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Intra-Arterial Treatment for Acute Ischemic Stroke: a Meta-Analysis

ORIGINAL RESEARCH

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Abstract

Objective: To assess the potential benefit of treating patients with acute ischemic stroke using intra-arterial methods.

Methods: A meta-analysis of published randomized controlled trials that compared standard therapy with intravenous tissue plasminogen activator (IVtPA) for thrombolysis to intra-arterial therapies in patients with acute stroke was performed. All studies reported were analyzed as one group and studies documenting patients with large vessel obstruction were analyzed as a second group. The standardized mean difference (SMD) and the odds ratio (OR) of the dichotomized outcomes of Modified Rankin Scale (mRS) of these trials was calculated.

Results: Nine trials were identified with 2,711 patients treated. Meta-analysis of all studies, with and without large vessel obstruction documented, showed a significant benefit with intra-arterial therapy (SMD: 0.22 +/- 0.041; P=0.003). The dichotomized outcomes of mRS of these trials showed significant improvement (OR: 1.66 - 2.43 in four of the five treatment arm groups examined). Meta-analysis of all publications with large vessel obstruction documented as an entry criteria showed a greater significant benefit with intra-arterial therapy (SMD: 0.35 +/- 0.05; P<0.001). The dichotomized outcomes of mRS of these trials showed significant improvement (OR: 1.36 - 2.38 in all five treatment arm groups examined). Some heterogeneity was observed between studies.

Conclusion: Treatment of patients with acute ischemic stroke was associated with improved outcomes as measured by mRS. Patient selection, standard treatment, and study treatment factors contributed to the statistical evaluation of inter study heterogeneity and may have contributed to different study outcomes.

Keywords
Stroke; Thrombus; Interventional Neurology; Endovascular Neurology; Vascular Neurology; Ischemia.

Introduction

Stroke is a major cause of disability, with more than 795,000 individuals affected and about 130,000 deaths in the United States each year. About 87% of strokes are caused by vascular obstruction. [1] A number of medical advances over the last twenty years have positively impacted patient outcome in patients with acute ischemic stroke. The use of intravenous tissue plasminogen activator (IV tPA) for thrombolysis was first approved by the FDA in 1996. [2] It was estimated that 1% to 6% of ischemic stroke patients were treated with IV tPA in the early years following its approval. This low number was largely due to the strict 3-hour time window recommended for treatment and fears about complications related to its use. [3, 4] The use of IV tPA became more widely accepted after 2008 when a randomized controlled trial reported significantly improved clinical outcomes in patients treated less than 4.5 hours after symptom onset. [5, 6]

New treatments are being developed for patients with acute stroke, including the use of mechanical devices to remove arterial obstructions. Endovascular mechanical devices for thrombus removal became widely available in about 2005. [7] These devices have significantly improved in efficacy and safety over time, as demonstrated by randomized controlled trials. [8, 9] The benefit of intra-arterial thrombus treatment using mechanical devices is still under investigation. The use of intra-arterial thrombolysis with enzymatic materials is also under active investigation and may result in similar outcomes as those found with thrombus removal devices. [10] Outcomes of studies of these treatments in patients with acute ischemic stroke have not been consistent. We performed a meta-analysis to better understand the potential benefit associated with the intra-arterial treatment of patients with acute ischemic stroke and risk factors for good or poor outcomes after treatment.

Outcomes of studies of these treatments in patients with acute ischemic stroke have not been consistent. We performed a meta-analysis to better understand the potential benefit associated with the intra-arterial treatment of patients with acute ischemic stroke and risk factors for good or poor outcomes after treatment.

Methods

A meta-analysis was performed of published peer-reviewed randomized controlled trials comparing standard therapy to intra-arterial therapeutic procedures for the treatment of patients with acute thrombotic stroke per PRISMA standards (see **Supplemental File I** for PRISMA Checklist). Standard of care was defined as the use of IV tPA in the control arm. [5] Trials not using IV tPA in the control arm were excluded. [11-15] Non-randomized prospective studies, studies with historical controls, and retrospective series were excluded from the analysis.

