Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke – a systematic review and meta-analysis

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Title

Endovascular therapy versus medical care alone for ischemic stroke: a systematic review and meta-analysis

Registration

The protocol of this systematic review was registered in Prospective Register of Systematic Reviews (PROSPERO 2015:CRD42015019340).

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Abstract

Background: Early reperfusion with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) improves survival and functional outcomes among ischemic stroke patients. Uncertainty exists whether endovascular therapy helps further improve outcomes.

Objectives: To evaluate the efficacy and safety of endovascular therapy, in particular adjunctive intra-arterial mechanical thrombectomy (AIMT), in ischemic stroke patients.

Data sources: MEDLINE, EMBASE, CENTRAL, Web of Science, SciELO, LILACS, and clinical trial registries from inception to December 2015. Reference lists were crosschecked.

Study eligibility criteria, participants and intervention: Ischemic stroke randomized controlled trials (RCTs) comparing endovascular treatment, including thrombectomy, with medical care alone, including IV rt-PA. No language or time restrictions.

Data extraction: Two reviewers.

Study appraisal and synthesis methods: Primary outcomes were modified Rankin Scale [mRS]≤2 and mortality at 90 days. Cochrane risk of bias assessment tool was applied. Random-effects meta-analysis was performed to estimate pooled risk ratio (RR) and 95% confidence intervals (95%CI). The GRADE approach was used.

Findings: Pooled analysis from ten RCTs (n=2925) showed that endovascular therapy, including thrombectomy, is associated with an increased proportion of patients experiencing good (mRS≤2) and excellent (mRS≤1) outcomes 90 days after

stroke, without differences in mortality or symptomatic intracranial haemorrhage rates, compared with patients randomized to medical care alone – including IV rt-PA. Heterogeneity was high among studies. Due to more accurate patient selection, higher rate and earlier administration of IV rt-PA, and use of more efficient thrombectomy devices, the more recent studies (seven RCTs; published or presented in 2015) proved better suited to evaluate the effect of AIMT on its index disease. In most of these studies, above 86% of the patients were treated with stent retrievers, and recanalization rates were higher (above 58%) than previously reported. Subgroup analysis of these seven studies yielded a RR of 1.56 (95%CI:1.38-1.75) and 2.03 (95%CI:1.62-2.53) for good and excellent outcomes, respectively, without heterogeneity among studies results.

Limitations: All RCTs were open-label. Risk of bias was moderate across studies. The full results of two RCTs are yet to be published.

Conclusions and implications of key findings: There is moderate-to-high quality evidence that endovascular thrombectomy as add-on to intravenous thrombolysis performed within 6 to 8 hours after anterior circulation large vessel ischemic stroke provides beneficial functional outcomes, without increased detrimental effects when compared to medical care alone.

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Keywords

Stroke, thrombectomy, meta-analysis

Introduction

Stroke is the second leading cause of death worldwide[1], its incidence is rising in individuals under 75 years old[2] and the global burden attributable to stroke is increasing.[3] Therefore, along with preventive measures, effective treatments are needed to reduce the deleterious consequences of stroke.

Arterial occlusion is the culprit of ischemic stroke. Lack of blood supply leads to functionally and radiologically distinct areas, namely the infarct core and the potentially salvageable ischemic penumbra.[4] The amount of viable tissue among the penumbra area is reduced over time. Consequently, early reversal of vascular occlusion limits the volume of damaged tissue and correlates with outcome.[5] By achieving timely reperfusion, thrombolysis improves survival and functional recovery.[6 7] However, the recanalization rates of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) alone are not ideal[8] – approximately 46%[9] – and the use of endovascular interventions, may reverse vessel occlusion more effectively and thus help further improve outcomes. Both pharmacologic and mechanical endovascular interventions have been evaluated in acute ischemic stroke. Thrombectomy can be performed using devices that disrupt, aspirate, and/or retrieve clots, and can be used alone or as an add-on to intravenous or intra-arterial chemical thrombolysis – i.e. adjunctive intra-arterial mechanical thrombectomy (AIMT).

Results from published randomized controlled trials (RCTs) on AIMT are heterogeneous and uncertainty exists regarding its clinical benefit.[10-13] Therefore, we

conducted a systematic review with meta-analysis to evaluate the efficacy and safety of endovascular therapy (in particular AIMT) versus standard medical care alone (in particular IV rt-PA) in adult patients with ischemic stroke.

Methods

Protocol and guidance

The protocol of this study was reported following PRIMA-P guidelines[14] and was registered at PROSPERO (registration number CRD42015019340; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019340). The methods of the systematic review followed PRISMA[15] guidelines. Reporting of statistical data followed SAMPL[16] guidelines.

Eligibility criteria

This review included RCTs reporting on the efficacy and safety of AIMT, independently of the device used, compared with medical care alone including IV rt-PA for ischemic stroke in adults (≥18 years old). To be included, studies had to mention functional outcome and mortality at 90 days after symptom onset as trial endpoints. Studies were not dismissed *a priori* due to poor quality, language, or time restrictions. Observational, non-controlled, or non-randomized interventional studies were excluded. Since our primary aim was to evaluate AIMT in comparison to IV rt-PA, we excluded RCTs that did not include patients submitted to mechanical thrombectomy in the experimental arm (for example, trials evaluating only patients

submitted to other types of endovascular therapy, such as intra-arterial rt-PA and urokinase-type plasminogen activator) and RCTs that did not include patients submitted to IV rt-PA in the control arm.

Information sources

Electronic identification of reports was conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SciELO, and LILACS. Grey literature was searched via appropriate databases (i.e.: OpenGrey, Database of Abstracts of Reviews of Effects (DARE), British Library Thesis Service). Clinical trial registries were also consulted (i.e.: ClinicalTrials.gov, European Union Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform, ISRCTN Registry, Stroke Trials Registry). The last electronic search was on 14 December 2015.

The references of potentially eligible RCTs were crosschecked.

Search strategy

The strategy combined the terms (cerebrovascular disorder OR stroke) with (mechanical thrombolysis OR embolectomy OR thrombectomy). The Cochrane Highly Sensitive Search Strategy was used to retrieve RCTs.[17] See *Annexe S1* for an exemplified search strategy.

Study selection

Reports retrieved were screened for potential eligibility by title and abstract analysis. Afterwards, the full text was screened for appropriateness of inclusion. Two independent screeners (FBR, JBN) conducted this process. Disagreements were solved by consensus or by a third party (DC). The inter-observer bias was calculated as the percentage of agreement achieved.[18]

Data collection process

Two independent parties (FBR, JBN) extracted data from the included RCTs to a standardised electronic form. Disagreements were solved by consensus or by a third party (DC). Gathered data was double-checked (JC).

Outcomes and prioritization

The primary efficacy outcome was the proportion of patients achieving a good functional outcome at 90 days after symptom onset defined as a modified Rankin Scale (mRS)[19] score between 0 and 2 – that is, functional independency. The primary safety outcome was all-cause mortality at 90 days. The secondary efficacy outcome was the proportion of patients achieving an excellent functional outcome at 90 days (mRS≤1). The secondary safety outcome was the proportion of patients with symptomatic intracerebral haemorrhage (sICH) as defined in the SITS-MOST study.[8] When sICH was not defined using SITS-MOST criteria, other definitions were accepted.

Risk of bias in individual studies

Risk of bias of individual studies was independently assessed by two authors (FBR, JBN) using the Cochrane Collaboration Risk of Bias Tool.[17] Three additional criteria were sought: independent funding, trial stopped early, and clinical trial registration to assess whether the trial was retrospective or prospectively registered. The risk of bias was considered high if the trial was retrospectively registered due to risk of reporting bias.

Data synthesis

Random-effects meta-analyses (RevMan 5.3.3 software) weighted by the inverse-variance method were performed to estimate pooled risk ratio (RR) and 95% confidence interval (95%CI). Sample size and event rates were considered when using the Mantel-Haenszel method. RR was chosen as effect measure due to greater similarity of relative estimates between studies with different designs, populations and lengths of follow-up.[20] Raw data was converted to RR. Heterogeneity was assessed with the Cochran Q test and the I^2 test.[21] When significant risk differences were found ($p<0.05$), we also determined absolute effects and derived the additional number of participants with events per 1000 who benefitted or suffered harm from receiving the studied intervention.

Trial Sequential Analyses (TSA) (see "TSA" Box) were performed for primary outcomes using TSA version 0.9 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) to explore whether cumulative data were adequately powered to evaluate outcomes.[22] The required information size and the O'Brien-Fleming adjacent trial sequential alpha spending monitoring

boundaries were calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), risk reduction based on pooled analysis, the weighted incidence of events in the control group, and heterogeneity. Power of the primary outcomes findings was interpreted if significance was reached with either a minimum sample size, or crossing trial sequential alpha spending monitoring boundary.

Due to inequalities in trial design, including patient populations and interventions,[23] (see results section), data for all outcomes were presented a priori separately according to the year of publication/presentation of trial results (2013 and 2015). Further subgroup analysis was planned for: gender; trials with different risk of bias; thrombectomy devices (according to rate of stent retriever use: ≥85% versus <85%); time to treatment; IV rt-PA administration; and stroke characteristics.

Meta-biases

Publication bias was assessed through visual inspection of funnel plots' asymmetry if more than ten studies per outcome were available[17]. Egger's[24] and Peters' tests[25] were performed.

Confidence in cumulative evidence

Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology.[26]

Results

Study selection

Electronic searches yielded 758 records after deduplication. The inter-observer agreement between screeners was good, as quantified by a Cohen's kappa coefficient of 0.75 (95%CI 0.56 to 0.93).[18] Ten studies were included (Figure 1), three published in 2013 (IMS III[27], SYNTHESIS Expansion[28], MR RESCUE[29]) and seven published/presented in 2015 (MR CLEAN[30], ESCAPE[31], EXTEND-IA[32], SWIFT-PRIME[33], REVASCAT[34], THERAPY[35], and THRACE[36]). Published protocols, supplementary material, and press releases of these studies were consulted whenever needed.[37-46] THERAPY and THRACE are not published. The principal investigators of these trials were contacted for data retrieval without success. Therefore, data extraction for these trials was based solely on results presented at scientific meetings and press releases.

Study characteristics

All studies were multicentre, parallel, prospective randomised open blinded endpoint (PROBE) clinical trials (Table 1). All but four – SYNTHESIS, MR CLEAN, REVASCAT, and THRACE - were international. The number of participants ranged from 70 to 656. Altogether, the studies involved 2925 participants, 1564 in the endovascular therapy arm and 1361 in the standard medical care (intravenous thrombolysis) arm, either based in an intention to treat (ITT) or in a modified-ITT population.

The main inclusion criteria entailed adult stroke patients with time from symptom onset to intravenous thrombolysis of 3 to 4.5 hours and time from symptom onset to endovascular therapy between 5 and 12 hours. In contrast to IMS III, SYNTHESIS, EXTEND-IA, SWIFT-PRIME, THERAPY, and THRACE trials, that only included patients who were also treated with IV rt-PA, some trials – MR RESCUE, MR CLEAN, ESCAPE, and REVASCAT – accepted patients who were not eligible for intravenous thrombolysis.

The overall baseline characteristics of included patients were similar between arms across studies (Table 2). Mean age ranged from 62 to 71 and gender distribution was approximately 1:1 in all studies. Stroke severity ranged from 13 to 19 points in the National Institute of Health Stroke Scale (NIHSS).

All studies focused on anterior circulation strokes, but IMS III, SYNTHESIS, and THRACE also allowed posterior circulation strokes. MR RESCUE, ESCAPE, EXTEND-IA, MR CLEAN, and THERAPY included strokes on the territory of the internal carotid artery, M1 or M2 portions of the middle cerebral artery while SWIFT-PRIME, REVASCAT, and THRACE included only internal carotid or M1 strokes. The Alberta Program Stroke Early Computed Tomography Score (ASPECTS) was also an enrolment criterion in IMS III, ESCAPE, SWIFT PRIME and REVASCAT (Table S1). All 2015 studies required radiological confirmation of large vessel occlusion as an inclusion criterion. This was not the case in 2013 trials (IMS III, SYNTHESIS, and MR RESCUE). For patient inclusion, perfusion imaging depicting

potentially salvageable brain tissue was only required in ESCAPE, EXTEND-IA and SWIFT-PRIME.

All studies evaluated endovascular therapy (with or without IV rt-PA) versus standard medical therapy, namely IV rt-PA (Table 3). In the intervention arm, thrombolysis (IV rt-PA) use ranged from 0% in SYNTHESIS to 100% in IMS III, EXTEND-IA, SWIFT PRIME, THERAPY, and THRACE. In SYNTHESIS, IV rt-PA was not administered due to study design (the aim of the study was to compare endovascular therapies, such as intra-arterial rt-PA and thrombectomy, with intravenous thrombolysis). In IMS III, the study design contemplated a planned dose reduction in IV rt-PA in the thrombectomy arm due to concomitant administration of intra-arterial rt-PA. In the control arm (standard medical therapy), IV rt-PA was administered in all studies. However, in MR RESCUE, only 28.1% of patients were given intravenous thrombolysis due to lack of illegibility. In all other trials, IV rt-PA was administered to 77% to 100% of the patients in the medical care arm.

All studies included thrombectomy as an endovascular treatment option. Overall, about two thirds of the patients randomised to the intervention arm (64.1%) underwent thrombectomy. IMS III, MR RESCUE, SYNTHESIS, and MR CLEAN allowed other endovascular interventions (intra-arterial rt-PA and urokinase-type plasminogen activator) in addition to thrombectomy. In fact, in SYNTHESIS and IMS III, only 30.9% and 39.2% of the patients were treated with AIMT, respectively. In SYNTHESIS, the intervention arm included intra-arterial thrombolysis with rt-PA, mechanical clot disruption or retrieval, or a combination of these approaches. In IMS

III, the intervention arm included thrombectomy or endovascular delivery of rt-PA. In all other trials, 77.1% to 91.5% of the patients in the intervention arm were treated with AIMT (data on THERAPY and THRACE patients are not yet available).

Selected thrombectomy devices varied among studies and some studies allowed for more than one device to be used (Table S2). In MR RESCUE, and THERAPY no stent retrievers were used. In IMS III, and SYNTHESIS the rate of stent retriever use was low, respectively, 2.9% and 41%. On the other hand, the stent retriever use rate among most 2015 studies was above 86%. The time from stroke ictus to endovascular treatment ranged from 225 to 355 minutes.

In the intervention arm, recanalization rates varied between 25.0% and 88.0% according to a score ≥2b/3 on Thrombolysis in Cerebral Infarction perfusion scale (TICI) or modified TICI (Table S3). SYNTHESIS did not report reperfusion rates. For THRACE this data is still unavailable. Recanalization rates above 58% were observed in MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, and THERAPY. With the exception of THERAPY trial participants, most (86.1% to 100%) of the patients in these last trials showing higher recanalization rates were treated with stent retrievers.

The follow-up period was 90 days in all trials and all provided data for our primary efficacy and safety outcomes. In IMS III, MR RESCUE, SYNTHESIS, and ESCAPE, sICH was defined by either authors' own criteria or according to previously defined

criteria other than the SITS-MOST study[8] definition. sICH criteria used in THRACE is still unkown.

Risk of bias within studies

The overall risk of bias was moderate among studies (Figure 2). Random sequence generation, blinding of outcome assessment, and selective reporting were considered as low risk items across studies. For THERAPY and THRACE, the bias associated with random sequence generation is not known due to lack of information. Outcome assessment at 90 days was conducted in person on ESCAPE, EXTEND-IA, and SWIFT-PRIME, in person or through video visualisation on REVASCAT, through video visualisation on THERAPY, and by telephone on SYNTHESIS and MR CLEAN. IMS III and MR RESCUE did not report the method used for outcome assessment evaluation. For THRACE this information is still unavailable. Allocation concealment and blinding of participants and personnel were classified as high risk due to study design (i.e. PROBE design). All studies but THRACE were, at least partially, industry sponsored. In SYNTHESIS, some of the supplies for the study (rt-PA) came from industry. IMS III and MR RESCUE were publicly funded (NIH-funded) but had industry support. MR CLEAN, EXTEND-IA and REVASCAT had mixed funding from both governmental bodies and industry (unrestricted grants). ESCAPE, SWIFT PRIME, and THERAPY had predominantly industry support.

