

# Mechanical Thrombectomy for Acute Ischemic Stroke



## A Meta-Analysis of Randomized Trials

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### ABSTRACT

**BACKGROUND** Acute ischemic stroke is a leading cause of serious disability and death worldwide. Individual randomized trials have shown possible benefits of mechanical thrombectomy after usual care compared with usual care alone (i.e., intravenous thrombolysis) in the management of acute ischemic stroke patients.

**OBJECTIVES** This study systematically determined if mechanical thrombectomy after usual care would be associated with better outcomes in patients with acute ischemic stroke caused by large artery occlusion.

**METHODS** The authors included randomized trials that compared mechanical thrombectomy after usual care versus usual care alone for acute ischemic stroke. Random effects summary risk ratios (RR) were constructed using a DerSimonian and Laird model.

**RESULTS** Nine trials with 2,410 patients were available for analysis. Compared with usual care alone, mechanical thrombectomy was associated with a higher incidence of achieving good functional outcome, defined as a modified Rankin scale (mRS) of 0 to 2 (RR: 1.45; 95% confidence interval [CI]: 1.22 to 1.72;  $p < 0.0001$ ) and excellent functional outcome defined as mRS 0 to 1 (RR: 1.67; 95% CI: 1.27 to 2.19;  $p < 0.0001$ ) at 90 days. There was a trend toward reduced all-cause mortality with mechanical thrombectomy (RR: 0.86; 95% CI: 0.72 to 1.02;  $p = 0.09$ ). The risk of symptomatic intracranial hemorrhage was similar with either treatment modality (RR 1.06; 95% CI: 0.73 to 1.55;  $p = 0.76$ ).

**CONCLUSIONS** In acute ischemic stroke due to large artery occlusion, mechanical thrombectomy after usual care was associated with improved functional outcomes compared with usual care alone, and was found to be relatively safe, with no excess in intracranial hemorrhage. There was a trend for reduction in all-cause mortality with mechanical thrombectomy. (J Am Coll Cardiol 2015;66:2498-505) © 2015 by the American College of Cardiology Foundation.

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Despite advances in medical therapy, acute ischemic stroke remains a leading cause of serious disability and death worldwide (1,2). Intravenous tissue plasminogen activator (tPA) remains the only effective reperfusion therapy if administered in a timely manner (<4.5 h) (3-6). Unfortunately, only 21% of patients achieve effective recanalization with intravenous tPA even when administered within this ischemic window (7). Intra-arterial therapy was developed as a means to improve vessel recanalization. Intra-arterial thrombolysis for large-vessel occlusion was first described in the 1980s (8), and formally evaluated in the PROACT II (Prolyse in Acute Cerebral Thromboembolism) trial, which showed better outcomes with intra-arterial urokinase versus intravenous heparin alone (9).

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In contrast, subsequent trials that used first-generation thrombectomy devices failed to demonstrate clinical benefit compared with intravenous thrombolysis (10,11). An important cause of failure for those early mechanical thrombectomy devices was thought to be the lower rate of recanalization achieved with these devices (12). However, newer-generation retrievable stents achieve higher recanalization rates compared with first-generation thrombectomy devices (13,14). Because this field has undergone rapid development, the clinical utility of these devices for reducing mortality and morbidity in acute ischemic stroke remains uncertain. Accordingly, we performed a comprehensive meta-analysis to evaluate the efficacy and safety of mechanical thrombectomy after usual care versus usual care alone.

## METHODS

A computerized search of the Medline database, without language restriction, was performed from inception until May 2015 using the strategy illustrated in Online Figure 1. In addition, the Web of Science and Cochrane Register of Controlled Trials were searched using the key words “stroke,” “thrombectomy,” and “arterial thrombolysis.” Abstracts of the major scientific sessions from January 2013 to April 2015 (International Stroke Organization, European Stroke Organization Conference, and the American Heart Association) were also searched with the same key words. Furthermore, the reference lists of the retrieved articles and previous meta-analyses were reviewed (15-18). The planned analysis was registered at the International Prospective Register for Systematic Reviews or PROSPERO (CRD42015019201).