A search of PubMed, the Cochrane Central Register of Controlled trials, Science Direct, and ClinicalTrials.gov was performed for randomized controlled trials using the terms "stroke" AND "thrombectomy" (MeSH unique IDs D020521 and D017131, respectively). Abstracts for all articles published before March, 2016 were reviewed. Bibliographies of relevant articles were reviewed to identify any additional relevant articles. Articles, databases, and supplemental appendices were searched for supporting data. Data were extracted in an unblinded fashion and rechecked on three separate occasions. No abstracts or unpublished studies were included in the study. Modified Rankin Scale (mRS) at 90 days was used to measure neurologic outcomes in the identified studies. [16]

Statistical Analysis

Data were analyzed for all patients and also separately for patients in studies that screened for large vessel obstruction as entry criteria. StatsDirect (Version 3) was used to perform meta-analysis of standardized mean difference (SMD) of mRS and

odds ratio (OR) of outcome of different dichotomous outcomes of mRS. Both fixed effects model and random effects model were used to examine the overall effect of treatments. Hedges g statistic was used to assess the SMD in the fixed effects model. The Mantel-Haenszel method was used for calculating the weighted summary OR in the fixed effects model. Cochran's Q test and I^2 statistic were used to estimate study heterogeneity. The Chi square statistic was used to evaluate different sources of study heterogeneity in groups with non-zero outcomes. The Cochrane risk of bias tool was used to assess publication bias. [17] Additional study methods including risk of bias and study heterogeneity are elaborated in **Supplemental File II**.

Risk factors for variations in study outcome included the use of first generation devices for endovascular treatments, general anesthesia, intra-arterial tPA in the treatment arms, and variable use of IV tPA in the control and treatment arms of each study. Time to treatment with clot removal therapies is critical to patient outcome. Heterogeneity in reported data made evaluation of time from onset of stroke event to each treatment modality difficult to evaluate and this analysis was not performed.

Results

A total of 946 publications were identified from the literature search, from which 102 were identified for detailed review **(Figure 1)**. Eleven clinical trials met the search criteria. [18-29] Among these, a single trial of seven patients not presenting mRS outcome data was excluded. [18] Another trial that included

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) four-phase flow diagram of included and excluded studies for quantitative analysis.

