Title

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Journal

Neurology, 101(9)

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Publication Date

2023-08-29

DOI

10.1212/WNL.0000000000207536

Peer reviewed

RESEARCH ARTICLE

Mechanical Thrombectomy for Large Ischemic Stroke

A Systematic Review and Meta-analysis

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Neurology® 2023;101:e922-e932. doi:10.1212/WNL.0000000000207536

Abstract

Background and Objectives

There is growing evidence for endovascular thrombectomy (EVT) in patients with large ischemic core infarct and large vessel occlusion (LVO). The objective of this study was to compare the efficacy and safety of EVT vs medical management (MM) using a systematic review and meta-analysis of observational studies and randomized controlled trials (RCTs).

Methods

We searched the PubMed, Embase, Cochrane Library, and Web of Science databases to obtain articles related to mechanical thrombectomy for large ischemic core from inception until February 10, 2023. The primary outcome was independent ambulation (modified Rankin Scale [mRS] 0–3). Effect sizes were computed as risk ratio (RR) with random-effect or fixed-effect models. The quality of articles was evaluated through the Cochrane risk assessment tool and the Newcastle-Ottawa Scale. This study was registered in PROSPERO (CRD42023396232).

Results

A total of 5,395 articles were obtained through the search and articles that did not meet the inclusion criteria were excluded by review of the title, abstract, and full text. Finally, 3 RCTs and 10 cohort studies met the inclusion criteria. The RCT analysis showed that EVT improved the 90-day functional outcomes of patients with large ischemic core with high-quality evidence, including independent ambulation (mRS 0–3: RR 1.78, 95% CI 1.28–2.48, $p < 0.001$) and functional independence (mRS 0–2: RR 2.59, 95% CI 1.89–3.57, $p < 0.001$), but without significantly increasing the risk of symptomatic intracranial hemorrhage (sICH: RR 1.83, 95% CI 0.95–3.55, $p = 0.07$) or early mortality (RR 0.95, 95% CI 0.78–1.16, $p = 0.61$). Analysis of the cohort studies showed that EVT improved functional outcomes of patients without an increase in the incidence in sICH.

Discussion

This systematic review and meta-analysis indicates that in patients with LVO stroke with a large ischemic core, EVT was associated with improved functional outcomes over MM without increasing sICH risk. The results of ongoing RCTs may provide further insight in this patient population.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ANGEL-ASPECT = Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core; **ASPECTS** = Alberta Stroke Program Early CT Score; **DC** = decompressive craniectomy; **EVT** = endovascular thrombectomy; **GRADE** = Grading of Recommendations Assessment, Development, and Evaluation; **HERMES** = Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; **LVO** = large vessel occlusion; **MM** = medical management; **mRS** = modified Rankin Scale; **NOS** = Newcastle-Ottawa Scale; **RESCUE-Japan LIMIT** = Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial; **RCT** = randomized controlled trial; **RR** = risk ratio; **SELECT2** = Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; **sICH** = symptomatic intracranial hemorrhage.

Introduction

Several randomized controlled trials (RCTs) have indicated that endovascular thrombectomy (EVT) reduces disability of patients with acute ischemic stroke and large vessel occlusion (LVO).[1-8] The approach has achieved level 1a recommendation for select patients in stroke guidelines.[9-13] However, most of these trials had strict imaging inclusion criteria, recruiting patients with a baseline Alberta Stroke Program Early CT Score (ASPECTS) greater than 5 on noncontrast CT or with an infarct core volume less than 70 mL on CT perfusion.[3,4,6,14] Patients with a large infarct core (volume greater than 70 mL, ASPECTS score of 5 or less) who were believed to be less likely to benefit from thrombectomy and at increased risk of reperfusion injury or symptomatic intracranial hemorrhage (sICH) were excluded from the early EVT trials.[7,9,15-17] Therefore, the efficacy of EVT in patients with a larger ischemic burden has not been well studied.

The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) individual patient-level meta-analysis of the thrombectomy trials compared the effect of mechanical thrombectomy vs medical therapy across different strata of patients with small, medium, or large infarct core.[18] A subgroup analysis of 126 patients with ASPECTS 0 to 4 showed that the point estimates favored thrombectomy compared with medical management (MM) for the primary outcome of neurological disability (90-day ordinal modified Rankin Scale [mRS]), however with a higher rate of sICH (EVT vs MM: 19% vs 5%, $p = 0.016$). A prior meta-analysis of 9 observational studies including 1,196 patients with LVO and low ASPECTS (≤5) who received mechanical thrombectomy showed that favorable outcome could be achieved despite a trend of higher sICH.[19] The Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial (RESCUE-Japan LIMIT) showed that patients with large infarct core achieved better functional outcomes with mechanical thrombectomy than with medical therapy alone.[20] A similar treatment effect was reported in 2 other randomized trials, the Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2), and the Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ANGEL-ASPECT).[21,22]

This systematic review and meta-analysis aims to provide an updated summary of the relevant literature, combining the pooled results of 3 RCTs (RESCUE-Japan LIMIT, SELECT2, and ANGEL-ASPECT) and observational cohort studies, to investigate the efficacy and safety of mechanical thrombectomy in acute large ischemic stroke across a diverse population.

Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.[23] This study protocol was registered on the International Prospective Register of Systematic Reviews on February 12, 2023 (PROSPERO, CRD42023396232). Data are available on request to the corresponding authors.

Data Source and Search Strategy

We searched the PubMed, Embase, Cochrane Library, and Web of Science databases to obtain articles in all languages from inception until February 10, 2023. "Stroke," "Thrombectomy," and "large ischemic core" were the search terms. Synonyms were obtained from PubMed, Embase, and Cochrane Library with elimination of duplicates. Detailed search criteria of keywords and their synonyms are provided in eTable 1 (links.lww.com/WNL/C859).

Eligibility Criteria

The inclusion criteria for this large ischemic core systematic review and meta-analysis were as follows: (1) patients with ASPECTS ≤5 or infarct core volume ≥50 mL, (2) RCT or observational study, (3) interventional arm receiving EVT and MM, (4) control arm receiving MM, and (5) reporting of mRS score of 0–3 at 3 months, 90-day mortality, and sICH. Studies were excluded if it lacked report of the primary study outcomes or if it lacked reporting of a control group. Randomized trials with less than 100 patients were excluded.

Study Selection and Data Collection

The titles, abstracts, and full texts of the articles were read by 2 researchers working independently (Q.L., Y.D.), selected according to the inclusion and exclusion criteria from a predesigned table as detailed in eTable 2 (links.lww.com/WNL/C859). The 2 researchers conducted cross-checking after screening of the articles, and if there was disagreement, it was

resolved through discussion with the senior author (Z.Q.). Data of the baseline characteristics, primary, secondary, and safety end points of each study were extracted for analysis by 2 researchers independently (Q.L., Y.D.).

Risk of Bias Assessment and Quality of Evidence

The quality of the RCTs and risk of bias were evaluated with the Cochrane risk assessment tool. The cohort and case-control studies were evaluated by the Newcastle-Ottawa Scale (NOS). For retrospective studies, an evaluation result ≥5 ☆ was considered of good quality and was included in the meta-analysis. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to evaluate the overall quality of evidence. Publication bias was examined by funnel plot.

Effect Measures

The primary outcome was independent ambulation (defined as a mRS score of 0–3) at 90 days. The secondary outcomes were functional independence (mRS 0–2) and the rate of decompressive hemicraniectomy. The safety outcomes were sICH defined according to study criteria and mortality at 90 days.

Statistical Analysis

Statistical analysis was performed using RevMan5.4 and Stata Software (version 12.0). For the RCTs, data were reported as intention-to-treat analysis. Absolute counts are provided in addition to effect estimates, which are expressed as risk ratios (RR) with corresponding 95% CIs. The χ^2 test was used to analyze the heterogeneity of the results in each study. It was considered that an $I^2 < 50\%$ and $p > 0.1$ indicated that the combined results were homogeneous, and hence, the fixed-effect model was used for analysis. When I^2 was ≥50% or $p \leq 0.1$, this indicated that the combination result had heterogeneity, and therefore, the random-effect model was used to analyze and search for possible sources of heterogeneity.

Standard Protocol Approvals, Registrations, and Patient Consents

This systematic review and meta-analysis was registered prospectively PROSPERO on February 12, 2023, which used summary data from published manuscripts (crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396232). We did not use individual level data, so informed consent or IRB approval was not required.

Data Availability

Data not provided in the article because of space limitations may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Study Characteristics and Quality Evaluation

A total of 5,395 articles were obtained through search and articles that did not meet the inclusion criteria were excluded by reading the title, abstract, and full text (Figure 1). Finally, 3 RCTs and 10 observational cohort studies met the inclusion criteria, with basic characteristics shown in Tables 1 and 2, respectively (other baseline data are presented in eTable 3 and eTable 4, links.lww.com/WNL/C859). The 3 RCTs were at low risk of bias (Table 1, eFigure 1). Ten cohort studies were scored with the NOS, with a score of 8☆ to 9☆, thus meeting the conditions for inclusion in this meta-analysis (Table 1, eTable 5). A total of 2,861 patients were included in this analysis. The RCTs included 1,010 patients, of whom 509 patients were treated with EVT and 501 treated with MM. The cohort study included 1,851 patients of whom 879 patients were treated with EVT and 972 treated with MM.

Primary Outcome: Independent Ambulation (mRS 0–3)

Three RCTs and 10 observational cohort studies were combined and analyzed using the random-effect model (Figures 2A and 3A, respectively). Across the 3 RCTs, EVT improved the primary outcome of independent ambulation in patients with large ischemic core (RR 1.78, 95% CI 1.28–2.48, $p < 0.001$) and showed moderate heterogeneity ($I^2 = 58\%$). In 10 observational cohort studies, the same conclusion was reached (RR 2.33, 95% CI 1.62–3.35, $p < 0.001$), but exhibited high heterogeneity ($I^2 = 78\%$). The GRADE quality of the RCT evidence was high whereas the GRADE quality of the cohort studies was low (eFigure 2, links.lww.com/WNL/C859).

