Endovascular therapy for anterior circulation emergent large vessel occlusion stroke in patients with large ischemic cores: a report of the SNIS Standards and Guidelines Committee

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ABSTRACT

Background Early clinical trials validating endovascular therapy (EVT) for emergent large vessel occlusion (ELVO) ischemic stroke in the anterior circulation initially focused on patients with small or absent completed infarctions (ischemic cores) to maximize the probability of detecting a clinically meaningful and statistically significant benefit of EVT. Subsequently, real-world experience suggested that patients with large core ischemic strokes (LCS) at presentation may also benefit from EVT. Several large, retrospective, and prospective randomized clinical trials have recently been published that further validate this approach. These guidelines aim to provide an update for endovascular treatment of LCS.

Methods A structured literature review of LCS studies available since 2019 and grading the strength and quality of the evidence was performed. Recommendations were made based on these new data by consensus of the authors, with additional input from the full SNIS Standards and Guidelines Committee and the SNIS Board of Directors.

Results The management of ELVO strokes with large ischemic cores continues to evolve. The expert panel agreed on several recommendations: Recommendation 1: In patients with anterior circulation ELVO who present within 24 hours of last known normal with large infarct core (70–149 mL or ASPECTS 3–5) and meet other criteria of RESCUE-Japan LIMIT, SELECT2, ANGEL-ASPECT, TESLA, TENSION, or LASTE trials, thrombectomy is indicated (Class I, Level A). Recommendations 2–7 flow directly from recommendation 1. Recommendation 2: EVT in patients with LCS aged 18–85 years is beneficial (Class I, Level A). Recommendation 3: EVT in patients with LCS >85 years of age may be beneficial (Class I, Level B-R). Recommendation 4: Patients with LCS and NIHSS score 6–30 benefit from EVT in LCS (Class I, Level A). Recommendation 5: Patients with LCS and NIHSS score <6 and >30 may benefit from EVT in LCS (Class IIa, Level A). Recommendation 6: Patients with LCS and low baseline mRS (0–1) benefit from EVT (Class I, Level A). Recommendation 7: Patients with LCS and time of last known well 0–24 hours benefit from EVT (Class I, Level A). Recommendation 8: It is recommended that patients with ELVO LCS who also meet the criteria for on-label or guideline-directed use of IV thrombolysis receive IV thrombolysis, irrespective of whether endovascular treatments are being considered (Class I, Level B-NR).

Conclusions The indications for endovascular treatment of ELVO strokes continue to expand and now include patients with large ischemic cores on presentation. Further prospective randomized studies, including follow-up to assess the population-based efficacy of treating patients with LCS, are warranted.

INTRODUCTION

The advent of mechanical thrombectomy (MT) created the realistic possibility of reversing neurological deficits with successful recanalization of emergent large vessel occlusion (ELVO) acute ischemic strokes. Reticence to perform thrombectomy in many places around the world following the relatively disappointing IMS-3, SYNTHESIS, and MR RESCUE studies in 2013[1] swung the pendulum of treatment to one extreme, only to return to a more moderate position just a few years later with the publication of MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, DAWN, and DEFUSE3. With further rapid evolution of the field, MT became the first-line therapy for patients with large vessel occlusions.[2] The studies that paved the way for this generally excluded patients with large core ischemic stroke (LCS) (Alberta Stroke Program Early CT Score (ASPECTS) <6 or ischemic core ≥70 mL) despite the frequent presence of a penumbra. Retrospective studies, prospective studies, and meta-analyses have suggested that a subset of these excluded patients would benefit from MT.[3–9] Recently published prospective trials concluded that patients fared better with MT, even accounting for the increased rate of hemorrhagic complications.[8 9] The implications are significant for individual patients and society; thus, it is imperative to establish which patients with large core infarcts are likely to benefit from MT.

Endovascular therapy (EVT) consisting of MT dramatically improves clinical outcomes for patients with ELVO strokes. In this paper the SNIS Standards and Guidelines Committee updates and supplements the existing SNIS guidelines 'Embolectomy

for stroke with emergent large vessel occlusion (ELVO)' (2015 SNIS Guideline) and 'Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO)' (2019 SNIS Guideline), focusing on the application of data from new trials on patients with anterior circulation ELVO with large ischemic cores at presentation.[2 10 11]

METHODS

A structured literature review of studies that have become available since the 2019 SNIS Guidelines was performed. Recommendations were developed based on the existing literature that has become available, discussions regarding the interpretation of the literature, and the collective experience of the writing group members. Experts from North American academic institutions from neurosurgery, neurology, and interventional neuroradiology were recruited based on their expertise. A computerized search of the MEDLINE database (PubMed) from January 1, 2019 to December 1, 2023 was performed using search terms including 'large core', 'large ischemic core', 'emergent large vessel occlusion stroke', 'treatment', and 'endovascular' to identify published articles on the endovascular treatment of patients with large vessel occlusion strokes and large ischemic cores (with LCS defined as ≥70 mL). Relevant English language articles were taken into consideration while writing this consensus paper. The literature review included randomized controlled trials, case series, and non-randomized single-center studies. The strength and quality of the evidence were graded. Recommendations were determined by consensus of the authors, with additional input from the full SNIS Standards and Guidelines Committee and the SNIS Board of Directors.