Six studies were stopped early, either due to futility (in IMS III, according to interim analysis as per protocol, after 72.3% of the planned patients had been enrolled) or due to efficacy. The former five trials were stopped after the publication of MR CLEAN's

positive results: interim analyses were brought forward in ESCAPE (63.2% of the planned sample size), EXTEND-IA (70.0% of the planned sample size) and SWIFT PRIME (23.5% of the planned sample size), and enrolment was stopped because efficacy boundaries were met; in REVASCAT, and THERAPY indication of lack of equipoise led to stopping of enrolment without reaching the stopping efficacy boundary – in REVASCAT after enrolling 25.4% of the planned sample size, and in THERAPY after enrolling 15.6% of the planned sample size.

One trial (MR RESCUE) was retrospectively registered in 2006, two years after the study start. Concerning attrition bias, IMS III and MR CLEAN showed imbalances between withdrawals in the intervention and control arms. In MR RESCUE and REVASCAT the reduced number of participants limited considerations regarding the effect of withdrawals between arms on study results. Due to lack of information, attrition bias was not evaluable for THRACE.

Synthesis of results

All studies, with the exception of THRACE, reported all the sought outcomes: each study's primary outcomes are described on Table 1. Results of individual studies were incorporated in forest plots (Figures 3, 4, S1, S2, S5, S6, and S7).

Overall, 1129 out of 2907 patients (38.8%) reached a good functional outcome at 90 days. Endovascular-treated patients had a higher chance of achieving a good outcome (RR 1.37; 95% CI: 1.14 to 1.64; Figure 3) with an increase of 123 (95% CI: 46 to 212) patients attaining a good outcome per each 1000 additional endovascular-treated

patients compared with medical care alone. Considerable statistical heterogeneity (I^2=69%, p=0.0006) was present for overall pooled studies results, but not for pooled results of studies published in 2013 (I^2=0%; p=0.62) and in 2015 (I^2=0%; p=0.43), which further support our *a priori* hypothesis that heterogeneity would exist between 2013 and 2015 trials' results due to inequalities in study design, including patient populations and interventions. In fact, efficacy outcome results were significantly different (p<0.00001) between these two subgroups of trials. No differences were found in the proportion of patients reaching mRS≤2 (Figure 3) or mRS≤1 (Figure S1) among 2013 trials results. In contrast, pooled RR for 2015 trials was 1.56 (95% CI: 1.38 to 1.75), representing an increase of 167 (95%CI: 113 to 223) patients attaining a good outcome (mRS≤2) per each 1000 additional endovascular-treated patients compared with medical care alone. Additionally, pooled RR for 2015 trials for mRS≤1 (Figure S1) was 2.03 (95% CI: 1.62 to 2.53; I^2=0, p=0.99), representing an increase of 131 (95% CI: 79 to 195) patients attaining an excellent outcome per each 1000 additional endovascular-treated patients compared with medical care alone. Outcomes data for THRACE and THERAPY studies are not yet accurately published. Sensitivity analysis excluding these studies from pooled RR for 2015 trials yielded similar results. Further sensitivity analysis excluding trials with low rates of patients treated with rt-PA in the control arm (MR RESCUE) or with low rate of AIMT in the endovascular treatment arm (IMS III and SYNTHESIS) also yielded similar results for all efficacy outcomes as all these trials happened to be published in 2013.

At 90 days, 482 out of 2880 participants (16.7%) died, without differences between arms in all-cause mortality (RR 0.90; 95% CI: 0.76 to 1.06; I^2= 0%, p=0.52; Figure

4). Furthermore, no differences existed between results from trials published in 2013 and in 2015 (p=0.48).

Overall, 129 out of 2526 patients (5.1%) experienced sICH, without differences between treatment groups (RR 1.02; 95% CI: 0.72 to 1.44; I^2=0%, p=0.85; Figure S2). Furthermore, no differences existed between results from trials published in 2013 and in 2015 (p=0.86).

Additional analysis

The number of included studies limited the evaluation of publication bias with funnel plots. Egger's (p=0.435) and Peters' (p=0.483) tests were not suggestive of publication bias or small studies' effects.

Regarding TSA analysis, the proportion of patients with a favourable outcome (mRS≤2) was 33% and a RR increase of 37% was assumed based on the RR of 1.37 estimated for the independency outcome. The cumulative evidence overcame the minimum information size required (1873 patients) adjusted for the obtained RR increase and heterogeneity (Figure S3). The cumulative evidence was not adequately powered for mortality evaluation, reaching 20.1% of the required information size for a 9% RR reduction of mortality (Figure S4).

Predetermined subgroup analysis for the primary efficacy outcome based on gender (Figure S5) and IV rt-PA administration across all patients (rt-PA versus no rt-PA;

Figure S6) did not showed significant differences between subgroups (p=0.61 and p=0.05, respectively).

Subgroup analysis according to stent retriever use reached statistical significance (p=0.04; Figure S7), favouring high (≥ 85%) stent retriever use (RR 1.69; 95%CI 1.42 to 2.01) over low to no use (RR 1.18; 95%CI 0.88 to 1.58).

Subgroup analysis according to risk of bias, stroke characteristics, and time to treatment were not performed due to similarity of risk of bias across studies, and lack of robust data for posterior circulation strokes and for time to endovascular treatment.

Discussion

Summary of evidence

The main finding of this systematic review is that there is moderate-to-high quality evidence indicating that adding endovascular therapy, in particular thrombectomy, to best medical care alone, including intravenous rt-PA, improves the probability of an ischemic stroke patient being functionally independent at 90 days after stroke, without increased mortality or sICH (Table 4).

These conclusions are based on ten RCTs enrolling 2925 ischemic stroke patients. Although pooled analysis of these RCTs yielded statistical significant and clinical relevant effects, significant heterogeneity was found among studies' results. This heterogeneity was driven by differences in methodological and clinical features between studies. There were disparities in inclusion criteria and in the interventions considered in both the standard medical therapy arm and in the endovascular therapy arm, in particular, the proportion of patients that underwent intravenous thrombolysis and AIMT, as well as the type of devices used for thrombectomy. These divergences lead us to look separately at the results of the ten included RCTs, by creating two distinct subgroups of trials: the first, comprised of 2013 publications – including the IMS III, SYNTHESIS, and MR RESCUE trials –, and the second, comprised of 2015 publications – encompassing MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT, THERAPY, and THRACE.

As far as inclusion criteria are concerned, all studies focused on anterior circulation

strokes, but IMS II, SYNTHESIS, and THRACE also allowed posterior circulation strokes. THRACE also allowed proximal artery (internal carotid or M1) strokes. The former were the only types of strokes included in REVASCAT, and SWIFT-PRIME. ESCAPE, MR CLEAN, REVASCAT, SWIFT-PRIME, and THERAPY also included strokes of the M2 portion of the middle cerebral artery.

Large vessel occlusion – the index problem amenable by thrombectomy – was not required for enrolment in IMS III and SYNTHESIS, but was an obligatory criterion in MR RESCUE and in all 2015 studies. In four studies it was also needed to document potentially salvageable brain tissue: perfusion imaging and evidence of penumbra was required in three 2015 studies – ESCAPE, EXTEND-IA, and SWIFT PRIME –, and REVASCAT only included patients with high ASPECTS score, that is, with imaging features suggestive of less extensive brain damage. Of note, although MR RESCUE evaluated the existence of penumbra, this was not a criterion for enrollment.

Regarding intravenous thrombolysis, most patients in the medical care arm (>77%) were treated with intravenous rt-PA (the only exception being MR RESCUE), as well as in the endovascular therapy arm (>68% of the patients), except in SYNTHESIS and MR RESCUE (where the rate of administration of intravenous thrombolysis was low). In IMS III the dose of intravenous rt-PA was reduced due to study design and safety issues.

Although all studies evaluated patients submitted to thrombectomy in the endovascular arm, the rate of patients that underwent AIMT varied between studies. In 2015 trials this rate was high (>77%). On the other hand, less than 40% of the

patients were treated with thrombectomy in IMS III and SYNTHESIS in detriment of use of intra-arterial rt-PA, a strategy that has proven to be of little benefit with increased complications.[47] Also important, the use of stent retrievers was more prominent in the more recent trials, which were also the studies where the reperfusion rates were also higher. In agreement, Solitaire FR, the most frequently used stent retriever, is a newer generation device that has previously shown to contribute to higher recanalization rates and reduced deployment times when compared with previous devices.[48] The use of currently outdated first generation devices may have lead to the suboptimal revascularization rates observed in IMS III and MR RESCUE (respectively, 41% and 25%), and, at least in IMS III, may have contributed to substandard groin puncture to reperfusion times.[49]

The focus on large vessel occlusion scenarios, the selection of patients with less brain tissue damage, the use of two simultaneous endovascular reperfusion techniques – IV rt-PA and thrombectomy –, and the use of more efficient devices are probably pivotal factors that help explain the difference between the statistical significant and clinical relevant results observed among 2015 RCTs, but not among 2013 RCTs. It is therefore without surprise that some previous systematic reviews and meta-analysis, focusing mainly in 2013 publications[9, 10, 12], have failed to detect treatment differences. Our results are however supported by the quantitative analysis of more recent meta-analytic studies that include more recent published RCTs.[50-52]

Considering the pathophysiology of ischemic stroke and the knowledge acquired from IMS III[53], SYNTHESIS[54], as well as from previous rt-PA trials[7], it can be drawn that faster, more efficient recanalization is of paramount importance to reduce the

infarction of penumbral brain tissue and thus contribute to improved clinical outcomes. As such, the quick IV rt-PA administration as well as the timely intravascular intervention achieved in 2015 studies may have contributed to reduce brain tissue damage.

To sum up, due to the above-mentioned reasons, as well as due to the rate and dosage of IV rt-PA usage in both studies arms, the studies published or presented in 2015 are more suited to test the true effect of endovascular thrombectomy on its index disease. We therefore consider that pooled results from these studies evaluate more accurately the benefit of endovascular therapy in general, and adjunctive thrombectomy after IV rt-PA in particular, in ischemic stroke caused by large vessel occlusion. Based on these results, we conclude that patients undergoing AIMT are twice more likely to be without disability and 1.5 times more likely to be functionally independent, both 90 days after an ischemic stroke caused by anterior large vessel occlusion.

Weaknesses of the study

Despite gathering data from multicentric RCTs, the information included was not powered enough to evaluate the safety of endovascular therapy, including AIMT. Furthermore, observational studies may be more adequate than RCTs to evaluate safety, as these may include patients that are usually excluded from RCTs and the follow-up is frequently longer. Lastly, the magnitude of effects may have been exaggerated by a stricter patient selection, and by a higher level of study site selection and interventionist proficiency comparing with the real world.

The PROBE design of all studies has greater similarities with everyday clinical practice and is more cost-effective than double-blinded RCTs.[55] Nonetheless, PROBE studies eliminate placebo effect, a phenomenon not discarded in blind sham-controlled trials, and are more likely to lead to researcher and patient biases[55] and to patient drop-out after randomization.

In stroke trials it is customary to provide outcomes at 90 days.[56] However, spontaneous neurological recovery may take longer to cease[56], so longer follow-ups could have contributed to a better understanding of the evolution of functional endpoints through time.

Another limitation was the overall moderate risk of bias – all trials had PROBE design, some were mostly industry funded, six were stopped early, and one had retrospective registration. Nevertheless, previous reports noted that industry-sponsored studies can accurately report outcomes[57] and that in truncated trials for efficacy treatment effects may not be substantially larger than for completed trials.[58] Finally, data from THRACE and THERAPY trials have not yet been officially published. This data was extracted from scientific conferences and press releases. Therefore, the possibility exists that the available information is not completely accurate.

Implications for clinical practice

Recommending endovascular therapy, in particular AIMT with stent retrievers, as standard of care in ischemic stroke caused by anterior large vessel occlusion will

require restructuring of comprehensive stroke centres and of interventional neuroradiologists' training in order to enhance the available resources.

Due to the baseline characteristics of the included population, the pooled clinical benefit attributable to AIMT may only be applicable to patients younger than 85 years old with large vessel anterior circulation strokes where brain damage is not widespread and if the intervention is performed within 6 to 8 hours from ictus. Of note, adding thrombectomy to standard IV rt-PA opens the conventional treatment window from 4.5 hours to at least 6 hours in these scenarios. Still, the decision to use adjunctive thrombectomy should be taken shortly after beginning the administration of intravenous rt-PA.

Implications for research

Future studies should evaluate the optimal timeframe for AIMT, its benefit in patients who have contraindications for thrombolysis, in posterior circulation strokes and in older populations, and its safety profile. Also, longer follow-ups could help provide a better understanding of the cost-effectiveness and budget impact of implementing AIMT.

Conclusion

In contrast to some previous publications[10 11 13] and the results obtained in initial trials, this systematic review and meta-analysis shows that endovascular therapy, in particular thrombectomy as an add-on to intravenous rt-PA, provides beneficial functional outcomes after ischemic stroke secondary to anterior large vessel

occlusion, without increased detrimental effects when compared to medical care alone. Our results and recommendations are in accordance to other recently published systematic reviews on this field. [50-52] In addition to the studies already included in those recent systematic reviews, we have further included data from two unpublished studies, as well as performed a cumulative meta-analytic measurement – TSA – that re-enforces our results and recommendations. Also, our qualitative analysis allows for an in-depth view of the clinical and methodological disparities observed between the published trials. This, in turn, helps explain the shift in evidence regarding endovascular thrombectomy in acute stroke and also explore the clinical contexts where this invasive approach appears more beneficial. We think that the critical discussion here presented on how the obtained results translate into clinical practice is of particular interest to both neurologists and neuroradiologists when deciding the best therapeutic option for an individual patient with an acute stroke.

Finally, we believe that cost-effectiveness analysis should be pursued before widespread implementation of endovascular thrombectomy and restructuration of comprehensive stroke centres.

“What this paper adds” box

Section 1: What is already known on this subject

Intravenous thrombolysis is the standard therapy for acute ischemic stroke but recanalization rates are not ideal. The use of concomitant endovascular reperfusion

techniques, such as adjunctive intra-arterial mechanical thrombectomy (AIMT), may help to further improve clinical outcomes.

Section 2: What this study adds

This systematic review and meta-analysis of ten randomised controlled trials provide moderate-to-high quality evidence indicating that, in carefully selected patients, endovascular therapy, in particular AIMT, when provided up to 6 to 8 hours after anterior circulation large vessel ischemic stroke, leads to improved functional outcomes at 90 days without increased mortality or symptomatic intracerebral haemorrhage.

This evidence supports the need to restructure current neurointerventional resources and to change clinical practice.

"TSA" box

Trial-sequential analysis (TSA) is a methodology that evaluates whether statistically significant results of meta-analysis can be reliable taking into account its information size (cumulative sample sizes of all included randomized controlled trials). For example, significant results can occur due to play of chance. TSA adjusts the threshold of statistical significance to the data size to decrease the random error.

Contributorship statement and garantors

JJF and JC were the guarantors. All authors but JMF contributed to the drafting of the manuscript, the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. FBR developed the search strategy. FBR and JBN conducted the report screening, study inclusion, data extraction, and result interpretation and discussion. DC performed the statistical analysis, and conducted result interpretation and discussion. JMF, JJF and JC provided expertise on stroke. JJF and JC also provided expertise on methodology. All authors read, provided feedback and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) No author has support for the submitted work; (2) JJF have speaker and consultant relationships with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) FBR, JBN, DC, and JC have no non-financial interests that may be relevant to the submitted work. JMF received in the last 3 years speaker fees from Boehringer Ingelheim and consultancy fees from Boehringer Ingelheim, Lundbeck, and Daichi Sankyo.

Funding statement and statement of the independence of researcher from funders

No financial or non-financial support of any kind was provided. There is no dependency relation between researchers and funders or sponsors.

Data sharing statement

No additional data available.

Ethics committee approval

No required.