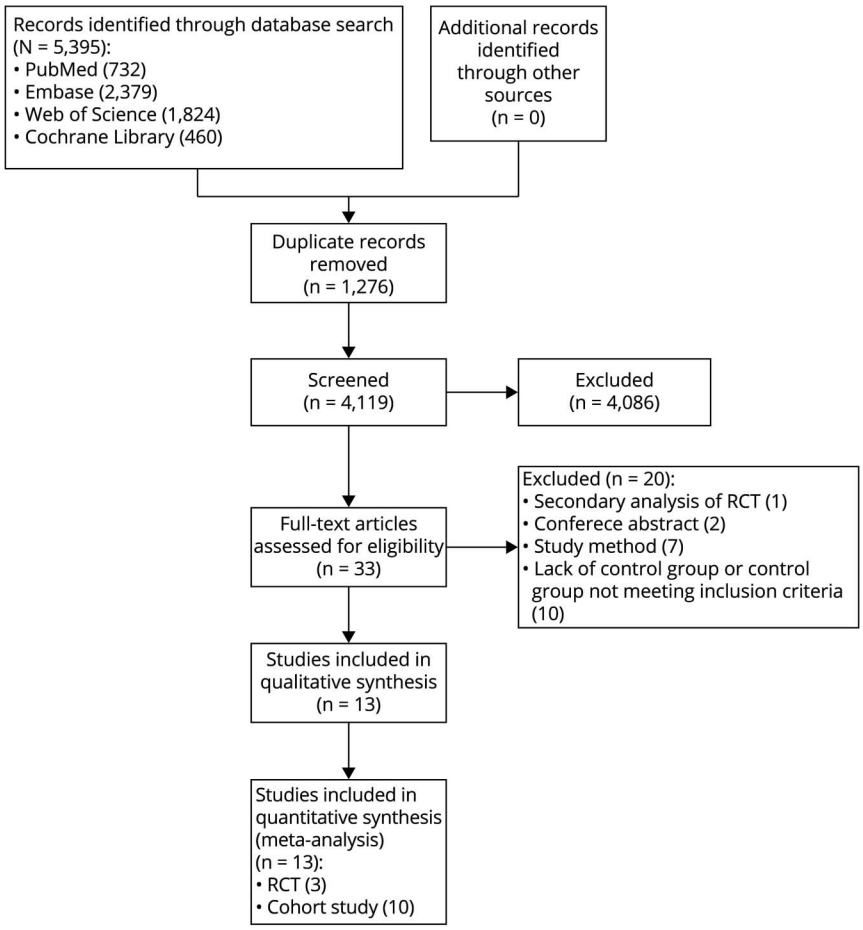
Secondary Outcome: Functional Independence (mRS 0–2)

The fixed-effect model was used to combine the results of the 3 RCTs (Figure 2B) and showed that for patients with large ischemic core, EVT improved the likelihood of functional independence (RR 2.59, 95% CI 1.89–3.57, $p < 0.001$), with very low heterogeneity ($I^2 = 0\%$). The same results were obtained after pooling 10 cohort studies with the random-effect model (RR 3.39, 95% CI 1.98–5.79, $p < 0.001$) (Figure 3B), but the heterogeneity was high ($I^2 = 74\%$). The GRADE quality of evidence for the 3 RCTs was high, and the GRADE quality of evidence for the observational cohort studies was low (eFigure 2, links.lww.com/WNL/C859).

Symptomatic Intracranial Hemorrhage

In the RCT analysis, there was a numerically higher rate of sICH in the EVT compared with the MM group; however, this was not significant (24/508, 4.7% vs 13/501, 2.6%, $p = 0.07$). Owing to the very low heterogeneity ($I^2 = 0\%$), the fixed-effect model was used to combine sICH data from the RCTs. The probability of sICH in patients with large infarct region treated with EVT was 1.83 times higher than that in patients treated with MM (RR 1.83, 95% CI 0.95–3.55, $p = 0.07$), also not significant (Figure 2C). Analysis of 8 cohort studies showed that the probability of sICH was similar between EVT and MM (RR 1.01, 95% CI 0.70–1.46; $p = 0.95$) (Figure 3C). Two of the cohort studies did not include sICH data and were not included in the sICH analysis.[24,25] The

Figure 1 PRISMA Flow Diagram



PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis; RCT = randomized controlled trial.

GRADE quality of the RCT evidence was high and that of the cohort studies was very low (eFigure 2, links.lww.com/WNL/C859).

Decompressive Hemicraniectomy

Two RCTs[20,22] and 2 cohort studies[26,27] reported data on decompressive craniectomy (DC). Analysis of the 2 RCTs showed that there was no difference in the rate of DC between the EVT and MM group (RR 1.22, 95% CI 0.43–3.41), whereas the cohort study showed that EVT was associated with a lower rate of DC (RR 0.21, 95% CI 0.07–0.59, eFigure 3, links.lww.com/WNL/C859).

