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Mechanical thrombectomy with retrievable stents and aspiration catheters for acute ischaemic stroke: a meta-analysis of randomised controlled trials

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KEYWORDS

- ischaemic stroke
- stent retrievers
- thrombectomy

Abstract

Background: Retrievable stents and aspiration catheters have been developed to provide more effective arterial recanalisation in acute ischaemic stroke.

Aims: The aim of this analysis was to test the effect of mechanical thrombectomy on mortality and long-term neurological outcome in patients presenting with acute large-vessel anterior circulation ischaemic stroke.

Methods: A structured search identified randomised controlled trials of thrombectomy (using a retrievable stent or aspiration catheter) versus control on a background of medical therapy which included intravenous thrombolysis if appropriate. The primary endpoint was disability at 90-day follow-up as assessed by the modified Rankin scale (mRS). Secondary endpoints included all-cause mortality and symptomatic intracranial haemorrhage. A Bayesian mixed-effects model was used for analysis.

Results: Twelve trials met the inclusion criteria, comprising a total of 1,276 patients randomised to thrombectomy and 1,282 patients to control. Randomisation to thrombectomy significantly reduced disability at 90 days (odds ratio [OR] 0.52, 95% credible interval [CrI] 0.46 to 0.61, probability$_{(\text{control better})}$<0.0001). Furthermore, thrombectomy reduced the odds of functional dependence at 90 days, indicated by an mRS score >2 (OR 0.44, CrI 0.37 to 0.52, p<0.0001). Thrombectomy reduced all-cause mortality at 90 days (16.1% vs 19.2%, OR 0.81, 95% CrI 0.66 to 0.99, p=0.024). The frequency of symptomatic intracranial haemorrhage was similar between thrombectomy (4.2%) and control (4.0%) (OR 1.12, 95% CrI 0.76 to 1.68, p=0.72).

Conclusions: In patients with an acute anterior circulation stroke, modern device thrombectomy significantly reduces death and subsequent disability. The magnitude of these effects suggests that universal access to this treatment strategy should be the standard of care.

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Abbreviations

CrI	credible interval
ICH	intracranial haemorrhage
mRS	modified Rankin scale
NNT	number needed to treat
RCT	randomised controlled trial
tPA	tissue plasminogen activator

Introduction

The holy grail of treatment in acute ischaemic stroke caused by large vessel occlusion is prompt removal of the thrombus obstructing the cerebral artery to minimise permanent brain injury. This has become possible with the development of cerebral artery aspiration catheters and retrievable stents.

Acute ischaemic stroke accounts for 2.7 million deaths annually and is the leading cause of severe long-term disability in adults worldwide[1]. Administration of intravenous tissue plasminogen activator (IV-tPA) within 4.5 hours of symptom onset reduces subsequent disability, is first-line medical therapy, and is an established treatment target for healthcare systems globally[2]. However, IV-tPA does not achieve recanalisation in the majority of cases: success varies according to the length and composition of the occlusion, and long-term disability remains common[3].

In stroke caused by large vessel occlusion, higher rates of revascularisation have been reported when mechanical thrombectomy is used in addition to thrombolysis[4]. The advantage arises because mechanical extraction is more effective at removing established thrombus which is resistant to enzymatic destruction through fibrinolysis. The addition of thrombectomy may therefore allow treatment to be effective over a broader time window from symptom onset, thereby providing effective therapy to patients who may otherwise achieve a poor result, or even be contraindicated, from thrombolytics.

Aspiration catheter techniques for acute ischaemic stroke apply negative pressure to suction the thrombus through or into a dedicated neurothrombectomy catheter. Retrievable stents consist of a self-expanding mesh which is deployed alongside the thrombus, ensnaring the clot within its struts, which is then retrieved into the catheter. Both techniques may be used with or without thrombolysis, and crossover between these technologies is common in clinical practice.

In 2016, the HERMES collaboration published a pooled patient-level analysis of the first five randomised controlled trials (RCTs) of thrombectomy using second-generation devices[5]. This confirmed that thrombectomy reduced disability at 90-day follow-up, albeit in a narrow patient population. We have conducted an updated meta-analysis which permits consolidation of subsequent RCTs which have covered a range of devices[6], applied increasingly pragmatic protocols suitable for real-world service conditions[7,8], and also provided focus on patients presenting late (up to 24 hours) after stroke onset[9,10]. By synthesising these data, we have been able to calculate a contemporary, real-world, estimate of the effect size of thrombectomy for stroke, and test whether any benefits extend to a reduction in all-cause mortality.

Editorial, see page 1367

Methods

SEARCH STRATEGY

We performed a structured search of PubMed to identify all RCTs in any language which assigned patients to thrombectomy or control for the treatment of acute anterior circulation stroke, on a background of medical therapy, which could include intravenous thrombolysis. We searched for trials between January 2010 and July 2020. The search string is available in **Supplementary Appendix 1**.

The search was conducted independently by two investigators (C.A. Rajkumar and S. Ganesananthan) and the senior investigator (M. Shun-Shin) arbitrated any discrepancies.

INCLUSION AND EXCLUSION CRITERIA

We included any RCT which examined the effect of thrombectomy in addition to best medical therapy. This included the use of intravenous thrombolysis if appropriate. The use of any second-generation neurothrombectomy device (retrievable stent or aspiration catheter) was permitted. We excluded trials in which only a minority (<50%) of the thrombectomy group received thrombectomy with retrievable stents, aspiration catheters or a combination of the two (for example, trials which permitted wire manipulation in isolation as the thrombectomy technique).

ENDPOINTS

The primary efficacy endpoint for this meta-analysis was disability as assessed by the 90-day modified Rankin scale (mRS). The mRS is a validated 7-point scale of disability and dependence in activities of daily living for patients following stroke[11]. Higher grades indicate greater degrees of disability, where a score of 0 is equivalent to no symptoms at all, and 6 is equivalent to death. We additionally reported a dichotomised outcome from the mRS, which categorised an independent functional outcome (mRS ≤2) or a dependent outcome (mRS >2). The secondary efficacy endpoint was all-cause mortality at 90-day follow-up. The primary safety endpoint was the occurrence of symptomatic intracranial haemorrhage.

DATA ABSTRACTION AND ANALYSIS

Two authors (C.A. Rajkumar and S. Ganesananthan) independently abstracted the data from eligible studies and these data were verified by the senior author (M. Shun-Shin). For each trial, the number of patients in each mRS category at 90-day follow-up was abstracted from the intervention and control arms using the reported intention-to-treat analysis. This allowed us to construct, for each trial, a table with individual patient mRS scores that could be used to recreate the original analysis, rather than relying on a single summary effect size (such as a single odds ratio [OR] or mean difference) for each trial. We did not have access to the patient baseline covariates (e.g., time to reperfusion) that would allow the assessment of the impact of these on the effect size.

For the mRS endpoint, a Bayesian ordinal regression model was constructed for the individual patient's mRS score. For the death and symptomatic intracranial haemorrhage endpoints,

a Bayesian logistic regression model was constructed. Bayesian methods have multiple advantages over frequentist approaches. In addition to allowing external information or beliefs to be captured and made clear using prior distributions, they also allow direct probability statements to be made about parameters or their combinations[12].

All models included a randomisation arm as a fixed effect and the trial as a random intercept, without random slope. The model family was binomial with the logit link function – four chains with 5,000 burn-in iterations and 5,000 post burn-in iterations. Effect sizes, 95% credible intervals, and probabilities that the effect was greater than 0 were calculated. Package default priors (normal distributions with a standard deviation of 100 on coefficients, and exponential distribution with a mean of 1 on the random effects) were used. For familiarity we present the probability that the control arm had a better outcome than the intervention. Forest plots were generated for the individual trials and summary effect.

For reader familiarity, we present an I^2 equivalent statistic as a measure of heterogeneity. This was calculated from the effect sizes and standard errors from a Bayesian ordinal analysis of the individual trials and our model effect size.

Whilst the "number needed to treat" (NNT) has statistical and conceptual limitations[13], we present the NNT for disability and mortality as the inverse of the absolute rate reduction of the raw data to allow comparison with other reports.

A sensitivity analysis was generated to assess the impact of the prior on the primary endpoint **(Supplementary Table 1, Supplementary Table 2)** and the secondary endpoint of all-cause mortality **(Supplementary Table 3, Supplementary Table 4)**.

Publication bias for the primary endpoint was assessed with the construction of a funnel plot and asymmetry was assessed with Egger's test[14].

All analysis was performed on the statistical programming environment R[15] using the "rms" package (with the "blrm" function) for modelling and the "tidyverse" set of packages.

Individual RCTs were critically appraised using the Cochrane risk of bias tool[16] by two authors (C.A. Rajkumar and S. Ganesananthan), and results are reported in line with PRISMA guidance[17].

Results

SEARCH RESULTS

The results of the search strategy are shown in **Figure 1**.

Characteristics of eligible studies are summarised in **Table 1**.

Twelve trials[6-10,18-24] were eligible, comprising 2,558 patients. A total of 1,276 patients were randomised to thrombectomy and 1,282 to control. Patients in both the thrombectomy and control arms were also allowed to receive thrombolysis if indicated. The majority of trials aimed to recruit patients with a time from symptom onset to delivery of thrombectomy of less than eight hours. Two trials recruited patients with delayed presentation (up to 16[10] and 24[9] hours) from the time they were last known to be well; the majority of these patients were ineligible for IV thrombolysis. Excluding these trials, the median duration from symptom onset to groin puncture was 245 (224-259) minutes.

Median National Institutes of Health Stroke Scale (NIHSS) scores ranged from 16 to 18 in the thrombectomy arm and 14 to 20 in the control arm. The number of patients randomised to thrombectomy who received an attempt at thrombectomy with a dedicated device was 86.4% (1,103/1,276), in whom a retrievable stent (alone or in combination with another device) was used in 87.7% (967/1,103).

