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Improved clinical outcome 3 months after endovascular treatment, including thrombectomy, in patients with acute ischemic stroke: a meta-analysis

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ABSTRACT

Background and purpose Intravenous thrombolysis with tissue plasminogen activator is standard treatment in acute stroke today. The benefit of endovascular treatment has been questioned. Recently, studies evaluating endovascular treatment and intravenous thrombolysis compared with intravenous thrombolysis alone, have reported improved outcome for the intervention group. The aim of this study was to perform a meta-analysis of randomized controlled trials comparing endovascular treatment in addition to intravenous thrombolysis with intravenous thrombolysis alone.

Methods Databases were searched for eligible randomized controlled trials. The primary outcome was a functional neurological outcome after 90 days. A secondary outcome was severe disability and death. Data were pooled in the control and intervention groups, and OR was calculated on an intention to treat basis with 95% CIs. Outcome heterogeneity was evaluated with Cochrane's Q test (significance level cut-off value at <0.10) and I² (significance cut-off value >50%) with the Mantel–Haenszel method for dichotomous outcomes. A p value <0.05 was regarded as statistically significant.

Results Six studies met the eligibility criteria, and data from 1569 patients were analyzed. A higher probability of a functional neurological outcome after 90 days was found for the intervention group (OR 2, 95% CI 2 to 3). There was a significantly higher probability of death and severe disability in the control group compared with the intervention group.

Conclusions Endovascular treatment in addition to intravenous thrombolysis for acute ischemic stroke leads to an improved clinical outcome after 3 months, compared with patients receiving intravenous thrombolysis alone.

INTRODUCTION

Stroke is estimated to cause 5.7 million deaths globally each year and to cause major disability in patients who survive.¹ An aging global population has increased the annual incidence of death from ischemic stroke by 50% from 1990 to 2013. Acute stroke treatment has undergone major changes during the past decades.² Currently, intravenous tissue plasminogen activator (tPA) within 3–4.5 h of symptom onset is an established treatment for ischemic stroke and is associated with an improved functional outcome after 3 months. Endovascular

techniques of relieving vessel occlusion in acute ischemic stroke have been developed over the past decades and their clinical benefit has been questioned.³ Endovascular treatment can mainly be divided into loco-regional intra-arterial (IA) thrombolysis and mechanical thrombectomy. A randomized controlled trial (RCT) published in 1999 (Prolyse in Acute Cerebral Thromboembolism II (PROACT-II)) showed improved clinical outcome in patients treated with IA thrombolysis compared with IV heparin.⁴ However, the follow-up study, Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT), failed to prove a better outcome in patients treated with IA thrombolysis.⁵ An RCT by Ciccone *et al*⁶ (SYNTHESIS Expansion) comparing endovascular treatment (IA thrombolysis and mechanical thrombectomy) with IV thrombolysis failed to show the superiority of endovascular treatment. Kidwell *et al*⁷ (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE)), randomized patients to thrombectomy or standard medical care within 8 h from stroke symptom onset and found no improved clinical outcome in the intervention group. Despite previous discouraging results, new studies comparing first generation thrombectomy devices with modern generation of retrievable stents, favor the usage of the Trevo retriever and Solitaire flow restoration device compared with the older Merci retrieval system.^{8–9} Recently, studies evaluating endovascular treatment and IV thrombolysis compared with IV thrombolysis alone showed improved outcome for the intervention group.^{10–12}

Clinical outcome of stroke patients can be assessed using the modified Rankin Scale (mRS). mRS scores range from 0 to 6, and a score of 0 indicates no symptoms, 1=no significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death. A score between 0 and 1 reflects an excellent outcome and a score of 0–2 a functional outcome.¹³

A meta-analysis by Fargen *et al*¹⁴ showed improved outcome for endovascular treatment compared with medical management in acute ischemic stroke. Since the publication of this recent meta-analysis, several new RCTs have been published, highlighting the need for an updated meta-analysis in the field of neurointerventional treatment in acute ischemic stroke.

