National Institute for Health and Care Excellence

Draft for consultation

Stroke (update)

Evidence review D: Thrombectomy

NICE guideline

Intervention evidence review

November 2018

Draft for consultation

This evidence review was developed by the National Guideline Centre

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Contents

1 Endovascular therapy

1.1 Review question: What is the clinical and cost effectiveness of endovascular therapy (EVT) with or without intravenous thrombolysis versus intravenous thrombolysis to improve outcomes?

1.2 Introduction

Ischaemic stroke secondary to occlusion of a proximal intracerebral artery is a major and rising source of morbidity and mortality in the UK. Intravenous thrombolytic therapy has formed the mainstay of acute treatment over the last twenty years but increasingly there has been interest in alternative means of vessel recanalisation using neurointerventional endovascular techniques in order to achieve more effective brain reperfusion in an attempt to minimise the damage caused by an occluded artery. Initial evidence provided by randomised trials published in 2013 suggested that endovascular therapy offered no conclusive benefit to patients over standard medical therapy but these trials were criticised for speed of recruitment, use of out-dated technology and mode of patient selection. Since 2015 there have been numerous publications describing a large number of multi-centre randomised controlled trials that have investigated the use of more contemporary neurointerventional techniques. We aim to assess this evidence for the use of endovascular thrombectomy in acute stroke patients suffering a proximal intracerebral arterial occlusion.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with acute ischaemic stroke, with a proven large vessel occlusion on non-invasive angiography.
Intervention(s)	Endovascular therapy (mechanical thrombectomy) with or without alteplase
Comparison(s)	Intravenous thrombolysis (alteplase) or standard care (for example, aspirin)
Outcomes	Critical Modified Rankin scale (mRS) 0 – 2 or ordinal shift, 90 days and 1 year Mortality at 90 days and 1 year Important Intracerebral haemorrhage Symptomatic intracerebral haemorrhage Patient reported outcome measures Quality of life (both health- and social-related quality) Length of stay in hospital Procedural complications
Study design	Randomised controlled trials Systematic reviews and meta-analyses of the above Observational studies with multivariable analysis if no RCTs are identified

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[23] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy upto March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 Clinical evidence

1.5.1 Included studies

Ten studies detailed in 15 papers were included in the review;[6, 7, 15, 17, 21, 28, 30, 37, 42, 51, 66, 71, 76, 90, 91] these are summarised in Table 2 below and compare endovascular therapy (thrombectomy) with or without thrombolysis (alteplase) versus usual care (with or without) thrombolysis. All of the RCT evidence found was based on anterior circulation stroke. Evidence from these studies is summarised in the clinical evidence summary below (Table 2). See also the study selection flow chart in appendix C, forest plots in appendix E, study evidence tables in appendix D, GRADE tables in appendix F and excluded studies list in appendix H.

As no RCT study data was found for posterior circulatory stroke, an additional observational study search was carried out for this stratum. Two studies met the inclusion criteria[31 115]. Evidence from these studies is summarised in the clinical evidence summary below (Table 2).

1.5.1.1 Anterior circulation stroke

All the studies are PROBE design (prospective, randomized, open-label, controlled trial with blinded outcome evaluation). It is noted that although this is the highest quality of study design suitable for these trials, subjective outcomes (EQ-5D and mRS) have been downgraded due to no blinding of the interventions for the patient or care giver. All the trials are in people aged 18 and over, but this was considered similar enough to our protocol of 16 years and over not to warrant a downgrade in evidence. The majority of studies were funded by industry.

Following the results of MR CLEAN[15] which shows efficacy of thrombectomy, the majority of other trials stopped recruitment. Some conducted planned interim analysis; others state that they are underpowered.

A pre-planned subgroup analysis based on time to thrombectomy was performed due to heterogeneity. This resolved the inconsistency and so the results are reported according to the pre-specified subgroups based on time to thrombectomy. The DAWN[76] trial investigated thrombectomy performed 6 - 24 hours after a stroke and the DEFUSE 3 trial had time to treatment of 6 - 16 hours after symptom onset and has also been included in the 6 - 24 hour subgroup. The REVASCAT[51] and ESCAPE[42] trials have been reported individually as thrombectomy was performed within 8 and 12 hours respectively. The remaining studies all perform thrombectomy within 6 hours and have been meta-analysed.

1.5.2 Posterior circulation stroke

No RCT or observational data were found for this stratum that met the protocol criteria. It is noted that the BEST[60] trial, a multicentre randomised outcome blinded trial on acute ischemic stroke due to basilar artery occlusion, has a published protocol. The trial was due to have finished in March 2018 but no results have yet been published and therefore this trial is not

included in the review. The trial authors were contacted for further information but no response was received.

1.5.3 Excluded studies

1.5.3.1 Anterior circulation stroke

EASI, [53] and IMS III[1] were excluded as imaging was not conducted as standard prior to inclusion in study (therefore they do not meet the protocol criterion of having a proven large vessel occlusion on non-invasive angiography).

1.5.3.2 Posterior circulation stroke

Observational studies were excluded primarily for being non-comparative studies, wrong interventions or having a mixed stroke population with no separate analysis for the posterior circulation.

See the excluded studies list in appendix H.

1.5.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review for anterior circulation stroke

Study	Intervention and comparison	Population	Outcomes	Comments
Thrombectomy within 6 hours of stroke onset				
Berkhemer 2015 [15, 37] MR CLEAN	Intra-arterial thrombolysis (urokinase or alteplase), mechanical thrombectomy (within 6 hours) or both vs best medical practice Median (IQR) time from onset to alteplase: intervention 85 (67-110); control 87 (65-116) minutes IV alteplase = 87.1% intervention, 90.6% control Additional intra-arterial thrombolytics used in 10.3% and intra-arterial thrombolytics as monotherapy in 0.4%	n = 500 Netherlands Age ≥18 Mean age (range) = 65 (23 - 96) Patient selection criteria: evidence of occlusion on CTA, MRA or DSA; enrolment not limited according to ASPECTS or extension of early signs of infarction at baseline Median (IQR) NIHSS: Intervention = 17 (14-21) Control = 18 (14-22)	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Stroke at 90 days EQ-5D at 90 days	Of the intervention group 83.7% received thrombectomy; 15.9% received no intra-arterial intervention; 0.4% received intra-arterial thrombolysis alone Funded by industry
Bracard 2016[17] THRACE	Thrombectomy (within 5 hours) plus IV alteplase vs IV alteplase	n = 414 26 centres in France	Mortality at 90 days mRS at 90 days EQ-5D	Funded by academia/government

Study	Intervention and comparison	Population	Outcomes	Comments
	All received IV alteplase Median (IQR) time from stroke onset to IV thrombolysis: intervention 150 (120-178) minutes Control 153 (124-180) minutes Median (IQR) time from stroke onset to thrombectomy: 250 (210-290) minutes	Age 18 - 80 Median (IQR) intervention = 66 (54 - 74) control = 68 (54 - 75) Patient selection criteria: evidence of occlusion on CTA or MRA Median (IQR) NIHSS: Intervention = 18 (15-21) Control = 17 (13-20)		
Campbell 2015 [21] EXTEND IA	Mechanical thrombectomy (within 6 hours) plus IV alteplase vs IV alteplase All received thrombolysis Median (IQR) time from onset to alteplase: intervention 127 (93-162); control 145 (105-180) minutes	n = 70 10 study centres across Australia and New Zealand Age ≥18 Mean age (SD) intervention = 68.6 (12.3) control = 70.2 (11.8) Patient selection criteria: evidence of occlusion on CTA Median (IQR) NIHSS: Intervention = 17 (13-20) Control = 13 (9-19)	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage	Used CT perfusion imaging to select patients likely to benefit Trial stopped early because of efficacy. Funded by industry and academia
Saver 2015 [90, 91] SWIFT PRIME	Mechanical thrombectomy (within 6 hours) plus IV thrombolysis (tPA) vs IV thrombolysis (tPA) All received thrombolysis Median (IQR) time from onset to randomisation: intervention 190.5 (141-249); control 188 (130-268)	n = 196 39 centres in USA and Europe. Age 18 - 80 Mean age (SD) intervention = 65 (12.5) control = 66.3 (11.3) Patient selection criteria: initially used a 'target	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Procedural complications	Study stopped due to interim analysis showed evidence of efficacy Funded by industry.

Study	Intervention and comparison	Population	Outcomes	Comments
	minutes Median (IQR) time from stroke onset to groin puncture: 224 (165-275) minutes	mismatch' strategy, using multimodal CT or MRI, including perfusion sequences, to identify patients with salvageable tissue. Subsequently, a 'small to moderate core' strategy, using ASPECTS ratings of CT or MRI was used. Median (IQR) NIHSS: Intervention = 17 (13-19) Control = 17 (13-20)		
Mocco 2016[66] THERAPY	Thrombectomy (within 6 hours) plus alteplasevs IV alteplase All received IV alteplase Median (IQR) time from onset to groin puncture in intervention group: 227 (184-262) minutes Median time from onset to IV alteplase, intervention: 108 (86-138) and control: 102 (80-154) minutes	n = 108 36 USA and German centres 18 to 85 years of age Mean age (SD): Intervention = 67 (11) Control = 70 (10). Patient selection criteria: evidence of occlusion on CTA Median (IQR) NIHSS: Intervention = 17 (13-22) Control = 18 (14-22)	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Serious adverse events	Trial enrolment was halted after the presentation of the MR CLEAN study at the World Stroke Congress
Muir 2017 [71] PISTE	Mechanical thrombectomy (within 6 hours) plus IV thrombolysis vs IV thrombolysis All received thrombolysis Median time from	n = 65 10 centres in the UK Age ≥18 Mean age (SD) intervention = 67 (17) control = 64	Mortality at 90 days Fatal/serious adverse events at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Intracerebral haemorrhage	Trial recruitment suspended following other thrombectomy trial results Funded by industry and academia

Study	Intervention and comparison	Population	Outcomes	Comments
	onset to IV alteplase, intervention: 120 (61-242) and control: 120 (62-238) minutes	(16) Patient selection criteria: evidence of occlusion on CTA or MRA Median (IQR) NIHSS: Intervention = 18 (6-24) Control = 14 (6-29)		
Thrombectomy within 8 hours of stroke onset				
Jovin 2015[28, 51, 67] REVASCAT	Thrombectomy (within 8 hours) plus standard medical management including IV alteplase when eligible vs standard medical management: including IV alteplase when eligible IV alteplase: intervention 70/103 (68.0%); control 80/103 (77.7%) Median (IQR) time from onset to IV thrombolysis: intervention 117.5 (90-150); control 105 (86-137.5) minutes	N = 206 4 centres in Spain Age 18 - 80 Mean age (SD) intervention = 65.7 (11.3) control = 67.2 (9.5) Patient selection criteria: evidence of occlusion on CTA, MRA or angiogram Median (IQR) NIHSS: Intervention = 17 (14-20) Control = 17 (12-19)	Mortality at 90 days mRS at 90 days Symptomatic intracranial haemorrhage Stroke at 90 days EQ-5D	Recruitment stopped due to emerging study results of other thrombectomy trials. Funded by industry and academia/government
Thrombectomy within 12 hours of stroke onset				
Goyal 2015[30, 42] ESCAPE	Mechanical thrombectomy (within 12 hours) vs best medical practice IV alteplase = 72.7% intervention, 78.7% control Median (IQR) time from onset to IV	n = 316 22 centres worldwide Age ≥18 Mean age (range) intervention = 71 (60 - 81) control = 70 (60 - 81) Patient selection	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Stroke at 90 days EQ-5D at 90 days	Trial stopped early due to release of MR CLEAN results (efficacy of thrombectomy). Funded by industry and academia

Study	Intervention and comparison	Population	Outcomes	Comments
	thrombolysis: intervention 110 (80-142); control 125 (89-183) minutes Median time from stroke onset to groin puncture in intervention group: 185 minutes	criteria: evidence of occlusion on CTA Median (IQR) NIHSS: Intervention = 16 (13-20) Control = 17 (12-20)		
Thrombectomy between 6 and 24 hours after stroke onset				
Albers 2018[7] DEFUSE 3	Mechanical thrombectomy (6 - 16 hours) plus standard medical therapy vs standard medical therapy IV alteplase = 11% intervention, 9% control Median time from onset to randomisation, intervention: 288 (216-372) and control: 336 (216-468) minutes	n = 182 38 centres in the USA Age 18 - 90 Median age (IQR) intervention = 70 (59-79) control = 71 (59-80) Patient selection criteria: evidence of occlusion on CTA or MRA and a MRI diffusion and perfusion or CT perfusion scans showing an initial infarct volume of <70 ml, a ratio of volume of ischaeminc tissue to initial infarct volume of 1.8 or more and a penumbra of 15 ml or more. Median (IQR) NIHSS: Intervention = 16 (10-20) Control = 16 (12-21)	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage	Recruitment terminated early due to efficacy
Nogueira 2018[76] DAWN	Mechanical thrombectomy (6 - 24 hours) plus standard care vs standard care IV alteplase = 5% intervention, 13% control	n = 206 26 centres across USA, Canada, Europe and Australia Age ≥18 Mean age (SD) intervention = 69.4 (14.1) control	Mortality at 90 days mRS at 90 days Symptomatic intracerebral haemorrhage Procedural complications	Funded by industry

Study	Intervention and comparison	Population	Outcomes	Comments
	Median time from onset to randomisation, intervention: 653 (526-741) and control: 644 (522-784) minutes	= 70.7 (13.2) Patient selection criteria: evidence of occlusion on CTA or MRA and a mismatch between clinical severity and infarct volume assessed by DW MRI or perfusion CT. Median (IQR) NIHSS: Intervention = 17 (13-21) Control = 17 (14-21)		

ASPECTS: Alberta stroke program early CT Score; CTA; CT angiography; DSA: digital subtraction angiography; DW: diffusion-weighted; IQR: interquartile range; MRA: magnetic resonance angiography; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation; tPA: tissue plasminogen activator

See appendix D for full evidence tables.

1.5.5 Quality assessment of clinical studies included in the evidence review

1.5.5.1 Anterior circulation stroke

Table 3: Clinical evidence summary: thrombectomy within 6 hours with or without alteplase versus alteplase or standard medical care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
Mortality at 90 days	1334 (6 studies)	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.9 (0.7 to 1.16)	157 per 1000	16 fewer per 1000 (from 47 fewer to 25 more)
Modified Rankin scale (0 - 2) 90 days	1324 (6 studies)	⊕⊕⊕⊖ MODERATE2 due to risk of bias	RR 1.47 (1.28 to 1.68)	377 per 1000	177 more per 1000 (from 106 more to 256 more)
Modified Rankin scale ordinal shift at 90 days	1324 (6 studies)	MODERATE2 due to risk of bias	OR 1.78 (1.47 to 2.16)[3]	Control rate not reported	
Symptomatic intracerebral haemorrhage at 90 days	1312 (6 studies)	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.98 (0.6 to 1.6)	44 per 1000	1 fewer per 1000 (from 18 fewer to 26 more)
Intracerebral haemorrhage	65 (1 study)	⊕⊕⊖⊖ LOW1 due to imprecision	RR 0.97 (0.21 to 4.45)	94 per 1000	3 fewer per 1000 (from 74 fewer to 324 more)
Any serious adverse event at 90 days	800 (3 studies)	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 1.08 (0.92 to 1.28)	423 per 1000	34 more per 1000 (from 34 fewer to 118 more)
EQ-5D at 90 days Scores range from -0.33 to 1, with higher scores indicating a better quality of life	260 (1 study)	⊕⊕⊕⊖ MODERATE2 due to risk of bias		The mean EQ-5D in the control group was 0.515	The mean EQ-5D at 90 days in the intervention groups was 0.02 higher (0.08 lower to 0.11 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
EQ-5D at 90 days Scores range from -0.33 to 1, with higher scores indicating a better quality of life	500 (1 study)	⨁⨁⨁⨀ MODERATE2,5 due to risk of bias		The median EQ-5D in the control group was 0.66	The median EQ-5D at 90 days in the intervention group was 0.03 higher

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Five studies provided an adjusted odds ratio but one study provided only an unadjusted estimate.
4 Adjusted for age, NIHSS at baseline, time from stroke onset to randomisation, prior stroke, atrial fibrillation, diabetes mellitus and internal carotid artery terminus occlusion.
5 Imprecision could not be assessed because non-parametric statistics were reported.

Table 4: Clinical evidence summary: thrombectomy within 8 hours with or without alteplase versus alteplase or standard medical care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
Mortality at 90 days	206 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.19 (0.65 to 2.18)	155 per 1000	29 more per 1000 (from 54 fewer to 183 more)
Mortality at 12 months	206 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.96 (0.59 to 1.57)	243 per 1000	10 fewer per 1000 (from 100 fewer to 139 more)
Modified Rankin scale (0 - 2) 90 days	206 (1 study)	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.55 (1.06 to 2.27)	282 per 1000	155 more per 1000 (from 17 more to 358 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
Modified Rankin scale (0 - 2) at 1 year	206 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.45 (1.01 to 2.1)	301 per 1000	135 more per 1000 (from 3 more to 331 more)
Modified Rankin scale ordinal shift at 90 days	206 (1 study)	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	OR 1.7 (1.05 to 2.8)[3]	Control rate not reported	
Modified Rankin scale ordinal shift at 1 year	206 (1 study)	⨁⨁⊖⊖ LOW2 due to risk of bias, imprecision	OR 1.80 (1.09 to 2.99)[3]	Control rate not reported	
Symptomatic intracerebral haemorrhage at 90	206 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1.75 (0.53 to 5.8)	39 per 1000	29 more per 1000 (from 18 fewer to 187 more)
Recurrent stroke at 90 days	206 (1 study)	⨁⨁⊖⊖ LOW1 due to imprecision	RR 1.33 (0.31 to 5.81)	29 per 1000	10 more per 1000 (from 20 fewer to 139 more)
EQ-5D at 90 days Scores range from -0.33 to 1, with higher scores indicating a better quality of life	206 (1 study)	⨁⨁⨁⊖ MODERATE2,4 due to risk of bias		The median EQ-5D in the control group was 0.32	The median EQ-5D at 90 days in the intervention group was 0.33 higher

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Adjusted for minimisation factors (NIHSS, therapeutic window, occlusion site and participating centre) and alteplase use.
4 Imprecision could not be assessed because non-parametric statistics were reported.

Table 5: Clinical evidence summary: thrombectomy within 12 hours with or without alteplase versus alteplase or standard medical care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
Mortality at 90 days	311 (1 study)	⊕⊕⊕⊖ MODERATE1 due to imprecision	RR 0.54 (0.31 to 0.95)	191 per 1000	88 fewer per 1000 (from 10 fewer to 132 fewer)
Modified Rankin Scale (0 - 2) 90 days	311 (1 study)	⊕⊕⊕⊖ MODERATE2 due to risk of bias	RR 1.81 (1.36 to 2.42)	293 per 1000	237 more per 1000 (from 105 more to 416 more)
Modified Rankin Scale ordinal shift at 90 days	316 (1 study)	⊕⊕⊕⊖ MODERATE2 due to risk of bias	OR 3.1 (2.0 to 4.7)[3]	Control rate not reported	
Symptomatic intracerebral haemorrhage at 90 days	315 (1 study)	⊕⊕⊖⊖ LOW1 due to imprecision	RR 1.36 (0.39 to 4.74)	27 per 1000	10 more per 1000 (from 16 fewer to 101 more)
Malignant middle cerebral syndrome at 90 days	315 (1 study)	⊕⊕⊕⊕ HIGH	RR 0.26 (0.12 to 0.55)	187 per 1000	138 fewer per 1000 (from 84 fewer to 165 fewer)
EQ-5D at 90 days visual analogue scale Score ranges from 0 - 100. 0 indicating worst possible quality of life and 100 the best possible quality of life.	315 (1 study)	⊕⊕⊕⊖ MODERATE2,4 due to risk of bias		The median EQ-5D in the control group was 65	The median (IQR) EQ-5D at 90 days in the intervention group was 15 higher

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Adjusted for age, sex, baseline NIHSS, baseline ASPECTS, occlusion location and alteplase use.
4 Imprecision could not be assessed because non-parametric statistics were reported.

Table 6: Clinical evidence summary: thrombectomy between 6 - 24 hours onset of symptoms versus standard medical care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Thrombectomy plus medical management (95% CI)
Mortality at 90 days	388 (2 studies)	⨁⨁⨀⨀ VERY LOW1,2 due to inconsistency, imprecision	RR 0.76 (0.41 to 1.40)	219 per 1000	53 fewer per 1000 (from 129 fewer to 88 more)
Modified Rankin Scale (0 - 2) 90 days	388 (2 studies)	⨁⨁⨁⨀ MODERATE3 due to risk of bias	RR 3.16 (2.17 to 4.59)	149 per 1000	322 more per 1000 (from 174 more to 535 more)
Modified Rankin Scale ordinal shift at 90 days	182 (1 study)	⨁⨁⨁⨀ MODERATE3 due to risk of bias	OR 3.36 (1.96 to 5.77)[4]	Median 4 (IQR 3 - 6)	
Symptomatic intracerebral haemorrhage at 90 days	388 (2 studies)	⨁⨁⨀⨀ LOW2 due to imprecision	RR 1.63 (0.66 to 4.06)	37 per 1000	23 more per 1000 (from 13 fewer to 113 more)
Procedural complications	206 (1 study)	⨁⨁⨁⨁ HIGH	OR 7.27 (1.61 to 32.73)	0 per 1000	70 more per 1000 (from 20 more to 120 more)[5]

1 Downgraded by 1 increment for unexplained heterogeneity with I^2 >50%

2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

3 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

4 Odds ratio adjusted for stratification factors (age, core infarct volume, time from symptom onset to enrolment, baseline NIHSS, and trial site).

5 Calculated from risk difference

See appendix F for full GRADE tables.

1.5.5.2 Posterior circulation stroke

No studies were identified.

1.6 Economic evidence

1.6.1 Included studies

Two published health economic studies with the relevant comparison in the population of people presenting within 0-6 hours of onset of ischaemic stroke were identified and have been included in this review. [38] [61] One of the published economic studies was adapted by the authors for the population of people presenting within 6-24 hours of onset of ischaemic stroke. Unpublished data from this health economic study has also been included in this review. [84]These studies are summarised in the health economic evidence profile below (Table 7) and the health economic evidence table in appendix I.

1.6.2 Excluded studies

Twelve economic studies relating to this review question were identified but were selectively excluded due to the availability of more applicable evidence of a greater methodological quality. [2, 10, 16, 29, 46, 50, 104, 113] [107] [22] [88] [11] These are listed in appendix H, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

1.6.3 Summary of studies included in the economic evidence review

Table 7: Health economic evidence profile: intravenous tissue-type plasminogen activator and endovascular therapy versus intravenous tissue-type plasminogen activator alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Ganesalingam, 2015 [38] (UK NHS and Personal Social Services perspective)	Directly applicable[(a)]	Minor limitations[(b)]	Decision analytic model with treatment effect from meta-analysis of five RCTs. [15 42 90 51 21] Markov model simulating a lifetime time horizon.	£7,296 (pa) [(e)]	0.954 QALYs (pa)	ICER: £7,648 per QALY gained (pa)	95% CI: £5,481-£9,690 per QALY gained (pa) Probability IV-tPA and mechanical thrombectomy cost effective (£20K/30K threshold): 100%/100%
Lobotesis, 2016 [61] (UK)	Directly applicable[(a)]	Minor limitations[(c)]	Decision analytic model with treatment effect from SWIFT-PRIME study only. [90]. Markov model with seven health states based on mRS simulating a lifetime time horizon.	Saves £33,190 (da) [(e)]	2.31 QALYs (da)	Dominant[(f)] (da)	Probability IV-tPA and mechanical thrombectomy cost effective (£20K/30K threshold): 98.6%/99.0%
Pizzo, 2018 (Confidential draft) [84]	Directly applicable[(a)]	Minor limitations[(d)]	Decision analytic model with treatment effects at 12 and 24 hours after stroke onset from DAWN RCT and at 16 hours after stroke onset from DEFUSE-3 RCT. [7, 76] Markov model simulating a lifetime time horizon.	**12 hours after stroke onset:** £1,995 (pa)[(g)] **16 hours after stroke onset:** £6,919 (pa) [(g)] **24 hours after stroke onset:** £6,466 (pa)	**12 hours after stroke onset:** 1.63 QALYs (pa) **16 hours after stroke onset:** 1.69 QALYs (pa) **24 hours after stroke onset:** 2.23 QALYs (pa)	**12 hours after stroke onset:** **ICER:** £1,227 per QALY gained (pa) **16 hours after stroke onset:** **ICER:** £4,103 per QALY gained (pa) **24 hours after stroke onset:**	**12 hours after stroke onset:** 95% CI: Dominant[(f)] - £2,879 per QALY gained (pa) **16 hours after stroke onset:** 95% CI: £2,417 - £6,214 per QALY gained (pa) **24 hours after stroke onset:** 95% CI: £1,588 - £4,311 per QALY gained (pa)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
				(g)		**ICER:** £2,894 per QALY gained (pa)	Probability medical therapy followed by mechanical thrombectomy cost effective (£20K/30K threshold): 99.9%/99.9%.

