Original Investigation

Stent Retrievers for the Treatment of Acute Ischemic Stroke
A Systematic Review and Meta-analysis of Randomized Clinical Trials

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IMPORTANCE Stent retrievers are a promising alternative for the treatment of acute ischemic stroke (AIS). Several recently completed clinical trials have examined the use of stent retrievers with intravenous recombinant tissue plasminogen activator (rtPA) compared with rtPA alone.

OBJECTIVE To conduct a systematic review and meta-analysis of randomized clinical trials to quantify the benefits and risks of using stent retrievers in addition to rtPA for the treatment of AIS.

DATA SOURCES The MEDLINE, EMBASE, and Cochrane Library of Clinical Trials databases were searched from inception to July 2015 for the keywords *stent*, retriev*, Solitaire, Trevo, Revive*, and *stroke*. Trial registries were also searched. A total of 326 publications were identified and 213 potentially relevant records were screened.

STUDY SELECTION Randomized clinical trials that examined stent retrievers with rtPA vs rtPA alone were included in the meta-analysis.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers extracted study data and performed quality assessment using the Cochrane Risk of Bias Tool. DerSimonian and Laird random-effects models were used to estimate relative risks (RRs), risk differences (RDs), and numbers needed to treat.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients achieving functional independence (defined as a score of 0-2 on the modified Rankin Scale, with 0 indicating no disability and 6 indicating death) at 90 days. Risks of all-cause mortality, intracranial hemorrhage, and parenchymal hematoma at 90 days were also assessed.

RESULTS Five randomized clinical trials met our inclusion criteria (n = 1287 patients). Patients randomized to stent-retriever therapy with rtPA had significantly improved rates of functional independence at 90 days compared with those randomized to rtPA alone (RR, 1.72; 95% CI, 1.48-1.99; RD, 0.19; 95% CI, 0.13-0.25). When data were pooled across trials, the effect of stent-retriever therapy on all-cause mortality at 90 days was inconclusive (RR, 0.82; 95% CI, 0.60-1.11; RD, −0.04; 95% CI, −0.08 to 0.1). There were similarly no detectable differences in the risks of intracranial hemorrhage (RR, 1.15; 95% CI, 0.67-1.97; RD, 0.00; 95% CI, −0.02 to 0.03) or parenchymal hematoma (RR, 1.18; 95% CI, 0.71-1.94; RD, 0.01; 95% CI, −0.01 to 0.04), although the 95% CIs were wide. Fixed-effects sensitivity analyses produced similar results for all outcomes.

CONCLUSIONS AND RELEVANCE The use of stent retrievers in conjunction with rtPA vs rtPA alone is associated with significant improvement of functional independence 90 days after AIS.

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Editorial page 265

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For several decades, the standard of care for acute ischemic stroke (AIS) has been thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rtPA).[1] However, developments in intra-arterial therapy (IAT) in the form of stent-retriever devices for thrombectomy (used in combination with rtPA) have shown promise for AIS. Stent retrievers are deployed in an occluded vessel and are temporarily expanded into the body of a thrombus. This procedure recanalizes the vessel, allowing for reperfusion of ischemic sites and causing the thrombus to be partially entangled within the stent. Thrombectomy is performed by retracting the stent.[2]

In 2015, several randomized clinical trials (RCTs) revealed significant improvements in functional status (as defined by the modified Rankin Scale [mRS]) when comparing the use of stent retrievers with rtPA vs rtPA alone,[3-7] with 4 RCTs terminated early because of clear benefits with stent-retriever therapy. Hence, the individual trials had small sample sizes and a modest number of events. To allow for a more precise determination of the overall benefits and risks associated with these devices, we conducted a meta-analysis of RCTs to compare stent retrievers with rtPA vs rtPA alone for the treatment of AIS.

Key Points

Question: What are the overall benefits and risks associated with the use of stent retrievers in conjunction with thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) vs rtPA alone for acute ischemic stroke treatment?

Findings: In a meta-analysis of 5 randomized clinical trials, which included 1287 patients, patients randomized to stent retrievers plus rtPA were significantly more likely to be functionally independent at 90 days vs those randomized to rtPA alone.

Meaning: Stent retrievers used in conjunction with rtPA are a promising alternative for the treatment of acute ischemic stroke.