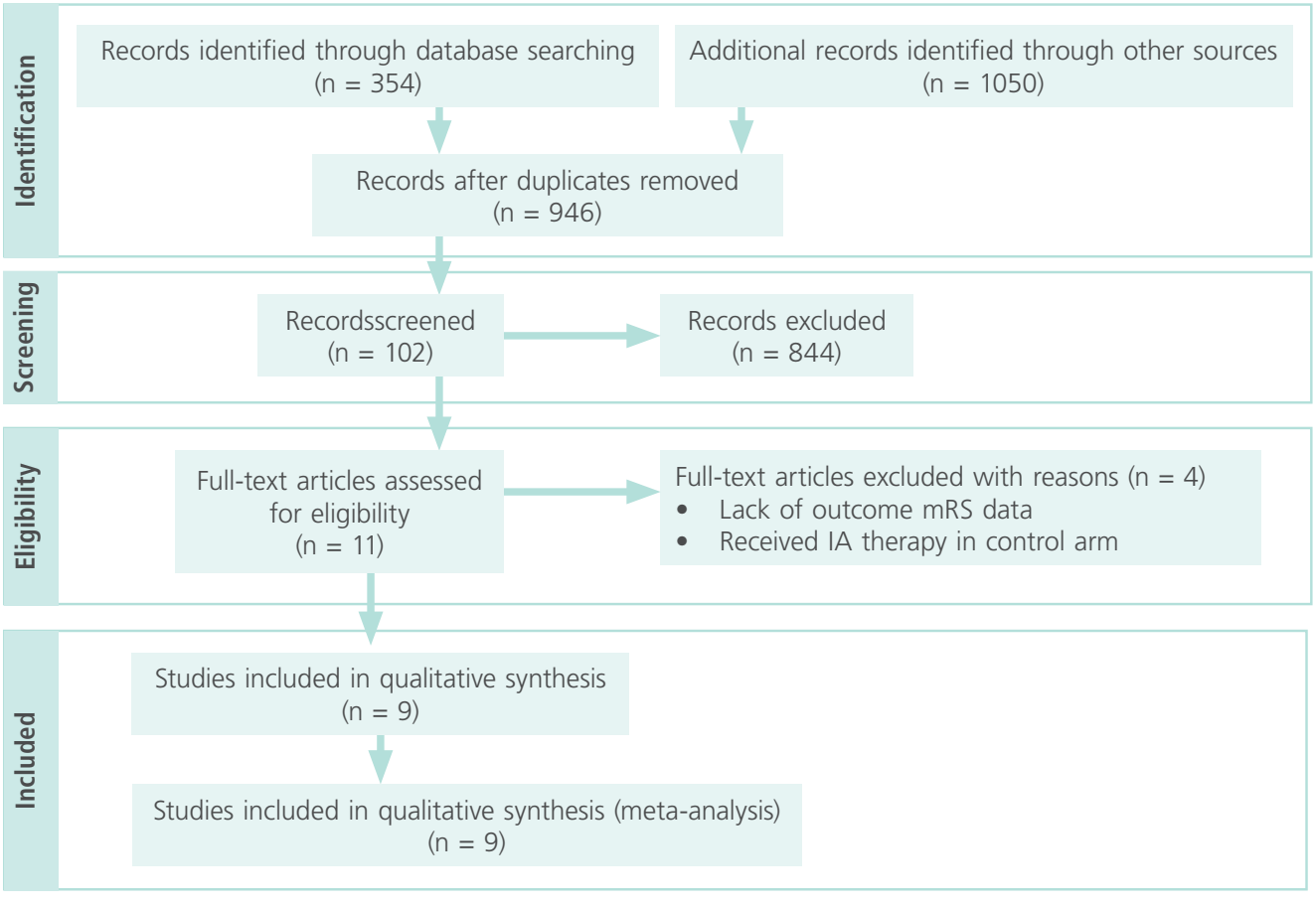


Table 1. Studies evaluated.

Study	Obstruction†	Treatment	Treated	Treatment	Treated
Synthesis pilot		IV tPA	29	IA tPA with mechanical thrombectomy if needed	25
Synthesis		IV tPA	181	IA tPA with mechanical thrombectomy if needed	181
IMS III		IV tPA	214	IV tPA plus IA tPA, mechanical thrombectomy, or both	415
MR rescue	X	IV tPA	54	IV tPA plus mechanical thrombectomy with rescue IA tPA	64
IMS III	X	IV tPA	91	IV tPA plus IA tPA, mechanical thrombectomy, or both	180
MR clean	X	IV tPA	267	IV tPA plus IA tPA, mechanical thrombectomy, or both	233
Escape	X	IV tPA	146	IV tPA plus mechanical thrombectomy	164
Extend-IA	X	IV tPA	35	IV tPA plus mechanical thrombectomy	35
Revascat	X	IV tPA	103	IV tPA plus mechanical thrombectomy	103
Swift prime	X	IV tPA	93	IV tPA plus mechanical thrombectomy	98

† X: All patients screened for large vessel proximal arterial obstruction. IV tPA: Intravenous tissue plasminogen activator. IA tPA: Intra-arterial tissue plasminogen activator

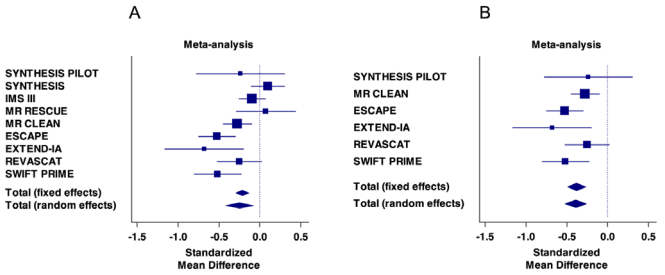
an intravascular therapeutic procedure in both arms was also excluded. [19] Nine trials were suitable for meta-analysis **(Table 1)**. [20-29] Of these trials, seven accepted patients after initial screening identified large vessel obstruction. [22, 24-29] These studies were also evaluated in a separate meta-analysis. Additional study results including risk of bias and study heterogeneity are elaborated in **Supplemental File II**.

All publications, with and without large vessel obstruction documented

Nine randomized controlled trials were identified that compared the use of IV tPA to that of intra-arterial treatment in patients with acute ischemic stroke **(Table 1)**. [20-23, 25-29] Not all trials had documentation of large vessel obstruction as an entry criteria. [20, 21, 23] Patients in the SYNTHESIS PILOT AND SYNTHESIS studies had a higher frequency of male gender than the other studies (Chi square test, P=0.000527) **(Supplemental File III)**. Patient age and race was not evaluable between studies.