The aim of this study was to perform a meta-analysis of current eligible RCTs comparing

endovascular treatment in addition to IV thrombolysis with IV thrombolysis alone, in order to evaluate and quantify the aggregated benefit for mechanical thrombectomy in acute ischemic stroke.

METHODS

Eligibility criteria

Only RCTs were considered for inclusion. The intervention group was endovascular treatment in addition to IV thrombolysis, and the control group was IV thrombolysis. Only complete studies published in whole were included. Only studies with at least two-thirds of all participants receiving IV thrombolysis were considered for inclusion. There were no restrictions in study language, study age, included patient age, imaging criteria, or National Institutes of Health Stroke Scale (NIHSS) score.

Information source

We searched PubMed, the Cochrane Central Register of Controlled Trials, and the National Institutes of Health Clinical Trials from the date of inception until 17 April 2015. Two searches were performed. The first search terms were 'thrombectomy' and 'thrombolysis'; the second search terms were 'endovascular treatment', 'stroke', and 'randomized'. All manuscript titles were assessed and eligible abstracts were read. Manuscripts to be read in whole were selected from abstracts that fulfilled the inclusion criteria. Manuscripts found in references lists from read manuscripts were also assessed for possible inclusion. Two independent reviewers assessed the retrieved manuscripts for possible inclusion in the meta-analysis. Any disagreements were resolved by discussion.

Data collection process

Two independent reviewers extracted data from the included studies from the published manuscripts, study protocols, and appendices. The primary specified outcome was the proportion of patients with an mRS score of 0–2 at 90 days from stroke onset. Secondary outcomes included mRS 0–1 at 90 days, mRS 0–3 at 90 days, mortality at 90 days, intracerebral hemorrhage within 90 days, and mRS 5–6 at 90 days. To maintain high homogeneity between the included studies, a subgroup of patients in the Interventional Management of Stroke-III (IMS-III) trial that did not have vessel occlusion on imaging were excluded from further analysis. Data were treated according to the intention to treat analysis, and randomized patients remained in their first allocated treatment arm in the outcome analysis. Data from patients lost to follow-up were imputed with mRS 5 in order not to overestimate the treatment effect in studies with a higher percentage of dropouts.

Statistical analysis

Two independent reviewers performed the statistical analyses (Review Manager, RevMan, V.5.3., Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Review Manager was used for data presentation. Data were pooled in the intervention group and the control group. Outcome heterogeneity was evaluated with Cochrane's Q test (significance level cut-off value at <0.10) and I^2 (significance cut-off value >50%). A p value <0.05 was considered statistically significant. The Mantel–Haenszel method was used for dichotomous outcomes with fixed effect or random effect (DerSimonian and Laird¹⁵) where appropriate, according to outcome heterogeneity. OR with 95% CI were calculated for all outcomes.

RESULTS

Search findings

A total of 2138 articles were identified; 1942 articles did not match the eligibility criteria. One hundred and ninety-six abstracts were eligible for evaluation and 22 of these were selected for full text evaluation. Of the 22 manuscripts analyzed in full text, 11 were not RCTs and hence were excluded. Five RCTs were further excluded for various reasons. The study of Miao *et al*¹⁶ was excluded as patients did not receive IV thrombolysis. In two studies (Solitaire with the Intention for Thrombectomy (SWIFT) study by Saver *et al*⁸ and Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2) by Nogueira *et al*⁹) patients were randomized to different endovascular treatments with no control group receiving IV thrombolysis. The intervention group in the SYNTHESIS Expansion trial did not receive systemic thrombolysis.⁶ MR RESCUE was excluded as <50% of the included patients received systemic thrombolysis.⁷ The remaining six articles met all of the eligibility criteria and hence were included in the meta-analysis.^{10–12 17–19}

Randomized controlled trials

All trials were randomized 1:1, except IMS-III, which was randomized 2:1, with more patients in the intervention group. All trials were prospective randomized, open label, blinded endpoint with intention to treat analyses. Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-1A) also included target group analysis. Study quality details are presented in the online supplementary table S1.