Abbreviations: 95% CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; mRS: modified Rankin Scale; pa: probabilistic analysis; QALY: quality-adjusted life years; pa: probabilistic analysis; RCT: randomised controlled trial

(a) UK NHS and Personal Social Services perspective

(b) Components of ongoing costs were not detailed. Start age of those entering the model nor male:female ratio were reported, but as UK stroke national audit data was used to populate the model these could likely be found from these data. Treatment effect used in study did not include data from THRACE, THERAPY and PISTE RCTs, which were included in the 0-6 hour pre-specified subgroup analysis in the clinical review, [17 66 71] The treatment effect included REVASCAT and ESCAPE RCTs, which were not included in the 0-6 hour pre-specified subgroup analysis as they considered thrombectomy within 8 hours and within 12 hours of stroke onset, respectively. [42 51].T. Sunderland in employment of Boehringer Ingleheim

(c) Health outcomes and treatment effects were based on the SWIFT-PRIME study only. The male:female ratio of those populating the model was not recorded, but could be elicited from the SWIFT-PRIME population. Funded by Medtronic, the manufacturer of Solitaire. Declarations of financial/other relationships with Medtronic, Boehringer Ingelheim and others.

(d) Components of ongoing costs not detailed.

(e) 2013-2014 UK pounds

(f) A dominant treatment option is one that is both less costly and results in better health outcomes than the comparator treatment2017 UK pounds

1.6.4 Unit costs

Table 8: UK costs of endovascular therapy, perfusion imaging and intravenous tissue-type plasminogen activator and endovascular therapy

Currency Description	Unit Cost
Endovascular therapy (YA12Z Percutaneous Transluminal, Other Procedures on, Intracerebral or Extracranial Blood Vessel, weighted average non-elective short stay and non-elective long stay inclusive of excess bed days; as recorded for Non-Elective Inpatients)	£8,115 (average length of stay: 7.1 days)
Computerised Tomography Perfusion (RD21A Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over, Direct Access)	£106
Computerised Tomography Angiography (Cardiac CT Angiography) (RD28Z Complex Computerised Tomography Scan, Direct Access)	£121
Post-Contrast Magnetic Resonance Imaging (RD02A Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over, Direct Access)	£202
Magnetic Resonance Angiography (RD02A Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over, Direct Access)	£202
Alteplase (rt-PA; Tissue-type plasminogen activator) 10mg (1 vial)[(a)]	£172.80
Alteplase (rt-PA; Tissue-type plasminogen activator) 20mg (1 vial)[(a)]	£259.20
Alteplase (rt-PA; Tissue-type plasminogen activator) 50mg (1 vial)[(a)]	£432.00

Sources: NHS Reference Costs, 2016-2017; British National Formulary

Table 9: UK costs of intravenous tissue-type plasminogen activator

Drug	Daily dose[(b)]	Cost per 50mg vial (£)	Cost per 20mg vial (£)	Total Cost (70mg)
Alteplase (rt-PA; Tissue-type plasminogen activator)	68.4mg[(c)]	£432.00	£259.20	£691.20

Sources: MIMS; British National Formulary
(a) Indications: adult 18-79 years
(b) Dose: initially 900 micrograms/kg (maximum per dose 90mg) treatment must begin within 4.5 hours of symptom onset, to be given over 60 minutes, the initial 10% of dose is to be administered by intravenous injection and the remainder by intravenous infusion
(c) Dose assuming an average weight of 76kg [75]

1.7 Resource costs

The recommendations made in this review that thrombectomy is offered are likely to have a substantial impact on resources for the NHS in England.

Additional costs are likely to be incurred for the following reasons: the population eligible for thrombectomy will be increased; more people with stroke will need to be transferred to centres offering thrombectomy, and additional training will be required. Further work is being carried out to quantify the potential resource impact in this area.

The committee also made a recommendation based on this review (see section 1.9: Recommendations) that thrombectomy should be 'considered' for people with acute ischaemic stroke last known to be well up to 24 hours previously (including wake up strokes) with confirmed occlusion of the proximal posterior circulation and with potentially salvageable brain tissue. Unlike for stronger recommendations stating that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS of recommendations regarding interventions that could be used, as uptake is too difficult to predict. However, the committee noted that this is already current best practice.

1.8 Evidence statements

1.8.1 Clinical evidence statements

1.8.1.1 Anterior circulation stroke

- Six trials in 1334 people were included investigating the use of mechanical thrombectomy with or without thrombolysis, within 6 hours after the onset of symptoms of acute ischemic stroke, compared to thrombolysis or usual care with follow up at 90 days. Thrombectomy showed a clinical benefit compared to control for functional independence, measured by mRS (increase in those with a score of 0–2) (moderate quality). No clinical difference in mortality, serious adverse events or quality of life was reported (moderate quality). It is uncertain if there are any differences in symptomatic and non-symptomatic intracerebral haemorrhage outcomes due to low event rates (low quality).
- One trial in 206 people receiving thrombectomy within 8 hours, with or without thrombolysis, compared to usual care showed a benefit of thrombectomy for functional independence (low quality) and for quality of life measured by EQ-5D (moderate quality). This trial also reported an uncertain impact on mortality rates, symptomatic intra-cranial haemorrhage and recurrent stroke (low quality).
- One trial in 316 people receiving thrombectomy, with or without thrombolysis, within 12 hours compared to control, again showed a clinical benefit of thrombectomy for functional independence and mortality (moderate quality). The study also reports a clinical benefit of thrombectomy for reduced incidence of malignant middle cerebral syndrome compared to control (high quality) and for improved quality of life (EQ-5D visual analogue scale) at 90 days (moderate quality) and an uncertain impact on symptomatic intracerebral haemorrhage (low quality).
- Two studies in 388 people investigated later presentation of acute ischemic stroke, with thrombectomy, with or without thrombolysis, after 6 hours, but within 24 hours of symptom onset. These studies show a clinical benefit of thrombectomy for functional outcome and mortality at 90 days follow up (very low to moderate quality) and no clinical difference in symptomatic intracerebral haemorrhage (low quality). Procedural complications were reported as a harm of thrombectomy (high quality).

1.8.1.2 Posterior circulation stroke

No studies were identified for this stratum.

1.8.2 Health economic evidence statements

- One cost-utility analysis found that IV t-PA and mechanical thrombectomy was cost effective compared with IV t-PA alone for treating acute ischaemic stroke, within 0-6 hours of stroke onset. (ICER: £7,648 per QALY gained). This analysis was assessed as directly applicable with minor limitations.

- One cost-utility analysis found that IV t-PA and mechanical thrombectomy was dominant over IV t-PA alone for treating acute ischaemic stroke, within 0-6 hours of stroke onset. This analysis was assessed as directly applicable with minor limitations.
- One cost-utility analysis found that mechanical thrombectomy following best medical therapy was cost effective compared with medical therapy alone for treating acute ischaemic stroke, 6-24 hours after stroke onset. This analysis was assessed as directly applicable with minor limitations.

1.9 Recommendations

D1. Offer thrombectomy within 6 hours of symptom onset, alongside intravenous thrombolysis (if not contraindicated and within the licensed time window) to people who have:

- acute ischaemic stroke and
- confirmed occlusion of the proximal anterior circulation demonstrated by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA). [2019]

D2. Offer thrombectomy to people who were last known to be well between 6 hours and 24 hours previously (including wake up strokes):

- who have acute ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and
- if there is the potential to salvage brain tissue, as shown by CT or MRI scanning techniques. [2019]

D3. Consider thrombectomy alongside intravenous thrombolysis (where not contraindicated and within the licensed time window) for people last known to be well up to 24 hours previously (including wake up strokes):

- who have acute ischaemic stroke and confirmed occlusions of the proximal posterior circulation (that is, basilar or posterior cerebral artery) demonstrated by CTA or MRA and
- if there is the potential to salvage brain tissue, as shown by CT or MRI scanning techniques. [2019]

D4. Take into account the following factors when considering thrombectomy (in addition to recommendations D1 to D3):

- pre stroke functional status
- clinical severity of stroke
- extent of established infarction on initial brain imaging. [2019]

1.10 Rationale and impact

1.10.1 Why the committee made the recommendations

Anterior circulation stroke

Overall, the evidence across time-frames showed that thrombectomy, with or without thrombolysis, improved functional outcome as measured by the mRS score in people last known to be well up to 24 hours previously, compared with usual care. There was also a potential benefit for improved quality of life. However, there was no clinical difference in mortality and there were low rates of symptomatic intracerebral haemorrhage. The committee noted there had been some procedural complications associated with thrombectomy, but agreed that these were outweighed by the benefits of improvements in functional outcome. The committee looked at the results of 2 published cost–utility analyses with a UK NHS perspective. The first estimated that thrombectomy alongside intravenous thrombolysis (where appropriate) is cost effective compared with intravenous thrombolysis alone, when performed within 6 hours of stroke onset (that is, from when a person was last known to be well). The second demonstrated the cost effectiveness of thrombectomy and best medical therapy compared with best medical therapy alone, when performed 6-24 hours after stroke onset. Therefore, the committee agreed to recommend thrombectomy up to 24

hours after stroke onset alongside intravenous thrombolysis if within the licensed time window in people with appropriate clinical and radiological characteristics. The benefit of thrombectomy was seen for people presenting between 6 and 24 hours after stroke onset. Few of them received thrombolyisis because this is outside the licenced time window. Therefore, the recommendation for those presenting beyond 6 hours is for thrombectomy alone.

The evidence for thrombectomy within 6 hours of symptom onset was from populations selected using CTA or MRA to identify proximal anterior circulation occlusions. For thrombectomy undertaken between 6 and 24 hours after stroke onset, the evidence was based on more highly selected populations using CT perfusion, MRI diffusion and MRI perfusion imaging, in addition to identifying a proximal anterior circulation arterial occlusion. As the effectiveness of thrombectomy is likely to be lower in a less selected population, the committee recommended that, in line with the evidence, CT or MR imaging is performed if presentation is 6-24 hours after stroke onset. This would ensure that there is vulnerable but salvageable brain tissue to be targeted for thrombectomy.

Posterior circulation stroke

No clinical or cost effectiveness evidence was identified for the population with posterior circulation stroke. The committee discussed that prognosis is usually very poor in basilar artery occlusion with around an 80% mortality. As few as 2-5% of people with basilar artery occlusion make a full neurological recovery in the absence of interventions to achieve recanalisation or reperfusion. The committee agreed that in their experience the prevalent current practice is to consider intravenous thrombolysis and mechanical thrombectomy, and that good outcomes can be achieved. This is the case even up to 24 hours after stroke onset, which is significant because diagnosis can be delayed in this population by a non-focal presentation, reduced conscious level, or both.

The main potential risk of thrombectomy and thrombolysis in this population relates to intervening when there is established disabling ischaemic brain injury. For example, if a person with basilar artery occlusions has irreversible bilateral damage to the pons, they may be left with locked-in-syndrome with complete face and body paralysis but clear consciousness, even if the basilar artery is opened. The committee agreed that it is standard practice to perform brain imaging and look for established tissue damage in the brain regions affected by the arterial occlusion, particularly in areas of the brain stem, before intervening. This avoids increasing the number of patients surviving with severe neurological disability. CT or MR imaging should be performed to demonstrate that there is salvageable brain tissue and to seek evidence of established injury to functionally critical areas of the posterior circulation.

The outlook for this population without intervention is poor. But good outcomes can be achieved with intervention, and there is supportive evidence from treating anterior stroke. Therefore the committee agreed that thrombectomy, and thrombolysis within its licensed indications, should be considered for people with posterior circulation proximal occlusions and without evidence of irreversible infarction who were last known well up to 24 hours previously.

1.10.42 Impact of the recommendations on practice

The committee noted that in current practice around 10% of people presenting with all strokes in the UK are eligible for thrombectomy. More people are likely to be offered thrombectomy as a result of these recommendations. The recommendation on thrombectomy alongside thrombolysis within 6 hours is aligned with current best practice and the NHS England Cinical Commissioning Policy on Mechanical Thrombectomy for Acute Ischaemic Stroke, published in March 2018. The recommendation for thrombectomy between 6 and 24 hours requires a change from current practice by most providers.

Currently, the NHS England Cinical Commissioning Policy states that mechanical thrombectomy will be commissioned where substantial salvageable brain tissue is identified up to 12 hours. However, we reviewed new evidence from health economic modelling that supports the extension of the eligibility period up to 24 hours.The recommendation to consider thrombectomy for posterior circulation stroke reflects current best practice.

Overall, the new recommendations are likely to have a substantial resource impact on the NHS. Thrombectomy is already performed in most neuroscience centres, but the recommendations will mean 24 hour access to appropriate staffing and imaging..

The committee discussed the possibility that the new recommendations could initially result in a large increase in referrals to centres that already have thrombectomy services. The committee also noted that there are likely to be additional costs incurred in transferring people to these centres. This will have implications for the spoke site for arranging transfers, for the ambulance service and at the hub site where more patients will be received. There will need to be networked arrangements for spoke sites around a thrombectomy 'hub' with fast image transfer, referral, eligibility assessment, and responsive repatriation systems.

Balanced against thisare the positive implications for other aspects of stroke care. For example, it is expected that there will be a decrease in demand for decompressive hemicraniectomies and in-patient rehabilitation. There may also be a reduction in the need for long-term social care.

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The outcomes that matter most

The critical outcomes identified for this review were functional outcome (modified Rankin Scale) and mortality at 90 days and 1 year. The committee considered both outcomes to be vital in decision making. Important outcomes included intracerebral haemorrhage, procedural complications and quality of life (EQ-5D). Patient reported outcome measures were also considered, but no evidence was identified.

1.11.1.2 The quality of the evidence

Ten RCTs detailed in 15 papers were included in the review. The studies included people with large vessel occlusion demonstrated by CTA or MRA. All were in the anterior circulation population No randomised trials were found for the posterior circulation stroke population so observational studies were sought, but none that met the inclusion criteria were identified. The trials were all prospective randomised open blinded end-point (PROBE) trials. This meant that patients and care givers were not blinded to the intervention, but the outcome assessors were. Subjective outcomes (mRS and quality of life) were therefore downgraded for risk of bias. Some outcomes, including symptomatic intracerebral haemorrhage and recurrent stroke, had very few events and therefore had estimates of effect with wide confidence intervals and were downgraded for imprecision.

A subgroup analysis of timing of thrombectomy was performed for all outcomes. The studies were grouped into those performing thrombectomy within 6 hours of the onset of stoke, up to 8 hours, up to 12 hours and those conducted at any time more than 6 hours and up to 24 hours.

The majority of studies were funded by industry, but the committee considered that the evidence should not be downgraded for publication bias and that the study design ensured robustness of evidence. It was noted that following the results of MR CLEAN,[15] which shows efficacy of thrombectomy, the majority of other trials stopped recruitment early due to superior efficacy of thrombectomy. Some conducted planned interim analysis; others state that they are underpowered. Although the committee recognised the potential for an overestimation of treatment effect in the trials that were stopped early, evidence was not downgraded because of this.

Evidence ranged from very low to high quality, with the majority of the evidence rated as moderate quality.

Three cost utility analyses from the UK NHS perspective were included in the health economic review and were assessed as directly applicable with minor limitations.

1.11.1.3 Benefits and harms

Anterior circulation stroke

The evidence shows a clear clinical benefit in functional outcome (higher functional independence; mRS score of 0–2 and by ordinal shift analysis) compared to usual care, which was IV thrombolysis in the majority of studies, when thrombectomy is performed within 6, 8, or 12 hours. IV thrombolysis was administered in both the thrombectomy and usual care groups in the majority of patients. This benefit was even seen in studies recruiting between 6 and 24 hours of stroke onset, when few patients in either the thrombectomy or usual care group received thrombolyisis as this is outside the licenced time window, with either no clinical difference or a clinical benefit of thrombectomy for mortality. The committee

discussed the evidence from the study of thrombectomy within 8 hours, which had a direction of effect suggesting a possible harm of thrombectomy for increased mortality. This was not consistent with the other trials or the mortality outcome at 12 months from the same trial, where the direction of effect favoured thrombectomy. The committee agreed that this small absolute difference from a single trial with imprecision around the estimate was not convincing enough to indicate a true clinical harm of thrombectomy, but may reflect a small increase in intracerebral haemorrhages seen in this trial among those receiving thrombectomy.

The majority of people also received IV alteplase across both arms of the studies, as part of best medical practice. The committee noted that people receiving thrombectomy between 6 and 24 hours after stroke onset were outside of usual eligibility criteria and treatment with alteplase is less likely in this group as it is indicated for use within 4.5 hours of symptom onset. The committee discussed the studies that included people up to 8 and 12 hours after onset, noting that the majority of participants recived IV alteplase, which was likely to reflect the proportion who were included within the licenced time window for IV thrombolysis. As a minority of patients in the studies including only those who had thrombectomy 6-24 hours received IV thrombolysis and a benefit of thrombectomy alone was still seen, the committee agreed that, in line with the licencing criteria, those presenting during this later time window should not routinely be offered IV thrombolysis.

There was also specific evidence from a trial that included people with the procedure performed up to 12 hours after stroke onset, that thrombectomy was associated with fewer cases of malignant middle cerebral artery syndrome at 90 days. No evidence was identified for this outcome for thrombectomy performed within other time frames.

The committee discussed the findings for the adverse event symptomatic intracerebral haemorrhage. For thrombectomy plus thrombolysis within 6 hours there was no clinical difference for this outcome. For the later time points there were fewer cases of symptomatic intracerebral haemorrhage in the standard care group; however, the number of events was small and the effect estimates were imprecise. Since this potential harm was not reflected in the primary outcome measures and there was uncertainty in the true effect, the committee did not believe this to be a clinically important difference.

Quality of life (EQ-5D) was reported across several studies and showed either no difference or a benefit of thrombectomy with or without thrombolysis within 6, 8 and 12 hours, compared to control at 90 days. No data were available for this outcome from the 2 studies reporting on thrombectomy performed between 6 and 24 hours after stroke onset.

Some procedural complications associated with thrombectomy were noted, but were considered to be outweighed by the benefits of functional outcome improvement. Other studies reported on serious adverse events and recurrent stroke at 90 days and showed no clear clinical difference between treatment arms.

Overall there is strong evidence for a clinical benefit of thrombectomy, alongside intravenous thrombolyisis if within the licenced time window, for improving functional outcome when performed in people last known to be well up to 24 hours previously, with no clinical difference in mortality rates. Therefore, the committee made strong recommendations for thrombectomy up to 24 hours after stroke onset (that is, from when a person was last known to be well) in people with appropriate clinical and radiological characteristics. The committee agreed that it was important to specify that this should be done in people who present with an acute ischaemic stroke syndrome as it is possible to have an occlusion without stroke symptoms and intervention should not currently be attempted in these people. It is also important that the occlusion is confirmed by CTA or MRA in order to identify a target for reperfusion with thrombectomy.

The committee discussed their experience that the plain CT scan may be assessed using the Alberta Stroke Program Early CT Score (ASPECTS), with a score of more than 6 indicating a

good volume of salvageable brain tissue. They noted that in the presence of a low ASPECTS score, imaging with CT perfusion or MRI could be considered within an earlier timeframe. Even within 6 hours of stroke onset it is possible for there to be a malignant core of severe, established ischaemic change that cannot be salvaged as collaterals have already failed; in such cases there is no potential for benefit of intervention and the procedure could cause harm and so would not be indicated. When thrombectomy is undertaken between 6 and 24 hours after stroke onset, potential benefit must be demonstrated by further appropriate imaging with CT or MRI because the evidence of effectiveness from the trials was based on more highly selected populations using CT perfusion and MRI diffusion and perfusion scans and effectiveness in a broader population is likely to be lower. In terms of clinical characteristics, it is important to consider the NIHSS score and overall functional capacity prior to the stroke to determine suitability for this intervention. It is not possible to specify strict threshold criteria for eligibility based on pre-stroke functional status, clinical severity of stroke or the extent of established infarction on initial brain imaging as these factors will be considered as part of the clinical judgment on an individual basis. Some studies but not all, used an entry criteria of a pre morbid Rankin (mRS) <2 for thrombectomy. There was a range of NIHSS severity scores across the trials ranging from no NIHSS thresholds to an NIHSS score of 10 or more pre-thrombectomy. Some utilised an ASPECTs score of >6 as an entry criterion. It was the view of the committee that evidence on these clinical parameters will become clearer as experience with thrombectomy increases. There is therefore likely to be regional variation in how these criteria are applied, and at least initially, decision making will be on an individual patient basis. The committee agreed that providing additional criteria to take into account when considering thrombectomy would be helpful for those setting up a new service and also a helpful guide for referring centres.

The committee noted that although the benefit in mRS appeared to increase at later thrombectomy time thresholds, this does not mean that it is better to wait and perform thrombectomy later after stroke onset. This effect could be a consequence of the stricter patient selection criteria used, because the trials including thrombectomy performed later after stroke onset used more advanced imaging. This increased selectivity would have resulted in a population with a greater chance of benefit from the intervention by identifying and including only those with a favourable collateral flow. The larger effect size in the later time thresholds might also be explained by the difference between the people in the control groups. People in the control arm presenting within 4.5 hours of stroke onset are eligible for thrombolysis, whereas beyond this time threshold and up until 24 hours of stroke onset, this treatment option is no longer available to the people in the control group, for whom aspirin may be the only option. The difference in mRS score between the thrombectomy and control arms for those presenting within 6-24 hours of stroke onset may therefore be greater than the difference for those presenting 0-6 hours of stroke onset. The committee highlighted the need for rapid treatment for all patients with ischaemic stroke.

Posterior circulation stroke

In the absence of evidence on the effectiveness and safety of thrombectomy compared to thrombolysis or standard care in the posterior circulation stroke population the committee agreed to make a consensus recommendation. They agreed that the prognosis is usually very poor in those with basilar artery occlusion, which accounts for approximately 95% of interventions for proximal posterior artery occlusions, with around an 80% mortality and as few as 2-5% making a full neurological recovery in the absence of interventions to improve recanalisation or reperfusion interventions. The committee agreed that in their experience the prevalent current practice is to consider intravenous thrombolysis and/or mechanical thrombectomy in these people and that good outcomes can be achieved. Diagnosis may be delayed because posterior circulation strokes can present non-focally and/or with a reduced conscious level, and so thrombectomy is often performed later than 6 hours after onset and good outcomes can still be achieved at this time.