Methods

Our systematic review and meta-analysis were conducted using a prespecified protocol and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[8]

Search Strategy

We performed a systematic search of the MEDLINE (via Ovid), EMBASE (via Ovid), and Cochrane Library of Clinical Trials databases from inception to July 2015 (eTables 1, 2, and 3 in the Supplement). The search was executed by one of us (L.T.) using the keywords *stent*, retriev*, Solitaire, Trevo, Revive*, and *stroke*. Medical Subject Headings terms and EMTREE terms were used where applicable. We used a modified version of the Cochrane RCT hedge to restrict our search to RCTs.[9] We additionally searched by hand the references of published reviews and RCTs that met our prespecified inclusion and exclusion criteria for any additional potentially eligible RCTs. The ClinicalTrials.gov and ClinicalTrialsRegister.eu registries were also searched. We did not search the gray literature for unpublished reports, such as abstracts and conference proceedings, because often their data are incomplete or insufficient to assess trial quality.

Study Selection

The title and abstract of identified publications were screened, with any potentially eligible articles retrieved for full-text review. Inclusion was restricted to RCTs published in English or French that randomized adult patients (aged ≥18 years) to stent retrievers in conjunction with rtPA vs rtPA alone. Trials that randomized patients to IAT (ie, intra-arterial administration of rtPA, a first-generation thrombectomy device, or a stent retriever) were also included if 75% or more of patients received stent retrievers. We excluded observational studies, case reports, reviews, editorials, commentaries, abstracts, and conference proceedings. Abstracts and conference proceedings were excluded because their results are often incomplete or contain insufficient detail to assess trial quality. Final study selection was performed by one of us (L.T.).

Data Extraction

For each included RCT, data on study and patient characteristics were extracted independently and in duplicate (L.T. and L.H.S.) using a standardized, pilot-tested data collection form. Discrepancies were resolved by consensus (L.T. and L.H.S.) or, if necessary, by a third reviewer (K.B.F.). Extracted study and patient characteristics included year of publication, sample size, maximum allowable time from stroke symptom onset to treatment, follow-up duration, sex, age, diabetes mellitus, atrial fibrillation, previous stroke, hypertension, serum glucose level, and baseline National Institutes of Health Stroke Scale (NIHSS) score (which rates the severity of stroke on a scale of 0-42, with a higher score indicating more severe impairment).[10] The following 24-hour postprocedure outcomes were extracted: early neurologic improvement (defined by a change >8 on the NIHSS), median change in NIHSS score, infarct volume, and infarct growth. The following 90-day outcomes were then extracted: mRS score[11] (scale of 0-6 rating disability due to stroke, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death) (eTable 4 in the Supplement), proportion of patients with an mRS score of 0 to 2, all-cause mortality, intracranial hemorrhage, and parenchymal hematoma. We extracted count data and reported relative risks (RRs), hazard ratios, and odds ratios (ORs) where available.

Quality Assessment

Quality of included RCTs was assessed using the Risk of Bias Tool developed by the Cochrane Collaboration.[12] For each RCT, 2 reviewers (L.T. and L.H.S.) independently assigned a score of high, low, or unclear to each of the following domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential sources of bias. Disagreements were resolved by consensus or a third reviewer (K.B.F.). We included all eligible RCTs regardless of their assessed quality.

Table 1. Characteristics of Randomized Clinical Trials Comparing SRs With rtPA and rtPA Alone

Trial	Year	Patients per Arm, No.		SR Device Used in SR and rtPA Arm of the Trial	SR Use Among Patients Randomized to Treatment Arm, %		Neurologic Inclusion Criteria	Allowable Time to Treatment From Symptom Onset, h	Length of Follow-up, d	Lost to Follow-up, %[a]
		SR and rtPA	rtPA		SR and rtPA	rtPA				
MR CLEAN[3,b]	2015	233	267	Not specified, 100%	81.5	0[c]	NA	6	90	0
ESCAPE[5,b]	2015	165	150	Solitaire, 76.9%; not specified, 23.1%	78.8	0[c]	Barthel Index scores of ≥90	12[d]	90	1.3
REVASCAT[6]	2015	103	103	Solitaire, 100%	95.1	0	mRS scores of 0-1	6	90	0
SWIFT PRIME[7]	2015	98	98	Solitaire, 100%	88.8	0	mRS scores of 0-1	6	90	4.6[e]
EXTEND-IA[4]	2015	35	35	Solitaire, 100%	77.1	0	mRS scores of 0-2	4.5	90	0

Abbreviations: ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-arterial Therapy; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; NA, not applicable; REVASCAT, 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 8 Hours of Symptom Onset; rtPA, recombinant tissue plasminogen activator; SR, stent retriever; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment.