Study characteristics

In total, the six RCTs randomized 1943 patients to either the intervention group (55%) or the control group (45%). Study characteristics are shown in table 1.

Time to inclusion from symptom onset varied between <3 h in the IMS-III trial to <12 h in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial.¹⁰ Five of the six studies included patients with stroke symptoms from the anterior circulation. All studies required imaging of vessel occlusion status before inclusion, except the IMS-III trial. In the IMS-III trial, 284 patients had been randomized before CT angiography was allowed in the study. We therefore decided to perform a post hoc analysis including only patients with baseline CT angiography and vessel occlusion from the IMS-III trial.²⁰

Study design

In all studies both the intervention group and the control group received IV tPA if eligible. Time from symptom onset to treatment with IV thrombolysis varied from <3 h in IMS-III to <4.5 h in the other trials. In Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT), patients presenting with acute stroke without signs of revascularization after 30 min of IV tPA, or patients not eligible for IV tPA, received either thrombectomy or medical care.

Patient characteristics

A detailed description of the patients in each trial, divided into an experimental group and a control group, is presented in the

Table 1 Study details

Study name	Trial period	Location	Enrolled centers (n)	Study design	Randomized patients (n)	Intervention	Control	Inclusion criterion: NIHSS	Inclusion criterion: age (years)	Inclusion criterion: occluded vessel	Stroke imaging	Primary outcome	Safety measures
ESCAPE	2013–2014	Canada, USA, South Korea, Europe	22	RCT	316	IV tPA if eligible plus endovascular treatment	IV tPA if eligible	>5	≥18	Middle cerebral artery with or without occlusion of the internal carotid artery	Non-contrast CT and CTA, multiphase CT	mRS after 90 days	Mortality and other
EXTEND-1A	2012–2014	Australia, New Zealand	10	RCT	70	IV tPA if eligible plus endovascular thrombectomy	IV tPA if eligible	0–42	≥18	Internal carotid artery or middle cerebral artery and mismatch on CT perfusion or MR	Non-contrast CT, CTA/MRA and CT perfusion or diffusion MRI	Reperfusion at imaging after 24 h, early neurologic improvement	Mortality. Symptomatic intracranial hematoma
IMS-III	2006–2012	USA, Canada, Australia, Europe	58	RCT	656	IV tPA if eligible plus endovascular treatment	IV tPA if eligible	≥10*	18–82	Anterior or posterior circulation	Non-contrast CT, CTA†	mRS ≤2 after 90 days	Mortality within 90 days, symptomatic ICH within 24±6 h
MR CLEAN	2010–2014	Europe	16	RCT	502	IV tPA if eligible plus intra-arterial treatment with thrombolysis or mechanical thrombectomy, or both	IV tPA if eligible	≥2	≥18	Distal carotid artery, middle or anterior cerebral artery	Non-contrast CT or MRI. CTA/MRA/DSA	mRS ≤2 after 90 days	Neurologic deterioration within 24 h from inclusion in the study
SWIFT-PRIME	2012–2014	USA, Europe	39	RCT	196	IV tPA plus endovascular thrombectomy	IV tPA	≥8 and <30	18–80	Distal carotid artery or middle cerebral artery	Non-contrast CT or MRI. CTA/MRA	mRS after 90 days	Mortality within 90 days
REVASCAT	2012–2014	Europe	4	RCT	206	IV tPA if eligible plus endovascular thrombectomy	IV tPA	≥6	18–85 (80)‡	Middle cerebral artery with or without occlusion of the internal carotid artery	Non-contrast CT or MRI. CTA/MRA or angiogram	mRS after 90 days	Mortality within 90 days

*NIHSS >7 if occlusion of M1, internal carotid artery, or basilar artery on CTA at institutions where baseline CTA imaging is standard of care for acute stroke patient. Baseline CTA in n=306. No baseline CTA in n=350.

