Endovascular vs medical management of acute ischemic stroke

Ching-Jen Chen, MD
Dale Ding, MD
Robert M. Starke, MD, MSc
Prachi Mehndiratta, MD
R. Webster Crowley, MD
Kenneth C. Liu, MD
Andrew M. Southerland, MD, MSc
Bradford B. Worrall, MD, MSc

Correspondence to
Dr. Chen:
chenjared@gmail.com

ABSTRACT

Objective: To compare the outcomes between endovascular and medical management of acute ischemic stroke in recent randomized controlled trials (RCT).

Methods: A systematic literature review was performed, and multicenter, prospective RCTs published from January 1, 2013, to May 1, 2015, directly comparing endovascular therapy to medical management for patients with acute ischemic stroke were included. Meta-analyses of modified Rankin Scale (mRS) and mortality at 90 days and symptomatic intracranial hemorrhage (sICH) for endovascular therapy and medical management were performed.

Results: Eight multicenter, prospective RCTs (Interventional Management of Stroke [IMS] III, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS] Expansion, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN], Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness [ESCAPE], Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial [EXTEND-IA], Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment [SWIFT PRIME], and Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours [REVASCAT]) comprising 2,423 patients were included. Meta-analysis of pooled data demonstrated functional independence (mRS 0–2) at 90 days in favor of endovascular therapy (odds ratio [OR] = 1.71; $p = 0.005$). Subgroup analysis of the 6 trials with large vessel occlusion (LVO) criteria also demonstrated functional independence at 90 days in favor of endovascular therapy (OR = 2.23; $p < 0.00001$). Subgroup analysis of the 5 trials that primarily utilized stent retriever devices (≥70%) in the intervention arm demonstrated functional independence at 90 days in favor of endovascular therapy (OR = 2.39; $p < 0.00001$). No difference was found for mortality at 90 days and sICH between endovascular therapy and medical management in all analyses and subgroup analyses.

Conclusions: This meta-analysis provides strong evidence that endovascular intervention combined with medical management, including IV tissue plasminogen activator for eligible patients, improves the outcomes of appropriately selected patients with acute ischemic stroke in the setting of LVO. *Neurology®* 2015;85:1980–1990

GLOSSARY

AIS = acute ischemic stroke; **ASPECTS** = Alberta Stroke Program Early CT Score; **CI** = confidence interval; **ESCAPE** = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; **EXTEND-IA** = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; **IA** = intra-arterial; **ICA** = internal carotid artery; **IMS III** = Interventional Management of Stroke III; **ITT** = intent-to-treat; **LVO** = large vessel occlusion; **MR CLEAN** = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; **MR RESCUE** = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **RCT** = randomized controlled trial; **REVASCAT** = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; **sICH** = symptomatic intracranial hemorrhage; **SWIFT PRIME** = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; **SYNTHESIS** = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; **tPA** = tissue plasminogen activator; **TREVO 2** = Trevo versus Merci Retrievers for Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke.

Acute ischemic stroke (AIS) affects approximately 795,000 patients in the United States annually.[1] The presence of large vessel occlusion (LVO) of a major intracranial artery, most commonly the middle cerebral artery or internal carotid artery (ICA), is estimated to occur in approximately one-third to one-half of AIS.[2] Until recently, the only therapy for AIS with proven efficacy was IV

tissue plasminogen activator (IV-tPA) administered within 4.5 hours of symptom onset.[3,4] However, recanalization rates of AIS with LVO after IV-tPA are low and associated with poor clinical outcomes.[5]

Endovascular therapy is a potentially efficacious adjunct to IV-tPA for patients with acute LVO. However, 3 failed randomized controlled trials (RCTs) of endovascular stroke therapy significantly dampened the initial enthusiasm for endovascular intervention.[6–8] Methodologic weaknesses have been the main criticisms of these trials.[9] More recently, several endovascular stroke trials have addressed the shortcomings of the initial trials, and all have reported superior outcomes with endovascular therapy for AIS.[10–14] The aim of this meta-analysis is to compare the rates of functional independence, mortality, and symptomatic intracranial hemorrhage (sICH) between endovascular and medical management of AIS in modern RCTs. We hypothesize consistent safety and efficacy in the combined data.

METHODS **Inclusion criteria.** The inclusion criteria for this meta-analysis were as follows: (1) the study must be a multicenter, prospective, RCT published from January 1, 2013, to May 1, 2015; (2) the study must directly compare outcomes between endovascular therapy and medical management for patients with AIS.

Literature search. A systematic literature review was performed in PubMed on May 1, 2015, using the search term stroke from 2013 to present. Following the search, the articles were then screened by title and abstract for the aforementioned inclusion criteria. The remaining articles underwent further detailed review for relevance and usable data.

