NHS England

Evidence review: Mechanical thrombectomy for acute ischaemic stroke in the anterior cerebral circulation

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1. Introduction

Stroke is a devastating disease for the patient and family and is estimated to cost the NHS around £3b per year, with additional cost to the economy of a further £4b in lost productivity, disability and informal care (National Audit Office 2005). About 20% die within the first year (the majority within the first 3 months) and over 50% of survivors are left with long-term disability. A disproportionately high share of the disability burden arises within the 30-50% of patients with proximal large artery occlusive stroke. Many of these will have a mixture of cognitive, mood and physical function problems.

85% of strokes are ischaemic, resulting from a blood vessel becoming blocked and the brain tissue dependent on that blood vessel being damaged from a lack of nutrients and oxygen. Up to 20% of people with ischaemic strokes are suitable for intravenous thrombolysis, but many of those treated will not respond because the blood clot is too large and some cannot receive the treatment due to contraindications such as recent surgery or being on anticoagulant (blood-thinning) drugs. For some of these patients, the evidence suggests that intra-arterial clot extraction (mechanical thrombectomy) performed within six hours of the onset of symptoms is an effective treatment that can prevent permanent brain damage and prevent or limit long term disability. It acts mainly to reduce the probability of significant disability rather than impacting on overall mortality. Other than intravenous thrombolysis there are no other acute interventions that have been shown to reduce the size of the area of infarcted brain despite major investment by pharmaceutical firms to develop more effective thrombolytic agents or neuroprotective drugs.

The group that are likely to benefit are those with proximal occlusion of the internal carotid or middle cerebral arteries who present early after the stroke before there is irreversible ischaemic damage to the brain. These patients, often with extensive thrombus, are much less likely to respond to the conventional intravenous thrombolysis and more likely to end up with large strokes and consequent severe disability. Around 40% of ischaemic strokes are caused by a large artery occlusion (LAO).

For patients who do not respond to intravenous thrombolysis there has previously been no active intervention available to prevent brain damage: treatment is limited to rehabilitation and high quality nursing care.

The Intervention:
A catheter containing a specially-designed revascularisation device is inserted through the

femoral artery in the groin and advanced up to the blocked (occluded) artery in the brain to remove any clots (thrombus). In addition to introducing a new device and procedure, the intervention will require a new model of care which builds on existing acute stroke networks.

2. Summary of results

For every 4 to 6 people with an acute ischaemic stroke who present with an identifiable occlusion in the anterior cerebral circulation who undergo mechanical thrombectomy, one more person will be functioning independently at three months than if they had received iv thrombolysis alone.

Rapid treatment is important, as the benefit from mechanical thrombectomy falls by 3.4% for every hour of delay. Some patients may still have better outcomes from thrombectomy than best medical thrombectomy alone, even if delayed by up to 12 hours.

Symptomatic intracranial haemorrhage is no more common among people who had thrombectomy (4.4%) than best medical therapy (4.3%). Death rates at 3 months appear lower for those undergoing thrombectomy (15.3%) than for those receiving best medical therapy (18.9%), though these differences were not statistically significant.

3. Methodology

Searches were undertaken to identify potentially relevant material in Medline, Embase, CINAHL, the Cochrane database and NHS Evidence Search. Clinical members of the policy working group also offered relevant material. The titles and abstracts of all potentially relevant studies were extracted into an EndNote (v7.1) database. All were then assessed for relevance to the review using the following inclusion criteria.

- Comparisons of mechanical thrombectomy plus intravenous thrombolysis against best medical therapy (including intravenous thrombolysis)
- Randomised treatment allocation
- Majority of thrombectomy procedures undertaken using a device type in current use (list developed iteratively, with reference to an expert clinical member of PWG)
- Site of occlusion demonstrated using cerebral angiography, and (principally) located to the anterior circulation.

In addition, for reviews, meta-analysis and secondary data analysis:

- The method for identification and assessment of studies had to be explicit

The full text of each study meeting these inclusion criteria was obtained. Each of these studies was then reviewed again against the inclusion criteria. At this point, the number of studies meeting the inclusion criteria and the extent to which this material cross-referred (this was particularly true of review and meta-analysis studies) indicated that a review of the inclusion criteria was required. The inclusion criteria were refined on the basis of this pool to only examine in detail those studies published in full (i.e. excluding conference abstracts).

Each was then appraised for its methodological quality and relevance to the study purposes, summarised and then scored for quality and relevance.

4. Results

1417 citations were identified from database searches and 25 from expert advisors. These together yielded 1116 unique records. 86 were considered potentially relevant to the review and the full text obtained. Sixteen of these studies; seven trials, and a further nine systematic literature reviews and meta-analyses (two of which use secondary analyses of pooled trial data) met all the inclusion criteria.

All trials that met the inclusion criteria were conducted in multiple centres; with two genuinely international trials (Goyal et al., 2015) (Saver et al., 2015), four undertaken in Europe: The Netherlands Berkhemer et al. (2015), France (Bracard et al., 2016), Spain (Jovin et al., 2015), and the UK (Muir et al., 2016), one each in Australasia (Campbell et al., 2015). These trials were funded by a mixture of industry and government grants.

All seven trials were designed to test rapid access to stroke treatment for those with confirmed ischaemic stroke. All included the principle of establishing early the need for thrombectomy- i.e. those individuals in whom intravenous thrombolysis fails to resolve neurological symptoms, and identifying a lesion that is amenable to this form of therapy. Some, such as REVASCAT, waited a short period to determine whether iv thrombolysis was resolving symptoms before starting the workup for thrombectomy.

The trials varied as to whether patients with contraindications to iv thrombolysis were included. One reason why iv thrombolysis cannot be used is late presentation, as Alteplase is licenced only for use up to 4.5 hours from onset of stroke symptoms. So,

patients presenting beyond this time are therefore excluded from most trials in this review. However, two of these trials: REVASCAT (Jovin et al., 2015), and ESCAPE (Goyal et al., 2015) included patients who presented late but nonetheless had angiographic features suggesting that reperfusion could still have positive results. Both included a relatively large proportion of patients with delayed treatment onset; a quarter of REVASCAT participants did not start their procedure until 7 hours or more after onset of symptoms, and among ESCAPE participants a quarter of achieved reperfusion only after four or more hours from onset.