Transparency statement

The lead authors (JC and JJF) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;**380**(9859):2095-128.
2. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology 2012;**79**(17):1781-7.
3. Thrift AG, Cadilhac DA, Thayabaranathan T, et al. Global stroke statistics. Int J Stroke 2014;**9**(1):6-18.
4. Fisher M. Characterizing the target of acute stroke therapy. Stroke 1997;**28**(4):866-72.
5. Ueda T, Sakaki S, Kumon Y, et al. Multivariable analysis of predictive factors related to outcome at 6 months after intra-arterial thrombolysis for acute ischemic stroke. Stroke 1999;**30**(11):2360-5.
6. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2014;**7**:CD000213.
7. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;**384**(9958):1929-35.
8. Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;**369**(9558):275-82.
9. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007;**38**(3):967-73.
10. Lin C, Li N, Wang K, et al. Efficacy and safety of endovascular treatment versus intravenous thrombolysis for acute ischemic stroke: a meta-analysis of randomized controlled trials. PLoS One 2013;**8**(10):e77849.
11. Singh B, Parsaik AK, Prokop LJ, et al. Endovascular therapy for acute ischemic stroke: a systematic review and meta-analysis. Mayo Clin Proc 2013;**88**(10):1056-65.
12. Fargen KM, Neal D, Fiorella DJ, et al. A meta-analysis of prospective randomized controlled trials evaluating endovascular therapies for acute ischemic stroke. J Neurointerv Surg 2015;**7**(2):84-9.
13. Osanai T, Pasupuleti V, Deshpande A, et al. Acute endovascular reperfusion therapy in ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2015;**10**(4):e0122806.
14. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;**349**:g7647.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;**151**(4):W65-94.
16. Lang TA, Altman DG. Basic Statistical Reporting for Articles Published in Biomedical Journals: The "Statistical Analyses and Methods in the Published Literature" or The SAMPL Guidelines". Science Editors' Handbook, European Association of Science Editors 2013.
17. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions*: Wiley Online Library, 2008.
18. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;**33**(1):159-74.
19. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;**19**(5):604-7.
20. Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Stat Med 2002;**21**(11):1575-600.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;**21**(11):1539-58.
22. Brok J, Thorlund K, Gluud C, et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008;**61**(8):763-9.
23. Fiorella DJ, Fargen KM, Mocco J, et al. Thrombectomy for acute ischemic stroke: an evidence-based treatment. J Neurointerv Surg 2015;**7**(5):314-5.
24. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**(7109):629-34.

25. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. JAMA 2006;**295**(6):676-80.
26. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;**328**(7454):1490.
27. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;**368**(10):893-903.
28. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med 2013;**368**(10):904-13.
29. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 2013;**368**(10):914-23.
30. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;**372**(1):11-20.
31. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;**372**(11):1019-30.
32. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;**372**(11):1009-18.
33. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;**372**(24):2285-95.
34. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;**372**(24):2296-306.
35. Mocco J, Zaidat O, Von Kummer R, et al. Results of the THERAPY trial: A prospective, randomized trial to define the role of mechanical thrombectomy as adjunctive treatment to iv rtpa in acute ischemic stroke. International Journal of Stroke 2015;**10**:10.
36. Bracard S, Guillemin F, Ducrocq X. THRACE study: Intermediate analysis results. International Journal of Stroke 2015;**10**:31.
37. Khatri P, Hill MD, Palesch YY, et al. Methodology of the Interventional Management of Stroke III Trial. Int J Stroke 2008;**3**(2):130-7.
38. Ciccone A, Valvassori L, Nichelatti M, et al. SYNTHESIS expansion: design of a nonprofit, pragmatic, randomized, controlled trial on the best fast-track endovascular treatment vs. standard intravenous alteplase for acute ischemic stroke. Int J Stroke 2011;**6**(3):259-65.
39. Kidwell CS, Jahan R, Alger JR, et al. Design and rationale of the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) Trial. Int J Stroke 2014;**9**(1):110-6.
40. Fransen PS, Beumer D, Berkhemer OA, et al. MR CLEAN, a multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke in the Netherlands: study protocol for a randomized controlled trial. Trials 2014;**15**:343.
41. Demchuk AM, Goyal M, Menon BK, et al. Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE) trial: methodology. Int J Stroke 2015;**10**(3):429-38.
42. Campbell BC, Mitchell PJ, Yan B, et al. A multicenter, randomized, controlled study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits with Intra-Arterial therapy (EXTEND-IA). Int J Stroke 2014;**9**(1):126-32.
43. Saver JL, Goyal M, Bonafe A, et al. Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. Int J Stroke 2015;**10**(3):439-48.
44. Molina CA, Chamorro A, Rovira A, et al. REVASCAT: a randomized trial of revascularization with SOLITAIRE FR device vs. best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight-hours of symptom onset. Int J Stroke 2015;**10**(4):619-26.
45. Mocco J, Khatri P, Zaidat O. Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY). Secondary Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) 2011. https://clinicaltrials.gov/ct2/show/study/NCT01429350.
46. Bracard S. Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE). Secondary Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE) 2010. https://clinicaltrials.gov/ct2/show/study/NCT01062698?term=thrace&rank=1.
47. Mullen MT, Pisapia JM, Tilwa S, et al. Systematic review of outcome after ischemic stroke due to anterior circulation occlusion treated with intravenous, intra-arterial, or combined intravenous+intra-arterial thrombolysis. Stroke 2012;**43**(9):2350-5.

48. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012;**380**(9849):1241-9.
49. Goyal M, Almekhlafi MA, Fan L, et al. Evaluation of interval times from onset to reperfusion in patients undergoing endovascular therapy in the Interventional Management of Stroke III trial. Circulation 2014;**130**(3):265-72.
50. Chen CJ, Ding D, Starke RM, et al. Endovascular vs medical management of acute ischemic stroke. Neurology 2015.
51. Yarbrough CK, Ong CJ, Beyer AB, et al. Endovascular Thrombectomy for Anterior Circulation Stroke: Systematic Review and Meta-Analysis. Stroke 2015;**46**(11):3177-83.
52. Badhiwala JH, Nassiri F, Alhazzani W, et al. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. Jama 2015;**314**(17):1832-43.
53. Khatri P, Yeatts SD, Mazighi M, et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol 2014;**13**(6):567-74.
54. Ciccone A, Investigators SE. Complexity of the endovascular intervention and clinical outcomes in acute ischaemic stroke. Lancet Neurol 2014;**13**(9):865.
55. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press 1992;**1**(2):113-9.
56. Duncan PW, Jorgensen HS, Wade DT. Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke 2000;**31**(6):1429-38.
57. Naci H, Dias S, Ades AE. Industry sponsorship bias in research findings: a network meta-analysis of LDL cholesterol reduction in randomised trials of statins. BMJ 2014;**349**:g5741.
58. Korn EL, Freidlin B, Mooney M. Stopping or reporting early for positive results in randomized clinical trials: the National Cancer Institute Cooperative Group experience from 1990 to 2005. J Clin Oncol 2009;**27**(10):1712-21.

Figures

Figure 1 – Study selection flow diagram

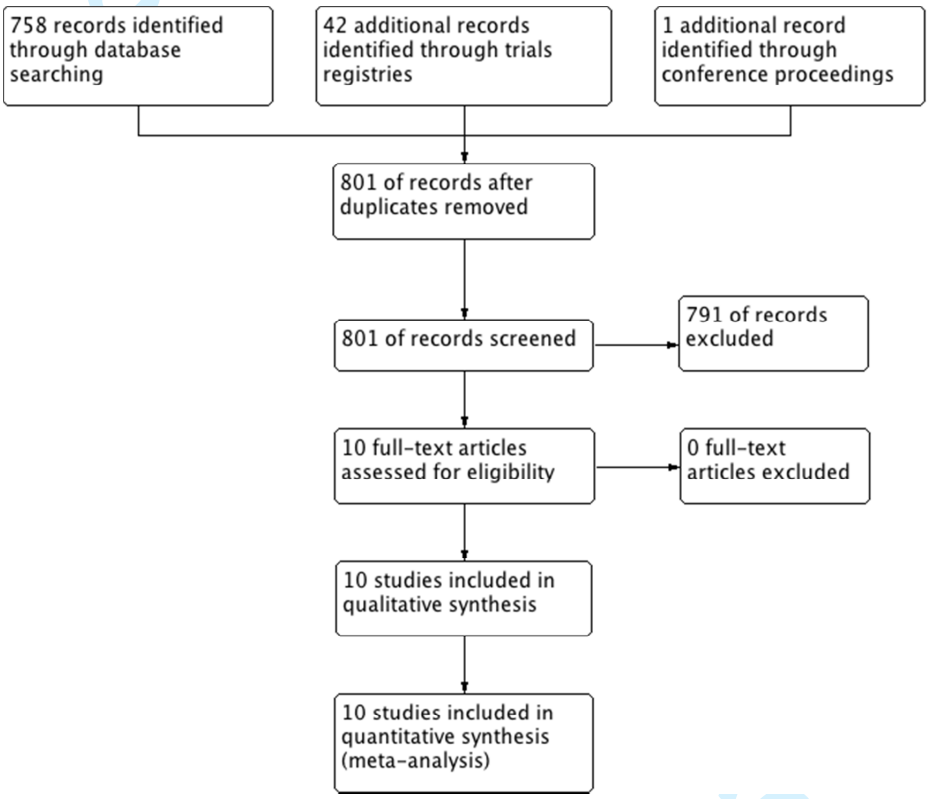


Figure 2 – Risk of bias summary

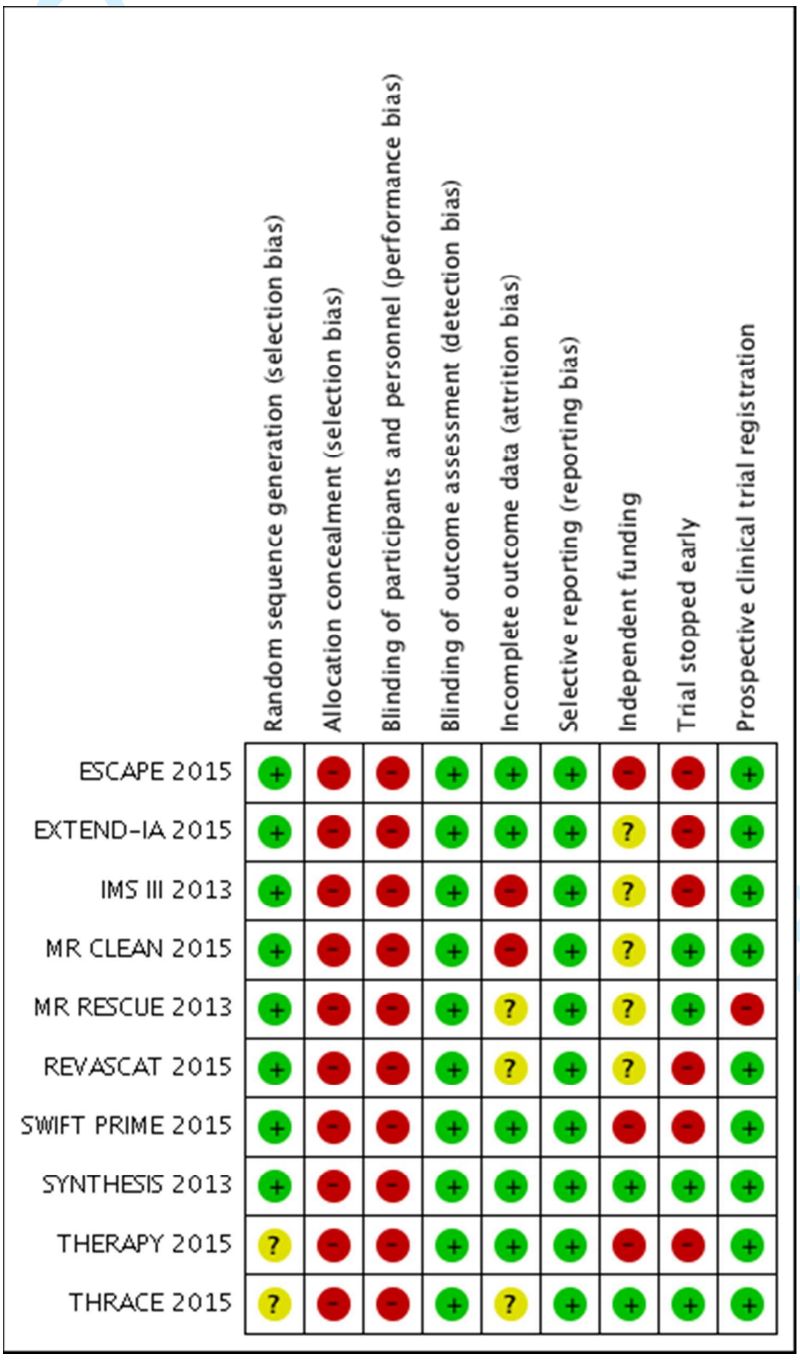


Figure 3 – Forest plot for a good outcome (mRS≤2) at 90 days, including year of study publication subgroup analysis. Mantel-Haenszel method; CI, Confidence interval.

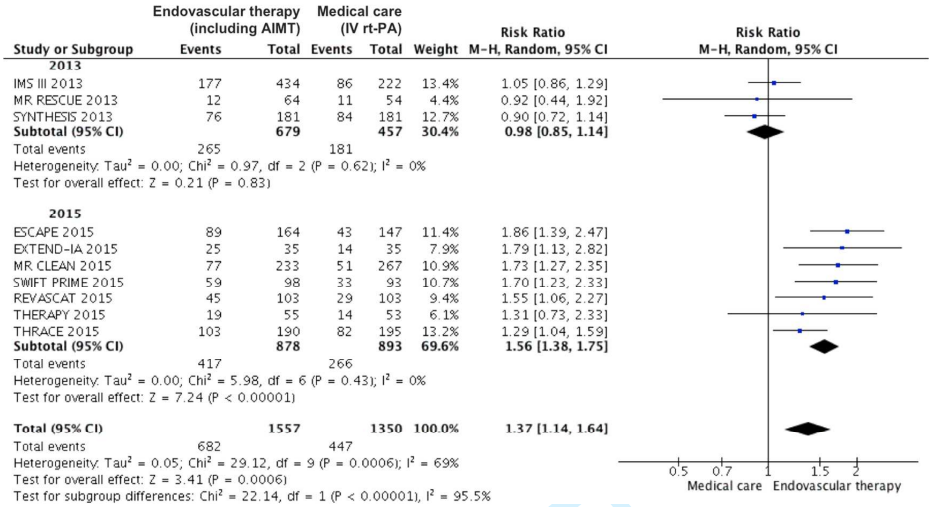
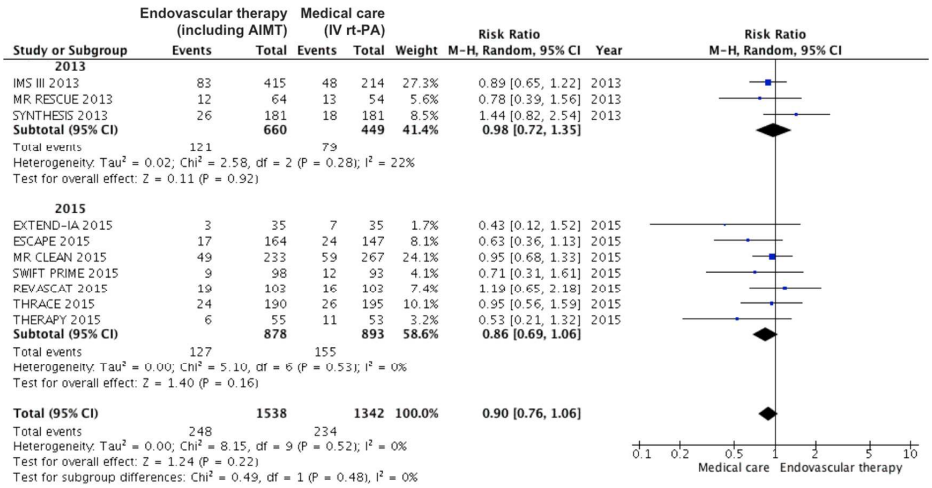


Figure 4 – Forest plot for mortality at 90 days, including year of study publication subgroup analysis. M-H, Mantel-Haenszel method; CI, Confidence interval.



