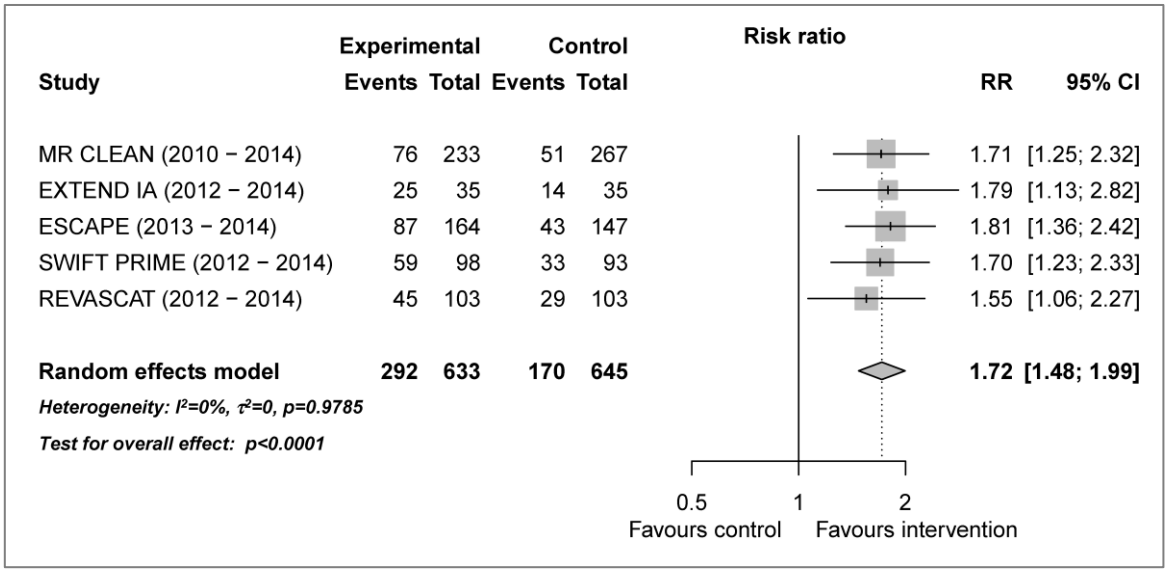
All eight trials reported data for mRS at 90 days, with data available on 2,387 patients. In total, 42.8% (553/1,293) of patients in the intervention arm were reported to have achieved an mRS of 0–2 at 90 days; compared with 32.0% (350/1,094) of patients who were assigned to the control arms of the studies (Appendix 1, Table 12). The risk ratio for achieving an mRS of 0–2 at 90 days was 1.37 (95% CI: 1.09 to 1.73; p = 0.008) in favour of the intervention. The evidence presented suggests that the intervention is associated with higher likelihood of being independent, as assessed using the mRS, at 90 days post acute ischaemic stroke (Figure 3).

Figure 3: Random effects meta-analysis modified Rankin Scale at 90 days



While the studies exhibit a high degree of statistical heterogeneity overall (I^2 = 76.0%; p=0.0001), this heterogeneity is completely eliminated by only including the five studies which began enroling from 2010 onwards (Figure 4). When limiting the analysis to these five studies, 46.1% (292/633) of patients in the intervention arm were reported to have achieved an mRS of 0–2 at 90 days; compared with 26.4% (170/645) of patients who were assigned to the control arms of these studies. The absolute benefit of the intervention on mRS at 90 days across these latter five trials ranged from 13.5% in MR CLEAN to 31.4% in EXTEND IA. In a subgroup analysis of these five trials, the risk ratio for achieving an mRS of 0–2 at 90 days was 1.72 (95% CI: 1.48 to 1.99; p<0.0001) in favour of the intervention (Figure 4).

Figure 4: Subgroup random effects meta-analysis modified Rankin Scale at 90 days

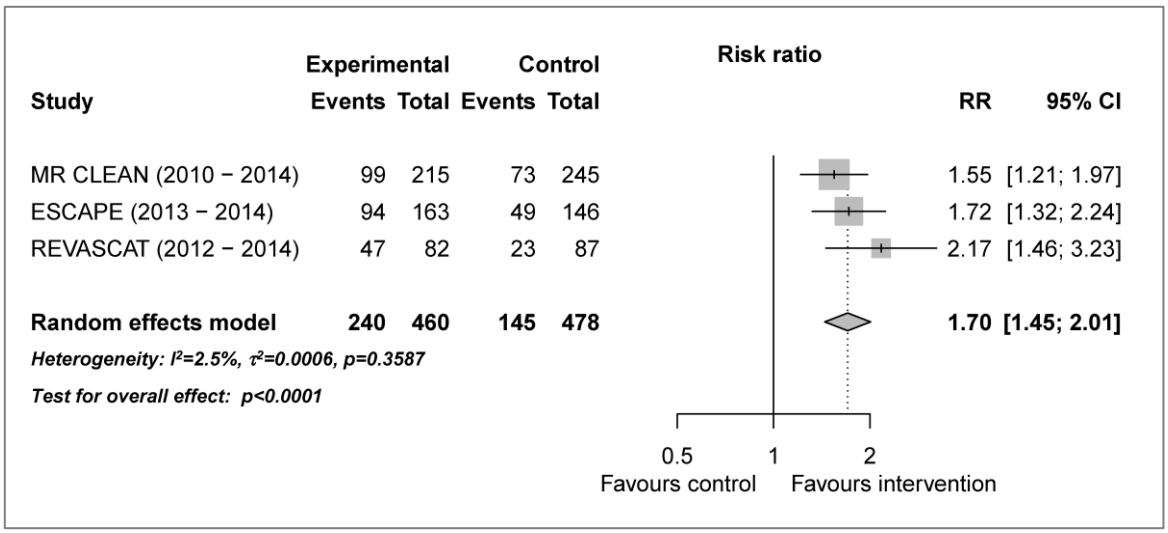


Barthel Index at 90 days

Three trials (MR CLEAN, REVASCAT, ESCAPE) provided data which were amenable to comparison in relation to the Barthel Index (Appendix 1, Table 12). All three reported the proportion of patients in the control and intervention groups (total = 938 patients) who achieved a score of ≥95 at 90 days; 52.2% (240/460) of patients achieved this score in the intervention groups with 30.3% (145/478) achieving it in the control arms. The risk ratio for achieving a Barthel Index of 95 or higher at 90 days was 1.70 (95% CI: 1.45 to 2.01; p<0.0001) in favour of the intervention. This evidence suggests that the intervention is associated with better outcomes in relation to ADL, as measured using the Barthel Index, at 90 days, with all three studies individually demonstrating a statistically significant benefit from the intervention (Figure 5).

A fourth trial, SWIFT PRIME, reported median Barthel Index scores at 90 days for those in the intervention (n = 88/98) and control groups (n = 77/98) for whom the information was available; the median scores at 90 days were 100 (IQR 10–100) and 90 (IQR 0–110) for the intervention and control groups, respectively.

Figure 5: Random effects meta-analysis Barthel Index at 90 days



NIHSS

The NIHSS ranges from 0 to 42, and quantifies neurological deficits into 11 categories, with higher scores indicating more severe neurological deficit. Six studies provided data on NIHSS scores post-stroke (Appendix 1, Table 12). This data varied in how it was reported, however, and thus a meta-analysis is not possible. In addition, while the project plan for this assessment specified that NIHSS score change at 24 hours would be evaluated, again this was not possible because of inadequate reporting of this outcome by the studies under consideration.

Two trials (MR CLEAN and ESCAPE) reported the median NIHSS at 24 hours in the control and intervention groups. Both reported better median NIHSS scores in the intervention versus the control groups. The intervention group in ESCAPE had a median NIHSS of 6 (IQR 3–14), while the control group had a median NIHSS of 13 (IQR 6–18). The MR CLEAN trial reported a median NIHSS of 13 (IQR 6–20) in the intervention group, and a median NIHSS of 16 (IQR 12–21) in the control group.

Two further studies reported different measures of NIHSS at 24–27 hours and another reported at 3 days only. Regardless of the reporting method, all studies reported better scores in the intervention versus the control groups. SWIFT PRIME reported mean change at 27 hours (intervention group –8.5 [±7.1]; control group –3.9 [±6.2]), while REVASCAT reported the proportion of patients who achieved a reduction of ≥8 NIHSS points or a score of ≤2 at 24 hours (intervention group 59/100; control group 20/100). EXTEND IA reported the proportion of patients who achieved a reduction of ≥8 NIHSS points or a score of 0 or 1 at 3 days (intervention group 28/35; control group 13/35).

Reperfusion at 24 hours and/or revascularization at final angiography

Three studies (EXTEND IA, MR RESCUE, SWIFT PRIME) reported on reperfusion, but only one of these was at 24 hours; EXTEND IA reported that the median percentage reduction in the reperfusion–lesion volume between initial and 24 hour imaging was 100% (IQR 100–100) in the intervention group and 37% (IQR -0.50–0.96) in the control group. EXTEND IA also reported the proportion of patients in the control and intervention groups who achieved >90% reperfusion at 24 hours without SICH; the proportions were 31/35 (89%) and 12/35 (34%) for the intervention and control groups, respectively.

SWIFT PRIME reported on reperfusion, but at 27 hours rather than at 24 hours; 83% (53/64) and 40% (21/52) of the intervention and control groups achieved ≥90% reperfusion at 27 hours, respectively.

MR RESCUE assessed reperfusion (defined as a reduction of ≥90% in the volume of the perfusion lesion from baseline) at Day 7; of those for whom information was available, 48.9% (23/47) and 51.3% (20/39) of the intervention and control groups achieved this degree of reduction, respectively.

Six studies reported the proportion of patients in their intervention group who demonstrated a TICI (ESCAPE, MR RESCUE) or an mTICI score (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME) of 2a-3 or 2b-3 (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME and ESCAPE) (Appendix 1, Table 12). These latter five studies reported proportions of mTICI 2b-3 which ranged from 58.7% (MR CLEAN) to 88% (SWIFT PRIME) while MR RESCUE reported that 40/56 (71.4%) had a TICI score of 2a-3 at Day 7.

A seventh study, IMS III, reported final mTICI scores based on the location of the vessel occlusion which had caused the stroke; the percentage of the intervention group who achieved an mTICI score of 2b-3 ranged from 23% (multiple M2 occlusions) to 44% (M1 occlusion or single M2 occlusion).

Health-related quality of life

D0012 – What is the effect of mechanical thrombectomy on generic health-related quality of life?

D0013 – What is the effect of mechanical thrombectomy on disease-specific quality of life?

Health-related quality of life (EQ-5D)

Not all trials included health-related quality of life as a primary or secondary endpoint.

Three trials reported on health-related quality of life using the EQ-5D, a generic measure, with higher scores reflecting better quality of life. It was not clear whether the studies used the ‘3L’ or ‘5L’ version of this measure. The scales used were either from 0 to 100 (ESCAPE) or from –0.33 to 1 (REVASCAT, MR CLEAN).

ESCAPE reported median scores at 90 days in the intervention group of 80 (IQR 60–90) and control group of 65 (IQR 50–80), along a scale from 0 to 100.

REVASCAT and MR CLEAN also reported median scores at 90 days, but reported these along a different scale (–0.33 to 1). REVASCAT reported median scores in the intervention and control groups of 0.65 (IQR 0.21–0.79) and 0.32 (IQR 0.13–0.70), respectively. MR CLEAN reported median scores in the intervention and control groups of 0.69 (IQR 0.33–0.85) and 0.66 (IQR 0.30–0.81), respectively.

No data were available on disease-specific quality of life.

Patient satisfaction

D0017 – Was the use of mechanical thrombectomy worthwhile?

No evidence was found to answer the research question.

4.4 Discussion

The assessment of the clinical effectiveness of thrombectomy for acute ischaemic stroke is based on eight RCTs, with a total of 2,423 patients. As noted above, while the risk of bias was generally rated as low, the quality of the pooled data for the outcomes under review was rated as low or moderate. In addition, a number of important points about the trials need to be reiterated.

Mechanical thrombectomy versus endovascular intervention

While mechanical thrombectomy is the subject of this analysis, the RCTs examined 'endovascular intervention' which includes both mechanical thrombectomy and intra-arterial thrombolysis, in which tPA is infused directly into the artery close to the occlusion. Two of the studies, in particular, had markedly lower proportions of their intervention groups undergoing mechanical thrombectomy (IMS III 16.1%, SYNTHESIS Expansion 30.9%); this compared with the other six trials where the proportion of the intervention group undergoing mechanical thrombectomy ranged between 77.1% and 100%. There were a number of reasons for the different rates across the trials, including the use or non-use of imaging in patient selection, clinical deterioration or improvement, and system or process issues (that is, the availability of an interventionist). That said, all of the trials randomised patients on the basis that they were eligible for mechanical thrombectomy, and analysis in seven trials was performed on an intention-to-treat basis, with the eighth based on a per-protocol analysis (MR RESCUE).

Older versus newer generation mechanical thrombectomy devices

The type of devices used has changed over time; this is significant because the year of commencement of enrolment across the eight trials ranged from 2004 (MR RESCUE) to 2013 (ESCAPE). The first three trials to begin enrolment used first-generation devices alone (MR RESCUE) or in the majority of cases (IMS III, SYNTHESIS Expansion). In contrast, the later trials used newer generation 'stent retrievers' in all (EXTEND IA, REVASCAT, SWIFT PRIME) or the majority of cases (MR CLEAN, ESCAPE).

Anterior versus posterior circulation ischaemic stroke

Six of the eight trials focused exclusively on patients with anterior acute ischaemic stroke. IMS III included those with occlusion in the basilar artery, but this consisted of just four patients, while SYNTHESIS Expansion included 30 patients (8%) with posterior circulation stroke as assessed on Day 7. The results presented here should therefore be taken to be indicative of the effectiveness or otherwise of mechanical thrombectomy in the management of anterior circulation acute ischaemic stroke; further studies are required before a determination on the efficacy of mechanical thrombectomy in the posterior circulation can be made.

The use of vessel imaging to select patients

Neither MR RESCUE nor SYNTHESIS Expansion used non-invasive arterial imaging to identify patients for enrolment. IMS III, which began enrolment in 2006, did not begin using CTA to identify the site of occlusion until after 284 participants had undergone randomisation; from then on, CTA was used to determine trial eligibility for patients with an NIHSS score of 8 or 9. The other five trials used either CTA or MRA to guide patient selection.

Summary and conclusion

There are thus a number of caveats to the interpretation of the evidence presented in this pilot assessment of effectiveness. The quality of the pooled data for the outcomes under review was rated as low or moderate and the individual trials span a time frame in which both the technology itself and the process of identifying patients who could potentially benefit from the technology have changed significantly.

The intervention had no effect on all-cause mortality either in the overall or subgroup analysis.

The effectiveness outcome for which this analysis is most consistent is mRS ≤2 at 90 days, with the pooled data suggesting that mechanical thrombectomy is significantly more likely to result in functional independence when compared with the current standard of care (medical treatment).It has been argued that the methodology and devices (predominantly stent retrievers) employed in the later five trials are those which are more relevant to current clinical practice. It is therefore pertinent to note that subgroup analysis of these five trials demonstrated an improved effect of the intervention on mRS at 90 days, when compared with its overall effect as analysed across all eight trials.

Similarly to mRS, the Barthel Index can also be used to measure disability or dependence in ADL following a stroke. While concerns have been raised in general that there is a lack of consensus across these two measures, this does not appear to be the case here; in keeping with the positive association between thrombectomy and mRS as discussed above, the pooled data from the three trials which provided information on median Barthel Index score at 90 days further suggest that mechanical thrombectomy has a significant positive effect on morbidity and function; all three trials were performed with newer generation devices with all commenced in 2010 or later [64].

While six trials reported on NIHSS in different ways and at different time points, all indicated better outcomes in the intervention groups – the significance of this is difficult to assess, however, given the aforementioned heterogeneity in reporting. Similarly, while just two trials reported on reperfusion at 24 hours, and again did so in different ways, both reported markedly improved rates of reperfusion in the intervention versus the control groups (it should be noted, however, that MR RESCUE, which reported on reperfusion at 7 days, suggested no difference at this time point).