Literature review and data extraction. No registered review protocol was utilized in this study. This review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Available study, demographic, baseline clinical and radiographic, intervention, and outcomes data were extracted from studies included for analysis. Study, demographic, and baseline clinical and radiographic data included trial period, number of centers involved, trial locations, number of patients, and trial enrollment criteria, such as time from symptom onset, age, LVO, Alberta Stroke Program Early CT Score (ASPECTS), and NIH Stroke Scale (NIHSS).[15] LVO refers to the presence of thrombus within proximal intracranial vessels on imaging, which may be due to carotid disease, cardioembolism, or other sources of thromboembolus. Treatment data included the therapeutic modalities utilized in the intervention and control arms, number of intent-to-treat (ITT) patients, number of patients who underwent mechanical thrombectomy, IV/intra-arterial (IA)–tPA, median/mean NIHSS score, median/mean ASPECTS, median/mean age, LVO on imaging, number of patients who

underwent general anesthesia, and median/mean time from symptom onset to IV-tPA or groin puncture. Outcomes data included successful angiographic revascularization, defined as modified Thrombolysis in Cerebral Ischemia grade 2b or 3, modified Rankin Scale (mRS) score at 90 days following intervention, sICH, neurologic deterioration, malignant cerebral edema, and recurrent stroke.

Statistical analysis. Descriptive statistics were determined using SPSS version 20.0.0 (IBM, Armonk, NY; 2011), while statistical analyses of pooled data comparing mRS scores and sICH were performed using Review Manager version 5.2.8 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Odds ratios (ORs) for the included studies were computed using the Mantel-Haenszel test. Under the assumptions of possible clinical diversity and methodologic differences among the included studies, a random-effects model was implemented in the analyses to account for sampling variation and random variation from each individual study. Study heterogeneity was detected using the χ^2 and I^2 test statistics. Significant heterogeneity was considered to be present when both the χ^2 value was within 10% level of significance ($p < 0.10$) and the I^2 value exceeded 50%. Risks of bias were assessed at study level in accordance with the guidelines set forth by the Cochrane Handbook for Systematic Reviews of Interventions.[16] All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant.

RESULTS **Study selection.** The search yielded 8 multicenter, prospective RCTs: Interventional Management of Stroke (IMS) III, Local Versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) Expansion, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA), Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), and Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT), comprising a total of 2,423 patients for inclusion in the meta-analysis.[6–8,10–14] All studies were reviewed for risks of bias, and all demonstrated low risks for selection, detection, attrition, and reporting biases. However, the studies were judged to have high risk for performance bias, since the participants and treatment teams were not blinded. Other biases included early study termination in 5 studies (REVASCAT, SWIFT PRIME, IMS III, EXTEND-IA, and ESCAPE), a limited number of patients who underwent mechanical thrombectomy in one study (SYNTHESIS Expansion), and imaging protocol violations in one study (ESCAPE).[6,8,11–14]

Demographics and study characteristics. Table 1 summarizes the designs of the included studies. Of the 8 multicenter, prospective RCTs included in this review, 3 studies were published in 2013 and 5 in 2015. The total number of participating centers was 195 (range 4–58 centers). Table 2 summarizes the characteristics of the intervention and control arms of the included studies. The numbers of ITT patients in the intervention and control arms were 1,313 and 1,110 patients, respectively. IV-tPA was administered in 988 (75%) and 989 (89%) patients of the intervention and control arms, respectively. Mechanical thrombectomy using retrievable stent (stent retriever) devices was performed in 569 (43%) patients of the intervention arm. IA-tPA was administered in 498 (38%) patients of the intervention arm. LVO was present in 888 (78%) and 799 (86%) patients of the intervention and control arms, respectively. General anesthesia was administered in 143 (30%) patients of the intervention arm.

Outcomes and complications after intervention vs medical management stratified by LVO criteria. Table 3 details the mRS scores at 90 days for intervention and control arms of the included studies. Of the 1,293 patients in the intervention arms with follow-up assessment, 140 (11%), 216 (17%), 201 (16%), 225 (17%), 209 (16%), 84 (6%), and 218 (17%) patients had mRS scores of 0, 1, 2, 3, 4, 5, and 6 at 90 days, respectively. Follow-up assessment at 90 days was available in 1,094 patients of the control arms; 81 (7%), 130 (12%), 140 (13%), 181 (17%), 240 (22%), 121 (11%), and 201 (18%) patients had mRS scores of 0, 1, 2, 3, 4, 5, and 6, respectively (figure e-1 on the *Neurology*® Web site at Neurology.org). Three studies found no difference between the 2 arms, whereas 5 studies found endovascular therapy to yield significantly better outcomes than medical management. Angiographic revascularization was achieved in 565 (56%) of 1,005 patients. Compared to the 2013 studies, all recent studies in 2015 achieved higher successful reperfusion rates with endovascular intervention.

Meta-analysis of pooled data based on the random effects model from the 8 included trials (figure 1A) demonstrated functional independence (mRS score 0–2) at 90 days in favor of endovascular stroke intervention (OR 1.71; 95% confidence interval [CI] 1.18–2.49; $p = 0.005$). There was heterogeneity among the included trials in this analysis ($\chi^2 = 28.47$; $p = 0.0002$; $I^2 = 75\%$). Subgroup analysis of the 6 trials which included only those patients with evidence of LVO on baseline neuroimaging (LVO criteria) also demonstrated functional independence in favor of endovascular therapy (OR 2.23; 95% CI 1.70–2.93; $p < 0.00001$). Subgroup analysis of the 2 trials without LVO criteria demonstrated no difference in functional independence between the 2 arms (OR 0.99; 95% CI 0.76–1.30; $p = 0.94$). There was a difference between the subgroups ($\chi^2 = 17.46$; $p < 0.0001$; $I^2 = 94.3\%$).