## SELECTION CRITERIA AND DATA EXTRACTION.

Trials that randomized acute ischemic stroke patients within 4.5 h of symptom onset and who received usual care were randomized to undergo mechanical thrombectomy versus no mechanical thrombectomy were included. For usual care, most patients received intravenous thrombolysis, unless there were contraindications or an extended time window. Trials that prohibited intravenous thrombolysis before mechanical thrombectomy were excluded.

Data on study design, sample characteristics, sample size, intervention strategies, outcomes, and other study characteristics from the selected studies were extracted by 2 independent investigators (I.Y.E. and A.M.). Discrepancies were resolved by consensus of the investigators. For all clinical outcomes, the number of events that occurred in each arm of each trial was tabulated.

**OUTCOMES AND DEFINITIONS.** The modified Rankin scale (mRS) is a widely accepted and objective tool to measure post-stroke functional outcome and has been used in most of the major acute ischemic stroke trials, with scores ranging from 0 (fully independent without deficit) to 6 (death). We defined excellent functional outcome as mRS 0 to 1, good functional outcome as mRS 0 to 2, and fair functional outcome as mRS 0 to 3 (19). Our primary outcome of interest was good functional outcome at 90 days. The secondary efficacy outcomes assessed were all-cause mortality, excellent functional outcome, fair functional outcome, and recanalization as defined by the individual studies. The safety outcomes evaluated were symptomatic intracranial hemorrhage (sICH) (range: 27 h to 7 days) and recurrent stroke.

**STATISTICAL ANALYSIS.** Outcomes were analyzed by intention-to-treat analysis. Random effects summary risk ratios (RRs) were constructed using a DerSimonian and Laird model (20). Fixed-effects summary odds ratios (ORs) were performed using Peto’s model (21). Statistical heterogeneity was examined using the  $I^2$  statistic, with  $I^2$  statistic values <25%, 25% to 50%, and >50% considered as low, moderate, and high degree of heterogeneity, respectively (22). The method of Egger (23) was used to calculate the risk of publication bias. This meta-analysis was conducted in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24). The quality of the trials was evaluated on the basis of the adequate description of treatment allocation, blinded outcome assessment, and description of losses to follow-up (25). All p values were 2-tailed, with statistical

## ABBREVIATIONS AND ACRONYMS

CI = confidence interval  
mRS = modified Rankin scale  
OR = odds ratio  
RR = risk ratio  
sICH = symptomatic intracranial hemorrhage  
tPA = tissue plasminogen activator

**TABLE 1** Baseline Characteristics and Treatment Strategies

Study (Ref. #)	Year	n*	Age* (yrs)	Male* (%)	NIHSS*	Time to Mechanical Thrombectomy	IV Thrombolysis* (%)	Time to IV Thrombolysis*	Major Artery Occlusion Documented Before Inclusion?
MR RESCUE: penumbral (26)	2013†	34/34	66 ± 13/66 ± 17	50/44	NR†	NR†	47/26	NR†	Yes
MR RESCUE: non-penumbral (26)		30/20	62 ± 12/69 ± 16	43/60			40/35		
IMS III (10)	2013	434/222	69/68	50/55	17/16	208‡§	100/100	122/121	No
MR CLEAN (27)	2015	233/267	66/66	58/59	17/18	260§	87/91	85/87	Yes
ESCAPE (28)	2015	165/150	71/70	48/47	16/17	241	73/79	110/125	Yes
EXTEND-IA (29)	2015	35/35	69 ± 12/70 ± 12	49/49	17/13	248	100/100	127/145	Yes
SWIFT PRIME (30)	2015	98/98	65 ± 13/66 ± 11	55/47	17/17	252	100/100	161/168	Yes
REVASCAT (31)	2015	103/103	66 ± 11/67 ± 10	53/52	17/17	355	68/78	118/105	Yes
THERAPY (32)	2015	41/41	NR	NR	NR	226	NR	NR	Yes
THRACE (33)	2015	190/195	62	NR	17	225	NR	NR	Yes

Values are mean ± SD unless otherwise indicated. \*Values are presented for mechanical thrombectomy/usual care alone groups. †Data for both subgroups in this study were combined together. ‡Mean was reported. §Time to groin puncture was reported. ||Data were reported as combined for both arms.