Restoration of cerebral blood flow on final angiography, as assessed using the TICI or mTICI score, varied markedly across the seven trials for which data were presented and, while there are reasons for this variability (i.e. the absence of appropriate imaging in some patients in MR CLEAN), it is difficult to arrive at any firm conclusions in relation to this outcome measure.

Finally, three trials reported health-related quality of life, as measured using the EQ-5D; the results from all three are consistent in suggesting that mechanical thrombectomy has a positive effect on this outcome measure.

In conclusion, while there are a number of caveats as discussed, the evidence suggests that mechanical thrombectomy, when used in conjunction with non-invasive arterial imaging, in selected patients with anterior circulation acute ischaemic stroke, and when using second-generation (stent retriever) devices, has a beneficial effect on morbidity and function, and health-related quality of life at 90 days, but no effect on all-cause mortality at 90 days.

5 SAFETY

5.1 Domain framing

The initial wording of some of the outcomes from the project plan has been modified in this pilot assessment.

5.2 Research questions and methods

Research questions

Element ID	Research Question	Outcomes
C0004	What are the variables associated with the use of mechanical thrombectomy devices that may impact the frequency and/or severity of harms?	Patient safety
C0005	Which patient groups are more likely to be harmed by the use of mechanical thrombectomy devices? Are there any relevant contraindications or interactions with other technologies?	Patient safety
C0007	Are mechanical thrombectomy devices associated with user-dependent harms? Specifically, are there potential harms that can be caused by those who undertake mechanical thrombectomy? Is there a learning curve, or potential for intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care?	Patient safety
C0008	Relative to current standard of care alone, how safe is mechanical thrombectomy (technology- and procedure-related adverse events) when used in combination with standard of care relative to standard of care? Specifically: • What is the frequency of serious adverse events (SAEs)? • What are the most serious adverse events? • What is the frequency of SAEs leading to death? • What are the most frequent adverse events? • How frequently do they occur?	Patient safety

Sources

The following sources were used to obtain information:

- PubMed
- Embase
- Cochrane Register of Controlled Trials
- ClinicalTrials.gov
- ICTRP
- ISRCTN
- EU Clinical Trials Registry
- mRCT
- Stroke Trials Registry
- Request to the manufacturer
- Health Products Regulatory Authority, Ireland

We selected RCTs and prospective clinical studies in which relevant safety data were reported.

Relevant studies were identified as part of the systematic review of clinical effectiveness. Search results were supplemented by studies identified as part of a systematic review and meta-analysis performed by Puñal-Riobóo et al., which included studies published up to March 2015 [65]. All major databases were included in their search and the authors used the GRADE system to evaluate the quality of their evidence. In addition to the studies identified from this review, relevant prospective studies, published between March and August 2015, inclusive were included – although no additional studies were identified. The outcome of interest in the additional studies was device-related adverse events; other adverse events (that is, SICH, mortality, all haemorrhage) were sufficiently reported in the RCTs and hence data on these events were not extracted from the six additional studies, none of which had compared mechanical thrombectomy with standard medical care.

A detailed description of the search strategy and selection process is available in Appendix 1, page 66.

Analysis

The GRADE methodology was used to assess the quality of the pooled evidence. The risk of bias was assessed using the Cochrane risk of bias tool for RCTs.

Synthesis

The questions were asked in plain text format with reference to the evidence tables included in Appendix 1, page 70. Due to the expected heterogeneity across studies in terms of devices used and time to procedure, random effects meta-analysis was used. Binary outcomes were pooled as risk ratios. Heterogeneity was assessed on the basis of I^2 values. Values in excess of 75% were interpreted as considerable heterogeneity, and values between 50% and 90% were interpreted as potentially substantial heterogeneity. If sufficient studies were available (n ≥10), assessment of small study bias using funnel plots and Egger's test was planned. Meta-analysis was performed for three outcomes: SICH, any cerebral haemorrhage and recurrent ischaemic stroke within 90 days.

There are a number of important methodological differences between the first three trials included in this assessment (MR RESCUE, IMS III, SYNTHESIS Expansion) and the other five, as discussed in Sections 4.3 (Study characteristics) and 4.4 (Discussion). In particular, these trials used older generation devices which, it has been argued, are no longer clinically relevant [62]. Therefore, a subgroup analysis including the latter five trials only (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE), was performed for SICH, any cerebral haemorrhage and recurrent ischaemic stroke at 90 days.

5.3 Results

Included studies

All eight RCTs included in the clinical effectiveness assessment were also included in the safety assessment. Their characteristics have been described previously.

An additional six studies (four prospective observational studies and two RCTs) with data on device-related adverse events were identified and included for analysis (Appendix 1, Table 13) [66-71]. A total of 641 patients were evaluated across these six studies. All six were performed between 2010 and 2012 and all were published in 2012 or 2013. The devices included in these studies were the Solitaire™ FR and AB, the Merci retriever and the Trevo® device. For additional information on these six studies, please see Appendix 1, page 89.

Patient characteristics

The patient characteristics of the eight RCTs are described in Section 4 (Clinical effectiveness).

The mean patient age across the six additional studies ranged from 64 to 68.4 years [66-71]. The median baseline NIHSS score ranged from 17 to 19 across the six studies. Pereira et al. included patients with anterior circulation acute ischaemic strokes only; the other five studies included a variable proportion (2.8–11.1%) of patients with pathology in the posterior circulation. Four of the six studies had a maximum time to mechanical thrombectomy of 8 hours; Nogueira et al. stated that the lesion had to have been angiographically confirmed within 8 hours of onset [68], while Soize et al. included patients with anterior circulation strokes who presented within 6 hours of onset and those with posterior circulation strokes who presented within 24 hours of onset [67].

Quality assessment

The quality of the eight RCTs is described in the Section 4 (Clinical effectiveness). With the exception of mortality at 90 days (see Section 4) and SICH, there was inconsistency in how these eight trials reported their safety outcomes, making comparability and interpretation difficult.

The quality of the six additional studies was assessed on the basis of risk of bias (see Appendix 1, page 102). It was noted that two of the studies had a small number of participants (Soize et al., n = 36 [67]; de Castro-Afonso et al., n = 21 [69]). The only outcome data extracted from the six additional studies was that concerning device-related adverse events.

Patient safety

C0004 – What are the variables associated with the use of mechanical thrombectomy devices that may impact the frequency and/or severity of harms?

No evidence was found to answer the research question.

C0005 – Which patient groups are more likely to be harmed by the use of mechanical thrombectomy devices? Are there any relevant contraindications or interactions with other technologies?

No evidence was found to answer the research questions.

C0007 – Are mechanical thrombectomy devices associated with user-dependent harms? Specifically, are there potential harms that can be caused by those that undertake mechanical thrombectomy? Is there a learning curve, or potential for intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care?

No evidence was found to answer the research questions.

C0008 – Relative to current standard of care alone, how safe is mechanical thrombectomy (technology- and procedure-related adverse events) when used in combination with standard of care relative to standard of care? Specifically:

- **What is the frequency of serious adverse events (SAEs)?**
- **What are the most serious adverse events?**
- **What is the frequency of SAEs leading to death?**
- **What are the most frequent adverse events?**
- **How frequently do they occur?**

Note: while individual studies report adverse events and/or serious adverse events, a lack of clarity regarding what constitutes ‘serious’ and inconsistencies in reporting makes comparative analysis across studies difficult.

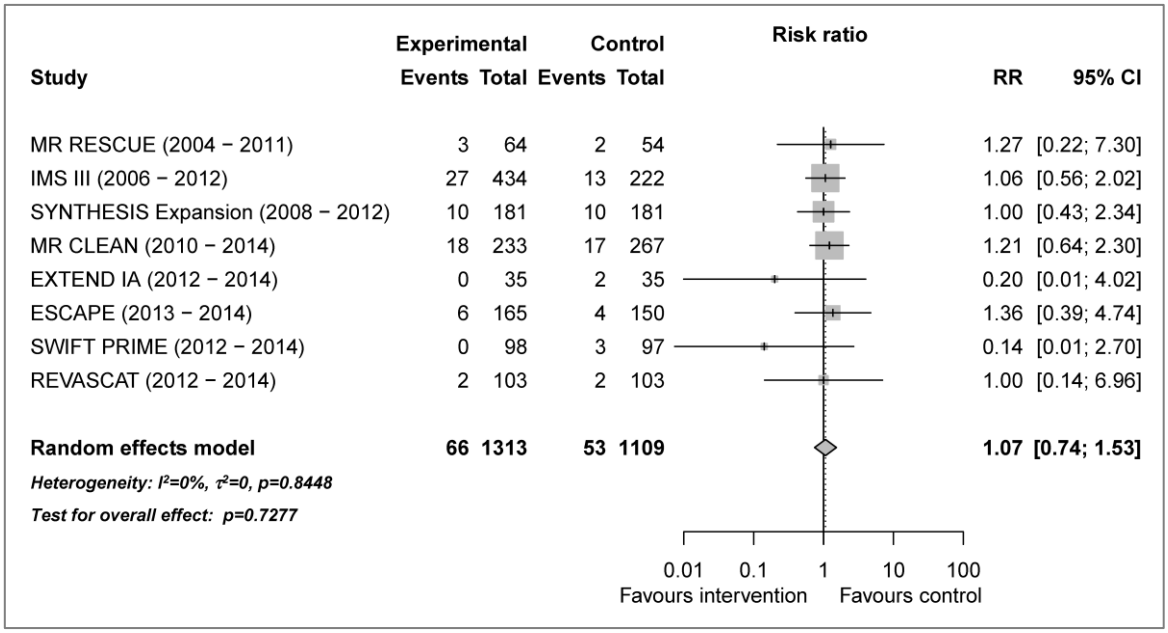
All-cause mortality at 90 days

Please see Section 4 (Clinical effectiveness) for further information on this outcome.

Symptomatic intracerebral haemorrhage

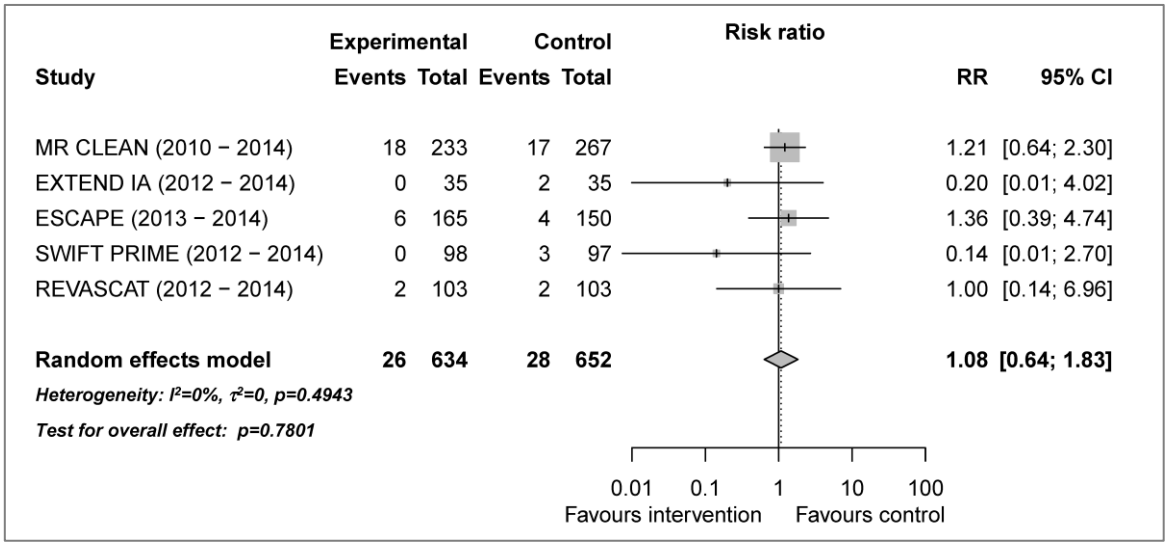
All eight trials reported data on SICH across a total cohort of 2,422 patients. In total, 5% (66/1,313) of patients in the intervention arm and 4.8% (53/1,109) of patients in the control arm experienced an SICH. This evidence suggests that the intervention is not associated with a higher overall rate of SICH when compared with the control (risk ratio = 1.07; 95% CI: 0.74 to 1.53; p = 0.73) (Figure 6).

Figure 6: Random effects meta-analysis of symptomatic intracerebral haemorrhage



A subgroup analysis was performed using data from the five trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE) (Figure 7). In these trials, there were 26 events in 634 patients in the intervention arm (4.10%) and 28 events in 652 patients in the control arm (4.29%). The pooled risk ratio for SICH was 1.08 (95% CI: 0.64 to 1.83; p = 0.78) (Figure 7). This evidence suggests that the intervention is not associated with a higher overall rate of SICH when compared with the control.

Figure 7: Subgroup random effects meta-analysis of symptomatic intracerebral haemorrhage



Perforation/dissection

There were insufficient data to address this question. Please see the section below *Device-and/or procedure-related adverse events* for additional information.

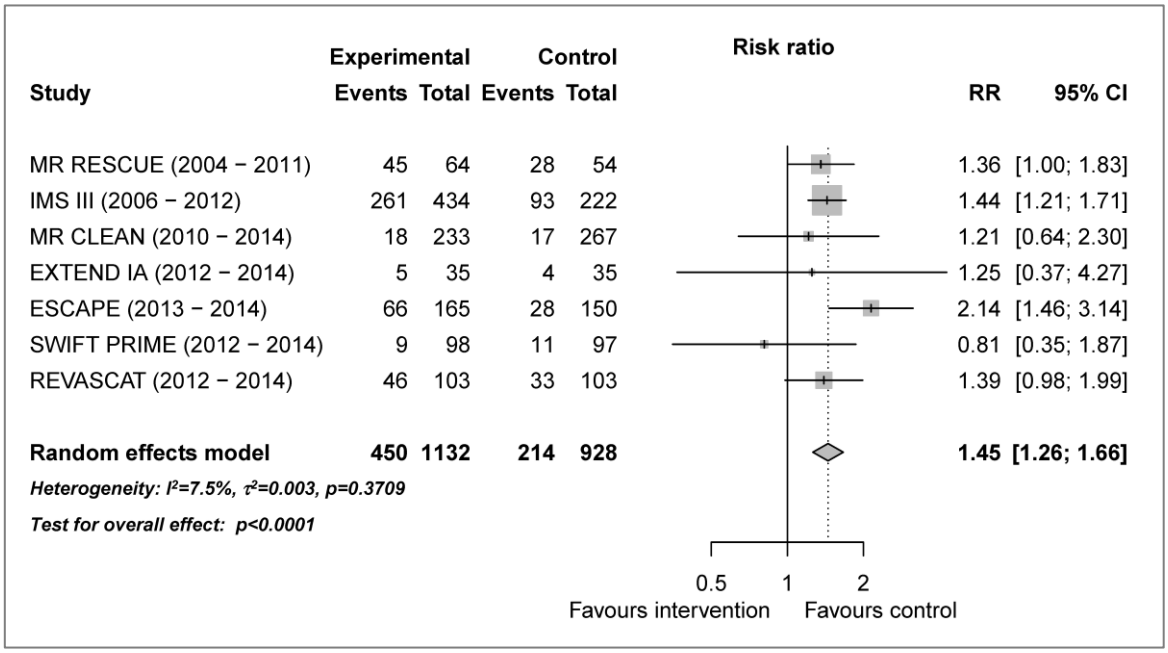
Other haemorrhage

There were insufficient data to address this question. Please see the section below *Device-and/or procedure-related adverse events* for additional information.