†Arterial occlusion on CTA or MRA of the internal carotid artery, M1, or M2. CTA was performed in 306 of 656 patients and mismatch, using CT or MRI, with a Tmax above 6 s delay perfusion volume and either CT-regional cerebral blood flow or diffusion weighted imaging infarct core volume.

‡After enrollment of 160 patients, the inclusion criteria were modified to include patients up to the age of 85 years with an Alberta Stroke Program Early CT score of >8.

Studies: ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; IMS-III, Interventional Management of Stroke-III; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; REVASCAT, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment; CTA, CT angiography; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; IV tPA, intravenous tissue plasminogen activator; MRA, MR angiography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial.

Table 2 Intervention group characteristics

Study name	Allocated to intervention group (n)	Received endovascular therapy (n (%))	Received IA tPA (n (%))	Mechanical thrombectomy (n (%))	Time from onset to groin puncture (min)	mTICI of $\geq 2b$ (n)*	Treatment with IV tPA (n (%))
ESCAPE	165	151 (92)	NA	151 (92)	75†	113	120 (73)
EXTEND-1A	35	27 (77)	0	27 (77)	210	25	35 (100)
IMS-III‡	190	190 (100)	NA	NA	NA	86§	190 (100)
MR CLEAN	233	196 (84)	24 (10)	195 (84)	260	115	203 (87)
SWIFT-PRIME	98	87 (89)	NA	87 (89)	224	73	98 (100)
REVASCAT	103	98 (95)	1 (0)	98 (95)	269	67	70 (68)

* mTICI score between 0 and 3; 0 is no perfusion and 3 is complete reperfusion. A score of $\geq 2b$ is considered successful reperfusion.

†Time from randomization to groin puncture.

‡Subgroup with CT angiography verified vessel occlusion.

§Successful recanalization was defined as grade 3–5 flow in previously occluded (grade 1–2) segments of symptomatic intracranial arteries on 24 h CT angiography and/or MR angiography.

Studies: ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; IMS-III, Interventional Management of Stroke-III; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; REVASCAT, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment. IA tPA, intra-arterial tissue plasminogen activator; mTICI, modified Thrombolysis in Cerebral Infarction; NA, assessed.

online supplementary table S2. Median or mean age of the patients in all groups varied from 65 to 71 years. Median NIHSS score (0–42, higher score indicates more severe stroke symptoms) was 13–18. The intervention group received endovascular treatment if eligible (77% in EXTEND-1A to 100% in IMS-III). Full intervention group characteristics are presented in table 2.

Control group characteristics are presented in the online supplementary table S3. Overall, all patients in Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), EXTEND-1A, and the subgroup of patients in IMS-III with vessels occlusion received IV thrombolysis. The percentages receiving IV thrombolysis in the other three studies varied between 78% and 91% in the control groups and between 68% and 87% in the intervention groups.

Primary and secondary outcomes

The primary outcome measure, mRS score of 0–2 at 90 days from symptom onset, was favored in the intervention group. The proportion of patients with mRS 0–2 after 90 days was 46% in the intervention group and 27% in the control group (figure 1A). The absolute risk reduction for the intervention group compared with the control group was 19% (95% CI 14% to 23%). Number needed to treat for mRS 0–2 in the intervention group was 6 (95% CI 4 to 7). Results from analyses of secondary outcomes showed a significantly increased proportion of patients in the intervention group with an excellent outcome (mRS 0–1, figure 1B) and of mRS 0–3 after 90 days. There was a significantly reduced risk of mortality in the intervention group compared with the control group, with an absolute risk reduction for death of 4% (95% CI 1% to 8%) in the intervention group. The number needed to treat in the intervention group to avoid one death was 23 (95% CI 12 to 149). There was a significantly higher probability for severe disability and death in the control group (table 3). There were no differences regarding symptomatic intracerebral hemorrhage between the intervention and control groups. To more specifically evaluate the effect of stent retrievers on stroke outcome, we performed a sensitivity analysis excluding the IMS-III trial due to its limited use of stent retrievers. In general, the outcomes for the intervention group improved after exclusion of the IMS-III trial (figure 1C, D). The proportion with a functional outcome (mRS 0–2) in the intervention group was 47% and 26% in the control