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-Intra-arterial; IMS III = Third Interventional Management of Stroke; IV = intravenous; 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; NIHSS = National Institutes of Health Stroke Scale; NR = not reported; REVASCAT = Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT PRIME = Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; THERAPY = Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke; THRACE = Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke.

significance set at  $p < 0.05$ , and confidence intervals (CIs) were calculated at the 95% level for the overall estimates effect. All analyses were performed using STATA software version 11 (StataCorp, College Station, Texas).

A pre-specified analysis was conducted excluding unpublished trials, and another was performed excluding trials that tested other modalities of endovascular therapy aside from mechanical thrombectomy

(i.e., intra-arterial thrombolysis). Random effects meta-regression analyses were pre-specified for the primary outcome with time to mechanical thrombectomy and publication year.

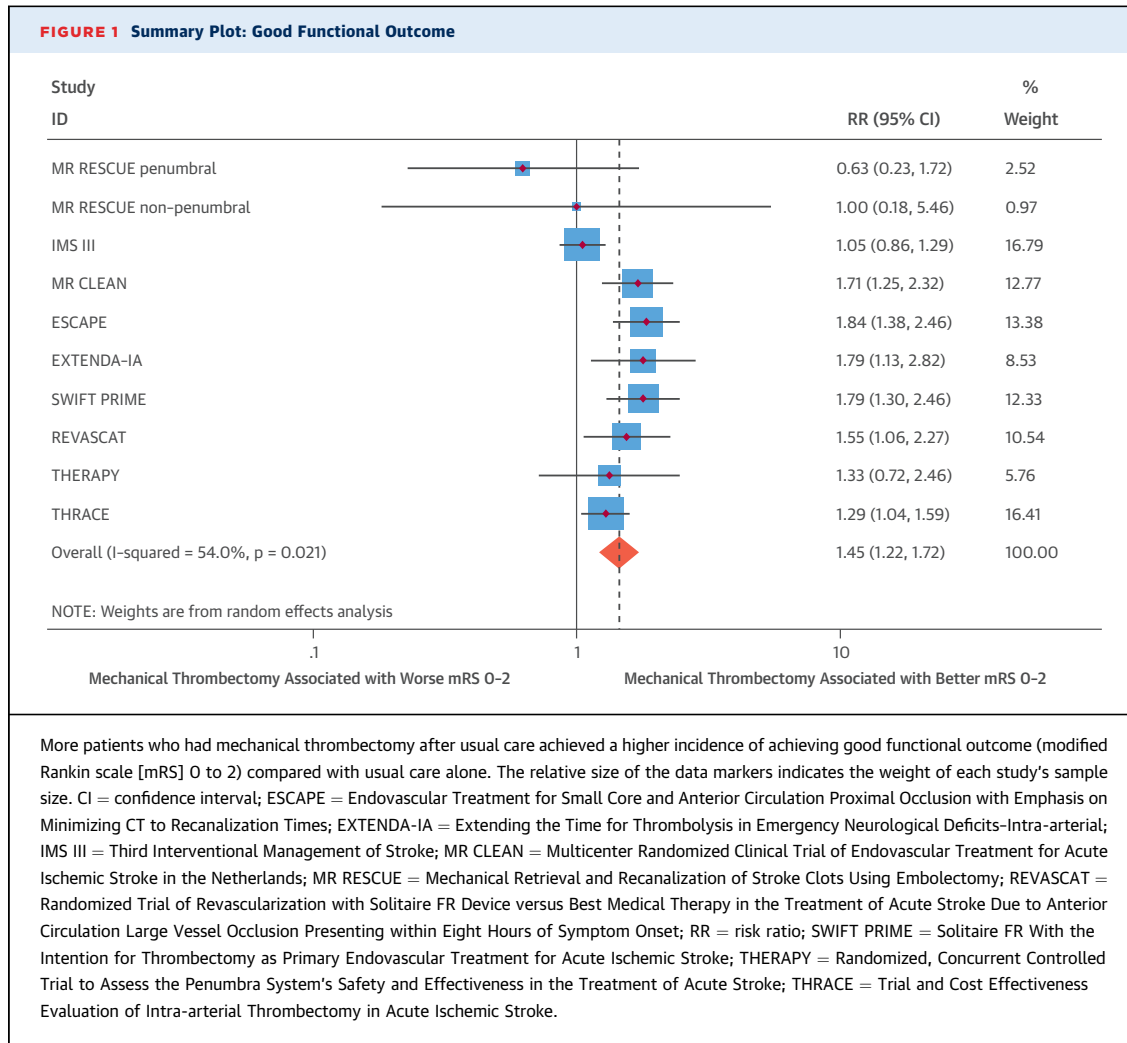
**RESULTS**

Overall, 9 trials met our inclusion criteria, with a total of 2,410 patients (10,26-33). Seven studies were retrieved from Medline (10,26-31), and 2 studies were presented at the European Stroke Organization Conference (32,33). Retrievable stents were mandated in 3 studies (29-31), encouraged in 2 studies (27,28), and allowed in 2 other studies (10,26). The THERAPY trial (Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) tested