Stroke

AHA SCIENCE ADVISORY

Large-Core Ischemic Stroke Endovascular Treatment: A Science Advisory From the American Heart Association

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ABSTRACT: Several trials of endovascular treatment for patients with large-core acute ischemic stroke have been completed. Whereas future stroke clinical guidelines will provide specific recommendations, this advisory aims to summarize the results of these trials, analyze the commonalities and differences among the studies, and discuss the clinical implications of these new results.

Key Words: AHA Scientific Statements ■ ischemia ■ ischemic stroke ■ stroke

Core, in the setting of ischemic stroke, is defined as the volume of cerebral tissue that is irreversibly injured or infarcted. Core size estimated by the semiquantitative Alberta Stroke Program Early CT Score (ASPECTS) at early and late time windows, although imprecise,[1–3] was used to select participants in the majority of the pivotal trials establishing endovascular thrombectomy (EVT) for patients within 6 hours of last known well (LKW).[4–9] The area of the core can also be predicted by perfusion imaging measures based on cerebral blood flow <30% on computed tomography (CT) or magnetic resonance perfusion, and these criteria were used to select patients for EVT in the pivotal trials to demonstrate the benefit of EVT at 6 to 24 hours from LKW.[10,11] However, this definition overestimates core within hours of stroke onset,[12] and does not consistently detect areas of subacute ischemia seen on CT. Thus, the working definitions in clinical practice for large core ischemic stroke (LCIS) have been delineated in a time-qualified manner by the pivotal trials[4–11] and previous guidelines[13] to (1) ASPECTS ≤5 by noncontrast head CT (NCCT) or brain magnetic resonance imaging (MRI) within 6 hours of stroke onset[4–9] and (2) ischemic core volume >50 mL[10] to 70 mL[11] within 6 and 24 hours of stroke onset. In routine clinical practice,[14] CT perfusion (CTP) volumes are combined with any additional hypodensity present on NCCT, but not visualized on CTP, to consider the full extent of core.

Until recently, with the premise that reperfusion therapies would have low or no benefit in patients with large vessel occlusion stroke with substantial amounts of completed infarction (core), most randomized clinical trials for endovascular thrombectomy (EVT) excluded patients with LCIS.[4–9] Within 6 hours of onset, patients were typically excluded from trials if the baseline ASPECTS on presentation to the emergency department was <6.[13] Beyond 6 hours up to 24 hours, in addition to ASPECTS criteria, trials did not allow enrollment of patients with core volumes >50 mL (eg, DAWN [Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo], <24 hours) or >70 mL (eg, DEFUSE 3 [Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3], <16 hours, and other 2015 <6- to 8-hour trials); they also required some level of clinical or penumbra mismatch with core volume as measured by CTP.[10,11]

This American Heart Association science advisory summarizes recent randomized trials on the efficacy of EVT in LCIS, analyzes the similarities and differences

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among these trials, and discusses the clinical implications of their findings. LCIS represents ≈25% of ischemic strokes attributable to large vessel occlusion among those presenting within 8 hours of onset to referral centers,[15] highlighting the substantial clinical relevance of interventions that could improve outcomes for these patients.

METHODS

After the identification, acceptance, and approval of writing group members by the American Heart Association, an initial meeting was conducted on January 31, 2024, which included American Heart Association staff. An agenda, outline, and calendar schedule were formulated. Several virtual meetings among subsets of members of the writing group were completed to develop a consensus on the final scientific statement. Writing group members had access to the list of publications for review and used this information to develop this science advisory. We systematically searched PubMed, Cochrane Library, and Ovid databases for prospective randomized controlled clinical trials that compared EVT with medical management (MM) in patients with an acute ischemic stroke presenting with a large core infarct. By consensus of the writing group, we restricted our primary analysis to clinical trials published within the past 3 years to capture the evidence most relevant to current clinical practice. The search strategy for studies was comprehensive, including published and unpublished studies (gray literature). The full electronic search strategies for each database were developed meticulously using a combination of MeSH terms and free text. Specific search strings, along with filters and limits, are detailed in the Supplemental Material. We evaluated the available studies on the basis of intervention protocols, patient population characteristics, and outcome measures. Two authors (R.M. and C.-H.T.) evaluated the quality of the studies using the revised Cochrane risk-of-bias tool for randomized trials and GRADE (Grading of Recommendations Assessment, Development and Evaluations) quality evaluation system.[16,17] All authors discussed those assessments to form a consensus opinion. Using these criteria, the summary and analysis presented is based on 6 randomized clinical trials: RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial),[18] ANGEL-ASPECT (Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core),[19] SELECT2 (SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke),[20] TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke),[21] TENSION (The Efficacy and Safety of Thrombectomy in Stroke),[22] and LASTE (Large Stroke Therapy Evaluation).[23] We used the inverse variance method to incorporate the adjusted odds ratios (ORs) and their CIs from each study into a unified analysis. This method maintains the integrity of adjustments for confounders in each trial by weighting their contributions according to the precision of their estimates. In brief, the ORs were transformed into their natural logarithms (log ORs), the variance for these log ORs was derived from their CIs, and standard errors were calculated using the Z value for a 95% CI. The weight assigned to each study in the analysis is inversely proportional to the variance of its log OR. A weighted average of the log ORs was computed using the previously calculated weights. The exponential of this weighted average gives the combined OR, representing the synthesized effect estimate across all included studies.