The primary outcome measures differed between studies, but all reported changes in the modified Rankin scale, which categorises the degree of disability following stroke from 0 (no symptoms) to 5 (severe disability) and 6 death (see BOX). So aggregating study results is relatively straightforward. The most commonly reported outcome measures were: median changes in scores on the mR scale, and the proportion of people who can function independently (mR scale scores 0-2).

BOX Modified Rankin scale (mR scale)

This is a functional assessment scale that measures the degree of disability or dependence of people who have suffered a stroke. The scale runs from perfect health without symptoms to death:

0: No symptoms.

1: No significant disability. Able to carry out all usual activities, despite some 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 own bodily needs without assistance, and unable to walk unassisted.

5: Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6: Death

All these trials reported strongly positive findings, with the proportion of people who could function independently at 90 days increasing by between 19-35%.

All trials also examined the safety of the mechanical thrombectomy, usually by monitoring total mortality and the probability of an intracranial haemorrhage. None of the trials showed a significant excess of either of these outcomes.

The conduct and outcome assessment of these trials means that synthesising the findings in meta analyses and pooling results in secondary analyses are both realistic undertakings. The six systematic literature reviews and meta analyses of these trials included here are a small proportion of those the search identified. Many were excluded for lack of detail of method (which excluded, for example, all those reported as conference abstracts), and many more because they included one or more of the older trials examining the effects of using obsolete devices. They still varied a little in the trials included, depending on the focus (and precision) of the inclusion criteria and on when the search for relevant research was undertaken. None of the reviews included every one of the trials identified by the searches undertaken for this analysis, not least because the last of these trials (Muir et al., 2016) identified by clinical members of the policy working group was published shortly after the search for this review was undertaken.

The source of funding for these reviews was mixed, with a mixture of industry and government funding being reported, and some declaring no explicit funding, but not all reports documented the source of funding for their work.

Given that these studies synthesised the results of the same pool of studies, it is no surprise that the findings of the individual meta-analyses are also very similar. They calculate the absolute chance of being able to function independently at 90 days after stroke were improved by around 20% (19-22%) among those undergoing mechanical thrombectomy (Bush et al., 2016, Marmagkiolis et al., 2015, Lambrinos et al., 2016, Touma et al., 2016, Anonymous, 2016). This suggests that for every 4 to 6 patients undergoing thrombectomy following stroke, one more will be able to function independently at 90 days, compared to those that receive iv thrombolysis alone.

As trial conduct was similar, but most trials terminated early, there is a potential pool of data about individual patients from studies that on their own have limited statistical power, but if pooled could provide more powerful insights. Two collaborations undertook their meta-analyses by pooling individual patient data in this way. The HERMES collaboration publishing results of pooling data from five recent trials (Goyal et al., 2016) (Saver et al., 2016) and the SEER collaboration from four trials. (Campbell et al., 2016)

The larger of these pooled analyses calculated median disability scores and 90 days, and concluded that the median score on the mR scale for those who received best medical therapy was 4- i.e. that they were moderately severely disabled. In contrast, the median

scope at this time for those who had also undergone mechanical thrombectomy was 2- i.e. they were able to function independently. Further, using a “differences in differences” approach- mechanical thrombectomy increases the odds of being in a less disabled category at 90 days (one point different on the mR scale) by more than two fold (Odds ratio 2.26 p<0.0001) (Goyal et al., 2016)

Pooled analysis allowed other factors to be explored, particularly the significance of time from symptom onset to key events in the treatment pathway, such as decision to treat (randomisation), start of procedure, and restoration of cerebral blood flow. HERMES identified that the absolute chance of being functionally independent 90 days after thrombectomy diminish by 3.4% with each hour’s delay to starting the procedure (Saver et al., 2016), and the probability of a beneficial reduction in decline in disability (one point on the mR scale at 90 days) fell by 5.3% for each hour’s delay. This decline in treatment benefit remained statistically significant up to 7 hours after treatment.

Further analysis by the HERMES investigators identified that the benefits to patients in this pooled analysis randomised after 3 hours were statistically no different to those randomised before 3 hours (Goyal et al., 2016). Similarly the SEER collaboration again found no statistically significant difference in benefit between those randomised before or after 5 hours from onset of treatment. (Campbell et al., 2016)

5. Discussion

Trials meeting the inclusion criteria had consistently strongly positive findings of a very similar order, in favour of mechanical thrombectomy. Whilst this is heartening, the fact that most were stopped early following planned or unplanned interim analyses means that it is hard to get a reliable estimate of treatment effects from any one of them.

A brief history of trial developments in this field is necessary to understand the evidence now available on treatment effects. Trials examining the effects of an earlier generation of thrombectomy devices and clinical practice (Kidwell et al., 2013, Broderick et al., 2013, Ciccone et al., 2013, Mocco et al., 2016) identified little benefit on stroke outcomes from mechanical thrombectomy. Then a head to head comparison of different device types found in favour of stent-retrievers; (Nogueira et al., 2012) (themselves an adaption of vascular stents in routine use for arterial recanalisation). These stent-retrievers then became the main type of device used in clot extraction, usually with supplemental clot aspiration.

The first of the trials testing these newer devices against best medical therapy that reported its findings: MR CLEAN then became highly influential on the conduct of many similar trials recruiting across the world, including the UK PISTE trial, sponsored by the National Institute for Health Research. The Dutch MR CLEAN study findings were so strong (Berkhemer et al., 2015) that the monitoring committees of the remaining active trials were prompted to review their own interim data and consider the equipoise required to continue randomising patients. All trials were subsequently stopped either because the evidence from interim analysis was sufficiently strong, or because equipoise had been lost.

Whilst all these trial monitoring decisions were entirely justified, and in the best interests of patients, it highlights the hazard of multiple trials of the same intervention running in parallel. In practice, this means that the estimates of treatment effect reported in individual trials are uncertain. To address this limitation, trial results need to be pooled. Indeed, the searches undertaken for this review identified many meta-analyses of these trial results. All such meta-analyses meeting the inclusion criteria for the review identified strong homogeneity between recent trial findings, with the statistical indicator of heterogeneity of effects on functional outcome at 90 days typically being reported as very low (0%). This finding is strikingly different from attempts to pool both earlier and more

recent studies- where heterogeneity was high- 69% (Rodrigues et al., 2016) being typical.