an aspiration thrombectomy device (32). In 3 trials—MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy), IMS III (Third Interventional Management of Stroke) trial, and MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)—intra-arterial thrombolysis could be given alone or in combination with mechanical thrombectomy (10,26,27). Intravenous tPA was the sole thrombolytic agent used in all the studies, except for MR CLEAN, which also allowed intravenous urokinase (27). The occluded arteries were mainly the internal carotid artery, and the M1 and M2 segments of the middle cerebral artery. The follow-up duration in all the included

**TABLE 2** Measures of Study Quality

Study (Ref. #)	Single/Multicenter	Blinded Endpoint	Generation of Treatment Assignment	Follow-Up Completion (%)	Primary Outcome
MR RESCUE (26)	Multicenter	Yes	Centralized website	100/100	mRS
IMS III (10)	Multicenter	Yes	Sealed envelope	100/100	mRS 0-2
MR CLEAN (27)	Multicenter	Yes	Centralized website	100/100	mRS
ESCAPE (28)	Multicenter	Yes	Centralized website	99/98	mRS
EXTEND-IA (29)	Multicenter	Yes	Centralized website	100/100	mRS 0-1
SWIFT PRIME (30)	Multicenter	Yes	Interactive web response or interactive voice response system	100/95	mRS 0-2
REVASCAT (31)	Multicenter	Yes	Real-time computerized randomization procedure	100/100	mRS
THERAPY (32)	Multicenter	NR	NR	NR	mRS 0-2
THRACE (33)	Multicenter	NR	NR	NR	mRS 0-2

Values are presented for mechanical thrombectomy/intravenous thrombolysis groups. ESCAPE = Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; mRS = modified Rankin scale; other abbreviations as in Table 1.