ANALYSIS OF CLINICAL TRIAL METHODS

Clinical Eligibility Criteria

All 6 clinical trials—RESCUE-Japan LIMIT,[18] ANGEL-ASPECT,[19] SELECT2,[20] TESLA,[21] TENSION,[22] and LASTE[23]—ascertained by our search methods and criteria included adult patients 18 years or older with large acute ischemic stroke and major arterial occlusions at the anterior circulation (internal carotid artery or middle cerebral artery). TESLA data are included on the basis of a preprint and personal communications with the lead author.

Age

Three studies (ANGEL-ASPECT, SELECT2, and TESLA) had upper age limits for enrollment (80, 85, and 85 years, respectively); the other 3 studies (RESCUE-Japan LIMIT, TENSION, and LASTE) did not specify upper age boundaries, although LASTE has an upper age limit of 80 years for participants with ASPECTS 0 through 3.

Baseline Stroke Severity

The minimum National Institutes of Health Stroke Scale score for eligibility was 6 in all studies except TENSION, which had no lower limit. TENSION had an upper limit of 26 and ANGEL-ASPECTS had an upper limit of 30; the remainder of the studies did not report an upper limit.

Time

The MRI-based stroke studies (RESCUE-Japan LIMIT and LASTE) consisted of participants primarily in earlier time windows from witnessed stroke onset or LKW. RESCUE-Japan LIMIT included patients within 6 hours and LASTE allowed up to 6.5 hours, but both allowed patients with unknown onset up to 24 hours from LKW if the diffusion-weighted MRI lesion had no corresponding fluid-attenuated inversion recovery lesion to suggest >4.5 hours from onset.

Among the CT-based studies, TENSION had an intermediate window, randomizing within 11 hours and completing thrombectomy by 12 hours. ANGEL-ASPECT, SELECT2, and TESLA enrolled patients up to 24 hours from LKW.

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Exclusion Criteria

Studies had distinct clinical exclusion criteria influencing patient cohort composition. Common exclusions included contrast allergies, pregnancy, coagulation issues, or severe renal impairment. Other exclusion criteria were more heterogeneous and specific for each study, such as hypertension, life expectancy, infective endocarditis, and seizure at stroke presentation. Table 1 summarizes the eligibility criteria for each trial.

Imaging Eligibility Criteria

Table 2 presents imaging criteria for trial eligibility, which exhibit heterogeneity in several aspects. Commonalities included enrollment of patients with ASPECTS of 3 to 5 in most studies and systematic enrollment of patients with ASPECTS 0 to 2 in 1 study (LASTE) if <80 years old. RESCUE-Japan LIMIT and LASTE selected participants mainly by MRI-ASPECTS, whereas ANGEL-ASPECT and SELECT2 selected participants on the basis of a combination of criteria derived from NCCT and CTP. TENSION and TESLA required predominantly NCCT selection criteria. CTP data were available for almost half of participants (46%) in TESLA but not reported in TENSION.

Study Designs

All studies were centrally randomized and stratified by baseline variables, with participants assigned in a 1:1 ratio to either EVT with standard care or standard care alone (ie, medical treatment). Group assignment was not blinded to patients or physicians. The EVT technique (ie, stent retriever, aspiration, or both, with or without balloon protection) was left to the discretion of the treating physician in all trials, and acute angioplasty, stenting, and intra-arterial thrombolysis were variably permitted. The primary outcome measure—modified Rankin Scale (mRS) score at 90 days—was assessed by blinded assessors in all the studies. Whereas 4 studies used mRS shift analysis as the primary end point, RESCUE-Japan LIMIT used mRS 0 to 3, and TESLA used utility-weighted mRS scores. Intravenous thrombolysis (IVT) candidates received alteplase in all studies (standard 0.9 mg/kg, or 0.6 mg/kg in RESCUE-Japan LIMIT). ANGEL-ASPECT also allowed intravenous urokinase (1.0 to 1.5 million IU) in some patients. Table 3 provides information on the study end points.

CLINICAL TRIAL RESULTS

Table S1 presents a detailed summary of the complete clinical trial results.