No difference in mortality at 90 days was demonstrated in the meta-analysis of pooled data based on the random effects model (figure 1B) from the 8 included studies (OR 0.87; 95% CI 0.67–1.12; $p = 0.27$). Subgroup analysis of the 6 trials with LVO criteria also demonstrated no difference in mortality between the 2 arms (OR 0.79; 95% CI 0.59–1.05; $p = 0.11$). Subgroup analysis of the 2 trials without LVO criteria also demonstrated no difference in mortality (OR 1.08; 95% CI 0.63–1.86; $p = 0.77$). No difference between the subgroups was found ($\chi^2 = 1.04$; $p = 0.31$; $I^2 = 4.0\%$).

Meta-analysis of pooled data based on the random effects model (figure 1C) from the 8 included studies for sICH demonstrated no difference between the 2 arms (OR 1.12; 95% CI 0.77–1.63; $p = 0.56$). Subgroup analyses of the 6 trials with LVO criteria (OR 1.20; 95% CI 0.71–2.03; $p = 0.50$) and 2 trials without LVO criteria (OR 1.04; 95% CI 0.60–1.80; $p = 0.88$) also demonstrated no difference in sICH between the 2 arms. No difference between the subgroups was found ($\chi^2 = 0.13$; $p = 0.72$; $I^2 = 0\%$).

Outcomes and complications after intervention vs medical management stratified by use of stent retriever device. Subgroup analysis (figure 2A) of the 5 trials that primarily utilized ($\geq 70\%$) stent retriever devices in the intervention arm demonstrated functional independence at 90 days in favor of endovascular therapy (OR 2.39; 95% CI 1.88–3.04; $p < 0.00001$). Subgroup analysis of the 3 trials that did not primarily utilize stent retriever devices demonstrated no difference in functional independence between the 2 arms (OR 0.98; 95% CI 0.77–1.26; $p = 0.90$). There was a difference between the subgroups ($\chi^2 = 25.11$; $p < 0.00001$; $I^2 = 96.0\%$).

Subgroup analyses (figure 2B) of the 5 trials that primarily utilized stent retrievers (OR 0.77; 95% CI 0.54–1.11; $p = 0.17$) and the 3 trials that did not primarily utilize stent retrievers (OR 0.99; 95% CI 0.67–1.46; $p = 0.95$) did not find difference in mortality at 90 days between the 2 arms. No difference between the subgroups was found ($\chi^2 = 0.80$; $p = 0.37$; $I^2 = 0\%$).

No difference in rates of sICH between the 2 arms was found in the subgroup analyses (figure 2C) of the 5 trials that primarily utilized stent retriever devices (OR 1.17; 95% CI 0.63–2.18; $p = 0.61$) and the 3 trials that did not primarily utilize stent retrievers

Table 1	Randomized controlled trials included in the meta-analysis											
	Enrollment criteria											
Trial	Publication year	Trial period	Location	No. of centers	No. of patients	Time from symptom onset to endovascular treatment, h	Age, y	NIHSS score	LVO	ASPECTS	Intervention arm	Control arm	Primary endpoint
IMS III	2013	2006–2012	North America, Europe, Australia	58	656	≤5	≥18[a]	≥10, or ≥8 with LVO[b]	NA[b]	NA[c]	IA thrombectomy, IA-tPA, IV-tPA	IV-tPA	mRS ≤2 at 90 d
SYNTHESIS Expansion	2013	2008–2012	Italy	24	362	≤6	18–80	NA	NA	NA	IA thrombectomy, IA-tPA	IV-tPA	mRS ≤1 at 90 d
MR RESCUE	2013	2004–2011	North America	22	118	≤8	18–85	6–29	Occlusion of ICA or MCA (M1 or M2)	NA	IA thrombectomy, IA-tPA, IV-tPA	IV-tPA	mRS at 90 d
MR CLEAN	2015	2010–2014	Netherlands	16	500	≤6	≥18	≥2	Occlusion of distal intracranial ICA, MCA (M1 or M2), or ACA (A1 or A2)	NA	IA thrombectomy, IA-tPA, IV-tPA	IV-tPA	mRS at 90 d
EXTEND-IA	2015	2012–2014	Australia, New Zealand	10	70	≤6	NA	NA	Occlusion of ICA, or MCA (M1 or M2)	NA[d]	IA thrombectomy, IA-tPA, IV-tPA	IV-tPA	Reperfusion + early neurologic improvement[e]
ESCAPE	2015	2013–2014	North America, Asia, Europe	22	315	≤12	≥18	NA	Occlusion of MCA and its immediate branches with/ without intracranial occlusion of ICA and ≥50% MCA pial arterial circulation on CTA[f]	≥6 on CT[g]	IA thrombectomy, IV-tPA	IV-tPA	mRS at 90 d
SWIFT PRIME	2015	2012–2014	United States, Europe	39	196	≤6	18–80	8–29	Occlusion of intracranial ICA, MCA (M1), or carotid terminus	≥6 on CT or MRI	IA thrombectomy, IV-tPA	IV-tPA	mRS at 90 d
REVASCAT	2015	2012–2014	Spain	4	206	≤8	18–85[h]	≥6	Occlusion of intracranial ICA, MCA (M1), or tandem proximal ICA/MCA (M1)	≥7 on CT, or ≥6 on MRI[h]	IA thrombectomy, IV-tPA	IV-tPA	mRS at 90 d