Mortality

Three RCTs and 8 cohort studies were combined and analyzed using the fixed-effect model. In the 3 RCTs, there was no increased mortality in the EVT group compared with the MM group (RR 0.95, 95% CI 0.78–1.16, $p = 0.61$) (Figure 2D), showing an extremely low heterogeneity ($I^2 = 0\%$). In 8 observational cohort studies, EVT reduced mortality of patients with large ischemic core (RR 0.60, 95% CI 0.51–0.71, $p < 0.001$) (Figure 3D), and there was a moderate heterogeneity ($I^2 = 49\%$). As 2 of the cohort studies did not include mortality data, they were not included in the mortality analysis.[24,25] The GRADE quality of the RCT evidence was moderate and that of the cohort studies was very low (eFigure 2, links.lww.com/WNL/C859).

Risk of Bias

A funnel plot of the 3 RCTs was symmetric indicating that there was no publication bias (Egger test $p > 0.05$, eFigure 4, links.lww.com/WNL/C859).

Discussion

In the present systematic review and meta-analysis comprising patients of diverse international representation with anterior circulation LVO and large ischemic core infarct, we found from the analysis of 3 pooled RCTs that patients who underwent EVT had a nearly twofold higher chance of independent ambulation at 90 days, over twofold higher probability of achieving 90-day functional independence, a numerically higher rate of sICH, and comparable mortality rate when compared with standard care alone. These treatment effects were generally concordant with the 10 observational studies except that

Table 1 Characteristics and Quality Evaluation of Randomized Controlled Trials

Study	Inclusion criteria	No. of patients	Age, y	Occlusion site, n (%)				Median ASPECTS value (IQR)	Median infarct core volume (IQR), mL	Median time of interval between time of stroke onset and time of randomization (IQR), min	Quality evaluation (Cochrane)
				ICA	M1 segment	M2 segment	Tandem occlusions				
Yoshimura et al., 2022[20]	ASPECTS (3–5)	EVT: 101 MM: 102	76.6 ± 10.0 75.7 ± 10.2	47 (46.5) 49 (48.0)	74 (73.3) 70 (68.6)	0 (0%) 3 (2.9)	20 (19.8) 20 (19.6)	3 (3–4) 4 (3–4)	94 (66–152) 110 (74–140)	229 (144–459) 214 (142–378)	Low risk
Sarraj et al., 2023[21]	ASPECTS (3–5) OR ischemic core (≥50 mL)	EVT: 178 MM: 174	66 (58–75) 67 (58–75)	80 (44.9) 66 (37.9)	91 (51.1) 100 (57.5)	7 (3.9) 8 (4.6)	56 (31.5) 44 (25.3)	4 (3–5) 4 (4–5)	81.5 (57–118) 79 (62–111)	587 (349–919) 544 (316–920)	Low risk
Huo et al., 2023[22]	ASPECTS (3–5) OR ASPECTS (0–2) within ischemic core (70–100 mL) OR ASPECTS (>5) within ischemic core (70–100 mL)	EVT: 230 MM: 225	68 (61–73) 67 (59–73)	83 (36.1) 81 (36.0)	145 (63.0) 142 (63.1)	2 (0.9) 2 (0.9)	— —	3 (3–4) 3 (3–4)	60.5 (29–86) 63 (31–86)	453 (299–712) 463 (305–781)	Low risk

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; EVT = endovascular thrombectomy; ICA = internal carotid artery; IQR = interquartile range; MM = medical management.

mortality was noted to be lower in the EVT group from the observational studies.

The pooled treatment effect favoring EVT over MM across these 3 large ischemic core randomized trials is less than that observed in the HERMES meta-analysis comprising patients with small core infarct (adjusted common odds 2.49, 95% CI 1.76–3.53; $p < 0.0001$). HERMES selected ordinal mRS shift as the primary outcome, while we selected the primary outcome as independent ambulation as defined by mRS 0–3.[5] As patients with large ischemic stroke have more extensive infarction at baseline, a clinically meaningful outcome for these patients can be widened to mRS 0–3, which translates to requiring some help, but the patient is independent with ambulation.[16,28] With data from these 3 RCTs, our findings now lend support that EVT confers benefit across a broader strata of patients with moderate-sized to large-sized infarcts in an up to 24 hours window from time last known well. As such, advanced imaging modalities to triage patients with LVO in the 6–24 hour window may no longer be necessary to select patients with widening of thrombectomy eligibility criteria to include patients with large ischemic core.[12,29,30] However, as patients with very large infarct core as defined by ASPECTS 0–2 were excluded from RESCUE-Japan LIMIT and underrepresented in ANGEL-ASPECT and SELECT2, we could not establish the benefit of EVT in this subgroup of patients with very large ischemic core.