Baseline Demographic and Clinical Characteristics

The 6 clinical trials enrolled a total of 1887 patients. In the EVT group, 514 of 945 patients (54.4%) were men;

Table 1. Summary of the Clinical Eligibility Criteria

Trial name	Region	ASPECTS	NIHSS score	Occlusion site	Prestroke mRS score	Age category, y	Clinical exclusion	Randomized within time, h
RESCUE-Japan LIMIT[18]	Japan	3–5: MRI	≥6	ICA, M1	0–1	≥18	A, P, C	6 (or <24 if FLAIR-negative)
ANGEL-ASPECT[19]	China	3–5: CT	6–30	ICA, M1	0–1	18–80	A, P, C, B, RF, E <1 mo, biopsy <1 mo	24
SELECT2[20]	Australia, Canada, New Zealand, Spain, United States	3–5: CT	≥6	ICA, M1	0–1	18–85	A, RF, E <3 mo, previous thrombolytic treatment	24
TESLA[21]	United States	2–5: CT	>6	ICA, M1	0–1	18–85	A, P, C, E <3 mo, hypertension >185/110 mm Hg, VTo	24
TENSION[22]	Austria, Canada, Czechia, Denmark, Norway, Slovakia	3–5: CT	<26	ICA, M1	0–2	≥18	E <6–12 mo, infective endocarditis	11
LASTE[23]	France	0–5, 4–5 in patients ≥80 y: MRI	≥6	ICA, M1, M2	0–1	≥18 if ASPECTS 4–5; 18–80 if ASPECTS 0–3	A, E <6 mo, seizures at time of stroke (affecting NIHSS assessment), VTo	6.5 (or <24 if FLAIR-negative)

A indicates allergy to contrast; ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; ASPECTS, Alberta Stroke Program Early CT Score; B, active bleeding; biopsy <1 mo, biopsy performed within the past month; C, coagulopathy; CT, computed tomography; E, life expectancy; FLAIR, fluid-attenuated inversion recovery; ICA, internal carotid artery; LASTE, Large Stroke Therapy Evaluation; M1, stroke in the M1 segment of the middle cerebral artery; M2, acute ischemic stroke that occurs when the M2 segment of the middle cerebral artery is blocked; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; P, pregnancy; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial; RF, renal failure; SELECT2, SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; TENSION, The Efficacy and Safety of Thrombectomy in Stroke; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; and VTo, vessel tortuosity limiting endovascular intervention.

Table 2. Summary of Imaging Eligibility Criteria

Trial name	Baseline imaging	Time window, h	ASPECTS criteria
RESCUE-Japan LIMIT[18]	MRI (14% with CT)	<6*	3–5
ANGEL-ASPECT[19]	CT and CTP (8% with MRI)	<24	3–5†
SELECT2[20]	CT and CTP (2% with MRI)	<24	3–5‡
TESLA[21]	CT	<24	2–5
TENSION[22]	CT (18% with MRI)	<11	3–5
LASTE[23]	MRI (16% with CT)	<6.5*	0–5 (4–5 if >80 y)

ANGEL-ASPECT indicates Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; CT, computed tomography; LASTE, Large Stroke Therapy Evaluation; MRI, magnetic resonance imaging; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial; SELECT2, SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; TENSION, The Efficacy and Safety of Thrombectomy in Stroke; and TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke.

*Allowed 6 to 24 h if no signal change on fluid-attenuated inversion recovery (FLAIR).

†Allowed Alberta Stroke Program Early CT Score (ASPECTS) 0 to 2 if core volume on computed tomography perfusion (CTP) was 70 to 100 mL; also allowed ASPECTS ≥6 h if core volume on CTP was 70 to 100 mL.

‡Allowed ASPECTS ≥6 if core volume on CTP >50 mL.

in the MM group, 525 of 942 patients (55.7%) were men. The mean ages of the patients enrolled were mid- to late 60s in the trials with upper age limits, and mid-70s in the 2 without upper age limits. Median National Institutes of Health Stroke Scale score ranged from 16 to 22. Across all trials, 930 patients were randomized within 6 hours of the LKW time, and an additional 153 patients were randomized on the basis of MRI evidence of early onset, totaling 1083 (57%) of the 1887 patients. At least 433 patients were enrolled at >12 hours from LKW, and 1130 within 12 hours. IVT was given in 265 (28%) patients in the EVT group, compared with 254 (27.0%) in the MM group. Large vessel involvement included 714 (37.3%) in the internal carotid artery, 1164 (60.8%) in the M1 middle cerebral artery, and 35 cases of M2 occlusions. See details in Tables S2 and S3.