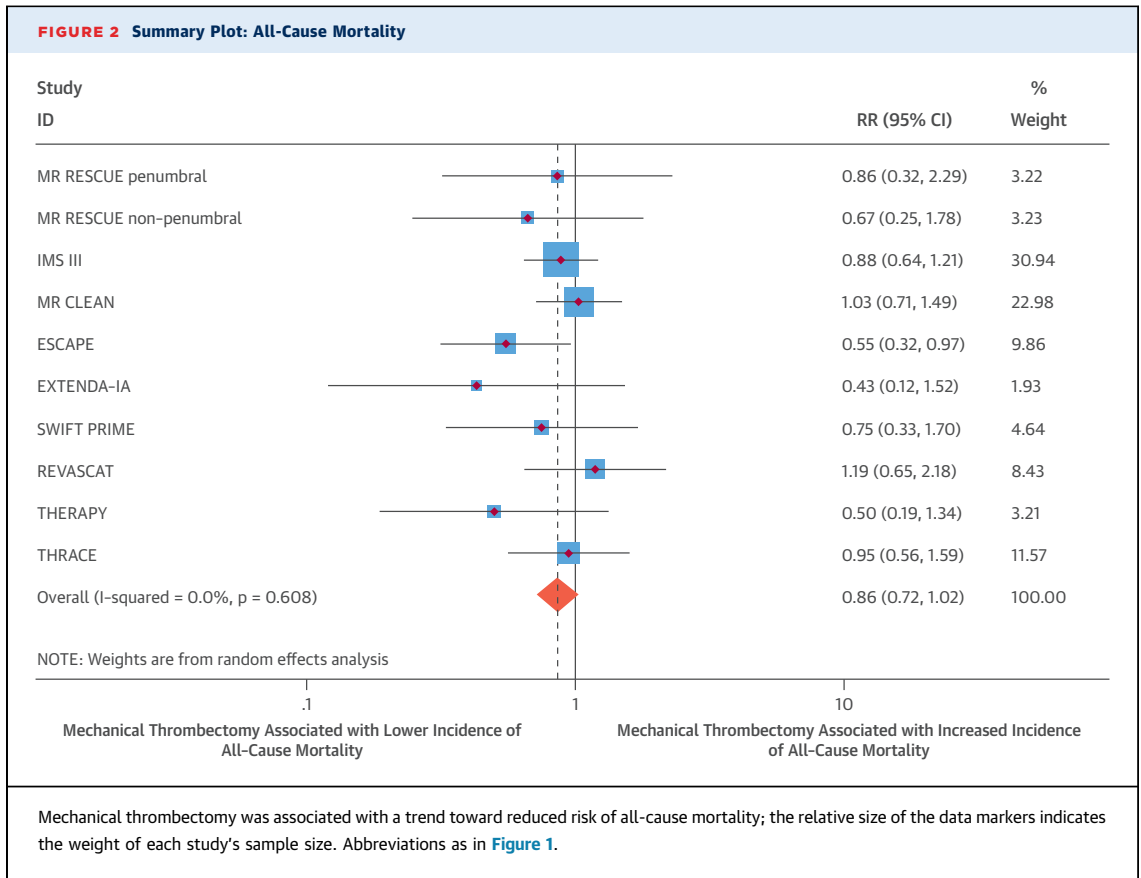


studies was 90 days. Baseline characteristics and treatment strategies of these studies are listed in **Table 1**, whereas **Table 2** lists the measures of study quality. Two studies have not yet been published; therefore information regarding treatment allocation and blinded endpoint assessment was lacking (32,33); the remaining studies were classified as having a low risk for bias.

**PRIMARY OUTCOME.** Mechanical thrombectomy after usual care was associated with a higher incidence of achieving good functional outcome (mRS 0 to 2) at 90 days compared with usual care alone (43.7% vs. 30.9%; RR: 1.45; 95% CI: 1.22 to 1.72;  $p < 0.0001$ ) with no evidence of publication bias using the test by Egger et al. (23) ( $p = 0.74$ ) (Figure 1). Findings from the pre-specified analyses yielded similar results: 1) excluding unpublished trials (RR: 1.49; 95% CI: 1.20 to 1.87,  $p < 0.0001$ ); and 2) excluding trials that

allowed intra-arterial thrombolysis (MR RESCUE, IMS III, and MR CLEAN: RR: 1.55; 95% CI: 1.35 to 1.79;  $p < 0.0001$ ). Meta-regression analysis revealed better outcomes with recent publication year ( $p = 0.02$ ), but did not identify a difference in treatment effect on the basis of time to mechanical thrombectomy ( $p = 0.28$ ).