Abbreviations: ACA = anterior cerebral artery; ASPECTS = Alberta Stroke Program Early CT score; CTA = CT angiography; ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IA = intra-arterial; ICA = internal carotid artery; IMS III = Interventional Management of Stroke III; LVO = large vessel occlusion; MCA = middle cerebral artery; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; mRS = modified Rankin Scale; NA = not applicable; NIHSS = NIH Stroke Scale; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; tPA = tissue plasminogen activator.

[a] After 284 patients had undergone randomization, protocol was changed from 18 to 82 to no upper limit for age of exclusion.

[b] After 284 patients had undergone randomization, identification of occlusion with CTA (occlusion of ICA, MCA-M1, or basilar artery) was allowed to determine trial eligibility for patients with NIHSS score of 8 or 9.

[c] ASPECTS <4 used as guideline when evaluating >1/3 region of territory involvement, but not exclusion criteria.

[d] T_{max} >6 seconds delay perfusion volume using CT or MRI, and either CT regional cerebral blood flow or diffusion-weighted imaging infarct core volume mismatch ratio >1.2, and absolute mismatch volume >10 mL, and infarct core lesion volume <70 mL.

[e] Percentage reduction in perfusion lesion volume between initial imaging and imaging at 24 hours, reduction of 8 points or more on NIHSS, or a score of 0 or 1 at 3 days.

[f] A total of 14 of 315 patients had inappropriate vessel occlusion, and 20 of 315 patients had poor collateral circulation.

[g] A total of 11 of 308 patients in whom ASPECT score could be evaluated had a score of <6.

[h] After enrollment of 160 patients, inclusion criterion was changed from 80 years old to up to 85 years old with >8 ASPECTS.

Table 2   Characteristics of intervention and control arms of the included randomized controlled trials

Trials	Intervention arm										Control arm						
	ITT patients, n	Stent retriever device, n (%)	IA-tPA, n (%)	IV-tPA, n (%)	Mean/median NIHSS score	Mean/median ASPECTS	Mean/median age, y	LVO, n (%)	GA, n (%)	Mean/median time from onset to groin puncture, min	ITT patients, n	IV-tPA, n (%)	Mean/median NIHSS score	Mean/median ASPECTS	Mean/median age, y	LVO, n (%)	Mean/median time to tPA, min
IMS III	434	14 (3)	266 (61)	434 (100)	17	NA	69	190 (44)[a]	NR	208	222	222 (100)	16	NA	68	92 (41)[a]	121.2
SYNTHESIS Expansion	181	23 (13)	165 (91)	0 (0)	13	NA	66	NR	NR	225	181	178 (98)	13	NA	67	NR	165
MR RESCUE	64	0 (0)	8 (13)	28 (44)	17.4	NA	64.2	64 (100)	NR	381	54	16 (30)	17.7	NA	67.1	54 (100)	NR
MR CLEAN	233	190 (82)	24 (10)	203 (87)	17	9	65.8	233 (100)	88 (38)	260	267	242 (91)	18	9	65.7	267 (100)	87
EXTEND-IA	35	27 (77)	35 (100)	35 (100)	17	NA	68.6	35 (100)	12 (34)	210	35	35 (100)	13	NA	70.2	35 (100)	127
ESCAPE	165	130 (79)	0 (0)	120 (73)	16	9	71	165 (100)	NR	241[b]	150	118 (79)	17	9	70	150 (100)	125
SWIFT PRIME	98	87 (89)	0 (0)	98 (100)	17	9	65	98 (100)	36 (37)	224	98	98 (100)	17	9	66.3	98 (100)	117
REVASCAT	103	98 (95)	0 (0)	70 (68)	17	7	65.7	103 (100)	7 (7)	269	103	80 (78)	17	8	67.2	103 (100)	105
Total	1,313	569 (43)	498 (38)	988 (75)				888 (78)	143 (30)		1,110	989 (89)				799 (86)	

Abbreviations: ASPECTS = Alberta Stroke Program Early CT score; ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; GA = general anesthesia; IA = intra-arterial; IMS III = Interventional Management of Stroke III; ITT = intention-to-treat; LVO = large vessel occlusion; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; NA = not applicable; NIHSS = NIH Stroke Scale; NR = not reported; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; tPA = tissue plasminogen activator.