Table 3. Study Planned Recruitment and End Points

Trial design	Planned sample, n	Primary outcome, 90 d	Secondary outcomes, <1 d	Secondary outcomes, 1–3 d	Secondary outcomes, 1 wk	Secondary outcomes, 90 d	Secondary outcomes, 180 d	Secondary outcomes, 360 d
RESCUE-Japan LIMIT[18]	203	mRS 0–3	NA	NIHSS improvement ≥8, sICH, ICH	Decompressive craniectomy rate	mRS (0–2, 0–1), mRS shift, death, new AIS	NA	NA
ANGEL-ASPECT[19]	488	Shift mRS	NA	NIHSS 0–1 or improved ≥10, infarct volume change, ICH, recanalization	Decompressive craniectomy rate	mRS (0–2, 0–3), death	NA	NA
SELECT2[20]	560	Shift mRS	sICH, NIHSS worsening ≥4	AE, infarct volume	LOS, NIHSS	QoLa, mRS (0–2), death	NA	NA
TESLA[21]	300	Utility–weighted mRS	sICH, NIHSS, recanalization	NA	NA	NA	NA	NA
TENSION[22]	665	Shift mRS	Infarct volume, growth, sICH	NA	AE, death, malignant edema, new AIS	mRS (0–2, 0–3), QoLb, ICH	NA	mRS (4–6), new AIS, QoL, cost analysis
LASTE[23]	450	Shift mRS	sICH, AE	Infarct volume growth	NIHSS 0–1 or NIHSS decrease ≥8	mRS (0–2, 0–3), death	mRS (0–2, 0–3, 5–6), QoLc, DC rate, cost analysis	NA

AE indicates adverse event; AIS, acute ischemic stroke; ANGEL-ASPECT, Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; DC, decompressive craniectomy; ICH, intracerebral hemorrhage; LASTE, Large Stroke Therapy Evaluation; LOS, length of stay; mRS, modified Rankin Scale; NA, not available, NIHSS, National Institutes of Health Stroke Scale; QoL, quality of life; QoLa, Neuro-QoL; QoLb, PROMIS-10, EQ-5D, PHQ-4; QoLc, EuroQol 5D-5L; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial; SELECT2, SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; sICH, symptomatic intracerebral hemorrhage; TENSION, The Efficacy and Safety of Thrombectomy in Stroke; and TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke.

Baseline Imaging Characteristics

Of the 1914 vascular occlusion sites, 1878 (98.11%) were in the internal carotid artery and the proximal (M1) middle cerebral artery. Only 36 (1.88%) were reported as M2 occlusions. See details in Table S1.

Among the 1887 patients, 1475 (78.2%) had baseline ASPECTS 3 to 5, and 320 (16.9%) had ASPECTS 0 to 2. LASTE contributed 181 participants (56.6%) with ASPECTS 0 to 2, and the majority were assessed by MRI. According to the central imaging evaluations, 90 participants (5%) had ASPECTS 6 to 10. Tables S4 and S5 describe imaging features of enrolled patients.

In studies that reported ischemic core volumes based on CTP or MRI,[19,20,23] out of 1131 patients, 654 (57.8%) had core volumes <100 mL, 289 (25.5%) had core volumes 100 to 150 mL, and 188 (16.6%) had volumes >150 mL. LASTE contributed 133 (70.7%) of the patients with cores >150 mL. See details in Table S6.

Primary and Secondary End Points

Table 4 and Figure 1 present a summary of the event rates for the primary and secondary end points.

Functional Independence

Higher rates of functional independence were observed after EVT compared with MM in all trials. The difference was most apparent in ANGEL-ASPECT, in which 30% of EVT-treated patients achieved functional independence, compared with 11.6% of those receiving MM. Other trials showed more modest but still favorable results for EVT.

Only one-fifth of patients (19.5%) treated with EVT achieved functional independence across all of the trials. This underscores the severe disease in this patient population. However, this rate is more than double that of MM (7.5%), suggesting a number needed to treat of ≈8 to prevent 1 functionally dependent outcome.

Independent Ambulation

Independent ambulation was achieved more frequently by patients treated with EVT. ANGEL-ASPECT most notably underscored this advantage, with 47.0% of patients receiving EVT regaining the ability to walk independently versus 33.3% for MM. SELECT2 also demonstrated EVT's benefit, although with a slightly narrower gap of 37.9% for EVT versus 18.7% for MM. This pattern persisted throughout the trials, confirming the robustness of the effects of EVT on mobility outcomes.

Symptomatic Hemorrhage

Symptomatic hemorrhage rates were relatively low for both treatment modalities across all trials, with numerically but not significantly higher rates in EVT groups compared with MM groups. Several trials did not include subarachnoid hemorrhage as a qualifying symptomatic hemorrhage. TESLA showed the largest difference among the trials, reporting symptomatic hemorrhage rates of 4.0% for EVT compared with 1.3% for MM. Whereas EVT is an invasive procedure, it did not demonstrate a substantial increase in the risk of symptomatic hemorrhage compared with MM.