**SECONDARY OUTCOMES.** At 90 days, mechanical thrombectomy after usual care was associated with a trend toward reduction in the risk of all-cause mortality compared with usual care alone (15.9% vs. 17.9%; RR: 0.86; 95% CI: 0.72 to 1.02;  $p = 0.09$ ) (Figure 2). A similar trend was observed after excluding the trials that allowed intra-arterial thrombolysis (MR RESCUE, IMS III, and MR CLEAN) (RR: 0.77; 95% CI: 0.57 to 1.03;  $p = 0.08$ ). Mechanical thrombectomy after usual care was associated with a higher incidence of achieving both



excellent (mRS 0 to 1) functional outcomes (26.3% vs. 15.5%; RR: 1.67; 95% CI: 1.27 to 2.19;  $p < 0.0001$ ), and fair (mRS 0 to 3) functional outcomes (59.0% vs. 45.1%; RR: 1.32; 95% CI: 1.12 to 1.56;

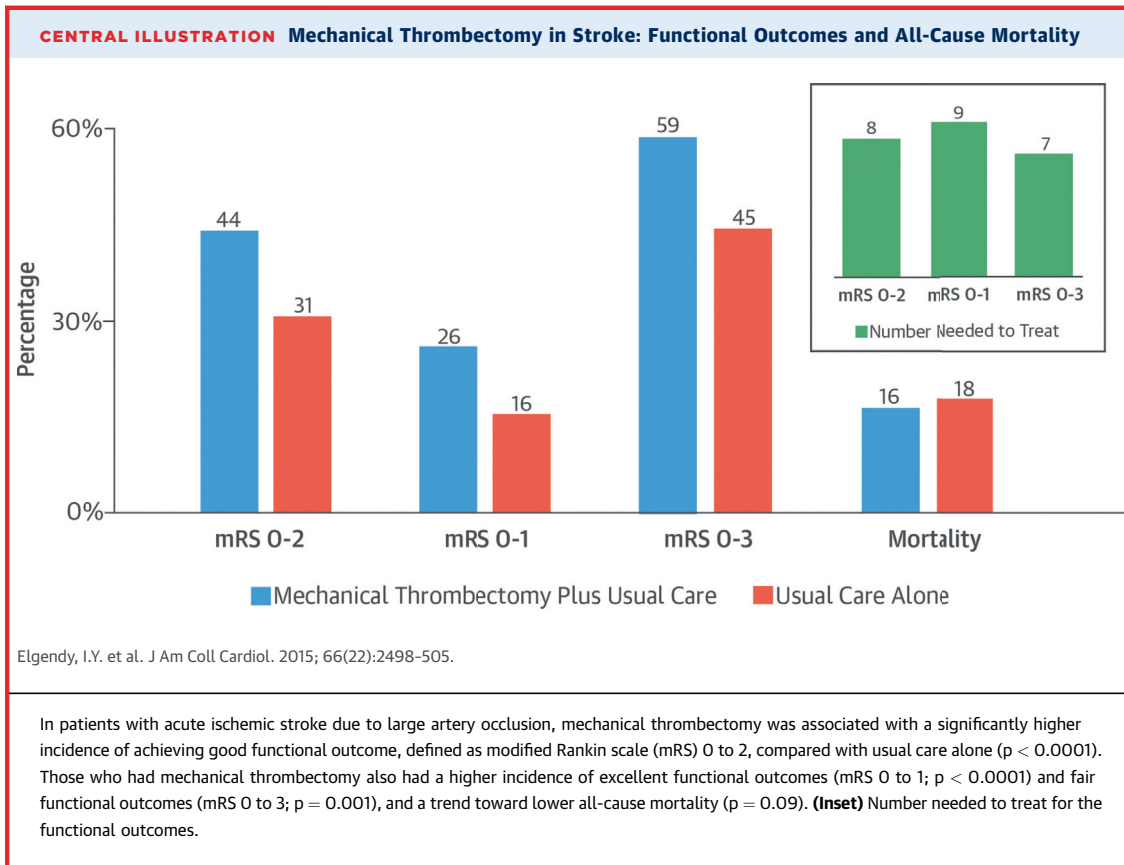
$p = 0.001$ ) compared with intravenous thrombolysis alone (Online Figures 2 and 3). Recanalization rates were reported by 6 trials (Online Table 1) (10,27-31). Mechanical thrombectomy after usual care was associated with improved recanalization compared with usual care alone (66.6% vs. 39.2%; RR: 1.57; 95% CI: 1.11 to 2.23;  $p = 0.01$ ).