Three trials did not meet eligibility criteria for our main analysis, MR-RESCUE[25], IMS III[26] and SYNTHESIS Expansion[27]. In each case only a minority of patients were treated with a retrievable

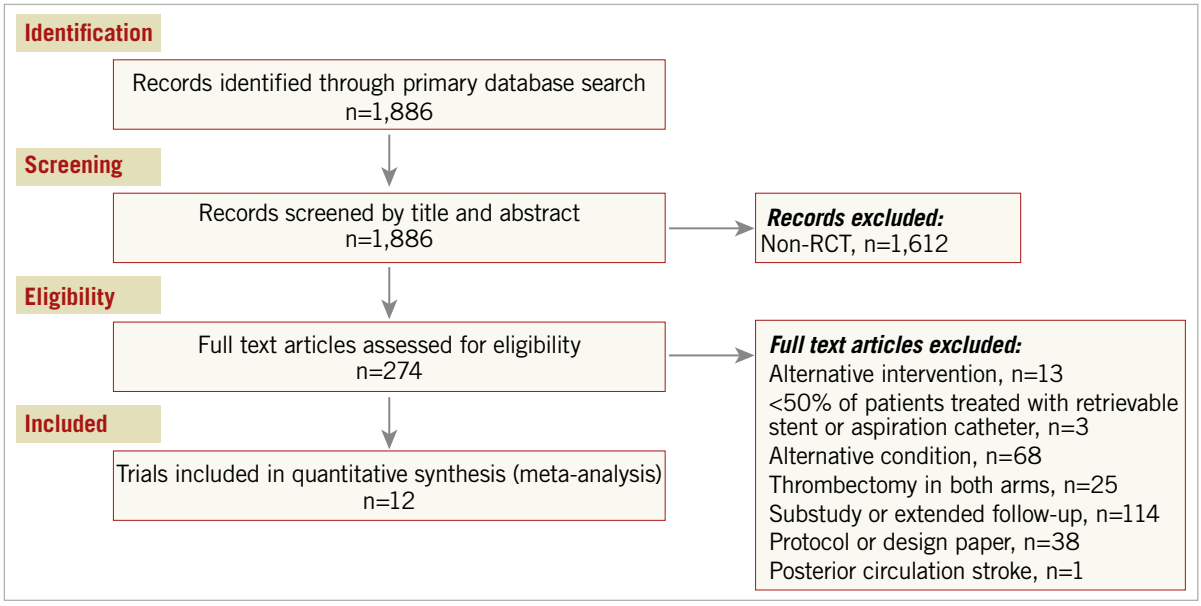


Figure 1. *Consort diagram of search strategy. RCT: randomised controlled trial*

Table 1. Summary characteristics of included trials.

TRIAL n MT/CON	Journal	Year	Sites	Median NIHSS MT/CON	MT from symptom onset (hours)	Imaging modality for inclusion	Proportion received IV thrombolytic therapy MT/CON	Protocol mandated thrombectomy technique	Symptom onset to groin puncture (mins)	Attempt with any MT device	MT with stent retriever	MT with aspiration catheter	TICI 2b-3 at procedure end
ESCAPE[20] 165/150	NEJM	2015	22 sites, worldwide	16 / 17	≤12	NCCT + CTA	72.7 / 78.7	Retrievable stent recommended	241[◊] (176-359)	91.5% 151/165	86.1% 130/151	Not specified	72.4% 113/156
EXTEND-IA[21] 35/35	NEJM	2015	10 sites, AUS + NZ	17 / 13	<4.5	CTA + CT perfusion	100 / 100	Solitaire	210 (166-251)	77.1% 27/35	100% 27/27	0.0% 0/27	86.2 25/29
MR CLEAN[22] 233/267	NEJM	2015	16 sites, Netherlands	17 / 18	≤6	CTA / MRA / DSA	87.1 / 90.6	Any CE marked or FDA approved device	260 (210-313)	81.9% 193/233	98.4% 190/193	Not specified	58.7% 115/196
REVASCAT[23] 103/103	NEJM	2015	4 sites, Spain	17 / 17	≤8	CTA / MRA / DSA	68.0 / 77.7	Solitaire	269 (201-340)	95.1% 98/103	100% 98/98	0.0% 0/98	65.7% 67/102
SWIFT PRIME[24] 98/98	NEJM	2015	39 sites, USA, Europe	17 / 17	≤6	CTA / MRA	100 / 100	Solitaire	224 (165-275)	89.0% 87/98	100% 87/87	0.0% 0/87	88.0% 73/83
THRACE[18] 204/208	Lancet Neurology	2016	26 sites, France	18 / 17	<5	CTA / MRA	100 / 100	Any CE marked device	250 (210-290)	68.6% 140/204	90.0% 126/140	20.7% 29/140	68.8% 95/138
THERAPY[6] 55/53	Stroke	2016	36 sites, USA, Germany	17 / 18	Not specified	NCCT + CTA	100 / 100	Penumbra	227 (184-263)	81.8% 45/55	15.5% 7/45	95.6% 43/45	73.3% 33/45
PISTE[7] 33/32	J Neurol Neurosurg Psychiatry	2017	10 sites, UK	18 / 14	≤6	CTA / MRA	100 / 100	Any CE marked device	209	97.0% 32/33	68%[§]	32%[§]	86.7% 26/30
EASI[19] 40/37	J Neurorad	2017	1 site, Canada	18 / 20	<6	NCCT	57.5 / 62.2	Any approved stent retriever	245 (105-580)	75.0% 30/40	96.7% 29/30	Not specified	76.7% 23/30
DAWN[9] 107/99	NEJM	2018	26 sites, worldwide	17 / 17	6-24	CTA / MRA + dwMR / CT perfusion	4.7 / 13.1	Trevo	768[◊◊] (636-1002)	98.1% 105/107	100% 105/105	0.0% 0/105	84.1% 90/107
DEFUSE3[10] 92/90	NEJM	2018	38 sites, USA	16 / 16	6-16	CTA / MRA + dwMR / CT perfusion	10.8 / 8.9	Any FDA approved device	688*	97.8% 90/92	82.2% 74/90	27.8%** 25/90	75.8% 69/91
RESILIENT[8] 111/110	NEJM	2020	12 sites, Brazil	18 / 18	≤8	CTA / MRA / DSA	68.5 / 71.8	Solitaire FR / Penumbra	259*	94.6% 105/111	68.6% 72/105	66.7% 70/105	82.0% 91/111

Values indicate mean±SD, unless indicated as a median (IQR). [◊]Time from stroke onset to reperfusion. [◊◊] Time since last known to be well to arterial puncture. [§]Proportion of patients undergoing thrombectomy procedure in which a stent retriever was used as the first device. *Derived value from available values. **Number of patients who underwent aspiration alone. CON: control arm; CTA: CT angiogram; DSA: digital subtraction angiography; dwMR: diffusion weighted magnetic resonance; INT: intervention arm; MRA: magnetic resonance angiography; MT: mechanical thrombectomy; NCCT: non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis In Cerebral Infarction score

stent or aspiration catheter. We additionally performed a sensitivity analysis of the totality of the available data, in which these three trials were added **(Supplementary Appendix 2)**.

RISK OF BIAS OF INCLUDED STUDIES

In all trials, patients were aware of treatment allocation. Two trials, THRACE[18] and EASI[19], did not blind the outcome assessor to treatment allocation. No other significant issues were identified. The risks of bias of the included studies are summarised in **Supplementary Table 5**.

PRIMARY EFFICACY ENDPOINT: MODIFIED RANKIN SCALE AT 90 DAYS

The distribution of mRS scores at 90-day follow-up is displayed in **Figure 2**. Thrombectomy reduced the level of disability at 90 days compared with medical therapy alone (OR 0.52, 95% credible interval [CrI] 0.46 to 0.61, p<0.0001, I^2=48%) **(Figure 3A)**. The median mRS at follow-up was 3 in the thrombectomy group and 4 in the control group (mean 2.8 vs 3.5).

Thrombectomy reduced the odds of patients being functionally dependent (mRS >2) at 90 days (OR 0.44, CrI 0.37 to 0.52, p<0.0001). For every 5.4 patients treated with thrombectomy, one fewer patient will be dependent at 90 days **(Central illustration)**.

SECONDARY EFFICACY ENDPOINT: ALL-CAUSE MORTALITY

At 90 days, death occurred in 16.1% (204/1,266) of patients randomised to thrombectomy and 19.2% (242/1,259) randomised to control. Thrombectomy reduced all-cause mortality (OR 0.81, 95% CrI 0.66 to 0.99, p=0.024, I^2=0%) **(Figure 3B)**. The NNT to prevent one death at 90 days was 32.

PRIMARY SAFETY ENDPOINT: SYMPTOMATIC INTRACRANIAL HAEMORRHAGE

Symptomatic intracranial haemorrhage occurred in a small proportion of patients randomised to thrombectomy (4.2%, 54/1,276) and control (4.0%, 51/1,282). The odds of symptomatic intracranial haemorrhage were similar between the arms (OR 1.12, 95%

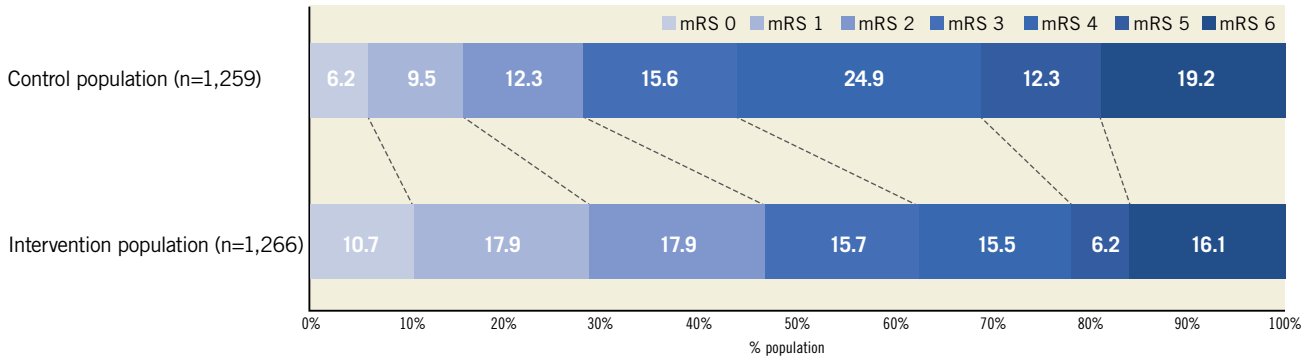


Figure 2. *Distribution of modified Rankin Scale scores at 90-day follow-up. Higher scores indicate greater disability. mRS: modified Rankin Scale*

CrI 0.76 to 1.68, p=0.72, I^2=0%) **(Figure 3C)**; however, the small number of events limits certainty.

PUBLICATION BIAS

There was no strong evidence of publication bias in the trials included in this meta-analysis (funnel plot, **Supplementary Figure 1**, Egger's test p=0.2).