Decompressive Craniectomy

In the case of decompressive craniectomy, the data did not indicate a consistent advantage for either treatment approach across the trials. TESLA showed a numerically but not statistically higher rate of decompressive craniectomies in the EVT group (21.9%) relative to the MM group (15.1%). SELECT2 lacked data for this outcome. The remainder of the trials also did not show a significant difference in the rate of this type of intervention.

Table 4. Summary of Clinical End Points: Absolute Event Rates

	End points, n (%)									
	Functional independence		Independent ambulation		Symptomatic hemorrhage		Decompressive craniectomy		Death	
Trial name	EVT	MM	EVT	MM	EVT	MM	EVT	MM	EVT	MM
RESCUE-Japan LIMIT[18]	14 (14.0)	8 (7.8)	31 (31.0)	13 (12.7)	9 (9.0)	5 (4.9)	10 (10.0)	14 (13.7)	18 (18.0)	24 (23.5)
ANGEL-ASPECT[19]	69 (30.0)	26 (11.6)	108 (47.0)	75 (33.3)	14 (6.1)	6 (2.7)	17 (7.4)	8 (3.6)	50 (21.7)	45 (20.0)
SELECT2[20]	36 (20.3)	12 (7.0)	67 (37.9)	32 (18.7)	1 (0.6)	2 (1.2)	NA	NA	68 (38.4)	71 (41.5)
TENSION[21]	21 (16.9)	3 (2.4)	39 (31.4)	16 (13.1)	7 (5.6)	6 (5.1)	11 (8.8)	9 (7.0)	49 (39.2)	63 (51.2)
TESLA[22]	22 (14.6)	13 (8.9)	45 (29.8)	29 (19.9)	6 (4.0)	2 (1.3)	33 (21.9)	22 (14.8)	53 (35.3)	49 (33.3)
LASTE[23]	21 (13.3)	8 (4.9)	53 (33.5)	20 (12.2)	15 (9.6)	9 (5.7)	14 (8.8)	19 (11.5)	57 (36.1)	91 (55.5)
Total %	183 (19.5)	70 (7.5)	343 (36.5)	185 (19.9)	52 (5.5)	30 (3.3)	85 (11.1)	72 (9.5)	295 (31.5)	343 (36.8)
Treatment effect*	12		16.6		−2.2		−1.6		5.3	

ANGEL-ASPECT indicates Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core; LASTE, Large Stroke Therapy Evaluation; MM, medical management; NA, not available; RESCUE-Japan LIMIT, Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial; SELECT2, SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; TENSION, The Efficacy and Safety of Thrombectomy in Stroke; and TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke.

*Positive numbers indicate the advantage of endovascular thrombectomy (EVT).