The meta-analyses (Bush et al., 2016, Marmagkiolis et al., 2015, Lambrinos et al., 2016, Touma et al., 2016, Anonymous, 2016) conducted on the more recent trials all show a high degree of statistical homogeneity among estimates of treatment effect on the chances of functioning independent at 90 days. The proportion of people able to function independently falls close to 20% in all these analyses, meaning that for every 5 people undergoing thrombectomy, one more of them will be able to function independently.

Other than requirements about timing of procedure and location of occlusion, these were pragmatic trials, with few exclusion criteria that might limit the generalisability of findings. This pragmatic approach to trial design means that the experimental and control interventions varies between studies. For example, the MR CLEAN protocol permitted intra-arterial thrombolysis in the control regimen, an intervention which would not now be standard practice. The statistical homogeneity between headline results of the studies included in meta-analyses is therefore reassuring. Equally the strongly positive findings of the (smaller than planned) PISTE study, the one trial in current UK context, provides some further reassurance.

The wealth of review and meta-analytic studies provides a choice about which summary results best summarise the available research. The main choice here is between studies that are meta-analyses of trial results and those which have obtained and used individual patient level data. None of the meta-analyses included all of the published trials- so none can claim to provide a comprehensive overview. Some meta-analyses were more inclusive than others, some such as the helpful Rodrigues review (Rodrigues et al., 2016), for example, included the THRACE (Bracard et al., 2016) study, in which most patients were treated with technology that is now obsolete. Irrespective of which trial results were pooled, the fact that so many were stopped early (some from the results of preliminary or outside protocol analysis) means that every effort should be made to minimise the chance of false-positive findings. The findings from meta-analyses conducted on individual patient level data perhaps gives a better chance of avoiding this than pooling trial results, although in practice the effect estimates from the two approaches are very similar, for example the Rodrigues review found that 47.5% of patients undergoing mechanical thrombectomy were functioning independently at 90 days, compared to 29.8% in those undergoing best medical therapy. In contrast, the HERMES analysis of individual level data found 46.0% had this outcome after

thrombectomy, compared to 26.5% among those undergoing best medical therapy.

All the multi-centre thrombectomy trials set (more or less explicit) standards about the organisation and delivery of treatment and care including the facilities, operators (experienced & passed a credentialing process) and the efficiency of services. The implication of this selection is that these trials give little insight into the importance of any one of these factors for patient outcomes.

Whilst none of the trials showed a significant excess of important adverse outcomes, all these trials were powered to detect a clinically important difference in functioning, rather than a change in either these relatively uncommon (in the case of intracranial haemorrhage) or dichotomous (in the case of death) outcomes. The largest meta-analyses of individual patient level data identifies that mortality at three months is lower among those undergoing mechanical thrombectomy (15.3%), than among those receiving best medical therapy (18.9%), though this does not reach statistical significance.

Much of the evidence identified for this review has already been extensively reviewed, and much already incorporated into clinical guidelines. The Intercollegiate Stroke Working Party has considered its relevance for UK clinical practice using methods accredited by the National Institute for Health and Care Excellence (2016b)
Their recommendations for the use of mechanical thrombectomy in acute ischaemic stroke include:
(G) Patients … should be considered for combination intravenous thrombolysis and intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.

Recommendation (G) is uncontroversial in light of the evidence reviewed

(H) Patients with … a contraindication to intravenous thrombolysis but not to thrombectomy should be considered for intra-arterial clot extraction (using stent retriever and/or aspiration techniques) if they have a proximal intracranial large vessel occlusion causing a disabling neurological deficit (National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) and the procedure can begin (arterial puncture) within 5 hours of known onset.

Recommendation (H) is well supported by the evidence reviewed here

(I) Patients with acute ischaemic stroke causing a disabling neurological deficit (a National Institutes of Health Stroke Scale [NIHSS] score of 6 or more) may be considered for intraarterial clot extraction (using stent retriever and/or aspiration techniques, with prior intravenous thrombolysis unless contraindicated) beyond an onset-to-arterial puncture time of 5 hours if:

– the large artery occlusion is in the posterior circulation, in which case treatment up to 24 hours after onset may be appropriate;

This recommendation is outside the scope of the review reported here, and no view can be formed about it

– a favourable profile on salvageable brain tissue imaging has been proven, in which case treatment up to 12 hours after onset may be appropriate.

The wording of this recommendation is cautious and the evidence contains findings that are difficult to resolve. Most recent trials excluded patients who presented late, but ESCAPE and REVASCAT included those presenting late, but who had a favourable profile on angiography. In REVASCAT, a quarter participants started their thrombectomy seven hours or more after the onset of stroke (Jovin et al., 2015). 14% of ESCAPE participants were not randomised until at least 6 hours after their stroke (Goyal et al., 2015). As both these trials were stopped early (for different reasons), neither is adequately powered to give a definitive view on the benefits of later intervention, but the two pooled analyses of individual patient data are the most likely to be helpful in establishing effects of delayed treatment.

The HERMES collaborators (which included ESCAPE and REVASCAT participants in its pooled analysis) demonstrated that, just as in trials of intravenous thrombolysis, timing of thrombectomy with respect to the onset of stroke symptoms (that indicate the onset of infarction) is crucial. The absolute chance of having being functionally independent after treatment diminish by 3.9% with each hour's delay to thrombectomy (Saver et al., 2016). The odds of a benefit thrombectomy over best medical therapy (as measured by the change in mR scale score) also appeared greater among patients who were randomised early-within 3 hours (OR=2.66) than for those who were randomised after 3 hours (OR=1.76) but there was no statistically significant difference between these estimates (Goyal et al., 2016). Similarly the SEER collaboration (which also

included ESCAPE and REVASCAT participants in its pooled analysis of four trials) used a longer cut-off and again found no statistically significant difference in benefit between those randomised before or after 5 hours from onset of treatment. (Campbell et al., 2016)

So, on the one hand there is a real decline in benefit over time, but on the other it is not possible to identify a point statistically significant time from stroke where beyond which the benefits of thrombectomy are significantly inferior to medical therapy alone. Given that these findings are difficult to resolve, a cautious approach is required to offering mechanical thrombectomy to patients who present late.

(J) Hyperacute stroke services providing endovascular therapy should participate in national stroke audit to enable comparison of the clinical and organisational quality of their services with national data, and use the findings to plan and deliver service improvements.