SENSITIVITY ANALYSIS

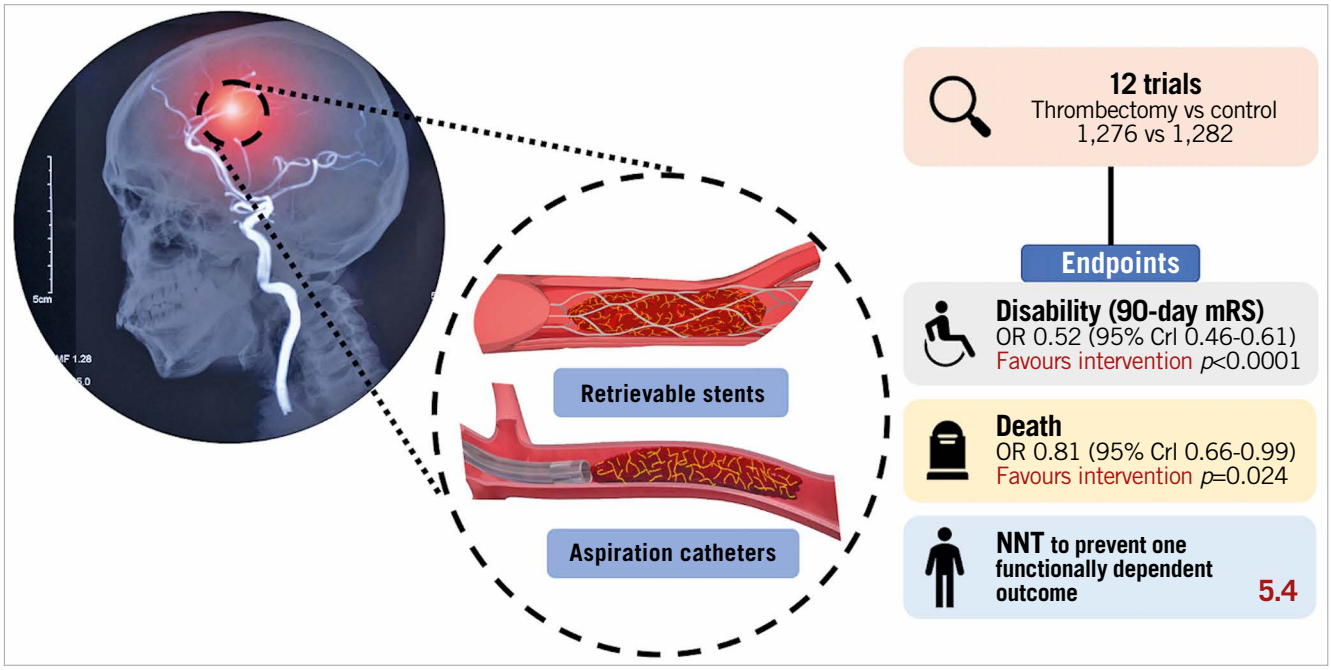
Our sensitivity analysis extended the scope of eligible trials to those that did not routinely use retrievable stents or aspiration devices **(Supplementary Table 6)** but instead used wire manipulation, first-generation devices (such as the Merci retriever) or even attempted intra-arterial catheter-directed ultrasound. The results of this analysis are reported in **Supplementary Figure 2**.

SAMPLE DIAGNOSTIC PLOTS

Sample diagnostic plots (trace, density and autocorrelation) for each endpoint are shown in **Supplementary Figure 3-Supplementary Figure 5**.

Discussion

The RCTs of modern thrombectomy for acute ischaemic stroke (covering a diverse range of trial protocols, encompassing delays to treatment onset, differential use of thrombolytics, a variety of second-generation devices, and pragmatic treatment settings) show that thrombectomy (i) significantly reduces disability at 90-day follow-up, (ii) significantly reduces all-cause mortality at 90 days, and (iii) is not associated with an increase in the rate of symptomatic intracranial haemorrhage, although the small number of events limits certainty.



Central illustration. *Mechanical thrombectomy with retrievable stents and aspiration catheters for acute ischaemic stroke: a meta-analysis of randomised controlled trials. CrI: credible interval; mRS: modified Rankin scale; NNT: number needed to treat*

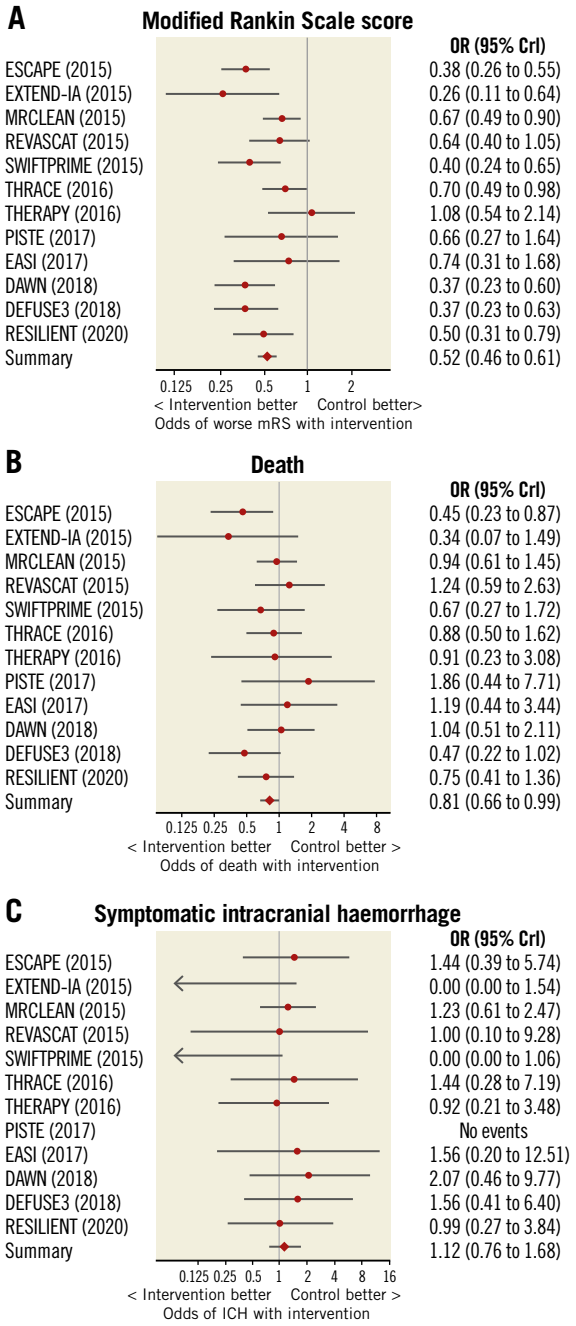


Figure 3. *Forest plots of outcome measures. Forest plots indicating the effect of mechanical thrombectomy versus control for the treatment of acute ischaemic stroke on 90-day outcomes of (A) modified Rankin Scale score, (B) all-cause mortality, and (C) symptomatic intracranial haemorrhage. CrI: credible interval; ICH: intracranial haemorrhage; mRS: modified Rankin Scale score; OR: odds ratio*

DISABILITY REDUCTION WITH THROMBECTOMY

A 1-grade better outcome in those randomised to thrombectomy is a substantial reduction in disability. It is the difference between being bedridden and not (mRS 5 vs 4). Alternatively, it is the difference between only being able to walk when someone is available to help and being able to walk whenever one wants to (mRS 4 vs 3).

The strength of our analysis is that it was sensitive across the full 7-point mRS scale, rather than draining statistical power by dichotomising at a particular threshold. However, some dichotomies are clinically important. For example, by dichotomising the results into independent (mRS ≤2) and dependent (mRS >2) categorisations, we can calculate that, for every 5.4 patients treated with the addition of thrombectomy to medical care, one fewer patient is dependent at 90 days. Put into context, the equivalent figure for functional independence with the addition of thrombolysis to medical therapy for stroke is 18[28].

MORTALITY REDUCTION WITH THROMBECTOMY

This is the first complete meta-analysis to demonstrate a significant reduction in all-cause mortality following mechanical thrombectomy. Thrombectomy reduced mortality from 19.2% to 16.1%. The NNT to prevent one death at 90 days was 32. Not only has mortality reduction not been found with thrombolysis for stroke[28], but this effect size of three absolute percentage points is similar to that of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) (which has been estimated at 2%)[29].

IMPLICATIONS FOR SERVICE PROVISION

Timely intervention, to obtain the best clinical outcome, requires services that are available locally in many hospitals around a given country rather than isolated in small numbers of super-specialised centres to which the patient has to be transported. The lesson from primary PCI is that it was feasible and effective to have dozens of hospitals providing 24/7 emergency intervention, to which patients presenting anywhere in the country could be transported within tens of minutes.

In acute ischaemic stroke, as in acute myocardial infarction, early intervention is beneficial. Each 15-minute reduction in the time from stroke onset to tPA is associated with a 4% increase in the odds of walking independently at discharge[30]. Despite this, it is notable that the selected populations enrolled in the delayed presentation DEFUSE 3[10] and DAWN[9] trials did not have the smallest effect sizes of trials of thrombectomy in this meta-analysis. Similarly, the EXTEND[31] trial for thrombolysis for stroke found benefit up to nine hours. Whilst it must be stressed that the delayed presentation trials randomised a highly selected patient cohort in comparison to trials restricted to a six-hour time window, the RCT evidence for thrombectomy for stroke for delayed presentation exceeds that for primary PCI for STEMI[9,10].

Services implemented for acute ischaemic stroke have mirrored those for acute myocardial infarction. First, there is thrombolysis made available locally. Then comes procedural intervention offered only in a small number of super-specialised centres. Finally, with recognition of mortality benefit, the health service moves to ensure universal access to prompt procedural intervention[32,33].

For stroke intervention, the sites providing it need interdisciplinary teams with complementary expertise. Routine, 24/7 access to CT imaging, high dependency care and rehabilitation services

are required. They also need 24/7 teams of proceduralists, catheter laboratory staff, and anaesthetists on-call for this intervention. Minimum practice standards for acute stroke care have been defined previously[34]. It is recommended that mechanical thrombectomy is available in all level 1 and level 2 stroke centres. However, routine access to thrombectomy remains limited in most European countries[35].

No more RCTs are required on the general question of whether modern thrombectomy for acute ischaemic stroke is better than medical therapy alone for large artery acute ischaemic stroke. Although questions remain over the risk-benefit ratio of mechanical thrombectomy in certain subgroups, such as occlusions of the M2 segment of the middle cerebral artery, the overall benefit is seen across numerous trials with increasingly pragmatic protocols, performed in increasingly diverse healthcare systems. We can therefore be confident that the benefits of thrombectomy are both large and generalisable.

A mechanical thrombectomy service is a multidisciplinary effort. The next step for the healthcare system is rapid expansion of the pool of specialists able to perform the technique and an increase in the provision of 24/7 CT vascular imaging and interpretation, and advanced stroke care. For the provision of imaging, cost efficiency may be improved through artificial intelligence to screen large numbers of images for eligibility[36].

Limitations

This meta-analysis addressed retrievable stent and aspiration catheter therapies. There have been previous technologies. The Merci device from 2004 used a retrievable coil, rather than a stent. It achieved Thrombolysis In Cerebral Infarction (TICI) 2b-3 recanalisation in only 25% of cases in the MRRESCUE trial[25]. There have been other trials in which the only mechanical intervention in most patients in the active arm was simple disruption of the thrombus with a guidewire. These trials also generally had lower standards of prior imaging confirmation of vascular occlusion amenable to thrombectomy. Those trials were not eligible for our analysis[25-27]. However, we have performed a sensitivity analysis in which they are added and found that the primary endpoint continues to show significant benefit of the intervention.