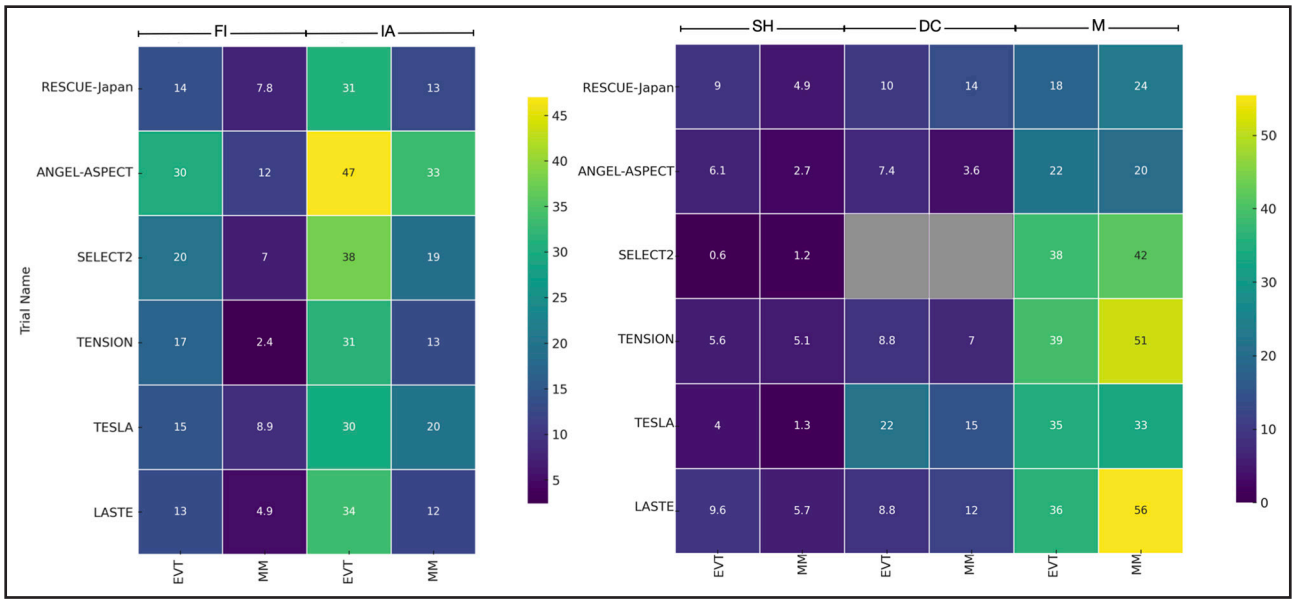

Figure 1. Comparative outcomes of endovascular therapy and medical management across clinical trials.
Heatmaps display the comparative endovascular thrombectomy (EVT) and medical management (MM) results for the clinical trial outcomes: functional independence (FI), independent ambulation (IA), symptomatic hemorrhage (SH), decompressive craniectomy (DC), and mortality (M). Each cell represents the proportion of a specific outcome within a trial, color-coded from yellow (lower proportions) to dark blue (higher proportions). The color scale represents the proportion of outcomes, with yellow indicating lower values and dark blue indicating higher values. Trials included RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial)[18]; ANGEL-ASPECT (Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core)[19]; SELECT2 (SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke)[20]; TENSION (The Efficacy and Safety of Thrombectomy in Stroke)[21]; TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke)[22]; and LASTE (Large Stroke Therapy Evaluation).[23]

Mortality Risk

Mortality outcomes were nominally favorable for EVT in 4 of the 6 clinical trials. In TESLA and ANGEL-ASPECT, mortality rates were numerically greater for EVT, but the differences were not significant. TENSION and LASTE found a statistically significant advantage of EVT over MM in mortality rates, whereas in RESCUE-Japan LIMIT and SELECT2, the differences were not significant.

Analysis of Adjusted Primary End Points

In the original analysis of each study, the primary end points of the 6 trials were presented as adjusted ORs for confounding variables. A simple comparison of raw proportions could overlook these adjustments. To reflect the study outcomes accurately, the combined OR calculated using the generic inverse variance method was used. The results of that analysis are summarized in Figure 2.

Analysis of Study Strengths and Limitations

The 6 published clinical trials were similar in their execution; they all were individually randomized and open-labeled, and had blinded end point assessments. The risk of internal bias from the randomization process, missing outcome data, measurement of the outcomes, and selection of the reported result (based on predetermined relevant clinical outcomes) was considered low by consensus. There was some concern of bias attributable to deviations from the intended interventions, which occurred in all the studies. Protocol violations were limited in number overall, except in TENSION, with 25% to 30% protocol violations, primarily because of core laboratory ASPECTS values exceeding the intended range in the inclusion criteria. The open-label design may also influence deviations from the intended interventions. Generalizability considerations are addressed in the Discussion.

The certainty of the results obtained for the primary end point—functional independence—and independent ambulation is high. The findings regarding symptomatic ICH have lower certainty because of the inconsistency of results across clinical trials and the overlapping 95% CI with the noninterventional group.

Summary Analysis of Primary End Point Results

The combined analysis of the 6 clinical trials, using the generic inverse variance method, produced a combined OR of 1.57 (95% CI, 1.40–1.76). Across all studies, EVT treatment is associated with a statistically significant increase in the likelihood of a favorable shift in the mRS at 90 days compared with MM, with adjustments

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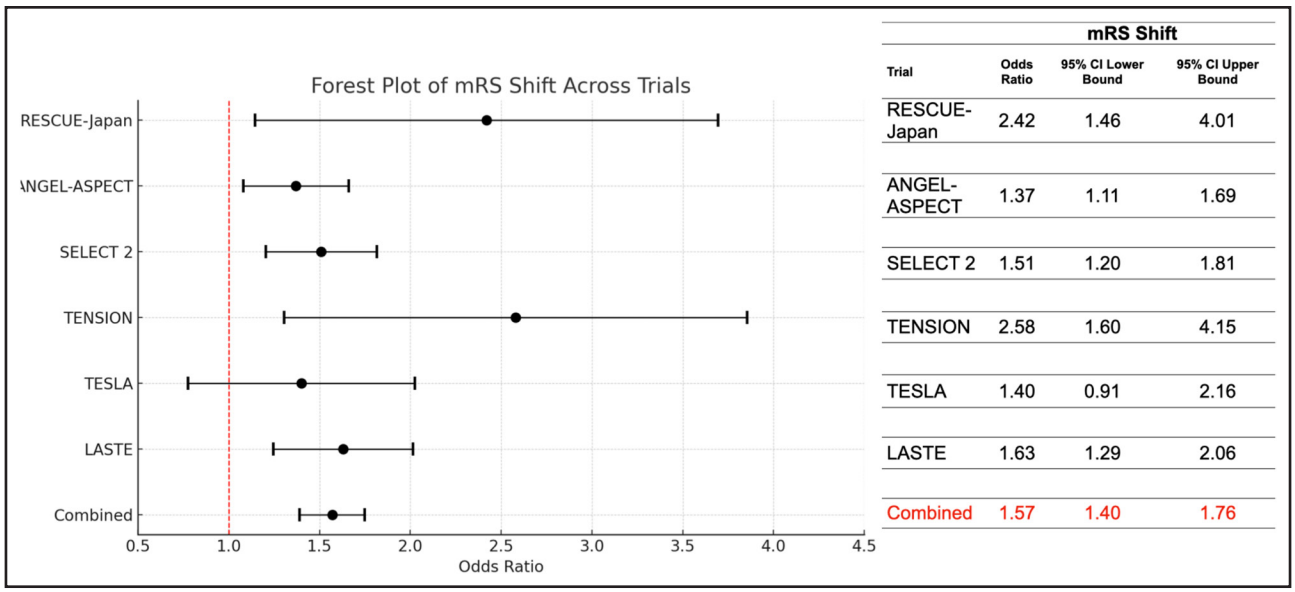