This recommendation is consistent with Interventional Procedure Guidance that "Selection of patients… should be done by clinicians experienced in the use of thrombolysis for stroke and in interpretation of relevant imaging. The procedure should only be carried out by appropriately trained specialists with regular experience in intracranial endovascular interventions, with appropriate facilities and neuroscience support."(2016a) As there is no experimental evidence about the relative importance of different arrangements for the organisation and delivery of care, this recommendation is supported by the evidence review reported here.

Finally, this review stands out as it is characterised by an impressive number of well-designed and well-conducted randomised controlled trials, which represents a strong testament to the clinical and academic communities in seeking to understand the potential benefits and risks of stroke treatments, particularly of thrombectomy.

6. Conclusion

Mechanical thrombectomy minimises disability among people who present early with an acute ischaemic stroke (without increasing mortality), where the occlusion can be localised to the proximal anterior cerebral circulation.

7. Evidence Summary Table

Trials of mechanical thrombectomy supplementing intravenous thrombolysis vs. best medical therapy (including iv thombolysis) to treat ischaemic stroke secondary to proximal anterior circulation occlusion

Study reference	Trial name	Study type	Study Design	Population characteristics	randomisation: 2004- 2016	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
BERKHEMER, O. A., et al 2015. NEJM STARKE, R. M., 2015. Neurosurgery, FRANSEN, P. S. S. et al 2016. JAMA Neurology,	MR CLEAN	P1: Primary research (quantitative)	RCT	502 , 16 centres in Netherlands cerebral angiography to demonstrate anterior circulation occlusion I=233, C= 267 randomised 12/2010 - 3/2014 median age I= 66, C= 66 median NIHSS score I= 17, C= 18		intervention block randomised by centre, severity and intended treatment and use of iv thrombolysis Among those allocated to I: 84% had mechanical extraction retreivable stents used in 82% stroke to procedure time: median 206 min, interquartile range 210-313	Primary Clinical effectiveness	median Modified Rankin score	90 days I=3, C=4	10	Direct	well conducted multi-centre pragmatic RCT, requiring angiography on entry, clot extraction principally using stent retreivers. Release of strongly positive trial findings precipitated review of many other concurrent trials
							Secondary Clinical effectiveness	Modified Rankin (0-2)	90 days I= 32.6%, C=19.1%			
							Secondary Clinical effectiveness	Median EQ5D	90 days I= 0.69, C=0.66			
							Secondary Safety	Symptomatic intracranial haemorrhage	90 days I= 7.7%, C= 6.4%			
BRACARD, S. et al 2016. Lancet Neurology,	THRACE	P1: Primary research (quantitative)	RCT	26 centres in France I=204, C=208 randomised 2010- 2015 cerebral angiography to demonstrate site (basilar occlusions not excluded, but none such cases randomised) thrombectomy to take place within 5 hours of symptom onset median age I=68, C= 66 median NIHSS score I=17, C=18		randomisation by number sequence, held by trial centre, stratified by centre device choice by operator, from prescribed list maintained by investigators 9% with aspiration device alone 77% with stentreiver alone 14% with multiple systems time to thrombectomy median = 250min interquartile range 210-290 min trial terminated early by steering committee as 2nd unplanned interim analysis on release of MR CLEAN results showed superiority I vs C trial funded by French Ministry of Health	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=53%, C=42% OR 1.55 95%CI 1.05, 2.30 p=0.028	9	Direct	well designed and executed government funded trial of angiographically determined anterior circulation occlusion. Trial terminated early after unplanned interim analysis following release of MR CLEAN results
							Secondary Clinical effectiveness	All cause mortality	90 days I=12%, C=13% OR 0.81 95%CI 0.53, 1.24 p= 0.70			
							Secondary Safety	Symptomatic intracranial haemorrhage	24 hours I=2%, C=2% OR 1.39 95%CI 0.53, 1.24 p=0.71			
CAMPBELL, B. C.,et al 2015. NEJM	EXTEND- IA	P1: Primary research (quantitative)	RCT	14 Centres in Australia and New Zealand patients with angiographically confirmed occlusion of 1st or 2nd segment of middle cerebral artery patients receiving iv thrombolysis witin 4.5 hours of stroke onset n=70: I=35, C=35 mean age: I=68.6, C=70.2 median NIHSS score: I=17, C=13		I: endovascular thrombectomy using stent retreivers trial suspended after release of MR CLEAN results, unplanned interim analysis demonstrated superiority of I time from stroke to procedure median 210 interquartile range 166-251 trial supported by Australian government grants. Devices (and infrastructure grant) supplied by Convidien	Primary Clinical effectiveness	early neurological improvement (>7 point fall or zero NIHSS score)	3 days I=80%, C=37% OR 6.0, p=0.002	9	Direct	well designed and executed government and industry supported trial of stent-retreivers. Trial terminated early after publication of MR CLEAN results. Results were positive, but of uncertain magnitude, given total study size
							Secondary Clinical effectiveness	Modified Rankin (0-2)	90 days I=71%, C=40% OR= 4.2, p=0.01			
							Secondary Safety	Death	90 days I=9%, C=20% OR=0.45, p=0.31			