Any cerebral haemorrhage

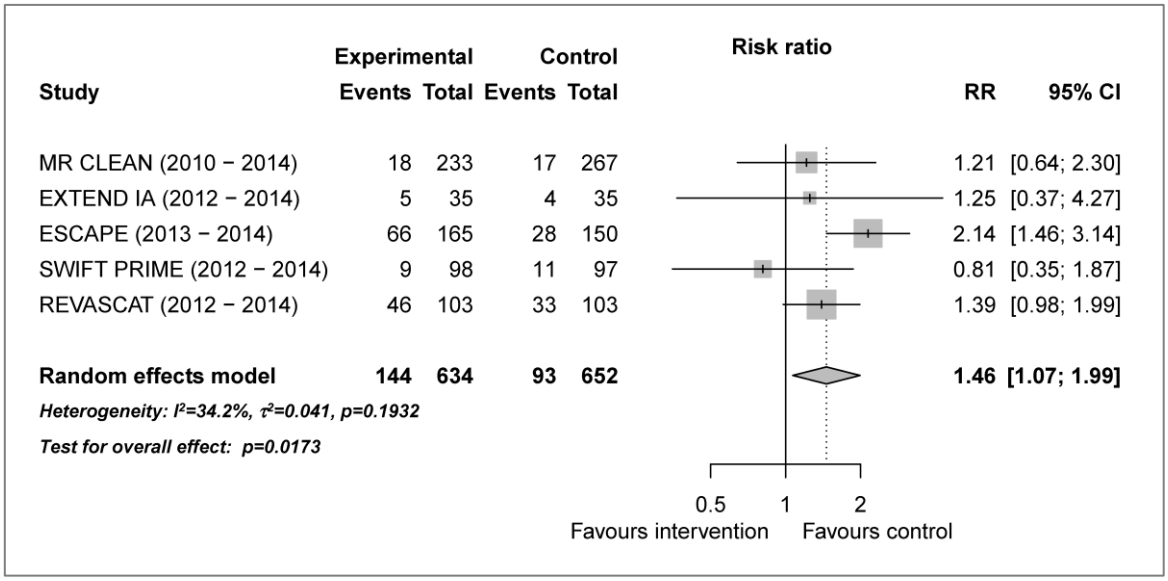
Seven of the eight studies reported comparable data on any cerebral haemorrhage at between 24 and 30 hours (it was unclear which events qualified in SYNTHESIS Expansion and hence this was not included). A total of 39.8% (450/1,132) patients in the intervention arm and 23.1% (214/928) patients in the control arm experienced a cerebral haemorrhage (Figure 8). The risk ratio for any cerebral haemorrhage was 1.45 (95% CI: 1.26 to 1.66; p<0.0001). The evidence suggests that the intervention is associated with a higher overall rate of cerebral haemorrhage when compared with the control.

Figure 8: Random effects meta-analysis of any cerebral haemorrhage



A subgroup analysis of any cerebral haemorrhage was performed using data from the five trials commenced from 2010 onwards (MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, ESCAPE) (Figure 9). In these trials, there were 144 events in 634 patients in the intervention arm (22.7%) and 93 events in 652 patients in the control arm (14.3%). The pooled risk ratio for any cerebral haemorrhage at 90 days was 1.46 (95% CI: 1.07 to 1.99; p = 0.02). This evidence suggests that the intervention is associated with a higher overall rate of any cerebral haemorrhage at 90 days when compared with the control.

Figure 9: Subgroup random effects meta-analysis of any cerebral haemorrhage



Recurrent ischaemic stroke within 90 days

Four trials (IMS III, MR CLEAN, ESCAPE, REVASCAT) provided data on the number of patients who suffered a recurrent ischaemic stroke within 90 days; the proportion of the intervention group suffering this adverse event ranged from 3.9% (in REVASCAT) to 5.6% (in MR CLEAN). The proportion of patients with recurrent ischaemic stroke in the control group ranged from 0.4% (in MR CLEAN) to 6.3% (in IMS III). The pooled data from these four trials do not suggest that the intervention is associated with a higher overall rate of recurrent ischaemic stroke within 90 days, when compared with the control (risk ratio = 1.97; 95% CI: 0.64 to 6.03; p = 0.24) (Figure 10). While substantial statistical heterogeneity is noted between the four included studies (I^2 = 67.8%; p = 0.03), this is reduced by exclusion of the earliest trial (IMS III) with all three later trials indicating that the intervention is not associated with a higher rate of recurrent ischaemic stroke. Subgroup analysis, including only these latter three trials, again suggests that the intervention is not associated with a statistically significant higher overall rate of recurrent ischaemic stroke within 90 days, when compared with the control (risk ratio = 3.09; 95% CI: 0.86 to 11.11; p = 0.08) (Figure 11).

One additional trial, SYNTHESIS Expansion, reported that 2.2% (4/181) of patients in the intervention group had experienced a new stroke at 7 days.

Figure 10: Random effects meta-analysis of recurrent ischaemic stroke within 90 days

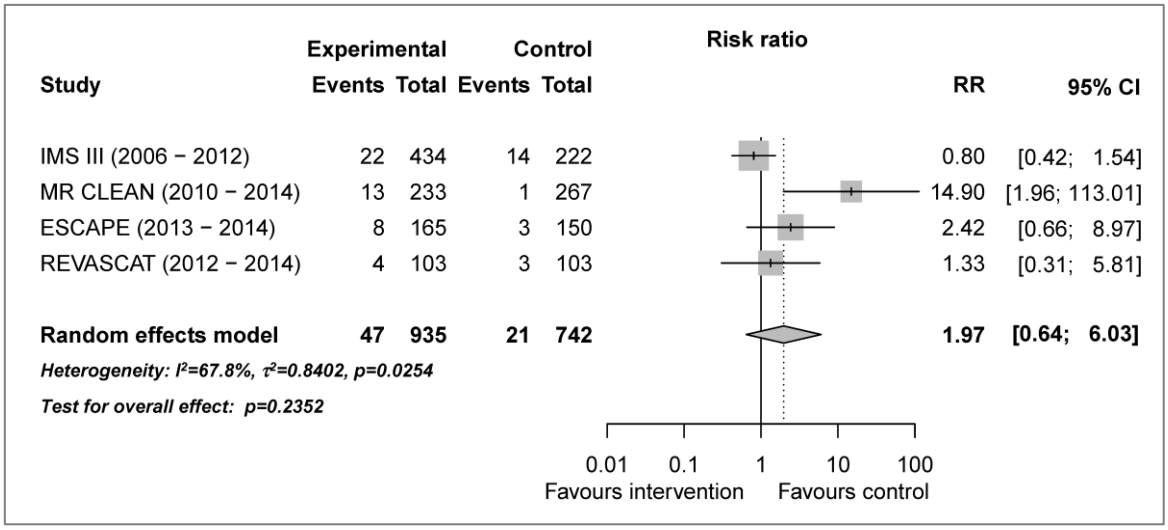
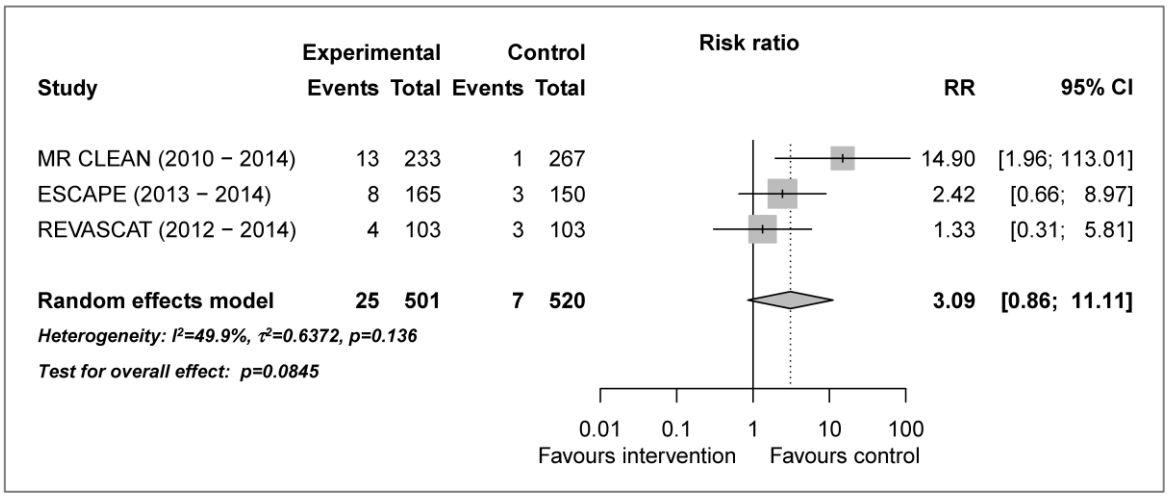


Figure 11: Subgroup random effects meta-analysis of recurrent ischaemic stroke within 90 days



Device- and/or procedure-related adverse events

Seven of the eight trials provided data on device- and/or procedure-related adverse events (SYNTHESIS Expansion did not) (Appendix 1, Table 14). These were reported differently across the seven trials, however, making comparability difficult. Five trials did not differentiate between device-related and procedure-related adverse events – MR RESCUE, IMS III, EXTEND IA, REVASCAT and ESCAPE.

The earliest trial to have begun enrolment, MR RESCUE, reported that there were ten such events among the intervention group cohort of 64 patients; it was not clear whether these events were in ten individual patients. The adverse events included one device fracture, seven vessel perforations, one vessel dissection and one embolus to a previously uninvolved territory.

IMS III reported that 16.1% (70/434) of patients in the intervention group experienced a device- or procedure-related adverse event, including groin haematoma, vessel dissection or perforation and emboli to previously uninvolved territories.

EXTEND IA reported that 11.4% (4/35) of patients experienced an adverse event which could be classified as device- or procedure-related, specifically, wire perforation (n = 1), groin haematoma (n = 1) and emboli to previously uninvolved territories (n = 2).

REVASCAT reported that there were 30 complications in their intervention cohort of 103 patients which could be classified as device- or procedure-related, specifically, arterial dissection or perforation (n = 9), emboli to previously uninvolved territories (n = 5), groin haematoma (n = 11) or pseudoaneurysm (n = 1) and vasospasm requiring treatment (n = 4). It was not clear whether these events were experienced by 30 different patients or if some patients experienced more than one of these complications.

The ESCAPE trial reported that 10.9% (18/165) of patients experienced a total of 19 adverse events which could be classified as device- or procedure-related – these included four serious adverse events (haematoma at access site, n = 3; perforation of middle cerebral artery, n = 1) and 15 'non-serious' adverse events (access site femoral haematoma, n = 11; carotid dissection, n = 1; cranial nerve palsy (cavernous sinus syndrome), n = 1; and subarachnoid haemorrhage, n = 1).

SWIFT PRIME reported that there were seven device-related adverse events in five patients (5.1%, 5/98), all of which were classified as 'non-serious', specifically, cerebral vasospasm (n = 4), intraventricular haemorrhage (n = 1), subarachnoid haemorrhage (n = 1) and subarachnoid contrast extravasation (n = 1). Procedure-related adverse events were not reported.

MR CLEAN reported that 11.2% (26/233) of patients in the intervention group experienced a procedure-related adverse event. These included emboli to previously uninvolved territories in 20 patients (8.6%), procedure-related vessel dissections in four patients (1.7%) and vessel perforations in two patients (0.9%). Device-related adverse events were not reported.

Data on device-related adverse events were available from six additional studies as discussed above (see Appendix 1, Table 11). The proportion of patients experiencing a device-related adverse event in these studies ranged from 2.8% (1/36, Soize et al. [67]) to 13.5% (24/178, Nogueira et al. [68]).

5.4 *Discussion*

This assessment of the safety of mechanical thrombectomy in acute ischaemic stroke is based on evidence from eight RCTs. For device-related events, the data from six additional studies were also included. The limitations inherent in pooling data from the eight RCTs were discussed in detail in the Section 4 (Clinical effectiveness). There are additional limitations inherent in pooling data from the additional six studies included in this domain and hence only data on device-related events were extracted from the additional studies identified as part of this safety assessment. It should also be noted that the patients undergoing mechanical thrombectomy across the various trials and prospective studies received standard medical care including IV tPA to a greater or lesser extent, and this may have influenced subsequent safety outcomes.

These limitations notwithstanding, the evidence presented suggests that mechanical thrombectomy is not associated with an increased risk of all-cause mortality at 90 days (as discussed in Section 4), SICH or with recurrent ischaemic stroke at 90 days, when compared with standard medical therapy – although it should be noted that the evidence for recurrent ischaemic stroke at 90 days is based on four trials only. Pooled data from seven trials suggest that the intervention may be associated with a higher rate of any cerebral haemorrhage when compared with standard medical therapy; the significance of this is difficult to quantify, however, because it includes all reported cases of cerebral haemorrhage, some of which would have been clinically insignificant.

While seven of the eight RCTs reported on device- and/or procedure-related events, differences in reporting make comparability difficult. Five of the trials did not differentiate between device- and procedure-related adverse events and the range of these events across the five trials varied widely; from 10.9% to 29.1% of the intervention cohort. Just one of the eight RCTs specifically reported device-related events (SWIFT PRIME, 5.1% of intervention group). Relevant data on device-related adverse events was identified in six additional studies – these reported a range from 2.8% to 13.5% of patients affected.

5 REFERENCES

[1] Pierot L, Soize S, Benaissa A, Wakhloo AK. Techniques for Endovascular Treatment of Acute Ischemic Stroke: From Intra-Arterial Fibrinolytics to Stent-Retrievers. Stroke 2015;46(3):909-14.

[2] European Stroke Organisation. Update Guidelines January 2009 New Elements. 2009; Available from: http://www.eso-stroke.org/eso-stroke/education/guidelines.html.

[3] Chen M. An Evidence-based Update on Acute Endovascular Stroke Therapy. US Neurology 2015;11(1):62-3.

[4] Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372(24):2285-95.

[5] Grotta JC, Hacke W. Stroke Neurologist's Perspective on the New Endovascular Trials. Stroke 2015;46(6):1447-52.

[6] Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. N Engl J Med 2015;372(1):11-20.

[7] Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372(11):1009-18.

[8] Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372(11):1019-30.

[9] Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. N Engl J Med 2015;372(24):2296-306.

[10] American Stroke Association. Ischemic Strokes (Clots). [Last accessed August 2015]; Available from: http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/IschemicClots/Ischemic-Strokes-Clots_UCM_310939_Article.jsp.

[11] Jayaraman MV, Hussain MS, Abruzzo T, Albani B, Albuquerque FC, Alexander MJ. Embolectomy for stroke with emergent large vessel occlusion (ELVO): report of the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery. Journal of neurointerventional surgery 2015;7(5):316-21.

[12] World Health Organization. The Atlas of Heart Disease and Stroke. [Last accessed August 2015]; Available from: http://www.who.int/cardiovascular_diseases/resources/atlas/en/.

[13] World Health Organization. The top 10 causes of death. 2014 [Last accessed August 2015]; Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

[14] Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;368(10):914-23.

[15] Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368(10):893-903.

[16] Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;368(10):904-13.

[17] Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC. 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015.

[18] ESO-Karolinska Stroke Update Conference. Consensus statement on mechanical thrombectomy in acute ischemic stroke – ESO-Karolinska Stroke Update 2014 in collaboration with ESMINT and ESNR. 2015 [Last accessed 2015 20 Feb]; Available from: http://2014.strokeupdate.org/consensus-statement-mechanical-thrombectomy-acute-ischemic-stroke.

[19] European Medicines Agency. Points to consider on clinical investigation of medicinal products for the treatment of acute stroke 2001; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003342.pdf.

[20] European Stroke Organisation. Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack. 2008; Available from: http://www.eso-stroke.org/eso-stroke/education/guidelines.html.

[21] Raychev R, Saver JL. Mechanical thrombectomy devices for treatment of stroke. Neurol Clin Pract 2012;2(3):231-5.

[22] British Association of Stroke Physicians. Standards for providing safe acute ischaemic stroke thrombectomy services. [Last accessed August 2015]; Available from: http://www.basp.ac.uk/Portals/2/Standards%20for%20providing%20safe%20acute%20ischaemic%20stroke%20thrombectomy%20services%20Oct14%20final.pdf.

[23] Pereira VM, Narata AP, Gonzalez AM, Sztajzel R, Lovblad KO. Use of stentrievers in acute stroke: tips, tricks, and current results. Tech Vasc Interv Radiol 2012;15(1):68-77.

[24] Dobkin BH. Impairments, disabilities, and bases for neurological rehabilitation after stroke. J Stroke Cerebrovasc Dis 1997;6(4):221-6.