[a] Percentage represents the total number of patients lost to follow-up in the trial.

[b] Trial randomizing patients to intra-arterial therapy (ie, intra-arterial administration of rtPA, a first-generation thrombectomy device, or an SR).

[c] One patient randomized to the control group crossed over to the treatment group, but it is not specified if that patient received an SR as part of the intra-arterial therapy.

[d] The rtPA must be administered within 4.5 hours.

[e] Nine patients were lost to follow-up: 4 were included in the analyses using the last observation carried forward method, 2 were withdrawn by the investigator because of deviation from trial entry criteria, and 3 withdrew their consent.

Statistical Analysis

DerSimonian and Laird random-effects models with inverse variance weighting were used to pool count data across trials and estimate RRs and their corresponding 95% CIs for all outcomes. Our primary outcome was functional independence at 90 days, defined as achieving an mRS score of 0 to 2, in patients randomized to receive stent retrievers with rtPA vs rtPA alone. I^2, Q, and τ^2 were calculated to assess heterogeneity among the included RCTs. I^2 was estimated via a weighting approach using a Mantel-Haenszel fixed-effects approach. Sensitivity analyses were conducted using Mantel-Haenszel fixed-effects models to assess the effect of using a random-effects model on our estimates. Risk differences (RDs) and numbers needed to treat (NNTs) were calculated for all outcomes of interest, and influence analyses using random-effects models were performed to assess the effect of each trial on meta-analytic results. Statistical analyses were conducted using STATA software, version 11.2 (StataCorp).

Results

Search Results

Our systematic search identified 326 potentially relevant publications, including 1 found through searching by hand the references of included RCTs (eFigure 1 in the Supplement). There were 113 duplicates, leaving 213 to be screened by title and abstract. We identified 9 publications for full-text review. Of those, 5 met our prespecified criteria for inclusion in our meta-analysis[3-7]: a randomized trial of IAT for AIS (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN]),[3] randomized assessment of rapid endovascular treatment of ischemic stroke (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE]),[5] thrombectomy within 8 hours after symptom onset in ischemic stroke (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 8 Hours of Symptom Onset [REVASCAT]),[6] stent-retriever thrombectomy after intravenous tPA vs tPA alone in stroke (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME]),[7] and endovascular therapy for ischemic stroke with perfusion-imaging selection (Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-arterial Therapy [EXTEND-IA]).[4]

Study Characteristics

Together, these 5 RCTs randomized a total of 1287 patients to receive stent retriever with rtPA or rtPA alone (**Table 1**). Sample sizes ranged from 70 to 500. All studies included patients with an imaging-confirmed stroke of the anterior circulation, and 4 studies[4-7] restricted inclusion to patients who were previously functionally independent. Functional independence was defined as a Barthel Index score of 90 or higher (a scale assessing the ability to perform activities of daily living; scored from 0-100, with higher scores indicating more independence),[13] mRS score of 0 to 1, or mRS score of 0 to 2. Studies[4-7] differed in their acceptable time from stroke symptom onset to stent-retriever therapy, ranging from 4.5 to 12 hours after stroke symptoms began.

REVASCAT, SWIFT PRIME, and EXTEND-IA specifically examined the use of the Solitaire stent retriever (Covidien) along

Table 2. Outcomes at 90 Days in Randomized Clinical Trials Comparing SRs With rtPA and rtPA Alone