The mean mRS of the control and treatment groups was evaluated. The SMD of the treatment group mRS was decreased compared to the control group in the fixed effects model 0.22 +/- 0.041 and the random effects model 0.25 +/- 0.085. The standardized mean difference of the two groups was significantly different (Funnel plot, **Figure 2A**, Fixed effects model, P<0.001; Random effects model, P=0.003). Significant study heterogeneity was observed (Cochran's Q test for heterogeneity, P=0.0003, I^2 statistic for inconsistency, 72.5%). Significant heterogeneity was observed with inclu-

Figure 2: The size of the square marker is relative to study weight. The location of the diamond represents the estimated effect size and the width the precision of the estimate.



A) Standardized mean difference of control and treatment group mRS, including all patient studies. A significant reduction in mRS was associated with intravascular treatment. B) Standardized mean difference of control and treatment group mRS, including all patient studies and removal of studies associated with heterogeneity. A significant reduction in mRS was associated with intravascular treatment.

sion of the Synthesis, [21] MR Rescue, [22] and IMS III [23] trials in the meta-analysis (Funnel plots, **Figures 2A** and **2B**). Excluding these trials, the SMD of the treatment group was decreased compared to the control group in the fixed effects model 0.38 +/- 0.055 and the random effects model 0.39 +/- 0.067. The standardized mean difference of the two groups was significantly different (**Figure 2B**, Fixed effects model, P<0.001; Random effects model, P<0.001). Minimal heterogeneity was observed after exclusion of these trials (Cochran's Q test for heterogeneity, P=0.26, I^2 statistic for inconsistency, 23.7%).

The OR of different dichotomized outcomes of the mRS was evaluated **(Table 2)**. Increments in mRS of the positive dichotomous outcome were associated with a monotone increase in the number of patients in that group. Significant heterogeneity was observed with inclusion of the Synthesis, [21] MR Rescue, [22] and IMS III [23] trials in the meta-analysis. Excluding these trials, meta-analysis of the remaining six trials showed minimal heterogeneity. The meta-analysis of the OR of the dichotomized outcomes of these six trials showed significant association with improvement in four of the five treatment arm groups examined. The OR benefit ranged from 1.66 to 2.43, with the largest benefit seen in the best outcome mRS subgroup.

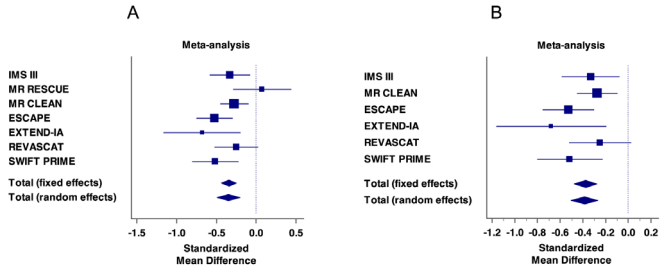
Series with large vessel obstruction as entry criteria

Nine randomized controlled trials were identified that compared the use of IV tPA to that of intra-arterial treatment in patients with acute ischemic

Table 2. Odds ratio meta-analysis and study heterogeneity. All patients (excluding SYNTHESIS, MR RESCUE, and IMS III trials) and studies with large vessel obstruction as entry criteria (excluding MR RESCUE trial).