RESULTS

Anterior circulation stroke with large ischemic core: recent trials and meta-analyses

EVT has been the standard of care for patients with anterior circulation ELVO and small to medium-sized ischemic cores (ASPECTS 6–10 and core volumes <70 mL) for several years. LCS were not included in prior trials due to concerns over hemorrhagic risk and futility. The SELECT2, ANGEL-ASPECT, RESCUE-Japan LIMIT, TESLA, and TENSION trials (as well as preliminary results from LASTE and MAGNA) challenge this previous limitation and demonstrate the benefit of MT of the intracranial internal carotid artery (ICA) and M1 middle cerebral artery (MCA) in patients with larger baseline ischemic cores.[8 9 12]

The Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMIc core Trial (RESCUE-Japan LIMIT),[12] a multicenter, open-label, randomized clinical trial in Japan, randomized 203 patients with either CT or MR ASPECTS 3–5, although MRI was used for triage most often (in 86% of patients). The percentage of patients achieving a modified Rankin scale (mRS) score of 0–2 at 90 days was 14.0% in the EVT group versus 7.8% in the standard medical management (MM) group. The ordinal shift of mRS scores favored EVT. The incidence of symptomatic intracranial hemorrhage (sICH) was not significantly higher with EVT than with standard medical care.

The Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2) trial enrolled 352 patients with LCS defined as ASPECTS 3–5 or CT perfusion-derived core volume >50 mL.[8] Note that SELECT2 includes patients with infarct cores of 50–70 mL, in contradistinction to the other LCS trials. The patients were enrolled from the USA, Canada, Europe, Australia, and New Zealand to undergo EVT and receive standard medical care or to receive standard medical care alone within 24 hours since last known well (LKW). EVT was associated with a 90-day mRS score of 0–2 in 20% in the EVT group versus 7% in the standard MM group. Rates of sICH were similar between the groups. Furthermore, EVT reduced by 50% the number of patients with mRS 5.[13]

The Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ANGEL-ASPECT) trial randomized 456 patients in China with ELVO ischemic stroke and LCS, defined as ASPECTS 3–5, core infarct volume 70–100 mL, presenting within 24 hours since LKW.[9] Results at 90 days were mRS 0–2 in 30% of the EVT group versus 11.6% in the standard MM group. Like SELECT2, EVT reduced by 50% the number of patients with mRS 5.[13]

The Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke Trial (TESLA), which treated 300 patients with ASPECTS 2–5, was presented in May 2023 at the European Stroke Organization Conference. Although TESLA did not meet its primary intention-to-treat analysis of EVT superiority over medical treatment (90-day utility weighted mRS), multiple secondary efficacy endpoints did favor EVT, and its results were broadly in the direction of benefit for thrombectomy.[14] EVT was associated with 90-day mRS 0–3 in 30% of patients compared with 20% of patients in the MM arm (OR 1.6, P=0.03). sICH occurred in 3.97% in the EVT arm and 1.34% in the MM arm. Major neurological improvement was seen in 26% of patients in the EVT group and 13% in the MM group (P=0.0008). The treatment effect of EVT was smaller in the TESLA trial (9.9%) than in the RESCUE-Japan LIMIT (18.3%), ANGEL-ASPECT (13.7%), and SELECT2 (19.2%) trials.

The Endovascular Thrombectomy for Acute Ischaemic Stroke with Established Large Infarct: Multicentre, Open-label, Randomised Trial (TENSION) was a prospective multicenter, open-label, randomized trial which randomized 253 patients with ASPECTS 3–5 presenting within 12 hours of symptom onset to receive either EVT with medical treatment or medical treatment alone.[15] The trial was stopped early after 222 patients reached the primary outcome for efficacy at the first pre-planned interim analysis, revealing an ordinal shift of mRS towards a better outcome in the EVT cohort (adjusted common OR 2.58 (95% CI 1.60 to 4.15); P=0.0001), with lower mortality (HR 0.67 (95% CI 0.46 to 0.98); P=0.038) and no significant difference in sICH (6% vs 5%).

The Large Stroke Therapy Evaluation (LASTE) trial for the treatment of patients with LCS including ASPECTS 0–5 presenting within 7 hours from LKW was presented in November 2023 at the Society of Vascular and Interventional Neurology Annual Meeting. The trial had a planned sample size of 450, but was terminated early for ethical reasons after the publication of ANGEL-ASPECTS and SELECT2. At the time of termination 333 patients had been randomized; 159 to medical therapy plus MT and 165 to medical therapy alone. Data for 3- and 6-month follow-up were presented, showing an ordinal shift of mRS towards a better outcome in patients receiving MT (GenOR 1.63 (95% CI 1.29 to 2.06), P<0.0001) as well as lower mortality and a significant reduction in infarct growth and 24-hour infarct volumes (119.5 mL vs 51.6 mL). While all patients with LCS had high rates of poor outcomes and mortality, core size was found not to be a treatment effect modifier, allowing the authors to suggest that core size alone should not exclude patients from receiving EVT.