group, with an absolute risk reduction of 21% (95% CI 15% to 26%) in the intervention group and a number needed to treat of five patients (95% CI 4 to 7). There was no statistically significant differences in mortality or intracerebral hemorrhage between the intervention and control groups in the sensitivity analysis. Comparisons between the outcomes are presented in table 4.

DISCUSSION

In this meta-analysis, we analyzed six RCTs with 1569 patients, evaluating the outcome in patients with acute ischemic stroke with a documented occlusion who received either IV thrombolysis (control) or IV thrombolysis plus endovascular treatment (intervention group).

The aim of this meta-analysis was to evaluate the role of endovascular treatment, in particular for stent retrievers, in acute ischemic stroke. Our results indicate that treatment with endovascular treatment, including mechanical thrombectomy, leads to a higher ratio of patients with an improved clinical outcome after 3 months from stroke onset compared with the control group receiving IV thrombolysis alone. Patients receiving IV thrombolysis alone had a higher probability of mRS 5–6 and death after 3 months; this has not been shown in previous single RCTs. However, this was not significant when the IMS-III trial was excluded.

There were a number of differences between the six trials. The IMS-III trial included patients over 8 years and used several different devices for mechanical thrombectomy, due to the technological and scientific evolution of stent retrievers during the study period.^{8,9} Percentages of patients in the intervention groups that received mechanical thrombectomy varied between trials. In the IMS-III trial, only 39% received mechanical thrombectomy in the intervention group. This was due to inclusion of patients without a CT angiography verified vessel occlusion. After confirmed vessel occlusion on CT angiography was used as an inclusion criterion, all patients in the intervention group received endovascular treatment. This was adjusted for in our analysis by using patients from the cohort of CT angiography verified vessel occlusions. Study heterogeneity decreased after inclusion of only CT angiography confirmed vessel occlusion from the IMS-III trial. There was wide use of stent retrievers among the RCTs, except for the IMS-III trial. To more specifically evaluate clinical outcome after treatment with stent retrievers in combination