[25] European Stroke Organisation. What Are the Costs of Stroke? [Last accessed August 2015]; Available from: http://www.eso-stroke.org/eso-stroke/stroke-information/faq/epidemiology-of-stroke.html#c39517.

[26] Marshall IJ, Wang Y, McKevitt C, Rudd AG, Wolfe CD. Trends in risk factor prevalence and management before first stroke: data from the South London Stroke Register 1995-2011. Stroke 2013;44(7):1809-16.

[27] Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B. A prospective community-based study of stroke in Germany--the Erlangen Stroke Project (ESPro): incidence and case fatality at 1, 3, and 12 months. Stroke 1998;29(12):2501-6.

[28] Kolominsky-Rabas PL, Wiedmann S, Weingartner M, Liman TG, Endres M, Schwab S. Time trends in incidence of pathological and etiological stroke subtypes during 16 years: the Erlangen Stroke Project. Neuroepidemiology 2015;44(1):24-9.

[29] Lainay C, Benzenine E, Durier J, Daubail B, Giroud M, Quantin C. Hospitalization within the first year after stroke: the Dijon stroke registry. Stroke 2015;46(1):190-6.

[30] Acandis GmbH & Co. KG. Submission File Acandis GmbH & Co. KG. 2015.

[31] MicroVention Europe. Submission File MicroVention Europe. 2015.

[32] phenox GmbH. Submission File phenox GmbH. 2015.

[33] Neuravi Ltd. Submission File Neuravi Ltd. 2015.

[34] Medtronic. Submission File Medtronic. 2015.

[35] Stryker Neurovascular. Submission File Stryker Neurovascular. 2015.

[36] Codman Neuro - Johnson & Johnson Medical. Submission File Codman Neuro - Johnson & Johnson Medical. 2015.

[37] European Stroke Organisation. Stroke Facts. 2015; Available from: http://www.eso-stroke.org/eso-stroke/strokeinformation/stroke-facts.html.

[38] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376(9735):112-23.

[39] Chen CL, Tang FT, Chen HC, Chung CY, Wong MK. Brain lesion size and location: effects on motor recovery and functional outcome in stroke patients. Arch Phys Med Rehabil 2000;81(4):447-52.

[40] Coffey C. Edward CJL, Starkstein Sergio, Robinson Robert. Stroke - the American Psychiatric Press Textbook of Geriatric Neuropsychiatry. Second Edition ed. Washington DC: American Psychiatric Press; 2000. p. 601–17.

[41] Schweizer TA, Macdonald, L. The Behavioral Consequences of Stroke. New York: Springer; 2014. p. 119–33.

[42] Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 2011;118(1-2):40-50.

[43] Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol 2005;4(11):752-9.

[44] Coulthard E, Singh-Curry V, Husain M. Treatment of attention deficits in neurological disorders. Curr Opin Neurol 2006;19(6):613-8.

[45] Lim C, Alexander MP. Stroke and episodic memory disorders. Neuropsychologia 2009;47(14):3045-58.

[46] Murray ED, Buttner N, Prize BH. Depression and Psychosis in Neurological Practice. In: Bradley WG DR, Fenichel GM, Jankovic J, editor. Bradley's Neurology in Clinical Practice: Expert Consult - Online and Print, 6th edition. Philadelphia, PA: Elsevier/Saunders; 2012. p. 100-1.

[47] Reith J, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. Stroke 1997;28(8):1585-9.

[48] Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. BMJ 1997;315(7122):1582-7.

[49] Jungehulsing GJ, Heuschmann PU, Holtkamp M, Schwab S, Kolominsky-Rabas PL. Incidence and predictors of post-stroke epilepsy. Acta Neurol Scand 2013;127(6):427-30. Epub 2013/02/13.

[50] Berglund A, Svensson L, Wahlgren N, von Euler M. Face Arm Speech Time Test use in the prehospital setting, better in the ambulance than in the emergency medical communication center. Cerebrovasc Dis 2014;37(3):212-6.

[51] Robinson TG, Reid A, Haunton VJ, Wilson A, Naylor AR. The face arm speech test: does it encourage rapid recognition of important stroke warning symptoms? Emerg Med J 2013;30(6):467-71.

[52] Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. The Lancet;383(9913):245-55.

[53] Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19(1):155-62.

[54] Kolominsky-Rabas PL, Heuschmann PU, Marschall D, Emmert M, Baltzer N, Neundorfer B. Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry: the Erlangen Stroke Project. Stroke 2006;37(5):1179-83.

[55] Truelsen T, Piechowski-Jóźwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. Eur J Neurol 2006;13(6):581-98.

[56] The European Registers of Stroke Investigators. Incidence of Stroke in Europe at the Beginning of the 21st Century. Stroke 2009;40(5):1557-63.

[57] Campbell BC, Donnan GA, Lees KR, Hacke W, Khatri P, Hill MD. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. Lancet Neurol 2015;14(8):846-54.

[58] Tatlisumak T. Implication of the recent positive endovascular intervention trials for organizing acute stroke care: European perspective. Stroke 2015;46(6):1468-73.

[59] Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified Rankin Scale: a systematic review. Stroke 2009;40(10):3393-5.

[60] Fisher M. Stroke Part III: Investigation and management. Elsevier ed2008.

[61] Duffy L, Gajree S, Langhorne P, Stott DJ, Quinn TJ. Reliability (inter-rater agreement) of the Barthel Index for assessment of stroke survivors: systematic review and meta-analysis. Stroke 2013;44(2):462-8.

[62] Palaniswami M, Yan B. Mechanical Thrombectomy Is Now the Gold Standard for Acute Ischemic Stroke: Implications for Routine Clinical Practice. Interv Neurol 2015;4(1-2):18-29.

[63] Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 2010;303(12):1180-7.

[64] Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke; a journal of cerebral circulation 1999;30(8):1538-41.

[65] Punal-Rioboo J, Atienza G, Blanco M. Safety and Efficacy of Mechanical Thrombectomy Using Stent Retrievers in the Endovascular Treatment of Acute Ischaemic Stroke: A Systematic Review. Interv Neurol 2015;3(3-4):149-64.

[66] Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet (London, England) 2012;380(9849):1241-9.

[67] Soize S, Kadziolka K, Estrade L, Serre I, Bakchine S, Pierot L. Mechanical thrombectomy in acute stroke: prospective pilot trial of the solitaire FR device while under conscious sedation. AJNR American journal of neuroradiology 2013;34(2):360-5.

[68] Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet 2012;380(9849):1231-40.

[69] Castro-Afonso LH, Abud TG, Pontes-Neto OM, Monsignore LM, Nakiri GS, Cougo-Pinto PT. Mechanical thrombectomy with solitaire stent retrieval for acute ischemic stroke in a Brazilian population. Clinics (Sao Paulo) 2012;67(12):1379-86.

[70] Jansen O, Macho JM, Killer-Oberpfalzer M, Liebeskind D, Wahlgren N. Neurothrombectomy for the treatment of acute ischemic stroke: results from the TREVO study. Cerebrovascular diseases (Basel, Switzerland) 2013;36(3):218-25.

[71] Pereira VM, Gralla J, Davalos A, Bonafe A, Castano C, Chapot R. Prospective, multicenter, single-arm study of mechanical thrombectomy using Solitaire Flow Restoration in acute ischemic stroke. Stroke; a journal of cerebral circulation 2013;44(10):2802-7.

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

METHODS AND EVIDENCE INCLUDED

A preliminary working version of the HTA Core Model® for Rapid Relative Effectiveness Assessment, based on the 'HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0', was used as the primary source for selecting the assessment elements. Additionally, assessment elements from other EUnetHTA Core Model Applications were screened and included if believed relevant to the present assessment.

The following domains were developed within the present assessment:

- Description and technical characteristics of the technology (TEC);
- Health Problem and Current Use of Technology (CUR);
- Clinical effectiveness (EFF);
- Safety (SAF).

Researchers at each of the 2 authoring agencies (HIQA, IZPH) identified the studies and relevant data sources necessary to answer the research questions for their selected domains (HIQA, EFF and SAF; IZPH, TEC and CUR).

Inclusion and exclusion of the studies was based on the PICO protocol.

For the 'Description and technical characteristics of the technology' and 'Health Problem and Current Use of Technology' domains, no restrictions in terms of study design were applied.

The accepted study design for 'Clinical Effectiveness' was RCTs. For the 'Safety' domain, prospective clinical studies could also be included where relevant data was presented. Searches were limited to 2005 to the present. All search terms used were in the English language only. The following sources were used to obtain information:

- PubMed (Medline)
- Embase
- Cochrane Register of Controlled Trials
- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)
    - ISRCTN
    - EU Clinical Trials Registry
- metaRegister of Controlled Trials (mRCT)
- Stroke Trials Registry
- Request to the manufacturer
- Health Products Regulatory Authority, Ireland

Two researchers independently extracted (RG, CT) and rated (RG, CT) the studies included. Any disagreements were resolved through discussion.

Effectiveness and safety were assessed by using the GRADE methodology as this allows for a transparent summary of the evidence in a qualitative manner. Risk of bias was assessed using the Cochrane risk of bias tool for RCTs; assessment was based on the presence or absence of evidence of random sequence generation, allocation concealment, blinding of participants and

personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Other potential biases were also considered on a study by study basis.
Deviations to the project plan are outlined in section 1 (Scope).

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategy for Pubmed (Medline), Date of Search 11th August 2015

((((((embolectomy[Title/Abstract]) OR "mechanical thrombus removal"[Title/Abstract]) OR "mechanical embolus removal"[Title/Abstract]) OR "endovascular intervention"[Title/Abstract]) OR "mechanical device"[Title/Abstract]) OR "endovascular recanalisation"[Title/Abstract]) OR "endovascular embolectomy"[Title/Abstract]
OR
(((((((((stroke[MeSH]) OR stroke[tiab])) OR “Cerebrovascular accident”[Title/Abstract]) OR "Large vessel occlusion"[tiab]) OR "Large artery occlusion"[tiab])) AND ((((((((((((thrombectomy[MeSH terms] OR Thrombectomy[Text Word])))) OR ((“mechanical thrombolysis”[MeSH terms] OR mechanical thrombolysis[Text Word])))) OR ((“endovascular procedures”[MeSH terms] OR endovascular procedures[Text Word])))) OR ((angioplasty[MeSH terms] OR angioplasty[Text Word])))) OR "endovascular therapy"[Title/Abstract]) OR “revascularization”[Title/Abstract]) OR “stent retriever”[Title/Abstract]) OR "mechanical recanalization"[Title/Abstract]) OR "stent recanalization"[Title/Abstract]) OR "clot retrieval"[Title/Abstract]) OR "retrievable stent"[Title/Abstract]) OR "intra-arterial"[Title/Abstract])))
AND
((((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR drug therapy [sh]) OR randomly [tiab]) OR trial [tiab]) OR groups [tiab])) NOT ((animals [mh] NOT humans [mh])))) AND (((((((embolectomy[Title/Abstract]) OR "mechanical thrombus removal"[Title/Abstract]) OR "mechanical embolus removal"[Title/Abstract]) OR "endovascular intervention"[Title/Abstract]) OR "mechanical device"[Title/Abstract]) OR "endovascular recanalisation"[Title/Abstract]) OR "endovascular embolectomy"[Title/Abstract]) AND ("2005/01/01"[PDat] : "3000/12/31"[PDat]))
3,766 results

Search strategy for EMBASE, Date of Search 11th August 2015

1	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR 'randomi?ed controlled' NEXT/1 trial* OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR allocated NEAR/2 random OR single NEXT/1 blind* OR double NEXT/1 blind* OR (treble OR triple) NEAR/1 blind* OR placebo*	1531314
2	'thrombectomy'/exp OR 'thrombectomy'	14046
3	'endovascular therapy':ab,ti	3550
4	'revascularisation':ab,ti	7943
5	'stent retriever':ab,ti	193
6	'mechanical recanalization':ab,ti	233
7	'stent recanalization':ab,ti	20

8	'clot retrieval':ab,ti	174
9	'retrievable stent':ab,ti	88
10	'intra-arterial':ab,ti	15947
11	'mechanical thrombectomy'/exp OR 'mechanical thrombectomy'	2830
12	'endovascular procedure'/exp OR 'endovascular procedure'	21669
13	'angioplasty'/exp OR 'angioplasty'	82897
14	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	134822
15	'stroke'/exp OR 'stroke'	343742
16	'cerebrovascular accident':ab,ti	4837
17	'large vessel occlusion':ab,ti	403
18	'large artery occlusion':ab,ti	133
19	15 OR 16 OR 17 OR 18	345003
20	1 AND 14 AND 19 AND [2005-2015]/py	3140
21	'embolectomy':ab,ti	3239
22	'endovascular recanalization':ab,ti	373
23	'endovascular embolectomy':ab,ti	28
24	'mechanical thrombus removal':ab,ti	14
25	'mechanical embolus removal':ab,ti	33
26	'endovascular intervention':ab,ti	1557
27	'mechanical device':ab,ti	742
28	21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27	5901
29	1 AND 28 AND AND [2005-2015]/py	300
30	29 OR 20	3382

3,382 results

Search strategy for International Clinical Trials Registry Platform (ICTRP)

Date of Search 10th August 2015
Condition: Stroke or cerebrobascular accident
AND
Intervention: thrombectomy OR mechanical OR endovascular OR angioplasty OR revascularization OR stent OR embolectomy 01/01/2005 to present
74 results

Search strategy for MetaRegister of Controlled Trials (mRCT)

Date of Search 10th August 2015

Not available. Directed to ICTRP and UKCTG (this latter one pools data from ICTRP and clinicaltrials.gov and therefore not searched).

Search strategy for Stroke Trials Registry

Date of Search 10th August 2015
Search terms: thrombectomy OR mechanical OR endovascular OR angioplasty OR revascularization OR stent
Limited to randomized trials
Thrombectomy – 17
Mechanical Thrombolysis – 2
Mechanical – 0
Endovascular – 40
Angioplasty – 14
Revascularization – 24
Stent – 93
Embolectomy – 0
Mechanical thrombus removal – 0
Mechanical embolus removal – 0