mRS outcomes		All Patients					Patients with Visualized Obstruction				
		Odds ratio	95% CI	P	Study Heterogeneity Cochran's Q, P value	Study Heterogeneity I^2 Statistic (%)	Odds ratio	95% CI	P	Study Heterogeneity Cochran's Q, P value	Study Heterogeneity I^2 Statistic (%)
0-1 vs 2-6	Fixed effects model	2.43	1.83-3.24	<0.001	0.93	0.0	2.38	1.82-3.10	<0.001	0.92	0.0
	Random effects model	2.43	1.82-3.24	<0.001			2.38	1.82-3.10	<0.001		
0-2 vs 3-6	Fixed effects model	2.4	1.90-3.03	<0.001	0.75	0.0	2.17	1.75-2.70	<0.001	0.34	11.9
	Random effects model	2.4	1.90-3.03	<0.001			2.17	1.73-2.76	<0.001		
0-3 vs 4-6	Fixed effects model	2.23	1.78-2.78	<0.001	0.24	25.4	2.12	1.73-2.61	<0.001	0.17	37.4
	Random effects model	2.26	1.71-2.99	<0.001			2.17	1.64-2.86	<0.001		
0-4 vs 5-6	Fixed effects model	1.66	1.30-2.13	<0.001	0.16	36.9	1.74	1.38-2.19	<0.001	0.29	18.3
	Random effects model	1.71	1.21-2.42	0.003			1.77	1.36-2.31	<0.001		
0-5 vs 6	Fixed effects model	1.22	0.92-1.63	0.17	0.29	18.5	1.36	1.05-1.78	0.022	0.23	27.1
	Random effects model	1.24	0.88-1.74	0.23			1.41	1.01-1.96	0.044		

Figure 3: The size of the square marker is relative to study weight. The location of the diamond represents the estimated effect size and the width the precision of the estimate.



A) Standardized mean difference of control and treatment group mRS, including studies using large vessel obstruction as inclusion criteria. A significant reduction in mRS was associated with intravascular treatment. B) Standardized mean difference of control and treatment group mRS, including studies using large vessel obstruction as inclusion criteria, and removal of one study associated with heterogeneity. A significant reduction in mRS was associated with intravascular treatment.

stroke. [20-29] Two trials did not document large vessel obstruction as an entry criteria [20, 21] and were excluded from this analysis. One trial, IMS III, [23] was modified late in its accrual history to have absence of large vessel obstruction as an exclusion criteria. [24] Outcomes of patients with large vessel obstruction from this study were reported separately and were available for analysis. [24] Seven of the identified randomized controlled trials that included large vessel obstruction as an entry criteria were used for this meta-analysis **(Table 1)**. [22, 24-29] Patient demographics were similar for the two treatment arms **(Supplemental File III)**.

The mean mRS of the control and treatment groups was evaluated. The SMD of the treatment group mRS was decreased compared to the control group 0.35 +/- 0.05 in the fixed effects model and 0.35 +/- 0.074 in the random effects model. The standardized mean difference of the two groups was significantly different (Funnel plot, **Figure 3A**, Fixed effects model, P<0.001, Random effects model, P< 0.001). Significant heterogeneity was observed with inclusion of the MR Rescue [22] trial in the meta-analysis (Cochran's Q test for heterogeneity, P= 0.0615, I^2 statistic for inconsistency, 50.1%; Funnel plots, **Figures 3A** and **3B**). Excluding this trial, the SMD of the treatment group was decreased compared to the control group, 0.38 +/- 0.052 in the fixed effects model and 0.39 +/- 0.060 in the random effects model. The standardized mean difference of the two groups was significantly different **(Figure 3B)** (Fixed effects model, P<0.001; Random effects model, P<0.001). Minimal heterogeneity was observed after exclusion of this trial (Cochran's Q test for heterogeneity, P= 0.27, I^2 statistic for inconsistency, 22.0%).

The OR of different dichotomized outcomes of the mRS was evaluated **(Table 2)**. Increments in mRS of the positive dichotomous outcome was associated with a monotone increase in the number of patients in that group. Significant heterogeneity was observed with inclusion of the MR Rescue [22] trial in the meta-analysis. Meta-analysis of the six remaining trials, the same trials as those examined for the SMD mRS analysis, showed minimal heterogeneity. The meta-analysis of the OR of the dichotomized outcomes of these six trials showed significant association with improvement in all five treatment arm groups examined. The OR benefit ranged from 1.36 to 2.38, with the largest benefit seen in the best outcome mRS subgroup.