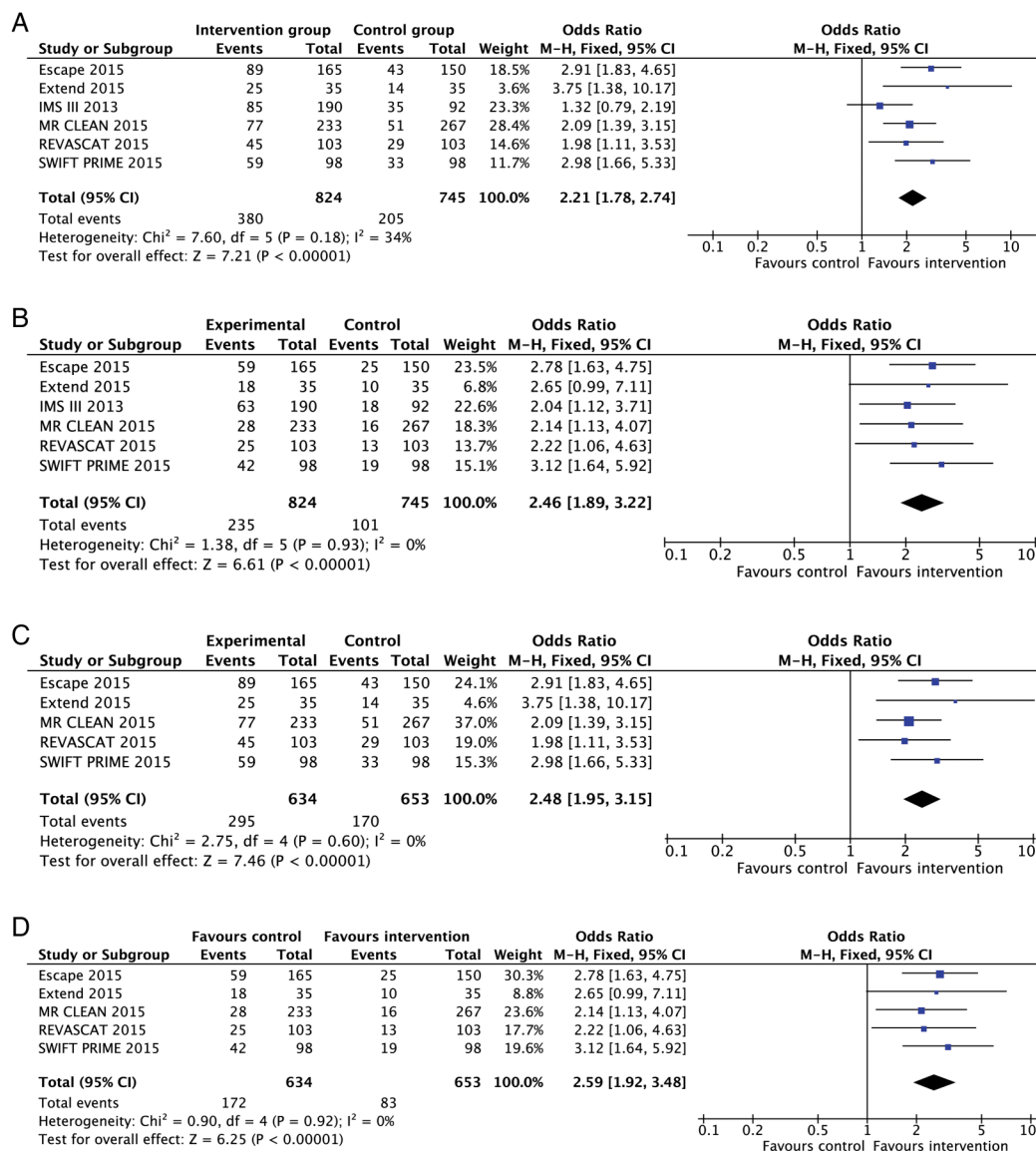


Figure 1 Forest plot of the modified Rankin Scale (mRS) in the intervention and control groups. (A) OR of mRS 0–2 (functional outcome) in the intervention and control groups after 90 days. (B) OR of mRS 0–1 (excellent outcome) in the intervention and control groups after 90 days. (C) OR of mRS 0–2 (functional outcome) in the intervention and control groups after 90 days, excluding IMS-III. (D) OR of mRS 0–1 (excellent outcome) in the intervention and control groups after 90 days, excluding IMS-III. Studies: ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; IMS-III, Interventional Management of Stroke-III; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands; REVASCAT, Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT-PRIME, Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment.

Table 3 Outcome 90 days after stroke symptom onset comparing the intervention and control groups*

Outcome	Endovascular group (n (%))	Control group (n (%))	OR (95% CI)	p Value
mRS 0–2 (functional outcome)	380 (46)	205 (28)	2.21 (1.78 to 2.74)	<0.00001
mRS 0–1 (excellent outcome)	235 (29)	101 (14)	2.46 (1.89 to 3.22)	<0.00001
mRS 0–3	509 (62)	320 (43)	2.15 (1.75 to 2.64)	<0.00001
Mortality	125 (15)	146 (20)	0.73 (0.56 to 0.96)	0.02
Symptomatic intracerebral hemorrhage	41 (5)	34 (5)	1.05 (0.65 to 1.68)	0.85
mRS 5–6	188 (23)	249 (33)	0.58 (0.46 to 0.73)	<0.00001

*Subgroup from IMS-III with CT angiography verified vessel occlusion.
IMS-III, Interventional Management of Stroke-III; mRS, modified Rankin Scale score.