**TABLE 3 Summary Estimates for the Outcomes of Interest**

Outcome	Incidence (%)*	Model	RR†	95% CI	p Value	I <sup>2</sup> (%)
mRS 0-2	43.7/30.9	DL	1.45	1.22-1.72	<0.0001	54
		Peto	1.74	1.48-2.06	<0.0001	58
mRS 0-1	26.3/15.5	DL	1.67	1.27-2.19	<0.0001	47
		Peto	1.78	1.44-2.21	<0.0001	48
mRS 0-3	59.0/45.1	DL	1.32	1.12-1.56	0.001	67
		Peto	1.73	1.45-2.07	<0.0001	73
All-cause mortality	15.9/17.9	DL	0.86	0.72-1.02	0.09	0
		Peto	0.82	0.67-1.02	0.08	0
Recanalization	66.6/39.2	DL	1.57	1.11-2.23	0.01	88
		Peto	3.09	2.46-3.89	<0.0001	83
sICH	5.1/5.0	DL	1.06	0.73-1.55	0.76	0
		Peto	1.02	0.69-1.52	0.92	0
Recurrent stroke	5.0/2.8	DL	1.97	0.64-6.03	0.24	68
		Peto	1.62	0.98-2.67	0.06	73

\*Values are presented for mechanical thrombectomy/intravenous thrombolysis groups. †Odds ratio was reported for Peto's method.  
CI = confidence interval; DL = DerSimonian and Laird; mRS = modified Rankin scale; RR = risk ratio; sICH = symptomatic intracranial hemorrhage; other abbreviations as in Tables 1 and 2.

**SAFETY OUTCOMES.** The risk of in-hospital sICH was similar between both arms (5.1% vs. 5.0%; RR: 1.06; 95% CI: 0.73 to 1.55;  $p = 0.76$ ) (Online Figure 4). The risk of recurrent stroke at 90 days was nonsignificantly higher with mechanical thrombectomy (5.0% vs. 2.8%; RR: 1.97; 95% CI: 0.64 to 6.03;  $p = 0.24$ ) (Online Figure 5). This was driven predominantly by a higher embolic stroke rate in the MR CLEAN trial (5.6% vs. 0.4%) (27). In a sensitivity analysis, excluding MR CLEAN, the risk of recurrent stroke was similar with both modalities (4.8% vs. 4.2%; RR: 1.10; 95% CI: 0.59 to 2.06;  $p = 0.77$ ). No evidence of publication bias was observed for any of the secondary or safety outcomes. Table 3 provides the summary estimates for the outcomes of interest using the methods by DerSimonian and Laird and Peto.



## DISCUSSION

In this meta-analysis of 9 randomized trials with 2,410 patients with acute ischemic stroke caused by large artery occlusion who presented within 4.5 h of symptom onset, mechanical thrombectomy after usual care was associated with improved recanalization rates, better functional outcomes, and a similar risk of sICH compared with usual care alone (i.e., intravenous thrombolysis). In particular, mechanical thrombectomy after usual care was associated with a 45% higher relative likelihood and a 13% higher absolute likelihood of achieving a good functional outcome at 90 days (mRS 0 to 2) compared with usual care alone administered within the recommended ischemic window (number needed to treat = 8) (Central Illustration). The meta-regression analysis demonstrated that outcomes were improved in the more recent studies (i.e., those that used stent retrievers). In addition, there was a trend for reduced all-cause mortality with mechanical thrombectomy.

All studies included in this analysis showed a trend for better outcomes with mechanical thrombectomy,

except for MR RESCUE (26). In this study, the investigators had incorporated advanced imaging before mechanical thrombectomy, resulting in a delay in the time to recanalization (34). In the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-arterial), SWIFT PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke), REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset), and THERAPY trials, functional perfusion imaging was encouraged before randomization, yet investigators emphasized workflow efficiency to speed up study enrollment (29-32). Moreover, a strategy of advanced imaging has not been shown to affect patient outcomes or reduce the risk of intracerebral hemorrhage (35). Physical examination, along with non-contrast computed imaging, might be sufficient to select appropriate patients for mechanical thrombectomy (36). The American Heart Association/American Stroke Association recently gave a new 1A



recommendation for endovascular treatment (in particular stent retrievers) as an adjunctive therapy to intravenous thrombolysis for patients with acute ischemic stroke secondary to a clot in a major artery and with evidence of salvageable brain tissue on noninvasive imaging when presenting within 6 h of symptom onset (37).