In the pooled analysis of independent ambulation, the 3 RCTs showed moderate heterogeneity, while the heterogeneity decreased to 0% after removing ANGEL-ASPECT but only combining the results of SELECT2 and RESCUE-Japan LIMIT (eFigure 5, links.lww.com/WNL/C859). We surmise that this may be due to the fact that the median infarct core volume of patients included in ANGEL-ASPECT was smaller than that of the other 2 trials (Table 1). Subgroup analysis of SELECT2 also showed that patients with larger infarction volume (≥100 mL) were likely to benefit from EVT.[21] Similarly, subgroup analysis of patients with larger infarct core volume (>70 mL) in ANGEL-ASPECT also suggested the point estimates in favor of EVT, although this did not achieve significance.

With regard to adverse events, the RCTs showed that the sICH rate of patients with large ischemic core treated with EVT was 1.83 times higher than that of MM, whereas there was no difference between the EVT and MM groups with regard to sICH from the observational cohort studies. This

Table 2 Characteristics and Quality Evaluation of Cohort Studies

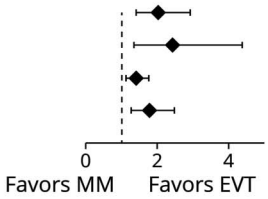
Study	Inclusion criteria	No. of patients	Age, y	Occlusion site, n (%)				Median ASPECTS value (IQR)	Median infarct core volume (IQR), mL	Intravenous thrombolysis, n (%)	Quality (NOS)
				ICA	M1 segment	M2 segment	Tandem occlusions				
Chen et al., 2018[40]	Ischemic core (≥70 mL)	EVT: 28 MM: 76	EVT: 68.4 ± 14.0 MM: 73.8 ± 11.8	14 (50.0) 31 (40.8)	14 (50.0) 45 (59.2)		— —	— —	97.8 (80.8–115.7) 114.6 (85.4–143.9)	— —	8☆
Garcia-Esperon et al., 2022[24]	Ischemic core (≥70 mL)	EVT: 121 MM: 148	EVT: 69 (61–77) MM: 75 (61–82.5)	64 (52.9) 83 (56.1)	49 (40.5) 62 (41.9)	5 (4.1) 2 (1.4)	— —	7 (4–9) n = 116 5 (3–7) n = 141	92 (79–116.5) 105.5 (85.7–138)	60 (49.6) 74 (50.0)	8☆
Mourand et al., 2018[26]	ASPECTS (≤5)	EVT: 60 MM: 48	EVT: 66 (22–86) MM: 67 (41–87)	8 (13.3) 9 (18.8)	34 (56.7) 27 (56.3)	5 (8.3) 3 (6.3)	13 (21.7) 9 (18.8)	5 (2–5) 3 (0–5)	— —		8☆
Kaesmacher et al., 2019[41]	ASPECTS (≤5)	EVT: 165 MM: 71	EVT: 66.4 ± 14.8 MM: 68.6 ± 13.5	63 (38.1) 25 (35.2)	96 (58.2) 45 (63.4)	6 (3.6) 1 (1.4)	30 (18.2) 12 (16.9)	— —	— —		8☆
Seners et al., 2021[25]	Ischemic core (≥50 mL)	EVT: 56 MM: 51	EVT: 73 (61–80) MM: 69 (57–80)	19 (33.9) 12 (23.5)	28 (50.0) 29 (56.9)	9 (16.1) 10 (19.6)	— —	— —	105 (76–133) 97 (65–124)	32 (57.1) 46 (90.2)	9☆
Kakita et al., 2019[42]	ASPECTS (≤5)	EVT: 172 MM: 332	EVT: 74.6 (10.8) MM: 80.4 (11.3)	97 (56.4) 184 (55.4)	77 (44.8) 158 (47.6)	— —	— —	5 (4–5) 3 (2–4)	— —	67 (39.0) 41 (12.4)	7☆
Kerleroux et al., 2020[43]	Ischemic core (≥70 mL)	EVT: 130 MM: 42	EVT: 66.2 ± 15 MM: 77.7 ± 13.5	24 (18.5) 7 (16.7)	— —	— —	— —	— —	104 ± 37.7 96.7 ± 33	63 (48.5) 42 (100.0)	8☆
Sarraj et al., 2019[44]	ASPECTS (≤5) OR Ischemic core (≥50 mL)	EVT: 62 MM: 43	66 (59–74) 66 (60–81)	19 (30.6) 16 (37.2)	37 (59.7) 20 (46.5)	6 (9.7) 7 (16.3)	— —	5 (4–7) 4 (3–5)	97 (43–189) 190 (127–252)	43 (69.4) 26 (60.5)	7☆
Yoshimoto et al., 2021[27]	Ischemic core (70–300 mL)	EVT: 49 MM: 108	EVT A: 76 (71–85)[a] B: 80 (71–85)[b] C: 77 (65–81)[c] MM A: 79 (67–87)[a] B: 77 (71–84)[b] C: 84 (77–87)[c]	20 (40.8) 43 (54.6)	16 (32.7) 35 (32.4)	3 (6.1) 6 (5.6)	9 (18.4) 3 (2.8)	5 (4–6) 6 (4–6) 3 (3–6) 4 (3–5) 3 (1–5) 2 (1–3)	80 (74–87) 107 (101–117) 178 (175–194) 85 (77–91) 113 (107–124) 182 (150–210)	19 (38.8) 3 (2.8)	8☆
Jiang et al., 2018[45]	ASPECTS (≤5)	EVT: 36 MM: 53	EVT: 60.83 ± 14.22 MM IVT: 66.19 ± 6.79 CC: 63.13 ± 12.30	1 (2.7) 3 (5.7)	24 (66.7) 33 (62.3)	2 (5.4) 16 (30.2)	9 (25) 1 (1.9)	3.06 ± 1.47 4.10 ± 1.09 3.13 ± 1.70	— — —	— — —	7☆