The main potential risk of thrombectomy and thrombolysis in this population relates to outcomes of intervening when there is already established disabling ischaemic brain injury. For example, in basilar artery occlusions if there is irreversible bilateral damage to the pons, even if the basilar artery is opened the person may be left with “locked-in-syndrome” with complete face and body paralysis but clear consciousness. The committee agreed that it is standard practice to perform brain imaging and look for established tissue damage in the brain regions affected by the arterial occlusion, particularly in areas of the brain stem before intervening to avoid increasing the number of patients surviving with severe neurological disability. Imaging with CT or MRI techniques should be performed regardless of how soon after onset a person presents with posterior circulation stroke to demonstrate that there is salvageable brain tissue. Furthermore, even if there may be some salvageable brain tissue it is important to identify whether small but functionally critical areas of the posterior circulation have been damaged, although the committee acknowledge that this can be difficult to identify. A small infarct in specific areas, for example, in areas of the brain supplied by the basilar artery, can have devastating consequences for functional outcomes.

The committee also agreed that, as the technique is similar, it would be reasonable to extrapolate the lack of clinically significant harm for mortality and intracerebral haemorrhage seen in anterior circulation stroke evidence. Alongside the potential for benefit in a severely ill population this supports the use of thrombectomy and thrombolysis when appropriate.

In conclusion, given the poor outlook without intervention, clinical experience of good outcomes being achieved with intervention and supportive evidence from the anterior stroke population, the committee agreed that thrombectomy and thrombolysis should be considered. The population included in the recommendation is people last known well up to 24 hours previously with acute ischaemic stroke and confirmed occlusions of the proximal posterior circulation where potentially salvageable brain tissue has been demonstrated by imaging with MRI or CT techniques. It is also important to consider the initial NIHSS score and overall functional capacity prior to the stroke to determine suitability for this intervention. The committee did not make a research recommendation as they are aware of ongoing research in this area including the BEST trial and the BASICS (Basilar Artery International Cooperation Study) trial. BASICS t is currently recruiting participants in Europe. The population is those with CTA or MRA confirmed basilar occlusion and people will be randomised between standard care with additional intra-arterial therapy within 6 hours of onset versus standard care alone.

1.11.4 Cost effectiveness and resource use

The results of a published cost–utility analysis with a UK NHS perspective estimated that thrombectomy alongside intravenous thrombolysis (where appropriate) is cost effective compared with intravenous thrombolysis alone, when performed within six hours of stroke onset. The study estimated the incremental cost effectiveness ratio to be £7,648 per QALY gained with a 100% likelihood of being cost effective at both a £20,000 and £30,000 threshold. A second cost utility analysis with a UK NHS perspective estimated that thrombectomy and intravenous thrombolysis was dominant (more effective and less costly) compared with intravenous thrombolysis alone.

The economic studies considered the cost effectiveness of thrombectomy alongside intravenous thrombolysis (compared with intravenous thrombolysis alone) in a refined population of people presenting within 6 hours of stroke onset, who had already undergone CT angiography or MR angiography (to determine whether they might benefit from thrombectomy) prior to randomisation. While CT/MR angiography is necessary to perform thrombectomy, intravenous thrombolysis can be administered following a CT head with no contrast. The committee noted that the economic analyses did not include the costs of CT/MR angiography, as all people in the trials received imaging. The committee therefore

considered the current NHS reference cost of £121 for CT angiography and £202 for MR angiography.

To consider how including the costs of CT/MR angiography might affect the cost effectiveness of mechanical thrombectomy within 0-6 hours of ischaemic stroke onset, the committee noted the results of a threshold analysis which showed that the cost of mechanical thrombectomy would need to increase by 139% to render it borderline cost effective at a cost effectiveness threshold of £20,000 per QALY. The committee was informed by a published modelling study which used data from the Sentinel Stroke National Audit Programme[a]. The modelling study indicates that 40% of people with CT-confirmed ischaemic stroke (presenting within 12 hours) are found to have an occlusion of a large artery on CT Angiography, and so are potentially eligible for thrombectomy. Therefore, to find one person potentially eligible for thrombectomy, 2.5 CT angiography scans would be required. The committee judged that including the costs of the 2.5 scans needed to find one person potentially eligible for thrombectomy in the intervention arm would be unlikely to change the results of the cost–utility analyses.

The committee was confident that the economic evidence accurately demonstrates that offering thrombectomy alongside intravenous thrombolysis (where not contraindicated) to people with confirmed occlusion of the proximal anterior circulation determined by CT/MR angiography is cost-effective compared with current practice (intravenous thrombolysis alone following a CT head with no contrast) and would therefore be a good use of NHS resources.

The results of a cost utility analysis with a UK NHS perspective demonstrated the cost effectiveness of thrombectomy and best medical therapy compared with best medical therapy alone, when performed between 6-24 hours after stroke onset. The study estimated the incremental cost effectiveness ratio to be £1,227 per QALY gained when thrombectomy was performed between 6-12 hours of stroke onset, £4,103 per QALY gained when performed within 6-16 hours of stroke onset and £2,984 per QALY gained when performed within 6-24 hours of stroke onset.

The population of the trials investigating thrombectomy in people presenting between 6 and 24 hours after stroke onset is refined to those that would benefit from thrombectomy compared with the entire population of people presenting in this later timeframe, as the inclusion criteria of the clinical trials specified that perfusion imaging was performed. The economic study therefore considered the cost effectiveness of thrombectomy, delivered in the later timeframe, in a population of people who had already undergone perfusion imaging.

The committee agreed that it was not current practice to offer perfusion imaging to all those presenting within 6-24 hours of onset of ischaemic stroke and so considered the costs of perfusion imaging in the context of the results of the cost utility analysis. Threshold analyses found that the cost of thrombectomy would need to exceed £35,517 using the efficacy data at 12 hours, £33,185 at 16 hours and £43,140 at 24 hours to be borderline cost effective at a cost effectiveness threshold of £20,000 per QALY gained. The committee estimated that 2-4 perfusion scans would need to be carried out to yield one person eligible for thrombectomy[b]. Using the results of the threshold analyses and the current unit costs of CT angiography and perfusion, the committee judged that including the costs of four additional scans in the thrombectomy arm would be unlikely to change the results of the cost–utility analysis.

a McMeekin P, White P, James MA, Price CI, Flynn D, Ford GA. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. 2017; 2(4): 319-326

b Jadhav AP, Desai, SM, Kenmuir CL, Rocha M, Starr MT, et al. Eligibiilty for endovascular trial enrolment in the 6- to 24-hour time window: analysis of a single comprehensive stroke center. 2018; 49(4): 1015-1017

The economic and clinical evidence informed the committee's decision to make a strong recommendation to offer thrombectomy for people presenting between 6-24 hours of stroke onset, where occlusion of the proximal anterior circulation is confirmed and where potential benefit has been determined by further appropriate imaging with CT or MRI and appropriate clinical radiological mismatch.

No economic or clinical evidence was identified for the use of thrombectomy for posterior circulation stroke. The committee noted that around 5-10% of all strokes are in the posterior circulation. Prognosis is poor in basilar artery occlusion in the absence of reperfusion. The committee chose to make a consensus recommendation that thrombectomy alongside intravenous thrombolysis (where not contraindicated and within the licensed time window) is considered for those last known to be well up to 24 hours previously (including wake up strokes), aligning with current practice. thrombectomy should be considered only for those with salvageable brain tissue demonstrated with MRI or CT techniques. The committee stressed the need to demonstrate salvageable brain tissue in all people presenting up to 24 hours of stroke onset, as damage to functionally important areas of the brain could have a significant impact on functional outcomes. The committee thought that this would mitigate the risk of locked-in syndrome or other poor outcomes in this population.

The committee was aware of the significant change to current practice and the substantial resource impact which will arise from these recommendations. In current practice, around 10% of people presenting with stroke in the UK are eligible for thrombectomy. This population will likely increase as a result of these recommendations. The prevalence of thrombectomy is increasing; it is currently performed in most of the neuroscience centres in England. In addition, most neurointervention centres currently operate on a 9:00-17:00 basis. To implement these recommendations, radiographers and staff at neurointervention centres will be required 24 hours per day. The committee also discussed the possibility that the new recommendations could result in a large increase in referrals to centres which deliver thrombectomy services. The committee noted that there are likely to be additional costs incurred in transferring people to centres where thrombectomy is available. The new recommendations are therefore expected to result in a significant change from current practice, which is likely to have a substantial resource impact on the NHS. However, the committee were highly confident that increasing the provision of thrombectomy will be a cost effective use resources, due to the downstream cost savings it will produce such as decreased demand for rehabilitation, long term care and decompressive hemicraniectomies.

In conclusion, the committee agreed the cost effectiveness evidence accurately demonstrates that offering thrombectomy with best medical therapy beyond six hours of stroke and up to 24 hours after stroke onset as well as thrombectomy with intravenous thrombolysis within six hours of stroke onset would be an efficient use of NHS resources. No health economic evidence was identified for the cost effectiveness of thrombectomy for posterior circulation ischaemic stroke and a consensus recommendation to consider thrombectomy was made. The committee was aware of the significant up-front investment that will be required for the implementation of these recommendations.

1.11.6 Other factors the committee took into account

The committee discussed age as an equality consideration and noted that three studies had inclusion criteria of up to 80 years of age, one at up to 85 and one of up to 90 years, the remaining studies included all those aged over 18 years old. The group considered that the evidence was applicable to the population of those aged 16 years and over with no separate recommendations for any age group and no upper age limit. It was also noted that the included studies allowed clinical judgement about the use of general anaesthetic when performing thrombectomy.

Current practice is for IV thrombolysis administered as soon as ischaemic stroke is diagnosed, if the patient is within 4.5 hours of onset of symptoms and has no contraindications. Thrombectomy should then be undertaken if appropriate, checking as the procedure is about to start whether the thrombolysis has already achieved recovery and the thrombectomy is no longer required. Access to thrombectomy services varies across the country; rapid access remains a logistical challenge with different pathway models under evaluation. The committee discussed that few centres offer a 24-hour service and that most operate within 9 to 5 working hours Monday to Friday. It was also noted that staff at district general hospitals will always contact a stroke or neurointerventional specialist before deciding to transfer the patient for thrombectomy. The receiving centres will decide whether or not there would be a benefit of thrombectomy based on imaging evidence and the clinical scenario. Detailed consideration of detection of salvageable tissue was considered to be beyond the scope of this guideline. The optimal neuroimaging pathways should be determined by individual clinical networks based on local expertise and resources.

The committee discussed implementation of this recommendation and that this would increase the numbers of people undergoing thrombectomy, particularly those with stroke onset more than 6 hours prior to possible intervention. This may require more specialist centres or increased transport to areas where this procedure can be performed, and may present challenges for implementation, including access to imaging (in particular CT angiography) to select those who can benefit from treatment.

The committee noted the risk that if further imaging with CT or MRI is not available, people who would be eligible may not receive thrombectomy.

The committee agreed that providing additional criteria to take into account when considering thrombectomy would be helpful for those setting up a new service and also a helpful guide for referring centres.

The current model is to access local stroke centre for diagnosis and intravenous thrombolysis and transfer to a specialist thrombectomy centre. Service models include ‘mother ship’ model where all cases are triaged to a very large stroke centre with centralisation, which may be better for urban areas; and the ‘drip and ship’ models where the IV thrombolysis is started in the spoke hospital pending transfer to the larger centre (hub). Optimal networked arrangements will depend on the geography of region.

NICE have published other guidance which is relevant to this review:

- Mechanical clot retrieval for treating acute ischaemic stroke (IPG548); and
- Alteplase for treating acute ischaemic stroke (TA264).

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1 Appendices

2 Appendix A: Review protocols

3 **Table 10: Review protocol: thrombectomy**

Field	Content
Review question	What is the clinical and cost effectiveness of endovascular therapy (EVT) with or without intravenous thrombolysis versus intravenous thrombolysis to improve outcomes?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	Thrombolysis and thrombectomy are separate interventions, however there is some overlap of populations: some people can have both treatments, and some can have alteplase only, some can have thrombectomy only. Guidance on identifying patients who would benefit from thrombectomy and transporting patients to a centre that can perform thrombectomy was thought to be needed.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with acute ischaemic stroke People with a proven large vessel occlusion on non invasive angiography
Eligibility criteria – interventions	Endovascular therapies Mechanical thrombectomy including stent retrievers/technology and aspiration catheters (thrombo aspiration, mechanical suction, clot retrievers, ADAPT, solitaire, trevo) With or without intravenous thrombolysis (alteplase)
Eligibility criteria – comparators	Intravenous thrombolysis (alteplase) Aspirin, no IV thrombolysis, As above, compared to each other or no treatment (e.g. outside the time window, poor pre-morbid state, rapidly improving symptoms)
Outcomes and prioritisation	<u>Critical</u> Degree of disability or dependence in daily activities: Modified Rankin Scale at 90 days and 1 year (0–2 for anterior circulation stroke stratum and 0–3 for posterior circulation stroke stratum because this condition carries a much higher mortality) Mortality at 90 days and 1 year <u>Important</u> Intracerebral haemorrhage. Symptomatic intracranial haemorrhage Patient reported outcome measures. Quality of life (both health- and social-related quality). Length of stay in hospital Procedural complications
Eligibility criteria – study design	Randomised controlled trials Systematic reviews and meta-analyses of the above Observational studies with multivariable analysis if no RCTs are identified
Other inclusion exclusion criteria	Inclusion Language: Restrict to English only

	Date restriction: 2015 for anterior circulation stroke population because newer devices for mechanical thrombectomy are known to be more effective than those used in trials published before 2015. Therefore, the results from trials before 2015 are not applicable to current practice. However, for posterior circulation stroke there has been no such "evolution" of technology either diagnostically or interventionally and it is not necessarily the case that the newer devices would be better because the physiology of the occlusions differ from those in the anterior circulation. Settings: Hospital, Emergency department, Stroke Unit, CT scanning suite, Angiography suite
Proposed sensitivity / subgroup analysis, or meta-regression	<u>Strata</u> People with posterior circulation stroke / anterior circulation strokes <u>Subgroups</u> People aged over 80 Perfusion based imaging for selection for endovascular therapy Time from symptom onset to treatment <6 hr, >6 People with lower NIHSS scores than 4 (or higher than 22), People with "wake-up strokes" but no changes on plain CT imaging. GA versus no GA
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.

Information sources – databases and dates	Databases: Medline, Embase, Cochrane Library Key papers • NICE IPG 548 Mechanical clot retrieval for treating acute ischaemic stroke. • Broderick JP, Palesch YY, Demchuk AM et al. (7-3-2013) Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl.J Med 368:893-903. • O'Rourke K, Berge E, Walsh CD et al. (2010) Percutaneous vascular interventions for acute ischaemic stroke. [Review]. Cochrane Database of Systematic Reviews CD007574. • Saver JL, Goyal M, Bonafe A et al. (11-6-2015) Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. New England Journal of Medicine 372:2285-2295. • Campbell BC, Mitchell PJ, Kleinig TJ et al. (12-3-2015) Endovascular therapy for ischemic stroke with perfusion-imaging selection. New England Journal of Medicine 372:1009-1018. • Broderick JP, Berkhemer OA, Palesch YY et al. (2015) Endovascular Therapy Is Effective and Safe for Patients With Severe Ischemic Stroke: Pooled Analysis of Interventional Management of Stroke III and Multicenter Randomized Clinical Trial of Endovascular Therapy for Acute Ischemic Stroke in the Netherlands Data. Stroke 46:3416-3422. • Jovin TG, Chamorro A, Cobo E et al. (11-6-2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. New England Journal of Medicine 372:2296-2306. • Goyal M, Demchuk AM, Menon BK et al. (12-3-2015) Randomized assessment of rapid endovascular treatment of ischemic stroke. New England Journal of Medicine 372:1019-1030. • Berkhemer OA, Fransen PS, Beumer D et al. (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. New England Journal of Medicine 372:11-20.
Identify if an update	No. Thrombectomy was not reviewed in CG68, but alteplase was reviewed. **Recommendations from CG68 2008** What is the safety and efficacy of anticoagulants versus placebo for the treatment of patients with acute ischaemic stroke? No question was asked regarding endovascular therapy. 1.4.1.1 Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if: • •treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and • •intracranial haemorrhage has been excluded by appropriate imaging techniques. 1.4.1.2 Alteplase should be administered only within a well organised stroke service with: • •staff trained in delivering thrombolysis and in monitoring for any complications associated with thrombolysis • •level 1 and level 2 nursing care staff trained in acute stroke and thrombolysis • •immediate access to imaging and re-imaging, and staff trained to interpret the images. 1.4.1.3 Staff in A&E departments, if appropriately trained and supported, can

	administer alteplase for the treatment of acute ischaemic stroke provided that patients can be managed within an acute stroke service with appropriate neuroradiological and stroke physician support. 1.4.1.4 Protocols should be in place for the delivery and management of thrombolysis, including post-thrombolysis complications.
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report. For non-randomised studies, we will note which confounding variables have been accounted for in the analysis and by what method. The following confounding variables were agreed to be important: • age (any age cut offs) • pre-intervention measures of stroke severity/Glasgow coma scale • pre-morbid mRS • imaging confounders (e.g., excluding those with evidence of brain stem infarction/compromise) • IV thrombolysis before intervention (yes/no) • time from symptom onset to intervention
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ [Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.]
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.

Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

2 **Table 11: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[74] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and

it will be included in the health economic evidence profile.

- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.
- Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 02 August 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 02 August 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp "Intracranial Embolism and Thrombosis"/

10.	exp Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or vertebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
12.	exp Brain Ischemia/
13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or vertebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	Ischemic Attack, Transient/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
39.	37 not 38
40.	Tissue Plasminogen Activator/
41.	(tPA or TPA or t-PA or rtPA or rt-PA or alteplase or activase or actilyse).ti,ab.
42.	'recombinant human tissue-type plasminogen activator'.ti,ab.
43.	exp thrombectomy/
44.	(thrombecto* or neurothrombecto*).ti,ab.
45.	(aspirat* or thromboaspirat*).ti,ab.
46.	((removal or disrupt* or excis* or retriev* or incorporat* or manipulat* or technolog*) adj3 (coil* or catheter* or stent*)).ti,ab.
47.	(suction adj2 catheter*).ti,ab.
48.	(first pass adj3 technique*).ti,ab.

49.	(suction adj2 mechanic*).ti,ab.
50.	ADAPT.ti,ab.
51.	(solitaire or trevo).ti,ab.
52.	*Endovascular Procedures/
53.	(endovascular adj2 (therap* or treatment* or procedure* or surger*)).ti,ab.
54.	or/40-53
55.	39 and 54
56.	randomized controlled trial.pt.
57.	controlled clinical trial.pt.
58.	randomi#ed.ti,ab.
59.	placebo.ab.
60.	randomly.ti,ab.
61.	clinical trials as topic.sh.
62.	trial.ti.
63.	or/56-62
64.	Meta-Analysis/
65.	Meta-Analysis as Topic/
66.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
67.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
68.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
69.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
70.	(search* adj4 literature).ab.
71.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
72.	cochrane.jw.
73.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
74.	or/64-73
75.	55 and (63 or 74)

1 **Embase (Ovid) search terms**

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*brain embolism/
10.	*Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or

	vertebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
12.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or vetebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	*Transient ischemic attack/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	*plasminogen activator/ or alteplase/ or plasminogen activator derivative/ or recombinant plasminogen activator/
39.	(tPA or TPA or t-PA or rtPA or rt-PA or alteplase or activase or actilyse).ti,ab.
40.	'recombinant human tissue-type plasminogen activator'.ti,ab.
41.	exp thrombectomy/
42.	*mechanical thrombectomy/
43.	fibrinolytic therapy/
44.	(thrombecto* or neurothrombecto*).ti,ab.
45.	(aspirat* or thromboaspirat*).ti,ab.
46.	((removal or disrupt* or excis* or retriev* or incorporat* or manipulat* or technolog*) adj3 (coil* or catheter* or stent*)).ti,ab.
47.	(suction adj2 catheter*).ti,ab.
48.	(first pass adj3 technique*).ti,ab.
49.	(suction adj2 mechanic*).ti,ab.
50.	ADAPT.ti,ab.

51.	(solitaire or trevo).ti,ab.
52.	*Endovascular surgery/ or *endovascular aneurysm repair/
53.	(endovascular adj2 (therap* or treatment* or procedure* or surger*)).ti,ab.
54.	or/38-53
55.	37 and 54
56.	random*.ti,ab.
57.	factorial*.ti,ab.
58.	(crossover* or cross over*).ti,ab.
59.	((doubl* or singl*) adj blind*).ti,ab.
60.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
61.	crossover procedure/
62.	single blind procedure/
63.	randomized controlled trial/
64.	double blind procedure/
65.	or/56-64
66.	systematic review/
67.	Meta-Analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	55 and (65 or 76)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Stroke] explode all trees
#2.	(stroke or strokes):ti,ab
#3.	((cerebro* or cerebral*) near/2 (accident* or apoplexy)):ti,ab
#4.	(CVA or poststroke or poststrokes):ti,ab
#5.	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#6.	(brain near/2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)):ti,ab
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab
#8.	MeSH descriptor: [Brain Infarction] explode all trees
#9.	MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#10.	MeSH descriptor: [Carotid Artery Thrombosis] explode all trees
#11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or vertebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) near/3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab

#12.	MeSH descriptor: [Brain Ischemia] explode all trees
#13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or vertebro basil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#14.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#15.	(isch?emi* near/2 attack*):ti,ab
#16.	TIA*:ti,ab
#17.	(or #1-#16)
#18.	MeSH descriptor: [Tissue Plasminogen Activator] explode all trees
#19.	(tPA or TPA or t-PA or rtPA or rt-PA or alteplase or activase or actilyse):ti,ab
#20.	'recombinant human tissue-type plasminogen activator':ti,ab
#21.	MeSH descriptor: [Thrombectomy] explode all trees
#22.	(thrombecto* or neurothrombecto*):ti,ab
#23.	(aspirat* or thromboaspirat*):ti,ab
#24.	((removal or disrupt* or excis* or retriev* or incorporat* or manipulat* or technolog*) near/3 (coil* or catheter* or stent*)):ti,ab
#25.	(suction near/2 catheter*):ti,ab
#26.	(first pass near/3 technique*) ti,ab
#27.	(suction near/2 mechanic*):ti,ab
#28.	ADAPT:ti,ab
#29.	(solitaire or trevo):ti,ab
#30.	MeSH descriptor: [Endovascular Procedures] explode all trees
#31.	(endovascular near/2 (therap* or treatment* or procedure* or surger*)):ti,ab
#32.	(or #18-#31)
#33.	#17 and #32

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the stroke population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 –	None

Database	Dates searched	Search filter used
	March 2015	

1 **Medline (Ovid) search terms**

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/
32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language

37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

1 **Embase (Ovid) search terms**

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.