Tables

Trial	Source	Trial period	Location	No. of centres	No. of patients*	Primary outcome	Enrolment criteria			
							Age, y	Symptom onset to		NIHSS
								rt-PA, h	Endovascular therapy (AIMT), h	
IMS III[27]	Broderick et al., 2013	2006 - 2012	USA, CAN, AUS, ESP, DEU, FRA, NLD	58	656	mRS ≤ 2 at 90d	18 - 82	3	5	≥ 10***
SYNTHESIS[28]	Ciccone et al., 2013	2008 - 2012	ITA	24	362	mRS ≤ 1 at 90d	18 - 80	4.5	6	≤ 25
MR RESCUE[29]	Kidwell et al., 2013	2004 - 2011	USA, CAN	22	127	mRS scores at 90d	18 - 85	4.5**	8	6 - 29
MR CLEAN[30]	Berkhemer et al., 2015	2010 - 2014	NLD	16	500	mRS scores at 90d	≥18	4.5**	6	≥ 2
ESCAPE[31]	Goyal et al., 2015	2013 - 2014	CAN, USA, KOR, IRL, GBR	22	315	Median mRS at 90d	≥18	4.5**	12	Unrestricted
EXTEND-IA[32]	Campbell et al., 2015	2012 - 2014	AUS, NZL	10	70	Reperfusion at 24h and NIHSS at 3d	≥18	4.5	6	Unrestricted
SWIFT PRIME[33]	Saver et al., 2015	2012 - 2015	USA, FRA, DEU, ESP, CHE, DNK, AUT	39	196	mRS scores at 90d	18 - 80	4.5	6	8 - 29
REVASCAT[34]	Jovin et al., 2015	2012 - 2014	ESP	4	206	mRS scores at 90d	18 - 85	4.5**	8	≥ 6
THERAPY[35]	Mocco et al., 2015	2012 - 2015	USA, GER	36	108	mRS ≤ 2 at 90d	18 - 85	4.5****	5*****	≥ 8
THRACE[36]	Bracard et al., 2015	2010 - 2015	FRA	26	385	mRS scores at 90d	18 - 80	4	5	10 - 25

Table 1 - Characteristics of included studies.

y, years; rt-PA, recombinant tissue plasminogen activator; h, hours; AIMT, adjuvant intra-arterial mechanical thrombolysis; NIHSS, National Institute of Health Stroke Scale; USA, United States of America; CAN, Canada; AUS, Australia; ESP, Spain; DEU, Germany; FRA, FRANCE; NLD, Netherlands; mRS, modified Rankin Scale; d, days; ITA, Italy; KOR, South Korea; IRL, Ireland; GBR, United Kingdom; NZL, New Zealand; CHE, Switzerland; DNK, Denmark; AUT, Austria.

* Intention to treat population; ** If illegible; *** ≥8 if CT or MR angiographic evidence of internal carotid artery, first division of middle cerebral artery (M1) or basilar artery occlusion; **** a time limit of 3 hours was used for participants over 80 years old, with a history of stroke and diabetes, anticoagulant use and NIHSS > 25; ***** Initial protocol allowed up to 8 hours but revision limited to up to 5 hours (6.5% of participants were over 5 hours).

Trial	Endovascular therapy (AIMT) arm					Medical care (IV rt-PA) arm				
	Intervention	**n***	**Age, y** mean ± SD	**Male,** no. (%)	**NIHSS,** mean ± SD	**Intervention**	**n***	**Age, y** mean ± SD	**Male,** no. (%)	**NIHSS,** mean ± SD
IMS III[27]	IV rt-PA ± IV heparin ± thrombectomy and/or IA rt-PA	434	63 ± 11.07	218 (50.2)	20 ± 5.54	IV rt-PA	222	61 ± 10.23	122 (55.0)	18 ± 3.69
SYNTHESIS[28]	IV heparin ± thrombectomy and/or IA rt-PA	181	66 ± 11	106 (59)	13 ± 5.98	IV rt-PA	181	67 ± 11	103 (57)	13 ± 6.73
MR RESCUE[29]	Thrombectomy ± IA rt-PA ± IV heparin ± IV rt-PA	70*/64***	64 ± 12.78***	30 (46.9)***	17 ± 4.72***	± IV rt-PA	57*/54***	67 ± 16.48***	27 (50)***	17 ± 5.73***
MR CLEAN[30]	± IV rt-PA + thrombectomy ± IA rt-PA or IA uPA	233	65 ± 16.04	135 (57.9)	17 ± 5.22	± IV rt-PA	267	66 ± 15.58	157 (58.8)	18 ± 5.96
ESCAPE[31]	Thrombectomy ± IV rt-PA	165	71 ± 15.71	79 (47.9)	16 ± 5.24	± IV rt-PA	150	70 ± 15.72	71 (47.3)	16 ± 5.99
EXTEND-IA[32]	IV rt-PA ± thrombectomy	35	69 ± 12.3	17 (49)	17 ± 5.41	IV rt-PA	35	70 ± 11.8	17 (49)	14 ± 7.73
SWIFT PRIME[33]	IV rt-PA ± thrombectomy	98*/98***	65 ± 12.5***	54 (55.1)***	17 ± 5.27***	IV rt-PA	98*/93***	66 ± 11.3***	45 (48.4)***	16 ± 4.52***
REVASCAT[34]	Thrombectomy ± IV rt-PA	103	66 ± 11.3	55 (53.4)	17 ± 4.51	± IV rt-PA	103	67 ± 9.5	54 (52.4)	16 ± 5.26
THERAPY[35]	IV rt-PA ± thrombectomy	55	67 ± 11.4	34 (61.8)	17 ± 6.05	IV rt-PA	53	70 ± 10.3	23 (43.9)	18 ± 5.38
THRACE[36]	IV rt-PA ± thrombectomy	190	N/S	N/S	N/S	IV rt-PA	195	N/S	N/S	N/S

Table 2 - Characteristics of included patients.

AIMT, adjuvant intra-arterial mechanical thrombolysis; IA, intra-arterial; IV, intravenous; NIHSS, National Institute of Health Stroke Scale; N/S, Not Specified; rt-PA, recombinant tissue plasminogen activator; uPA, urokinase-type plasminogen activator.

* Intention to treat population; ** Per protocol population; *** Modified intention to treat population.

Trial	Both arms		Endovascular therapy (AIMT) arm					Medical care (IV rt-PA) arm	
	n*	IV rt-PA no. (%)	n*	Thrombectomy no. (%)	IV rt-PA no. (%)	IA rt-PA no. (%)	Thrombectomy + IV rt-PA no. (%)	n*	IV rt-PA no. (%)
IMS III[27]	656	656 (100)	434	170 (39.2)	434 (100)**	266 (61.3)	170 (39.2)	222	222 (100)
SYNTHESIS[28]	362	178 (49.2)	181	56 (30.9)	0 (0)	109 (60.2)	0 (0) / 56 (30.9)***	181	178 (98.3)
MR RESCUE[29]	127	44 (34.6)	70	61 (87.1)	28 (40.0)	8 (11.4)	28 (40.0)	57	16 (28.1)
MR CLEAN[30]	500	445 (89.0)	233	195 (83.7)	203 (87.1)	25 (10.7)	N/S	267	242 (90.6)
ESCAPE[31]	315	238 (75.6)	165	151 (91.5)	120 (72.7)	N/A	120 (72.7)	150	118 (78.7)
EXTEND-IA[32]	70	70 (100)	35	27 (77.1)	35 (100)	N/A	27 (77.1)	35	35 (100)
SWIFT PRIME[33]	191	191 (100)	98****	87 (88.8)****	98 (100)****	N/A	87 (88.8)****	93****	93 (100)****
REVASCAT[34]	206	150 (72.8)	103	98 (95.1)	70 (68.0)	1 (1.0)	N/S	103	80 (77.7)
THERAPY[35]	108	108 (100)	55	N/S	55 (100)	0 (0.0)	N/S	53	53 (100)
THRACE[36]	385	385 (100)	190	N/S	190 (100)	0 (0.0)	N/S	195	195 (100)

Table 3 - Characteristics of the intervention within treatment arms.

AIMT, Adjuvant intra-arterial mechanical thrombolysis; IV, intravenous; IA, Intra-arterial; N/A, Not applicable; N/S, Not specified; rt-PA, recombinant tissue plasminogen activator.

* Intention to treat population; ** Approximately two thirds of the standard dose *** IA rt-PA; **** Modified intention to treat population

Table 4 – Summary of findings table

Endovascular therapy (including AIMT) compared to medical care (IV rt-PA) for ischemic stroke – pooled analyses from all included studies and 2015 trials only

Outcomes	№ of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical care (IV rt-PA)	Risk difference with endovascular therapy (including AIMT)
mRS≤2 90d (independency outcome)	2907 (10 RCTs)	□□□○ MODERATE [1]	RR 1.37 (1.14 to 1.64)	**Study population**	
				331 per 1000	**123 more per 1000** (46 more to 212 more)
mRS≤2 90d (independency outcome) - year of publication subgroup analysis - 2015	1771 (7 RCTs)	□□□○ MODERATE [1]	RR 1.56 (1.38 to 1.75)	**Study population**	
				298 per 1000	**167 more per 1000** (113 more to 223 more)
Mortality 90d	2880 (10 RCTs)	□□○○ LOW [1,2]	RR 0.90 (0.76 to 1.06)	**Study population**	
				174 per 1000	**17 fewer per 1000** (42 fewer to 10 more)
mRS≤1 90d (excelente outcome)	2522 (9 RCTs)	□□□○ MODERATE [1]	RR 1.53 (1.15 to 2.04)	**Study population**	
				188 per 1000	**100 more per 1000** (28 more to 195 more)
mRS≤1 90d (excellent outcome) - year of publication subgroup analysis - 2015	1386 (6 RCTs)	□□□□ HIGH [1]	RR 2.03 (1.62 to 2.53)	**Study population**	
				128 per 1000	**131 more per 1000** (79 more to 195 more)
Symptomatic intracerebral hemorhage	2526 (9 RCTs)	□□○○ LOW [1,2]	RR 1.02 (0.72 to 1.44)	**Study population**	
				51 per 1000	**1 more per 1000** (14 fewer to 22 more)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE: Grading of Recommendations Assessment, Development and Evaluation working group; CI: Confidence interval; RR: Risk ratio; AIMT: Adjunctive intra-arterial mechanical thrombectomy; mRS: modified Rankin Scale; RCT: Randomized controlled trial, d: day

Endovascular therapy (including AIMT) compared to medical care (IV rt-PA) for ischemic stroke – pooled analyses from all included studies and 2015 trials only

Outcomes	№ of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical care (IV rt-PA)	Risk difference with endovascular therapy (including AIMT)

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. The overall risk of bias was moderate among included studies
2. Confidence interval fails to excluded important benefit or harm

Supplementary material

Annexe S1 - Exemplified search strategy for MEDLINE (OvidSP)

1 exp cerebrovascular disorders/

2 exp basal ganglia cerebrovascular disease/

3 exp brain ischemia/

4 exp carotid artery diseases/

5 exp carotid artery thrombosis/

6 exp intracranial arterial diseases/

7 exp cerebral arterial diseases/

8 exp stroke/

9 (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.

10 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

11 or/1-10

12 exp mechanical thrombolysis/

13 exp embolectomy/

14 exp thrombectomy/

15 (mechanical adj3 (thrombectom* or thromboembolectom* or thrombo-

embolectom* or thrombolys* or remov* or disrupt* or clot* or embolectom* or recanalis* or recanaliz* or retriev*)).tw.

16 neurothrombectom*.tw.

17 merci.tw.

18 penumbra system.tw.

19 solitaire.tw.

20 trevo.tw.

21 or/12-20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 clinical trials as topic.sh.

27 randomly.ab.

28 trial.ti.

29 or/22-28

30 and/11,21,29

31 exp animals/ not humans.sh.

32 30 not 31

Figure S1 - Forest plot for an excellent outcome (mRS≤1) at 90 days, including year of study publication subgroup analysis. M-H, Mantel-Haenszel method; CI, Confidence interval.

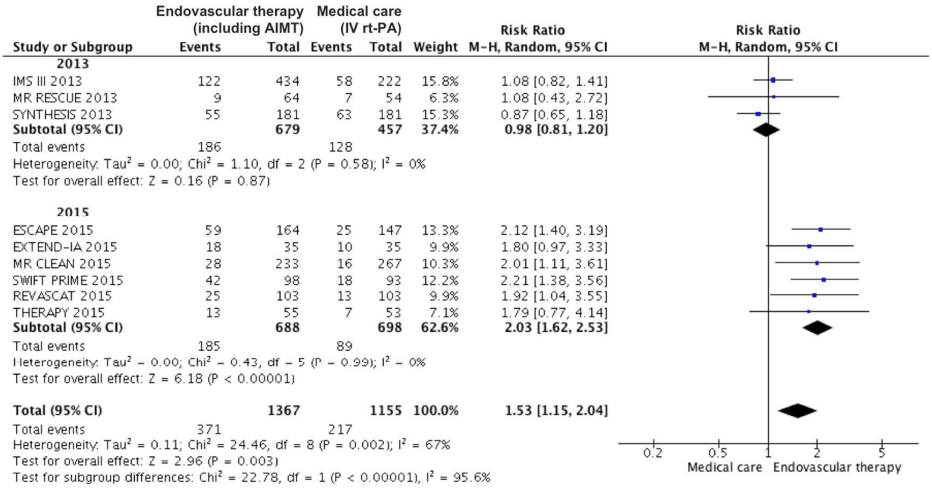
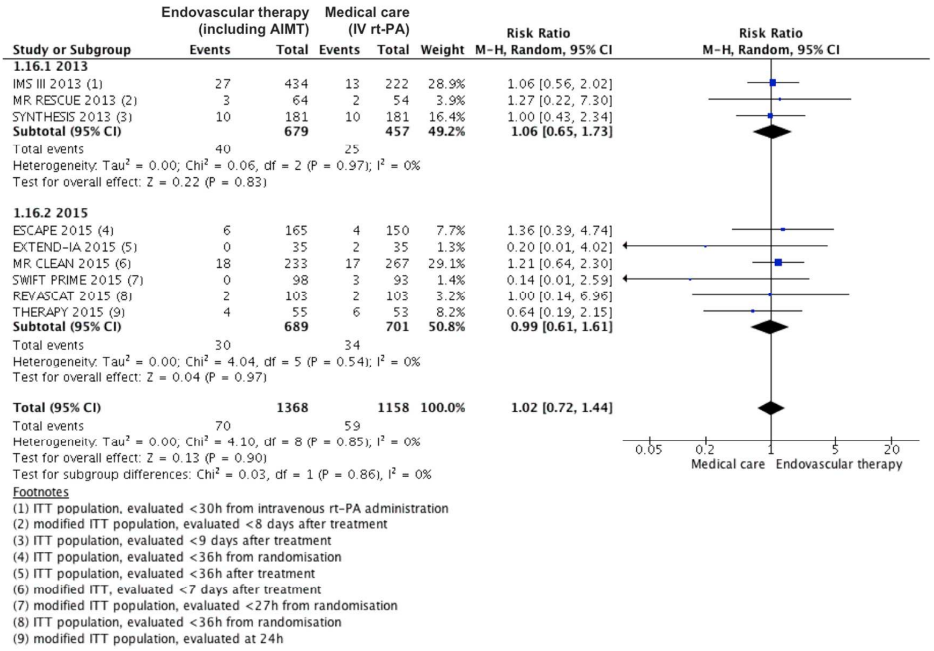
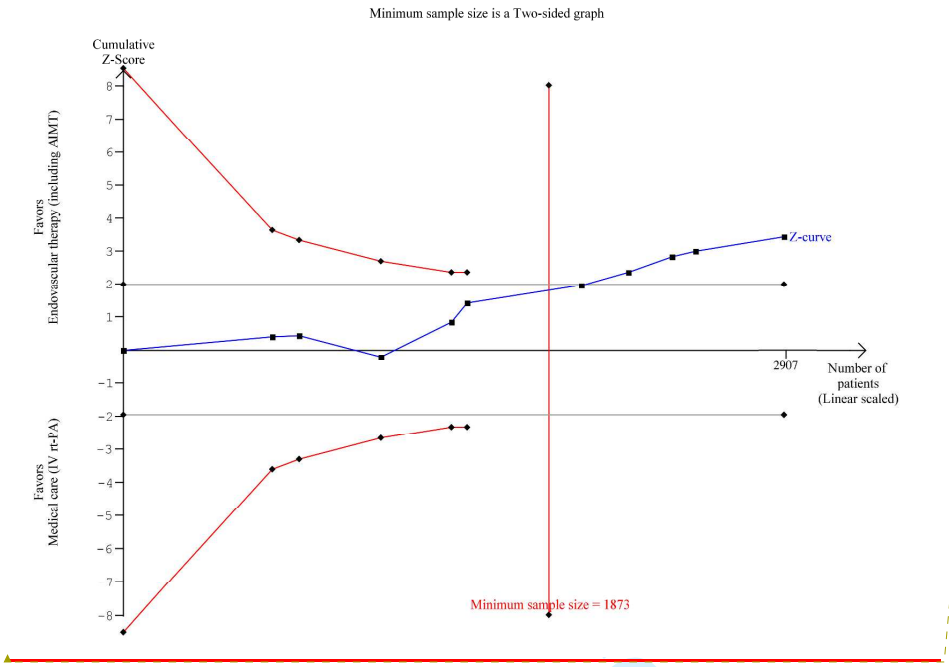


Figure S2 - Forest plot for symptomatic intracerebral haemorrhage, including year of study publication subgroup analysis. M-H, Mantel-Haenszel method; CI, Confidence interval.