Trial	mRS Scores of 0-2, No./Total No. (%)			OR for a 1-Point Decrease in mRS score[b] (95% CI)	All-Cause Mortality, No./Total No. (%)			Intracerebral Hemorrhage, No./Total No. (%)			Parenchymal Hematoma, No./Total No. (%)		
	SR and rtPA	rtPA	RR (95% CI)[a]		SR and rtPA	rtPA	RR (95% CI)[a]	SR and rtPA	rtPA	RR (95% CI)[a]	SR and rtPA	rtPA	RR (95% CI)[a]
MR CLEAN[3,c]	76/233 (32.6)	51/267 (19.1)	1.71 (1.25-2.32)	1.66 (1.21-2.28)	49/233 (21.0)	59/267 (22.1)	0.95 (0.68-1.33)	18/233 (7.7)	17/267 (63.7)	1.21 (0.64-2.30)	14/233 (6.0)	16/267 (6.0)	1.02 (0.51-2.04)
ESCAPE[5,d]	87/164 (53.0)	43/147 (29.3)	1.81 (1.36-2.42)	2.6 (1.7-3.8)	17/164 (10.4)	28/147 (19.0)	0.54 (0.31-0.95)	6/165 (3.6)	4/150 (2.7)	1.36 (0.39-4.74)	8/165 (4.8)	3/150 (2.0)	2.38 (0.64-8.80)
REVASCAT[6]	45/103 (43.7)	29/103 (28.2)	1.55 (1.06-2.27)	1.7 (1.04-2.7)	19/103 (18.4)	16/103 (15.5)	1.19 (0.65-2.18)	2/103 (1.9)	2/103 (1.9)	1.00 (0.14-6.96)	6/103 (5.8)	6/103 (5.8)	1.00 (0.33-3.00)
SWIFT PRIME[7]	59/98 (60.2)	33/93 (35.5)	1.70 (1.23-2.33)	2.63 (1.57-4.40)	9/98 (9.2)	12/98 (12.2)	0.75 (0.33-1.70)	NR	NR	NR	NR	NR	NR
EXTEND-IA[4]	25/35 (71.4)	14/35 (40.0)	1.79 (1.13-2.82)	2.1 (1.2-3.8)	3/35 (8.6)	7/35 (20.0)	0.43 (0.12-1.52)	0/35 (0.0)	2/35 (5.7)	0.20 (0.01-4.02)	4/35 (11.4)	3/35 (8.6)	1.23 (0.30-5.13)
Pooled[e]	...	...	1.72 (1.48-1.99)	2.03 (1.65-2.50)	...	...	0.82 (0.60-1.11)	...	...	1.15 (0.67-1.97)	...	...	1.18 (0.71-1.94)
I^2, %	...	...	0.0	11.4	...	...	23.9	...	...	0.0	...	...	0.0
Q	...	...	0.45	...	...	...	5.26	...	...	1.44	...	...	1.38
τ^2	...	...	0.0000	...	...	...	0.0297	...	...	0.0000	...	...	0.0000

Abbreviations: ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-arterial Therapy; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NR, not reported; OR, odds ratio; REVASCAT, 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 8 Hours of Symptom Onset; RR, relative risk; rtPA, recombinant tissue plasminogen activator; SR, stent retriever; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment. Ellipses indicate data not applicable.

[a] Data in these columns are RR (95% CI) except for I^2, Q, and τ^2.

[b] Unadjusted OR for a 1-point improvement in mRS score if randomized to SR therapy in combination with rtPA vs rtPA alone.

[c] Intra-arterial therapy with 190 out of 233 randomized patients (81.5%) receiving SR therapy.

[d] Intra-arterial therapy with 130 out of 165 randomized patients (78.8%) receiving SR therapy.

[e] Results were pooled using random-effects models.

with rtPA vs the use of rtPA alone.[4,6,7] In contrast, ESCAPE and MR CLEAN examined the use of any IAT (ie, intra-arterial administration of rtPA, a first-generation thrombectomy device, or a stent retriever) vs rtPA alone, with most patients randomized to the interventional arms receiving stent-retriever therapy (n = 130 [78.8%] and n = 190 [81.5%], respectively).[3,5] In ESCAPE, 76.9% of patients received the Solitaire and 23.1% received unspecified stent-retriever device types, whereas the device type was not specified in MR CLEAN.[3,5] Furthermore, the ESCAPE, REVASCAT, and MR CLEAN trials allowed the inclusion of patients who could not be treated with rtPA because they were trials of IAT vs no IAT against a background of best medical management, which could include rtPA.[3,5,6]

All included RCTs had a maximum follow-up of 90 days after the procedure. The 90-day mRS score was the primary outcome for all included RCTs except EXTEND-IA, where it was a secondary outcome. The proportion of patients achieving an mRS score of 0 to 2 at 90 days was among the secondary outcomes of all included RCTs. Significant improvements in mRS-defined functional status with the use of stent retrievers with rtPA vs rtPA alone led to the early termination of 4 of the 5 RCTs.[4-7]

Quality Assessment

Overall, studies had a low risk of bias, as assessed by the Cochrane Risk of Bias Tool (eTable 5 in the Supplement). Four studies[4-7] had an unclear risk of bias in the other sources of bias category because of their early termination and corresponding increase in the role of chance in their findings.