Search strategy for Cochrane register of controlled trials

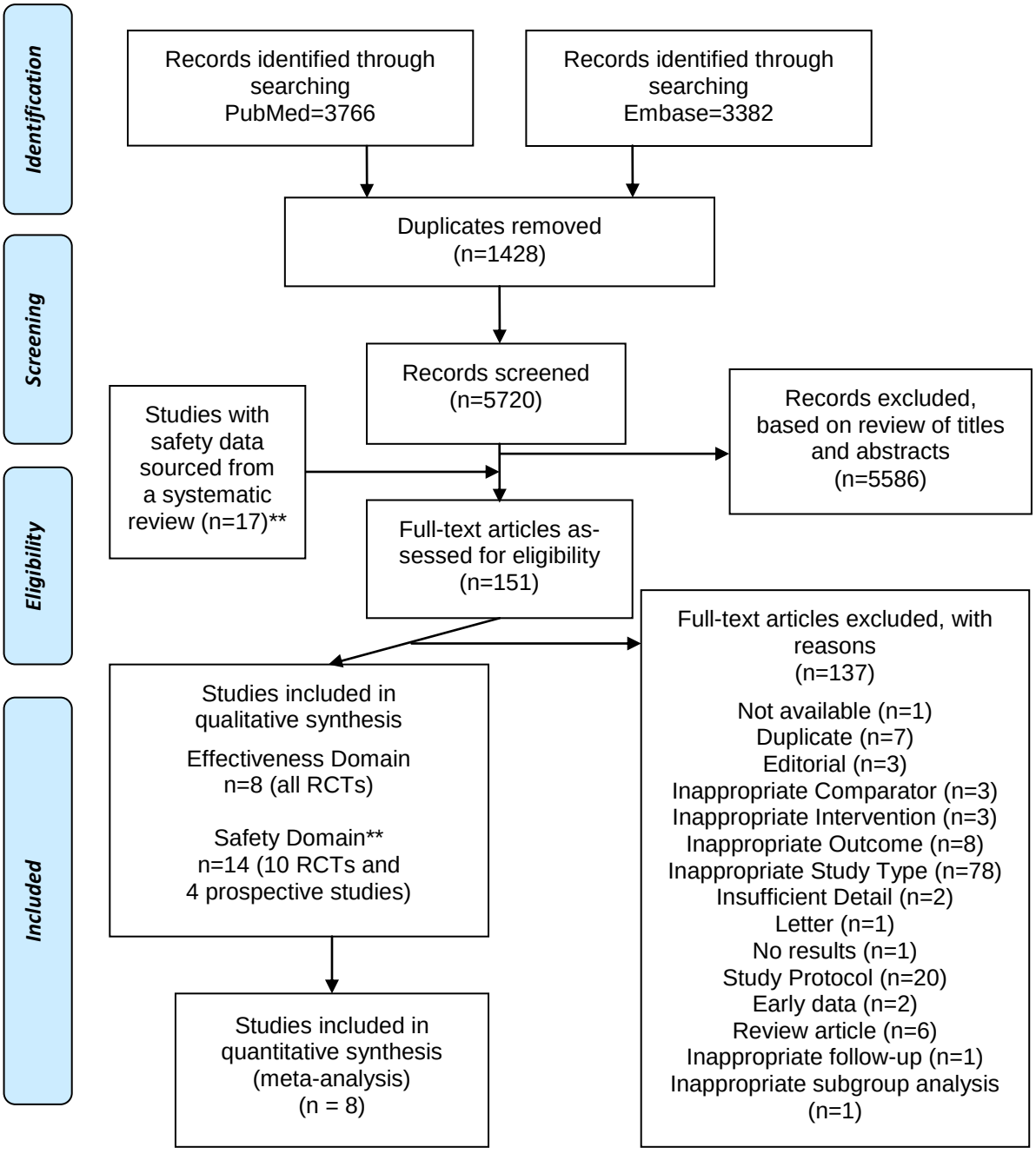
Date of search: 11 August 2015
'("stroke" OR "cerebrovascular accident") AND ("thrombectomy" OR "endovascular" OR "stent" OR "mechanical" OR "angioplasty" OR "revascularization" OR "embolectomy") in Record Title in Trials' 2005 to present.
170 results

Search strategy for ClinicalTrials.gov

Date of search: 11 August 2015
("stroke" OR "cerebrovascular accident") AND ("thrombectomy" OR "endovascular") | Adult, Senior | received on or after 01/01/2005
130 results

FLOW CHART OF STUDY SELECTION

(PUBMED (MEDLINE) AND EMBASE – NO ADDITIONAL STUDIES IDENTIFIED THROUGH OTHER DATABASES)



** The safety domain includes analysis of 2 RCTs and 4 prospective studies identified in a systematic review and meta-analysis performed by Puñal-Riobóo et al. in 2015 [65].

DESCRIPTION OF THE EVIDENCE *USED*

Evidence tables of individual studies for health problem and current use of the technology

Table 6: Indications of authorised mechanical thrombectomy devices

Source: [30-36]

Aperio® Thrombectomy Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
European countries (i.e. Germany, Italy, Spain, UK, Finland, Poland, Croatia, Austria, Switzerland)	DQS Medizinprodukte GmbH	Authorised	The Aperio® Thrombectomy Device is intended for restoration of the arterial flow in patients diagnosed with ischemic stroke due to large intracranial vascular occlusion (i.e. in the internal carotid artery, M1 and M2 segments of the MCA,). Patients who fail intravenous thrombolytic therapy or who are ineligible for thrombolysis may be suited for treatment with the Aperio® Thrombectomy Device	• For occlusions in vessels with a diameter not within the recommended vessel diameter range (see label). • For patients with anatomic conditions or vessel pathologies (i.e. stenosis proximal to the occlusion to be treated) that may preclude a safe thrombus removal. • For calcified lesions which cannot be removed by percutaneous transluminal angioplasty (PTA). • In cases of recent, non-lysed, non-organized thrombotic or embolic material	17 Apr 2014 Exp. 16 Apr 2019	YES	516327 MRA

EmboTrap® Revascularization Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	BSI	Authorised	The EmboTrap® Revascularization Device (the Device) is intended to be used to restore blood flow in patients experiencing an acute ischemic stroke due to a large vessel neurovascular occlusion. The Device is designed for use in the anterior and posterior neurovasculature in vessels of diameter 1.5mm to 5mm, such as the internal carotid artery, the M1 and M2 segments of the middle cerebral artery, the A1 and A2 segments of the anterior cerebral artery, the basilar, the posterior cerebral and the vertebral arteries. The Device should only be used by physicians trained in neurointerventional catheterization and the treatment of ischemic stroke.	• Allergy or hypersensitivity to Nickel-Titanium.	EU	BSI	Authorised

ERIC® Retrieval Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	DQS	Authorised	The ERIC® Retrieval Device is intended for use in the revascularization of acute ischemic stroke caused by the intracranial occlusive vessels of patients who are not eligible for intravenous tissue plasminogen activator, IV tPA, or who fail IV tPA therapy.	• Patients with known hypersensitivity to nickel-titanium. • Patients with stenosis proximal to the thrombus site that may prevent safe recovery of the ERIC® Retrieval De-	05 May 2014 (12 Aug 2018)	YES	Cert# 512594 MRA ID# 170594250

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				vice. • Patients with angiographic evidence of carotid dissection.			

Mind Frame Capture™ LP Revascularization Device

Country	Institution (EMA, FDA, TGA etc)	Authorisation yes/no/ongoing	If authorised verbatim wording of the indication(s)	Specified contraindications	Approval number (if known)
US	FDA	Authorised	The Capture™ LP Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	Use of the MindFrame Capture™ LP Device is contraindicated under these circumstances: • Patients with known sensitivity to nickel-titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the MindFrame Capture™ Device • Patients with angiographic evidence of carotid dissection.	K141516
EU	DQS Medizinprodukte GmbH	Authorised	The MindFrame Capture™ LP is indicated for temporary use to restore blood flow in the cerebral vasculature of patients suffering from an acute ischemic stroke. The MindFrame Capture™ LP is positioned across the embolus or blood clot and is used to facilitate the restoration of blood flow and removal of the clot obstruction. The MindFrame Capture™ LP is indicated for: • Endovascular temporary use in patients with acute ischemic stroke • Endovascular temporary use to restore blood flow in patients who are experiencing symptoms of an acute ischemic stroke caused by an embolus in a cerebral vessel.	• Delivery of pharmacological agents not routinely used to treat ischemic stroke. • Patient presents with nickel allergy. • Patients with suspected or known allergies to contrast media. • Pregnancy • Glucose <50mg/dl • Excessive vessel tortuosity that prevents the placement of the device. • Known haemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy with INR>3.0. • Patient received heparin within 48 hours with a PTT greater than 2 times the lab normal. • Patient has baseline platelets <30,000. • Evidence of rapidly improving neurological signs of stroke.	CE Certificate: 281863 MR2

				• Coma • Pre-existing neurological or psychiatric disease. • Patient has severe sustained hypertension. • CT/MRI scan reveals significant mass effect with midline shift. • Patient's angiogram shows an arterial stenosis >50% proximal to the embolus.	

pREset LT Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	DQS Medizinprodukte GmbH	Authorised	The pRESET (LT) Thrombectomy Stent is designed for mechanical clot retrieval from intracranial arteries as acute ischemic stroke treatment • for patients who are ineligible for intravenous thrombolysis or • for patients who failed thrombolysis therapy and • as a supplement treatment of initiated thrombolysis therapy.	No specified contraindications	PRE-4-20: 22 Aug 2011; PRE-6-30: 01 Jun 2012; Pre-LT-X-XX: 11 Nov 2013 Expiry Date (EC-Design Examination Certificate: 18 Aug 2016	Date of approval is date of launch.	Certificate registration No.: 495569 MRA Certificate unique ID: 170582491

REVIVE™ Self Expanding (SE) Thrombectomy Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	BSI	Authorised	The REVIVE SE Thrombectomy Device is intended to restore blood flow in patients with acute ischemic stroke secondary to intracranial occlusive vessel disease by providing temporary bypass across the occlusion and/or by the nonsurgical removal of emboli and thrombi. It may be used with aspiration and with the injection or infusion of contrast media and other fluids.	• Blood vessel with extreme tortuosity or other conditions preventing the access of the device; • Patients with a known hypersensitivity or allergy to nitinol; • Reference vessel diameter less than 1.5 mm.	31 January 2012	YES	CE582680
Israel	BSI	Authorised	Same as above	Same as above	20 July 2012	YES	CE582680
Venezuela	BSI	Authorised	Same as above	Same as above	2 October 2013	YES	CE582680
Guatemala	BSI	Authorised	Same as above	Same as above	27 June 2013	YES	CE582680
Colombia	BSI	Authorised	Same as above	Same as above	15 October 2013	YES	CE582680
Peru	BSI	Authorised	Same as above	Same as above	20 Nov 2013	YES	CE582680
Mexico	BSI	Authorised	Same as above	Same as above	17 Jan 2014	YES	CE582680
Uruguay	BSI	Authorised	Same as above	Same as above	11 June 2014	YES	CE582680
China	BSI	Authorised	Same as above	Same as above	10 July 2014	YES	CE582680
South Korea	BSI	Authorised	Same as above	Same as above	13 Aug 2014	YES	CE582680
Taiwan	BSI	Authorised	Same as above	Same as above	24 June 2014	YES	CE582680
India	BSI	Authorised	Same as above	Same as above	30 Jan 2015	YES	CE582680

SOFIA™ Aspiration Catheter, SOFIA™ PLUS

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	DQS	Authorised	The SOFIA™ Catheter is indicated for general intravascular use, including the neuro and peripheral vasculature. The SOFIA™ Catheter can be used to facilitate introduction of diagnostic or therapeutic agents. The SOFIA™ Catheter is not intended for use in coronary arteries. Moreover, the SOFIA™ Catheter is intended for use in removal/aspiration of emboli and thrombi from selected blood vessels in the arterial system, including the peripheral and neuro vasculatures.	There are no known contraindications.	18 Feb 2015 (15 Sep 2018)	YES	Cert # 487703 MRA ID# 170616782

Solitaire™ 2 Revascularization Device

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Australia	Therapeutic Goods Administration	Authorised	The Solitaire™ 2 Revascularization Device is designed to restore blood flow in patients experiencing ischemic stroke due to large intracranial vessel occlusion. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The device is designed for use in the neurovasculature such as the internal carotid artery, M1 and M2	• Patients with known sensitivity to nickel-titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the Solitaire™ 2 Revascularization Device • Patients with angiographic evidence of carotid dissection.	18 Nov 2014	YES	ARTG ID: 230784

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
			segments of the middle cerebral artery, basilar and vertebral arteries.				
European Union	DQS Medizinprodukte GmbH	Authorised	The Solitaire™ 2 Revascularization Device is designed for use in the flow restoration of patients with ischemic stroke due to large intracranial vessel occlusion. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment. The Solitaire™ 2 Revascularization Device should only be used by physicians trained in interventional neuroradiology and treatment of ischemic stroke.	• Patients with known sensitivity to nickel-titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the Solitaire™ 2 Revascularization Device • Patients with angiographic evidence of carotid dissection.	13 Aug 2013	YES	CE Certificate: 281863 MR2
Japan	Ministry of Health, Labor and Welfare (MHLW)	Authorised	The Solitaire™ 2 Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	• Patients with known sensitivity to nickel-titanium, radiographic contrast agents or nickel-chroimium. • Arterial tortuosity that would prevent the Solitaire™ 2 Revascularization Device from reaching the target vessel. • Patients with angiographic evidence of carotid dissection, occulusion or vasculitis of whole carotid artery • Patient with highly suspected cerebral bleeding as follows 1. CT or MRI evidence of haemorrhage on presentation 2. CT or MRI showing marked compression observation such as median line excursion 3. CT showing hypodensity	08 Jun 2015	YES	22500BZX 00543000

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				or MR showing hyperintensity involving greater than 1/3 of the middle cerebral artery (MCA) territory (or in other territories, >100 cc of tissue) on presentation 4. Uncontrolled hypertension defined as systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg 5. Bleeding diathesis such as cranial tumor 6. Anticoagulated patient with PT-INR>3.0 or APTT elevated 7. Platelet count < 30,000/mm3			
US	US Food and Drug Administration – Center For Devices and Radiological Health	Authorised	The Solitaire™ 2 Revascularization Device is intended to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	Use of the Solitaire™ 2 Revascularization Device is contraindicated under these circumstances: • Patients with known sensitivity to nickel-titanium. • Patients with stenosis and/or pre-existing stent proximal to the thrombus site that may preclude safe recovery of the Solitaire™ 2 Revascularization Device • Patients with angiographic evidence of carotid dissection.	30 Nov 2012	YES	K123378

Trevo® ProVue™ Retrieval System, Trevo® XP ProVue™ Retrieval System

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
EU	LNE (laboratoire national de métrologie et d'essais)	Authorised	The Trevo® Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment	None	Effective date 16 Jun 2015 Expiry date: 29 Sep 2017	YES	
US	FDA	Authorised	The Trevo® Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment	None	TREVO: 03 Aug 2012 TREVO ProVue: 13 Jan 2014 Trevo XP ProVue: 06 Apr 2015	Yes	
Japan (TREVO ProVue)	MHLW	Authorised	Retrievers are intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	• Known serious allergy for Ni-Ti Alloy, Platinum /iridium alloy and Stainless Steel. • Known haemorrhagic diathesis. • Known coagulation factor deficiency. • Oral anti-coagulant therapy with INR > 3.0 • Platelets < 30,000. • Uncontrolled and sustained severe hypertension (systolic blood pressure >185 mmHg or diastolic blood pressure > 110mmHg. • CT or MRI shows significant mass effect with midline shift. • History of severe allergy (more than a rash) to contrast media.	28 Mar 2014 (effective period:5 years)	YES	22600BZX00166000

Country	Institution issuing approval	Authorisation status yes/no/ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contraindications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				• Patients who have arterial tortuosity to prevent device delivery to target vessel. • Following patients who will have highly possible intracranial hemorrhage. 1) CT/MR evidence of haemorrhage 2) CT showing hypodensity or MR showing hyperintensity involving greater than 1/3 of MCA territory. For non-MCA territory, CT showing hypodensity or MR showing hyperintensity involving >100cc of tissue.			
Australia (TREVO ProVue)	Therapeutics Goods Administration (TGA)	Authorised	The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	As per DFU	27 Apr 2013	YES	208795
(TREVO XP ProVue)	Therapeutics Goods Administration (TGA)	Authorised	The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV tPA) or who fail IV tPA therapy are candidates for treatment.	As per DFU	20 Nov 2014 (3mm, 4mm XP) 14 Jul 2015 (6mm XP)	YES	230859