Sarraj *et al* presented a patient-level data meta-analysis of more than 1000 patients from SELECT2, ANGEL-ASPECT,

and RESCUE-Japan LIMIT at the 2023 European Stroke Organization Conference. MAGNA (MechanicAl thrombectomy for larGe braiN infArctions) demonstrated meaningful improvement in mRS shifts (with good outcomes defined as either mRS 0–2 or mRS 0–3) for patients with ASPECTS 3, ASPECTS 4, and ASPECTS 5 who underwent EVT.[16] This positive result was also evident for patients with ischemic cores of <70 mL (OR 1.97, 95% CI 1.27 to 3.05), 70–99 mL (OR 1.77, 95% CI 1.30 to 2.39), and 100–149 mL (OR 1.94, 95% CI 1.49 to 2.51). Notably, EVT did not show a statistically significant benefit in the cohort of patients with ischemic cores of ≥150 mL (OR 1.2, 95% CI 0.83 to 1.73).

Despite differences in design, methodology, and inclusion/exclusion criteria, recently published trials have demonstrated benefits of EVT on mortality, severe morbidity (reducing the proportion of patients who survive with mRS 5 disability), and more traditional good functional outcomes (mRS 0–2). The results of these studies and the more recently reported, but not yet published, TESLA trial and MAGNA meta-analysis support the use of EVT for patients with ELVO compared with standard MM, thus warranting re-examination of treatment guidelines.[2 10]

Recommendation 1: In patients with anterior circulation ELVO who present within 24 hours of last known normal (LKN) with large infarct core (70–149 mL or ASPECTS 3–5) and meet other criteria of RESCUE-Japan LIMIT, SELECT2, ANGEL-ASPECT, TESLA, TENSION, or LASTE trials, thrombectomy is indicated (Class I, Level A)

Clinical selection criteria

Age

Eligibility for enrollment by age in SELECT2, ANGEL-ASPECT, RESCUE-Japan LIMIT, TESLA, TENSION, and LASTE trials differed slightly, although they all enrolled patients aged 18–80 years. The RESCUE-Japan LIMIT trial had no upper age limit, SELECT2 and TESLA enrolled patients up to 85 years of age, ANGEL-ASPECT and LASTE allowed a maximum age of 80 years, and TENSION enrolled patients 18 years and older (table 1). The mean age was greater in the RESCUE-Japan LIMIT trial due in part to the fact that there was no upper age limit.

Age-based subgroup analysis (SELECT2) showed better functional recovery at 90 days (as reflected by a shift in the distribution of mRS scores towards more favorable outcomes) in the EVT group compared with the medical care group for both younger (patients <70 years of age, OR 1.66, IQR 1.22–2.27) and older patients (≥70 years of age, OR 1.36, IQR 1.01–1.84). ANGEL-ASPECT showed a functional recovery benefit at 90 days for patients <75 years of age undergoing MT versus medical care only (OR 1.39, IQR 1.09–1.76), but there was no benefit for patients ≥75 years of age (OR 1.36, IQR 0.84–2.19).

Table 1 Age of patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ANGEL-ASPECT (EVT vs MM)
Age, target enrollment	≥18 years	18–85 years	18–80 years
Age, actual enrollment	76.6 vs 75.7	66 vs 67	68 vs 67
	TESLA	**LASTE**	**TENSION**
Age, target enrollment	18–85 years	≥18 years	>18 years
Age, actual enrollment	66 vs 67.5	73 vs 74	73 vs 74

EVT, endovascular therapy; MM, medical management.

The opposite was found in RESCUE-Japan LIMIT: patients ≥75 years of age showed functional benefit of EVT over MM (OR 3.05, IQR 1.19–7.89), but not in the <70 years subgroup (OR 2.05, IQR 0.98–4.27). However, the trials were not powered to allow definite conclusions for these age-based subgroup analyses. There was no significant effect modification for EVT based on age <70 years or >70 years in the TESLA and LASTE trials. Because the TENSION trial was halted early due to efficacy, the study was underpowered to complete subgroup analysis. However, the results of subgroup assessment, including age, were generally in favor of EVT.

Recommendation 2: EVT in patients with LCS aged 18–80 years (5 RCT evidence) and 80–85 years of age (4 RCT evidence) is beneficial (Class I, Level A)

Recommendation 3: EVT in patients with LCS >85 years of age (2 RCT) may be beneficial (Class I, Level B-R)

NIHSS score

In the SELECT2 trial the NIHSS score on hospital arrival was not part of the selection criteria to participate but was recorded. The RESCUE-Japan LIMIT trial included patients with an NIHSS score ≥6 whereas the ANGEL-ASPECT trial only included patients with an NIHSS score of 6–30. Therefore, there are randomized controlled trial (RCT) data from three trials for patients with large volume strokes with an NIHSS score of 6–30 and two RCTs with patients included with an NIHSS score of >30 (table 2). The NIHSS score was also used to define early neurological improvement (reduction of ≥8 points from baseline to 24 hours after presentation in the SELECT2 trial, ≥8 points 8 hours after presentation in the RESCUE-Japan LIMIT trial, and ≥10 points at 36 hours after randomization in the ANGEL-ASPECT trial) and neurological worsening (an increase of ≥4 points in the NIHSS score within 24 hours after presentation in the SELECT2 trial and 48 hours after randomization in the ANGEL-ASPECT and RESCUE-Japan LIMIT trials).

In the RESCUE-Japan LIMIT trial the median NIHSS score of 22 was higher than in the other two trials, with a median of 22 in the EVT cohort (IQR 18–26) and the MM group (IQR 17–26). Both subgroups above and below a cut-off NIHSS score of 21 favored EVT over MM: patients with an NIHSS score <21 (n=87) had an OR of 2.22 (IQR 0.76–6.55) and patients with an NIHSS score ≥21 (n=115) had an OR of 3.21 (IQR 1.12–9.16).