Patient Characteristics

Patient characteristics were similar across studies (eTable 6 in the Supplement). Most participants were in their middle 60s to early 70s, with men representing 48% to 59% of trial participants. Three trials reported rates of prior stroke; stroke rates ranged from 9% to 18% and were similar in the study arms. The NIHSS scores varied from a median of 13 to 18 across all studies.

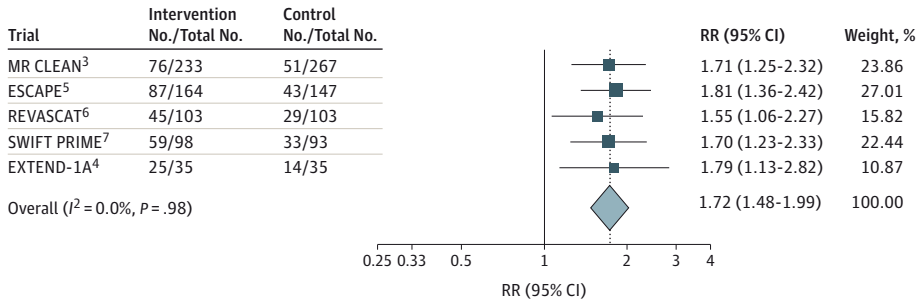
Early Neurologic Function

Reporting of early outcomes was inconsistent across trials (eTable 7 in the Supplement). Two trials assessed early neurologic improvement: 1 at 24 hours[6] and the other at 3 days.[4] Both studies[4,6] reported significant benefit from the use of stent retrievers (OR, 5.5; 95% CI, 2.9-10.3, and OR, 6.8; 95% CI, 2.3-20.0, respectively). Two studies[4,7] examined the mean and median reduction in NIHSS score at 27 and 24 hours, respectively, and found that stent-retriever therapy was associated with significant reductions, indicating improved outcomes.

90-Day Outcomes

Individual and pooled 90-day outcomes are reported in **Table 2**. In all trials, patients randomized to stent-retriever therapy with rtPA had significantly greater functional independence (defined as mRS scores of 0-2) vs rtPA alone (RR, 1.72; 95% CI, 1.48-1.99) (**Figure**). All trials also found that patients randomized to stent retrievers had a greater odds of a 1-unit decrease in mRS score at 90 days (pooled OR, 2.03; 95% CI, 1.65-2.50). Reduced 90-day all-cause mortality was also observed among

Figure. Forest Plot of the RR for Functional Independence in Patients Randomized to Receive Stent Retrievers With rtPA vs rtPA Alone



Functional independence was defined as a modified Rankin Scale score of 0 to 2 (a score of 0 indicates no symptoms; 1, no clinically significant disability; and 2, slight disability). ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-arterial Therapy; 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 vs Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset; RR, relative risk; rtPA, recombinant tissue plasminogen activator; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment.

Table 3. Summary of Pooled Analyses of Randomized Clinical Trials Comparing SRs With rtPA and rtPA Alone[a]

Outcome	Relative Risk (95% CI)	Risk Difference (95% CI)	No. Needed to Treat (95% CI)	No. of Excess Events per 1000 (95% CI)
mRS score of 0-2[b]	1.72 (1.48 to 1.99)	0.19 (0.13 to 0.25)	6 (4 to 8)	188.5 (125.4 to 262.0)
All-cause mortality	0.82 (0.60 to 1.11)	−0.04 (−0.08 to 0.1)	30[c]	34.1[d] (−20.8 to 74.6)
Intracranial hemorrhage	1.15 (0.67 to 1.97)	0.00 (−0.02 to 0.03)	−145[e]	6.9[d] (−14.7 to 43.8)
Parenchymal hematoma	1.18 (0.71 to 1.94)	0.01 (−0.01 to 0.04)	−114[f]	8.8[d] (−14.5 to 47.2)

Abbreviations: mRS, modified Rankin Scale; rtPA, recombinant tissue plasminogen activator; SR, stent retriever.