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; CC = conventional care; EVT = endovascular thrombectomy; ICA = internal carotid artery; IQR = interquartile range; IVT = intravenous thrombolysis; MM = medical management; NOS = Newcastle-Ottawa Scale.
[a] Infarct volume was 70–100 ml.
[b] Infarct volume was 100–130 ml.
[c] Infarct volume was >130 ml.

Figure 2 Forest Plots of RCTs About (A) Independent Ambulation (mRS ≤3), (B) Functional Independence (mRS ≤2), (C) Incidence of sICH (per Study Definition), and (D) Mortality

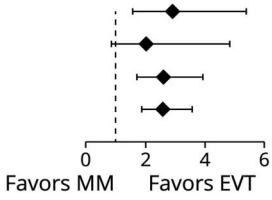
A. mRS 0–3

RCTs	EVT Events/total (%)	MM Events/total (%)	Risk ratio M-H, random, 95% CI	Risk ratio M-H, random, 95% CI	Weight (%)
Ref. #21	67/177 (37.29)	32/171 (18.71)		2.02 (1.40, 2.91)	34.00
Ref. #20	31/100 (31.00)	13/102 (12.75)		2.43 (1.35, 4.37)	20.50
Ref. #22	108/230 (46.96)	75/225 (33.33)		1.41 (1.12, 1.77)	45.40
Total	206/507 (40.63)	120/498 (24.10)		1.78 (1.28, 2.48)	100.00
Heterogeneity: Tau² = 0.05; Chi² = 4.78, df = 2 (p = 0.09); I² = 58%					
Test for overall effect: z = 3.43 (p = 0.0006)					



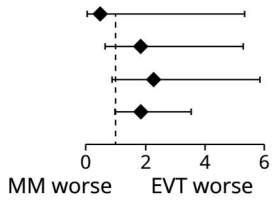
B. mRS 0–2

RCTs	EVT Events/total (%)	MM Events/total (%)	Risk ratio M-H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI	Weight (%)
Ref. #21	36/177 (20.34)	12/171 (7.01)		2.90 (1.56, 5.38)	26.90
Ref. #20	14/100 (14.00)	7/102 (6.86)		2.04 (0.86, 4.84)	15.30
Ref. #22	69/230 (30.00)	26/225 (11.56)		2.60 (1.72, 3.92)	57.90
Total	119/507 (23.47)	45/498 (9.04)		2.59 (1.89, 3.57)	100.00
Heterogeneity: Chi² = 0.42, df = 2 (p = 0.81); I² = 0%					
Test for overall effect: z = 5.86 (p < 0.00001)					



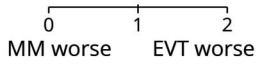
C. sICH

RCTs	EVT Events/total (%)	MM Events/total (%)	Risk ratio M-H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI	Weight (%)
Ref. #21	1/178 (0.56)	2/174 (1.15)		0.49 (0.04, 5.34)	15.50
Ref. #20	9/100 (9.00)	5/102 (4.90)		1.84 (0.64, 5.29)	38.00
Ref. #22	14/230 (6.09)	6/225 (2.67)		2.28 (0.89, 5.83)	46.50
Total	24/508 (4.72)	13/501 (2.59)		1.83 (0.95, 3.55)	100.00
Heterogeneity: Chi² = 1.38, df = 2 (p = 0.50); I² = 0%					
Test for overall effect: z = 1.80 (p = 0.07)					



D. Mortality

RCTs	EVT Events/total (%)	MM Events/total (%)	Risk ratio M-H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI	Weight (%)
Ref. #21	68/177 (38.42)	71/171 (41.52)		0.93 (0.72, 1.20)	51.00
Ref. #20	18/100 (18.00)	24/102 (23.53)		0.77 (0.44, 1.32)	16.80
Ref. #22	50/230 (21.74)	45/225 (20.00)		1.09 (0.76, 1.56)	32.20
Total	136/507 (26.82)	140/498 (28.11)		0.95 (0.78, 1.16)	100.00
Heterogeneity: Chi² = 1.19, df = 2 (p = 0.55); I² = 0%					
Test for overall effect: z = 0.51 (p = 0.61)					