In SELECT2, the median NIHSS score was 19 (IQR 15–23) at hospital arrival, with a median NIHSS of 19 (IQR 15–23) for the EVT group and 19 (IQR 15–22) for the MM group. Subgroup analysis showed better functional recovery at 90 days for patients with baseline NIHSS <20 (n=197, OR 1.53, IQR 1.12–2.10 and NIHSS ≥20 (n=155, OR 1.52, IQR 1.12–2.07) undergoing MT versus MM only.

In ANGEL-ASPECT, the median baseline NIHSS score of 16 was similar to that in SELECT2, and given the NIHSS range of 6–30 as an inclusion criterion for the trial, 20 patients were excluded during screening due to an NIHSS score other than 6–30. Two additional patients were excluded after being randomized into the endovascular arm before treatment worsening to an NIHSS score >30. The NIHSS score was slightly higher in the EVT group (median 16, IQR 13–20) than in the MM cohort (median 15, IQR 12–19). The cut-off for subgroup analysis was defined as an NIHSS score of <16 versus ≥16, and patients with an NIHSS score of <16 who underwent EVT had a better functional recovery at 90 days (n=219, OR 1.62, IQR 1.18–2.23)

Table 2 NIHSS score in patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ASPECT-ANGEL (EVT vs MM)
NIHSS at time of randomization, target	≥6	N/A	6–30
NIHSS, actual enrollment (median)	22 vs 22	19 vs 19	16 vs 15
	TESLA	**LASTE**	**TENSION**
NIHSS at time of randomization, target	>6	≥6	<26
NIHSS, actual enrollment (median)	19 vs 18	21 vs 21	19 vs 18

EVT, endovascular therapy; MM, medical management; NIHSS, National Institutes of Health Stroke Scale.

compared with MM only. In patients with a baseline NIHSS score of ≥16 at baseline there was no benefit of EVT over MM (n=236, OR 1.31, IQR 0.98–1.75).

In the TESLA trial the median baseline NIHSS score was 19 (IQR 15–23) in the EVT group and 18 (IQR 14.5–21) in the MM cohort. Patients receiving EVT showed significantly greater rates of major neurological improvement at 90 days following treatment (26% vs 13%, P=0.0008). Patients receiving IA therapy also tended to have a lower mean NIHSS score at 5–7 days/discharge relative to those who received MM (15.3 vs 16.4, P=0.117). Subgroup analysis showed no difference in the effect of EVT when stratified by NIHSS score of <16 versus ≥16.

In TENSION, patients with an NIHSS score <26 were included. Similar to TESLA, the median baseline NIHSS score was 19 in the EVT group and 18 in the MM arm. Although underpowered to detect significance, subgroup analysis tended to favor EVT in patients with an NIHSS score <18 (OR 3.54, 1.89–6.66) as well as those with an NIHSS score >18 (OR 1.73, 0.87–3.47).

In LASTE, patients with an NIHSS score ≥6 were included. The median NIHSS score at randomization was the same for both groups at 21 (IQR 18–24). NIHSS was used to assess rapid neurologic decline, which was observed to occur more frequently in the MM arm (32% vs 36.1%, RR 0.89, 0.64–1.21).

Recommendation 4: Patients with LCS and NIHSS 6–30 (5 RCT evidence) benefit from EVT in LCS (Class I, Level A)

Recommendation 5: Patients with LCS and NIHSS <6 and >30 (2 RCT evidence) may benefit from EVT in LCS (Class IIa, Level A)

Baseline mRS

SELECT2, ANGEL-ASPECT, RESCUE-Japan LIMIT, TESLA, and LASTE all required a baseline mRS score of 0 or 1, while TENSION included patients with mRS 0–2. Four patients were excluded in the ANGEL-ASPECT trial with baseline mRS of ≥2. Because of the narrow selection criteria, there is a lack of high-quality evidence with regard to what extent, if any, patients with baseline disability and an mRS score >1 may also derive benefit from EVT in the setting of an acute LCS.

Recommendation 6: Patients with LCS and low baseline mRS (0–1) (5 RCT evidence) benefit from EVT (Class I, Level A)

Last known well (LKW)

Time from LKW was a selection criterion for EVT in patients with LCS (table 3). In the RESCUE-Japan LIMIT trial, patients were eligible if randomization could be completed within 6 hours from the time of LKW or 6–24 hours from the time of LKW if there were no changes on the FLAIR-MRI image, indicating a recent stroke. EVT had to be initiated within 60 min from randomization. This resulted in a mean time from LKW to randomization of 229 min (IQR 144–459) in the EVT group and 214 min (IQR 142–378) in the MM group.

Similarly, selection criteria for the LASTE trial required symptom onset within 7 hours or in those within an unknown LKW time and negative FLAIR-MRI imaging. Within their study population, median data for LKW to qualifying imaging was 169 min (IQR 115–273) for those receiving MM and 170 min (IQR 112–301) for the EVT group. Subgroup analysis found no significant difference in mRS outcomes between patients presenting less than or more than 4.5 hours.