Study reference	Trial name	Study type	Study Design	Population characteristics	randomisation: 2004- 2016	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
JOVIN, G., et al . 2015. NEJM	REVASCAT	P1: Primary research (quantitative)	RCT	4 study centres in Catalonia, Spain patients aged 18- 80 who EITHER received iv alteplase within 4.5 hours, without revascularisation in 30 mins OR who had contraindication to alteplase AND where occlusion of the proximal anterior circulation was identified and could be operated on within 8 hours of symptom onset AND had pre-stroke functional status 0-1 on modified Rankin scale excluded on evidence of large ischaemic core to stroke (on CT) 206 patients: I= 103, C=103 mean age I=66, C=67 median NIHSS I=17, C=17		Centres had to: treat > 500 acute stroke patients/yr and undertake > 60 mechanical thromectomies/yr Randomisation stratified by age, severity, occlusion site, timing & participating centre I- iv alteplase plus extraction with stent-retrievers Outcome assessment by investigators blind to treatment assignment Stroke to procedure time: median 269 min interquartile range 269- 340 min *Trial terminated early* by monitoring committee due to loss of equipoise among investigators trial funded by government and industry sponsors	Primary Clinical effectiveness Secondary Safety Secondary Safety Secondary Clinical effectiveness	score on modified Rankin scale All cause mortality Symptomatic intracranial haemorrhage Modified Rankin (0-2)	90 days OR= 1.7 (95%CI 1.04 - 2.7) 90 days I=18.4%, C=15.5% 90 days I=1.9%, C=1.9% 90 days I=43.7%, C=28.2%	9	Direct	well conducted multi-centre trial in Spain, funded by government and industry, of stent retreivers, terminated early due to loss of equipoise quarter of participants had time to procedure >7hrs
SAVER, J. L., et al 2015.	SWIFT	P1: Primary research (quantitative)	RCT	39 Centres in USA and Europe patients with angiographically confirmed occlusion of internal carotid or 1st segment middle cerebral arterty able to undergo thrombectomy within 6 hours 196 patients I=98, C=98 age C = 66.3, I=65.0 NIHSS score median I= 17, C= 17		thrombectomy to be performed by Solitaire FR or Solitaire 2 device Study centres required to have performed at least 40 mechanical thrombectomies a year, including at least 20 each year using Solitaire stent retreivers time from stroke to procedure (mins) median 224 interquartile range 165-275 *trial terminated early* by steering committee after unplanned interim analysis following release of MR CLEAN results Study funded by *Convidien*	Primary Clinical effectiveness Secondary Safety Secondary Clinical effectiveness Primary Safety Primary Safety	Median Rankin Score All cause mortality Modified Rankin (0-2) Any serious adverse event Symptomatic intracranial haemorrhage	90 days I= 2, C=3 p<0.001 90 days I=9%, C=12% Risk ratio 0.74, p=0.50 95%CI 0.33, 1.68 90 days I=60%, C=35% Risk ratio 1.70, p<0.001 95%CI 1.23, 2.33 90 days I=36%, C=31% Risk ratio 1.15, p=0.54 95%CI 0.78, 1.72 90 days I=0%, C=3% Risk ratio 0, p=0.12	9	Direct	well designed and conducted international industry supported study, evauluating patients with angiographically confirmed anterior circulation occlusion who could be treated within 12 hours. Trial was stopped early after unplanned interim analysis showed positive findings.
Goyal, M., et al. NEJM (2015).	ESCAPE	P1: Primary research (quantitative)	RCT	22 centres worldwide. Sites chosen after visits to demonstrate efficient work practices. patients with angiographically confirmed proximal occulsion of anterior circulation within 12 hours of symptom onset 316 patients I=165, C=150 median age I=71, C=70 median NIHSS score I=16, C=17		Use of stent retrievers where possible Time from stroke to first reperfusion (mins) median 241 interquartile range 176-359 75% received iv thrombolysis onset to randomisation time 100 (32%) 3-6 hrs 46 (15%) 6-12 hours Outcome assessment by investigators blind to treatment assignment Funded by *Convidien* and other sources *Study terminated early* after unplanned interim analysis on release of MR CLEAN results	Primary Clinical effectiveness Secondary Clinical effectiveness Secondary Safety	Modified Rankin score Modified Rankin score 0-2 death	90 days OR= 2.6 95%CI 1.7, 3.8 90 days I=53.0%, C=29.3% rate ratio 1.8 95%CI 1.4, 2.4 90 days I=10.4%, C=19.0% Rate ratio 0.5 95%CI 0.3, 1.0	9	Direct	Well designed, industry supported study, on patients with angiographically confirmed occlusions of anterior cerebral circulation, mechanical thrombectomy undertaken using stent retreivers. Quarter of participants' time to reperfusion >4hrs Terminated early because of positive findings from unplanned interim analysis precipitated on release of MR CLEAN findings

Study reference	Trial name	Study type	Study Design	Population characteristics	randomisation: 2004- 2016	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Muir et al JNNP 2016	PISTE	P1: Primary research (quantitative)	RCT	10 UK centres. Centre eligibility: >1 operator, each with >9 thrombectomies in previous 18 months AND 120 endovascular procedures/yr for 3 years patients with angiographically confirmed proximal occulsion of anterior circulation within 12 hours of symptom onset 65 patients: I=33, C=32 median age I=67, C=64 median NIHSS score I=18, C=14		Randomisation stratified by centre, severity and time to presentation Time from stroke to procedure end (mins) median 251 interquartile range 181,390 Outcome assessment by investigators blind to treatment assignment Funded by Stroke Association and NIHR *Study terminated early* on release of other trial results	Primary Clinical effectiveness Secondary Safety	Modified Rankin score 0-2 death	90 days I=51%, C=40% OR 2.12 95%CI 0.65, 6.95 p=0.204 90 days OR 1.56 0.29, 8.40 p=0.599	9	Direct	Well designed, government and charity supported study, on patients with angiographically confirmed occlusions of anterior cerebral circulation. Terminated early because of release of other trial findings

Reviews and meta-analyses of mechanical thrombectomy supplementing intravenous thrombolysis Vs. best medical therapy (including iv thombolysis) to treat ischaemic stroke secondary to proximal anterior circulation occlusion