Furthermore, among the trials that did meet our inclusion criteria, there was substantial between-trial and within-trial heterogeneity in the specific devices used for thrombectomy. However, direct head-to-head RCTs comparing a strategy of direct aspiration versus retrievable stents as the first-line technique have been performed, with little evidence of difference between the two[37,38].

There was significant variation in the inclusion criteria between trials. For example, the DAWN[9] and DEFUSE 3[10] trials are distinct in design by their inclusion of patients presenting late after stroke onset. This is an important source of heterogeneity. However, whilst an attenuated benefit of thrombectomy might have been predicted in this setting, the effect sizes observed in these "late-presenter" trials were entirely consistent with trials restricted to patients with earlier presentation. The consistent effect seen across patient populations therefore gives confidence that the findings are generalisable. The HERMES collaboration have previously published predictors of response to thrombectomy based on individual patient data from a more limited number of trials[39,40]. Access to equivalent covariate data would be required for similar analyses to be performed for the expanded RCT data presented here.

Trials included in this meta-analysis typically recruited patients in centres with experienced interventional neuroradiologists in North America, Western Europe and Australasia. It could be argued that comparable results may not be achieved in less specialist centres. However, on account of the infancy of this therapy, the majority of operators in these trials would not have vast experience in thrombectomy. Furthermore, the purpose of the PISTE[7] and RESILIENT[8] trials was to assess whether the benefits of thrombectomy were reproducible in more pragmatic settings and public health systems. Reassuringly, they were found to be so.

Our conclusions are limited to patients presenting with acute large-vessel anterior circulation strokes as this is what was studied in the included trials. Vertebrobasilar occlusions are typically associated with more devastating neurological consequences, and intravenous therapy is limited by the fact that many patients present late with ill-defined symptoms or are delayed by diagnostic uncertainty[41]. Randomised trials of thrombectomy for vertebrobasilar occlusions have therefore been hampered by poor recruitment rates, and a high frequency of crossover from control to thrombectomy arms has been observed[42]. In addition, limited evidence suggests that mechanical thrombectomy in the posterior circulation may be more prone to complications than in the anterior circulation[43].

Our primary endpoint, disability as assessed by the mRS, is subject to a number of limitations. First, there is substantial inter-observer variability in scores awarded using the mRS, even by experienced researchers[44]. Second, its reporting is subject to bias in the absence of assessor blinding. Two trials[18,19] included in this meta-analysis did not blind the assessor to treatment allocation; their results are therefore subject to this potential limitation.

Recruitment was halted prior to the planned randomisation target in 10/12 trials included in this meta-analysis. For seven trials[6,7,19-21,23,24] this was because of evidence of efficacy from an external trial. Three trials were halted due to achievement of an internal efficacy margin on a pre-specified interim review[8-10]. A different result may have been obtained if these trials had run to completion.

Conclusions

Mechanical thrombectomy with retrievable stents and aspiration catheters significantly reduces disability at 90 days in anterior circulation ischaemic stroke. The available evidence now demonstrates that these benefits extend to a reduction in all-cause mortality. There is no significant increase in symptomatic intracranial

haemorrhage. The absolute mortality effect is similar to primary PCI which has long been rolled out universally. Innovative action by healthcare policy makers could transform the disability and mortality outcomes for patients with acute ischaemic stroke, with limited ongoing cost if efficiently integrated with existing services.

Impact on daily practice

Contemporary trials of mechanical thrombectomy confirm a reduction in disability with a large effect size. For every 5.4 patients treated, one fewer patient is functionally dependent at 90 days. The available evidence now supports a significant reduction in all-cause mortality, a 3% absolute risk reduction at 90-day follow-up. The benefits of mechanical thrombectomy for acute ischaemic stroke are both large and generalisable. Urgent action is required to expand access to this life-saving therapy.

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Conflict of interest statement

I. Grunwald is a co-founder and a shareholder of Brainomix. R. Al-Lamee reports speakers' honoraria from Philips Volcano and Menarini Pharmaceuticals. H. Seligman declares research funding from Amgen. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Details of PubMed search terms.

Supplementary Appendix 2. Supplementary results.

Supplementary Table 1. Impact of setting increasingly flat priors for the β coefficients for the primary outcome (mRS score at 90 days).

Supplementary Table 2. Impact of setting increasingly flat priors for the random effect on primary outcome (mRS score at 90 days).

Supplementary Table 3. Impact of setting increasingly flat priors for the β coefficients for the endpoint of mortality.

Supplementary Table 4. Impact of setting increasingly flat priors for the random effect on the endpoint of mortality.

Supplementary Table 5. Cochrane risk of bias assessment tool for included studies.

Supplementary Table 6. Summary characteristics for trials added to the sensitivity analysis.

Supplementary Figure 1. Funnel plot for risk of publication bias.

Supplementary Figure 2. Forest plots inclusive of trials not restricted to the use of second-generation devices.

Supplementary Figure 3. Sample diagnostic plots for modified Rankin Scale (mRS).

Supplementary Figure 4. Sample diagnostic plots for death.

Supplementary Figure 5. Sample diagnostic plots for symptomatic intracranial haemorrhage.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00343

Supplementary data

Supplementary Appendix 1. Details of PubMed search terms

We performed a structured search of PubMed to identify trials which randomly assigned patients to mechanical thrombectomy or control on a background of medical therapy which could include thrombolysis where eligible. We applied limits on the available dates from 1 January 2010 to 2 July 2020. No language restriction was applied.

The search string was as follows: randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] NOT (animals [mh] NOT humans [mh]) AND ((thrombectomy [tiab]) OR (clot retrieval [tiab]) OR intraarterial[tiab]) AND (stroke[tiab]).

Supplementary Appendix 2. Supplementary results

With the addition of these three trials, there were a total of 3,694 patients, of whom 1,955 were randomised to thrombectomy and 1,739 to control.

Including these data, thrombectomy reduced disability at 90 days assessed using the mRS (OR 0.64, 95% CrI 0.57 to 0.72, pr <0.0001) **(Supplementary Figure 2A)**. The reduction in all-cause mortality with thrombectomy was less certain (OR 0.88, 95% CrI 0.73 to 1.04, pr=0.070) **(Supplementary Figure 2B)**. Finally, the odds of SIH were similar between the two groups (OR 1.11, 95% CrI 0.81 to 1.51, pr=0.74) **(Supplementary Figure 2C)**.

Supplementary Table 1. Impact of setting increasingly flat priors for the β coefficients for the primary outcome (mRS score at 90 days).

SD of prior (normal distribution)	Odds of a higher mRS score with thrombectomy
0.25	OR 0.99 (95% CrI 0.97 to 1.01)
1	OR 0.86 (95% CrI 0.80 to 0.92)
10	OR 0.54 (95% CrI 0.47 to 0.61)
100	OR 0.52 (95% CrI 0.45 to 0.60)
10000	OR 0.52 (95% CrI 0.46 to 0.60)

mRS: modified Rankin Scale; OR: odds ratio; SD: standard deviation

Supplementary Table 2. Impact of setting increasingly flat priors for the random effect on primary outcome (mRS score at 90 days).

Mean of prior (exponential distribution)	Odds of a higher mRS score with thrombectomy
10	OR 0.53 (95% CrI 0.45 to 0.60)
1	OR 0.53 (95% CrI 0.46 to 0.60)
0.25	OR 0.52 (95% CrI 0.46 to 0.60)
0.1	OR 0.53 (95% CrI 0.46 to 0.61)

mRS: modified Rankin Scale; OR: odds ratio;. SD: standard deviation

Supplementary Table 3.
Impact of setting increasingly flat priors for the β coefficients for the endpoint of mortality.

SD of prior (normal distribution)	Odds of a higher risk of mortality with thrombectomy
0.25	OR 1.00 (95% CrI 0.98 to 1.02)
1	OR 0.97 (95% CrI 0.90 to 1.04)
10	OR 0.82 (95% CrI 0.67 to 1.00)
100	OR 0.81 (95% CrI 0.65 to 0.99)
10000	OR 0.81 (95% CrI 0.66 to 0.99)

OR: odds ratio; SD: standard deviation

Supplementary Table 4. Impact of setting increasingly flat priors for the random effect on the endpoint of mortality.

Mean of prior (exponential distribution)	Odds of a higher risk of mortality with thrombectomy
10	OR 0.81 (95% CrI 0.66 to 0.99)
1	OR 0.81 (95% CrI 0.66 to 0.99)
0.25	OR 0.81 (95% CrI 0.66 to 1.00)
0.1	OR 0.81 (95% CrI 0.66 to 1.00)

OR: odds ratio; SD: standard deviation

Supplementary Table 5. Cochrane risk of bias assessment tool for included studies.

Trial	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
ESCAPE [20]	Low risk "A real-time, dynamic, internet-based, randomised minimisation procedure (minimal sufficient balance method)"	Unclear	High risk Open label trial	Low risk "The primary outcome was assessed by trained personnel who were unaware of the treatment-group assignments"	Low risk One patient removed due to improper consent just after randomisation. One patient was lost to follow-up in the intervention arm and three patients were lost to follow-up in the control arm.	Low risk Most endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment.
EXTEND-1A [21]	Low risk "Patients were randomised - by means of a centralised website and stratified according to the site of arterial occlusion"	Unclear	High risk Open label trial	Low risk "Neurological impairment and functional scores were measured by a clinician trained in their administration and blinded to treatment assignment"	Low risk Eight patients in the intervention arm did not receive intervention (2 patients did not have angiogram performed due to change in their clinical status, 4 had no retrievable thrombus remaining on first angiographic run, 1 had mTICI 2b flow after stenting of extracranial ICA, 1 patient had vessel perforation and extravasation with microcatheter manipulation)	Low risk All endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment.
MR CLEAN [22]	Low risk "The randomisation procedure was Web-based, with the use of permuted blocks"	Unclear	High risk Open label trial	Low risk "A single experienced trial investigator, who was unaware of the treatment-group assignments, conducted the follow-up interviews at 90 days by telephone with the patient, proxy, or healthcare provider. This interview provided reports for the	Low risk 2 patients declined participation after randomisation to control arm. 17 patients in the intervention arm did not undergo catheter angiogram (8 had clinical improvement before intervention, 6 protocol violations by local investigators, 1 had no femoral access, 1 withdrew consent for intervention, 1 was	Low risk All pre-specified endpoints reported	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment