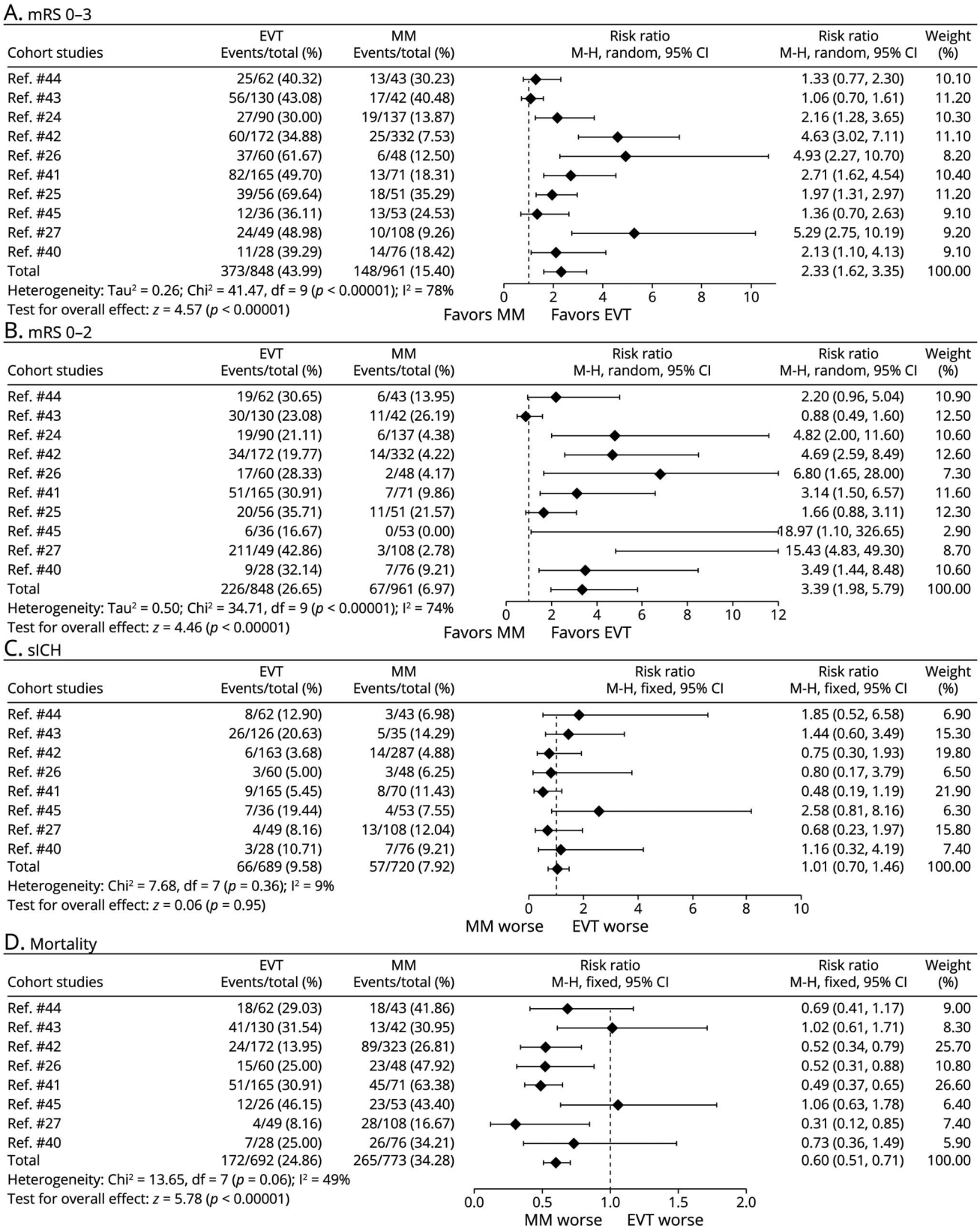


EVT = endovascular thrombectomy; MM = medical management; mRS = modified Rankin Scale; RCT = randomized controlled trial; sICH = symptomatic intracranial hemorrhage.

may be due to the variable criteria for evaluating sICH across different studies, such as use of the Heidelberg bleeding classification in ANGEL-ASPECT or Safe Implementation of Thrombolysis in Stroke-Monitoring Study in RESCUE-Japan LIMIT and SELECT2. Moreover, the overall rate of sICH was surprisingly low across all 3 randomized trials (EVT vs MM: 4.7% vs 2.6%) whereas the overall rates of sICH were more than twofold higher across the 8 observational cohorts (EVT vs MM 9.5% vs 7.9%). Perhaps the rigor by which patients are being managed in RCTs may, in part, explain safety differences between trial and real-world patients.[31,32]

Regarding mortality in patients with large ischemic core, EVT did not increase mortality in the RCT analysis, while cohort studies showed that EVT significantly reduced mortality. From the distribution plot of mRS scores of RCTs, the

Figure 3 Forest Plots of Observational Cohort Studies About (A) Independent Ambulation (mRS ≤3), (B) Functional Independence (mRS ≤2), (C) Incidence of sICH, and (D) Mortality