Risk of Bias

The risk of bias tool indicated a low risk of publication bias in the evaluated studies **(Supplemental File I)**. All studies used a random component in the sequence generation process and a recommended procedure to conceal allocation prior to assignment. While patients and providers were not blinded to their treatment, the mRS outcome was not likely to be influenced by the lack of blinding. All studies used an assessor of mRS outcome that was blinded to treatment arm. Six of the studies had no missing outcome data and the remaining 4 studies had 0 to 3.7% missing mRS values in the intra-arterial arm and 2 to 5.1% missing in the IV tPA arm. These

missing outcome data are unlikely to be related to true outcome. This missing data was balanced across treatment groups and the reasons for their absence were similar. No missing data was imputed. Nine of the 10 treatment protocols were available for review. Six studies had all planned outcomes reported, two were only missing financial outcomes, and two were missing redundant secondary outcomes. Other bias included patients randomized, but not receiving treatment, usually due to lack of obstruction found during imaging studies, marked clinical improvement or deterioration, or technical problems. All these patients were included in the mRS analyses.

Discussion

The study of intra-arterial treatment of acute ischemic stroke has mixed outcomes. While IV tPA has been significantly associated with improved outcomes, [5] intra-arterial thrombolytic treatments have not been uniformly successful. This meta-analysis of nine studies showed superior outcome in patients treated with intra-arterial thrombus-removing therapy, compared to patients treated with standard IV tPA therapy alone. This finding was observed in four of five dichotomous mRS subgroups derived from all patients treated in this fashion **(Table 2)**. The finding of superior outcome was stronger in studies where large vessel obstruction was a criterion for protocol entry. All five dichotomous mRS subgroups derived from studies with large vessel obstruction as a criterion for protocol entry had better outcomes than the control groups **(Table 2)**. The random effects model showed minimal benefit over the fixed effects model, suggesting there was one true benefit in all the studies evaluated.

The mixed results found in treated patients could be attributed to variations in protocol entry criteria and patient management, and changes in treatment modalities over time. [30] We examined how these factors contributed to inter-study heterogeneity that could result in different treatment outcomes and their relationship with reported outcomes.

Early trials often did not include large vessel obstruction as entry criteria. This likely resulted in unnecessary intra-arterial treatments, possible with the under general anesthesia, administered to stroke patients without large vessel obstruction. Early administration of IV tPA, before the administration of intra-arterial treatment, has the potential to clear an occluding arterial thrombus, making detection of benefit from intra-arterial therapy more difficult. From 2.9 to 3.4% of patients randomized to intra-arterial treatment in studies evaluated here had marked clinical improvement after the start of IV tPA that led to not receiving their intra-arterial treatment. [21, 25, 27] Receiving intra-arterial therapy after IV tPA can be an unnecessary treatment associated with serious complications including intracranial hemorrhage, arterial perforation, air emboli, and adverse reactions to general anesthesia. [10, 31] Inclusion of patients like these could have confounded the benefit analyses of intra-arterial therapies. From 3.4 to 18.4% of study patients evaluated here did not have large vessel obstruction at the time of intra-arterial treatment imaging [22-27, 32] and the frequency of obstruction in patients not having obstruction evaluated is not known. Patients in the SYNTHESIS PILOT, SYNTHESIS, and early IMS III trials were accepted on the basis of clinical findings of acute stroke, without any demonstration of thrombus obstruction. [21] There was no clear benefit associated with the use of intra-arterial treatment in these trials. Based on our analysis, the patients most likely to benefit from intra-arterial therapy would have a thrombus occluding a large artery after IV tPA treatment. The most commonly obstructed large arteries were the internal carotid artery and M1 and M2 middle cerebral arteries. Treatment of obstruction in these arteries appears to be associated with the best responses. Further study is needed to better evaluate outcomes in patients with extra-cranial internal ca-

rotid artery, M3 middle cerebral artery, and basilar artery obstruction.

Differences in patient management also contributed to study heterogeneity. While all patients in studies' control arm were scheduled for IV tPA by protocol, not all patients received treatment. In addition, some studies did not include IV tPA as part of the treatment arm, and when IV tPA was included, not all patients received this treatment. These unpredictable variations in the numbers of patients receiving IV tPA likely affect study outcome. IV tPA was not used in patients receiving endovascular treatment in the Synthesis Pilot and Synthesis trials, and used inconsistently in treated patients in MR RESCUE. No clear benefit was observed with the use of intra-arterial treatment in these trials. The effect of initial treatment with IV tPA on subsequent inra-arterial treatment needs further study.