[a] After 284 patients had undergone randomization, identification of occlusion with CT angiography was allowed to determine trial eligibility for patients with NIHSS score of 8 or 9.

[b] Symptom onset to first reperfusion.

Table 3 Randomized controlled trial outcomes

Trials	Intervention arm: mRS scores at 90 d								Control arm: mRS scores at 90 d								Primary endpoint result	Successful reperfusion after endovascular intervention, n/n (%)[a]
	0	1	2	3	4	5	6	Total, n	0	1	2	3	4	5	6	Total, n		
IMS III	53	69	55	71	64	20	83	415	19	39	28	35	30	15	48	214	No difference, absolute adjusted difference 1.5 (−6.1 to 9.1)	156/383 (41)
SYNTHESIS Expansion	22	33	21	37	32	10	26	181	28	35	21	28	38	13	18	181	No difference, OR 0.71 (0.44 to 1.14, p = 0.16)	NR
MR RESCUE	2	7	3	10	15	15	12	64	3	4	4	12	12	6	13	54	No difference (p = 0.99)	16/64 (25)
MR CLEAN	6	21	49	43	52	13	49	233	0	16	35	44	81	32	59	267	Endovascular superior, OR 1.67 (1.21 to 2.30)	115/196 (59)
EXTEND-IA	9	9	7	6	1	0	3	35	6	4	4	4	6	4	7	35	Endovascular superior: ischemic territory with reperfusion, effect size 4.7 (2.5 to 9.0, p < 0.001); early neurologic improvement effect size 6.0 (2.0 to 18.0, p = 0.002)	25/29 (86)
ESCAPE	24	34	29	27	22	11	17	164	11	15	17	22	36	18	28	147	Endovascular superior, OR 3.1 (2.0 to 4.7, p < 0.001)	113/156 (72)
SWIFT PRIME	17	25	17	12	15	3	9	98	8	10	15	16	20	12	12	93	Endovascular superior (p < 0.001)	73/83 (88)
REVASCAT	7	18	20	19	8	12	19	103	6	7	16	20	17	21	16	103	Endovascular superior, OR 1.7 (1.05 to 2.8)	67/102 (66)
Total, n (%)	140 (11)	216 (17)	201 (16)	225 (17)	209 (16)	84 (6)	218 (17)	1,293	81 (7)	130 (12)	140 (13)	181 (17)	240 (22)	121 (11)	201 (18)	1,094	—	565/1,005 (56)

Abbreviations: ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IMS III = Interventional Management of Stroke III; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; mRS = modified Rankin Scale; NR = not reported; OR = odds ratio; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.
[a] Modified Thrombolysis in Cerebral Infarction score 2b + 3.

(OR 1.06; 95% CI 0.63–1.78; p = 0.83). No difference between the subgroups was found ($\chi^2 = 0.06$; p = 0.80; $I^2 = 0\%$).

Table e-1 summarizes the major complications in the intervention and control arms of the included studies.

DISCUSSION Despite the therapeutic benefits of IV-tPA for AIS, outcomes for patients with LVO remain poor. Recanalization rates with IV-tPA have been reported to range from 17% to 38% in the literature.[5,17–19] There is a strong correlation between recanalization and good functional outcome. Bhatia et al.[5] found a higher rate of functional independence (relative risk 2.5, 95% CI 1.4–4.3) and reduced mortality in patients with recanalization compared to those without recanalization. Additionally, the same study observed that patients with early recanalization had better outcome than those with late recanalization. In light of the better outcomes associated with successful and earlier recanalization, the search for additional therapies to improve recanalization rates have led to recent trials investigating the efficacy and safety of mechanical thrombectomy for AIS.