Study reference	Subsidiary studies included	Study type	Study type	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
BUSH, C. K., 2016. PLoS ONE	MR CLEAN 2015 ESCAPE 2015 EXTEND IA 2015 SWIFT PRIME 2015 REVASCAT 2015	S1: Meta analysis of existing data analysis	R1: Systematic reviews of existing research	5 trials including 1,287 patients	estimate treatment effects of thrombectomy using principally stent retreivers database search, independent data extraction and critical appraisal no funding or conflicts of interest reported	Primary Clinical effectiveness	shift in modified Rankin score	90 days cOR 2.22 p<0.0001 95%CI 1.66, 2.98 I^2= 46%	8	Direct	well conducted systematic literature review and meta-analysis, examining the effect of thrombectomy, principally using stent retreivers, finding relatively consistent results between trials
						Primary Safety	All cause mortality	90 days cOR 0.78 p=0.11 95%CI 0.54, 1.12 I^2= 15%			
						Primary Safety	Symptomatic intracranial haemorrhage	90 days cOR 1.19 p=0.53 95%CI 0.69, 2.05 I^2= 0%			
CAMPBELL, B. C. V., et al. 2016. Stroke,	SWIFT PRIME 2015 ESCAPE 2015 REVASCAT 2015 EXTEND IA 2015	S2: Secondary analysis of existing data	S1: Meta analysis of existing data analysis	787 patients from 4 trials	pooled individual level data from trials where Solitaire was principal or only device mixed methods logistic regression used to determine treatment effects random effects model used to summarise finding, taking account of differences in trial protocols funded by Medtronic	Primary Clinical effectiveness	Modified Rankin score	90 days I=2, C=4 OR 2.7 p<0.0001 95%CI 2.0, 3.5	10	Direct	well conducted secondary analysis of recent trials, identifying magnitude of effect and important subgroup analysis
						Secondary Clinical effectiveness	Modified Rankin (0-2)	90 days I=54%, C=32% OR 3.1 95%CI 2.2, 4.4 p<0.0001 NNT for 1 additional independent patient= 4			
						Secondary Clinical effectiveness	Modified Rankin score, odds of favourable outcome by onset to randomisation	90 days <5hrs OR 2.76 95%CI 2.05, 3.72 >5hrs OR 2.0 95%CI 1.04,3.84			
						Secondary Clinical effectiveness	Modified Rankin score, odds of favourable outcome by age	90 days <80yr OR 2.57 95%CI 1.90, 3.50 ≥80 yr OR 3.46 95%CI 1.58, 7.60			
Ferri et al 2016		R1: Systematic reviews of existing research			summary of recent and ongoing clinical trials. No numerical summary given Brazilian government funded				9	*Direct*	well conducted systematic literature review, without accompanying meta analysis

Study reference	Subsidiary studies included	Study type	Study type	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Hussein M., et al 2016. Interventional Neurology,	MR CLEAN 2015 ESCAPE 2015 REVASCAT 2015 SWIFT PRIME 2015 EXTEND IA 2015 THERAPY 2016	S1: Meta analysis of existing data analysis		6 studies comaring mechanical thrombectomy + intravenous thrombolysis	benefits and risks of stent retreivers over the use of recombinant tissue plasminogen activator (rTPA) alone Database search, critical appraisal of studies Findings summarised by meta analysis (fixed effects model) no funding declared	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=46%, C=27% NNT 5 I^2=0%	9	Direct	well conducted meta analysis, of trials examining effects of stent retreivers identifying consistent treatment effect
						Secondary Safety	All cause mortality	90 days I= 14%, C= 18% I^2=27%			
MARMAGKIOLIS, K.,2015. JACC: Cardiovascular Interventions,	MR CLEAN 2015 REVASCAT 2015 EXTEND IA 2015 SWIFT PRIME 2015 ESCAPE 2015	S1: Meta analysis of existing data analysis		5 trials where thrombectomy was principally (86-100% of patients) performed using using stent retreivers	database search, meta analysis using random effects model no declaration about funding or conflicts of interest	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=46.2%, C=26.2% I^2=0%	7	Direct	Meta analysis of trials where patients were prinicipally treated with stent retreivers, identifying relatively consistent trial findings
						Primary Safety	All cause mortality	90 days I=15.1%, C=18.7% I^2=29%			
						Primary Safety	Symptomatic intracranial haemorrhage	90 days I=4.3%, C=4.3% I^2=0%			
RODRIGUES, F. B., 2016. BMJ, NEVES, J. B., et al. 2016. European Journal of Neurology, 23, 43. **2013 trials**	IMS III 2013 MR RESCUE 2013 SYNTHESIS 2013	R1: Systematic reviews of existing research	S1: Meta analysis of existing data analysis	I=679, C=457	Database search, Two independent reviews for inclusion, appraisal and summary. Results summarised by random effects model. Significant inconsistency identified among study findings (I^2=69%) among whole whole sample, hence results presented as subsets (2013 and 2015) No specific funding for this work Authors made declarations about prior industry links and funding	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=39.0%, C=39.6% I^2=0%	10	Direct	well conducted systematic literature review and meta analysis, based on subgroup analysis of all identified trials, identifying lack of a consistent treatment effect
						Primary Safety	All cause mortality	90 days I=18.3%, C=17.6%			
2015 trials	EXTEND IA 2015 ESCAPE 2015 MR CLEAN 2015 SWIFT PRIME 2015 REVASCAT 2015 THERAPY 2016 THRACE 2016	R1: Systematic reviews of existing research	S1: Meta analysis of existing data analysis	I=878, C=893		Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=47.5%, C=29.8% I^2=0%	10	Direct	well conducted systematic literature review and meta analysis, based on subgroup analysis of all identified trials, identifying a consistent treatment effect
						Primary Safety	All cause mortality	90 days I=14.5%, C=17.4%			

Study reference	Subsidiary studies included	Study type	Study type	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
SAVER, L.,et al. 2016. JAMA: Goyal, M., et al. (2016). Lancet HERMES	MR CLEAN 2015 ESCAPE 2015 REVASCAT 2015 SWIFT PRIME 2015 EXTEND IA 2015	S2: Secondary analysis of existing data	S1: Meta analysis of existing data analysis	1,231 patients, I=634, C=653 NIHSS I=17, C=17	Database search, characterisation of studies, extraction and collation of individual patient-level data. Mixed effects analysis used to take account of between-trial differences Funded by Medtronic	Primary Clinical effectiveness	modified Rankin Score reduction	90 days OR=2.26, p<0.0001	10	Direct	well conducted systematic literature review, and pooled analysis of individual patient data, likely to give a reliable estimate of treatment effect, with mixed findings around treatment timing
						Secondary Safety	All cause mortality	90 days I=15.3%, C=18.9%			
						Secondary Clinical effectiveness	Modified Rankin (0-2)	90 days I=46.0%, C=26.5%			
						Secondary Safety	Symptomatic intracranial haemorrhage	90 days I=4.4%, C=4.3%			
						Secondary Clinical effectiveness	modified Rankin Score reduction- absolute risk difference between I and C of lower disability score	90 days @3hr 39.2% cOR 2.79 95%CI 1.96, 3.98 @6hr 30.2% cOR 1.98 95%CI 1.30-3.00 @8hr 15.7% cOR 1.57 95% CI 0.86, 2.88 falling by 3.4% for every hour to arterial puncture			
						Secondary Clinical effectiveness	modified Rankin (0-2) absolute risk difference	90 days @3hr 23.9% cOR 2.83 95%CI 2.07, 3.86 @6hr 18.1% cOR 2.32 95%CI 1.56-3.44 @8hr 14.3% cOR 2.03 95% CI 1.03, 3.99			
						Secondary Clinical effectiveness	modified Rankin Score reduction - odds of favourable outcome by age	90 days cOR (95%CI) <80yrs 2.44 (1.70, 3.50) ≥80 yrs 3.68 (1.95, 6.92)			
						Secondary Clinical effectiveness	modified Rankin Score reduction - odds of favourable outcome by time to randomisation	90 days cOR (95%CI) ≤300 min 2.66 (1.83, 3.87) >300min 1.76 (1.05, 2.97) p(interaction)= 0.10			