Approximately 6.8 to 38.8% of patients undergoing endovascular treatments receive general anesthesia. This variation suggests a range in technical expertise of the physicians performing these special procedural treatments. General anesthesia has been reported as a risk factor for poor outcome in patients affected by stroke. [33, 34] However, patients we evaluated in the studies with frequently reported use of general anesthesia during administration of intra-arterial treatment did as well as patients in the studies with infrequent use. The reason for the good outcome observed in these studies with more frequent use of general anesthesia is not clear. Further study is needed to understand the safety of general anesthesia use in patients with acute ischemic stroke.

Improvements in mechanical devices to remove thrombi have been reported. The Merci Retriever, a first generation device, used corkscrew-shaped coil loops of flexible nitinol wire to ensnare and remove thrombus. Second generation thrombectomy devices used a different design resembling intracranial stents. The use of second generation devices has been shown to result in significant benefit over the Merci Retriever, as measured by recanalization studies and long term functional outcome. [8, 9] The use of the Merci Retriever was associated with higher risk of arterial perforation, [8] worse neurologic outcome, [8, 9] and higher mortality [9] than other stents. First generation devices were most frequently used as the sole intra-arterial treatment in MR RESCUE and IMS III, studies not associated with improved outcome after intra-arterial therapy.

Intra-arterial administration of thrombolytic agents for the treatment of acute stroke is not as well studied as intravenous treatment. Intra-arterial administration of thrombolytic agents appears to be associated with a modest benefit, although their evaluation is on-going. [10, 35] Some studies have shown a higher rate of arterial recanalization compared to intravenous treatments, spurring interest in this treatment modality. [35] The use of intra-arterial thrombolytic agents appears to be associated with more frequent occurrences of intracranial hemorrhage. [10] In IMS III, Synthesis Pilot, and Synthesis, intra-arterial tPA was most frequently used to remove obstructing clot. These studies were not associated with improved outcome after intra-arterial therapy.

Patients with larger ischemic cores are at higher risk for poor outcome after removal of proximal large arterial occlusions. [30, 36, 37] Patients with small infarct volumes have been reported to do better than those with larger infarct volumes. [38] Early studies did not use ischemic core size cutoff to select patients and were associated with worse outcome. Studies treating patients with a relatively small ischemic core volume, Extend-IA, MR Clean, Escape, Revascat, and Swift Prime, were associated with improved outcomes after intra-arterial treatment.

This study was limited by data not adequately reported or unavailable for retrospective analyses and differences in methodologies used in patient selection and treatment. This made the statistical evaluation of heterogeneity limited in nature. Clinical heterogeneity, including variations in physi-

cian patterns of treatment, patient selection and patient variability, could not be compared between studies. The use of different mechanical devices for thrombus removal, varying times to standard and intra-arterial treatments after onset of stroke, and pooling of different interventions in the treatment arm also contributed to inter-study heterogeneity and could not be accounted for.

The best outcomes were seen in a small subgroup of patients who developed stroke. These patients were treated with newer generation mechanical thrombectomy devices, had evidence of large vessel obstruction on initial imaging studies, had obstruction of the internal carotid artery and M1 and M2 middle cerebral arteries, had small core stroke volumes, and had the most consistent and apparently rapid use of IV tPA (less than 4.5 hours) and mechanical thrombectomy devices (less than 6 to 8 hours) to remove thrombus. Treatment of patients without apparent obstruction, cerebral hemorrhage, more distal large artery obstruction or small artery obstruction, larger ischemic stroke core size, and who present in a delayed fashion is still controversial. Further studies are needed to better delineate patient outcomes in these varied clinical scenarios.

Conclusion

This meta-analysis demonstrated improved outcomes as measured by mRS in patients with acute thrombotic stroke undergoing intra-arterial treatment. This improvement appears to be complementary to the improvement seen with IV tPA. Patient selection, standard treatment, and study treatment factors contributed to inter study heterogeneity, which may have resulted in different study outcomes in the different reports. These factors need further study to determine best outcome in different patient populations.

Contributorship Statement

Conceived and designed the experiments: SEL, MMW, DRM. Performed the experiments: SEL, MMW, DRM. Analyzed the data: SEL, MMW, DRM, TN. All authors participated in the preparation of the manuscript, and read and approved the final manuscript.

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Competing Interests Statement

The authors declare that they have no competing interests and report no disclosures.

Data Sharing

There are no additional unpublished data available. All data are found in the manuscript and supplemental files.

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