Three early trials (IMS III, SYNTHESIS Expansion, and MR RESCUE) published in 2013 attempted to evaluate the efficacy and safety of endovascular therapy compared to medical management for AIS.[6–8] All 3 trials reported a lack of significant difference in outcome between endovascular therapy and medical management, thus casting skepticism on the clinical benefit of endovascular stroke therapy. However, these earlier trials have substantial limitations, most notably the lack of LVO confirmation on initial neuroimaging and the use of early generation endovascular devices leading to low recanalization rates.[20,21] In fact, a significantly higher rate of recanalization in proximal occlusions with endovascular therapy were observed in subgroup analyses of patients who underwent screening for LVO in IMS III, and ICA T- or L-type and tandem ICA and M1 occlusions demonstrated a trend toward better outcome with endovascular treatment.[22,23]
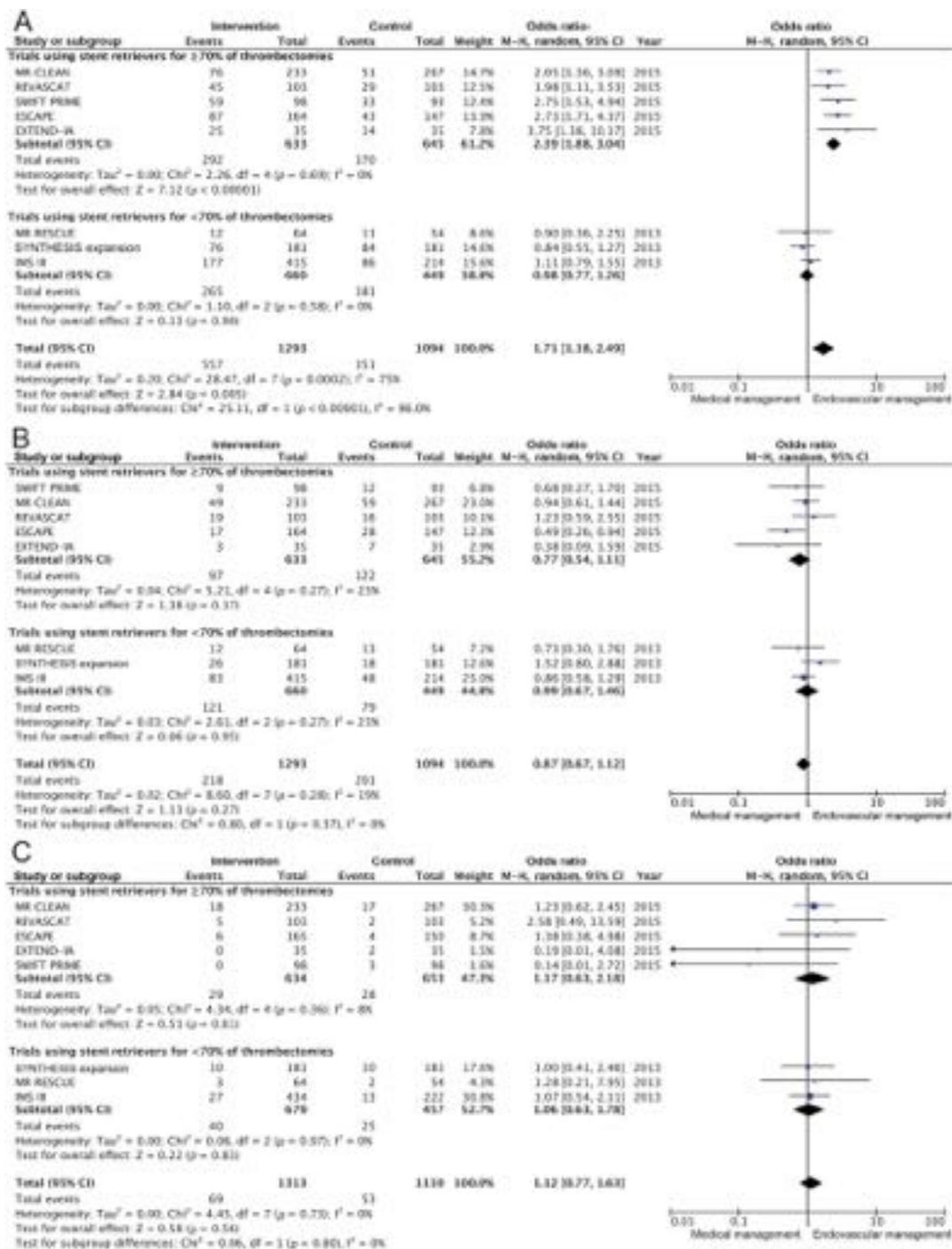
Two prior RCTs, Trevo versus Merci Retrievers for Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke (TREVO 2) and SWIFT, demonstrated significantly higher recanalization rates associated with stent retriever devices compared to the early generation Merci Retriever (Concentric Medical, Fremont, CA).