In the SELECT2 trial, patients were eligible if their LKW to groin puncture or MM was 0–24 hours. In this trial the median time from LKW to randomization was 9.31 hours (IQR 5.66–15.33), with similar distributions between the

Table 3 Time since last known well for patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ASPECT-ANGEL (EVT vs MM)
LKW, eligibility criteria	Either 0–6 hours or 6–24 hours without hyperintensity on FLAIR-MRI	0–24 hours	0–24 hours
Actual LKW to randomization	229 min vs 214 min	9.79 hours vs 9.07 hours	453 min vs 463 min
Percentage of patients in 6–24 hour time window	28.6%	71.6%	63.3%
	TESLA	**LASTE**	**TENSION**
LKW, eligibility criteria	0–24 hours	0–6.5 hours	0–12 hours
Actual LKW to randomization	Not reported	271 min vs 268 min	120 min vs 126 min
Percentage of patients in the 6–24 hour time window	72.4% vs 72.3%	Data presented for >6.5 hours 16.4% vs 12.1% (eligibility required presentation within 7 hours of LKW or unknown LKW with negative FLAIR)	N/A; 47.2% of patients in 6–11 hour cohort, 50.5% of whom underwent EVT and 49.5% underwent MM

EVT, endovascular therapy; LKW, last known well; MM, medical management.

two subgroups (EVT 9.79 hours (IQR 5.82–15.32) vs MM 9.07 hours (IQR 5.27–15.33)).

Time since LKW varied between trials. In the ANGEL-ASPECT trial, patients were eligible if randomization was completed within 24 hours of LKW. The median time from LKW to randomization was 453 min (IQR 299–712) in the EVT group and 463 min (IQR 305–781) in the MM group. By looking into different time points, patients with LKW <6 hours (n=100, OR 1.63, IQR 1.09–2.46), ≥6 hours (n=252, OR 1.49, IQR 1.14–1.94), <12 hours (n=211, OR 1.48 (IQR 1.12–1.96), and ≥12 hours (n=141, OR 1.58, IQR 1.09–2.28) all benefited from EVT over MM only in the SELECT2 trial. In the ANGEL-ASPECT trial, only patients with LKW of ≥6 hours benefited from EVT over MM only (n=188, OR 153, IQR 1.17–2.00), whereas there was no difference between the two groups with <6 hours of LKW (n=167, OR 1.15, IQR 0.80–1.63). The opposite was the case in the RESCUE-Japan LIMIT trial with patients with a shorter time period of LKW (<6 hours) benefitting from EVT (n=144, OR 2.43, IQR 1.04–6.52) whereas patients with LKW ≥6 hours had no difference in benefit between EVT and MM (n=58, OR 2.49, IQR 0.73–8.45).

Similar to the SELECT2 and ANGEL-ASPECT trials, patients in the TESLA trial were eligible if randomization was completed within 24 hours of LKW. In this population, 27.6% of patients receiving EVT and 27.7% in the MM arm were randomized within 6 hours, but no difference in the effect of IA therapy was noted in subgroup analysis with cut-offs at the 6-hour timepoint.

In the TENSION trial, patients were randomized within 11 hours of symptom onset with EVT expected to be completed within 12 hours of onset. This resulted in a median time from LKW to randomization of 120 min (IQR 72–210) in the EVT group and 126 min (IQR 72–216) in the MM group. The median interval between symptom onset to groin puncture was 252 min (IQR 204–354) and the median interval between randomization and recanalization was 144 min (IQR 108–180). In this trial, while sample size was underpowered to demonstrate significance, time from symptom onset <6 hours (OR 2.16, 1.19–3.95) and 6–11 hours (OR 2.64, 1.24–5.63) both tended to favor EVT.

Recommendation 7: Patients with LCS and time of last known well 0–24 hours (<6 hours with 3 RCT evidence and 6–24 hours with 5 RCT evidence) benefit from EVT (Class I, Level A)

Neuroimaging selection criteria

Imaging modalities

The RESCUE-Japan LIMIT trial, SELECT2, ANGEL-ASPECT, TESLA, TENSION, and LASTE trials all required either a non-contrast head CT or brain MRI with diffusion-weighted imaging (DWI) to determine the ASPECTS score. Vascular imaging by either CT angiography (CTA) or MR angiography (MRA) was required to confirm the site of occlusion. In the TESLA trial, non-contrast head CT was used alone to determine the ASPECTS score and assessments were reported for both investigator-interpreted ASPECTS scores and core laboratory-generated ASPECTS scores. In the SELECT2 study, patients also underwent penumbral imaging by either CT perfusion (CTP) or perfusion-diffusion MRI. RAPID AI automated software (iSchemaView) was used to assess trial eligibility. Where CTP was used, the ischemic core was determined using the relative cerebral blood flow of <30% according to the RAPID automated software. Where diffusion-weighted MRI was used, the ischemic core was determined using apparent diffusion coefficient (ADC) values $<620\times10^{-6}$ mm^2/s according to RAPID automated software.

Location of occlusion

The location of the occlusion varied between trials. The RESCUE-Japan LIMIT trial, SELECT2, and ANGEL-ASPECT trials required large vessel occlusions involving either the ICA, the M1 segment of the MCA, or both on CTA or MRA (table 4). The TESLA and TENSION trials required either the terminal ICA or M1 segment of the MCA, and the LASTE trial required either the intracranial ICA, M1 segment of the MCA, or M1–M2 segment of the MCA. In each of the trials the M1 segment of the MCA was affected the majority of the time.