Study reference	Subsidiary studies included	Study type	Study type	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Lambrinos A et al 2016. Canadian Journal of Neurological Sciences, Anon 2016. Health Quality Ontario	MR CLEAN 2015 EXTEND IA 2015 ESCAPE 2015 SWIFT PRIME 2015 REVASCAT 2015	S1: Meta analysis of existing data analysis	R1: Systematic reviews of existing research	1,278 patients in 5 trials thrombectomy with new-generation devices compared to iv thrombolysis alone	database search, critical appraisal meta-analysis of studies using fixed-effects model funded by Health Quality Ontario	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days I=46.1%, C=26.4% I^2=0%	10	Direct	well conducted systematic literature review and meta analysis of RCTs assesssing benefits of new generation stent-retriever devices, meta-analysis identified consistent treatment benefits
						Secondary Safety	All cause mortality	90 days I=15.3%, C=18.8% I^2=22%			
						Secondary Safety	Symptomatic intracranial haemorrhage	90 days I=4.6%, C=4.3% I^2=0%			
TOUMA, L., et al 2016. JAMA Neurology,	MR CLEAN 2015 ESCAPE 2015 REVASCAT 2015 SWIFT PRIME 2015 EXTEND IA 2015	S1: Meta analysis of existing data analysis	R1: Systematic reviews of existing research	5 studies using principlally stent retreivers	benefits and risks of stent retreivers over the use of recombinant tissue plasminogen activator (rTPA) alone Database search, critical appraisal of studies Findings summarised by meta analysis (random effects model) Funded by grants within McGill University	Primary Clinical effectiveness	Modified Rankin (0-2)	90 days RR=1.72 95% CI 1.48, 1.99 NNT 6 (4 to 8) I^2=0%	10	Direct	well conducted systematic literature review and meta analysis, of trials examining effects of stent retreivers identifying consistent treatment effect
						Secondary Safety	All cause mortality	90 days RR 0.82 95%CI 0.60, 1.11			
						Secondary Safety	Intracranial haemorrhage	RR= 1.15 95%CI 0.67, 1.97			

Abbreviations

I^2	measure of inconsistency in among results included in meta-analysis — http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm
NIHSS	National Institutes for Health Severity Score — score 0-42, higher score indicating greater severity
mR scale	Modified Rankin scale Score
RR	relative risk
95% CI	95% confidence interval

8. Grade of evidence table

Grade of evidence for mechanical thrombectomy supplementing intravenous thrombolysis Vs. best medical therapy (including iv thombolysis) to treat ischaemic stroke secondary to proximal anterior circulation occlusion.

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Modified Rankin Score (0-2) at 3 months	HERMES (Goyal et al 2016, Saver et al 2016)	10	Direct	*A*	The modified Rankin Score is a categorical scale measuring disability from stroke. The rating of 0-2 describes those with little or no disability who are able to function independently. This outcome measures the proportion of individuals who are functioning independently after 3 months. For every 4 to 6 people who undergo mechanical thrombectomy, one more person will be functioning independently than if they had received iv thrombolysis alone. The magnitude of this benefit falls every hour by 3.4%.
Modified Rankin Score probabiliy of favourable outcome at 3 months	HERMES (Goyal et al 2016, Saver et al 2016)	10	Direct	*A*	The modified Rankin Score is a categorical scale measuring disability from stroke. The rating of 0-2 describes those with little or no disability who are able to function independently. This outcome measures the proportion of individuals who obtain a favourable outcome as assessed by change in rating category, after 3 months. The odds of an improved favourable outcome as a result of thrombectomy was greater among those randomised 3 hours or less from stroke (OR=2.66) than those who were randomised after 3 hours (OR=1.76), though these differences were not statistically significant.
Symptomatic intracranial haemorrhage	HERMES (Goyal et al 2016, Saver et al 2016)	10	Direct	A	Intracranial haemorrhage is a potential complication of stroke associated with cerebral reperfusion. It is therefore a potentially very important complication of mechanical thrombectomy. Symptomatic intracranial haemorrhage is no more common among those who undergo mechanical thrombectomy (4.4%) than among those who receive best medical therapy (4.3%)
Mortality	HERMES (Goyal et al 2016, Saver et al 2016)	10	Direct	A	Death is unfortunately common in the weeks following stroke, and evaluation of any stroke treatment needs to take account of potential for (adversely) influencing montality. Death rates at 90 days were lower among those undergoing thrombectomy (15.3%) than among those undergoing best medical therapy (18.9%), though these differences were not statistically significant.

9. Literature Search Terms

Search Terms *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	*People suffering severe Acute ischaemic stroke* *Aged over 16 (no upper limit)* *Previously functioning independently* *Large vessel occlusion*
I – Intervention Which intervention, treatment or approach should be used?	Thrombectomy Clot retrieval
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Stroke unit care/best medical care
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Mortality Morbidity – impairment, disability, participation, quality of life *Important to decision-making:* cost effectiveness length of hospital stay
Assumptions / limits applied to search *Section to be completed in accordance with section 2.4*	
Inclusion Criteria	Randomised controlled trials, systematic reviews, meta-analyses, English only, last 10 years,
Exclusion Criteria	Patients less than 16 years