Footnotes
(1) ITT population, evaluated <30h from intravenous rt-PA administration
(2) modified ITT population, evaluated <8 days after treatment
(3) ITT population, evaluated <9 days after treatment
(4) ITT population, evaluated <36h from randomisation
(5) ITT population, evaluated <36h after treatment
(6) modified ITT, evaluated <7 days after treatment
(7) modified ITT population, evaluated <27h from randomisation
(8) ITT population, evaluated <36h from randomisation
(9) modified ITT population, evaluated at 24h

Figure S3 - Trial sequential analysis for the primary efficacy outcome.



Solid blue curve represents the cumulative Z curve. Horizontal grey line represent the 5% statistical significance level. Solid red curve represents trial sequential alpha spending monitoring boundaries. Vertical red line determines the sample size required to evaluate the independency outcome assuming the RR of the meta-analysis.

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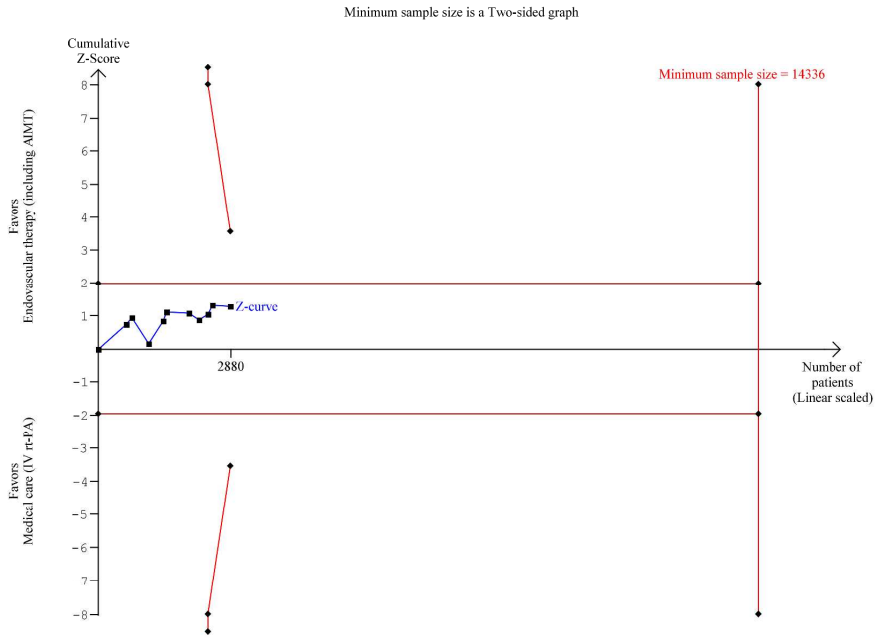
Figure S4 - Trial sequential analysis for the primary safety outcome.



Solid blue curve represents the cumulative Z curve. Horizontal grey line represent the 5% statistical significance level. Solid red curve represents trial sequential alpha spending monitoring boundaries. Vertical red line determines the sample size required to evaluate the independency outcome assuming the RR of the meta-analysis.

Figure S5 – Forest plot for a good outcome (mRS≤2) at 90 days, including gender subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval.

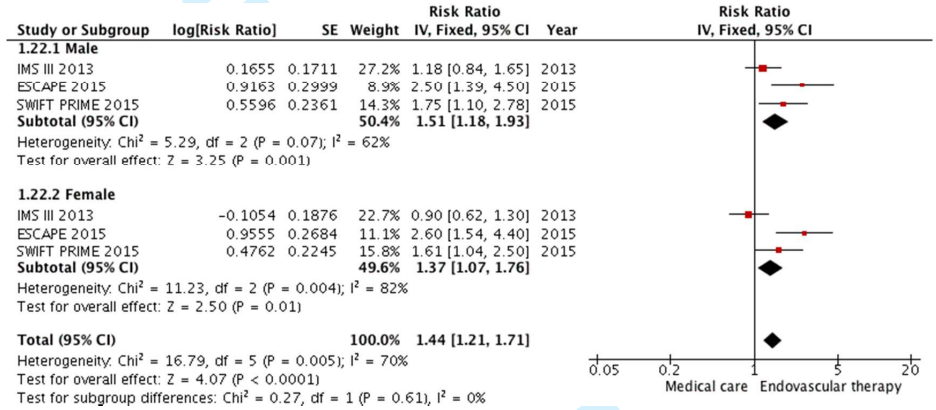


Figure S6 – Forest plot for a good outcome (mRS≤2) at 90 days, including rt-PA administration subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval.

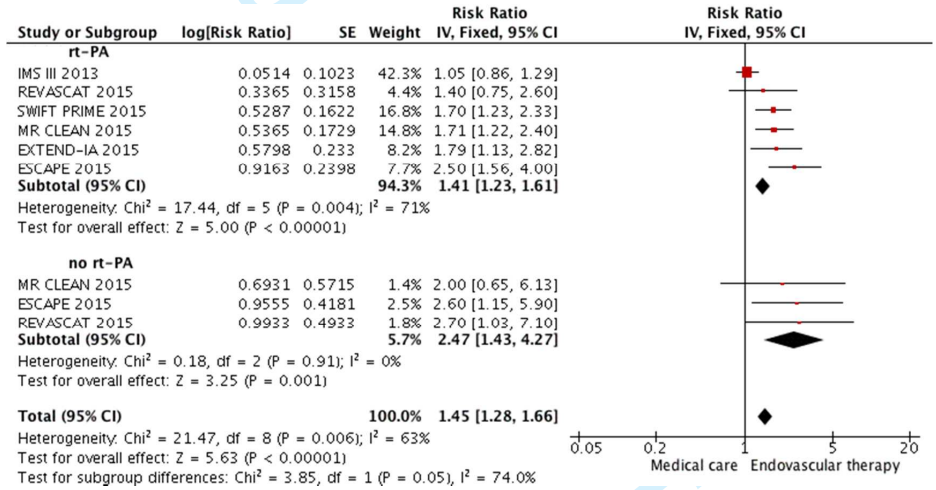
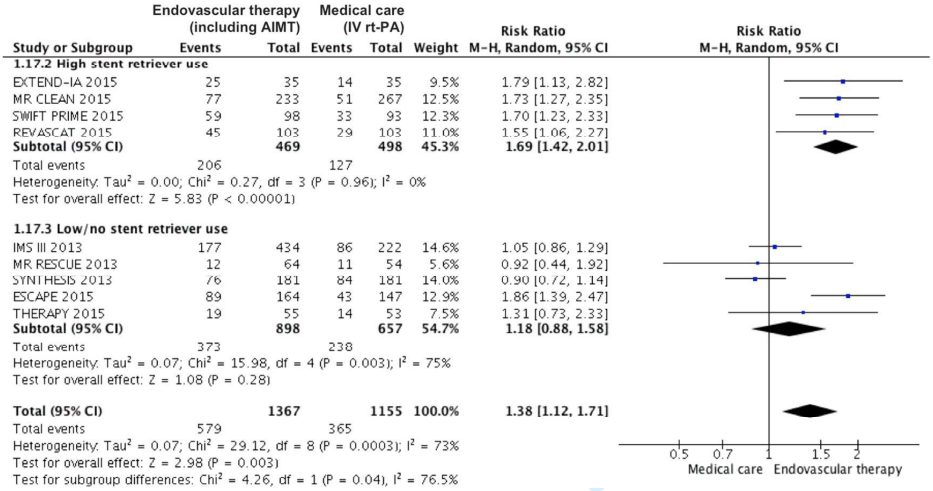


Figure S7 – Forest plot for a good outcome (mRS≤2) at 90 days, including high (≥85%) stent retriever use versus low (<85%) to no stent retriever use subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval.



Trial	Imaging methods	Imaging criteria required for enrolment		
		ASPECTS	Confirmation of large vessel occlusion	Perfusion study
IMS III[27]	CT; angiography, or CTA	<4	No	No
SYNTHESIS[28]	CT; angiography	-	No	No
MR RESCUE[29]	CT or MRI; CTA or MRA	-	No*	No
MR CLEAN[30]	CT or MRI; Angiography, CTA, or MRA	-	Yes	No
ESCAPE[31]	CT; CTA	>5	Yes	Yes
EXTEND-IA[32]	CT or MRI; CTA or MRA	-	Yes	Yes
SWIFT PRIME[33]	CT or MRI; CTA or MRA	>5	Yes	Yes
REVASCAT[34]	CT or MRI; angiography, CTA or MRA	≥6 in MRI, ≥7 in CT, >8 if >80 years old	Yes	No
THERAPY[35]	CT; angiography	-	Yes**	No
THRACE[36]	CT; angiography	N/S	Yes	N/S

Table S1 – Imaging methods and enrolment criteria. ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; CTA, CT angiography; MRI, magnetic resonance imaging; MRA, MRI angiography; N/S, Not specified.

* MR RESCUE required documentation of an anterior circulation stroke but not documentation of a vascular occlusion. While MR RESCUE was evaluating the value of penumbral imaging for patient selection for endovascular thrombectomy, the appearance on imaging was not an inclusion or exclusion criterion. ** Clot length ≥ 8 mm from thin-sliced non-contrast CT.

Trial	Thrombectomy no.*	Thrombectomy devices	
		Stent retrievers (%)	Coil retrievers and aspiration devices (%)
IMS III[27]	170	Solitaire FR (2.9%)	Merci retriever (55.9%), Penumbra system (31.8%), other** (9.4%)
SYNTHESIS[28]	56	Solitaire FR (32.1%), Trevo (8.9%)	Merci retriever (8.9%), Penumbra system (16.1%), other** (33.9%)
MR RESCUE[29]	61	-	Merci retriever (60.7%), Penumbra system (22.9%), both devices (16.4%)
MR CLEAN[30]	195	Solitaire FR (97.5%)	Merci retriever (1.0%), Thromboaspiration** (0.5%), Wire disruption** (1.0%)
ESCAPE[31]	151	Solitaire (66.2%), other** (19.9%)	Thromboaspiration** (13.9%)
EXTEND-IA[32]	27	Solitaire FR (100%)	-
SWIFT PRIME[33]	87	Solitaire FR or Solitaire 2 (100%)	-
REVASCAT[34]	98	Solitaire FR (100%)	-
THERAPY[35]	N/S	-	Penumbra system (N/S)***
THRACE[36]	N/S	Solitaire FR (N/S), Catch (N/S)	Merci retriever (N/S), Penumbra system (N/S)

Table S2 – Thrombectomy devices used.

N/S, Not specified.

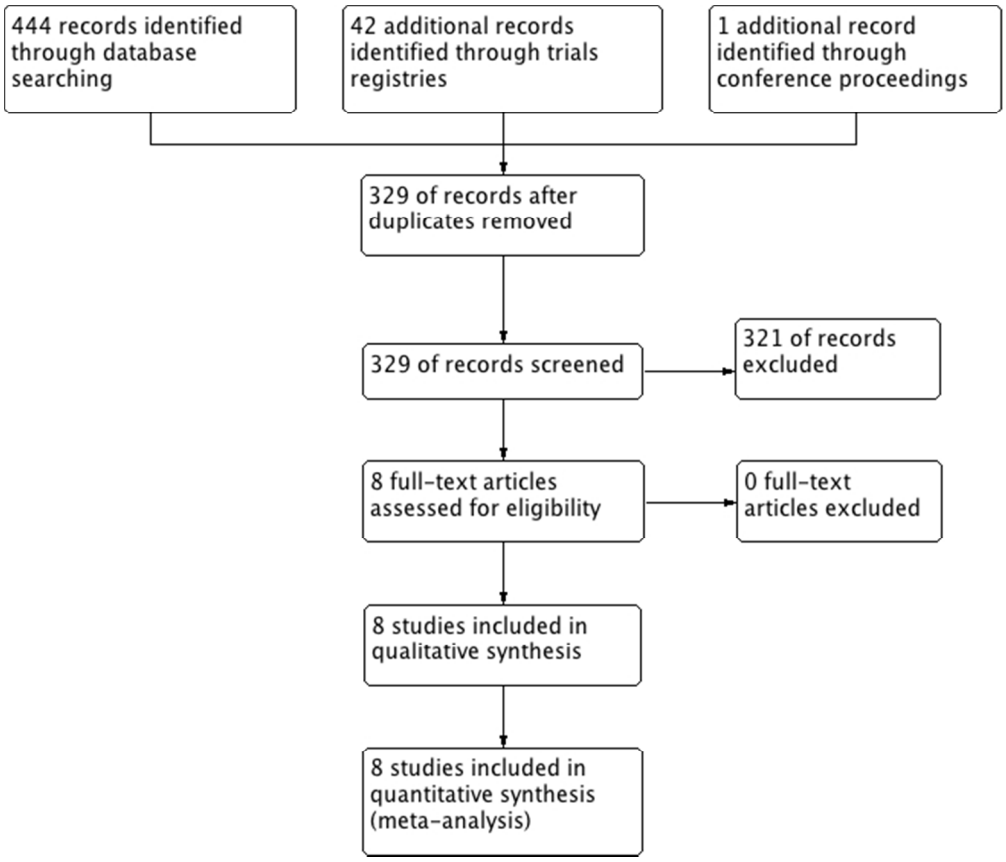
* Per protocol population; ** Device brand not named; *** 7 participants had additional treatment with Solitaire or Trevo stent retrievers.

Trial	Intervention arm no.*	Recanalization	
		Criteria	no. (%)
IMS III[27]	434	TICI≥2b/3	178 (41.0)
SYNTHESIS[28]	181	N/S	N/S
MR RESCUE[29]	70	TICI≥2b/3	16 (22.9)
MR CLEAN[30]	233	mTICI≥2b/3	115 (49.4)
ESCAPE[31]	165	TICI≥2b/3	113 (68.5)
EXTEND-IA[32]	35	mTICI≥2b/3	25 (71.4)
SWIFT PRIME[33]	98**	mTICI≥2b/3	73 (74.5)
REVASCAT[34]	103	mTICI≥2b/3	67 (65.0)
THERAPY[35]	55	mTICI≥2b/3	39 (70.9)
THRACE[36]	190	N/S	N/S

Table S3 – Recanalization rates in intervention arm.

N/S, Not specified; TICI, Thrombolysis In Cerebral Infarction perfusion scale, TICI; mTICI, modified TICI.

* Intention to treat population, ** Modified intention to treat.