16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	(((cerebro* or cerebral*) adj2 (accident* or apoplexy)))
#4.	((CVA or poststroke or poststrokes))

#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	(((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

1
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1 Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of thrombectomy for anterior circulation stroke

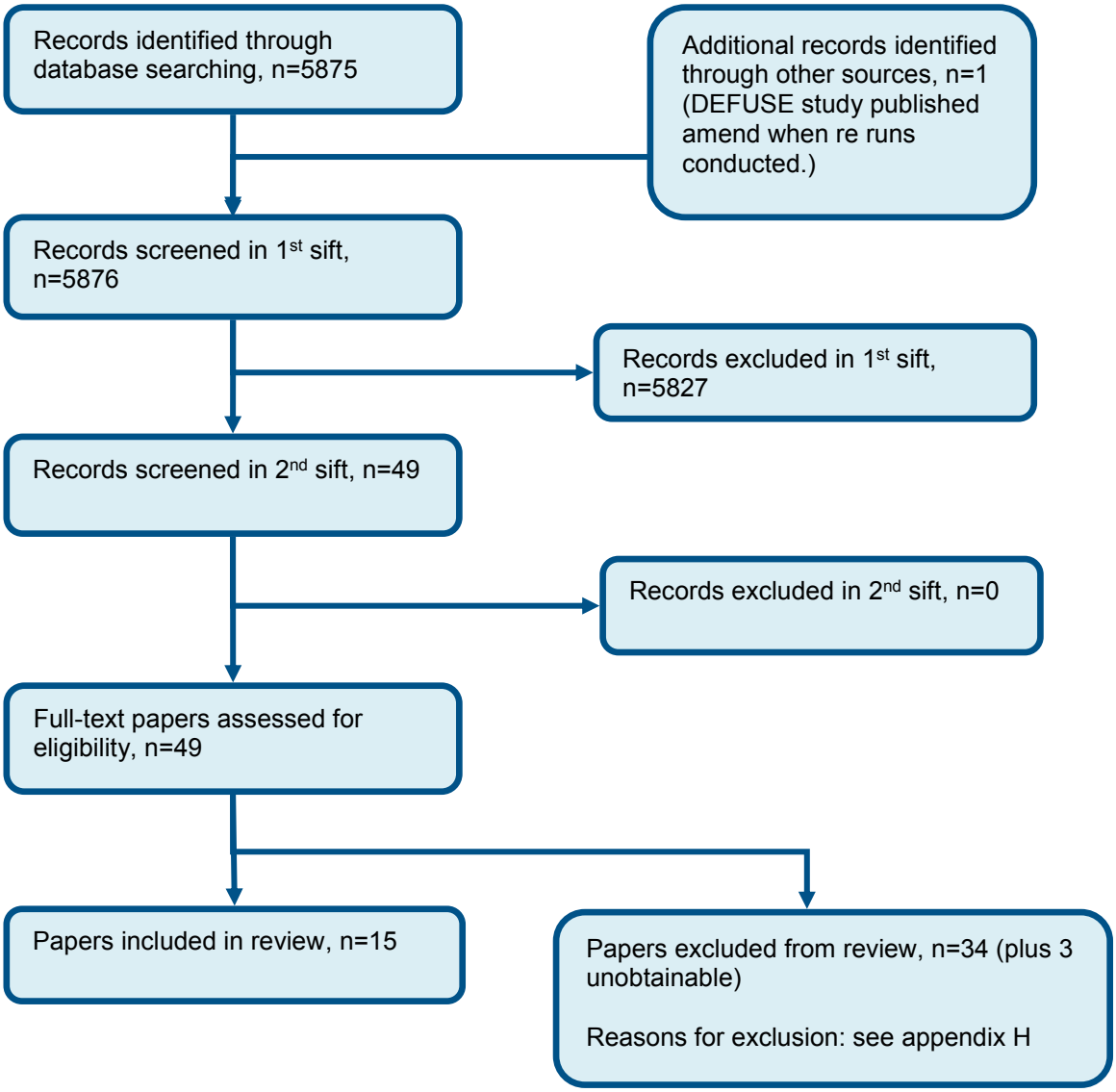
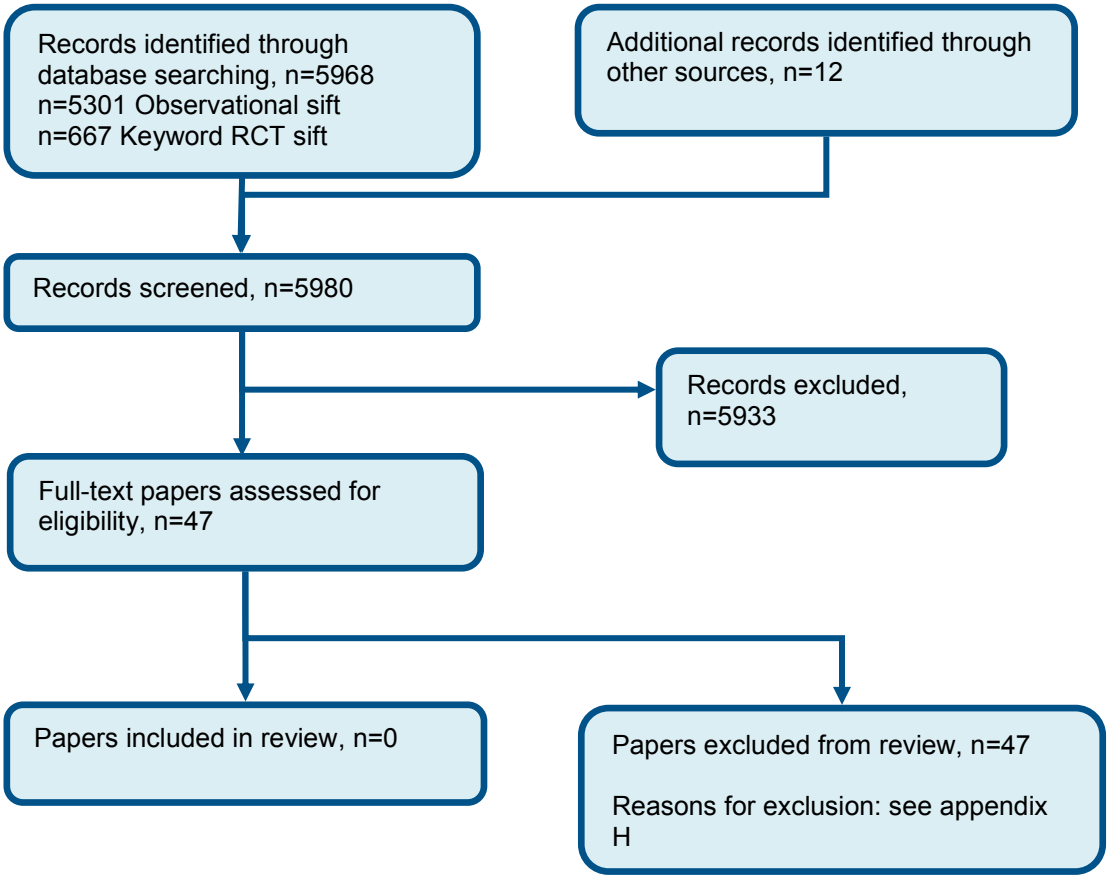


Figure 2: Flow chart of clinical study selection for the additional search on thrombectomy for posterior circulatory stroke



1

2

Appendix D: Clinical evidence tables

D.1 Anterior circulation stroke (randomised studies)

Study	DAWN trial: Nogueira 2018[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=206)
Countries and setting	Conducted in Canada, France, Germany, Spain, USA; Setting: 26 centres across the US, Canada, Europe and Australia
Line of therapy	1st line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: For the purpose of trial enrollment subjects must have an occlusion identified within the intracranial internal carotid artery (ICA), and/or middle cerebral artery (MCA)-M1 arteries by pre-procedure MRA or CTA. The MCA-M1 segment is defined as the first branch of the intracranial ICA which courses horizontally from its branching point off the ICA, through the Sylvian fissure up to the first bifurcation distal to the lenticulostriate arteries, in the most lateral aspect of Sylvian fissure.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Clinical signs and symptoms consistent with the diagnosis of an acute ischemic stroke, and subject belongs to one of the following subgroups: a. Subject has failed IV t-PA therapy (defined as a confirmed persistent occlusion 60 min after administration) b. Subject is contraindicated for IV t-PA administration 2. Age ≥18 3. Baseline NIHSS≥10 (assessed within 1 h of measuring core infarct volume) 4. Subject can be randomized between with 6 to 24 h after time last known well 5. No significant pre-stroke disability (pre-stroke mRS must be 0 or 1) 6. Anticipated life expectancy of at least 6 months 7. Subject willing/able to return for protocol required follow-up visits 8. Subject or subject's legally authorized representative (LAR) has signed the study informed consent form

	Imaging criteria 1. <1/3 MCA territory involved, as evidenced by CT or MRI 2. Occlusion of the intracranial ICA and/or MCA-M1 as evidenced by MRA or CTA 3. Clinical imaging mismatch (CIM) defined as one of the following on MR-DWI or CTP-rCBF maps: a. 0<21cm3 core infarct and NIHSS≥10 (and age□80 years old) b. 0<31cm3 core infarct and NIHSS≥10 (and age<80 years old) c. 31cm3 to □51cm3 core infarct and NIHSS ≤20 (and age<80 years old)
Exclusion criteria	1. History of severe head injury within past 90 days with residual neurological deficit, as determined by medical history 2. Rapid improvement in neurological status to an NIHSS<10 or evidence of vessel recanalization prior to randomization 3. Pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, e.g. dementia with prescribed anti-cholinesterase inhibitor (e.g. Aricept) 4. Seizures at stroke onset if it makes the diagnosis of stroke doubtful and precludes obtaining an accurate baseline NIHSS assessment 5. Baseline blood glucose of <50 mg/dL (2.78 mmol) or >400 mg/dL (22.20 mmol) 6. Baseline hemoglobin counts of <7 mmol/L 7. Baseline platelet count <50,000/uL 8. Abnormal baseline electrolyte parameters as defined by sodium concentration <130 mmol/L, potassium concentration <3 mEq/L or >6 mEq/L 9. Renal failure as defined by a serum creatinine >3.0 mg/dL (264mmol/L) Note: subjects on renal dialysis may be treated regardless of serum creatinine levels 10. Known hemorrhagic diathesis, coagulation factor deficiency, or on anticoagulant therapy with INR>3.0 or PTT>3 times normal. Patients on factor Xa inhibitor for 24–48 h ago must have a normal PTT. 11. Any active or recent hemorrhage within the past 30 days 12. History of severe allergy (more than rash) to contrast medium 13. Severe, sustained hypertension (systolic blood pressure >185mm Hg or diastolic blood pressure >110mmHg) Note: If the blood pressure can be successfully reduced and maintained at the acceptable level using medication the subject can be enrolled 14. Female who is pregnant or lactating at time of admission 15. Current participation in another investigational drug or device study 16. Presumed septic embolus, or suspicion of bacterial endocarditis 17. Treatment with any cleared thrombectomy devices or other intra-arterial (neurovascular) therapies prior to randomization
Age, gender and ethnicity	Age - Mean (SD): Intervention = 69.4 (14.1) Control = 70.7 (13.2) . Gender (M:F): Intervention = 42/65 Control = 51/48. Ethnicity: Not reported

Further population details	Not reported
Extra comments	At 31 months, enrollment in the trial was stopped because of the results of a prespecified interim analysis.
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Intra-arterial treatment - Mechanical therapy plus medical management. Trevo thrombectomy. The procedure must be started (defined as the time of arterial access) no earlier than 6 h, but before 24 h. No more than six retrieval attempts in the same vessel using any of the available Trevo devices and no more than three passes per Trevo device are allowed. Duration 90 day follow up. Concurrent medication/care: All subjects enrolled into this study are admitted to acute stroke units or ICU if needed and medically managed according to the 2013 AHA guidelines, according to the 2008 European Stroke Organization ESO Guidelines, according to the 2007 Australian Clinical Guidelines for Acute Stroke Management, and according to the 2015 Canadian Acute Stroke Best Practice recommendations depending on geographical location and hospital specific policies. In the first 24h after randomization antiplatelet therapy (aspirin or clopidogrel) or dual antiplatelet therapy as per local management protocols is allowed but full heparinization (except low doses intra-procedurally) is not allowed. In subjects who received IV tissue plasminogen activator (tPA), blood pressure should be managed according to post IV tPA management guidelines within the first 24h. Indirectness: No indirectness (n=99) Intervention 2: Usual care - Best medical practice/standard care. In the first 24h after randomization antiplatelet therapy (aspirin or clopidogrel) or dual antiplatelet therapy as per local management protocols is allowed but full heparinization (except low doses intra-procedurally) is not allowed. In subjects who received IV tissue plasminogen activator (tPA), blood pressure should be managed according to post IV tPA management guidelines within the first 24h. Duration 90 day follow up. Concurrent medication/care: All subjects enrolled into this study are admitted to acute stroke units or ICU if needed and medically managed according to the 2013 AHA guidelines, according to the 2008 European Stroke Organization ESO Guidelines, according to the 2007 Australian Clinical Guidelines for Acute Stroke Management, and according to the 2015 Canadian Acute Stroke Best Practice recommendations depending on geographical location and hospital specific policies. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Stryker Neurovascular)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THERAPY PLUS MEDICAL MANAGEMENT versus BEST MEDICAL PRACTICE/STANDARD CARE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 20/107, Group 2: 18/99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS 0 - 2 at 90 days; Group 1: 52/107, Group 2: 13/99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 90 days; Group 1: 6/107, Group 2: 3/99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 4: Procedural complications at 90 days
- Actual outcome: Procedure-related complications at 90 days; Group 1: 7/107, Group 2: 0/99
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Length of stay in hospital; Quality of life

Study (subsidiary papers)	**DEFUSE 3 trial: Albers 2018[7] (Albers 2017[6])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=182)
Countries and setting	Conducted in USA; Setting: 38 US centres
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Signs and symptoms consistent with the diagnosis of an acute anterior circulation ischemic stroke 2. Age 18–90 years 3. Baseline NIHSS score is ≥6 and remains ≥6 immediately prior to randomization 4. Endovascular treatment can be initiated (femoral puncture) between 6 and 16 h of stroke onset. Stroke onset is defined as the time the patient was last known to be at their neurologic baseline (wake-up strokes

	are eligible if they meet the above time limits) 5. Modified Rankin Scale less than or equal to 2 prior to qualifying stroke (functionally independent for all ADLs) 6. Patient/Legally authorized representative has signed the informed consent form
Exclusion criteria	1. Other serious, advanced, or terminal illness (investigator judgment) or life expectancy is less than 6 months 2. Pre-existing medical, neurological or psychiatric disease that would confound the neurological or functional evaluations 3. Pregnancy 4. Inability to undergo a contrast brain perfusion scan with either MRI or CT 5. Known allergy to iodine that precludes an endovascular procedure 6. Treated with tPA >4.5 h after time last known well 7. Treated with tPA 3–4.5 h after last known well and any of the following; age >80, current anticoagulant use, history of diabetes and prior stroke, NIHSS score >25 8. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; recent oral anticoagulant therapy with INR>3 (recent use of one of the new oral anticoagulants is not an exclusion if estimated GFR>30 ml/min) 9. Seizures at stroke onset if it precludes obtaining an accurate baseline NIHSS 10. Baseline blood glucose of <50 mg/dl (2.78 mmol) or >400 mg/dl (22.20 mmol) 11. Baseline platelet count <50,000/ml 12. Severe, sustained hypertension (defined as systolic blood pressure >185mmHg or diastolic blood pressure >110mm Hg) 13. Current participation in another investigational drug or device study 14. Presumed septic embolus or suspicion of bacterial endocarditis 15. Clot retrieval attempted using a neurothrombectomy device prior to 6 h from symptom onset 16. Any other condition that, in the opinion of the investigator, precludes an endovascular procedure or poses a significant hazard to the subject if an endovascular procedure was performed
Age, gender and ethnicity	Age - Median (IQR): Intervention: 70 (59 - 79) Control: 46 (51). Gender (M:F): 90/92. Ethnicity: Not reported
Further population details	Not reported
Extra comments	Trial terminated early for efficacy.
Indirectness of population	No indirectness
Interventions	(n=92) Intervention 1: Endovascular therapy - Mechanical thrombectomy. Femoral artery puncture was performed within 60 min (maximum 90 min) of the completion of the qualifying imaging. FDA-cleared thrombectomy devices (stent-retrievers) or suction thrombectomy systems were used in the treatment of thrombus removal in patients experiencing an acute stroke within 8 h of symptom onset. These devices are

	used up to 16 h following symptom onset in DEFUSE 3 based on an FDA investigational device exemption (IDE). The devices that are currently approved are the Trevo Retriever (Stryker Neurovascular, Fremont CA), the Solitaire Revascularization Device (Medtronic, Irvine, CA), Covidien MindFrame Capture Revascularization Device (Medtronic), and the Penumbra thrombectomy system (Penumbra, Alameda, CA). Additional devices may be added during the course of the study if they receive FDA clearance. Duration 90 days. Concurrent medication/care: All randomized patients received standard medical therapy based on current American Heart Association guidelines. Intraarterial tissue plasminogen activator (t-PA) was not allowed (intravenous t-PA was allowed if begun within 4.5 hours after symptom onset). Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: (n=90) Intervention 2: Usual care - Best medical practice/standard care. All randomized patients received standard medical therapy based on current American Heart Association guidelines. Intraarterial tissue plasminogen activator (t-PA) was not allowed (intravenous t-PA was allowed if begun within 4.5 hours after symptom onset). Duration 90 days. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Academic or government funding (Supported by grants (U10NS086487 and U01NS092076) from the National Institute of Neurological Disorders and Stroke. The RAPID software platform was provided to all sites by iSchemaView.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THROMBECTOMY versus BEST MEDICAL PRACTICE/STANDARD CARE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: mortality 90 days at 90 days; Group 1: 13/92, Group 2: 23/90
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS at 90 days continuous at 90 days; OR; 2.67 (95%CI 1.6 to 4.48) (Median score (IQR) Intervention: 3 (1-4) Control: 4 (3-6)) ;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: mRS at 90 days (0 - 2) at 90 days; Group 1: 41/92, Group 2: 15/90
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days - Actual outcome: Symptomatic intracranial haemorrhage at 90 days at 90 days; Group 1: 6/92, Group 2: 4/90 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage at Define; Procedural complications at Define; Length of stay in hospital at Define; Quality of life at Define

Study (subsidiary papers)	ESCAPE trial: Goyal 2015[42] (Demchuk 2015[30])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=316)
Countries and setting	Conducted in Canada, Irish Republic, South Korea, United Kingdom, USA; Setting: 22 centres worldwide
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Noncontrast CT and CTA (preferably multiphase) were performed to identify participants with a small infarct core, an occluded proximal artery in the anterior circulation, and moderate-to-good collateral circulation.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Acute ischemic stroke 2. Age 18 or greater 3. Onset (last-seen-well) time to randomization time <12 h. 4. Disabling stroke defined as a baseline NIHSS > 5 at the time of randomization. 5. Pre-stroke (24 h prior to stroke onset) independent functional status in activities of daily living with modified Barthel Index > 90. Patient must be living in their own home, apartment or seniors lodge where no nursing care is required. 6. Confirmed symptomatic intracranial occlusion, based on single phase, multiphase or dynamic CTA, at one or more of the following locations: Carotid T/L, M1 MCA, or M1-MCA equivalent (2 or more M2-MCAs). Anterior temporal artery is not considered an M2. 7. Noncontrast CT/CTA for trial eligibility performed or repeated at ESCAPE stroke center with endovascular suite on-site. 8. Endovascular treatment intended to be initiated (groin puncture) within 60 min of baseline noncontrast CT with target CT to first recanalization of 90 min. 9. Signed informed consent or appropriate signed deferral of consent where approved.
Exclusion criteria	1. Baseline noncontrast CT reveals a moderate/large core defined as extensive early ischemic changes of ASPECTS 0–5 in the territory of symptomatic intracranial occlusion. 2. Other confirmation of a moderate to large core defined one of three ways: a. On a single phase, multiphase or dynamic CTA: no or minimal collaterals in a region greater than 50% of the MCA territory when compared with pial filling on the contralateral side (multiphase/dynamic CTA preferred) OR b. On CT perfusion (≥8 cm coverage): a low CBV and very low CBF ASPECTS <6 in the symptomatic MCA territory OR c. On CT perfusion (<8 cm coverage): a region of low CBV and very low CBF >1/3 of the CTP imaged

	symptomatic MCA territory. 3. Groin puncture is not possible within 60 min of the end of noncontrast CT acquisition (please note that if CTP is performed it should be done after CTA). 4. No femoral pulses or very difficult endovascular access will result in a CT-to-recanalization time that is longer than 90 min, or will result in an inability to deliver endovascular therapy. 5. Pregnancy; if a woman is of child-bearing potential a urine or serum beta HCG test is positive. 6. Severe contrast allergy or absolute contraindication to iodinated contrast. 7. Suspected intracranial dissection as a cause of stroke. 8. Clinical history, past imaging or clinical judgment suggests that the intracranial occlusion is chronic. 9. Patient has a severe or fatal comorbid illness that will prevent improvement or follow-up or that will render the procedure unlikely to benefit the patient. 10. Patient cannot complete follow-up treatment due to comorbid nonfatal illness.
Age, gender and ethnicity	Age - Mean (range): Intervention = 71 (60-81) Control = 70 (60-81). Gender (M:F): 151/165. Ethnicity: White =87%
Indirectness of population	No indirectness
Interventions	(n=165) Intervention 1: Endovascular therapy - Mechanical thrombectomy. Subjects in the intervention group will undergo rapid endovascular treatment. A cerebral angiogram will be performed by a neuro interventionist neuroradiologist/neurosurgeon/neurologist). The neuro-interventionist will use any available, approved off the-shelf device according to the manufacturer's label (stentriever or aspiration thrombectomy) to achieve safe reperfusion; Solitaire stentriever device is recommended. In addition the use of a balloon guide catheter in the relevant internal carotid artery is recommended. The stentriever or other device will be deployed to engage and snare the offending thrombus for removal, thereby restoring blood flow. It is recommended that this be performed in combination with aggressive aspiration through the balloon guide catheter after balloon inflation to stop antegrade flow in the internal carotid artery (46). Alternatively, aspiration thrombectomy or simple guidewire manipulation of the thrombus may be employed. Any approved and reasonable endovascular technique is allowable as long as the neurointerventionist deems the technique necessary to safely accomplish and maintain TICI 2b/3 reperfusion to the ischemic MCA territory within a reasonable time frame. Duration 90 day follow up. Concurrent medication/care: All patients will get stroke unit care.After the acute phase, all patients will be treated according to clinical routine. Indirectness: No indirectness Comments: An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy. The ESCAPE trial was stopped early on the advice of the data and safety monitoring board because the prespecified boundary for efficacy had been crossed. (n=150) Intervention 2: Usual care - Best medical practice/standard care. The control group will receive the best current standard of care as described in the current Canadian or local guidelines for acute stroke

	management (47). This means that they will receive intravenous tPA in a 4·5 h window if they meet accepted criteria for IV tPA treatment. Patients who do not meet IV tPA criteria – for example, anticoagulated patients or those in a later time window – will not receive IV tPA. Duration 90 day follow up. Concurrent medication/care: All patients will get stroke unit care.After the acute phase, all patients will be treated accord ing to clinical routine. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Study funded by industry (Supported by Covidien through an unrestricted grant to the University of Calgary. Also supported by the University of Calgary (Hotchkiss Brain Institute, the Department of Clinical Neurosciences and Calgary Stroke Program, and the Department of Radiology), Alberta Innovates–Health Solutions, the Heart and Stroke Foundation of Canada, and Alberta Health Services)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THROMBECTOMY versus BEST BEDICAL PRACTICE/STANDARD CARE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 17/164, Group 2: 28/147
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: a; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS at 90 days; OR; 2.6 (95%CI 1.7 to 3.8);
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: a; Blinding details: A blinded evaluator performed follow-up evaluation. 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.; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention
- Actual outcome: mRS 0-2 at 90 days; Group 1: 87/164, Group 2: 43/147
Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: A blinded evaluator performed follow-up evaluation. 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.; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 90 days; Group 1: 6/165, Group 2: 4/150
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: a; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention

Protocol outcome 4: Procedural complications at 90 days - Actual outcome: Large or malignant middle-cerebral artery stroke at 90 days; Group 1: 8/165, Group 2: 28/150 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: a; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention Protocol outcome 5: Quality of life at 90 days - Actual outcome: EQ-5D at 90 days; OR; 9.4 (95%CI 3.5 to 15.2) (median (interquartile range): Intervention = 80 (60 - 90) Control = 65 (50 - 80)) ; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: a; Blinding details: A blinded evaluator performed follow-up evaluation. 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.; Group 1 Number missing: 14, Reason: Did not receive intervention; Group 2 Number missing: 1, Reason: Switched to intervention	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Length of stay in hospital

Study	EXTEND-IA trial: Campbell 2015[21]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=70)
Countries and setting	Conducted in Australia, New Zealand; Setting: 10 study centres across Australia and New Zealand
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Patients presenting with anterior circulation acute ischemic stroke eligible using standard criteria to receive IV tPA within 4·5 h of stroke onset. 2. Patient, family member, or legally responsible person depending on local ethics requirements has given informed consent. 3. Patient's age is ≥18 years (with no upper age limit). 4. Intra-arterial clot retrieval treatment can commence (groin puncture) within six-hours of stroke onset. Imaging inclusion criteria Dual target: 5. Arterial occlusion on CT orMR angiography of the ICA, M1, or M2 6. Mismatch – using CT or MRI with a Tmax >6 s delay perfusion volume and either CT-rCBF or DWI ischemic core volume. (a) Mismatch ratio >1·2; (b) Absolute mismatch volume >10 ml; and (c) Ischemic core lesion volume <70 ml.
Exclusion criteria	Exclusion criteria 1. Standard contraindications to intravenous tPA. 2. Rapidly improving symptoms at the discretion of the investigator. 3. Prestroke mRS score of ≥2 (indicating previous disability) 4. Inability to access the cerebral vasculature in the opinion of the neurointerventional team or contraindication to use of the Solitaire FR device. 5. Contraindication to imaging with contrast agents. 6. Participation in any investigational study in the previous 30 days. 7. Any terminal illness such that patient would not be expected to survive more than one-year.