Size of core infarct

Estimated core infarct sizes varied between the trials, as did imaging criteria. In the RESCUE-JAPAN LIMIT trial the inclusion

Table 4 Location of arterial occlusion in patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ASPECT-ANGEL (EVT vs MM)
Number	101 vs 102	178 vs 174	230 vs 225
ICA, extracranial/tandem occlusion	19.8% vs 19.6%	31.5% vs 25.3%	17.8% vs 15.6%
ICA, intracranial	46.5% vs 48%	44.9% vs 37.9%	36.1% vs 36.0%
M1	73.3% vs 68.6%	51.1% vs 57.5%	63.0% vs 63.1%
M2	0 vs 2.9%	3.9% vs 4.6%	0.9% vs 0.9%
	TESLA (EVT vs MM)	**LASTE (EVT vs MM)**	**TENSION (EVT vs MM)**
Number	152 vs 148	159 vs 165	125 vs 127
ICA, extracranial/tandem occlusion	2.6% vs 4.7% (core lab)	N/A	N/A
ICA, intracranial	21.7% vs 16.2% 31.5% vs 28.3% (core lab)	74% vs 69%	33% vs 29%
M1	78.3% vs 83.8% 66.4% vs 64.8% (core lab)	84% vs 89%	66% vs 69%
M2	2.1% vs 6.9% (core lab)	4% vs 2%	0% vs 1%

EVT, endovascular therapy; ICA, internal carotid artery; MM, medical management.

Table 5 Estimated core infarct volume in patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ASPECT-ANGEL (EVT vs MM)
ASPECTS or estimated ischemic core volume, enrollment target	3–5 on CT or DW–MRI	One of these categories: ► 3–5 on CT; ► core volume ≥50 mL (with no upper limit) on CTP or DWI-MRI, with a mismatch ratio of ≥1.8 and mismatch volume of ≥15 mL	One of these categories: ► 0–2 with infarct core volume 70–100 mL; ► 3–5 with any core volume; ► >5 with infarct core volume 70–100 mL
Median (IQR) ASPECTS on baseline CT	3 (3–4) vs 3 (3–4)	4 (3–5) vs 4 (4–5)	4 (3–4) vs 3 (3–4)
Median estimated ischemic core volume	94 mL vs 110 mL	81.5 mL vs 79 mL	60.6 mL vs 63 mL
Median volume of critically hypoperfused lesions	N/A	171 mL vs 169 mL	N/A
Median volume of tissue with Tmax >10 s	N/A	107 mL vs 111 mL	N/A
	TESLA (EVT vs MM)	**LASTE (EVT vs MM)**	**TENSION (EVT vs MM)**
ASPECTS or estimated ischemic core volume, enrollment target	2–5	0–5 on NCCT or DWI-MRI	3–5 on NCCT or DWI-MRI
Median (IQR) ASPECTS on baseline CT	4 (3–5) vs 4 (3–5)	<3: 54% vs 58% 3–5: 46% vs 52%	Median values not reported 3 (29% vs 38%) 4 (36% vs 30%) 5 (35% vs 32%)
Median estimated ischemic core volume	N/A	132 mL vs 137 mL	N/A
Median volume of critically hypoperfused lesions	N/A	N/A	N/A
Median volume of tissue with Tmax >10 s	N/A	N/A	N/A

ASPECTS, Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; EVT, endovascular therapy; MM, medical management; NCCT, non-contrast CT.

criteria included an ASPECT score of 3–5 on non-contrast CT or diffusion-weighted MRI (DWI-MRI). It was noted that perfusion imaging was not available in most hospitals in Japan during the trial. If they underwent randomization within 6–24 hours after the time the patient was LKW, the initial image on fluid-attenuated inversion recovery (FLAIR) MRI had to show there was no signal change indicating a recent infarction. Using these criteria, the median ASPECT score was 3 (table 5).

Similarly, the TENSION trial included patients with an ASPECTS 3–5, as defined by non-contrast CT head (83% vs 81%) or DWI-MRI (17% vs 19%), interpreted locally. Core laboratory values were also reported. Of note, there was an imbalance in baseline ASPECTS as recorded by the core laboratory, in which a larger proportion of the patients in the MM arm were defined to have an ASPECTS of 0–2 (18%) compared with the interventional arm (12%).

In the SELECT2 trial, LCS was defined by either an ASPECTS score of 3–5 on a non-contrast head CT or a core volume of at least 50 mL on a CTP study or a DWI-MRI sequence. There was no upper limit for the ischemic core volume. A mismatch ratio of at least 1.8 with a mismatch volume of at least 15 mL was required. Exclusion factors included any evidence of ICH on neuroimaging. Using these selection criteria, 85% of patients had ASPECTS ≤5, 87% had an ischemic core volume of at least 50 mL, and 78% of patients met the large core volume criteria using both ASPECTS and ischemic core volume. Notably, CTP—rather than MRI—was used in nearly all cases (98.3% of EVT patients and 97.1% of MM patients).