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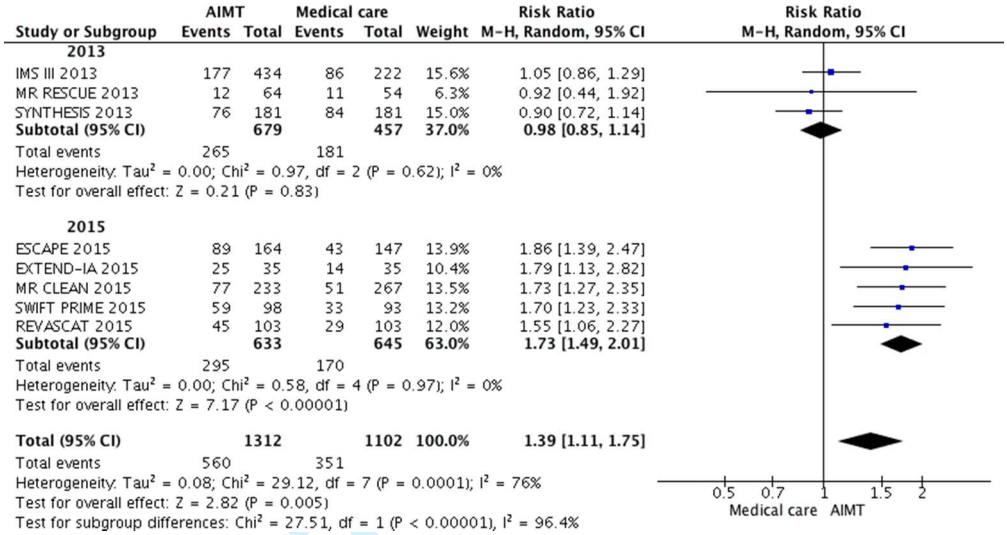

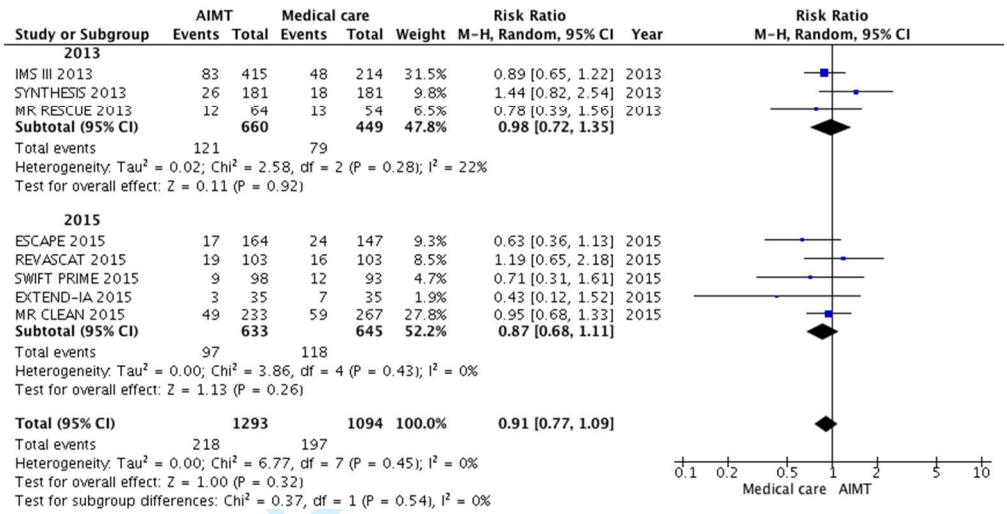

Supplementary material

Annexe S1 - Exemplified search strategy for MEDLINE (OvidSP)

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2 exp basal ganglia cerebrovascular disease/

3 exp brain ischemia/

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6 exp intracranial arterial diseases/

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8 exp stroke/

9 (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.

10 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

11 or/1-10

12 exp mechanical thrombolysis/

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14 exp thrombectomy/

15 (mechanical adj3 (thrombectom* or thromboembolectom* or thrombo-embolectom* or thrombolys* or remov* or disrupt* or clot* or embolectom* or recanalis* or recanaliz* or retriev*)).tw.

16 neurothrombectom*.tw.

17 merci.tw.

18 penumbra system.tw.

19 solitaire.tw.

20 trevo.tw.

21 or/12-20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 clinical trials as topic.sh.

27 randomly.ab.

28 trial.ti.

29 or/22-28

30 and/11,21,29

31 exp animals/ not humans.sh.

32 30 not 31

Figure S1 - Forest plot for a non-favourable functional outcome (mRS>2) at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

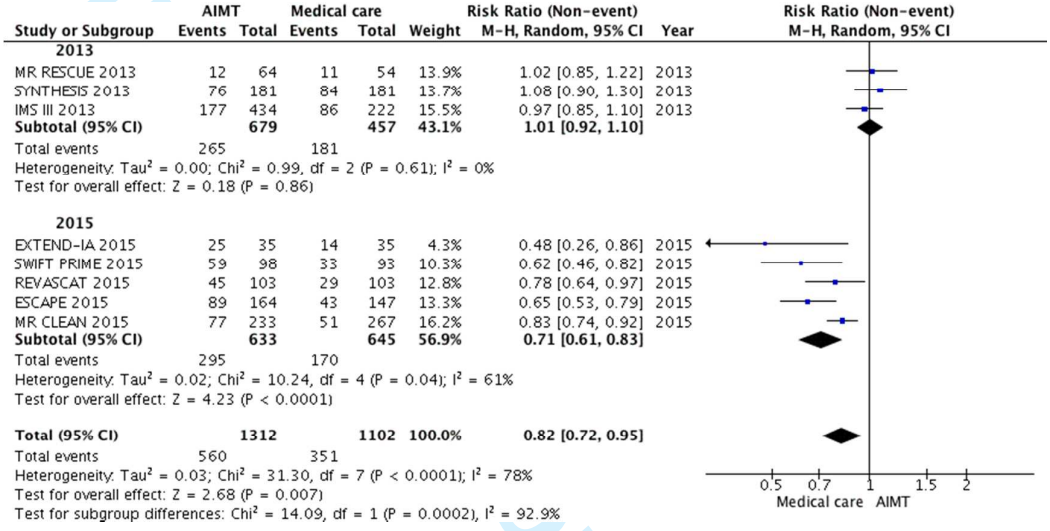


Figure S2 - Forest plot for an excellent outcome (mRS≤1) at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

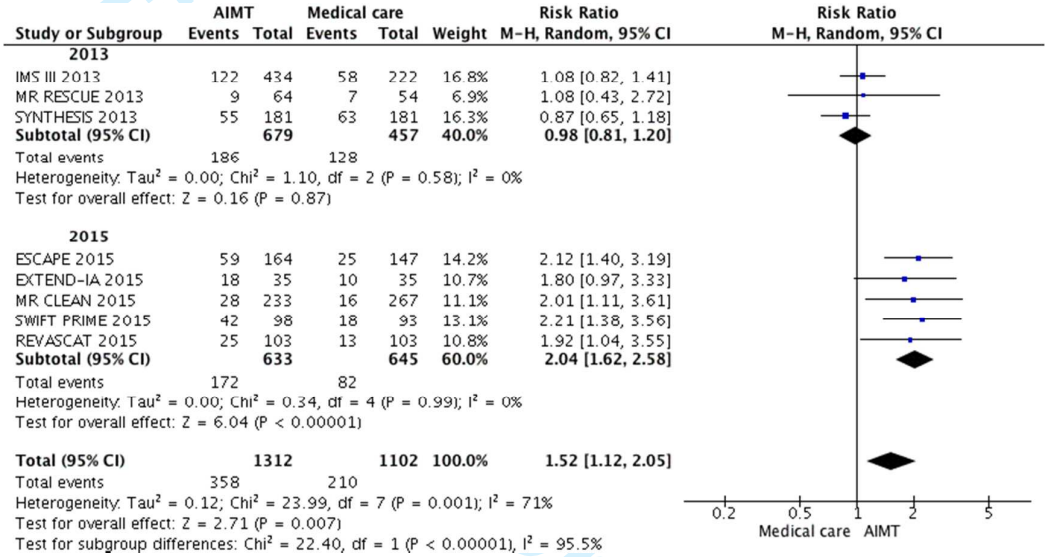
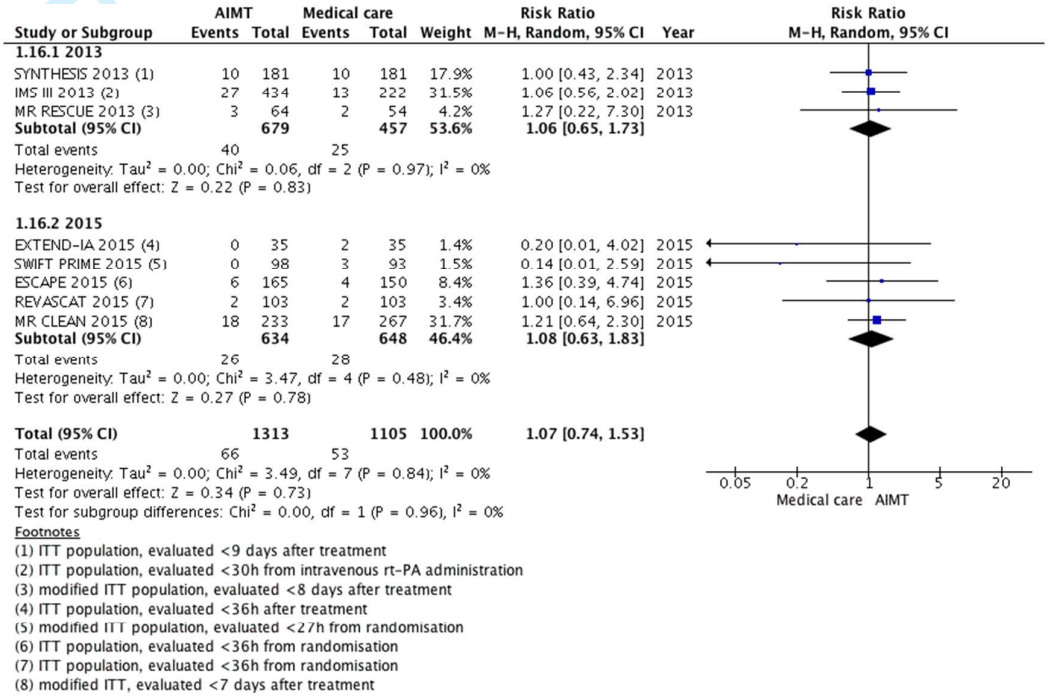


Figure S3 - Forest plot for symptomatic intracerebral haemorrhage, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.



Footnotes
(1) ITT population, evaluated <9 days after treatment
(2) ITT population, evaluated <30h from intravenous rt-PA administration
(3) modified ITT population, evaluated <8 days after treatment
(4) ITT population, evaluated <36h after treatment
(5) modified ITT population, evaluated <27h from randomisation
(6) ITT population, evaluated <36h from randomisation
(7) ITT population, evaluated <36h from randomisation
(8) modified ITT, evaluated <7 days after treatment

Figure S4 – Trial sequential analysis for the primary efficacy outcome.

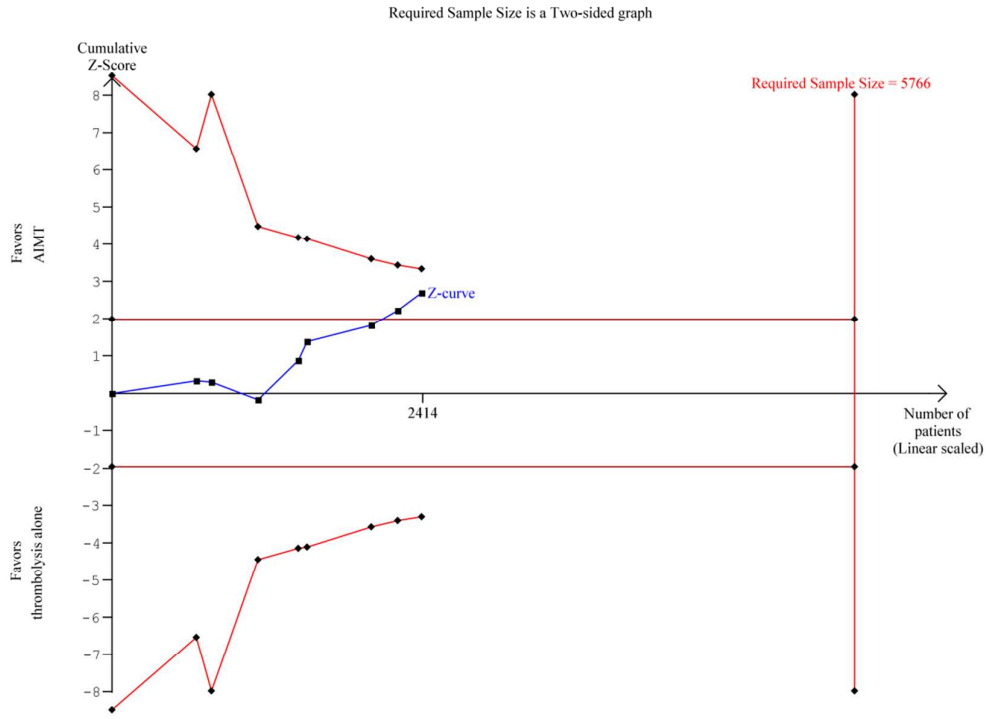


Figure S5 - Trial sequential analysis for the primary safety outcome.

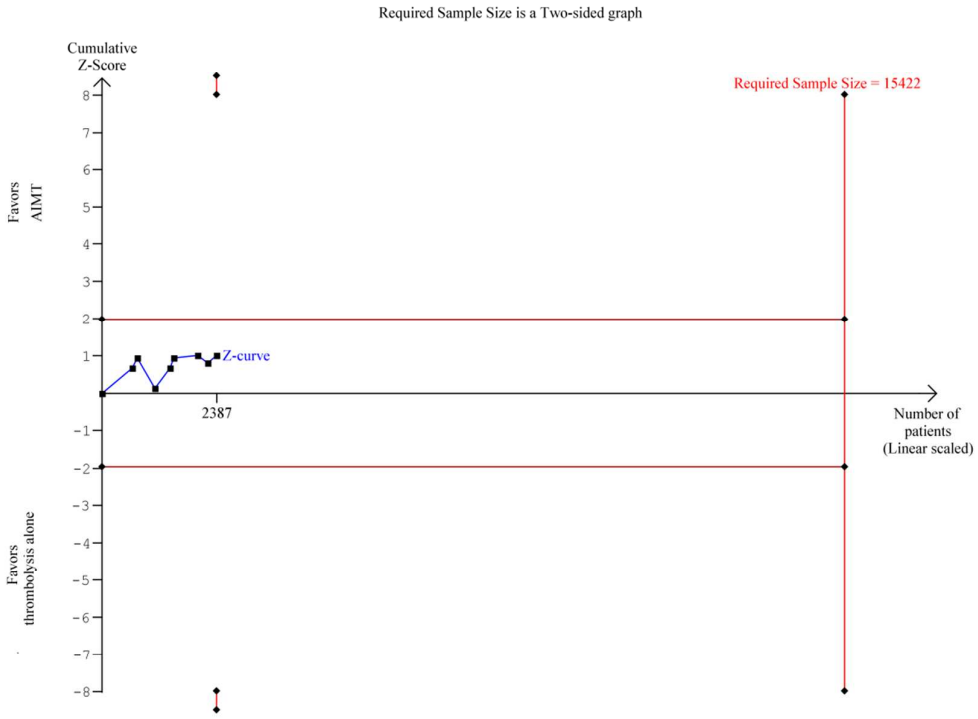


Figure S6 – Forest plot for a good outcome (mRS≤2) at 90 days, including gender subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval; AIMT, Adjuvant intra-arterial mechanical thrombectomy.

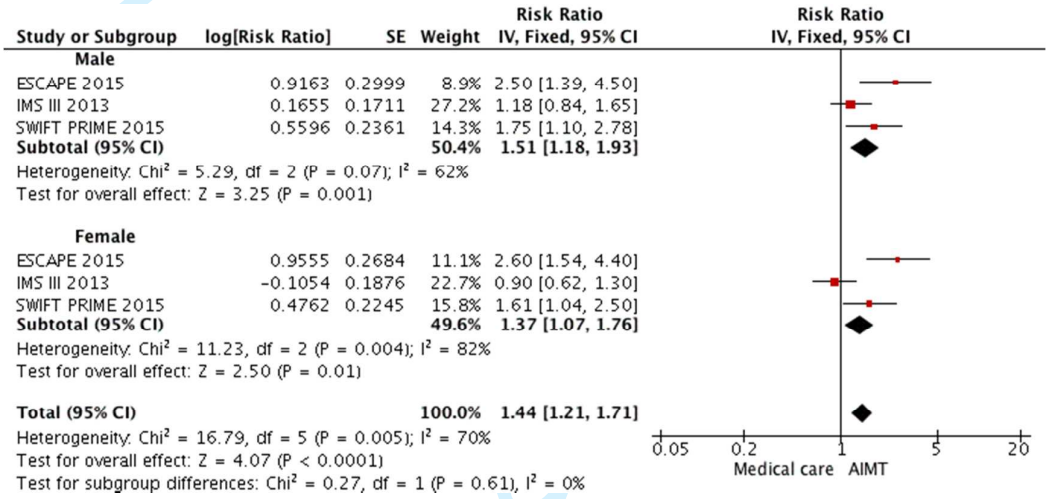


Figure S7 – Forest plot for a good outcome (mRS≤2) at 90 days, including rt-PA administration subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval; AIMT, Adjuvant intra-arterial mechanical thrombectomy.