Recruitment/selection of patients	Patients will be stratified by site of vessel occlusion into one of the following strata: (a) ICA occlusion; (b) proximal middle cerebral artery (MCA-M1); (c) distal middle cerebral artery (MCA-M2).
Age, gender and ethnicity	Age - Mean (SD): Intervention = 68.6 ± 12.3 Control = 70.2 ± 11.8. Gender (M:F): Define. Ethnicity: Not reported
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Thrombolysis - Alteplase. alteplase at a dose of 0.9 mg per kilogram as standard care. Duration 90 day follow up. Concurrent medication/care: N/A Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: Comments: After the release of the results of the MR CLEAN study, recruitment into the trial was suspended and the data and safety monitoring board reviewed data for the 70 enrolled patients. A prespecified Haybittle–Peto stopping boundary was applied to the coprimary outcome in the intention-to-treat population with the use of Holm's step-down procedure Planned to enroll a total of 100 people. (n=35) Intervention 2: Endovascular therapy - Mechanical thrombectomy. The use of conscious sedation or general anesthesia for endovascular treatment was at the discretion of the neurointerventionist. The site of vessel occlusion was confirmed with the use of digital subtraction angiography. If there was no lesion amenable to thrombectomy, the procedure was terminated. The Solitaire FR retrievable stent (Covidien) was deployed at the site of intracranial-vessel occlusion and then removed under negative-pressure aspiration. Control angiography was performed at the conclusion of the procedure and centrally graded for angiographic revascularization, with the use of the modified Treatment in Cerebral Ischemia classification, on a scale ranging from 0 (no flow) to 3 (normal flow), and any embolization of thrombus into previously uninvolved vascular territories. Duration 90 days. Concurrent medication/care: Alteplase at a dose of 0.9 mg per kilogram as standard care. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Study funded by industry (Supported by grants from the Australian National Health and Medical Research Council of Australia (1043242 and 1035688), Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, the National Heart Foundation of Australia, and the National Stroke Foundation of Australia; and by infrastructure funding from the state government of Victoria. The Solitaire FR device and trial infrastructure were provided under an unrestricted grant from Covidien.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THROMBECTOMY versus ALTEPLASE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 3/35, Group 2: 7/35

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Modified Rankin Scale at 90 days - Actual outcome: mRS at 90 days; OR; 2.1 (95%CI 1.2 to 3.8); Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: mRS 0-2 at 90 days; Group 1: 25/35, Group 2: 14/35 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation. indirectness Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days - Actual outcome: Symptomatic intracranial haemorrhage at 90 days; Group 1: 0/35, Group 2: 2/35 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: All those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Procedural complications; Length of stay in hospital; Quality of life

Study (subsidiary papers)	MR CLEAN trial: Berkhemer 2015[15] (Fransen 2014[37])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=500)
Countries and setting	Conducted in Netherlands; Setting: 17 large hospitals in the Netherlands
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The imaging committee evaluated the findings on baseline noncontrast CT for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with 1 point subtracted for any evidence of early ischemic change in each defined region on the CT scan), baseline vessel imaging (CTA, MRA, or DSA) for the location of the occlusion, and follow-up CTA or MRA at 24 hours for vessel recanalization.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 18 years or older with acute ischemic stroke and a symptomatic anterior proximal artery occlusion, which can be treated within 6 hours after stroke onset. General inclusion criteria are: a clinical diagnosis of acute stroke with a deficit on the NIHSS of at least 2 points, CT or MRI ruling out intracranial hemorrhage, occlusion of distal intracranial carotid artery or middle (M1 or M2 or anterior cerebral artery (A1) demonstrated with CT angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), the possibility to start treatment within 6 hours of onset, aged 18 years or over and informed consent given in writing.
Exclusion criteria	General exclusion criteria are: arterial blood pressure exceeding 185/110 mmHg, blood glucose less than 2.7 or over 22.2 mmol/L, treatment with IV thrombolysis in a dose exceeding 0.9 mg/kg or 90 mg or treatment with IV thrombolysis despite contraindications, and, finally, cerebral infarction in the distribution of the relevant occluded artery in the previous 6 weeks. A specific exclusion criterion for intended mechanical thrombectomy is laboratory evidence of coagulation abnormalities (that is, platelet count <40 × 109/L, activated partial Thromboplastin time (APTT) >50 seconds or International normalized ratio (INR) >3.0). Specific exclusion criteria for intended intra-arterial thrombolysis are: a history of cerebral hemorrhage, severe head injury (contusion) in the previous 4 weeks and clinical laboratory evidence of coagulation abnormalities, (that is, platelet count <90 × 109/L, APTT >50 seconds or INR >1.7), or treatment with oral thrombin or factor X antagonists.
Age, gender and ethnicity	Age - Mean (range): 65 (23 - 96). Gender (M:F): 292 men. Ethnicity: Not reported
Further population details	Not reported

Indirectness of population	No indirectness: Note that this study includes those aged 18 and over
Interventions	(n=233) Intervention 1: Intra-arterial treatment - Intra-arterial thrombolysis, mechanical treatment or both. Intraarterial treatment consisted of arterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both. The method of intraarterial treatment was left to the discretion of the local interventionist. The use of alteplase or urokinase for intraarterial thrombolysis was allowed in this trial, with a maximum dose of 90 mg of alteplase or 1,200,000 IU of urokinase. The dose was restricted to 30 mg of alteplase or 400,000 IU of urokinase if intravenous alteplase was given. Mechanical treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent. Duration 90 day follow up. Concurrent medication/care: The treatment is provided in addition to best medical management according to national and international guide lines, and may include IV thrombolysis. Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: Comments: Mechanical treatment was performed in 195 of the 233 patients (83.7%). Retrievable stents were used in 190 patients (81.5%), and other devices were used in 5 patients (2.1%). Additional intraarterial thrombolytic agents were given to 24 patients (10.3%). (n=267) Intervention 2: Usual care - Best medical practice/standard care. The treatment is provided in addition to best medical management according to national and international guidelines, and may include IV thrombolysis. Duration 90 day follow up. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Other (Supported by the Dutch Heart Foundation and by unrestricted grants from AngioCare Covidien/ev3, Medac/Lamepro, and Pen-umbra.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-ARTERIAL THROMBOLYSIS, MECHANICAL TREATMENT OR BOTH versus BEST MEDICAL PRACTICE/STANDARD CARE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 30 days; Group 1: 44/233, Group 2: 49/267
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS score at 90 days; OR; 1.66 (95%CI 1.21 to 2.28) (Median (interquartile range): Intervention = 3 (2 - 5) Control = 4 (3 - 5)) ;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intervention not initiated.; Group 2 Number missing: 1, Reason: Received intervention. - Actual outcome: mRS score of 0 - 2 at 90 days; Group 1: 76/76, Group 2: 51/267 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention Protocol outcome 3: Symptomatic intracranial haemorrhage - Actual outcome: Symptomatic intracerebral haemorrhage at 90 days; Group 1: 18/233, Group 2: 17/267 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention Protocol outcome 4: Procedural complications - Actual outcome: New ischemic stroke in a different territory at 90 days; Group 1: 13/233, Group 2: 1/267 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention - Actual outcome: Progressive ischemic stroke at 90 days; Group 1: 46/233, Group 2: 47/267 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention Protocol outcome 5: Quality of life - Actual outcome: EQ-5D at 90 days; Median (interquartile range): Intervention = 0.69 (0.33 - 0.85) Control = 0.66 (0.30 - 0.81) ; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Age: Intervention 65.8, control 65.7; Blinding details: Both patient and treating physician will be aware of the treatment assignment. Treatment assignment cannot be determined before inclusion and randomization.; Group 1 Number missing: 17, Reason: Intraarterial treatment not initiated; Group 2 Number missing: 1, Reason: Switching - received intervention	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Length of stay in hospital

Study	PISTE trial: Muir 2017[71]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=65)
Countries and setting	Conducted in United Kingdom; Setting: 10 centres in the UK
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: If non-invasive angiographic imaging with CT angiography (CTA) or magnetic resonance angiography showed occlusion of the intracranial ICA, M1 segment of the MCA or a single M2 MCA branch, patients were eligible for randomisation.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients ≥18 years were eligible if presenting with acute supratentorial ischaemic stroke and eligible for IVT started within 4.5 hours of symptom onset. If non-invasive angiographic imaging with CT angiography (CTA) or magnetic resonance angiography showed occlusion of the intracranial ICA, M1 segment of the MCA or a single M2 MCA branch, patients were eligible for randomisation.
Exclusion criteria	We excluded patients with contraindications to IVT, life expectancy imited to <90 days, with chronic extracranial ICA occlusion or with extensive early hypodensity on non-contrast CT brain involving more than one-third of the MCA territory.
Age, gender and ethnicity	Age - Mean (SD): Intervention 67 (17) Control 64 (16). Gender (M:F): Intervention 13/20 Control 16/16. Ethnicity: Not reported
Further population details	Not reported
Extra comments	Trial recruitment was suspended in April 2015 following presentation of other relevant thrombectomy trial results and ended in June 2015.
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Thrombolysis - Other. Intravenous thrombolysis - no specific details given. Duration 90 day follow up. Concurrent medication/care: Best medical therapy. Indirectness: No indirectness; Indirectness comment: Unknown if alteplase or other thrombolysis drug given. Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: (n=33) Intervention 2: Intra-arterial treatment - Mechanical thrombectomy plus intravenous thrombolysis. IVT with additional (adjunctive) MTwith any operator-selected CE-marked device approved for intracranial clot removal. Duration 90 day follow up. Concurrent medication/care: Best medical therapy. Indirectness: No indirectness

	Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: Comments: Intervention was to be initiated as fast as possible after confirming eligibility, and a maximum of 90 min from start of IVT to start of the MT procedure (groin puncture) was permitted. The target vessel should have been cannulated within a maximum of 6 hours of symptom onset. Stent-retriever devices were used first in 68% of procedures and aspiration devices in 32%.
Funding	Study funded by industry (The start-up phase of the trial was funded by grants from the Stroke Association (TSA 2011/2006) from 2012 to 2015 and the National Institute of Health Research (NIHR) Health Technology Assessment programme (HTA 14.08.47) from 2015 to 2016, and received unrestricted grants from Codman and Covidien (Medtronic).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THROMBECTOMY PLUS INTRAVENOUS THROMBOLYSIS versus INTRAVENOUS THROMBOLYSIS

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Fatal serious adverse events at 90 days; Group 1: 7/33, Group 2: 4/32
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Day 90 outcomes were assessed by site staff blind to treatment allocation.; Group 1 Number missing: 3, Reason: 1 = treatment allocation crossover and 2 = >33% MCA territory; Group 2 Number missing: 4, Reason: 1 = CTA occlusion ineligible, 1 = >33% MCA territory, 1 = mRS>2 on review, 1 = treatment allocation crossover
2 people lost to follow up.
- Actual outcome: Mortality at 90 days; OR; 1.56 (95%CI 0.29 to 8.4);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Day 90 outcomes were assessed by site staff blind to treatment allocation.; Group 1 Number missing: 3, Reason: 1 = treatment allocation crossover and 2 = >33% MCA territory; Group 2 Number missing: 4, Reason: 1 = CTA occlusion ineligible, 1 = >33% MCA territory, 1 = mRS>2 on review, 1 = treatment allocation crossover
2 people lost to follow up.

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS 0-2 at 90 days; OR; 2.59 (95%CI 0.93 to 7.24), Comments: ITT analysis used - per protocol also reported.);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Day 90 outcomes were assessed by site staff blind to treatment allocation.; Group 1 Number missing: 3, Reason: 1 = 1 treatment allocation crossover, 2 = >33% MCA territory; Group 2 Number missing: 4, Reason: 1 = CTA occlusion ineligible, 1 = >33% MCA territory, 1 = mRS>2 on review, 1 = treatment allocation crossover, plus 2 with no day 90 mRS
2 people lost to follow up.

Protocol outcome 3: Intracerebral haemorrhage at 90 days

- Actual outcome: Intracerebral haemorrhage at 90 days; Group 1: 3/33, Group 2: 3/32 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Day 90 outcomes were assessed by site staff blind to treatment allocation.; Group 1 Number missing: 3, Reason: 1 = treatment allocation crossover and 2 = >33% MCA territory; Group 2 Number missing: 4, Reason: 1 = CTA occlusion ineligible, 1 = >33% MCA territory, 1 = mRS>2 on review, 1 = treatment allocation crossover 2 people lost to follow up. Protocol outcome 4: Symptomatic intracranial haemorrhage at 90 days - Actual outcome: Symptomatic intracerebral haemorrhage at 90 days; Group 1: 0/33, Group 2: 0/32 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Day 90 outcomes were assessed by site staff blind to treatment allocation.; Group 1 Number missing: 3, Reason: 1 = treatment allocation crossover and 2 = >33% MCA territory; Group 2 Number missing: 4, Reason: 1 = CTA occlusion ineligible, 1 = >33% MCA territory, 1 = mRS>2 on review, 1 = treatment allocation crossover 2 people lost to follow up.	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Procedural complications; Length of stay in hospital; Quality of life

Study (subsidiary papers)	REVASCAT trial: Jovin 2015[51] (Davalos 2017[28], Molina 2015[67])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=206)
Countries and setting	Conducted in Spain; Setting: Four study centers in Catalonia, Spain.
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Patients with acute ischemic stroke ineligible for i.v. thrombolytic treatment (e.g. subject presents beyond recommended time from symptom onset), or treated with i.v. thrombolytic therapy without recanalization after a minimum of 30 mins from start of i.v. t-PA infusion. 2. Occlusion (TICI 0–1) of the intracranial ICA (distal internal carotid artery (ICA) or T occlusions), proximal middle cerebral artery (MCA-M1) segment or tandem proximal ICA/MCA-M1 suitable for endovascular treatment, as evidenced by computed tomography angiography (CTA), magnetic resonance angiography (MRA) or angiogram, with or without concomitant cervical carotid occlusion or stenosis. In patients treated with i.v. t-PA, the CTA or MRA confirming occlusion has to be performed at a minimum of 30 mins after start of i.v. t-PA infusion. 3. Patient treatable within eight-hours fromtime last seen well at baseline (i.e. subjects who have stroke symptoms upon awakening will be considered to have their ‘onset’ at beginning of sleep). 4. Age ≥ 18 and ≤ 80. 5. Baseline NIHSS score must be equal or higher than 6 points. 6. No significant pre-stroke functional disability (mRS ≤ 1). 7. Informed consent obtained frompatient or acceptable patient surrogate.
Exclusion criteria	Clinical 1. Known haemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulant therapy with INR > 3·0. 2. Baseline platelet count <30·000/μL. 3. Baseline blood glucose of <50 mg/dL or >400 mg/dl. 4. Severe, sustained hypertension (SBP > 185mmHg or DBP > 110mm Hg). 5. Patients in coma (NIHSS item of consciousness >1) (Intubated patients for transfer could be randomized only in case an NIHSS is obtained by a neurologist prior transportation). 6. Seizures at stroke onset thatwould preclude obtaining a baseline NIHSS. 7. Serious, advanced, or terminal illness with anticipated life expectancy of less than one-year.

	8. History of life-threatening allergy (more than rash) to contrast medium. 9. Subjects who have received i.v. t-PA treatment beyond 4·5 h from the beginning of the symptoms. 10. Renal insufficiency with creatinine ≥3 mg/dl. 11. Woman of childbearing potential who is known to be pregnant or lactating or who has a positive pregnancy test on admission. 12. Subject participating in a study involving an investigational drug or device that would impact this study. 13. Cerebral vasculitis. 14. Patients with a preexisting neurological or psychiatric disease that would confound the neurological or functional evaluations; mRS score at baseline must be ≤1. 15. Unlikely to be available for 90-day follow-up. Neuroimaging 16. Hypodensity on CT or restricted diffusion amounting to an Alberta Stroke Program Early CT score (ASPECTS) score of <7 on noncontrast CT, or <6 on DWI magnetic resonance imaging (MRI). ASPECTS may also be evaluated by cerebral blood flow maps of CT Perfusion, or CTA source imaging in patients whose vascular occlusion study (CTA/MRA) confirming qualify ing occlusion is performed beyond 4·5 h of last seen well. 17. CT or MR evidence of haemorrhage (the presence of micro bleeds is allowed). 18. Significant mass effect with midline shift. 19. Evidence of ipsilateral carotid occlusion, high-grade stenosis or arterial dissection in the extracranial or petrous segment of the internal carotid artery that cannot be treated or will prevent access to the intracranial clot or excessive tortuosity of cervical vessels precluding device delivery/deployment. 20. Subjects with occlusions in multiple vascular territories (e.g. bilateral anterior circulation, or anterior/posterior circulation). 21. Evidence of intracranial tumour (except small meningioma)
Age, gender and ethnicity	Age - Mean (SD): Intervention = 65.7 (11.3) Control = 67.2 (9.5). Gender (M:F): Intervention = 55/48 Control = 54/49. Ethnicity: Not reported
Further population details	Not reported
Indirectness of population	No indirectness: Does not include those over 80 years old.After the enrollment of 160 patients, the inclusion criteria were modified to include patients up to the age of 85 years with an ASPECTS score of more than 8.
Interventions	(n=103) Intervention 1: Intra-arterial treatment - Thrombectomy plus alteplase. Endovascular treatment with the Solitaire stent retriever. Thrombectomy was performed in 98 of 103 patients in the thrombectomy group. Ipsilateral carotid stenting was performed in 9 patients. Seven procedures in the thrombectomy group (6.7%) were performed under general anesthesia. Outside of protocol, 1 patient was treated with intracranial angioplasty after failed attempts with the stent retriever, and 1 patient received intraarterial alteplase. . Duration 1 year follow up. Concurrent medication/care: Medical therapy (including intravenous alteplase when eligible) 70 received alteplase. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:

	Comments: The first interim analysis was performed as planned after 25% patients (174 of the maximum sample size) had completed 90 days of follow-up. The steering committee accepted the recommendation of the data and safety monitoring board to stop recruitment because of loss of equipoise. Although the interim results did not reach the prespecified stopping boundaries, study recruitment was terminated because of emerging results from three other studies. (n=103) Intervention 2: Thrombolysis - Alteplase. Medical therapy (including intravenous alteplase when eligible). 80 people received alteplase. Duration 1 year follow up. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Other (Supported by Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien, by a grant from the Spanish Ministry of Health co-financed by Fondo Europeo de Desarrollo Regional (Instituto de Salud Carlos III, Red Temática de Investigación Cooperativa Invictus, RD 12/0014/008), and a grant from the Generalitat de Catalunya (SGR 464/2014).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THROMBECTOMY PLUS ALTEPLASE versus ALTEPLASE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 19/103, Group 2: 16/103
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0
- Actual outcome: Mortality at 12 months; Group 1: 24/103, Group 2: 25/103
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0, Reason: 0

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS at 90 days; OR; 1.7 (95%CI 1.04 to 2.7);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0
- Actual outcome: mRS 0 - 2 at 90 days; Group 1: 45/103, Group 2: 29/103
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up

evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0
- Actual outcome: mRS at 12 months; OR; 1.69 (95%CI 1.03 to 2.76);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0
- Actual outcome: mRS 0 - 2 at 12 months; Group 1: 45/103, Group 2: 31/103
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 90 days; Group 1: 7/103, Group 2: 4/103
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 4: Procedural complications at 90 days
- Actual outcome: Recurrent stroke at 90 days; Group 1: 4/103, Group 2: 3/103
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

Protocol outcome 5: Quality of life at 90 days
- Actual outcome: EQ-5D at 90 days; Median EQ-5D score (IQR): Intervention = 0.65 (0.21 - 0.79) Control 0.32 (0.13 - 0.7) ;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0
- Actual outcome: EQ-5D (utility) at 12 months; Group 1: mean 0.46 (SD 0.38); n=103, Group 2: mean 0.33 (SD 0.33); n=103
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Each site will designate one or more individual(s) to perform the follow-up evaluation at 24 (± 12) h, 5 (± 2) days or prior to discharge if discharge occurs before three-days and at three months who can remain blinded to the treatment of each subject.; Group 1 Number missing: 5, Reason: Did not receive thrombectomy; Group 2 Number missing: 0

	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Length of stay in hospital
Protocol outcomes not reported by the study	

Study (subsidiary papers)	SWIFT PRIME trial: Saver 2015[91] (Saver 2015[90])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=196)
Countries and setting	Conducted in Canada, France, Germany, Switzerland, USA; Setting: The study was performed at 39 centers in the United States and Europe.
Line of therapy	1st line
Duration of study	--: 90 day follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Thrombolysis in cerebral infarction (TICI) 0–1 flow in the intracranial internal carotid, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire™ FR device.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Age 18 – 80 2. Clinical signs consistent with acute ischemic stroke 3. Prestroke Modified Rankin Score ≤ 1 4. NIHSS ≥ 8 and < 30 at the time of randomization 5. Initiation of IV tPA within 4·5 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received/is receiving the correct IV tPA dose for the estimated weight prior to randomization. 6. Thrombolysis in cerebral infarction (TICI) 0–1 flow in the intracranial internal carotid, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire™ FR device. (Note: M1 segment of the MCA is defined as the arterial trunk from its origin at the ICA to the first bifurcation or trifurcation into major branches neglecting the small temporo-polar branch.) 7. Subject is able to be treated within six-hours of onset of stroke symptoms and within 1·5 hours (90 min) from CTA or MRA to groin puncture. 8. Subject is willing to conduct protocol-required follow-up visits. 9. An appropriate signed and dated informed consent form (or enrollment under exception from explicit informed consent if permitted under country regulations) 10. Subject is affiliated with a social security system (if required by individual country regulations). 11. Subject meets national regulatory criteria for clinical trial participation.
Exclusion criteria	1. Subject who is contraindicated to IV tPA as per local national guidelines. 2. Female who is pregnant or lactating or has a positive pregnancy test at time of admission. 3. As applicable by French law, subject who is a protected individual such as an incompetent adult or

	incarcerated person. 4. Rapid neurological improvement prior to study randomization suggesting resolution of signs/symptoms of stroke 5. Known serious sensitivity to radiographic contrast agents 6. Known sensitivity to nickel, titanium metals, or their alloys 7. Current participation in another investigation drug or device treatment study 8. Known hereditary or acquired haemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrollment.) 9. Renal failure as defined by a serum creatinine > 2·0 mg/dl (or 176·8 µmol/l) or glomerular filtration rate (GFR) < 30. 10. Subject who requires hemodialysis or peritoneal dialysis, or who has a contraindication to an angiogram for whatever reason. 11. Life expectancy of less than 90 days 12. Clinical presentation suggests a subarachnoid haemorrhage, even if initial CT or MRI scan is normal 13. Suspicion of aortic dissection 14. Subject with a comorbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments. 15. Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol (defined as regular or daily consumption of more than four alcoholic drinks per day). 16. Known history of arterial tortuosity, preexisting stent, and/or other arterial disease that would prevent the device from reaching the target vessel and/or preclude safe recovery of the device Imaging exclusion criteria 1. CT or MRI evidence of haemorrhage on presentation 2. CT or MRI evidence of mass effect or intra-cranial tumour (except small meningioma) 3. CT or MRI evidence of cerebral vasculitis 4. CT showing hypodensity or MRI showing hyperintensity involving greater than 1/3 of the MCA territory (or in other territories, > 100 cc of tissue) on presentation 5. *Baseline non-contrast CT or DWI MRI evidence of a moderate/large core defined as extensive early ischemic changes of Alberta Stroke Program Early CT score (ASPECTS) < 6. 6. CT or MRI evidence of a basilar artery (BA) occlusion or posterior cerebral artery (PCA) occlusion 7. CTA or MRA evidence of carotid dissection or complete cervical carotid occlusion requiring stenting at the time of the index procedure (i.e. mechanical thrombectomy)