Table 4 Outcome 90 days after stroke symptom onset comparing the intervention and control groups, excluding IMS-III

Outcome	Endovascular group (n (%))	Control group (n (%))	OR (95% CI)	p Value
mRS 0–2 (functional outcome)	295 (47)	170 (26)	2.48 (1.95 to 3.15)	<0.00001
mRS 0–1 (excellent outcome)	172 (27)	83 (13)	2.59 (1.92 to 3.48)	<0.00001
mRS 0–3	400 (63)	275 (42)	2.34 (1.87 to 2.94)	<0.00001
Mortality	97 (15)	122 (19)	0.80 (0.60 to 1.08)	0.14
Symptomatic intracerebral hemorrhage	26 (4)	28 (4)	1.00 (0.58 to 1.71)	0.99
mRS 5–6	139 (22)	217 (33)	0.57 (0.44 to 0.73)	<0.00001

IMS-III, Interventional Management of Stroke-III; mRS, modified Rankin Scale score.

with thrombolysis, we compared the five included RCTs after exclusion of the IMS-III trial in a sensitivity analysis. Excluding the IMS-III trial yielded a higher OR for functional and excellent outcome after 3 months, and a higher probability for a poor outcome (mRS 5–6) in the control group.

Time to intervention varied between included studies, with longer time to intervention in REVASCAT and Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN). Poorer result in clinical outcome in these two studies compared with ESCAPE, EXTEND, and SWIFT PRIME might be attributed to longer time to reperfusion and higher proportion of patients with successful recanalization, and emphasizes the importance of time in acute stroke care.

The generalizability of these results requires some caution. Included patients in these trials were a highly selected group and represent a small fraction of all stroke patients. Only 5–13% of all stroke patients present to hospital within the time window for thrombolysis. Contraindications for IV thrombolysis further reduce the number of eligible patients.²¹ For example, a total of 7798 patients presented with acute ischemic stroke and were assessed for eligibility in the EXTEND-1A trial; 1044 of these received IV tPA, but only 70 patients were enrolled in the study. Major reasons for exclusion after treatment with systemic thrombolysis was lack of occlusion of a major vessel, out of operating hours, or poor pre-morbid condition.

Five of the six included studies were stopped early. Premature stop because of efficacy has been shown to have a risk of result overestimation of the effect size and hence requires a certain degree of caution when interpreting the results.²²

A limitation of this meta-analysis is the lack of individual patient data for patients lost to follow-up, which might affect the results of the outcome analyses. Lack of individual patient data limits the possibility of subgroup analyses of patients with different clinical characteristics. Secondly, no specific search of unpublished studies was performed, possibly introducing a risk of publication bias. Although all included studies were of high scientific quality, the risk of bias due to funding from industry grants is not negligible. Considering that five of the six RCTs only included occlusions in the anterior circulation, this might also limit the generalizability of the results to patients with ischemic stroke in the posterior circulation. Furthermore, long time follow-up from these RCTs needs to be assessed in order to evaluate the treatment benefits after 3 months.

In addition to the six included RCTs, preliminary results from the Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE) trial have been presented.²³ This is a French multicentre study including, to date, 385 patients. Patients were randomized during IV thrombolysis treatment into intervention or no additional

treatment. Including these results in the meta-analysis yields an OR for functional outcome of 2 (95% CI 1 to 3), favoring intervention, with a numbers needed to treat of 8 (95% CI 6 to 10).

Conclusion

Patients with acute stroke treated with IV thrombolysis and additional endovascular treatment with mechanical thrombectomy show improved functional outcome and lower mortality after 3 months from stroke onset compared with patients receiving IV thrombolysis alone.

Contributors AnF-D and AIF-D contributed equally to this study. AnF-D and AIF-D planned the work, and were responsible for data collection, analysis, and interpretation, and writing of the manuscript. JF performed the statistical analysis and critically revised the content. ÅKS interpreted the data and critically revised the manuscript. All authors approved the final version and agreed on the integrity of the work.

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