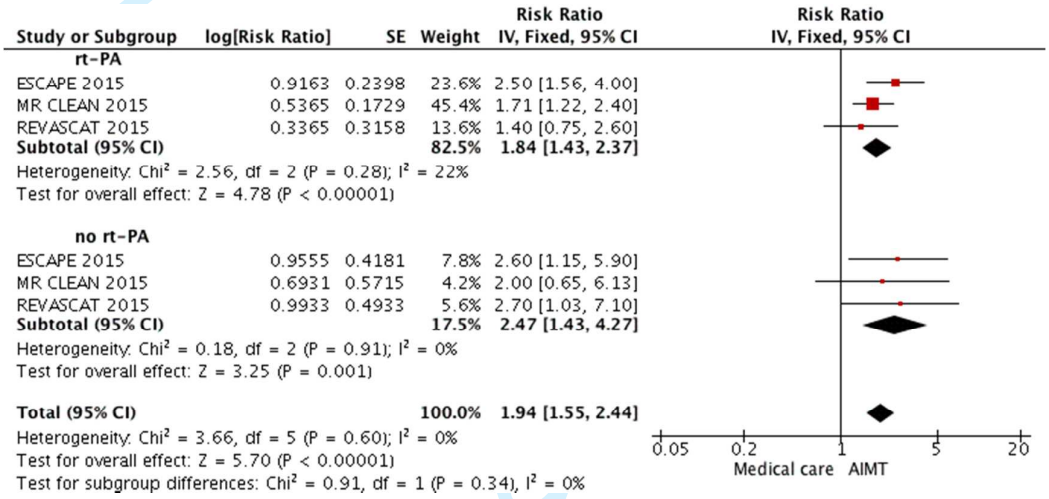
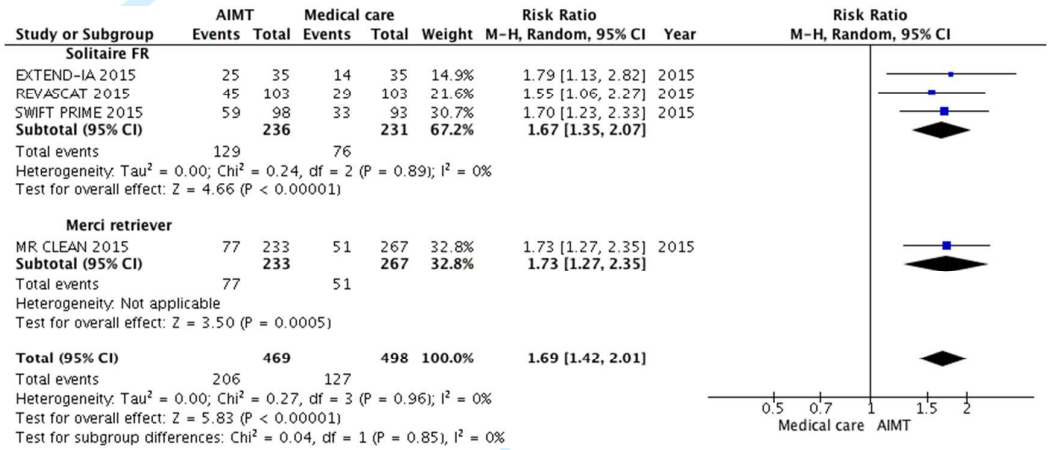
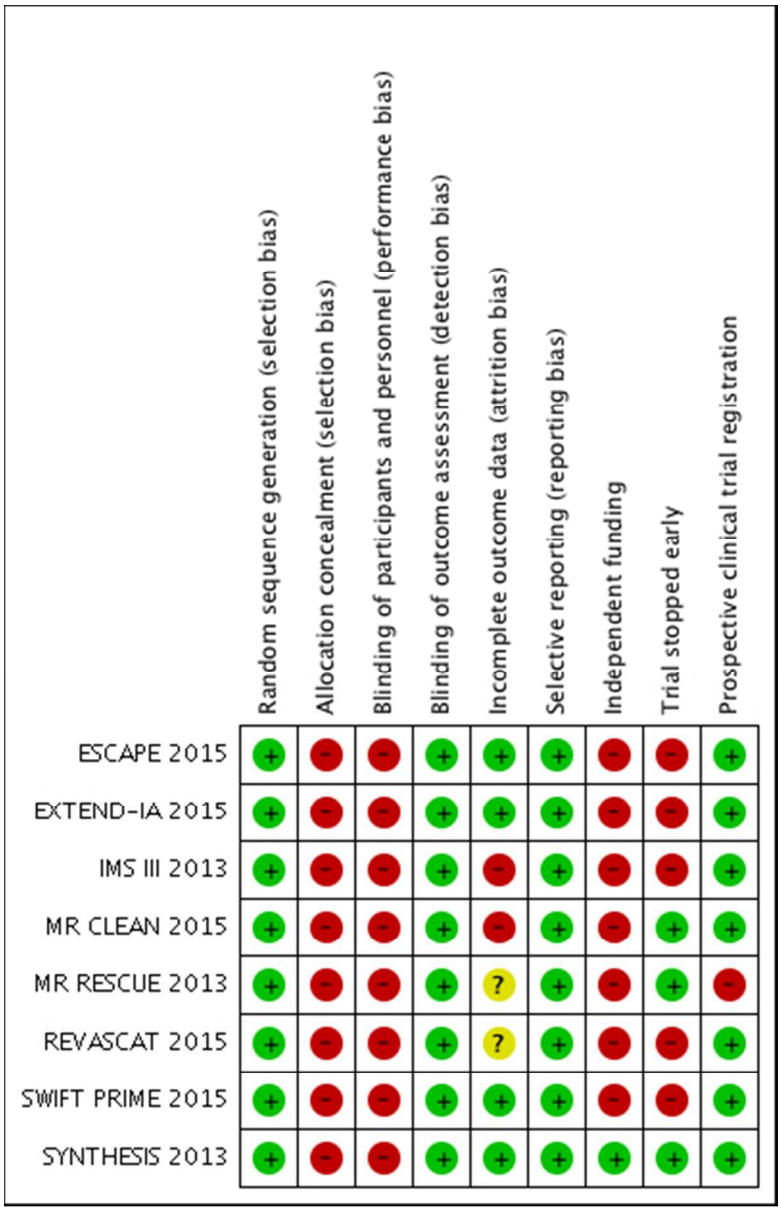


Figure S8 – Forest plot for a good outcome (mRS≤2) at 90 days, including thrombectomy device subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.





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Dear Dr. Alison Tonks
Associate editor BMJ

We would like to thank again for your keenness to publish our manuscript.

Please find below the answers to your comments, which we have very much appreciated and significantly helped improving our manuscript.

All changes made to the resubmitted manuscript were highlighted in yellow.

We would also like to underlie that in this revised version of the manuscript we have updated our search, which resulted in more than 400 additional references and that we were able to include two additional unpublished studies.

All comments and criticisms raised by Dr. Jose Merino were addressed and the final result is a manuscript different from others recently published, not only because we included more studies, but also because the resulting deep clinical critical discussion in our paper on how the obtained results translate into clinical practice is, we think, unique and help deciding the best therapeutic option for an individual patient with an acute stroke.

Following one strong suggestion of the Editorial Board, we have also included in the authors team José Manuel Ferro, a very experienced stroke specialist (Member of the Steering Committees of the EAFT, ESPS II, TESS II, TACIP, SCOPE, FOP/ASIA, SPIRIT, ESPRIT, and ICTUS trials; Past President of the European Neurological Society; Member of the Editorial Board of "Stroke" and of "Cerebrovascular Disease"). Professor José Manuel Ferro has significantly contributed to improve the critical clinical interpretation of the studies and of the overall results.

We hope that you find this version of the manuscript suitable for publication.

Sincerely,

Filipe Brogueira Rodrigues, on behalf of all authors.

***

09-Nov-2015

Dear Mr. Rodrigues:

Manuscript ID BMJ.2015.027448.R2 entitled "Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke – a systematic review and meta-analysis" which you submitted to BMJ,

Thank you for revising your paper.

Since my last letter, some important issues have surfaced and I hope you'll agree to work with us further to resolve them. Our clinical editor in the US, Jose Merino, identified a number of omissions and inconsistencies while drafting a linked editorial to accompany your paper in the BMJ. We all believe these are resolvable with further revision, and important for the correct clinical interpretation of your findings. His comments are at the end of this letter. Might you be willing to revise and respond again within a month or so?

Most of the problems lie with the clinical context of these studies, and you should consider recruiting a clinical stroke neurologist to help with the revision.

Answer: A highly experienced and renowned stroke neurologist (José Manuel Ferro) offered his consultancy to our project and was added to the list of contributing authors. Furthermore, two of the other authors (JJF and JC) are neurology and clinical pharmacology specialists.

A brief CV of José Manuel Ferro is attached.

It's unusual for us to ask for further work at this stage, but I hope you agree that it's worth it to improve your paper further, and enhance its value to both doctors and patients.

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How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I look forward to seeing the revision. As before, please include a point by point response to Dr Merino's comments, and a marked up copy showing the changes.

With thanks and best wishes

Alison Tonks
associate editor BMJ
atonks@bmj.com,

COMMENTS. Jose Merino

I think this MA has the potential to contribute to the literature because it is well done but I think it needs more detail to be better than others recently published, and more relevant to practicing clinicians. The authors can add additional data that can help explain why the newer trials had better results and also can guide doctors and patients when making decisions about the best course of action.

Answer: Please find below the answers to your comments, which we have very much appreciated and significantly helped improving our manuscript.

All changes made to the resubmitted manuscript were highlighted in yellow.

We would also like to underlie that in this revised version of the manuscript we have updated our search, which resulted in more than 400 additional references and that we were able to include two additional unpublished studies.
All comments and criticisms raised by Dr. Jose Merino were addressed and the final result is a manuscript different from others recently published, not only because we included more studies, but also because the resulting deep clinical critical discussion in our paper on how the obtained results translate into clinical practice is, we think, unique and help deciding the best therapeutic option for an individual patient with an acute stroke.

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*Use of "medical therapy"

An important issue that may be missed because the paper refers "medical therapy" is that for most patients in the analysis, "medical therapy" means IV tPA used according to local guidelines. Table 2 in the paper shows that IV tPA was the comparator in many studies and that it could be used in others. *But it may be helpful to readers to discuss the proportion of patients in these studies that actually received standard IV tPA (and perhaps the time window used).* This information is very important because it helps interpret the recent recommendations in updated guidelines that recommend the use of endovascular therapy in patients treated with IV tPA within 4.5 hours and who can be treated with a stent retriever within 6 hours (see the 2015 American heart Association/American Stroke Association focused update of the 2013 guidelines… (Stroke 2015; 46:3020-3035, http://stroke.ahajournals.org/content/46/10/3020) .

- SYNTHESE (randomized IV vs IA tPA)
- IMS-III: 100% had IV tPA
- MR RESCUE: 37% had IV tPA (long time window, recruit non-IV tPA eligible)
- MR CLEAN: 100% had IV tPA
- ESCAPE: 72% had IV tPA
- EXTEND IA: 100% had IV tPA
- SWIFT-PRIME: 100% had IV tPA
- REVASCAT 73% had IV tPA

The use of IV tPA in these studies highlights a major clinical issue: the evidence supports the use of thrombectomy devices early after onset of symptoms and preferably in patients who got standard IV tPA.

Answer: We agree with the reviewer that this important clinical issue was not clear in the manuscript. In this revised version we have specifically addressed this aspect.

*Use of devices

One of the possible reasons why the 2015 trials were positive while the 2013 were negative is that the former used a stent retriever and the latter did not (or did only for a few patients, particularly those enrolled late in the trial when the stent retrievers became available). Stent retrievers can be deployed more rapidly than other thrombectomy devices and lead to higher rates of recanalization. This may explain why the later studies had higher recanalization rates and higher rates of good outcome. The authors address this issue in the discussion but I think they should describe the devices used in each study in the results section. This is crucial information and should be included on *page 13.*

While the authors list the differences in terms of devices, they do not discuss this issue in sufficient detail. It is incorrect to say, as they do, that MR CLEAN used the Merci retriever *(see page 13).* MR RESCUE did. They also mention that some studies used the solitaire device. While this was the most commonly used device (and in some studies the only device) other stent retrievers were used and it may be helpful if they refer to these in generic terms *(stent retrievers)* rather than by brand name.

Endovascular interventions used in each study (some is included in supplemental appendices): the authors might consider creating a table using data from the studies:

- SYNTHESIS: 66% had intra-arterial tPA and guide wire fragmentation, 20% had MERCI, penumbra or another device, 14% had stent retriever
- IMS-III: 41% had IA tPA alone and 59% had a device with or without IA tPA(Merci retriever [Concentric Medical], Penumbra System [Penumbra], or Solitaire FR revascularization device [Covidien], or endovascular delivery of t-PA by means of the MicroSonic SV infusion system [EKOS] or a standard microcatheter). Only 1.5% had a stent retriever
- MR RESCUE: All had MERCI device or Penumbra +/- IA tPA (none had a stent retriever)
- MR CLEAN: Of 233 patients randomized to mechanical intervention, 81% were treated with a stent retriever, 2% had another mechanical therapy, 1 patient had IA tPA and 16% did not have a procedure.
- ESCAPE: Of 165 patients randomized to mechanical intervention, 86% had a stent retriever.
- SWIFT PRIME: 100% had stent retriever
- EXTEND-IA: 100% had stent retriever
- REVASCAT: 100% had stent retriever

The authors should confirm that all patients treated with a stent retriever were indeed treated with the *solitaire device* and not with other stent retrievers such as TREVO. (page 16)

Answer: We agree with the reviewer that the type of device is most probably a crucial variable for the obtained results and that in this case it can behave like a confounder. In the previously submitted version of the manuscript, we tried to call the attention of the reader to this aspect. However, looking again to the manuscript, we do agree with the reviewer that the emphasis and level of detail previously provided is insufficient. Therefore, more detail was added to the text, mainly in the results section and by creating an additional table (Table S2).

*Imaging and selection of patients

The authors address some issues around imaging selection of patients in the discussion. But the use of imaging criteria is a major difference between the 2013 and 2015 studies, and the criteria used in each study should be described in the results. These are critical aspects of the included studies.

Differences in the use of imaging criteria may explain why the studies published in 2015 were positive: they used imaging to identify patients most likely to benefit if they had the intervention (because there was a large vessel occlusion –the target pathology- documented before the procedure began) and also most likely to do poorly if only treated with IV tPA (because large vessel clots respond less well to IV tPA.)

The main difference is that the studies in 2015 used imaging criteria to identify those who had a small ischemic core (most often using non contrast CT brain and ASPECTS scores) and large vessel occlusion (with CTA, MRA and, in some studies, DSA). The studies published in 2013 did not use imaging to select patients for treatment. A table with the difference may be helpful.

Answer: More detail was added to the text, mainly in the results section. We also added a table (Table S1) to detail the imaging used to select patients.

*Other points.

Page 6, line 9: Ischemic heart disease AND ischemic stroke combined are the leading cause of death, if we separate all cancers by location according to the reference provided by the authors. The first statement in the paper needs qualification. Please review the cited reference.

Answer: Thank you for the correction.

Page 6, line 35. Please provide a figure to quantify recanalization rates with thrombolysis.

Answer: Figure added. Thank you for your suggestion.

Page 6, line 39. The studies included in this MA look at mechanical thrombectomy. The protocol in PROSPERO mentions the criteria of Saver and Jauch (as the combination of pharmacological fibrinolysis and mechanical thrombectomy, where arterial recanalization is achieved by thrombus fragmentation and retrieval, and enhancement of fibrinolytic penetration.) But some studies are limited to intravascular thrombolysis without mechanical disruption (SYNTHESIS, some patients in IMS-III) or intra-arterial thrombolysis along with mechanical disruption (IMS-III, MR RESCUE). While many of the studies in this analysis focus on mechanical thrombectomy, it is more accurate to refer to the MA as
for stroke. You could add a paragraph describing the different methods of endovascular therapy. I suggest you look at recent reviews that discuss the different embolectomy devices (and the pharmacological methods for embolectomy).

Answer: Thank you for the suggestion. We reformulated the paragraph according to the indications. It is now clearer what the goal of our work is.

Page 7, line 2: The study was REPORTED following PRISMA-P…

Answer: Corrected.

Page 7, line 27: Consider adding: "this review includes…" or something to that effect to make the text appear less telegraphic. Again, these studies are not limited to AIMT but to endovascular interventions (devices and drugs).

Answer: Thank you for the suggestion.

Page 7, line 29: Were there other inclusion criteria? Did you have any exclusion criteria a priori?

Answer: No other inclusion criteria were used. Exclusion criteria *a priori* included study design (as referred in the text) and trials in which the endovascular intervention did not included any patient treated with mechanical thrombectomy. We have now mentioned it clearer in the text.