Table 7: Management of ischaemic stroke according to guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
American Heart Association/American Stroke Association (AHA/ASA) 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	June 29, 2015	US, Healthcare Professionals World-wide	AHA/ASA recommendations on endovascular interventions are summarised below – refer to the guideline document for further recommendations on imaging and systems of stroke care.
			• Patients eligible for intravenous (IV) r-tPA should receive IV r-tPA even if endovascular treatments are being considered
			• Patients should receive endovascular therapy with a stent retriever if they meet the following criteria: pre-stroke mRS score (0–1), timing of IV r-tPA treatment from stroke onset (within 4.5 h), causative occlusion of the ICA or proximal MCA (M1), age (≥18 years), NIHSS score (≥6), ASPECTS (≥6), and ability to initiate treatment within 6 h of symptom onset.
			• Reperfusion to mTICI grade 2b/3 should be achieved as early as possible and within 6 h of stroke onset
			• When treatment is initiated >6 h from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1)
			• In carefully selected patients with anterior circulation occlusion who have contraindications to IV r-tPA, endovascular therapy with stent retrievers completed within 6 h of stroke onset is reasonable
			• Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries
			• Endovascular therapy with stent retrievers may be reasonable for some patients <18 years of age with acute ischemic stroke who have demonstrated large vessel occlusion in whom treatment can be initiated (groin puncture) within 6 h of symptom onset, but the benefits are not established in this age group
			• Although the benefits are uncertain, use of endovascular therapy with stent retrievers may be reasonable for patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score of >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the internal carotid artery or proximal MCA (M1)
			• Observing patients after IV r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended
			• Use of stent retrievers is indicated in preference to the MERCI device. • The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances.
			• The use of proximal balloon guide catheter or a large bore distal access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
			• The technical goal of the thrombectomy procedure should be a mTICI 2b/3 angiographic result to maximise the probability of a good functional clinical outcome. • Use of salvage technical adjuncts including intra-arterial (IA) fibrinolysis may be reasonable to achieve these angiographic results, if completed within 6 hours of symptom onset
			• Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered but the usefulness is unknown
			• Initial treatment with IA fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of <6 h duration caused by occlusions of the MCA • Endovascular therapy with stent retrievers is recommended over IA fibrinolysis as first-line therapy
			• IA fibrinolysis initiated within 6 h of stroke onset in carefully selected patients who have contraindications to the use of IV r-tPA might be considered, but the consequences are unknown
			• It might be reasonable to favour conscious sedation over general anaesthesia during endovascular therapy for acute ischemic stroke. However, the ultimate selection of anaesthetic technique during endovascular therapy for acute ischemic stroke should be individualised based on patient risk factors, tolerance of the procedure, and other clinical characteristics
European Stroke Organisation (ESO), the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) Consensus statement on mechanical thrombectomy in acute ischaemic stroke – ESO-Karolinska Stroke Update 2014 in collaboration with ESMINT and ESNR	February 2015	EU	• ESO recommendations on mechanical thrombectomy treatment are summarised below – refer to the guideline document for further recommendations on diagnostics and patient selection for treatment.
			• 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
			• Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved
			• If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions
			• Patients with acute basilar artery occlusion should be evaluated in centres with multimodal imaging and treated with mechanical thrombectomy in addition to intravenous thrombolysis when indicated alternatively they may be treated within a randomised controlled trial for thrombectomy approved by the local ethical committee
			• 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 neuroanesthesiology

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation
			• Mechanical thrombectomy should be performed by a trained and experienced neurointerventionalist who meets national and/or international requirements
			• The choice of anesthesia depends on the individual situation; independently of the method chosen, all efforts should be made to avoid thrombectomy delays

Source: [17, 18]

Evidence tables of individual studies for clinical effectiveness and safety

Table 8: Organisational characteristics of eight included randomised controlled studies

Author Year published	Trial Name	Country	No. Centres	Products Used	Sponsor	Study Duration
Kidwell 2013	MR RESCUE	US, Canada	22	Merci Retriever; Penumbra System;	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.	2004 - 2011
Broderick 2013	IMS3	USA, Canada, Australia, Europe	58	Merci Retriever; Penumbra System; Solitaire™ FR	National Institutes of Health, National Institute of Neurological Disorders and Stroke, Genentech, and industry (Genentech, EKOS, Concentric Medical, Cordis Neurovascular, Boehringer)	2006 - 2012
Ciccone 2013	Syntheis Expansion	Italy	24	Including: Solitaire, Penumbra Trevo, Merci	Italian Medicines Agency	2008 - 2012
Berkhemer 2015	MR CLEAN	Netherlands	16	Any device that was CE marked or had FDA approval could be used – retrievable stents were used in 81.5% of cases	Dutch Heart Foundation and others	2010 - 2014
Campbell 2015	EXTEND IA	Australia, New Zealand	10	Solitaire™ FR	Covidien	2012 - 2014
Jovin 2015	REVASCAT	Spain	4	Solitaire™ FR	Covidien	2012 - 2014
Saver 2015	SWIFT PRIME	US, Europe	39	Solitaire™ FR; Solitaire™ 2	Covidien	2012 - 2014
Goyal 2015	ESCAPE	Canada, Ireland, USA, UK, South Korea	22	Solitaire™ FR (n = 100) + unspecified others (n = 30)	Covidien and others	2013 - 2014

Table 9: Study characteristics of eight included randomised controlled studies

Author Year published Name	Objective	Comparator	Inclusion Criteria						Exclusion Criteria (Imaging/other)
			Age	Location of Stroke	Pre Stroke FA	Baseline NIHSS	IV tPA	Thrombectomy	
Kidwell 2013 MR RESCUE	Determine if patients selected for revascularization on basis of penumbral-imaging pattern have better outcomes than patients treated medically or those with nonpenumbral imaging patterns	Standard medical care	18-85	Anterior circulation	mRS≤2	≥ 6 & < 30	Within 4.5hrs of onset	Within 8hrs of onset	Proximal ICA occlusion, proximal carotid stenosis > 67% or dissection on MRA, CTA
Broderick 2013 IMS3	Determine efficacy of endovascular therapy after IV tPA	IV tPA (0.9 mg/kg body weight administered over a 1-hour period; maximum dose, 90 mg)	18-82	M1, ICA or Basilar Artery	mRS≤2	≥10 at start of IV tPA or >7 and <10 with occlusion seen in M1/ICA/Basilar artery on CTA	Within 3hrs of onset	Within 5hrs of onset	Large (> 1/3 of the MCA) regions of clear hypodensity on baseline imaging. (ASPECTS < 4 used as guideline when evaluating >1/3 region of territory involvement)
Ciccone 2013 SYNTHESIS Expansion	To assess whether endovascular treatment, including the options of a mechanical device and IA tPA, is more effective than the currently available treatment with IV tPA	IV tPA, 0.9 mg/kg body weight (maximum, 90mg for patients with a body weight of ≥100 kg) - to be delivered within 1 hour	18-80	-	-	-	Within 4.5hrs of onset in control group	Within 6hrs of onset	Intra-cranial haemorrhage
Author Year published Name	**Objective**	**Comparator**	**Inclusion Criteria**						**Exclusion Criteria (Imaging/other)**
			Age	**Location of Stroke**	**Pre Stroke FA**	**Baseline NIHSS**	**IV tPA**	**Thrombectomy**	
Berkhemer 2015 MR CLEAN	To test if IA treatment plus usual care is more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation	Usual care alone (which could include IV tPA	18+	Intracranial ICA, M1 or M2, ACA	-	NIHSS ≥ 2	-	Within 6hrs of onset	Intra-cranial haemorrhage

Campbell 2015 EXTEND IA	To test whether endovascular thrombectomy will improve outcomes in patients with anterior circulation ischemic stroke selected within 4.5hrs of stroke onset	IV tPA (0.9 mg/kg body weight)	18+	Anterior Circulation	mRS≤2	-	Within 4.5hrs of onset	Within 6hrs of onset	Irreversibly injured brain on CT perfusion imaging (diagnosed if the relative cerebral blood flow was <30% that in normal tissue)
Jovin 2015 REVASCAT	To determine efficacy & safety of neurovascular thrombectomy with the Solitaire™ stent retriever	Medical therapy alone	18-80	Proximal anterior circulation	mRS≤1	≥6	-£	Within 8hrs of onset	ASPECTS score <7 on non-contrast CT or ASPECTS score <6 on DWI MRI
Saver 2015 SWIFT PRIME	To establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with IV tPA versus IV tPA alone	IV tPA alone	18-80	Intracranial ICA, M1 or both	mRS≤1	≥8	Within 4.5hrs of onset	Within 6hrs of onset	ASPECTS score <6 on non-contrast CT or DWI MRI*
Author Year published Name	**Objective**	**Comparator**	**Inclusion Criteria**						**Exclusion Criteria (Imaging/other) Age**
			Age	**Location of Stroke**	**Pre-stroke FA**	**Baseline NIHSS**	**IV tPA**	**Thrombectomy**	
Goyal 2015 ESCAPE	To test if patients selected on the basis of results of CT and CTA, would benefit from rapid endovascular treatment	Current Standard of Care	18+	Proximal anterior circulation	Barthel Index ≥90	-	-£	Within 12hrs of onset	ASPECTS score <6 on non-contrast CT or CTA

FA = Functional Ability, IA = intraarterial, IV = intravenous, M1 = first segment of middle cerebral artery, ICA = internal carotid artery, ACA = Anterior Cerebral Artery, mRS = modified Rankin Scale, CTA = Computed Tomographic Angiography, MRA = Magnetic Resonance Angiography, DSA = Digital Subtraction Angiography

* Before imaging entry criteria revision, this criterion stated: “Core Infarct and hypoperfusion: a) MRI- or CT-assessed core infarct lesion greater than 50 cc; b) Severe hypoperfusion lesion (10 sec or more Tmax lesion larger than 100 cc); c) Ischemic penumbra < 15 cc and mismatch ratio ≤1.8.” After imaging entry criteria revision, sites could enroll based on ASPECTS findings only, but were still encouraged to obtain perfusion imaging and use this information if available. A total of 71 patients were enroled under the initial imaging entry criteria and 125 patients under the revised imaging entry criteria.

£ **Eligibility for IV thrombolysis was not mandatory in REVASCAT or ESCAPE.**

Table 10: Patient characteristics of eight included randomised controlled trials

Author Yr Published Name	No. Patients	Age (Mean)	Sex % Male	Pre Stroke NIHSS (Median (IQR))	Pre Stroke mRS	Proportion of intervention group who received... (%)			
						M.T.	GA	IV tPA	IA tPA
Kidwell 2013 MR RESCUE	I: 64 C: 54	I: 64 C: 67	I: 47 C: 50	I: 16 (12-18) AND 19 (17-22) C: 16 (11-18) AND 20.5 (17-23)	-	100[+] (64/64)	-	43.7	12.5
Broderick 2013 IMS3	I: 434 C: 222	I: 69 (Md) C: 68 (Md)	I: 50 C: 55	I: 17 (range 7-40) C: 16 (range 8-30)	mRS 0 = I – 87.3% C – 88.7%	27.6 (120/434)	-	100	61
Ciccone 2013 SYTHESIS Expansion	I: 181 C: 181	I: 66 C: 67	I: 59 C: 57	I: 13 (9-17) C: 13 (9-18)	-	30.9 (56/181)	12	0	-
Berkhemer 2015 MR CLEAN	I: 233 C: 267	I: 66 (Md) C: 66 (Md)	I: 58 C:59	I: 17 (14-21) C: 18 (14-22)	mRS 0 = I - 81.5% C - 80.1%	81.5 (190/233)	37.8	87.1	84.1
Campbell 2015 EXTEND IA	I: 35 C: 35	I: 69 C: 70	I: 49 C: 49	I: 17 (13-20) C: 13 (9-19)	All mRS < 2	77.1 (27/35)	36	100	-
Jovin 2015 REVASCAT	I: 103 C: 103	I: 66 C: 67	I: 53 C: 52	I: 17 (14-20) C: 17 (12-19)	mRS 0 = I - 83.5% C – 80.6%	95.1 (98/103)	6.7	68	1*
Saver 2015 SWIFT PRIME	I: 98 C: 98	I: 65 C: 66	I: 47 C: 55	I: 17 (13-19) C: 17 (13-20)	mRS 0 or 1 = I – 98% C – 99%	88.7 (87/98)	37	-	-
Goyal 2015 ESCAPE	I: 165 C: 150	I: 71 (Md) C: 70 (Md)	I: 48 C: 47	I: 16 (13-20) C: 17 (12-20)	-	91.5 (151/165)	9.1	72.7	-

I = Intervention Group, C = Controls, Md = Median, MT = Mechanical Thrombectomy, GA = General Anaesthetic, IV = intravenous, IA = intraarterial, tPA = tissue plasminogen activator

[+]Per-protocol analysis.

*The authors state that 1 patient received IA tPA outside of protocol – it is unclear whether any other patients in the intervention group received IA tPA.

Table 11: Timing characteristics of eight included randomised controlled trials

Author Year published Name	Median Time in minutes from stroke onset to.... (median and IQR, unless otherwise stated)			Duration of Procedure (median and IQR)
	Thrombolysis	Randomisation	Groin Puncture	
Kidwell 2013 MR RESCUE	-	I: 318 +/- 96 (mean, SD) C: 346 +/-69 (mean, SD)	I: 381 +/- 74 (mean, SD)	-
Broderick 2013 IMS3	I: 122.4 +/-33.7 (mean, SD) C: 121.2 +/-33.8 (mean, SD)	Within 40minutes of initiation of IV tPA	I: 208 +/- 46.7 (mean, SD)	-
Ciccone 2013 SYTHESIS Epansion	I: NA C: 165 (140-200)	I: 148 (124-190) C: 145 (119-179)	I: 225 (194-260)	-
Berkhemer 2015 MR CLEAN	I: 85 (67-110) C: 87 (65-116)	I: 204 (152-251) C: 196 (149-266)	I: 260 (210-313)	-
Campbell 2015 EXTEND IA	I: 127 (93-162) C: 145 (105-180)	I: 29 (23-46) C: 36 (18-55) (this is the time from initiation of IV tPA to randomisation)	I: 210 (166-251)	I: 43 (24-53)
Jovin 2015 REVASCAT	I: 117.5 (90.0–150.0) C: 105.0 (86.0–137.5)	I: 223 (170–312) C: 226 (168–308)	I: 269 (201–340)	I: 75 (50-114)
Saver 2015 SWIFT PRIME	I: 110.5 (85-156) C: 117 (80-155)	I: 190.5 (141-249) C: 188 (130-268)	I: 224 (165-275)	-
Goyal 2015 ESCAPE	I: 110 (80-142) C: 125 (89-183)	I: 169 (117-285) C: 172 (119-284)	Time from stroke onset to study CT: I: 134 (77-247) Time from study CT to groin puncture I: 51 (39-68)	-

I = Intervention Group, C = Controls, NA = not applicable

Note Re Kidwell, 2013: The intervention and control groups were split into those with and without favourable penumbral patterns.

Table 12: Effectiveness outcomes of eight included randomised controlled trials

Author Year published Name	mRS ≤2 at 90 days	Mortality at 90 days	NIHSS	Barthel Index at 90 days	mTICI score on final angiography
Kidwell 2013 MR RESCUE	I: 8/64 C: 10/54	I: 12/64 C: 13/54	-	-	2a-3 at day 7 I: 40/56
Broderick 2013 IMS3	I: 177/415 C: 86/214	I: 83/434 C: 48/222	-	-	2b-3 by vessel ICA occlusion: 38% M1 occlusion: 44% M2 occlusion: 44% Multiple M2 occlusions: 23%
Ciccone 2013 SYTHESIS Expansion	I: 76/181 C: 84/181	I: 26/181 C: 18/181	≤6 at day 7 I: 97/181 C: 100/181	-	-
Berkhemer 2015 MR CLEAN	I: 76/233 C: 51/267	I: 49/233 C:59/267	Median (IQR) at 24hrs I: 13 (6-20) C: 16 (12-21)	≥95 I: 99/215 C: 73/245	2b-3 I:115/196
Campbell 2015 EXTEND IA	I: 25/35 C: 14/35	I: 3/35 C: 7/35	A reduction of ≥8 points on NIHSS or a score of 0-1 at 3 days I: 28/35 C: 13/35	-	2b-3 I:25/29
Jovin 2015 REVASCAT	I: 45/103 C: 29/103	I: 19/103 C: 16/103	A reduction of ≥8 points on NIHSS or a score of ≤ 2 at 24 hrs I: 59/100 C: 20/100	≥95 I: 47/82 C: 23/87	2b-3 I:82/103
Saver 2015 SWIFT PRIME	I: 59/98 C: 33/93	I: 9/98 C:12/97	Mean change at 27hrs I: -8.5 (+/- 7.1) (n = 97) C: -3.9 (+/- 6.2) (n = 92)	Median (IQR) I: 100 (10-100) (n = 88) C: 90 (0-110) (n = 77)	2b-3 I:73/83
Goyal 2015 ESCAPE	I: 87/164 C: 43/147	I: 17/164 C: 28/147	Median (IQR) at 24hrs I: 6 (3-14) C: 13 (6-18)	≥95 I: 94/163 C: 49/146	2b-3 I:113/156

I, Intervention Group; C, Controls; mRS, modified Rankin Scale; IQR, Interquartile Range; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Treatment in Cerebral Ischaemia; M1, first segment of middle cerebral artery; M2, second segment of middle cerebral artery ; ICA = internal carotid artery.