[a] Pooled using random-effects models.

[b] A score of 0 indicates no symptoms; 1, no clinically significant disability; and 2, slight disability.

[c] The estimated number needed to treat is 30. It is not significant because the 95% CI, which spans from a number needed to treat of −48 (ie, number needed to harm) to a number needed to treat of 14, includes unity.

[d] Number of avoided events per 1000.

[e] The estimated number needed to treat is −145 (ie, a number needed to harm). It is not significant because the 95% CI, which spans from a number needed to treat of −23 (ie, number needed to harm) to a number needed to treat of 69, includes unity.

[f] The estimated number needed to treat is −114 (ie, number needed to harm). It is not significant because the 95% CI, which spans from a number needed to treat of −22 (ie, number needed to harm) to a number needed to treat of 70, includes unity.

patients randomized to stent retrievers in ESCAPE; however, this became inconclusive when pooling across trials (RR, 0.82; 95% CI, 0.60-1.11) (eFigure 2 in the Supplement). There were no significant differences in the rates of intracranial hemorrhage (RR, 1.15; 95% CI, 0.67-1.97) (eFigure 3 in the Supplement) and parenchymal hematoma (RR, 1.18; 95% CI, 0.71-1.94) (eFigure 4 in the Supplement) between groups at 90 days, although the 95% CIs were wide.

The RDs and NNTs were also assessed (**Table 3** and eTable 8 in the Supplement). The pooled NNT for our primary outcome of the proportion of patients achieving an mRS score of 0 to 2 at 90 days was 6 (number of excess events per 1000, 188.5; 95% CI, 125.4-262.0), revealing a clear benefit in functional status even with the treatment of a small number of patients. The pooled NNT (n=30) for all-cause mortality was inconclusive (number of avoided events per 1000, 34.1; 95% CI, −20.8 to 74.6). There were similarly no significant differences between groups in the occurrence of intracranial hemorrhage (number of avoided events per 1000, 6.9; 95% CI, −14.7 to 43.8) or parenchymal hematoma (number of avoided events per 1000, 8.8; 95% CI, −14.5 to 47.2), although these events were rare and the CIs were wide.

Sensitivity analyses conducted using fixed-effect models produced similar results for all outcomes (eTable 9 in the Supplement). Furthermore, influence analyses using random-effects models revealed that no study had a particularly large effect on the overall meta-analysis results (eTable 10 in the Supplement). This includes the omission of MR CLEAN, the largest trial (RR, 1.72; 95% CI, 1.45-2.04). To assess the potential effect of publication bias, we conducted a sensitivity analysis including data available from the registered but unpublished Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE; ClinicalTrials.gov Identifier: NCT01062698),[14] which compares mechanical thrombectomy with the Merci (Concentric Medical), Penumbra (Penumbra), Catch (Balt), or Solitaire devices plus rtPA vs rtPA alone. To date, only a 90-day mRS score of 0 to 2 and all-cause mortality are available, and it is unknown whether THRACE involves 75% or greater stent-retriever use. Our analyses yielded similar results regarding functional independence

(mRS score, 0-2; RR, 1.56; 95% CI, 1.38-1.77) and all-cause mortality (RR, 0.86; 95% CI, 0.68-1.09) (eTable 11 in the Supplement).

Discussion

Our study was designed to assess the benefits and risks of using stent retrievers in conjunction with rtPA vs rtPA alone for the treatment of AIS. We found that stent-retriever therapy was associated with better functional outcomes at 90 days, as assessed using the mRS, than standard therapy alone. Our findings at 90 days regarding all-cause mortality, intracranial hemorrhage, and parenchymal hematoma were inconclusive because the 95% CIs were wide. These findings are consistent with those of the constituent clinical trials but provide increased precision concerning the treatment effects of stent-retriever therapy.