Page 9, line 19: Do you have enough information to identify sICH by SITS-MOST criteria? Not all studies in the MA used this definition. In order to recode sICH using SITS-MOST you need access to the images and patient data. You may state that you are recording sICH as defined by the author in each study. In that case, it will be helpful to include a table with the definition. Upon review of a few of the studies, I found this info in the paper most often but sometimes more details in the appended protocol.

Answer: Thank again for the suggestion. We added a new paragraph detailing the sICH criteria in the results section.

Page 10, line 17: Explain the rationale for exploring the risk of non-event. How can a clinician interpret this information? Is it helpful for decision making? Same concern for TSA. other

Answer:

A secondary analysis of the primary efficacy outcome was performed in order to explore the risk of non -event: the risk of patients achieving an unfavourable functional outcome – dependency or death – at 90 days after symptom onset (mRS>2). Interventions in the acute phase of stroke, including endovascular thrombectomy, aim to reduce complications. Therefore, we thought that it was relevant to estimate the risk of becoming dead or dependent in addition to the probability of achieving a good ("positive") outcome.

Vascular interventions (device therapy or pharmacologic treatment) in the acute phase of stroke are meant to reduce complications of the condition. Customarily the impact of such interventions was measured in term of prevention of "negative" outcomes (Wardiaw et al. Cochrane Database Syst Rev. 2014;7:CD000213.), furthermore the relative risks of 'negative outcomes' are usually more consistent than relative risks of 'positive outcomes' (Deeks JJ. Stat Med. 2002 Jun 15;21(11):1575-600.).

Furthermore, the estimated result for risk of achieving an unfavourable functional outcome is expected to be different of the inverse of the pooled estimate for risk of achieving a good functional outcome because, despite the same sample size, the weighting method for statistical analysis takes into account the differences in event rates. Consistency between results of the primary and secondary analyses for the primary outcome would further increase confidence in the results.

Having stated the above mentioned reasons as rational for conducting the non-event analysis, we recognize that it does not add (in this case) vital information. Therefore, we have deleted this analysis.

For comment on TSA, please see our answer to a following comment.

Page 12, line 30: This statement is partially correct. The time to endovascular therapy was from 5-12 hours. But for inclusion, some trials had shorter time windows. IMS-III, for example, required treatment with IV tPA within 3 hours. Other studies required IV tPA within 4.5 hours. It may be more accurate to describe the inclusion criteria including the time constraints due to IV tPA requirements and then also the requirement for endovascular access by a certain point.

Answer: Thank you for the suggestion. This point was clarified

Page 12, line 36: Clarify that this refers to IV tPA. Mention the fact that some trials evaluated IV vs IA tPA (SYNTHESIS).

Answer: Added.

Page 13, line 3: It is necessary to qualify what you mean by proximal artery strokes. Only the studies published in 2015 required imaging confirmation of the vessel occlusion. All included patients with occlusion of the distal (intracranial) carotid artery or M1 portion of the MCA. Some studies allowed vessel occlusions of the M2 branches. Some also allowed basilar occlusions (please mention which study allowed which occlusions). This information is useful for a neurologist or neuroradiologist considering these therapies.

Answer: This information was added to the results section.

Page 13, line 17: The intervention was endovascular therapy (that could be AIMT or just IA lytics) compared with standard medical therapy. For some studies, standard medical therapy meant treatment with IV tPA. For other studies this meant other measures. And for some, IV tPA or other measures. See my comments above.

Answer: This comment related to a previous one. The reviewer was also previously right in that the way text was written is misleading regarding both intervention and control arms under consideration. We have changed the text to make it clearer that intervention was endovascular therapy providing that mechanical thrombectomy was at least one of the possible interventions in the endovascular treatment arm of the study. It is also clearer in this revised version of the manuscript what was considered under the control medical therapy arm.

Page 13, line 33: See comments above regarding endovascular devices. Also, correct statement about MR CLEAN requiring MERCI.

Answer: Corrected and further information was added in an additional table.

Page 14, line 10: Allocation concealment was not possible due to nature of procedure. The authors could discuss the PROBE design.

Answer: We elaborated on the PROBE design in the discussion section.

Page 14: what do the authors mean here: “Concerning attrition bias, IMS III and MR CLEAN showed imbalances between withdrawals in the active and control arms and in MR RESCUE and REVASCAT the reduced number of participants limited considerations”?

Answer: The concept was further developed.

Page 14: While all the trials report on mRS 0-2, mRS 0-1, mortality and sICH, these were not the primary outcome in all trials. Could the authors provide information on which were the primary and secondary outcomes for each trial?

Answer: The requested information was added.

Page 15: See my comments above regarding medical care alone. Need to qualify when IV tPA is medical care alone vs. other interventions.

Answer: The concept of medical care alone was more developed in the description of study interventions.

Page 15, line 32: “captured” is not the right word, it implies that the authors do not know if the other 95% of patients died. You may say that XX patients died…

Answer: Thank you for your correction

Page 15: An important piece of information for neurologists and neuroradiologists would be the recanalization rates achieved in the endovascular therapy arms. These numbers are provided in all the reports and can show how the newer studies had greater recanalization. This may explain the differences in outcomes. You should consider including this information.

Answer: The requested information was added to the results section and a new table (Table S3) was built.

Page 16, line 13: Can the authors interpret the results of the TSA analysis for readers not familiar with it? What does this paragraph mean?

Answer: This issue was further clarified in the manuscript. We created a box to explain to reader what TSA is – if that is acceptable from the editorial point of view.

Page 16, line 34: Clarify that you mean intravenous rt-PA (some studies, particularly those from 2013 but also some of the newer ones, used IA rt-PA)

Answer: Added.

Page 16, line 25: There are more than 2 thrombectomy devices used in all trials (Merci retriever, Penumbra System Solitaire FR revascularization device, TREVO, or endovascular delivery of t-PA by means of the MicroSonic SV infusion system or a standard microcatheter). The authors should make sure that the comparison mentioned here is limited to MERCI and Solitaire or change the wording in the text and tables. MR RESCUE allowed use of different iterations of the MERCI device as well as the Penumbra device. IMS-III used a variety of devices, as mentioned above. Some of the new trombectomy trials use several devices.

Answer: Subgroup analysis for the different devices was redone and the results were changed accordingly.

Page 17, line 47: Documentation of a large vessel occlusion was NOT required for enrollment into SYNTHESIS, IMS-III OR MR RESCUE (the authors do not list MR RESCUE here). MR RESCUE required documentation of an anterior circulation stroke but nor documentation of a vascular occlusion. While MR RESCUE was evaluating the value of penumbral imaging for patient selection for thrombectomy, the appearance on imaging was not an inclusion or exclusion criterion. The authors should clarify this issue.

Answer: Thank you for the correction.

Page 17, line 52: The difference in terms of the proportion of patients with atrial fibrillation between studies is most likely due to chance. When we speak about the trials looking for patients with vascular occlusion, we do not mean a difference in terms of patients with larger artery disease (typically cervical carotid artery) but rather an occlusion of the intracranial ICA or MCA.

Answer: This aspect was changed in accordance to editorial suggestion.

Page 18, line 3: You should clarify that IMS-III by design was designed to compare standard dose IV tPA with a combination of lower dose IV tPA PLUS intra-arterial therapy (in most cases, intra-arterial tPA). The reason why the lower dose of IV tPA was used was to prevent overdosing patients who later had IA tPA. The difference was by design and designed for safety. This should be clarified.

Answer: The issue was clarified in the results section

Page 18: Line 3: The authors write, “in SYNTHESIS IV rt-PA was withheld.” SYNTHESIS was a study to compare IV-tPA versus IA-tPA or other mechanical embolectomy in the standard time window. It is not that IV tPA was withheld. That was the point of the trial. The wording could be modified to reflect this fact.

Answer: Corrected.

Page 18, line 7: The authors write, “Compliance with thrombectomy in the intervention arm was low (<40%) in IMS-III and SYNTHESIS.” This is an incorrect statement.

- Compliance with thrombectomy in SYNTHESIS was 90%. (“Of the 181 patients assigned to endovascular treatment, 15 did not receive the treatment (6 because of clinical improvement, 3 because of a lack of evidence of occlusion, 3 because of dissection, 1 because of an unknown bleeding diathesis, 1 because of a groin hematoma, and 1 because of the delayed availability of the interventionist). Three procedures had to be interrupted, owing to equipment breakdown (in one procedure) and intraprocedural complications (in two procedures). Endovascular treatment was thus completed in 163 patients.”)
-

Answer: Thank you for your alert. We were referring to the proportion of patients that performed mechanical thrombectomy in the endovascular interventional arm and not to the proportion of patients assigned to thrombectomy that actually did it. We agree that this was unclear and we have changed the text.

Page 20: They write, “However, spontaneous neurological recovery usually ceases only after six months, so longer follow-ups could have more accurately predicted the endpoints.” I am not sure that this statement is correct. Most neurologists will tell you that most gains occur in the first few months and that is why stroke trial outcomes are usually measured at 3 months. Other comorbidities may affect recovery after 3 months. But neurologic recovery continues over months and even years. It is important to highlight this issue for patients and their families.

Answer: This sentence was rephrased according to the reviewer suggestion.

* Two recently published MAs on related research questions.

http://jama.jamanetwork.com/article.aspx?articleid=2467553

and

Stroke. 2015;46:3177-3183. DOI: 10.1161/STROKEAHA.115.009847

The authors should cite these two papers and discuss what their paper adds. We acknowledge both papers were published after the review process at the BMJ began and they will not influence our final decision.

Answer: Added.

- Statements about funding

The authors claim that all studies but one were industry funded. This is NOT an accurate statement. Only two studies had predominant industry support. In italics are the sources of funding as reported:

- SWIFT PRIME "Supported by Covidien."
- ESCAPE "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."

Other studies derive most of their funding from sources other than industry, and funders, authors and participants will be surprised to see some studies listed as industry-funded. MR RESCUE and IMS-III are considered as NIH-funded (to the tone of several million dollars) but some of the supplies used for the study at the sites (catheters, etc.) were donated by industry. Industry did not pay the investigators or the infrastructure of the trial. An more accurate statement would be that the studies were publicly funded but had industry support

- MR RESCUE: Supported by a grant (P50 NS044378) from NINDS. Concentric Medical provided study catheters and devices from the initiation of the study until August 2007; thereafter, costs for all study catheters and devices were covered by study funds or third-party payers. (This means that the manufacturer only provided a minority of the catheters. The rest of funds came from NIH and from insurance and government payers as part of routine care). The text of the paper states: "The trial was funded by the National Institute of Neurological Disorders and Stroke (NINDS). An independent medical monitor and a NINDSappointed data and safety monitoring board oversaw the conduct of the trial. There were no confidentiality agreements between NINDS and the investigators. Concentric Medical provided study devices until August 2007; thereafter, costs were covered by study funds or third-party payers. Concentric Medical had no involvement in the study design or in the analysis or interpretation of the data. No other commercial support for the study was provided."
- IMS III: Supported by grants from the National Institutes of Health and the National Institute of Neurological Disorders and Stroke (UC U01NS052220, MUSC U01NS054630, and U01NS077304) and by Genentech, EKOS, Concentric Medical, Cordis Neurovascular, and Boehringer Ingelheim. The industry players provided the drug and devices only.
- SYNTHESIS: Supported by a grant from the Italian Medicines Agency (AIFA) (FARM6LN3KS). The trial received t-PA from Boehringer Ingelheim Italia, which was paid by the AIFA for use in the experimental group and by the individual participating hospitals for use in the control group. The catheters and devices used in the study were those present in the participating interventional radiologists' apparatus and were refunded by Niguarda Ca' Granda Hospital (Milan) with the AIFA funding. This study only got the tPA from the manufacturer but all other trial expenses, including the catheters, were paid by a State organism. (NB The authors claim this was the only study free of industry ties. This is not an accurate statement either because some of the supplies in the study (tPA) came from industry).

These studies had support from governmental bodies and industry. Could state mixed funding. You will note that the industry support for these trials is different from that received from the studies listed above.

- EXTEND IA: 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 infra- structure funding from the state government of Victoria. The Solitaire FR device and trial infrastructure were provided under an unrestricted grant from Covidien.
- REVASCAT: Supported by Fundació Ictus Malaltia Vascular through an unrestricted grant from Covidien, by a grant from the Spanish Ministry of Health cofinanced 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).

Answer: We understand the point raised by the reviewer, although in pure terms study independency can only be ascertained when there is no industry support at all. However, we have clarified the type of support provided by the industry for each of the trials and we have amended the risk of bias table accordingly.

*Registration

MR RESCUE was indeed retrospectively registered. It is worth noting that the study started in 2004, before the 2005 ICMJE policy was implemented. The BMJ would not have requested registration for publication. Registration was done in 2006 (after journals began requesting it) and many years before the study data were collected or analyzed.

Answer: Added.

* Trials stopping early

As the authors state, five trials were stopped early. Four were stopped for efficacy and one for futility. The authors mention the information but it may help readers understand why so many trials were stopped early if they include some details about the percentage of patients included in the final sample as well as the reasons and justification for stopping the studies.

After MR CLEAN was published in 2015, investigators of the other five trials did interim analyses and decided to stop early because, in most cases, pre-specified criteria for stopping the studies were met (it is important that in one trial the DSMB felt equipoise had been lost but the stopping criteria were not met). Here are the relevant data (the authors can decide how much detail to include –This information is in the 2015 guidelines referenced below but the authors should look at the papers to confirm the information)

- ESCAPE: The interim analysis was done earlier than planned and it showed that the pre-specified O'Brien-Fleming a stopping boundary had been crossed and thus the trial was stopped.
- SWIFT PRIME: After the MR CLEAN results and the decision to stop ESCAPE were announced, an interim efficacy analysis was done earlier than planned and demonstrated that the pre-specified criteria for stopping the trial at the first interim analysis had been met and the trial was thus stopped.
- EXTEND-IA: "An unplanned interim efficacy analysis was implemented on the basis of a Haybittle-Peto stopping rule.
- REVASCAT: "When results of other similar trials became known, the DSMB recommended the recruitment be stopped because the emerging results showed that equipoise was lost, although the interim results did not reach the pre-specified stopping boundaries.

One trial was stopped early for futility.

- IMS-III was stopped for futility after 656 of the planned 900 patients had been enrolled. There was no difference between the treatment arms.

Answer: Thank you. Information added.

*Please add detail to your abstract. This is an important summary and should contain all the core details that doctors need for correct interpretation of your findings.

Answer: This aspect is now further developed on the manuscript.

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Essential Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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g. Footnotes and statements

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END

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- Member of the Steering Committees of the EAFT, ESPS II, TESS II, TACIP, SCOPE, FOP/ASIA, SPIRIT, ESPRIT, ICTUS
- Member of the Adjudication Committee of ICSS, CAVATAS 1 e CAVATAS 2 and PROFESS
- Member of the Executive Committee of TACIP and ICTUS
- Member of the Scientific Committee, European Stroke Conference (1st to present)

- Member of the Scientific Committee, 3rd World Stroke Congress
- Member of the Scientific Programme Committee, 8th World Stroke Congress
- Member of the Bylaws Committee and Education Committee, European Stroke Organisation
- Member of the Program Committee of the Stroke Conference (7th to present)
- Conference Chairman of the European Stroke Conference (2001 and 2012), and of the 21st Meeting of the European Neurological Society (2011)
- President - Elect – European Neurological Society Executive Committee (2007-2008)
- President - European Neurological Society Executive Committee (2009-2010)
- Past – President - European Neurological Society Executive Committee (2010-2011)
- Vice President of Sociedade Portuguesa de Neurologia (92-95)
- President of Grupo de Estudos de Doenças Cerebrovasculares da Sociedade Portuguesa de Neurologia (98-2001)
- Member of the Editorial Board of "Stroke" (2001-2003) and (since 2010)
- Member of the Editorial Board of "Cerebrovascular Disease"
- Member of the External Advisory Group of the Key Action "The Ageing Population and Disabilities" of the European Commission (99-02)
- Editor of "Functional Neurology" (2002)
- Member of the Advisory Board of "Cerebrovascular Disease" and "Journal of Neurology"
- Ad-Hoc reviewer for "Stroke", "European Neurology", "European Journal of Neurology", "Revista de Neurologia", "Acta Médica Portuguesa", "Lancet", "Lancet Neurology", "Neurology" and "Journal of Neurology, Neurosurgery and Psychiatry"
- Vice-Director of "Revista de Neurologia" (Barcelona) (96-present)

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PUBLICATIONS

Author or co-author of 224 publications in peer-review journals and 30 book chapters.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	43-44
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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