				assessment of the modified Rankin score by reviewers who remained unaware of the treatment-group assignments."	haemodynamically unstable. 20 patients in the intervention arm did not have intervention (10 had ICA disease, 8 had no clot visible, 2 technical problems)		
PISTE [7]	Low risk "Randomisation was conducted using an interactive voice-response system managed by the Robertson Centre for Biostatistics, University of Glasgow"	Unclear	High risk Open label trial	Low risk "Day 90 outcomes were assessed by site staff blinded to treatment allocation"	Low risk 3 patients in the intervention arm did not receive intervention (2 had more than 33% disease in MCA territory, 1 patient had treatment crossover). 4 patients in the control arm did receive IVT alone (1 patient had an ineligible CTA occlusion, 1 had more than 33% disease in MCA territory, 1 patient had mRS >2 on review, 1 patient had treatment crossover). In the control arm, two patients were lost to follow-up at 90 days.	Low risk All endpoints on CT.gov reported.	High Well conducted open-label trial with outcomes assessed by personnel unaware of treatment assignment
REVASCAT [23]	Low risk "a real-time computerised randomisation procedure" with stratification.	Unclear	High risk Open label trial	Low risk "Local and external certified assessors who were unaware of study-group assignments separately evaluated the primary outcome variable in each patient by means of a structured interview"	Low risk One patient withdrew consent just after randomisation. 33 patients in the intervention arm and 23 patients in the control arm did not receive tPA. Five patients in the intervention arm did not undergo intervention (3 had TICI 3 and 2 had TICI 2b perfusion score)	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by local and external assessors unaware of treatment assignment
SWIFT PRIME [24]	Low risk "Subject allocation to treatment will be accomplished by using	Unclear	High risk Open label trial	Low risk "The 90-day mRS was assessed by study personnel certified in the scoring of the mRS using the RFA-A, and	Low risk 11 patients in the intervention arm did not receive intervention (7 had complete or partial resolution of	Low risk All endpoints on CT.gov reported	High Well conducted open-label trial with outcomes

	an interactive web response or interactive voice response system.			blinded to treatment assignment"	target occlusion, 2 had no target occlusion at the time of enrolment and 2 had inaccessible target occlusions). Final assessment data were unavailable in 5 patients in the control arm (2 were withdrawn by the investigator after entry criteria deviation and 3 patients withdrew their consent)	in primary analysis.	assessed by staff blinded to treatment assignment
THRACE [18]	Low risk "Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients. Randomisation was done with a computer-generated sequence and was stratified by centre, and sequential minimisation with a factor of 85% was used to avoid imbalance in treatment."	Unclear	High risk Open label trial	High risk "Clinical assessments were done by vascular neurologists who were not masked to the treatment to which the patients had been allocated."	Low risk 2 patients withdrew consent after randomisation. 59 patients in the intervention arm did not have thrombectomy and 4 patients in the intervention group discontinued intervention because of catheterisation problems. 8 patients in the control arm eventually received intervention because of poor clinical evolution. 2 patients in the intervention arm and 2 patients in the control arm were lost to follow-up. 2 patients in the intervention arm and 4 patients in the control arm had missing data for efficacity analysis	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open-label trial but absence of blinded adjudication of clinical assessments reduces quality of trial
THERAPY [6]	Low risk "Randomisation was performed through a centralised interactive voice response system"	Unclear	High risk Open label trial	Low risk "The primary outcome measure (90-day mRS) was assessed by independent blinded adjudicators. Adjudicators reviewed videotapes of assessments performed by blinded, trained,	Low risk 3 patients in the intervention arm and 5 patients in the control arm were lost to follow-up. Two patients in the intervention arm and two patients in the control arm withdrew consent.	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by staff blinded to treatment assignment

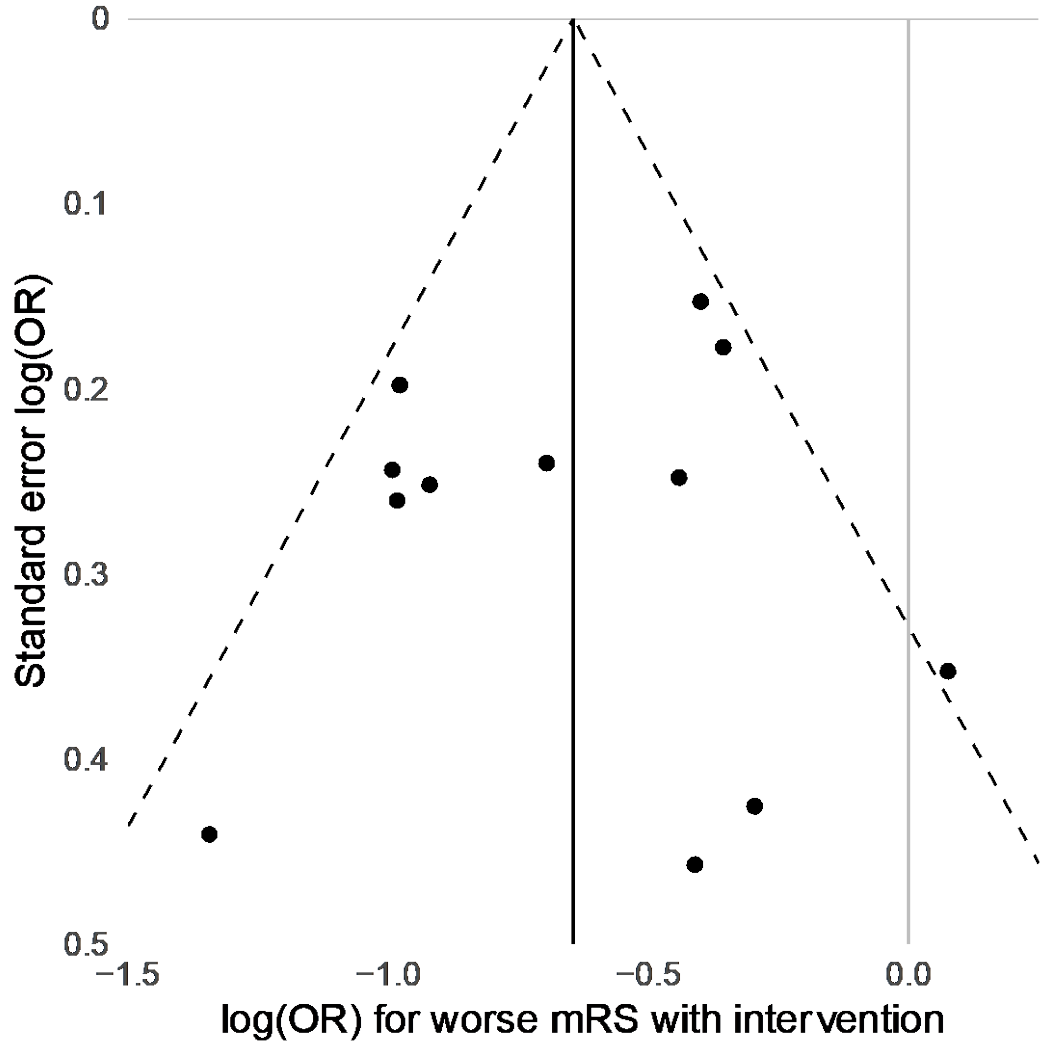
				and certified local investigators. “ “SiCH was defined as any new haemorrhage identified by the core laboratory with a concomitant ≥4-point worsening in NIHSS as recorded by a blinded, NIHSS-certified assessor.”			
DAWN [9]	Low risk “Randomisation was performed with the use of a central, Web-based procedure, with block minimisation processes to balance the two treatment groups, and was stratified according to mismatch criteria”	Unclear	High risk Open label trial	Low risk “For the coprimary endpoints, scores on the modified Rankin scale were obtained through in-person, formal, structured interviews with patients and caregivers that were performed by local certified assessors who were unaware of the treatment assignments.” Safety endpoints, procedure-related complications, and serious adverse events were adjudicated by an independent clinical events committee.	Low risk Two patients in the intervention arm did not receive intervention due to spontaneous recanalisation of target vessel on conventional angiogram	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open-label trial. Although safety endpoints were adjudicated by independent assessors, it is unclear if they were blinded to treatment allocation. This reduces the quality of the trial.
DEFUSE 3 [10]	Low risk “Randomisation - with the use of a Web-based dynamic randomisation system. Randomisation was stratified”	Low risk	High risk Open label trial	Low risk “The score (referring to mRS) was assessed in person, or by telephone if an in-person visit was not feasible, by a certified rater who was not aware of the trial-group assignments”	Low risk Two patients in the intervention group did not receive intervention due to intervention deemed unsafe/not feasible by the operator.	Low risk All endpoints on CT.gov reported in primary analysis.	High Well conducted open-label trial with outcomes assessed by independent staff, blinded to treatment assignment
RESILIENT [8]	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	High

	"Randomisation was performed through a real-time, dynamic, internet-based, randomised minimisation procedure to balance the numbers of patients across the two groups"		Open label trial	"Assessment was based on central adjudication by consensus of two certified neurologists, who were unaware of the treatment assignments and who viewed video recordings of structured patient or family interviews."	In the intervention arm, 35 did not receive intravenous tPA and 31 patients in the control group did not receive intravenous alteplase. One person in the control group did not receive intervention. One patient in the control group was lost to follow-up	All endpoints on CT.gov reported in primary analysis.	Well conducted open-label trial with outcomes assessed by independent staff, blinded to treatment assignment
EASI [19]	Low risk "Randomisation through a web-based application package. Minimisation was used as a method of adaptive stratified sampling"	Unclear Low risk	High risk Open label trial	High risk "All data and outcome measures were collected by routine care personnel in this care trial design and thus no blinding was involved"	Low risk 10 patients in the intervention arm did not receive intervention (1 patient had no angiography due to aortic dissection, 4 patients had distal thrombus, 3 patients had no thrombus found and 2 patients had inaccessible basilar artery). Three patients in the control arm received intervention due to request from the neurologist or family	Low risk All endpoints on CT.gov reported in primary analysis.	Intermediate Well conducted open label trial but lack of blinding for outcome evaluation reduces the quality of the trial.

Supplementary Table 6. Summary characteristics for trials added to the sensitivity analysis.