	mRS Shift		
Trial	Odds Ratio	95% CI Lower Bound	95% CI Upper Bound
RESCUE-Japan	2.42	1.46	4.01
ANGEL-ASPECT	1.37	1.11	1.69
SELECT 2	1.51	1.20	1.81
TENSION	2.58	1.60	4.15
TESLA	1.40	0.91	2.16
LASTE	1.63	1.29	2.06
Combined	1.57	1.40	1.76

Figure 2. Forest plot of adjusted odds ratios for clinical trials and summary of odds ratios.
This forest plot illustrates the adjusted odds ratios (ORs) and 95% CIs for the 6 clinical trials evaluating the shift in modified Rankin Scale (mRS) scores. Each row represents a different trial, with the point estimates of the ORs displayed as black dots and the 95% CIs shown as horizontal lines. The red vertical dashed line at an OR of 1.0 indicates no effect. The "combined" row at the bottom represents the meta-analytical pooled OR, indicating a significant effect in favor of endovascular therapy. Trials included RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism—Japan—Large Ischemic Core Trial)[18]; ANGEL-ASPECT (Study of Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core)[19]; SELECT2 (SELECT2: A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke)[20]; TENSION (The Efficacy and Safety of Thrombectomy in Stroke)[21]; TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke)[22]; and LASTE (Large Stroke Therapy Evaluation).[23]

for confounding variables maintained, as detailed in Figure 2. A recent meta-analysis of these 6 clinical trials[24] reported unadjusted combined OR of 1.49 (95% CI, 1.24–1.79), aligning with our summary analysis.

The τ^2 evaluations (0.0180) indicate that the estimated variance between studies is relatively low, showing moderate variability in effect sizes attributable to heterogeneity. The I^2 statistic 45.13% suggests moderate heterogeneity among the studies. An I^2 value of 45% indicates that ≈45% of the total variability in effect size estimates is attributable to heterogeneity rather than sampling error. The χ^2 test for heterogeneity showed a nonsignificant *P* value of 0.10, indicating that although there is some variation, it is not conclusively more than expected by chance. The analysis of heterogeneity summarized in the Figure S1 L'Abbé plot indicates moderate heterogeneity among studies despite the consistently positive effects of EVT compared with MM.

GENERALIZABILITY OF THE RESULTS

None of the subgroups examined in individual trials showed heterogeneity in the treatment effect, but those analyses were limited by power and must be considered in the context of the characteristics of those enrolled.

Patient-level pooled data are not available for precise considerations. However, based on a review of eligibility criteria and aggregate data from the individual trials, the generalizability of the results requires further consideration for the following subgroups.

1. Advanced age and vessel tortuosity: Among the 780 participants in the 3 trials that included participants >85 years of age (LASTE, RESCUE-Japan LIMIT, and TENSION), <25% of participants exceeded this age. This may be related to exclusion criteria of vessel tortuosity (TENSION and LASTE), restricted amounts of large core (only ASPECTS 4 or 5 in patients ≥80 years of age in LASTE), and prestroke disability.
2. Prestroke disability: All but 1 trial required no previous disability (prestroke mRS 0 or 1) for eligibility. TENSION allowed prestroke disability if the patient remained functionally independent (prestroke mRS 2). Available data from patients with ASPECTS ≥6 suggest that prestroke disability may not affect the magnitude of treatment effect of EVT, particularly for those with prestroke mRS 2 or 3.[25–29] Whether this can be extrapolated to patients with LCIS has not been evaluated.
3. Extended time from stroke onset: Close to 70% of patients were enrolled within 12 hours of LKW or showed fluid-attenuated inversion recovery–diffusion-weighted imaging mismatch to support early onset. Only ANGEL-ASPECT, SELECT2, and TESLA allowed enrollment of patients beyond 11 and up to 24 hours from onset with special

imaging selection. Based on published interquartile ranges, <25% of ANGEL-ASPECTS participants (n=455) were beyond 12 hours LKW, and <25% of SELECT2 (n=352) and TESLA (n=300) participants were beyond 16 hours LKW.