[24,25] TREVO 2 reported a higher rate of reperfusion (Thrombolysis in Cerebral Ischemia scores of 2 or greater) using the TREVO (Stryker Neurovascular, Fremont, CA) stent retriever compared to the Merci Retriever (OR 4.22, p < 0.0001).[24] Similarly, the SWIFT trial reported a higher rate of reperfusion
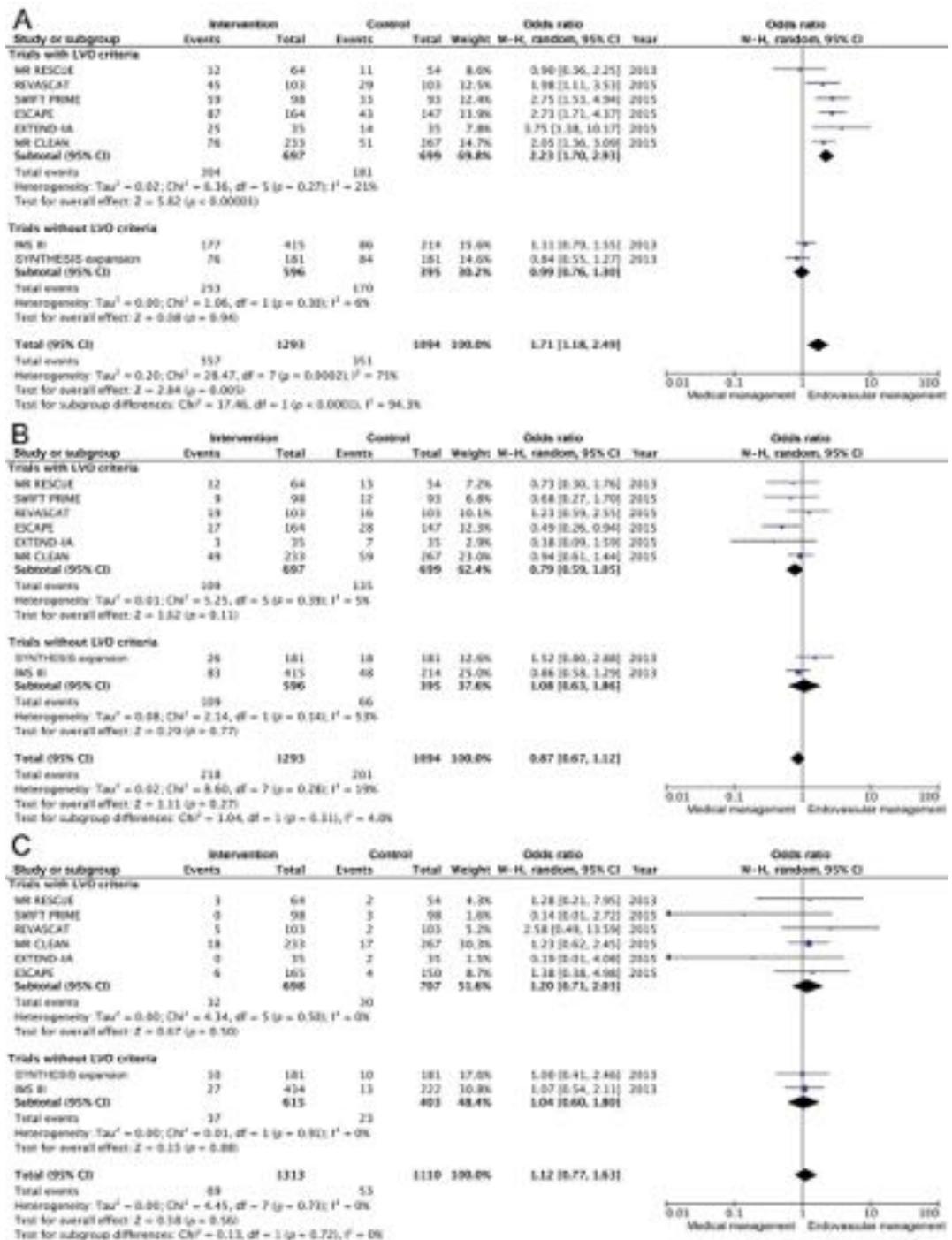
Forest plot of odds ratios (ORs) for (A) functional independence (modified Rankin Scale [mRS] 0–2) at 90 days, (B) mortality (mRS 6) at 90 days, and (C) symptomatic intracranial hemorrhage (sICH) for endovascular versus medical management of acute ischemic stroke (AIS). The included trials are divided into subgroups: trials with large vessel occlusion (LVO) criteria and trials without LVO criteria. The estimated OR and 95% confidence interval (CI) of each included study is represented by the center of the squares and the horizontal line, respectively. The summary OR and 95% CI are shown in bold, and are represented by solid diamond. Tests of heterogeneity and overall effect are given below the summary statistics. ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IMS III = Interventional Management of Stroke III; M-H = Mantel-Haenszel; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.