TRIAL n MT/CON	Journal	Year	Sites	Median NIHSS MT/CON	Max delay EVT from symptom onset (hrs)	Imaging modality for inclusion	Proportion received IV thrombolytic therapy MT/CON	Protocol-mandated thrombectomy technique	Symptom onset to groin puncture (mins)	Attempt with any MT device¶	Proportion of MT with stent retriever	Proportion of MT with aspiration catheter	TICI 2b-3 at procedure end (%)
MR RESCUE [25] 64/54	NEJM	2013	22 sites, N. America	16/19//16/20	≤8	MRA or CTA	43.8 / 29.6	Any FDA approved device. Merci retriever (77%)	381±74	95.3 61/64	0.0% 0/61	39.3% 24/61	25.0% 16/64
IMS III [26] 434/222	NEJM	2013	58 sites, N. America, AUS, Europe	17/16	<5	NCCT	100 / 100	IA tPA‡ and/or Merci (22%), Penumbra (12%), Solitaire (1%)	208±47	39.2% 170/434	8.2% 14/170	38.8% 66/170	39.6% 126/318
SYNTHESIS Expansion [27] 181/181	NEJM	2013	24 sites, Italy	13/13	<6	NCCT	0.0* / 98.3	IA tPA‡ +/- device utilisation (31%)	225 (194-250)	30.9% 56/181	41%‡‡ 23/56	16.1% 9/56	Not specified

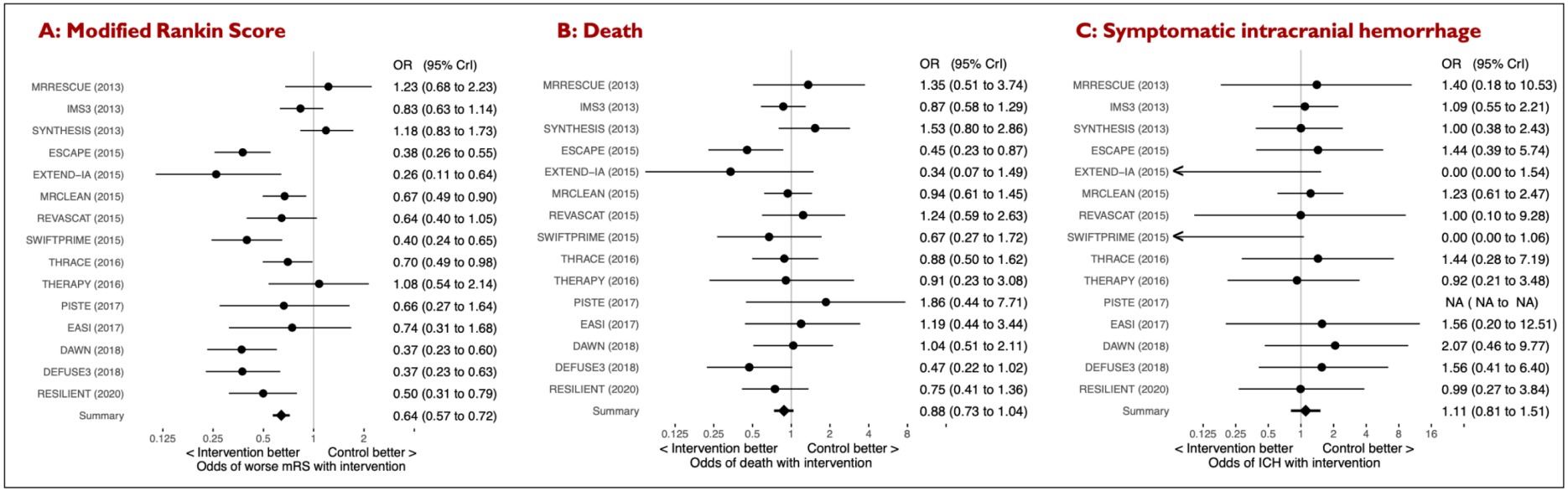
¶ Figure for proportion of patients in the intervention group who received an attempt at EVT with a dedicated EVT device.
‡ Intra-arterial tPA administered through a microcatheter +/- mechanical clot disruption typically using a guidewire.
‡‡ Only Solitaire and Trevo devices reported.
* Patients in the thrombectomy arm were eligible for intra-arterial thrombolysis at the discretion of the interventionalist.
CON: control arm; CTA: CT angiogram; DSA: digital subtraction angiography; dwMR: diffusion weighted magnetic resonance; INT: intervention arm; MRA: magnetic resonance angiography; MT: mechanical thrombectomy; NCCT: non-contrast computed tomography; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis In Cerebral Infarction score



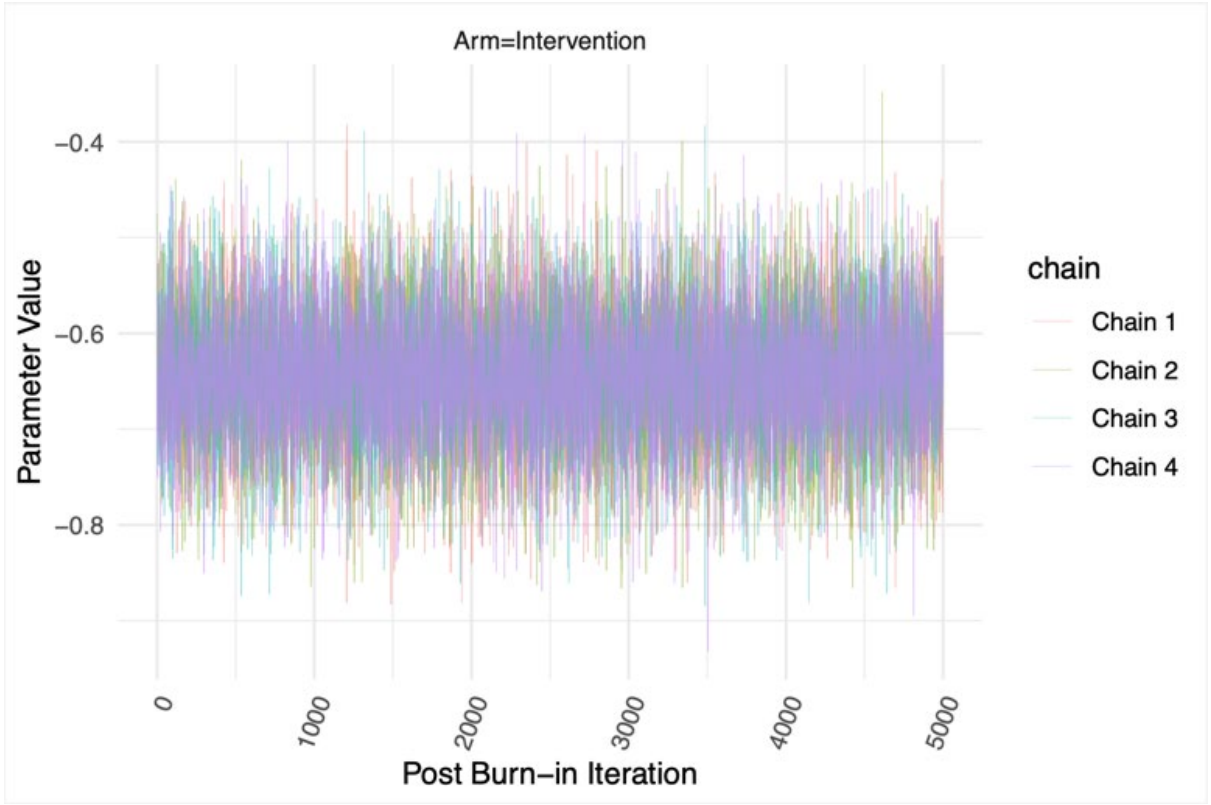
Supplementary Figure 1. Funnel plot.

Funnel plot demonstrating a low risk of publication bias for the primary endpoint across studies included in this meta-analysis (Egger's test, p=0.2).

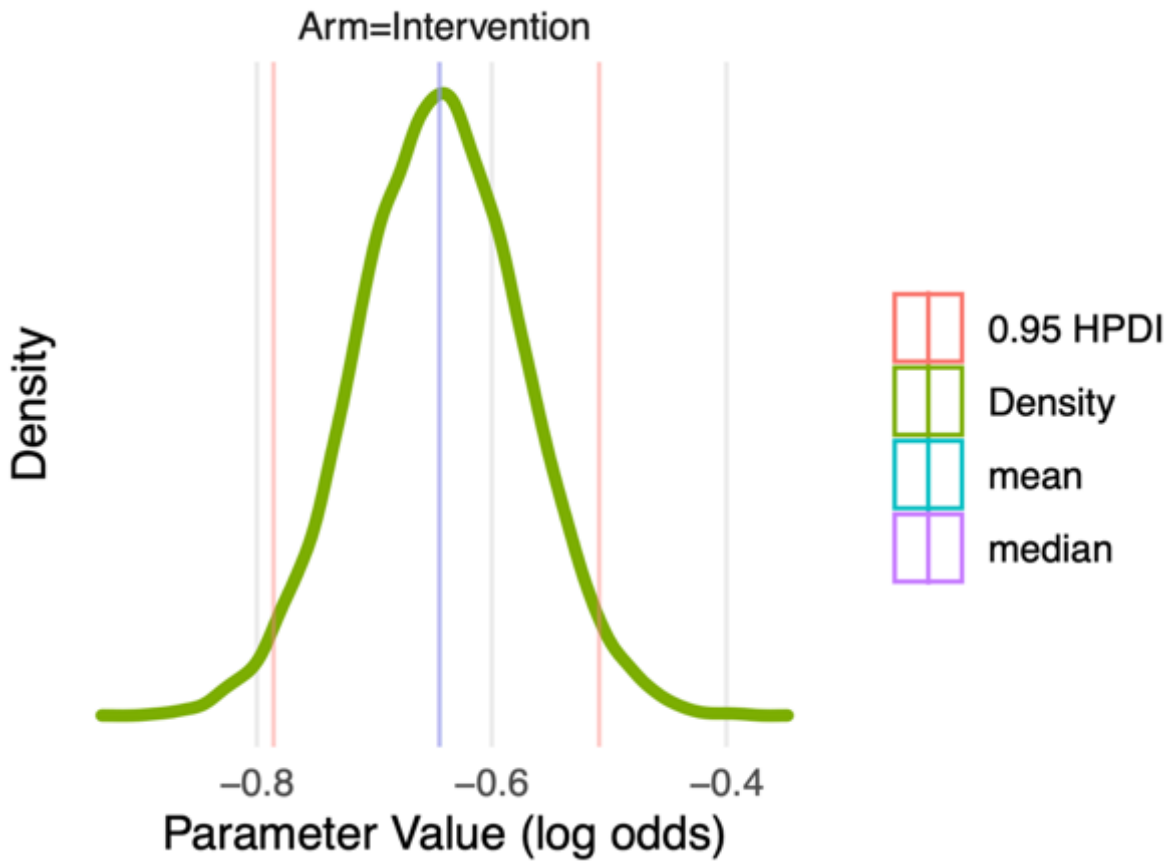
mRS: modified Rankin Scale score; OR: odds ratio



Supplementary Figure 2. Sensitivity analysis forest plots indicating the effect of mechanical thrombectomy versus control for the treatment of acute ischaemic stroke on 90-day outcomes of (A) modified Rankin Scale score, (B) all-cause mortality, and (C) symptomatic intracranial haemorrhage.
CrI: credible interval; mRS: modified Rankin Scale score; OR: odds ratio; ICH: intracranial haemorrhage