EVT = endovascular thrombectomy; MM = medical management; mRS = modified Rankin Scale; RCT = randomized controlled trial; sICH = symptomatic intracranial hemorrhage.

difference in mortality between the EVT group and the standard medical therapy group of the 3 RCTs was not significant, but the proportion of mRS 5–6 between the 2 groups was significantly different (SELECT2: EVT vs MM = 46.6% vs 59.2%; RESCUE-Japan LIMIT: EVT vs MM = 36% vs 64%; ANGEL-ASPECT: EVT vs MM = 33.4% vs 40%).[20-22] The above findings indicate that although EVT was not shown to reduce mortality and has a numerically higher risk of sICH, it can significantly reduce severe disability. Altogether, EVT, as a minimally invasive neurological procedure, can significantly improve the functional outcomes, and the incidence of adverse events is acceptable given the natural history of this condition.

We also analyzed the impact of DC on survival and functional outcomes in patients with large core infarction. Lack of a difference in the rates of DC between the EVT and MM groups in the RCT analysis was surprising considering that prior cohort or nation-wide analyses showed that EVT was associated with lower rates of DC.[33,34] It is possible the RCT analysis was underpowered to detect a potential difference. Moreover, there was no difference in preoperative clinical parameters, ASPECTS, and clinical outcome between DC patients who were treated with EVT and those who were not in a retrospective study.[35] In addition, the success of EVT (complete or near complete reperfusion) did not obviate need for DC.[35] In summary, EVT did not change the rate of subsequent DC in the RCT analysis.

Our study has limitations. First, the number of RCTs was limited. When evaluating the primary outcome for independent ambulation, the 3 RCTs had a low-to-moderate degree of heterogeneity whereas the cohort studies had moderate-to-severe heterogeneity. Second, there was wide variation in the imaging modality choice and definition of imaging parameters across these large ischemic core trials. There remains controversy in defining a true large ischemic core infarction in current clinical practice. Not all ASPECTS regions have the same infarct volume, which means that when ASPECTS ≤5 is the only criterion, patients with infarct core volume smaller than 50 mL may also be included. Third, owing to the lack of data on subgroup analysis, we did not identify the benefit of EVT and risk ratio of patients with very large ischemic core (i.e., ASPECTS 0–2) or as stratified by age.[36] Some studies have suggested that patients with ischemic core ≥130 mL do not benefit[27] or are at risk of increased edema after reperfusion.[37] However, in SELECT-2, even patients with >150 mL ischemic core seemed to benefit, and further analyses may be warranted.[21]

This systematic review and meta-analysis indicated that EVT is associated with better functional outcomes than standard medical therapy in acute LVO stroke with a large ischemic core. Less restrictive patient selection criteria lead to treatment benefit. The results of 3 additional RCTs, TESLA (ClinicalTrials.gov, NCT03805308),[38] TENSION (ClinicalTrials.gov, NCT03094715), and LASTE (ClinicalTrials.gov, NCT03811769) will provide further guidance on the management of these patients.[39] A meta-analysis of individual patient data is expected.

Study Funding

No targeted funding reported.

Disclosure

J. Kaesmacher is supported by the grants from the Swiss Academy of Medical Sciences/Bangerter Foundation, Swiss Stroke Society, Clinical Trials Unit Bern, and the Swiss National Science Foundation. A. Sarraj is Principal Investigator of the SELECT2 trial funding by grants from Stryker Neurovascular to University of Texas-McGovern Medical School and University Hospitals—Cleveland Medical Center. J.L. Saver has received contracts from Medtronic, Abbott, NeuroVasc, Phillips Medical, Bayer, Biogen, Roche, BrainsGate, BrainQ, and Occlutech and stock options from Rapid Medical and QuantalX for service on clinical trial steering committees and Data and Security Monitoring Committees and advising on rigorous study design and conduct. T.N. Nguyen received research support from Medtronic and served on advisory board of Idorsia. R.G. Nogueira reports consulting fees from Anaconda, Biogen, Cerenovus, Genentech, Philips, Hybernia, Imperative Care, Medtronic, Phenox, Philips, Prolong Pharmaceuticals, Stryker Neurovascular, Shanghai Wallaby and Synchron and stock options from Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, Vesalio, Viz-AI, RapidPulse, and Perfuze for advisory serve; is the Principal Investigator of the "Combined Thrombectomy for Distal MediUm Vessel Occlusion StroKe (DUSK)" trial funding by Stryker Neurovascular; and is an Investor in Viz-AI, Perfuze, Cerebrotech, Reist/Q'Apel Medical, Truvic, Vastrax, and Viseon. A.J. Yoo and O.O. Zaidat report PI of the Thrombectomy for Emergent Salvage of Large Anterior Ischemic Stroke (TESLA) trial. The remaining authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 21, 2023. Accepted in final form May 4, 2023. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

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Appendix *(continued)*

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Appendix *(continued)*

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