Table 13: Characteristics of six additional studies used for 'Safety' Domain

Study	Study type	Years of enrolment	No. patients	Mean age	Median NIHSS	Devices Used	Location of Stroke	Device-Related AEs
Saver, 2012	RCT (plus roll-in data)	2010-11	144	65.4-67.1 (3 groups)	18	Solitaire™ FR, Merci Retriever	ICA, M1, M2, Posterior circulation (4/144)	18 (25 events in 18 participants)[$]
Soize, 2012	Prospective	2010-11	36	64	17.5	Solitaire™ FR	ICA, MCA, ICA-MCA tandem, Basilar (4/36)	1**
Nogueira, 2012	RCT	2011	178	67.2	19	Trevo, Merci	ICA, M1,M2, VBA (12/178)	24[£]
de Castro-Afonso, 2012	Prospective	2011-12	21	65	18	Solitaire™ AB	MCA, ICA, tandem carotid, Basilar (2/21)	Not clear
Jansen, 2013	Prospective	2010-11	60	64.7	18	Trevo	ICA, M1,M2, VBA (5/60)	7[££]
Pereira, 2013	Prospective	2010-12	202	68.4	17	Solitaire™ FR	Anterior circulation	15^^

Abbreviations: AEs, Adverse Events; VBA, Vertebrobasilar artery; M1, M2 = first, second segment of middle cerebral artery, ICA = internal carotid artery

Notes: All six studies employed mechanical thrombectomy as monotherapy or as adjuntive therapy.

$ There were 5 events in 4 of 31 patients in the roll-in phase; the nature of these events is not described. The device related adverse events in the 113 patients included in the RCT proper included air embolism (n = 2), device separation (n = 1), difficulty in device delivery (n = 4), distal emboli to new territory (n = 4), vessel dissection (n = 3), vasospasm (n = 20) and vessel perforation (n = 4); the vessel perforations were associated with 2 symptomatic intra-cerebral haemorrhages (SICHs) and 2 which were asymptomatic.

*** This was a vessel dissection.*

£ This included 7 device related SICHs.Other device related adverse events not specified.

££ This included 3 device related SICHs,1 minor vessel performation, and 3 asymptomatic haemorrhages.^^This includes device OR procedure related serious adverse events, details not specified.

Table 14: Adverse events reported in the eight included randomised controlled trials

Study Year published Name	Device and/or Procedure Related	Serious	Non-Serious
Kidwell 2013 MR RESCUE	10/64[$]	79/127[£]	Not reported
Broderick 2013 IMS3	70/434	I: 256/434 C: 126/222	Not reported
Ciccone 2012 Synthesis Ex-pansion	Not reported	I: 10 (11 events) /181^ C: 5 (6 events) / 181^	^
Berkhemer 2015 MR CLEAN	26/233[$$$]	110/233 113/267	Not reported
Campbell 2015 EXTEND IA	4/35[$]	I: 7/35* C: 10/35*	*
Jovin 2015 REVASCAT	30/103[$]	Unable to interpret	Unable to interpret
Saver 2015 SWIFT PRIME	7/98[$]	I: 30/97 C: 35/98	Not reported
Goyal 2015 ESCAPE	18/165	I: 35/165 C: 27/150	I: 156/165 C:114/150

$ Not clear if these were unique patients

£ Not characterised according to whether intervention or control group

$$$ Not clear that this was the total number. All classified as 'procedure-related'.

*Not characterised as serious or non-serious. Included death, SICH, wire perforation, angiooedema, groin haematoma and embolization into another vessel territory

^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.

List of ongoing and planned studies

Table 15: List of completed (that have yet to report) and ongoing studies

Study Identifier	Estimated completion date*	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02142283 (DAWN)	July 2017 (Recruitment ongoing)	RCT	500	Mechanical thrombectomy with the Trevo Retriever plus medical management	Medical management alone	Aged ≥ 18 years with wake up and late presenting acute ischaemic stroke (NIHSS ≥10) with confirmed large vessel occlusion who have failed IV tPA or for whom IV tPA is contra-indicated. Patient can be randomised within 6 to 24 hours after time last known well	Weighted mRS at 90 days Stroke-related mortality
NCT01062698 (THRACE)	August 2015 (Terminated)	RCT	412	Mechanical thrombectomy plus intravenous thrombolysis	Intravenous thrombolysis	Aged 18 to 80 years with symptom onset <4 hours and confirmed occlusion of the proximal cerebral arteries (intracranial carotid, the middle cerebral artery or the upper third of the basilar artery) (10<NIHSS ≤25)	At 90 days: Weighted mRS QoL (Euroqol EQ-5D) Barthel score
NCT01745692 (PISTE)	July 2015 (Terminated)	RCT	65	Mechanical thrombectomy plus intravenous thrombolysis	Intravenous thrombolysis	Aged ≥ 18 years with clinical diagnosis of supratentorial stroke (NIHSS ≥6) and able to commence IV treatment in <4.5 hours and procedure onset within 90 minutes (groin puncture maximum 5.5 hours post stroke onset)	At 90 days: mRS Mortality NIHSS Angiographic patency Immediate recanalisation rate Home time SICH Intracranial haemorrhage Significant extracra-

							nial bleeding Barthel score
NCT02157532 (EASI)	January 2020 (Recruitment ongoing)	RCT	480	Mechanical thrombectomy (stent retriever) plus best standard treatment	Best standard treatment	Aged ≥ 18 years with occlusion of proximal cerebral arteries following moderate to severe stroke (NIHSS ≥8) within onset of symptoms < 5 hours or symptom/imaging mismatch	<u>At 90 days:</u> mRS SICH Infarct evolution (ASPECT score) TICI score Home time Intracranial haemorrhage Frequency and severity of complications
NCT01852201 (POSITIVE)	May 2016 (Recruitment ongoing)	RCT	750	Mechanical thrombectomy (aspiration or stent retriever separately or in combination) plus IV tPA	Intravenous thrombolysis (IV TPA)	Aged 18 to 80 years with 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.	<u>At 90 days:</u> mRS Mortality ICH with neurological deterioration Procedure-related SAE TICI score
NCT01584609	December 2016 (Recruitment ongoing)	RCT	230	Mechanical thrombectomy with Penumbra System with Separator 3D	Mechanical thrombectomy with Penumbra System	Aged 18 to 85 years with 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	Post procedure: TICI score <u>At 90 days:</u> mRS NIHSS SICH Device and procedure-related SAE
NCT01869478 (EARLY)	September 2015 (Completed)	RCT	1	Mechanical thrombectomy /clot disruption (Penumbra aspiration device, Solitaire™ device, and/or reflex catheter) and/or intracranial stent de-	Intravenous thrombolysis	Aged ≥ 18 years with definite or probable ischaemic stroke and CTA-confirmed intracranial vascular occlusion within 3.5 hours of symptom onset and able to receive treatment within 4.5 hours of symptom onset	At 24 hours Recanalisation rate <u>At 90 days:</u> mRS

				ployment			
NCT02216565 (EASYTRAL)	March 2017 (Recruitment ongoing)	RCT	270	Endovascular treatment plus conventional medical treatment	Conventional medical treatment	Aged 18 to 82 years with 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	NIHSS score at 24h and 7 days mRS at 90 days Mortality at 7 and 90 days
NCT02419781 (RESCUE-Japan)	July 2017 (Recruitment ongoing)	RCT	200	Endovascular therapy plus tPA plus best medical therapy	tPA plus best medical therapy	Aged 20 to 85 years with CT confirmed persistent large vessel occlusion (IC and MI proximal portion), 8≤NIHSS ≤29, who can reeive endovascular treatment within 8 hours of stroke onset and DWI-ASPECTs ≥ 5 OR CT-ASPECTs ≥ 6 just prior to CTA	At 72 hours: SICH Revascularisation rate At 90 days: mRS Mortality
NCT01429350 (THERAPY)	December 2016 (Active not recruiting	RCT	692**	Endovascular therapy with Penumbra device plus tPA	IV tPA	Aged 18 to 85 years with 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	24-hour infarct volume (ASPECTS score) NIHSS at 30 days At 90 days: mRS All SAE SICH and AICH
NCT01983644 (RESTORE)	November 2016 (Active not recruiting)	RCT	130	Endovascular therapy with the RECO flow restoration device	IV tPA	Aged 18 to 80 years with acute anterior circulation stroke an CTA/MRA confirmed large vessel occlusion, and presenting within 4.5 hours of symptom onset with 8≤NIHSS ≤24	At 24 hours: ICH NIHSS (and at 7 days) Revascularistion At 90 days: mRS Mortality
NCT02135926 (THRILL)	March 2018 (Suspended)	RCT	600***	Thrombectomy with stent retriever device in patients ineligible	Best medical care (no tPA)	Aged 18 to 80 years who are ineligible for tPA with symptoms consistent with acute ischaemic stroke and a new focal occlusion confirmed by imaging (MRA/CTA) to be accessible to the	TICI score Infarct volume At 90 days: mRS

				for tPA		thrombectomy device, and located in the M1 of the middle cerebral artery (MCA) and/or the intracranial segment of the distal internal carotid artery (ICA), 7<NIHSS<25 and randomised within 7 hours of stroke onset	Qol EQ-5D

Abbreviations: CTA – computed tomographic angiography; ICH – intra-cerebrall haemorrhage; IV tPA - intravenous tissue plasminogen activator; MRA – magnetic resonance angiography; mRS – modifed Rankin score; NIHSS – National Institutes of Health Stroke Scale; RCT – randomised controlled trial; SAE – serious adverse events; SICH – symptomatic intra-cerebral haemorrhage; TICI; QoL – quality of life;

* Reported as theestimated completion date for the study (and not the (earlier) date of the final data collection date for the primary outcome

** Reported that stopped early due to after 108 patients recruited due to publication of other positive trials http://www.medscape.com/viewarticle/843401#vp_3

*** This study has suspended participant recruitment with recruitment is on hold until MR CLEAN, ESCAPE, EXTEND-IA, and SWIFt PRIME have been evaluated.

Sources: International Clinical Trials Registry Platform (ICTRP http://apps.who.int/trialsearch/default.aspx (Updated search date 18112015), Clinical trials.gov https://clinicaltrials.gov/ (Updated search date 18112015), ISCTRN Meta-register of controlled clinical trials http://www.isrctn.com/page/mrct (Updated search date 18112015)

Risk of bias tables

Table 16: Cochrane risk of bias checklist

Study: Kidwell et al, MR RESCUE		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "employing a biased coin technique (weighted randomization to provide balanced assignments while maintaining uncertainty regarding next allocation)" or else "permuted block sequence" if there is a failure.
Allocation Concealment (selection bias)	Low	Randomisation occurred after imaging.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Unclear	Trial is described as a "blinded-outcome evaluator trial," but there is no clear description of this in the protocol or main paper other than "core laboratories completed primary neuroimaging analyses blinded to treatment assignment before database lock".
Incomplete outcome data (attrition bias)	High	9/127 excluded from the per protocol analysis (Intervention group 6; control group 3)
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Unclear	Quote (from main paper): "The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor"
Study: Broderick et al, IMS III		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "Randomization is implemented using a combination of a web-based minimization + biased coin scheme"
Allocation Concealment (selection bias)	Low	Quote (from protocol): "sealed randomization envelopes placed at each clinical site"
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	The assessor was blinded
Incomplete outcome data (attrition bias)	Unclear	mRS analysis on 415/434 in intervention group; 214/222 – in control group. Unfavourable imputation applied for 27 patients

Selective reporting (reporting bias)	High	EQ-5D, trail making test and Barthel Index all mentioned in protocol but no mention in the paper
Other bias	Low	Quote (main paper): "None of the industry sponsors were involved in the study design, study conduct, manuscript review, or protocol review, except to make sure that the specified use of devices in the study followed the instructions for use approved by the Food and Drug Administration (FDA)"
Study: Ciccone et al, SYNTHESIS Expansion		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from main paper): "The study protocol provided for centralized, simple randomization online. A single randomization list was prepared with the use of a hardware system, available at www.random.org. All patients underwent randomization within 4.5 hours after symptom onset."
Allocation Concealment (selection bias)	Unclear	Not stated when randomisation was carried out.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "A long-term patient's clinical condition is evaluated by a single neurologist, blinded to treatment allocation"
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Low	Quote (from main paper): "There was no industry support for or industry involvement in this trial."
Study: Berkhemer et al, MR CLEAN		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "The randomization procedure is computer- and web-based, using permuted blocks. Full-time back-up by telephone is provided."
Allocation Concealment (selection bias)	Low	Quote (from protocol): "Randomization is allowed when the intracranial occlusion has been established by CTA, MRA or DSA" and "Treatment assignment cannot be determined before inclusion and randomization."
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding

Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "Information on outcome at 3 months will be assessed with standardized forms and procedures, in a structured telephone interview by an experienced research nurse at the central trial office who is not aware of treatment allocation. Assessment of outcome on the mRS will be based on this information, by assessors who are blind to the allocated and actually received treatment. Results of neuroimaging will also be assessed by blinded observers."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up.
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Low	Quote (from main paper): "The study sponsors were not involved in the study design, study conduct, protocol review, or manuscript preparation or review."
Study: Campbell et al, EXTEND IA		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "randomization via a centralized website" with clinical assessment prior to randomisation.
Allocation Concealment (selection bias)	Unclear	Centralized website - not clear if investigators would have known what the next person out would be (intervention or control)
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary, secondary and tertiary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "Covidien supplied the Solitaire™ FR device and an unrestricted grant to support trial infrastructure, but the company was not involved in the study design or conduct or in the preparation of the manuscript, except to review the protocol to ensure that the specified use of devices in the study followed the approved instructions for use."
Study: Jovin et al, REVASCAT		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection	Low	From protocol: web-based real-time randomisation based on minimisation

bias)		
Allocation Concealment (selection bias)	Low	From protocol: randomisation is carried in real-time at point of confirming eligibility
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Primary endpoint of mRS evaluated by blinded assessors. Quote (from protocol): "All neuroimaging secondary end-points including recanalisation at 24 hours, infarct volume and haemorrhage will be determined by the CT/MR core-lab, which will be also blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Low	Quote (main paper): "The study was funded by an unrestricted grant from the manufacturer of the stent retriever (Covidien), which was not involved in the design or conduct of the study or in the writing of the protocol or the manuscript."
Study: Saver et al, SWIFT PRIME		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Unclear	"Subject allocation to treatment will be accomplished by using an interactive web response or interactive voice response system." Further detail on how this was actually done would have been preferable.
Allocation Concealment (selection bias)	Unclear	Not reported.
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "The 90-day mRS will be assessed by study personnel certified in the scoring of the mRS using the RFA-A and will be blinded to treatment assignment" and "the Core Lab will assess all CT and MR imaging blinded to treatment assignment"
Incomplete outcome data (attrition bias)	Unclear	Loss to follow-up in control arm (5 of 98). Last outcome carried forward (LOCF) used for 1/98 in intervention arm and 3/98 in control arm.
Selective reporting (reporting bias)	Low	Primary and secondary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "The trial was funded by Covidien and

		designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor."
Study: Goyal et al, ESCAPE		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from protocol): "Patients will be randomized using a real-time, dynamic Internet-based, minimal sufficient balance (MSB) randomization method"
Allocation Concealment (selection bias)	Low	Quote (from protocol): "Because randomization will occur dynamically in real-time, it will be fully concealed."
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to what procedure they were carrying out, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Quote (from protocol): "After enrollment of each subject the site will designate a blinded evaluator to perform the three-month follow-up evaluation including the primary end-point (mRS). This individual cannot be involved in care of the subject and must remain blinded to treatment assignment of the subject. Patients will be instructed not to disclose their treatment group to the evaluator. All neuroimaging secondary end-points will be determined by the CT core laboratory blinded to treatment allocation."
Incomplete outcome data (attrition bias)	Low	Loss to follow-up (1 case, 3 controls) represents small proportion of participants (165 cases, 150 controls).
Selective reporting (reporting bias)	Low	Primary outcomes all reported. Most secondary outcomes reported.
Other bias	Unclear	Trial stopped early after unplanned interim analysis. Study sponsorship. Quote (from main paper): "The study funders, including Covidien, were not involved in the design or conduct of the study, the preparation or review of the protocol, the collection or analysis of the data, or the preparation or review of the manuscript. All the authors collected data, provided comments on the analysis, contributed to the writing of the manuscript, and were independent of the sponsors."