	8. Imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention (e.g. inability to navigate to target lesion, moderate/large infarct with poor collateral circulation, etc.).
Recruitment/selection of patients	A subject is considered enrolled into the screening phase of the study after the informed consent form has been signed or country-specific requirements have been met for enrollment without explicit informed consent in emergency circumstances.
Age, gender and ethnicity	Age - Mean (SD): Intervention 65 (12.5) Control 66.3 (11.3). Gender (M:F): Intervention 54/44 Control 45/51 . Ethnicity: Intervention = White 79/90, Black 10/90, Asian or other 1/90 Control - 83/92, Black 8/92, 1/92
Further population details	Not reported
Indirectness of population	No indirectness: Patients aged over 80 excluded
Interventions	(n=98) Intervention 1: Intra-arterial treatment - Mechanical thrombectomy plus intravenous thrombolysis. In the intervention group, neurovascular thrombectomy was performed with the use of the Solitaire FR (Flow Restoration) or Solitaire 2 device. Concomitant stenting of the cervical internal carotid artery was not permitted, although angioplasty could be performed to permit intracranial access. The study target for the time from qualifying imaging to groin puncture was within 70 minutes. Duration 90 day follow up. Concurrent medication/care: Intravenous t-PA: Initiation of IV tPA within 4·5 hours of onset of stroke symptoms, with investigator verification that the subject has received/is receiving the correct IV tPA dose for the estimated weight prior to randomization.; Indirectness comment: t-PA - drug not stated Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: (n=98) Intervention 2: Thrombolysis - Other. Intravenous t-PA: Initiation of IV tPA within 4·5 hours of onset of stroke symptoms, with investigator verification that the subject has received/is receiving the correct IV tPA dose for the estimated weight prior to randomization. Duration 90 day follow up. Concurrent medication/care: None stated. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: Comments: After the preliminary results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Min- imizing CT to Recanalization Times (ESCAPE) trial were reported,16,18 our data and safety monitoring board recommended holding enrollment, and the first interim efficacy analysis was performed slightly early (including 196 rather than 200 patients). In February 2015, the study was halted when the interim efficacy analysis showed that the prespecified stopping-criteria boundary for efficacy had been crossed.

Funding	Study funded by industry (Supported by Covidien.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL THROMBECTOMY PLUS INTRAVENOUS THROMBOLYSIS versus IV TPA

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 day; Group 1: 9/98, Group 2: 12/97
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: Did not receive thrombectomy; Group 2 Number missing: 1, Reason: Patient requested deletion of all data (withdrew from study)

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS 0 - 2 at 90 day; Group 1: 59/98, Group 2: 33/93
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: 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.; Group 1 Number missing: 11, Reason: Did not receive thrombectomy; Group 2 Number missing: 1, Reason: Patient requested deletion of all data (withdrew from study)
- Actual outcome: mRS ordinal shift at 90 day; OR; 2.63 (95%CI 1.57 to 4.4);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: 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.; Group 1 Number missing: 11, Reason: Did not receive thrombectomy; Group 2 Number missing: 1, Reason: Patient requested deletion of all data (withdrew from study)

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 27 hour; Group 1: 0/98, Group 2: 3/97
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: Did not receive thrombectomy; Group 2 Number missing: 1, Reason: Patient requested deletion of all data (withdrew from study)

Protocol outcome 4: Procedural complications at 90 days
- Actual outcome: Any serious adverse event at 90 day; Group 1: 35/98, Group 2: 30/97
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 11, Reason: Did not receive thrombectomy; Group 2 Number missing: 1, Reason: Patient requested deletion of all data (withdrew from study)

Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Length of stay in hospital at Define; Quality of life

Study	THERAPY trial: Mocco 2016[66]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=108)
Countries and setting	Conducted in Germany, USA; Setting: 36 US and German centers
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT angiography was required to confirm intracranial occlusion and to rule out tandem cervical occlusion that would prevent thrombectomy without treatment.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	· From 18 to 85 years of age · Present with symptoms consistent with an acute ischemic stroke and eligible for IV rtPA therapy* · Evidence of a large vessel occlusion in the anterior circulation with a clot length of >8mm · NIH Stroke Scale (NIHSS) score > 8 at presentation · Signed informed consent *Patients presenting 3-4.5 hours from symptom onset are not eligible if they are >80 years of age, have a history of stroke and diabetes, anticoagulant use (even if INR is <1.7) and have a NIHSS score >25
Exclusion criteria	· History of stroke in the past 3 months. · Females who are pregnant · Pre-stroke mRS score >2 · Known severe allergy to contrast media · Uncontrolled hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg) · CT evidence of the following conditions at randomization: - Significant mass effect with midline shift - Any acute ischemic changes in >1/3 of the affected middle cerebral artery territory - Evidence of intracranial hemorrhage · Angiographic evidence of tandem extracranial occlusion or an arterial stenosis proximal to the occlusion that requires treatment prior to thrombus removal. Moderate stenosis not requiring treatment is not an

	exclusion. · Angiographic evidence of preexisting arterial injury · Rapidly improving neurological status prior to randomization · Bilateral stroke · Intracranial tumors · Known history of cerebral aneurysm or arteriovenous malformation · Known hemorrhagic diathesis, coagulation deficiency, or on anticoagulant therapy with an International Normalized Ratio (INR) of >1.7 · Baseline platelets <50,000 · Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal · Direct thrombin inhibitors or direct factor Xa inhibitors received within 48 hours · Pre-treatment glucose <50mg/dL or >300mg/dL · Life expectancy less than 90 days prior to stroke onset · Participation in another clinical investigation that could confound the evaluation of the study device
Age, gender and ethnicity	Age - Mean (SD): Intervention = 67 (11) Control = 70 (10). Gender (M:F): Intervention = 34/21 Control = 23/30. Ethnicity: Not reported
Further population details	Not reported
Extra comments	. Trial enrollment was halted by the steering committee after the presentation of the MR CLEAN study at the World Stroke Congress.
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Intra-arterial treatment - Thrombectomy plus alteplase. Aspiration thrombectomy after intravenous-alteplase administration . Duration 90 day follow up. Concurrent medication/care: Received full dose of intravenous-alteplase (0.9 mg/kg). Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: Comments: Among 55 patients randomized to ITT, traditional separator based aspiration system (Penumbra) was used in 30 patients (54%), the separator 3D in 14 patients (25%), the ACE catheter (Penumbra) in 15 patients (27%), and either a Solitaire (Covidien) or a Trevo (Stryker) was used in 7 patients (13%). (n=53) Intervention 2: Thrombolysis - Alteplase. Intravenous-alteplase alone. Full dose of intravenous-alteplase (0.9 mg/kg). Duration 90 day follow up. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:

Funding	Study funded by industry (This work was supported by Penumbra, Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THROMBECTOMY PLUS ALTEPLASE versus ALTEPLASE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 6/50, Group 2: 11/46
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Loss to follow up = 3 Withdrew consent = 2; Group 2 Number missing: 7, Reason: Loss to follow up = 5 Withdrew consent = 2

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS 0 - 2 at 90 days; Group 1: 19/50, Group 2: 14/46
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: 90-day mRS was assessed by independent blinded adjudicators. Adjudicators reviewed videotapes of assessments performed by blinded, trained, and certified local investigators. To minimize variability, local investigators used the Rankin Focused Assessment Tool.; Group 1 Number missing: 5, Reason: Loss to follow up = 3 Withdrew consent = 2; Group 2 Number missing: 7, Reason: Loss to follow up = 5 Withdrew consent = 2
- Actual outcome: mRS ordinal shift at 90 days; OR; 2.4 (95%CI 1.1 to 5.1);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: 90-day mRS was assessed by independent blinded adjudicators. Adjudicators reviewed videotapes of assessments performed by blinded, trained, and certified local investigators. To minimize variability, local investigators used the Rankin Focused Assessment Tool.; Group 1 Number missing: 5, Reason: Loss to follow up = 3 Withdrew consent = 2; Group 2 Number missing: 7, Reason: Loss to follow up = 5 Withdrew consent = 2

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 90 days; Group 1: 4/43, Group 2: 6/62; Comments: Available case (as treated)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: IV tPA alone = 9 Other thrombectomy device (not Penumbra) = 2 Withdrew = 1; Group 2 Number missing: 9, Reason: Switched from intervention = 9

Protocol outcome 4: Procedural complications at 90 days
- Actual outcome: Serious adverse events at 90 days; Group 1: 18/43, Group 2: 30/62; Comments: Available case analysis (as treated)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12, Reason: IV tPA alone = 9 Other thrombectomy device (not Penumbra) = 2 Withdrew = 1; Group 2 Number missing: 9, Reason: Switched from intervention = 9

Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage at Define; Length of stay in hospital at Define; Quality of life at Define

Study	THRACE trial: Bracard 2016[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=414)
Countries and setting	Conducted in France; Setting: 26 centres in France
Line of therapy	1st line
Duration of study	Follow up (post intervention): 90 days
Method of assessment of guideline condition	--: Occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confi rmed by CT or magnetic resonance angiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with acute ischaemic stroke were eligible for inclusion if they were aged 18–80 years; had a US National Institutes of Health Stroke Scale (NIHSS) score of 10–25; had an occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confirmed by CT or magnetic resonance angiography; could be administered intra venous thrombolysis within 4 h of symptom onset; and if thrombectomy could be initiated within 5 h of symptom onset.
Exclusion criteria	Patients who had cervical internal carotid artery occlusion and subocclusive stenosis were excluded
Age, gender and ethnicity	Age - Median (IQR): Intervention = 66 (54 - 74) Control 68 (54 - 75). Gender (M:F): Intervention 116/88 Control 104/104. Ethnicity: Not reported
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=208) Intervention 1: Thrombolysis - Alteplase. intravenous thrombolysis as per standard care—ie, 0·9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min. Duration 90 day follow up. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment: (n=204) Intervention 2: Intra-arterial treatment - Thrombectomy plus alteplase. dose/quantity, brand name, extra details. Duration 90 day follow up. Concurrent medication/care: All patients received intravenous thrombolysis as per standard care—ie, 0·9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min, irrespective of group assignment. Initially, patients allocated to the IVTMT group were to be clinically assessed after the completion of intravenous thrombolysis but before angiography. From Oct 12, 2012 All patients received intravenous thrombolysis as per standard care—ie, 0·9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min,

	irrespective of group assignment. Initially, patients allocated to the IVTMT group were to be clinically assessed after the completion of intravenous throm-bolysis but before angiography. From Oct 12, 2012 Furthermore, practitioners had to show proof of performance of at least five interventions with a given system before using it in the trial. A complementary intra-arterial injection of a maximum of 0·3 mg/kg of alteplase at the end of thrombectomy was authorised only in cases of persistent distal occlusions. Use of conscious sedation or general anaesthesia was left to the judgment of the interventional neuroradiologist. Indirectness: No indirectness Further details: 1. General anaesthetic: 2. Imaging: 3. Time from symptom onset to treatment:
Funding	Academic or government funding (This study was funded by the French Ministry for Health as part of its 2009 STIC programme for the support of costly innovations (grant number 2009 A00753-54).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THROMBECTOMY PLUS ALTEPLASE versus ALTEPLASE

Protocol outcome 1: Mortality at 90 days
- Actual outcome: Mortality at 90 days; Group 1: 24/202, Group 2: 27/206
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Masking of investigators and patients was not feasible because of the nature of the intervention.; Group 1 Number missing: 2, Reason: 2 = Lost to follow up ; Group 2 Number missing: 2, Reason: 2 = Lost to follow up

Protocol outcome 2: Modified Rankin Scale at 90 days
- Actual outcome: mRS 0-2 at 90 days; Group 1: 106/200, Group 2: 85/202
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Masking of investigators and patients was not feasible because of the nature of the intervention.; Group 1 Number missing: 4, Reason: 2 = Lost to follow up 2 = missing data; Group 2 Number missing: 6, Reason: 2 = Lost to follow up 4 = missing data
- Actual outcome: mRS ordinal shift at 90 days; OR; 1.39 (95%CI 0.99 to 1.97);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Masking of investigators and patients was not feasible because of the nature of the intervention.; Group 1 Number missing: 4, Reason: 2 = Lost to follow up 2 = missing data; Group 2 Number missing: 6, Reason: 2 = Lost to follow up 4 = missing data

Protocol outcome 3: Symptomatic intracranial haemorrhage at 90 days
- Actual outcome: Symptomatic intracranial haemorrhage at 24 hours; Group 1: 4/185, Group 2: 3/192
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Masking of investigators and patients was not

feasible because of the nature of the intervention.; Group 1 Number missing: 19, Reason: 2 = Lost to follow up 17 = missing data; Group 2 Number missing: 16, Reason: 2 = Lost to follow up 14 = missing data Protocol outcome 4: Quality of life at 90 days - Actual outcome: EQ-5D at 90 days; Group 1: mean 0.533 (SD 0.4); n=130, Group 2: mean 0.515 (SD 0.39); n=130 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Masking of investigators and patients was not feasible because of the nature of the intervention.; Group 1 Number missing: 74, Reason: 2 = Lost to follow up 76 = missing data or did not respond to EQ-5D; Group 2 Number missing: 78, Reason: 2 = Lost to follow up 76 = missing data or did not respond to EQ-5D	
Protocol outcomes not reported by the study	Mortality at 1 year; Modified Rankin Scale at 1 year; Intracerebral haemorrage; Procedural complications; Length of stay in hospital

D2. Posterior circulation stroke (observational studies)

No studies were identified

Appendix E: Forest plots and ordinal shift graphs

E.1 Anterior circulation stroke

E.1.1 Thrombectomy versus thrombolysis or best medical practice

Figure 3: Mortality at 90 days

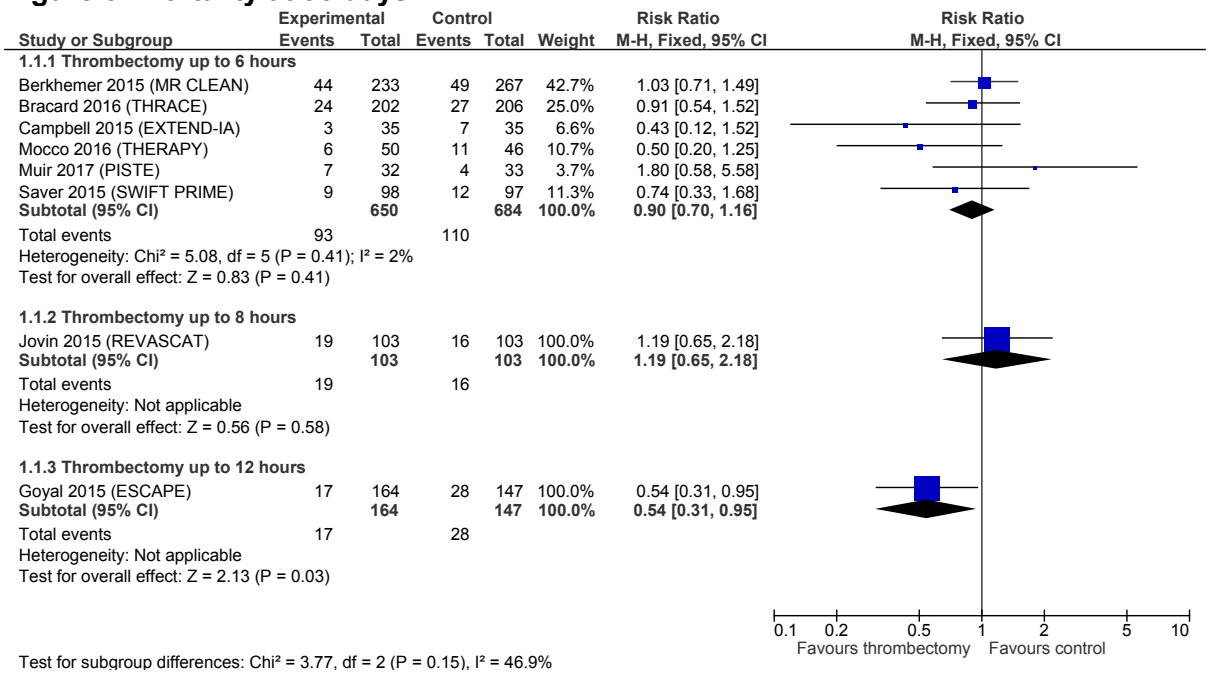


Figure 4: Mortality at 90 days

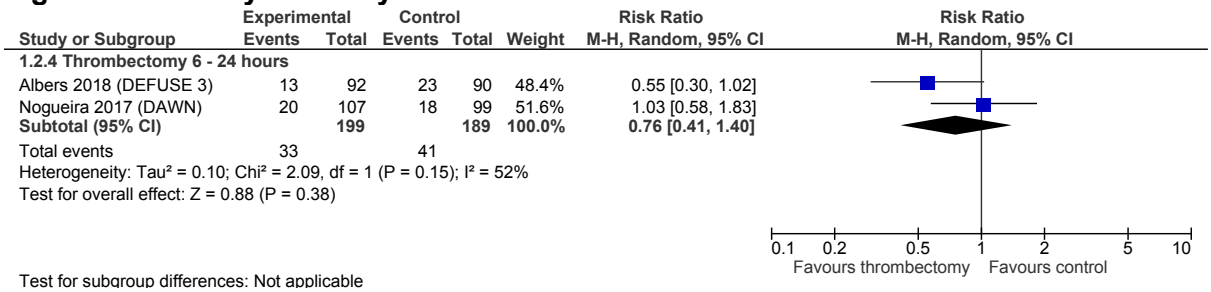


Figure 5: Mortality at 1 year (thrombectomy up to 8 hours)

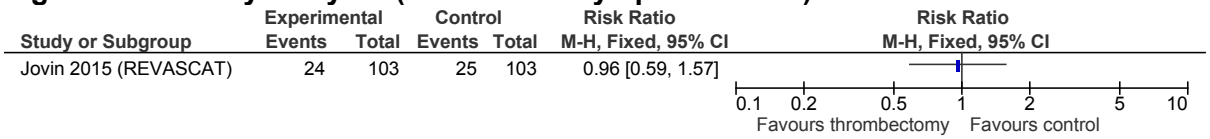
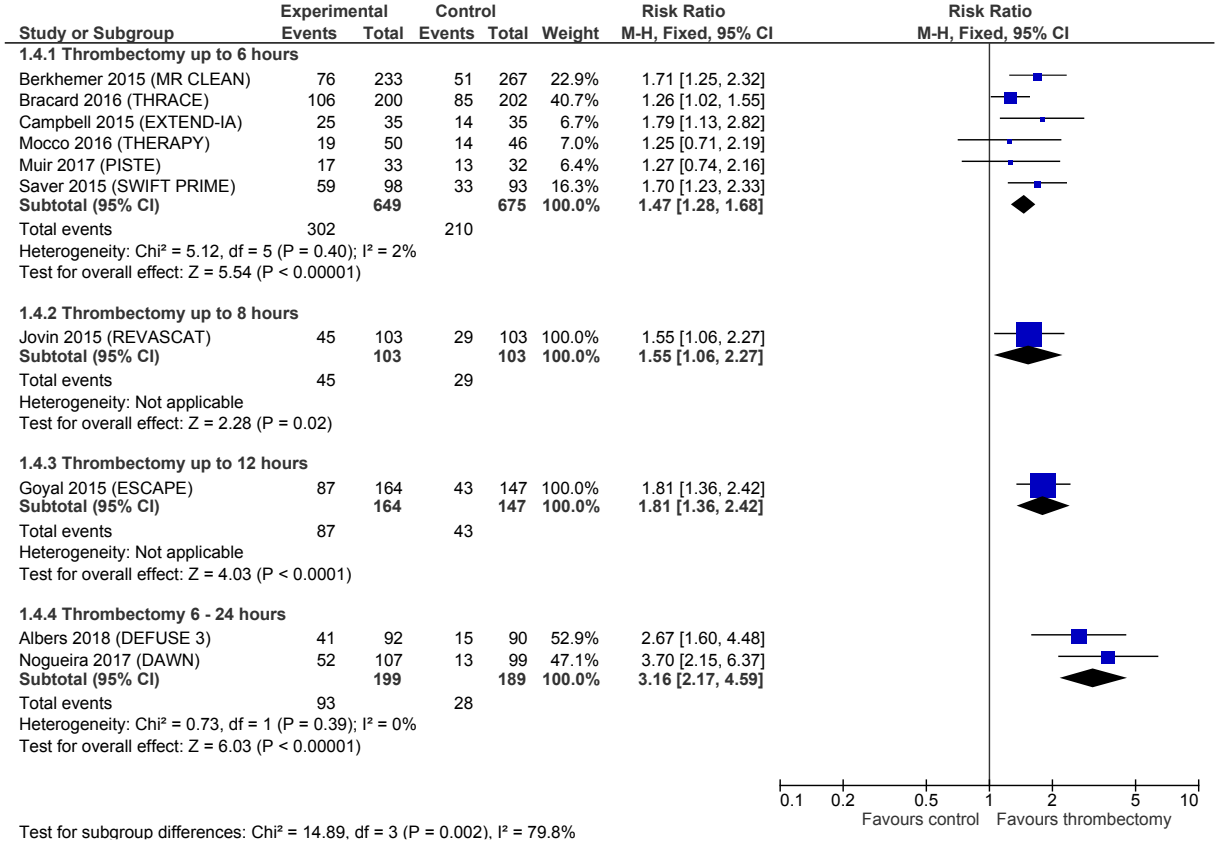


Figure 6: Modified Rankin Scale (0 - 2) at 90 days.



Test for subgroup differences: Chi² = 14.89, df = 3 (P = 0.002), I² = 79.8%

Figure 7: Modified Rankin Scale (0 - 2) at 1 year (thrombectomy up to 8 hours).