In the ANGEL-ASPECT trial, patients were eligible for the trial if they fell into one of the following three categories: ASPECTS 0–2 based on a non-contrast CT scan within 24 hours of onset and an infarct core volume of 70–100 mL; ASPECTS 3–5 based on a non-contrast CT scan within 24 hours of onset and no limitation of ischemic core volume; or ASPECTS >5 based on a non-contrast CT scan 6–24 hours from onset and an infarct core volume of 70–100 mL. Exclusion factors included signs of herniation, mass effect, high risk of hemorrhage, acute bilateral strokes, or multiple intracranial occlusions. Using these criteria, 14% of patients in the EVT arm and 13.4% of patients in the MM arm fell into the ASPECTS range of 0–2, and 86% of patients in the EVT arm and 86.6% in the MM arm fell into the ASPECTS range of 3–5. It is worth noting that no patients in the third tier (ie, ASPECTS >5 and infarct core volume 70–100 mL) were enrolled and therefore no conclusions can be drawn from this population.

The TESLA trial targeted enrollment of patients with ASPECTS 2–5 based solely on non-contrast CT scan of the head. Investigator analysis showed that 36.8% of patients in the EVT arm and 35.8% in the MM arm were in the ASPECTS 2–3 range, while 63.2% of patients in the EVT arm and 64.2% in the MM arm were in the ASPECTS range of 4–5. When assessed by the core laboratory, however, 2.0% of patients in the EVT arm and 5.4% in the MM arm were found to have ASPECTS<2; 10.6% of patients in the EVT arm and 12.9% in the MM arm had ASPECTS >5.

The LASTE trial included patients with ASPECTS 0–5 on non-contrast head CT or DWI-MRI. In patients aged ≥80 years, ASPECTS eligibility was >3. The overwhelming majority of patients underwent DWI-MRI in order to determine infarct core volume (85% in the MM arm and 82% in the EVT arm). Baseline ASPECTS was 0–2 in 58% of patients in the MM arm and 54% of patients receiving EVT. Importantly, the investigators reported no heterogeneity of treatment effect after subgroup analysis on patients with ASPECTS 0–2 versus 3–5.

Intravenous thrombolytic use

Intravenous thrombolytic medications were allowed in all six reported trials according to standard practices and guidelines but were not used as part of the selection criteria (table 6). Only about 20–40% of patients were eligible for tissue plasminogen activator (tPA), which was attributed to the large number of patients outside the 4.5-hour time window and possibly

Table 6 Intravenous thrombolytic use in patients enrolled in large ischemic core trials

	RESCUE-Japan LIMIT (EVT vs MM)	SELECT2 (EVT vs MM)	ASPECT-ANGEL (EVT vs MM)
Thombolytic medication	Alteplase	Alteplase or tenecteplase	Alteplase or urokinase
Thrombolytic usage	26.7% vs 28.4%	20.8% vs 17.3%	28.7% vs 28.0%
	TESLA (EVT vs MM)	**LASTE (EVT vs MM)**	**TENSION (EVT vs MM)**
Thombolytic medication	Alteplase	Unspecified	Alteplase
Thombolytic medication	20.4% vs 20.3%	34.6% vs 35.2%	39% vs 34%

EVT, endovascular therapy; MM, medical management.

physicians' concerns about using tPA in patients with signs of extensive ischemic changes already evident in this population. Furthermore, it was noted in the ASPECT-ANGEL trial that approximately 20% of patients were receiving anticoagulants.

Table 6 shows the relative usage of tPA in each of the trials. It is important to note that the thrombolytic regimens varied within and among the trials. The SELECT2 trial allowed for either alteplase or tenecteplase. In the ASPECT-ANGEL trial, a small percentage (3.5%) of patients received urokinase, which may be less effective than alteplase. In the RESCUE-Japan LIMIT trial, patients received a smaller dose of alteplase (0.6 mg/kg body weight) than is commonly used in many other countries.

Prior SNIS and AHA/ASA guidelines recommended that patients who meet the criteria for on-label or guideline-directed use of IV tPA should receive IV tPA irrespective of whether endovascular treatments are being considered (ASA Class I; Level of Evidence A). Large areas of established infarction (eg, more than one-third of the MCA territory) on initial imaging is a relative contraindication for IV tPA,[13] which has been shown to correlate with an increased risk of sICH.[17] Additionally, in the past 2 years, evidence continues to accrue regarding the relative outcomes between patients receiving thrombectomy alone versus IV thrombolysis plus thrombectomy. The MR CLEAN-NO IV trial, which attempted to compare thrombectomy alone versus the combination of thrombectomy and alteplase in patients with large vessel occlusion presenting <4.5 hours from LKW, was unable to demonstrate a difference and concluded that thrombectomy alone was 'neither superior nor non-inferior' statistically.[18] Similarly, although there were no significant differences in the observed primary outcomes between groups treated with thrombectomy with or without IV thrombolysis in the SKIP randomized trial, statistical significance for non-inferiority was not reached.[19] The DEVT randomized trial, in contrast, was stopped early after the prespecified non-inferiority endpoint was reached between the thrombectomy group and the thrombectomy plus IV thrombolysis group.[20] There were no significant differences in sICH or 90-day mortality.

Recent and ongoing trials in the LCS population do not exclude the administration of IV thrombolysis when it is indicated, but secondary analyses may provide further data in the future about the risks and benefits of IV thrombolysis in the setting of potentially larger core infarcts. Nonetheless, due to the lack of consensus among recent high-quality trials regarding the comparative efficacy of withholding IV thrombolysis among patients undergoing thrombectomy, and due to its clear benefit among eligible patients, the current recommendations are unchanged.