Figure 12: Risk of Bias Plot based on information in table above on the eight included randomised controlled trials

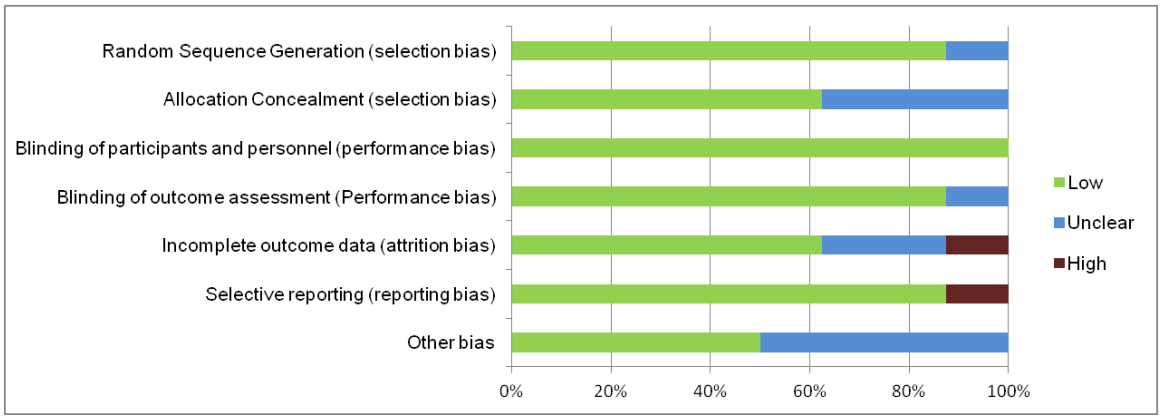


Table 17: GRADE assessment: effectiveness and safety of mechanical thrombectomy devices

Outcome	No. Studies	Study Design	Bias	Consistency	Directness	Imprecision	Other Factors	Quality	Importance
mRS at 90 days	8	RCTs	Moderate Risk[1]	Serious inconsistency[2]	No serious indirectness	Moderate imprecision	5 studies stopped early	Low[4]	Critical
All cause mortality at 90 days	8	RCTs	Moderate Risk[1]	No serious inconsistency	No serious indirectness	Moderate imprecision	5 studies stopped early	Moderate	Critical
Barthel Index at 90 days	3	RCTs	Moderate Risk[1, 3]	No serious inconsistency	No serious indirectness	Moderate imprecision	2 studies stopped early	Moderate	Critical
SICH	8	RCTs	Moderate Risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision	5 studies stopped early	Moderate	Critical
Any Haemorrhage	7	RCTs	Moderate Risk[1]	Serious inconsistency	No serious indirectness	Serious imprecision	4 studies stopped early	Low	Critical
Recurrent Stroke at 90 days	4	RCTs	Low Risk[1]	No serious inconsistency	No serious indirectness	Serious imprecision	3 studies stopped early	Low	Critical

1. See Risk of Bias Table
2. Lack of consistency between earliest three and latest five studies. Also lack of consistency in result with wide variation in % getting mRS≤2
3. One of the RCTs, IMS III, had planned to analyse Barthel Index at 90 days but did not report on this outcome measure
4. The overall quality of the 8 trials is deemed as low because of the serious inconsistency between earlier and later trials. If analysis was confined to studies which commenced after 2010, the evidence would be deemed moderate.

Table 18: Cochrane risk of bias checklist for additional included prospective studies, used in the assessment of safety

Study: Saver et al, 2012		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Quote (from paper): "Study patients were randomly allocated in a one-to-one ratio …the randomization sequence was computer generated and stratified by site and presenting stroke severity with block sizes of four"
Allocation Concealment (selection bias)	Low	Used sequentially numbered, opaque sealed envelopes
Blinding of participants and personnel (performance bias)	Low	Although personnel were not blinded to which device they were using, outcomes were unlikely to be influenced by this lack of blinding
Blinding of outcome assessment (Performance bias)	Low	Independent central core imaging laboratory, unaware of study assignments, assessed final revascularization grades on outcome angiograms and haemorrhagic transformation on outcome CT and MR examinations. A central, independent clinical events committee, whose members were unaware of study group assignments, categorized all adverse events by severity and relatedness to the study device and to the procedure.
Incomplete outcome data (attrition bias)	Low	All patients included in the analysis of safety endpoints
Selective reporting (reporting bias)	Low	All safety outcomes reported
Other bias	High	Quote (from main paper): "The trial was funded by Covidien/ev3"…. "The sponsor of the study was responsible for site management, data management, and safety reporting".
Study: Soize et al, 2012		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	High	Prospective, single-centre, single-arm, intention to treat study – no randomisation
Allocation Concealment (selection bias)	High	Prospective, single-centre, single-arm, intention to treat study – no allocation concealment
Blinding of participants and personnel (performance bias)	Low	No blinding possible but unlikely to have affected the results reported
Blinding of outcome assessment (Performance bias)	Low	No evidence presented of blinding of safety outcomes
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	All safety outcomes reported

Other bias	Unclear	One of the authors disclosed unrelated consultancy for the firm who responsible for production/sale of the device under consideration in the study
Study: Nogueira et al, 2012		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	Low	Patients randomly allocated in a 1:1 ratio. Stratifed on the basis of age and NIHSS scores. Randomisation performed at each study site with alternating blocks of various sizes, with first block chosen at random
Allocation Concealment (selection bias)	Low	Blocks chosen at random using sealed, opaque, sequentially numbered envelopes, prepared by an independent study statistician
Blinding of participants and personnel (performance bias)	Low	No blinding possible but unlikely to have affected the results reported
Blinding of outcome assessment (Performance bias)	Low	No evidence presented of blinding of safety outcomes
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	All safety outcomes reported
Other bias	Low	The study sponsor monitored and managed the data. However "the sponsor was masked to the results until after the study was completed and the database was locked. The sponsor had no role in data analysis or interpretation or writing of the report"
Study: de Castro-Afonso et al, 2012		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	High	Prospective study – no randomisation
Allocation Concealment (selection bias)	High	Prospective study – no allocation concealment
Blinding of participants and personnel (performance bias)	Low	No blinding possible but unlikely to have affected the results reported
Blinding of outcome assessment (Performance bias)	High	Not blinded
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	High	Unclear about device related complications

Other bias	Unclear	No information on study sponsorship or otherwise provided. Authors also not learning curve which may potentially have impacted outcomes.
Study: Jansen et al, 2013		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	High	Prospective, multi-centre, single arm study – no randomisation
Allocation Concealment (selection bias)	High	Prospective, multi-centre, single arm study – no allocation concealment
Blinding of participants and personnel (performance bias)	Low	No blinding possible but unlikely to have affected the results reported
Blinding of outcome assessment (Performance bias)	Low	No evidence presented of blinding of safety outcomes. Blinded outcome assessment may not be possible for device-related AEs.
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	All safety outcomes reported
Other bias	Unclear	Unclear re role of sponsor
Study: Pereira et al, 2013		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (selection bias)	High	Prospective, multi-centre, single arm study – no randomisation
Allocation Concealment (selection bias)	High	Prospective, multi-centre, single arm study – no allocation concealment
Blinding of participants and personnel (performance bias)	Low	No blinding possible but unlikely to have affected the results reported
Blinding of outcome assessment (Performance bias)	Low	No evidence presented of blinding of safety outcomes. Blinded outcome assessment may not be possible for device-related AEs.
Incomplete outcome data (attrition bias)	Low	No loss to follow-up
Selective reporting (reporting bias)	Low	All safety outcomes reported
Other bias	High	The study data was independently monitored; study management was provided by the sponsor……. "The sponsor of the study was responsible for site management, data management, and safety reporting".

Applicability tables

Table 19: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The 8 RCTs which form the basis for this assessment present data on 2,423 patients. All trials reported mean or median ages for their control and intervention groups between 64 and 71 years, and further investigation of the intervention in older cohorts is still required. Almost all patients assigned to the intervention groups had suffered ischaemic strokes in the anterior circulation and hence the evidence presented here should be regarded as applying to this population only, with further investigation in cohorts who suffer ischaemic strokes in the posterior region required. All eight trials reported median basline NIHSS scores in their intervention groups of between 13 and 19. In addition, the mean or median time to endovascular intervention in 7 of the 8 trials was less than 6 hours, and the applicability of the results to patients presenting outside this time frame is uncertain.
Intervention	The majority of the evidence presented here relates to just 4 devices and the applicability of the results to other devices used for Mechanical Thrombecomy is uncertain.
Comparators	The considered comparator of standard medical care is appropriate.
Outcomes	All studies report functional independence at 90 days (as measured using the Modified Rankin Scale) and on all-cause mortality at 90 days. Similarly, all provide data on rates of symptomatic intracranial haemorrhage. There is inconsistency in reporting or in the method of reporting of other outcomes of relevance to this patient cohort, including Barthel Index at 90 days, reperfusion at 24 hours, revascularisation at final angiography, NIHSS score at 24 hours, device- and procedure-related adverse events, any haemorrhage, and recurrent stroke at 90 days.
Setting	The results presented here must be considered with respect to the centres in which these trials took place, and it remains to be seen whether the stroke management systems in place in these institutions are replicable in other units.

APPENDIX 2: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
It is recognised that there are ethical implications of introducing (or not) a new intervention with significant upfront and ongoing running costs. While introduction of a comprehensive thrombectomy service may bring significant benefits for affected patients and their families that may well ultimately reduce overall health and social care costs, it may only be affordable if there is disinvestment from other currently funded healthcare interventions which bring less benefit at a population level. This could have consequences for individual patients and their families who may no longer have access to what was beneficial care for them.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparators require organisational changes?	Yes
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	Yes
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.	
3. Social	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

APPENDIX 3: ICD-10-CM DIAGNOSIS CODES

- I63 Cerebral infarction
  - I63.0 Cerebral infarction due to thrombosis of precerebral arteries
    - I63.00 Cerebral infarction due to thrombosis of unspecified precerebral artery
    - I63.01 Cerebral infarction due to thrombosis of vertebral artery
      - I63.011 Cerebral infarction due to thrombosis of right vertebral artery
      - I63.012 Cerebral infarction due to thrombosis of left vertebral artery
      - I63.019 Cerebral infarction due to thrombosis of unspecified vertebral artery
    - I63.02 Cerebral infarction due to thrombosis of basilar artery
    - I63.03 Cerebral infarction due to thrombosis of carotid artery
      - I63.031 Cerebral infarction due to thrombosis of right carotid artery
      - I63.032 Cerebral infarction due to thrombosis of left carotid artery
      - I63.039 Cerebral infarction due to thrombosis of unspecified carotid artery
    - I63.09 Cerebral infarction due to thrombosis of other precerebral artery
  - I63.1 Cerebral infarction due to embolism of precerebral arteries
    - I63.10 Cerebral infarction due to embolism of unspecified precerebral artery
    - I63.11 Cerebral infarction due to embolism of vertebral artery
      - I63.111 Cerebral infarction due to embolism of right vertebral artery
      - I63.112 Cerebral infarction due to embolism of left vertebral artery
      - I63.119 Cerebral infarction due to embolism of unspecified vertebral artery
    - I63.12 Cerebral infarction due to embolism of basilar artery
    - I63.13 Cerebral infarction due to embolism of carotid artery
      - I63.131 Cerebral infarction due to embolism of right carotid artery
      - I63.132 Cerebral infarction due to embolism of left carotid artery
      - I63.139 Cerebral infarction due to embolism of unspecified carotid artery
    - I63.19 Cerebral infarction due to embolism of other precerebral artery
  - I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
    - I63.20 Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries

- I63.21 Cerebral infarction due to unspecified occlusion or stenosis of vertebral arteries
  - I63.211 Cerebral infarction due to unspecified occlusion or stenosis of right vertebral arteries
  - I63.212 Cerebral infarction due to unspecified occlusion or stenosis of left vertebral arteries
  - I63.219 Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral arteries
- I63.22 Cerebral infarction due to unspecified occlusion or stenosis of basilar arteries
- I63.23 Cerebral infarction due to unspecified occlusion or stenosis of carotid arteries
  - I63.231 Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
  - I63.232 Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
  - I63.239 Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid arteries
- I63.29 Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries

- I63.3 Cerebral infarction due to thrombosis of cerebral arteries
  - I63.30 Cerebral infarction due to thrombosis of unspecified cerebral artery
  - I63.31 Cerebral infarction due to thrombosis of middle cerebral artery
    - I63.311 Cerebral infarction due to thrombosis of right middle cerebral artery
    - I63.312 Cerebral infarction due to thrombosis of left middle cerebral artery
    - I63.319 Cerebral infarction due to thrombosis of unspecified middle cerebral artery
  - I63.32 Cerebral infarction due to thrombosis of anterior cerebral artery
    - I63.321 Cerebral infarction due to thrombosis of right anterior cerebral artery
    - I63.322 Cerebral infarction due to thrombosis of left anterior cerebral artery
    - I63.329 Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
  - I63.33 Cerebral infarction due to thrombosis of posterior cerebral artery
    - I63.331 Cerebral infarction due to thrombosis of right posterior cerebral artery
    - I63.332 Cerebral infarction due to thrombosis of left posterior cerebral artery
    - I63.339 Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
  - I63.34 Cerebral infarction due to thrombosis of cerebellar artery
    - I63.341 Cerebral infarction due to thrombosis of right cerebellar artery

- I63.342 Cerebral infarction due to thrombosis of left cerebellar artery
- I63.349 Cerebral infarction due to thrombosis of unspecified cerebellar artery
- I63.39 Cerebral infarction due to thrombosis of other cerebral artery
- I63.4 Cerebral infarction due to embolism of cerebral arteries
  - I63.40 Cerebral infarction due to embolism of unspecified cerebral artery
  - I63.41 Cerebral infarction due to embolism of middle cerebral artery
    - I63.411 Cerebral infarction due to embolism of right middle cerebral artery
    - I63.412 Cerebral infarction due to embolism of left middle cerebral artery
    - I63.419 Cerebral infarction due to embolism of unspecified middle cerebral artery
  - I63.42 Cerebral infarction due to embolism of anterior cerebral artery
    - I63.421 Cerebral infarction due to embolism of right anterior cerebral artery
    - I63.422 Cerebral infarction due to embolism of left anterior cerebral artery
    - I63.429 Cerebral infarction due to embolism of unspecified anterior cerebral artery
  - I63.43 Cerebral infarction due to embolism of posterior cerebral artery
    - I63.431 Cerebral infarction due to embolism of right posterior cerebral artery
    - I63.432 Cerebral infarction due to embolism of left posterior cerebral artery
    - I63.439 Cerebral infarction due to embolism of unspecified posterior cerebral artery
  - I63.44 Cerebral infarction due to embolism of cerebellar artery
    - I63.441 Cerebral infarction due to embolism of right cerebellar artery
    - I63.442 Cerebral infarction due to embolism of left cerebellar artery
    - I63.449 Cerebral infarction due to embolism of unspecified cerebellar artery
  - I63.49 Cerebral infarction due to embolism of other cerebral artery
- I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
  - I63.50 Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
  - I63.51 Cerebral infarction due to unspecified occlusion or stenosis of middle cerebral artery
    - I63.511 Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
    - I63.512 Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery

I63.519 Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery

I63.52 Cerebral infarction due to unspecified occlusion or stenosis of anterior cerebral artery

I63.521 Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery

I63.522 Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery

I63.529 Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery

I63.53 Cerebral infarction due to unspecified occlusion or stenosis of posterior cerebral artery

I63.531 Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery

I63.532 Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery

I63.539 Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery

I63.54 Cerebral infarction due to unspecified occlusion or stenosis of cerebellar artery

I63.541 Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery

I63.542 Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery

I63.549 Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery

I63.59 Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery

I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

I63.8 Other cerebral infarction

I63.9 Cerebral infarction, unspecified