Previous reviews and meta-analyses[15-17] examining this issue have been published. However, some meta-analyses[15,16] pooled data from observational and nonrandomized trials with small sample sizes in addition to RCTs. These previous reviews are limited by the use of nonrandomized data and thus may be affected by confounding by indication and other variables. Another recent systematic review and meta-analysis[17] included only 2 RCTs comparing stent retrievers with the first-generation Merci coil retriever and none of the recently published stent-retriever RCTs. Although data were pooled in a commentary written by Goyal and Menon[18] that examined the 5 acute endovascular RCTs published in 2015, their meta-analysis was conducted outside the context of a systematic review.

In addition, 3 previous systematic reviews and meta-analyses[19-21] pooled data from RCTs comparing any IAT procedures vs medical management of AIS without focusing specifically on stent retrievers. These meta-analyses included the 3 negative RCTs published in 2013 that failed to demonstrate an improvement with endovascular treatment. A recent position statement by Mocco and colleagues[22] highlighted that these 3 RCTs had important limitations, including imaging techniques and thrombectomy devices studied that became outdated by the time recruitment was completed. Consequently, pooling their results with those of other trials may not be appropriate. The meta-analysis by Hong and colleagues[21] additionally pooled data from the 5 recent RCTs. However, they estimated pooled ORs, which are only unbiased estimates of the RR when the outcome is rare. Given how common the outcome of mRS scores of 0 to 2 is, these ORs are difficult to interpret. To our knowledge, our meta-analysis is the most recent one conducted within the context of a systematic review to include all the published evidence from RCTs and to specifically focus on stent retrievers.

The recent publication of the RCTs included in our meta-analysis resulted in updates to the American Heart Association/American Stroke Association guidelines for the management of AIS, which expanded the role of stent retrievers as part of the treatment algorithm for stroke.[23] Previous recommendations for the use of thrombectomy devices were based on weak evidence (Class 2a; Level of Evidence B).[1] The updated guidelines now strongly recommend their use and base this recommendation on the strongest level of evidence (Class 1a). The guidelines state that stent-retriever therapy should be considered if treatment can be initiated within 6 hours of symptom onset.[23]

These recommendations only apply to patients similar to those studied in currently published RCTs. With the exception of MR CLEAN, which placed no restrictions on age, comorbidity, and prestroke disability, all current RCTs examining stent retrievers with rtPA vs rtPA alone restricted their study samples to patients with excellent prestroke functional independence (ie, mRS score of 0-1). Moreover, most patients who became enrolled in MR CLEAN did not have prestroke disability. For all 5 RCTs, patients had confirmed anterior circulation obstructions on imaging and were able to receive stent-retriever therapy within 4.5 to 6 hours of stroke symptom onset (with the exception of one trial, which permitted stent-retriever therapy within 12 hours). However, only a small percentage of patients with AIS meet such criteria. Data on effectiveness will be required to determine the benefit of stent retrievers for patients falling outside these idealized parameters. On the basis of the strongly positive results of this meta-analysis, however, it is expected that stent retrievers will continue to be beneficial in real-world clinical practice.

Our study has several potential limitations. First, our sample size resulted in wide 95% CIs for the secondary end points. For instance, the point estimate for all-cause mortality suggests a protective effect but ultimately was inconclusive. Second, trials that are stopped early are more likely to suggest exaggerated benefits than if they had recruited their full sample.[24] However, because early stopping attributable to benefit occurred in 4 of the 5 trials, the observed benefits are unlikely to be owing to chance. Third, as with all meta-analyses, there is the potential for publication bias. The RCTs with positive findings are more likely to be published than those with null or negative findings. The limited number of included trials afforded modest ability to detect the presence of publication bias. Fourth, our search was restricted to French- and English-language publications. This practical limitation may have led to the exclusion of relevant studies, although this is unlikely because of the small number of records (n=12) removed when our search was limited to those 2 languages. Despite these limitations, this meta-analysis represents the best available evidence regarding the efficacy of stent retrievers.

Conclusions

Our study was designed to compare the efficacy and safety of stent retrievers used in conjunction with rtPA vs rtPA alone. Our meta-analysis found that stent-retriever therapy was associated with significantly improved functional outcomes at 90 days. Data on all-cause mortality and safety were inconclusive. Given the totality of the evidence regarding the benefits and risks of stent retrievers, our results suggest that the use of these devices in patients with AIS is warranted.

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