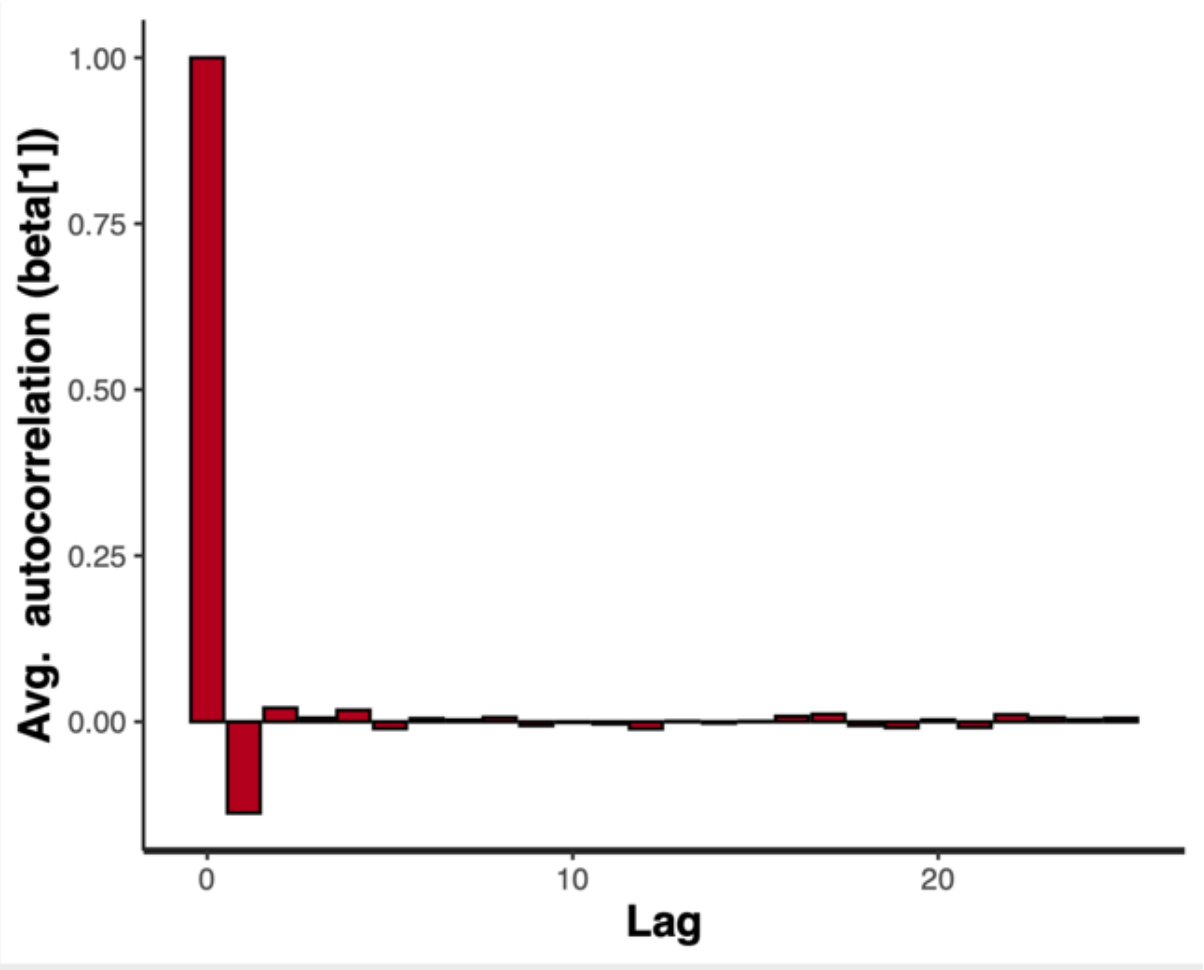


Supplementary Figure 3A. Sample diagnostic plot (mRS): trace.

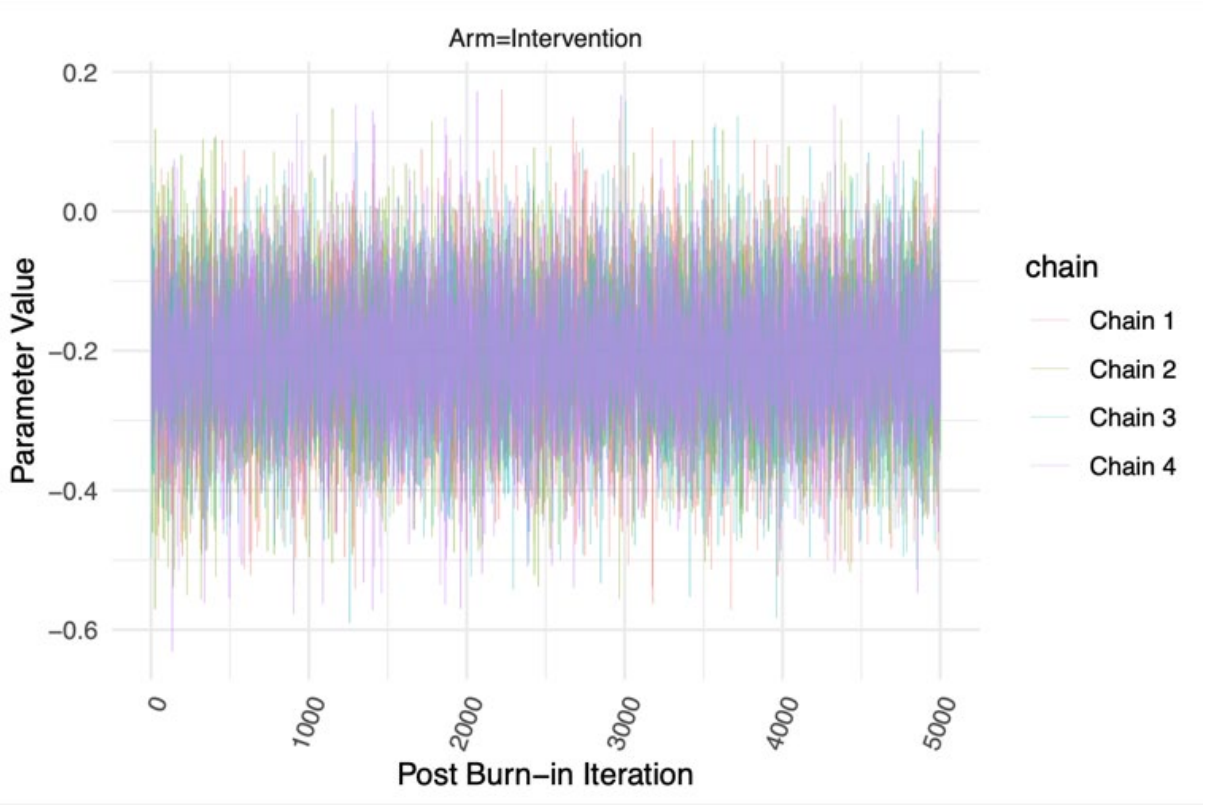


Supplementary Figure 3B. Sample diagnostic plot (mRS): density.

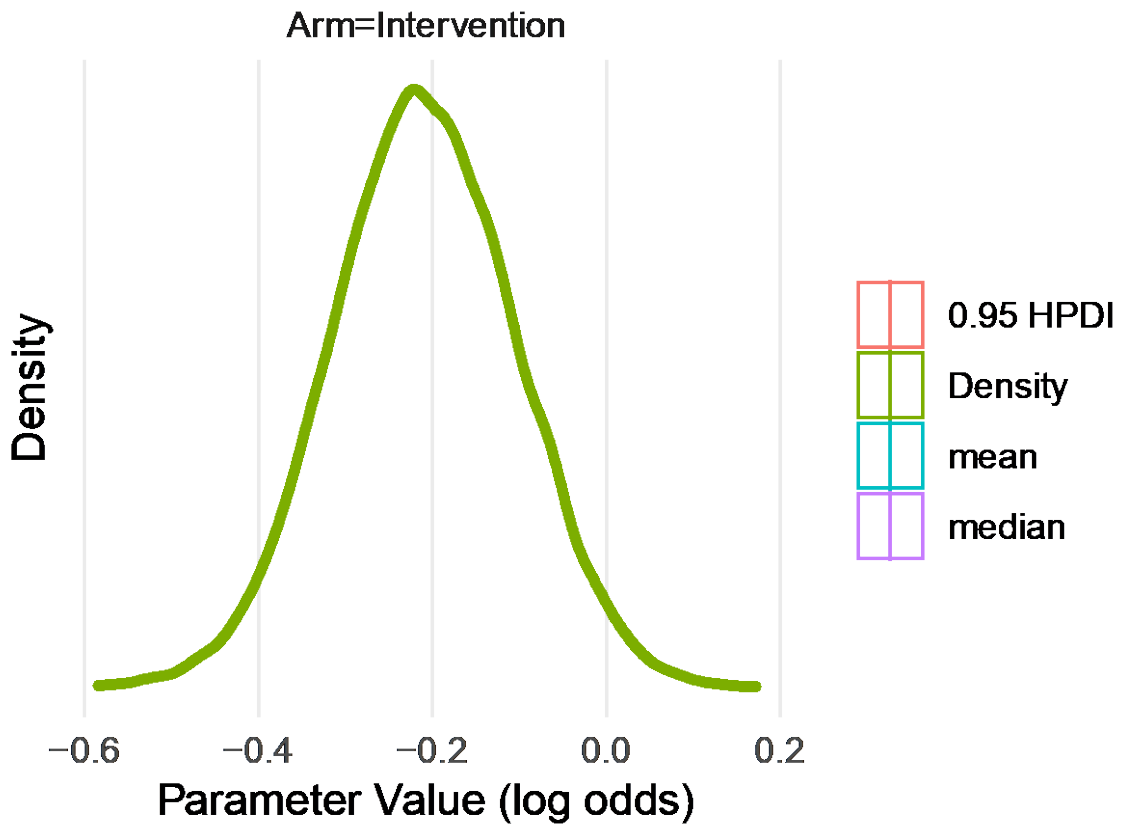
HPDI: highest posterior density interval



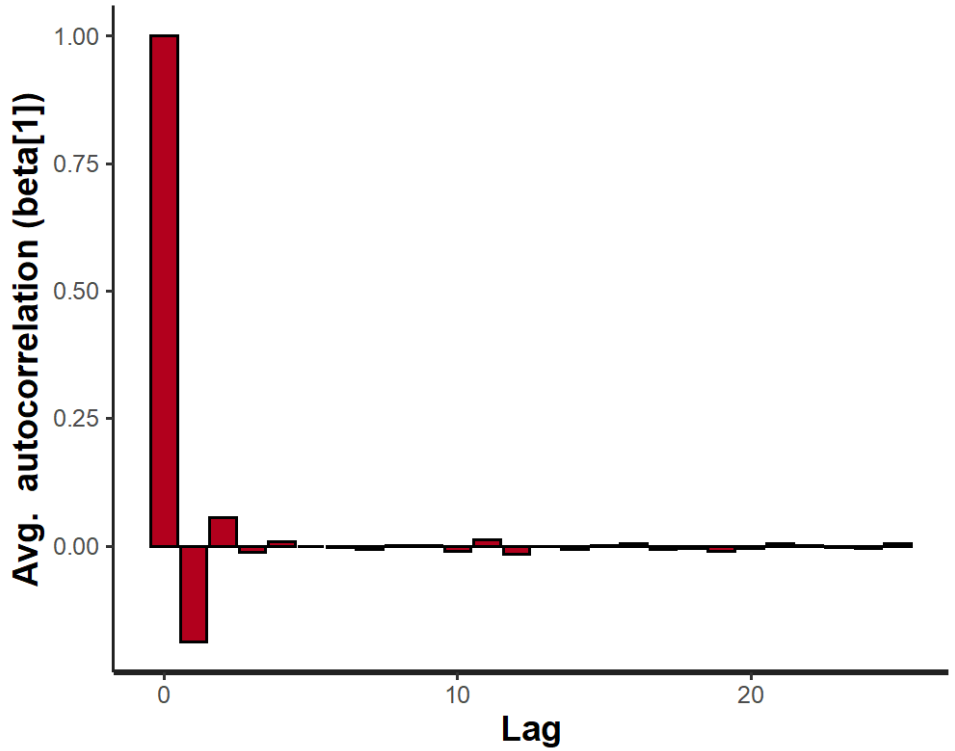
Supplementary Figure 3C. Sample diagnostic plot (mRS): autocorrelation.