Intravenous thrombolysis remains the cornerstone for acute ischemic stroke management; however, <30% of eligible patients receive intravenous thrombolysis within the recommended time window (6,38). Although mechanical thrombectomy is beneficial, this procedure requires specialized centers of excellence; therefore, the widespread application of this therapy for acute ischemic stroke patients will likely remain limited for the foreseeable future. A recent report from the national Get With The Guidelines-Stroke registry demonstrated that 41.8% of participating hospitals were capable of providing endovascular therapy to acute ischemic stroke patients (39). Future studies may need to explore the benefit of contemporary mechanical thrombectomy alone among patients who are not pre-treated with intravenous thrombolysis.

In the present analysis, we showed that mechanical thrombectomy after usual care was associated with a similar risk of sICH and recurrent stroke (in all arterial territories). In the MR CLEAN trial, the risk of recurrent stroke was significantly increased with mechanical thrombectomy, in contrast to other studies. In MR CLEAN, the investigators defined recurrent stroke as new ischemic stroke in a different vascular territory. In addition, a proportion of patients in the mechanical thrombectomy arm underwent a simultaneous acute cervical carotid stenting (i.e., second revascularization procedure) (27). Overall, our meta-analysis demonstrated that mechanical thrombectomy for acute ischemic stroke patients is relatively safe.

A recent meta-analysis demonstrated that endovascular therapy was associated with improved functional outcome with similar risk of mortality and sICH compared with intravenous thrombolysis (40).

In the present analysis, we evaluated only the studies that allowed intravenous thrombolysis before mechanical thrombectomy (i.e., we excluded SYNTHESIS Expansion [Local Versus Systemic Thrombolysis for Acute Ischemic Stroke] [12]). We also assessed the benefits of mechanical thrombectomy on a wide spectrum of outcomes with the totality of the available data, including the recently presented studies THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke) and THERAPY (32,33).

**STUDY LIMITATIONS.** The main outcome measure selected for this analysis was mRS 0 to 2, which has been used in all stroke trials. However, interobserver variability in describing the mRS is a potential limitation to the present study (41). Also, there was a significant degree of heterogeneity observed for several outcomes in this analysis, which can be explained by the variation in the study designs. We attempted to mitigate this by using random effects models when possible. Another limitation is the fact that some of the studies are yet unpublished; thus, a sensitivity analysis for the main outcome excluded these trials. In addition, we were not able to examine the impact of symptom duration on mechanical thrombectomy; however, 1 study delayed time to reperfusion due to advanced imaging and tended to have worse outcomes. Finally, lack of access to patient-level data precluded a full evaluation to identify patient characteristics and the National Institutes of Health Stroke Scale associated with the maximal clinical benefits.

## CONCLUSIONS

In acute ischemic stroke patients with large artery occlusion, mechanical thrombectomy after usual care was associated with improved functional outcomes compared with usual care alone (i.e., intravenous thrombolysis) and is relatively safe, with no excess in intracranial hemorrhage. There was a trend for reduction in all-cause mortality with mechanical thrombectomy.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND

**PROCEDURAL SKILLS:** In patients with acute ischemic stroke due to large artery occlusion who present in the appropriate timeframe, mechanical thrombectomy after intravenous thrombolytic therapy is associated with better functional outcomes than thrombolysis alone.

**TRANSLATIONAL OUTLOOK:** Further investigation is needed to identify specific characteristics of patients with acute ischemic stroke who benefit most from mechanical thrombectomy.

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**KEY WORDS** intracranial hemorrhage, outcomes, recanalization, thrombolysis

**APPENDIX** For supplemental figures and table, please see the online version of this article.