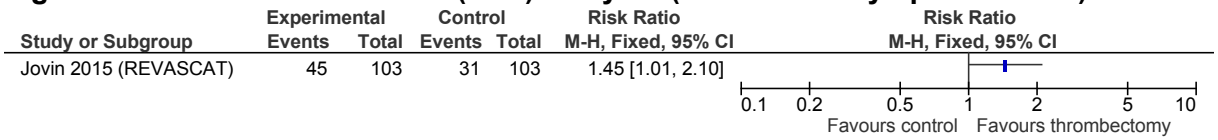
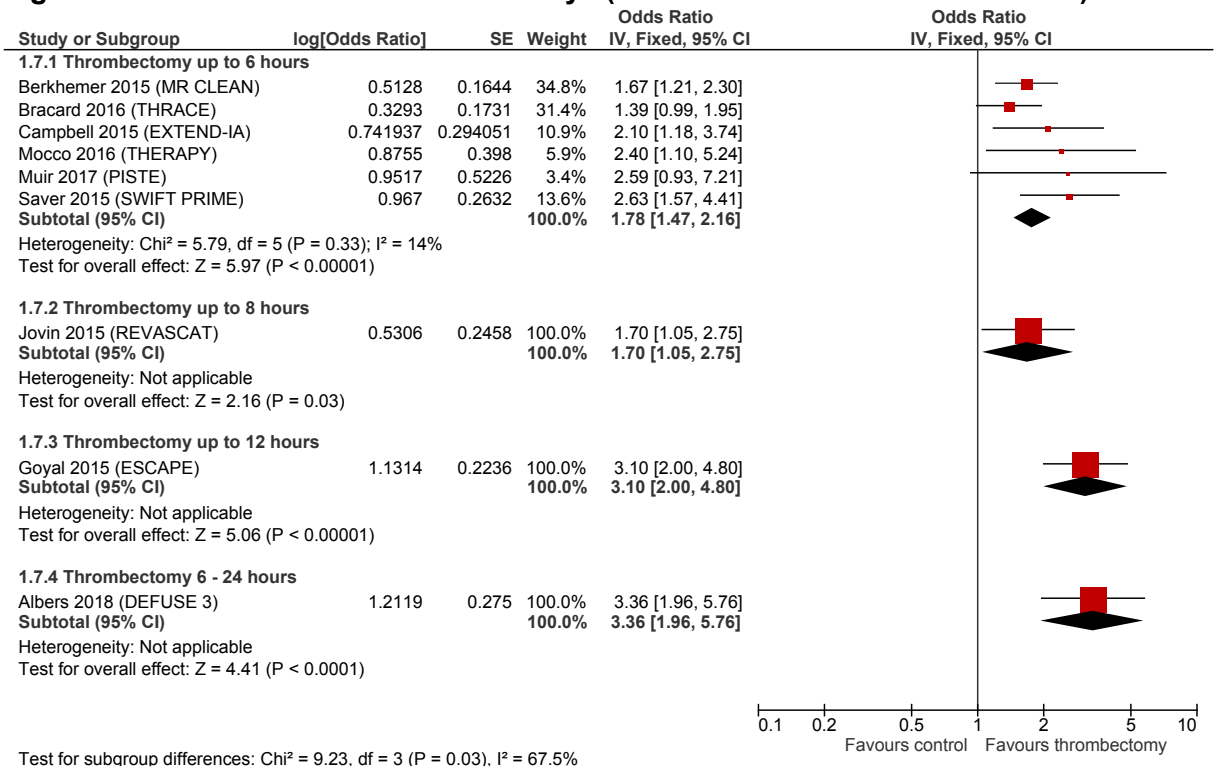
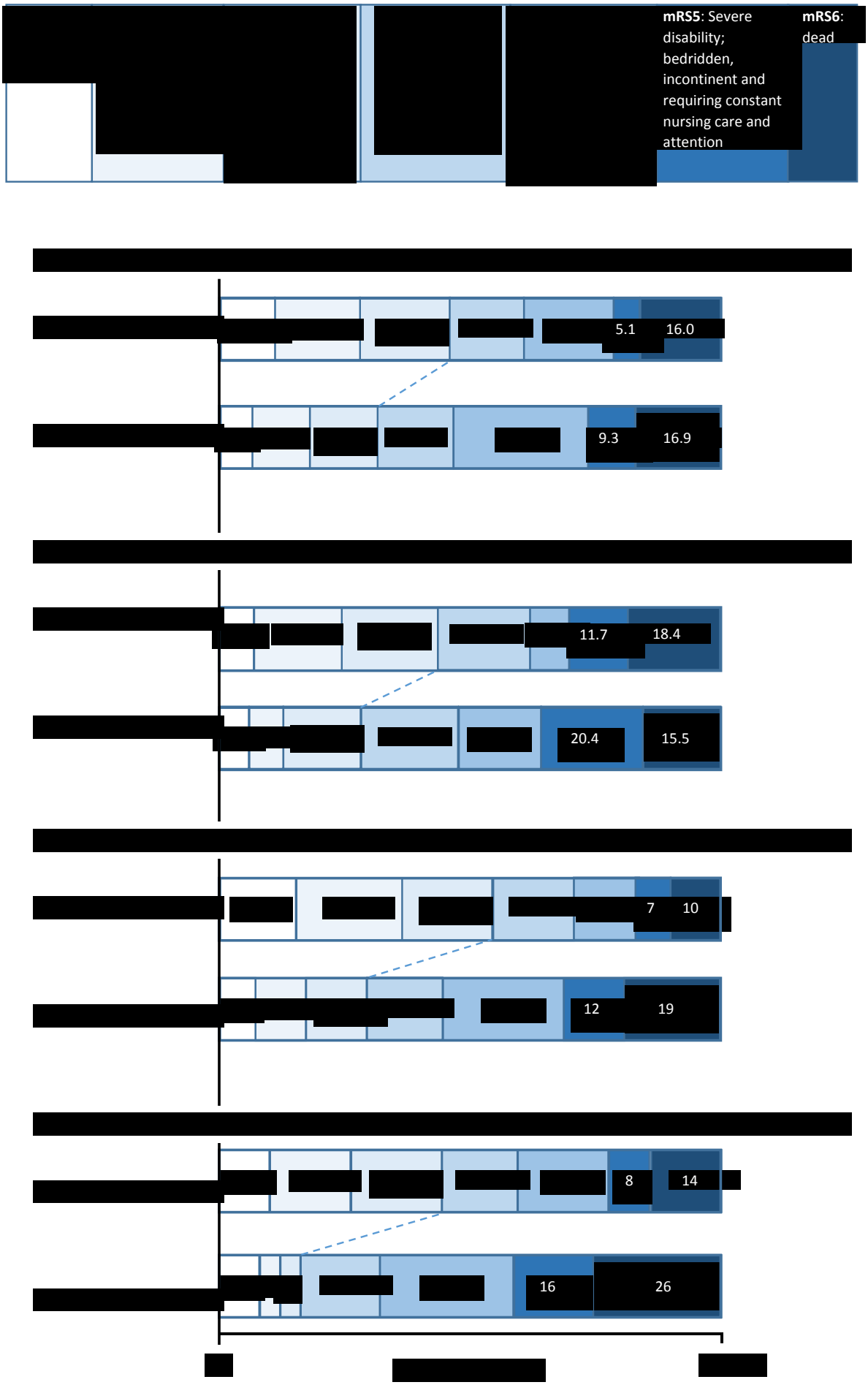


Figure 8: Modified Rankin Scale at 90 days (ordinal shift common odds ratios).



Test for subgroup differences: Chi² = 9.23, df = 3 (P = 0.03), I² = 67.5%

Figure 9: Modified Rankin Scale at 90 days (ordinal shift graphs)



1

Figure 10: Modified Rankin Scale at 1 year (thrombectomy up to 8 hours).

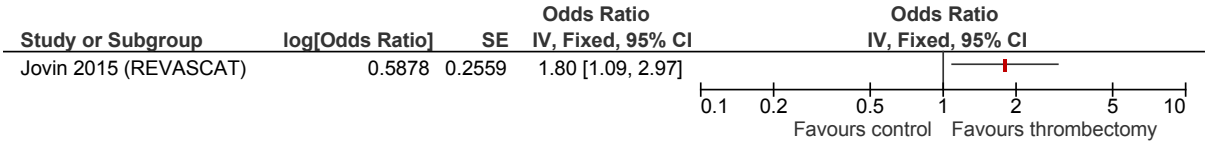


Figure 11: Symptomatic intracranial haemorrhage at 90 days.

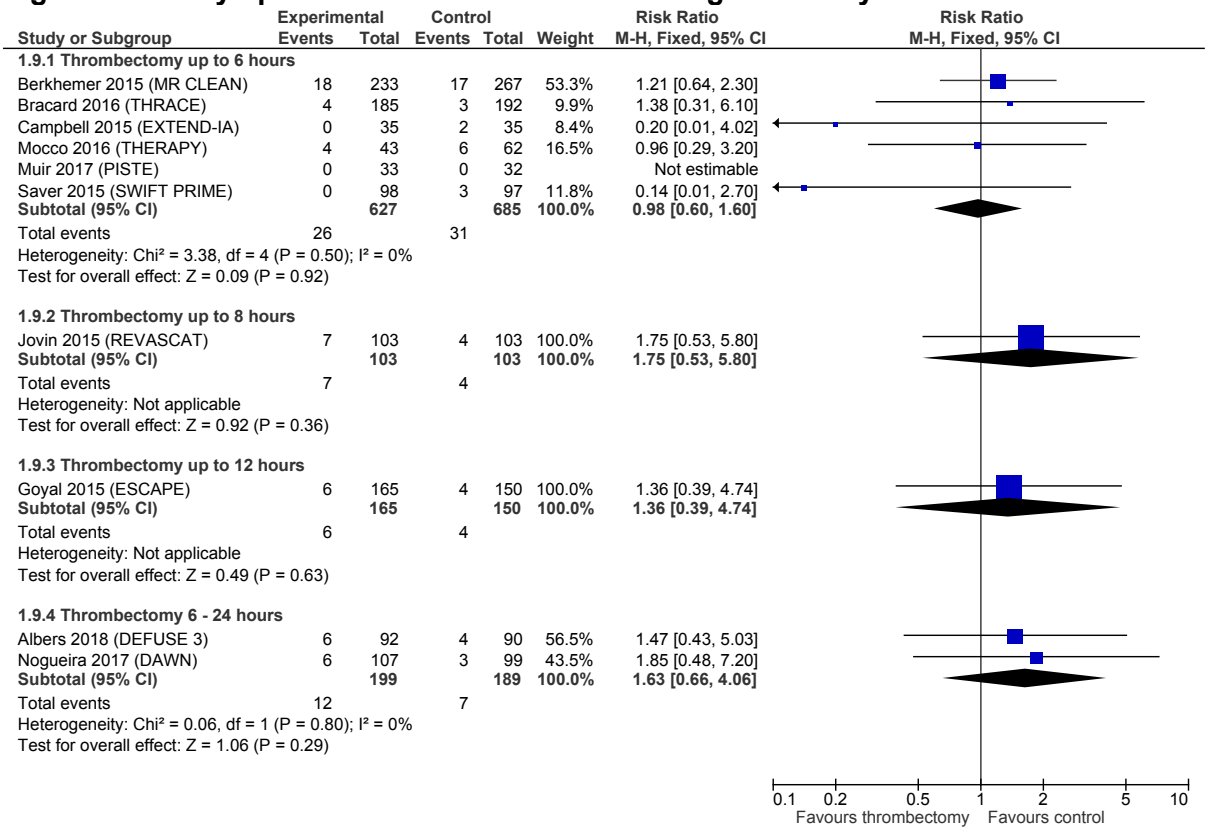


Figure 12: Intracerebral haemorrhage at 90 days (thrombectomy up to 6 hours).

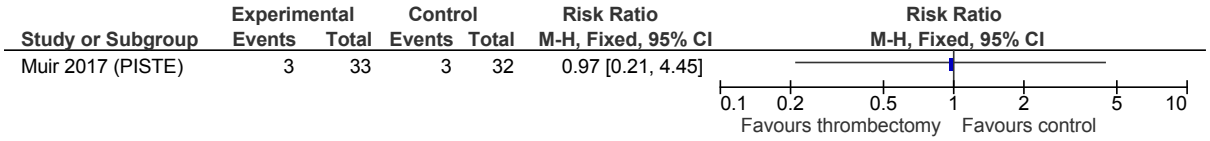


Figure 13: Recurrent stroke at 90 days (thrombectomy up to 8 hours).

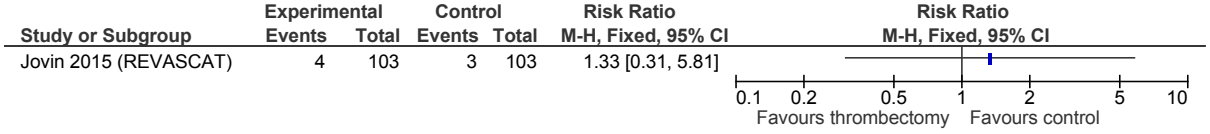


Figure 14: Malignant middle cerebral artery syndrome at 90 days (thrombectomy up to 12 hours).

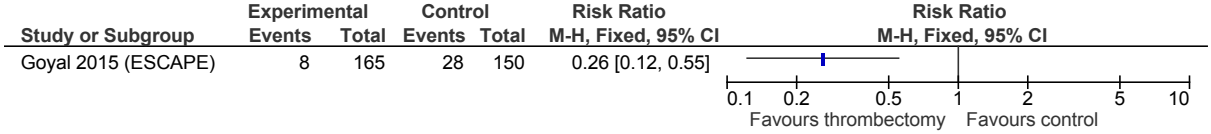


Figure 15: Any serious adverse event at 90 days (thrombectomy up to 6 hours).

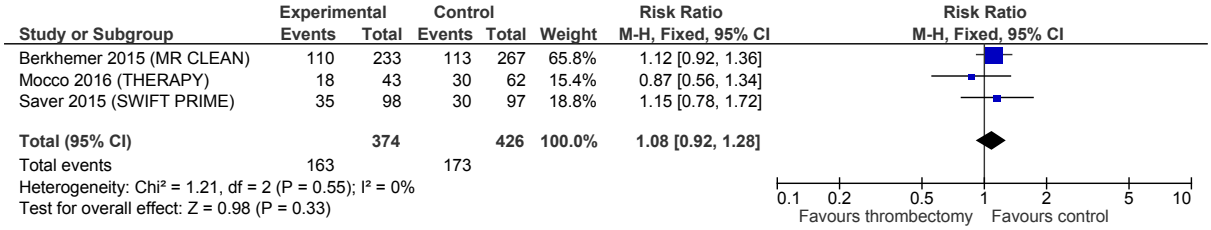


Figure 16: Procedural complications (thrombectomy 6-24 hours).

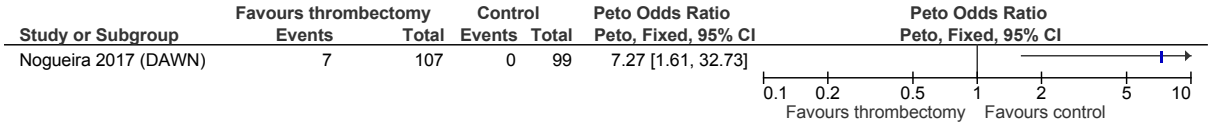
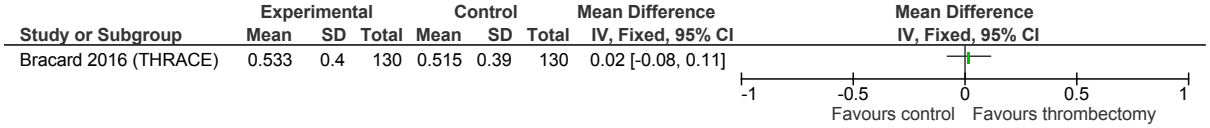


Figure 17: EQ-5D at 90 days (thrombectomy up to 6 hours).



E.21 Posterior circulation stroke

No studies were identified

Appendix F: GRADE tables

F.1 Thrombectomy within 6 hours with or without alteplase versus alteplase or standard medical care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thrombectomy plus medical management	Control	Relative (95% CI)	Absolute		
Mortality at 90 days												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	93/650 (14.3%)	15.7%	RR 0.9 (0.7 to 1.16)	16 fewer per 1000 (from 47 fewer to 25 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin Scale (0 - 2) 90 days												
6	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	302/649 (46.5%)	37.7%	RR 1.47 (1.28 to 1.68)	177 more per 1000 (from 106 more to 256 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin Scale at 90 days (Better indicated by higher values)												
6	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	649	675	Common OR 1.78 (1.47 to 2.16)[3]	-	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic intracranial haemorrhage at 90 days												

6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	26/627 (4.1%)	4.4%	RR 0.98 (0.6 to 1.6)	1 fewer per 1000 (from 18 fewer to 26 more)	⊕⊕OO LOW	IMPORTANT
Intracerebral haemorrhage												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/33 (9.1%)	9.4%	RR 0.97 (0.21 to 4.45)	3 fewer per 1000 (from 74 fewer to 324 more)	⊕⊕OO LOW	IMPORTANT
Any serious adverse event at 90 days												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	163/374 (43.6%)	42.3%	RR 1.08 (0.92 to 1.28)	34 more per 1000 (from 34 fewer to 118 more)	⊕⊕⊕O MODERATE	IMPORTANT
EQ-5D at 90 days (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	130	130	-	MD 0.02 higher (0.08 lower to 0.11 higher)	⊕⊕⊕O MODERATE	IMPORTANT
EQ-5D at 90 days (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	233	267		The median EQ-5D at 90 days in the intervention group was 0.03 higher	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] One study provided an odds ratio adjusted for age, NIHSS at baseline, time from stroke onset to randomisation, prior stroke, atrial fibrillation, diabetes mellitus and internal carotid artery terminus occlusion; the second study (23.8% weight) was an unadjusted estimate.
[4] Adjusted for age, NIHSS at baseline, time from stroke onset to randomisation, prior stroke, atrial fibrillation, diabetes mellitus and internal carotid artery terminus occlusion.
[5] Imprecision could not be assessed because non-parametric statistics were reported.

F.2 Thrombectomy within 8 hours with or without alteplase versus alteplase or standard medical care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thrombectomy plus medical management	Control	Relative (95% CI)	Absolute		
Mortality at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	19/103 (18.4%)	15.5%	RR 1.19 (0.65 to 2.18)	29 more per 1000 (from 54 fewer to 183 more)	⊕⊕OO LOW	CRITICAL
Mortality at 12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	24/103 (23.3%)	24.3%	RR 0.96 (0.59 to 1.57)	10 fewer per 1000 (from 100 fewer to 139 more)	⊕⊕OO LOW	CRITICAL
Modified Rankin Scale (0 - 2) 90 days												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	45/103 (43.7%)	28.2%	RR 1.55 (1.06 to 2.27)	155 more per 1000 (from 17 more to 358 more)	⊕⊕OO LOW	CRITICAL
Modified Rankin Scale (0 - 2) at 1 year												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	45/103 (43.7%)	30.1%	RR 1.45 (1.01 to 2.1)	135 more per 1000 (from 3 more to 331	⊕⊕OO LOW	CRITICAL

										more)		
Modified Rankin Scale at 90 days (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	103	103	Common OR 1.7 (1.05 to 2.78)[3]	-	⊕⊕OO LOW	CRITICAL
Modified Rankin Scale at 1 year (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	103	103	Common OR 1.80 (1.09 to 2.99)	-	⊕⊕OO LOW	CRITICAL
Symptomatic intracranial haemorrhage at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/103 (6.8%)	3.9%	RR 1.75 (0.53 to 5.8)	29 more per 1000 (from 18 fewer to 187 more)	⊕⊕OO LOW	IMPORTANT
Recurrent stroke at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/103 (3.9%)	2.9%	RR 1.33 (0.31 to 5.81)	10 more per 1000 (from 20 fewer to 139 more)	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	103	103		The median EQ-5D at 90 days in the intervention group was 0.33 higher	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[3]Adjusted for minimisation factors (NIHSS, therapeutic window, occlusion site and participating centre) and alteplase use.
4 Imprecision could not be assessed because non-parametric statistics were reported.

F.3 Thrombectomy within 12 hours with or without alteplase versus alteplase or standard medical care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thrombectomy plus medical management	Control	Relative (95% CI)	Absolute		
Mortality at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	17/164 (10.4%)	19.1%	RR 0.54 (0.31 to 0.95)	88 fewer per 1000 (from 10 fewer to 132 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin Scale (0 - 2) 90 days												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	87/164 (53%)	29.3%	RR 1.81 (1.36 to 2.42)	237 more per 1000 (from 105 more to 416 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin Scale at 90 days												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	164	147	Common OR 3.1 (2.0 to 4.7)[3]	-	⊕⊕⊕O MODERATE	CRITICAL

Symptomatic intracranial haemorrhage at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/165 (3.6%)	2.7%	RR 1.36 (0.39 to 4.74)	10 more per 1000 (from 16 fewer to 101 more)	⊕⊕OO LOW	IMPORTANT
Malignant middle cerebral syndrome at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/165 (4.8%)	18.7%	RR 0.26 (0.12 to 0.55)	138 fewer per 1000 (from 84 fewer to 165 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
EQ-5D VAS at 90 days (Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	164	147		The median EQ-5D at 90 days in the intervention group was 15 higher	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Adjusted for age, sex, baseline NIHSS, baseline ASPECTS, occlusion location and alteplase use.
4 Imprecision could not be assessed because non-parametric statistics were reported.

F.46 Thrombectomy between 6 - 24 hours onset of symptoms versus standard medical care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Thrombectomy plus medical management**	**Control**	**Relative (95% CI)**	**Absolute**		

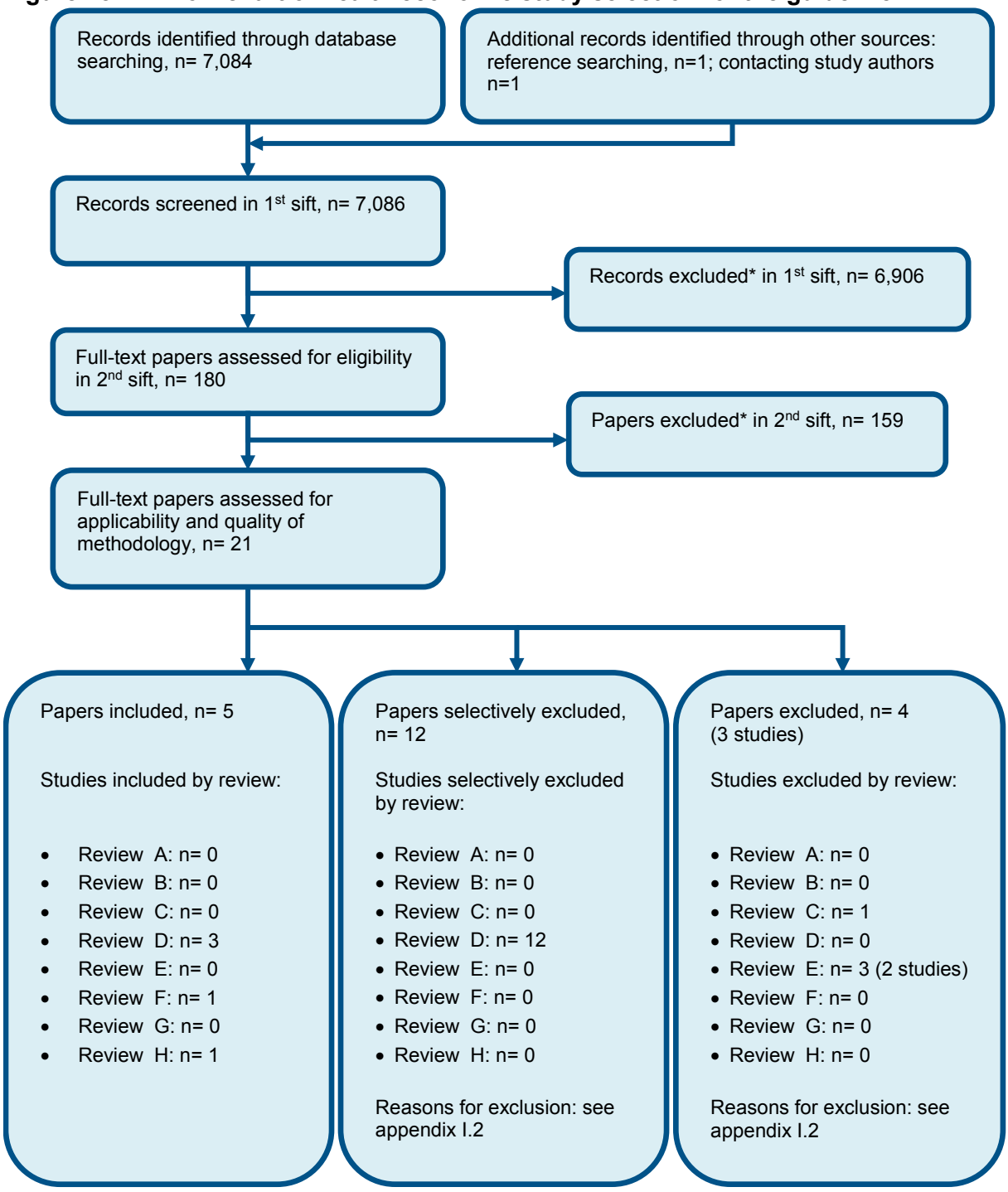
Mortality at 90 days												
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[2]	none	33/199 (16.6%)	21.9%	RR 0.76 (0.41 to 1.40)	53 fewer per 1000 (from 129 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Modified Rankin Scale (0 - 2) 90 days												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	93/199 (46.7%)	14.9%	RR 3.16 (2.17 to 4.59)	322 more per 1000 (from 174 more to 535 more)	⊕⊕⊕O MODERATE	CRITICAL
Modified Rankin Scale at 90 days												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92	90	Common OR 3.36 (1.96 to 5.77)[4]	-	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic intracranial haemorrhage at 90 days												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/199 (6%)	3.7%	RR 1.63 (0.66 to 4.06)	23 more per 1000 (from 13 fewer to 113 more)	⊕⊕OO LOW	IMPORTANT
Procedural complications												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/107 (6.5%)	0%	Peto OR 7.27 (1.61 to 32.73)	-	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 increment for unexplained heterogeneity with I^2 >50%

[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Odds ratio adjusted for stratification factors (age, core infarct volume, time from symptom onset to enrolment, baseline NIHSS, and trial site.