10. Search Strategy

Medline

1 Stroke/
2 Brain Ischemia/
3 Brain Infarction/
4 Cerebral Infarction/
5 "Intracranial Embolism and Thrombosis"/
6 Intracranial Embolism/
7 Intracranial Thrombosis/
8 (isch?emi* adj5 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)).tw.
9 ((brain or cerebr* or hemispher* or intracran* middle cerebr* or mca* or anterior circulation) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)).tw.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 Thrombectomy/
12 Mechanical Thrombolysis/
13 Embolectomy/
14 thrombectomy.tw.
15 embolectomy.tw.
16 (clot adj3 (retriev* or remov* or extract*)).tw.
17 (thromb* adj3 (retriev* or remov* or extract*)).tw.
18 (embol* adj3 (retriev* or remov* or extract*)).tw.
19 (mechanical adj3 (retriev* or remov* or extract* or intervention)).tw.
20 endovascular snare*.tw.
21 (thromboaspiration or atherect*).tw.
22 (interventional adj3 (radiolog* or radiograph* or neuroradiolog*)).tw.
23 stentriever.tw.
24 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 10 and 24
26 randomized controlled trial/
27 exp clinical trial/
28 (random* or RCT or control* trial).kf,ti.
29 26 or 27 or 28
30 limit 29 to yr="2009 -Current"
31 review/
32 meta analysis/
33 (systematic review or meta-analysis).kf,ti.
34 limit 33 to yr="2015 -Current"
35 30 or 34

36 25 and 35

Embase

1 cerebrovascular accident/
2 brain stem infarction/
3 brain infarction/
4 exp occlusive cerebrovascular disease/
5 (isch?emi* adj6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)).ab,ti.
6 ((brain or cerebr* or hemispher* or intracran* or middle cerebr* or mca* or anterior circulation) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ab,ti.
7 thromboembolism/
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 thrombectomy/
10 embolectomy/
11 percutaneous thrombectomy/
12 exp thrombectomy device/
13 thrombectomy.ab,ti.
14 embolectomy.ab,ti.
15 (clot adj3 (retriev* or remov* or extract*)).ab,ti.
16 (thromb* adj3 (retriev* or remov* or extract*)).ab,ti.
17 (embol* adj3 (retriev* or remov* or extract*)).ab,ti.
18 (mechanical adj3 (retriev* or remov* or extract* or intervention)).ab,ti.
19 "endovascular snare*".ab,ti.
20 (thromboaspiration or atherect*).ab,ti.
21 (interventional adj3 (radiolog* or radiograph* or neuroradiolog*)).ab,ti.
22 stentriever.ab,ti.
23 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 8 and 23
25 randomized controlled trial/
26 controlled clinical trial/
27 clinical trial/
28 controlled study/
29 (random* or RCT or control* trial).kw,ti.
30 25 or 26 or 27 or 28 or 29
31 limit 30 to yr="2009 -Current"
32 review/
33 systematic review/
34 meta analysis/
35 (systematic review or meta-analysis).kw,ti.
36 32 or 33 or 34 or 35
37 limit 36 to yr="2015 -Current"
38 31 or 37
39 8 and 23 and 38
40 limit 39 to english language
41 limit 40 to yr="2009 -Current"
42 (Conference Abstract or Conference Paper or Conference Review or Editorial or Erratum or Letter or Note).pt.
43 (40 not (Conference Abstract or Conference Paper or Conference Review or Editorial or Erratum or Letter or Note)).kw,ti.
44 exp animal/
45 nonhuman/
46 43 or 44
47 exp human/

48 45 not 46
49 42 not 47

CINAHL

1. CINAHL; STROKE/; 37038 results.
2. CINAHL; CEREBRAL ISCHEMIA/; 5483 results.
3. CINAHL; INTRACRANIAL EMBOLISM AND THROMBOSIS/; 871 results.
4. CINAHL; INTRACRANIAL EMBOLISM/; 194 results.
5. CINAHL; INTRACRANIAL THROMBOSIS/; 128 results.
6. CINAHL; ((ischemi* OR ischaem*) adj5 (stroke* OR apoplex* OR cerebral AND vasc* OR cerebrovasc* OR cva OR attack*)).ti,ab; 10096 results.
7. CINAHL; ((brain OR cerebr* OR hemispher* OR intracran* OR middle AND cerebr* OR mca* OR anterior AND circulation) adj5 (ischaem* OR ischem* OR infarct* OR thrombo* OR emboli* OR occlus* OR hypoxi*)).ti,ab; 8087 results.
8. CINAHL; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 46386 results.
9. CINAHL; THROMBECTOMY/; 461 results.
10. CINAHL; EMBOLECTOMY/; 159 results.
11. CINAHL; (thrombectomy OR embolectomy).ti,ab; 545 results.
12. CINAHL; ((clot adj3 (retriev* OR remov* OR extract*))).ti,ab; 80 results.
13. CINAHL; (thromb* adj3 (retriev* OR remov* OR extract*)).ti,ab; 161 results.
14. CINAHL; (embol* adj3 (retriev* OR remov* OR extract*)).ti,ab; 90 results.
15. CINAHL; (mechanical adj3 (retriev* OR remov* OR extract* OR intervention)).ti,ab; 367 results.
16. CINAHL; "endovascular snare*".ti,ab; 1 results.
17. CINAHL; (thromboaspiration OR atherect*).ti,ab; 166 results.
18. CINAHL; (interventional adj3 (radiolog* OR radiograph* OR neuroradiolog*)).ti,ab; 583 results.
19. CINAHL; stentriever.ti,ab; 4 results.
20. CINAHL; 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 2136 results.
21. CINAHL; 8 AND 20; 425 results.
22. CINAHL; RANDOMIZED CONTROLLED TRIALS/; 28252 results.
23. CINAHL; exp CLINICAL TRIALS/; 137064 results.
24. CINAHL; (random* OR RCT OR control* AND trial).ti; 40344 results.
25. CINAHL; 22 OR 23 OR 24; 146869 results.
26. CINAHL; 21 AND 25; 90 results.
27. CINAHL; 26 [Limit to: Publication Year 2009-2016]; 78 results.
28. CINAHL; SYSTEMATIC REVIEW/; 26649 results.
29. CINAHL; META ANALYSIS/; 17837 results.
30. CINAHL; ("systematic review" OR "meta analysis").ti; 25594 results.
31. CINAHL; 28 OR 29 OR 30; 48320 results.
32. CINAHL; 21 AND 31; 19 results.
33. CINAHL; 32 [Limit to: Publication Year 2015-2016]; 12 results.

11. Evidence selection

- 1116 unique records were identified.
- 86 were considered potentially relevant to the review and the full text obtained.
- Fifteen of these studies: seven trials, and a further nine systematic literature reviews and meta-analyses (two of which use secondary analyses of pooled trial data) met all the inclusion criteria.

12. References

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