4. Large core by ASPECTS: Among the 6 trials, 319 of 1887 participants (16.9%) had ASPECTS 0 to 2. More than half (n=181) were enrolled in LASTE, and participants were selected primarily on the basis of MRI–diffusion-weighted imaging, which is more sensitive to early ischemic change than CT, and enrolled predominantly within 6.5 hours of LKW. A minority (n=11) were enrolled in TESLA. The remainder were enrolled outside of eligibility criteria for the respective trials.[23]
5. Large core volumes by perfusion imaging: In the 3 studies with core volumes assessed by CTP or MRI–diffusion-weighted imaging (SELECT2, LASTE, and ANGEL-ASPECTS), only 188 of 1131 participants (16.6%) had core volumes >150 mL, and the majority (70.7%) were from LASTE, which enrolled patients predominantly within 6.5 hours from LKW and predominantly by MRI[20,23] (Xiaochuan Huo, MD, unpublished data from ANGEL-ASPECTS, March 4, 2024).
6. Core assessment as a summation of NCCT and CTP data: In routine clinical practice, when assessing patients with CTP in the extended time window, core volume is assessed by CTP in combination with any additional hypodensity present on CT, but not visualized on CTP, to capture the full extent of irreversible injury.[14] ANGEL-ASPECTS selected patients with additional CTP criteria only as a substitute for low (<3) or high (>5) ASPECTS. SELECT2 selected participants on the basis of the larger of the 2 assessments: ASPECTS by NCCT or core volume by CTP.
7. No-mismatch profiles on CTP or magnetic resonance perfusion: Data on whether enrolled participants would meet core–penumbra mismatch criteria are only available for SELECT2 and ANGEL-ASPECTS. In SELECT2, among 329 patients with data that were enrolled up to 24 hours from LKW, only 31 (9%) showed no mismatch (ie, ratio <1.2 and mismatch volume <10 mL). Among 426 patients in ANGEL-ASPECTS enrolled up to 24 hours from LKW, only 31 (7%) had no mismatch (Xiaochuan Huo, MD, unpublished data from ANGEL-ASPECTS, March 4, 2024).
8. IVT use: Large core features are typically not an exclusion criterion for IVT if a patient presents within 4.5 hours of LKW. Whereas the rates of IVT use in the trials (20%–40%) may be consistent with more participants at >4.5 hours from LKW, it raises the possibility that those within 4.5 hours of LKW were offered IVT less frequently in these trials. Further data are needed to assess generalizability in this regard.

The diverse geographic recruitment across centers in the United States, China, Japan, and European countries, among others, enhances the external validity of the study results, albeit with the notable absence of participants from low- and middle-income countries.

FUTURE CONSIDERATIONS

The results of these 6 trials reframe current evidence regarding the role of reperfusion therapies in those with larger areas of presumed irreversible ischemia. The benefit of EVT in this setting may reflect the prevention of further infarct expansion or potentially improved tissue outcomes within ischemic beds.[30] Further research is needed to elucidate the mechanisms at play.

Additional clinical data and analyses are pending from recently completed trials. Patient-level pooled clinical and imaging data might provide important insights that were not elucidated by individual trials, such as the role of advanced imaging, considerations for patient prognostication, and communication with families. Upcoming secondary end point data on quality of life will offer a further assessment of a patient's well-being after treatment, covering dimensions not captured by the mRS. Related analyses are also needed to quantify the cost-effectiveness of thrombectomy in this patient population. Post hoc studies to assess the degree of hypodensity in the large core region as a prognostic indicator or effect modifier are also awaited.[31]

CONCLUSION

The results from these 6 clinical trials examining the efficacy of EVT provide strong evidence of its benefit in patients who have good prestroke functional status (mRS 0–1) and substantial stroke severity (National Institutes of Health Stroke Scale score ≥6) with occlusion of the internal carotid artery or proximal middle cerebral artery and a large ischemic core (ASPECTS 3–5) on initial imaging. Data are limited to support EVT treatment of patients with matched core/perfusion, advanced age, or large core (ASPECTS 0–2) beyond 6 hours from LKW. Further appraisal of the EVT effects in the subgroups underrepresented in the trials is essential to determine the generalizability of the results to those cases.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

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*Modest.

†Significant.

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