Appendix G: Health economic evidence selection

Figure 18: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Abou-Chebl 2015[1]	Incorrect population: not proven large vessel occlusion on non-invasive angiography
Akins 2014[3]	Published prior to 2015
Al-Ajlan 2016[4]	Incorrect study design: secondary analysis with no relevant outcomes
Albers 2015[5]	Incorrect study design: secondary analysis with no relevant outcomes
Ali Raza 2017[8]	Incorrect interventions
Andersson 2013[9]	Inappropriate comparison: all had mechanical thrombectomy
Assis 2018[12]	Incorrect study design: secondary analysis with no relevant outcomes
Baek 2014[13]	Inappropriate comparison: all had mechanical thrombectomy.
Becktepe 2011[14]	Published prior to 2015
Broderick 2015[18]	Pooled analysis: individual studies included
Broussalis 2013[19]	Incorrect study design: observational and no adjustment for confounders
Campbell 2016[20]	IPD analysis - individual studies included
Ciccone 2013[24]	Published prior to 2015
Costalat 2011[26]	Inappropriate comparison: all had combination treatment in the posterior circulatory stroke subgroup
Costalat 2012[25]	Inappropriate comparison: all basilar stroke patients received combination treatment
Coutinho 2017[27]	Incorrect study design: posthoc analysis of pre-2015 trials
Dias 2017 [31]	Incorrect population: not proven large vessel occlusion on non-invasive angiography
Diener 2015[32]	Not English language (German)
Dorn 2012[34]	Inappropriate comparison: all had mechanical thrombectomy
Dornak 2015[35]	Incorrect interventions
Ecker-Schlipf 2009[36]	Not in English language
Ganesh 2016[39]	Incorrect study design: post hoc analysis of predictors for infarct in a new territory
Gerber 2017[40]	Inappropriate comparison: stent versus aspiration thrombectomy
Gory 2016[41]	Inappropriate comparison: all had mechanical thrombectomy.
Goyal 2016[43]	Systematic review: quality assessment is inadequate and methods are not adequate/unclear
Haussen 2018[44]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory stroke
He 2017[45]	Incorrect study design: non-comparative study
Health Quality Ontario 2016[46]	Systematic review: methods are not adequate/unclear
Heshmatollah 2017[47]	Incorrect population: subgroup analysis of people with atrial

Study	Exclusion reason
	fibrillation
Hong 2016[48]	Incorrect study design
Khatri 2013[52]	Published prior to 2015
Khoury 2017[53]	Incorrect population: not proven large vessel occlusion on non-invasive angiography
Kidwell 2013[55]	Published prior to 2015
Kidwell 2014[54]	Published prior to 2015
Kim 2015[56]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory strokes
Kocher 2014[57]	Not in English language
Kumar 2015[58]	Systematic review: study designs inappropriate and incorrect interventions
Lefevre 2014[59]	Incorrect interventions: all had mechanical thrombectomy
Maier 2017[62]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory stroke
Mazighi 2009[63]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory stroke
Menjot de Champfleur 2017[64]	Incorrect comparison: imaging techniques
Mistry 2017[65]	Systematic review: methods are not adequate/unclear and quality assessment is inadequate
Mordasini 2013[68]	Inappropriate comparison: all had mechanical thrombectomy
Mortimer 2012[69]	Systematic review published prior to 2015.
Mourand 2014[70]	Inappropriate comparison: all had mechanical thrombectomy
Mulder 2016[72]	Incorrect comparison
Nagel 2013[73]	Incorrect interventions: only 20/36 in EVT arm had EVT
Nogueira 2012[77]	Published prior to 2015
Nogueira 2012[78]	Published prior to 2015
O'rourke 2010[79]	Published prior to 2015
Ottomeyer 2012[80]	Incorrect comparison in multivariable analysis
Palesch 2015[81]	Incorrect population: not proven large vessel occlusion on non-invasive angiography
Park 2013[82]	Inappropriate comparison: all had mechanical thrombectomy
Phan 2016[83]	Systematic review: majority of studies included are pre-2015.
Raychev 2015[85]	Incorrect study design
Roth 2011[86]	Inappropriate comparison: all had mechanical thrombectomy
Rouchaud 2011[87]	Systematic review: methods are not adequate/unclear and quality assessment is inadequate
Saver 2012[94]	Incorrect interventions. Published prior to 2015
Saver 2014[93]	Published prior to 2015
Saver 2016[92]	IPD meta-analysis - individual studies included
Schonewille 2007[95]	Published prior to 2015
Schonewille 2009 [96]	Incorrect outcome (1 month follow-up)
Sherman 2000[97]	Published prior to 2015
Sheth 2015[98]	Incorrect study design
Sheth 2016[99]	Incorrect interventions

Study	Exclusion reason
Shi 2010[100]	Published prior to 2015
Singer 2013[102]	Inappropriate comparison: all had mechanical thrombectomy
Singer 2015[101]	Inappropriate comparison: all had mechanical thrombectomy
Smith 2015[103]	Systematic review: quality assessment is inadequate and methods are not adequate/unclear.
Tian 2017[105]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory stroke
Touma 2016[106]	Systematic review: quality assessment is inadequate and methods are not adequate/unclear
Von Kummer 2005[108]	Incorrect interventions
Webb 2012[109]	Inadequate adjustment for confounders
Wen 2017[110]	Incorrect study design: no comparator.
Wyszomirski 2017[111]	Systematic review: study designs inappropriate.
Xianxian 2017[112]	Observational study with no adjustment for confounders and unclear reporting
Yang 2017[114]	Incorrect interventions
Yang 2017 [115]	Incorrect interventions and outcomes.
Yoshimura 2011[116]	Observational study with no adjustment for confounders
Yoshimura 2014[117]	Incorrect population: observational study of a mixed stroke population with no separate analysis for the posterior circulatory stroke
Zaidat 2018[118]	Incorrect study design

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H.2 2 Excluded health economic studies

3 **Table 15: Studies excluded from the health economic review**

Reference	Reason for exclusion
Achit 2017[2]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Aronsson 2016[10]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Arora 2018[11]	This study was assessed as partially applicable with potentially serious limitations. However, the other available evidence was judged to be of greater applicability and methodological quality, and therefore this study was selectively excluded.
Bouvy 2013[16]	This study was assessed as partially applicable with potentially serious limitations. However, the other available evidence was judged to be of greater applicability and methodological quality, and therefore this study was selectively excluded.
Campbell 2017[22]	This study was assessed as partially applicable with potentially serious limitations. However, the other available evidence was judged to be of greater applicability and methodological quality, and therefore this study was selectively excluded.
De Andres-Nogales	This study was assessed as partially applicable with potentially serious limitations. However, the other available evidence was

Reference	Reason for exclusion
2017[29]	judged to be of greater applicability and methodological quality, and therefore this study was selectively excluded.
Health Quality Ontario 2016[46]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Jeong 2017[50]	This study was assessed as partially applicable with potentially serious limitations. However, the other available evidence was judged to be of greater applicability and methodological quality, and therefore this study was selectively excluded.
Ruggeri 2018[88]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Steen Carlsson 2017[104]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Trippoli 2018[107]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.
Xie 2016[113]	This study was assessed as partially applicable with minor limitations. However, the other available evidence was judged to be of greater applicability, and therefore this study was selectively excluded.

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Appendix I: Health economic evidence tables

Study	Ganesalingam 2015[38]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model with Markov state-transition model **Approach to analysis:** Decision analytic model covering three-month acute phase populates three health outcome states of Markov model. States based on predicted mRS scores: independent (mRS≤2), dependent (mRS 3-5), dead (mRS=6). 3 month cycles. If dependent state at 12 months, unable to transition to independent state. If independent state at 12 months, remain independent unless recurrent stroke. Recurrent stroke included (probability not differing between independent and dependent states). **Perspective:** UK NHS **Time horizon/Follow-up:**	**Population:** Patients with acute ischaemic stroke presenting within 6 hours of stroke symptom onset **Cohort settings:** Start age: NR (Cohort estimated using UK stroke national audit- median age for April 2016-March 2017: 77 years) Male: NR (Cohort estimated using UK stroke national audit- % male for April 2016-March 2017: 51.2%) **Intervention 1:** IV-tPA alone **Intervention 2:** IV-tPA and mechanical thrombectomy	**Total costs (mean per patient):** Intervention 1: £32,030 Intervention 2: £39,326 Incremental (2−1): £7,296 (95% CI: NR; p=NR) **Currency & cost year:** 2013-2014 UK pounds **Cost components incorporated:** Medication, average staff costs per hour at pay grade, materials, surgery (microcosted), acute management costs (lengths of stay in Hyper Acute Stroke Unity, Acute High Dependence Unit and rehabilitation ward, supported discharge cost and community care costs), ongoing costs (not detailed). Cost of average recurrent stroke not requiring thrombolysis or thrombectomy.	**QALYs (mean per patient):** Intervention 1: 3.723 Intervention 2: 4.677 Incremental (2−1): 0.954 (95% CI: NR; p=NR) **Deaths averted (per 1000 patients over 20 years):** Intervention 1: 787 Intervention 2: 716 Incremental (2−1): 71 deaths averted (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £7,648 per QALY gained (pa) 95% CI: £5,481-£9,690 per QALY gained Probability Intervention 2 cost effective (£20K/30K threshold): 100%/100% **Analysis of uncertainty:** Results were presented probabilistically. Univariate sensitivity analysis showed that increasing the cost of thrombectomy by 139% and decreasing utilities of independent patients (mRS 0-1-2) from 0.74 to 0.34 would make intervention 2 borderline cost-effective at a threshold of £20,000 per QALY.

lifetime (20 years) **Treatment effect duration:**(a) 3 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%				

Data sources

Health outcomes: Meta-analysis of 5 RCTs: [15 42 90 51 21] MR CLEAN, EXTEND IA and SWIFT PRIME studies considered thrombectomy within 6 hours of stroke onset, REVASCAT considered thrombectomy within 8 hours and ESCAPE within 12 hours of stroke onset **Quality-of-life weights:** EQ-5D UK tariff. Utility scores were obtained from the NICE technology assessment on Alteplase for ischaemic stroke [75] and from published literature. ([33, 89]) **Cost sources:** Unit Costs of Health and Social Care, British National Formulary, NICE technology assessment on Alteplase for ischaemic stroke and other published sources [75]

Comments

Source of funding: National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North Thames at Barts Health National Health Service Trust **Limitations:** Components of ongoing costs were not detailed. Start age of those entering the model nor male:female ratio were reported, but as UK stroke national audit data was used to populate the model, these were obtainable. Treatment effect used in study did not include data from THRACE, THERAPY and PISTE RCTs, which were included in the 0-6 hour pre-specified subgroup analysis in the clinical review, [17 66 71] The treatment effect included REVASCAT and ESCAPE RCTs, which were not included in the 0-6 hour pre-specified subgroup analysis as they considered thrombectomy within 8 hours and within 12 hours of stroke onset, respectively. [42 51] **Potential conflict of interest:** One of the authors in employment of Boehringer Ingleheim **Other:** Assumed that all aspects of care, including imaging needs, would be comparable between IV-tPA and mechanical thrombectomy arms, based on the inclusion criteria of the five RCTs from which the treatment effect was derived. The inclusion criteria of the trials specified that those included underwent CT Angiography/MR Angiography in both the mechanical thrombectomy and medical therapy arms to determine if they would benefit from thrombectomy. The population is therefore more refined to those that would benefit from treatment compared to the entire population of people presenting with ischemic stroke within 6 hours of symptom onset.

Overall applicability:(b) Directly Applicable **Overall quality:**(c) Minor limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IV-tPA: intravenous tissue-type plasminogen activator; mRS: modified Rankin Scale; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; RCT: randomised-controlled trial

(a) To extrapolate the treatment effect beyond the treatment effect duration (3 months) to the lifetime horizon (20 years), transition probabilities were obtained from the NICE technology assessment on Alteplase for ischaemic stroke [75]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

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Study	Lobotesis 2016[61]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model with Markov state-transition model **Approach to analysis:** Model consists of acute phase (90 days) and rest-of-life phase (91 days until death). One year cycle lengths. Seven health states are based on mRS 0-6: no symptoms (mRS 0), no clinically significant disability (mRS 1), slight disability (mRS 2), moderate disability (mRS 3), moderately severe disability (mRS 4), severe disability (mRS 5) and death (mRS 6) (death the only absorbing state). Different risks of recurrent stroke apply to the cycle up to 1 year and after the cycles thereafter. Patients remain in 90-day phase until recurrent stroke or death. Adverse events: symptomatic haemorrhage and vasospasm **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] 90 days **Discounting:** Costs: 3.5%;	**Population:** People presenting within 6 hours of ischaemic stroke with confirmed occlusions of proximal anterior intracranial circulation **Cohort settings:** Start age: 66 Male: NR **Intervention 1:** IV t-PA alone **Intervention 2:** IV t-PA and stent retriever thrombectomy	**Total costs (mean per patient):** Intervention 1: £143,512 Intervention 2: £110,322 Incremental (2−1): -£33,190 (95% CI: NR; p=NR) **Currency & cost year:** 2013-2014 UK pounds **Cost components incorporated:** Acute phase costs: medication, staff time, materials, surgery, acute management costs. Rest-of-life phase costs: data from Oxford Vascular Study, additional nursing and residential care costs. Consensus of three clinicians used to calculate long term costs for each mRS score from available data for mRS scores 0-2, 3-4 and 5.	**QALYs (mean per patient):** Intervention 1: 4.70 Intervention 2: 7.01 Incremental (2−1): 2.31 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Dominant (da) 95% CI: NR **Analysis of uncertainty:** Probabilistic sensitivity analysis was undertaken: Probability Intervention 2 cost effective (£20K/30K threshold): 98.6%/99.0% Deterministic sensitivity analysis found that stent retriever thrombectomy + IV t-PA remained cost effective when parameters were varied over a wide range of values. A higher starting age, lower utility values and lower long term costs were found to be key drivers of the model, associated with lower net monetary benefit. A scenario analysis was carried out which included a rehabilitation phase from 90 days to 1 year, during which mRS score could be maintained, improve or deteriorate by 1. The net monetary benefit was £72,883; lower than in the base case but still favourable for stent retriever thrombectomy + IV t-PA.

Outcomes: 3.5%				
Data sources				
Health outcomes: Based on the SWIFT-PRIME trial, [90]. Mortality data were from the 2011-2013 Office of National Statistics Life Tables and from published literature. **Quality-of-life weights:** EQ-5D UK tariff. Utility scores were obtained from the Oxford Vascular Study, UK. **Cost sources:** Treatment and device costs- Medtronic, Unit Costs of Health and Social Care, [75], NHS reference costs, British National Formulary, Information Services Division Scotland. Long term costs- Oxford Vascular Study, with calculations based on consensus of three clinical experts				
Comments				
Source of funding: Medtronic **Limitations:** Health outcomes and treatment effects were based on the SWIFT-PRIME study only, however this allowed the model to use health states based on mRS 0-6. [90]. The male:female ratio of those populating the model was not recorded, but could be elicited from the SWIFT-PRIME population. **Potential conflict of interest:** The study was funded by Medtronic, the manufacturer of Solitaire. Declarations of financial/other relationships with Medtronic, Boehringer Ingelheim and others. **Other:** The inclusion criteria of the SWIFT-PRIME RCT specified that those included underwent CT Angiography/MR Angiography in both the mechanical thrombectomy and medical therapy arms to determine if they would benefit from thrombectomy. The population in the trial is therefore more refined to those that would benefit from treatment compared to the entire population of people presenting with ischemic stroke within 6 hours of symptom onset.				
Overall applicability:(b) Directly applicable		**Overall quality:**(c) Minor limitations		

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IV t-PA: intravenous tissue-type plasminogen activator; mRS: modified Rankin Scale; NR: not reported; QALYs: quality-adjusted life years

(a) To extrapolate the treatment effect beyond the treatment effect duration (90 days) to the lifetime horizon, death and recurrent stroke probabilities were obtained from the literature

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Pizzo, Dumba and Lobotesis 2018 (Confidential draft) [84]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision analytic model with Markov state-transition model **Approach to analysis:** Decision analytic model covering three-month acute phase populates three health outcome states of Markov model. States based on predicted mRS scores: independent (mRS≤2), dependent (mRS 3-5), dead (mRS=6). 3 month cycles. If dependent state at 12 months, unable to transition to independent state. If independent state at 12 months, remain independent unless recurrent stroke or death. Recurrent stroke included (probability not differing between independent and dependent states).	**Population:** People presenting 12, 16 and 24 hours after onset of ischaemic stroke **Cohort settings:** Start age: 70 Male: NR **Intervention 1:** Medical therapy alone (which includes IV-tPA) **Intervention 2:** Medical therapy followed by mechanical thrombectomy	**12 hours after stroke onset: Total costs (mean per patient):** Intervention 1: £27,637 Intervention 2: £29,632 Incremental (2−1): £1,995 (95% CI: -£1,288 - £5,221; p=NR) **16 hours after stroke onset: Total costs (mean per patient):** Intervention 1: £31,705 Intervention 2: £38,621 Incremental (2−1): £6,916 (95% CI: £3,987 - £9,931; p=NR) **24 hours after stroke onset: Total costs (mean per patient):** Intervention 1: £26,846 Intervention 2: £33,312 Incremental (2−1): £6,466 (95% CI: £3,052 - £9,914; p=NR) **Currency & cost year:** 2017 UK pounds **Cost components incorporated:** IV-tPA medication (assuming average weight 76kg), average staff costs per hour at pay grade, materials, surgery (microcosted), acute management costs (lengths of stay in Hyper Acute Stroke Unity,	**12 hours after stroke onset: QALYs (mean per patient):** Intervention 1: 3.07 Intervention 2: 4.69 Incremental (2−1): 1.63 (95% CI: 0.76 – 2.47; p=NR) **16 hours after stroke onset: QALYs (mean per patient):** Intervention 1: 3.12 Intervention 2: 4.81 Incremental (2−1): 1.69 (95% CI: 0.95 – 2.39; p=NR) **24 hours after stroke onset: QALYs (mean per patient):** Intervention 1: 2.32 Intervention 2: 4.56 Incremental (2−1): 2.23 (95% CI: 1.49 – 2.96; p=NR) **Deaths averted (per 1000 patients over 20 years) (da):** Intervention 1: 875 deaths Intervention 2: 732 deaths Incremental (2−1): 143 deaths averted (95% CI: NR; p=NR)	**12 hours after stroke onset: ICER (Intervention 2 versus Intervention 1):** £1,227 per QALY gained (pa) 95% CI: Dominant - £2,876 per QALY gained **16 hours after stroke onset: ICER (Intervention 2 versus Intervention 1):** £4,103 per QALY gained (pa) 95% CI: £2,417 - £6,214 per QALY gained **24 hours after stroke onset: ICER (Intervention 2 versus Intervention 1):** £2,894 per QALY gained (pa) 95% CI: £1,588 - £4,311 per QALY gained **Analysis of uncertainty:** Probabilistic sensitivity analysis was undertaken. The probability thrombectomy was cost effective was 99.9% at both the £20,000 and £30,000 per QALY willingness to pay threshold. Univariate sensitivity analysis showed that the cost of thrombectomy must exceed

Perspective: UK NHS **Time horizon/Follow-up:** lifetime (20 years) **Treatment effect duration:**(a) 3 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%		Acute High Dependence Unit and rehabilitation ward, supported discharge cost and community care costs), ongoing costs (not detailed). Cost of average recurrent stroke not requiring thrombolysis or thrombectomy.		£35,518 using the DAWN trial data at 12 hours, £33,185 using the DEFUSE 3 trial data at 16 hours and £43,140 using the DAWN trial data at 24 hours to be borderline cost effective at a threshold of £20,000 per QALY gained.
Data sources				
Health outcomes: Treatment effects at 12 and 24 hours from DAWN RCT and at 16 hours from DEFUSE 3 RCT. [7, 76] **Quality-of-life weights:** EQ-5D UK tariff. Utility scores were obtained from the literature: NICE technology assessment on Alteplase for ischaemic stroke [75] and from published literature ([33, 89]) [49] **Cost sources:** Unit Costs of Health and Social Care, Ganesalingam et al 2015, NICE technology assessment on Alteplase for ischaemic stroke. [38 75]				
Comments				
Source of funding: National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North Thames at Barts Health National Health Service Trust **Limitations:** Components of ongoing costs not detailed. **Potential conflict of interest:** None **Other:** The inclusion criteria of the DAWN and DEFUSE-3 RCTs specified that those included underwent perfusion imaging in both the mechanical thrombectomy and medical therapy arms to determine if they would benefit from thrombectomy. The population in the trials is therefore more refined to those that would benefit from treatment compared to the entire population of people presenting with ischaemic stroke after 6 hours of symptom onset. Different device costs have been applied to the different time points, according to the trial data which was incorporated, as DEFUSE 3 used a stent retriever (£6,486) in 80% of cases whereas DAWN used Trevo® device in all cases (£4,952). For the 16 hour time point, it was assumed every patient was treated with Solitaire® rather than 80% treated with a stent retriever,however this conservative assumption is not likely to bias the results in favour of the intervention as Solitaire® is more expensive. In the DAWN trial, 5% of patients in the intervention arm had IV-tPA compared with 13% in the control arm so the cost was weighted accordingly.				
Overall applicability:(b) Directly Applicable **Overall quality:**(c) Minor limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; IV-tPA: intravenous tissue-type plasminogen activator; mRS: modified Rankin Scale; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; RCT: randomised-controlled trial

(a) To extrapolate the treatment effect beyond the treatment effect duration (3 months) to the lifetime horizon (20 years), transition probabilities were obtained from the NICE technology assessment on Alteplase for ischaemic stroke and published literature [33, 75, 89]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

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