Forest plot of odds ratios (ORs) for (A) functional independence (modified Rankin Scale [mRS] 0–2) at 90 days, (B) mortality (mRS 6) at 90 days, and (C) symptomatic intracranial hemorrhage (sICH) for endovascular versus medical management of acute ischemic stroke (AIS). The included trials are divided into subgroups: trials that used stent retriever device for ≥70% of endovascular therapies and trials that used stent retriever device for <70% of endovascular therapies. The estimated OR and 95% confidence interval (CI) of each included study is represented by the center of the squares and the horizontal line, respectively. The summary OR and 95% CI are shown in bold, and are represented by solid diamond. Tests of heterogeneity and overall effect are given below the summary statistics. ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial; IMS III = Interventional Management of Stroke III; M-H = Mantel-Haenszel; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT PRIME = Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.

(thrombolysis in myocardial ischemia score 2 or 3; OR 4.87, $p = 0.0001$), higher rate of good 3-month neurologic outcome (OR 2.78, $p = 0.02$), and lower rate of 90-day mortality (OR 0.34, $p = 0.02$) for patients treated with the Solitaire Flow Restoration (ev3 Neurovascular, Irvine, CA) stent retriever device compared to those treated with the Merci Retriever.[25]

The more recent trials (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, and REVASCAT) have addressed the major criticisms of the earlier studies by selecting for patients with LVO based on admission neuroimaging and using stent retrievers in the majority of patients undergoing endovascular intervention.[10–14] All of these trials individually demonstrated superiority of endovascular therapy over medical management for AIS with LVO. A meta-analysis of the trials with LVO enrollment criteria found higher rates of functional independence (OR 2.23; 95% CI 1.70–2.93; $p < 0.00001$) for endovascular therapy compared to medical management, with no statistical difference in mortality or sICH. Stratification by the primary ($\geq 70\%$) use of stent retrievers also found higher rates of functional independence with endovascular therapy (OR 2.39; 95% CI 1.88–3.04; $p < 0.00001$). Other contributors to the success of the recent trials included the use of more sophisticated radiographic criteria, such as AS-PECTS and volume mismatch ratios on perfusion imaging, to exclude patients with large core infarcts who are unlikely to attain clinical benefit from revascularization.[11–14] Despite the heterogeneity of the included RCTs, this meta-analysis provides strong evidence for the management of acute LVO with endovascular intervention combined with best medical therapy, including IV-tPA in eligible patients. Furthermore, our subgroup analyses suggest that employing baseline neuroimaging to identify patients with AIS with LVO and performing endovascular intervention with stent retriever devices may yield a greater benefit from endovascular stroke therapy. Given the improved functional outcomes with endovascular therapy in the recent trials, one would assume concurrent improvements in mortality. However, with the exception of ESCAPE, other trials demonstrated no difference in mortality rates.[12]

The recent trials are not without limitations. Early trial terminations occurred in ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT. EXTEND-IA and SWIFT PRIME were limited to only patients who were eligible for and treated with IV-tPA within 4.5 hours of symptom onset, and imaging protocol violations were observed in ESCAPE. Although outcome assessments were blinded, participants and treatment teams were not blinded, and thus susceptible to performance bias. Furthermore, endovascular therapy is not generalizable to all patients with AIS; patients selected for these trials comprise only a small proportion of patients presenting with AIS. In EXTEND-IA, only 70 of the 7,798 patients who were screened were ultimately enrolled in the trial (0.9%), and in SWIFT PRIME, only 196 of 1,470 patients who were screened were randomized (13%).[11,14]

Our meta-analysis is limited by the pooled data available from the RCTs, with all of the limitations and weakness inherent to these studies. The variability in the methods of clinical and radiographic evaluation and in the enrollment criteria among trials remains difficult to overcome. Additionally, not all patients in each study arm underwent the same treatments. Specifically, not all patients in the intervention arms underwent mechanical thrombectomy, thrombectomy using the same device, or IA- or IV-tPA, and not all patients in the control arms were treated with IV-tPA. It should also be noted that no direct comparison of different stent retrievers or imaging selection criteria were performed in these studies. Thus, generalization of our findings to stent retrievers not used in these trials may be limited. The endovascular trials primarily addressed AIS with LVO of the anterior circulation; therefore, the results may not be generalizable to LVO of the posterior circulation (i.e., vertebrobasilar system).

Future subgroup analyses at the individual patient level from trial investigators will help to guide endovascular intervention in AIS for elderly patients (age over 80 years) and those with severe strokes (NIHSS over 20). Current literature suggests better outcome associated with endovascular stroke therapy performed under local anesthesia, rather than general anesthesia. However, further trials are needed to clarify this benefit.[26,27] Efficient workflow, with coordination among emergency medical services, emergency departments, radiology, stroke neurology, and neurointerventionalists, needs to be optimized in order to quickly identify acute LVO, rule out large core infarcts, and appropriately transport select AIS patients to an angiography suite for endovascular thrombectomy at the earliest possible time. Policies and protocols regarding stroke systems of care will need to incorporate mechanisms for rapid triage of select AIS patients to facilities capable of providing endovascular therapy.

Meta-analyses of modern multicenter, prospective RCTs comparing endovascular therapy to medical management for AIS demonstrated significantly higher rates of functional independence at 90 days in favor of endovascular therapy, with no difference in the rates of mortality or sICH. Patients with LVO on initial neuroimaging who underwent endovascular mechanical thrombectomy using stent retriever devices also

demonstrated higher rates of functional independence at 90 days compared to medical management. This meta-analysis provides strong evidence that endovascular intervention combined with medical management, including administration of IV-tPA to eligible patients, is the standard of care for appropriately selected patients with acute ischemic stroke and LVO.

AUTHOR CONTRIBUTIONS

STUDY FUNDING

DISCLOSURE

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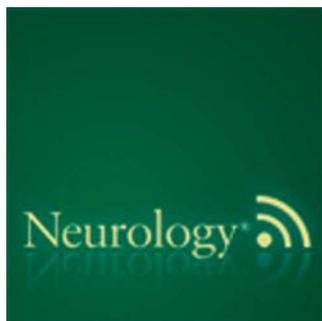
Endovascular vs medical management of acute ischemic stroke (see p. 1980)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the December 1, 2015, issue of *Neurology*. In the second segment, Dr. Kevin Barrett talks with Dr. Brad Worrall about his paper on endovascular versus medical management of acute ischemic stroke. Dr. Ted Burns interviews Dr. Daniel Kaufer about the AAN Behavioral Neurology Section Workgroup paper on improving clinical cognitive testing for our "What's Trending" feature of the week. In the next part of the podcast, Dr. Ted Burns focuses his interview with Dr. Steve Ringel on a Neurology Today® story about defective nuclear transport and endogenous retrovirus in ALS.

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