Recommendation 8: It is recommended that patients with LCS who also meet the criteria for on-label use of IV tPA receive IV tPA irrespective of whether endovascular treatments are being considered (Class I; Level B-NR)

Clinical and safety outcomes

The recent LCS trials showed a benefit from EVT compared with MM alone on functional independence and ambulatory status at 90 days. The RESCUE-JAPAN trial showed that MT was associated with increased odds of independent ambulation (mRS 0–3) (OR 2.43, 95% CI 1.35 to 4.37) and non-significantly higher functional independence (mRS 0–2) at 90 days (OR 2.04, 95% CI 0.86 to 4.84). Similarly, despite not meeting superiority thresholds for analysis of 90-day utility-weighted mRS of 0–2, the TESLA trial showed increased odds of mRS 0–3 with MT at 30% relative to MM at 20% (OR 1.6, P=0.03). Furthermore, the ANGEL-ASPECT trial showed that MT was associated with increased odds of independent ambulation (OR 1.41, 95% CI 1.12 to 1.77) and functional independence at 90 days (OR 2.60, 95% CI 1.72 to 3.92). The SELECT2 trial showed similar findings for functional independence (OR 2.90, 95% CI 1.56 to 5.38) and for independent ambulation (OR 2.02, 95% CI 1.40 to 2.91) and, in the primary outcome analysis for the TENSION trial including all 253 patients there was a shift in the distribution of mRS towards better outcomes, favoring EVT over MM (OR 2.58, 95% CI 1.60 to 4.15, P=0.0001). At interim analysis a similar shift was observed favoring EVT as well (OR 3.05, P<0.0001). Furthermore, both rates of independent function (mRS ≤2) and independent ambulation (mRS ≤3) at 90 days favored EVT (OR 7.16, 95% CI 2.12 to 24.21, P=0.0016 and OR 2.84, 95% CI 1.48 to 5.47, P=0.0018, respectively). Data from the LASTE trial show a shift in the distribution of 90-day mRS towards better outcomes favoring EVT (OR 1.63, 95% CI 1.29 to 2.06, P<0.0001) and, although they did not reach statistical significance, the data tended to favor EVT in achieving independent function and independent ambulation at 180 days. While the rates of sICH were slightly higher in the EVT group (9.6% vs 5.7%), the rates of all-cause mortality tended to be lower in the EVT group at both 90 days (36.1% vs 55.5%) and 180 days (40.8% vs 56.8%). Interestingly, the TENSION trial is the only LCS trial to show a mortality benefit favoring the EVT group (40% vs 51%, OR 0.67, 95% CI 0.46 to 0.98; P=0.038). On the other hand, 90-day mortality did not differ between the two groups across the other four studies: RESCUE-Japan (OR 0.77, 95% CI 0.44 to 1.32), ANGEL-ASPECTS (OR 1.09, 95% CI 0.76 to 1.56), SELECT2 (OR 0.93, 95% CI 0.72 to 1.20), TESLA (OR 2.00). Quality of life (QOL) domains at 90 days were studied in the SELECT2, TESLA, and TENSION trials. In SELECT2, MT was superior to MM in all domain-specific Neuro-QOL assessments (mobility domain, social domain, depression domain, cognitive domain), in the TESLA trial MT was similarly superior to MM as assessed by EQ-5D-5L (P=0.058), and the TENSION trial reported higher scores in measurements of QOL, mental, and physical health, favoring EVT.

DISCUSSION

Financial implications

Chen *et al* recently provided an overview of the socioeconomic implications of successful treatment of patients with large core infarcts.[13] As cited in their paper, a European consortium study showed a lifetime incremental cost-effectiveness ratio varying from US$2875 to US$11 202/

quality adjusted life year (QALY) with MT.[13] The most significant cost savings come from a decrease in the number of patients with mRS 4 and 5. As Chen *et al* noted, Sanmartin *et al* found that MT yielded higher lifetime benefits (2.20 QALYs vs 1.41 QALYs) despite marginal higher lifetime costs per patient (US$ 285 861 vs US$ 272954).[13 17] The difference of 0.79 QALYs equated to 288 additional days of healthy life per patient. The incremental cost-effectiveness ratio was US$ 16 239/QALY and the number needed to treat for one additional patient to achieve mRS 0–2 and mRS 0–3 were 7 and 5, respectively.[17]

Expanding indications to benefit more patients means tracking outcomes to avoid futility

Considering that LCS represent about 20% of all ischemic strokes due to proximal occlusion of a cerebral vessel, we anticipate that these recent trial results will likely increase the number of patients with ELVO who will be taken to the angiography suite for EVT. It is therefore incumbent on endovascular practitioners, hospitals, and health systems to understand the implications of these trials and to determine how best to incorporate the lessons from these trials into their own specific practice settings. It is incumbent on our field to prospectively track patient outcomes—ideally in a standardized manner so that data can be pooled across many sites—to assess the number needed to treat in real-world practice.

CONCLUSIONS

The indications for EVT of ELVO strokes continue to expand, now including patients with LCS prior to intervention. Further prospective randomized studies—including follow-up to assess the population-based efficacy of treating patients with LCS and outcomes in patients with baseline mRS ≥2—are warranted.

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