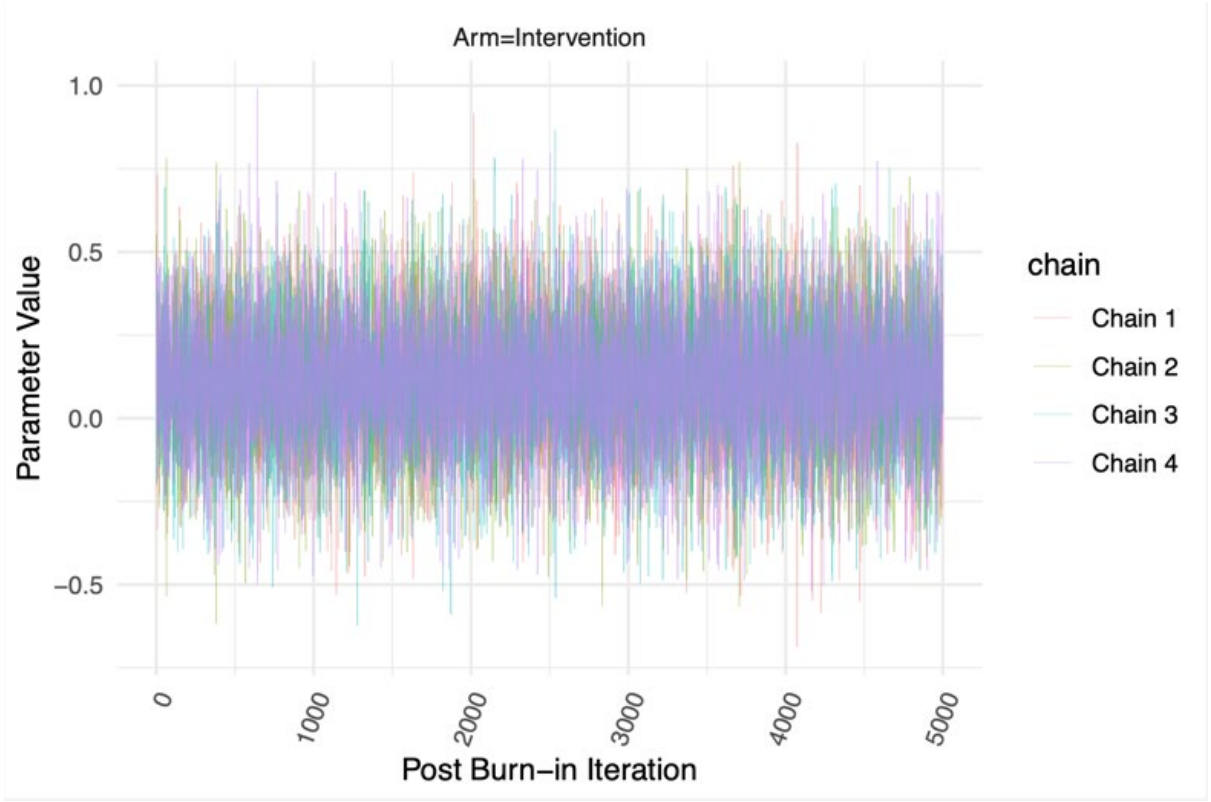
Supplementary Figure 4A. Sample diagnostic plot (death): trace.



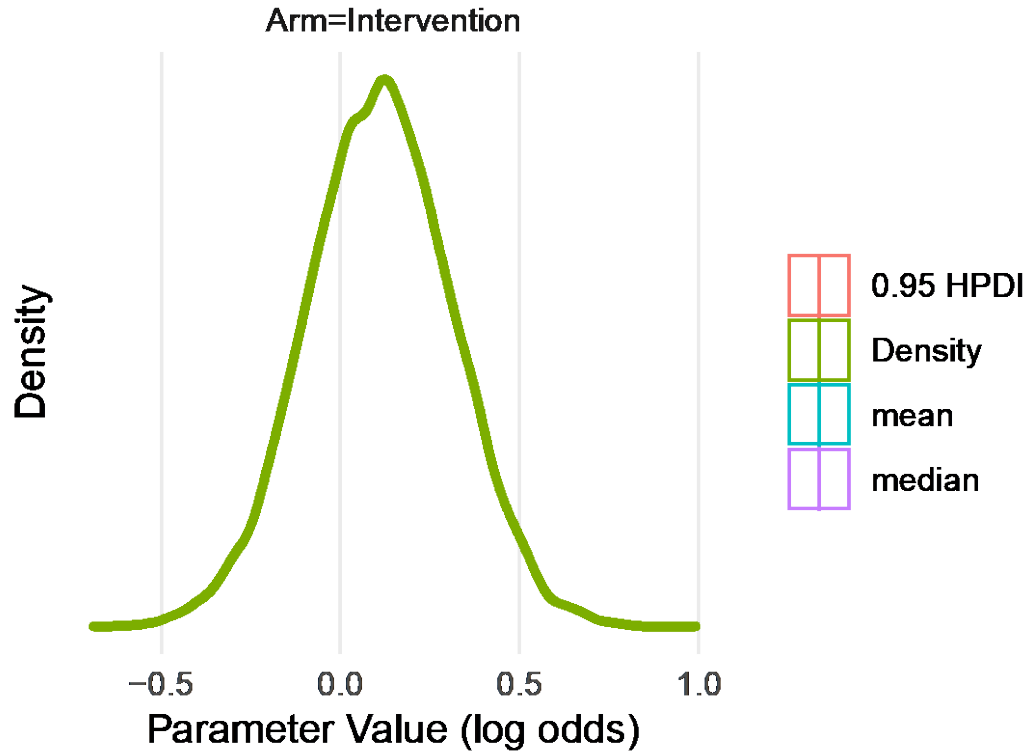
Supplementary Figure 4B. Sample diagnostic plot (death): density.
HPDI: highest posterior density interval



Supplementary Figure 4C. Sample diagnostic plot (death): autocorrelation.

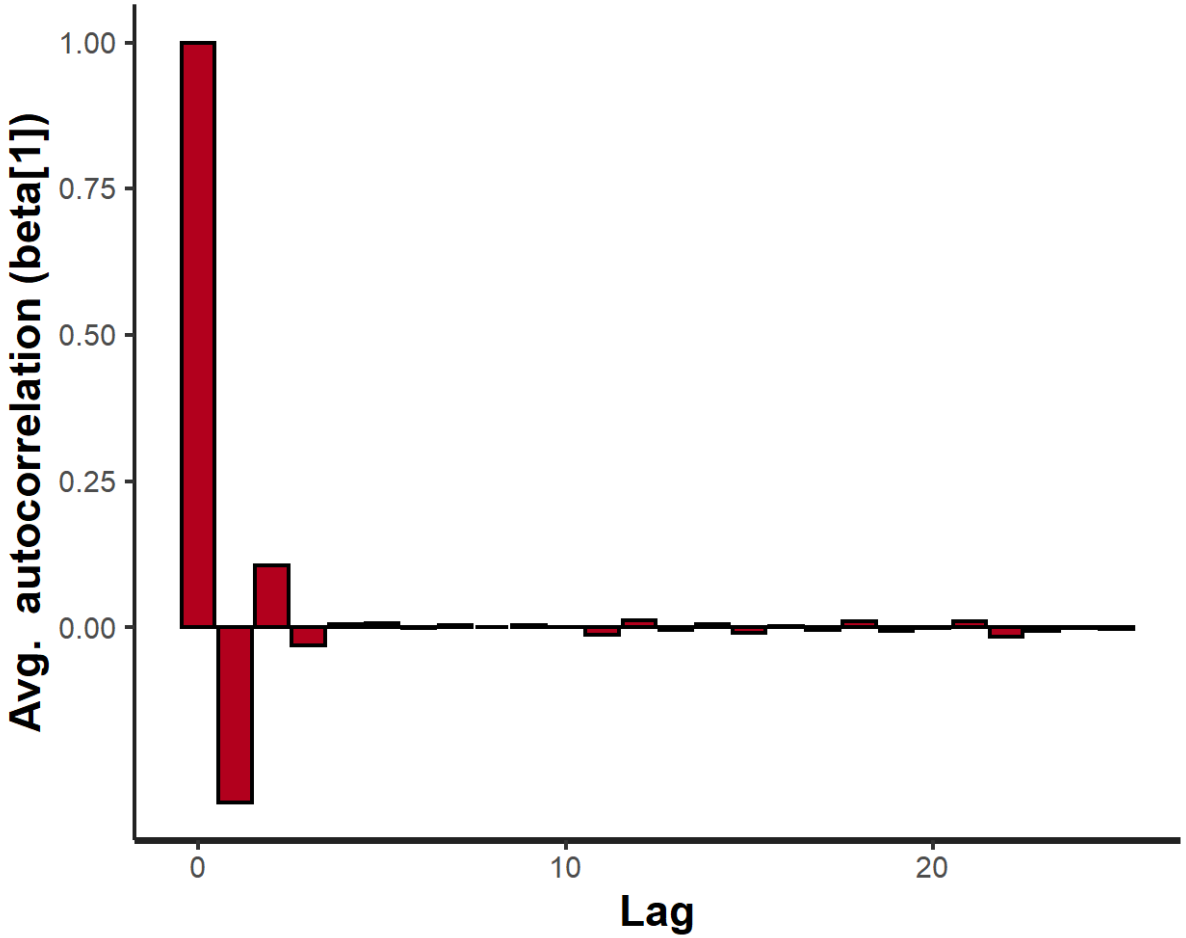


Supplementary Figure 5A. Sample diagnostic plot (symptomatic intracranial haemorrhage): trace.



Supplementary Figure 5B. Sample diagnostic plot (symptomatic intracranial haemorrhage): density.

HPDI: highest posterior density interval



Supplementary Figure 5C. Sample diagnostic plot (symptomatic intracranial haemorrhage): autocorrelation.