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Review

Endovascular Therapy for Extensive Infarction in Acute Ischemic Stroke

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Acute ischemic stroke is the leading cause of permanent disability and second leading cause of death worldwide. Over the past 10 years, mechanical thrombectomy has become a powerful technique for improving outcomes after large-vessel occlusion in patients with a small baseline infarct. Reperfusion in patients with extensive infarction has historically been considered futile or harmful. However, a recent series of trials showed that endovascular therapy benefits patients who present with extensive baseline infarction. These new data represent a paradigm shift in the approach to stroke therapy, leading to an expansion of indications. Therefore, more patients will benefit from mechanical thrombectomy. Furthermore, these data challenge current definitions of infarct and ischemia as seen on imaging. The data suggest a new era of reperfusion therapy that focuses on optimizing patient-specific approaches and developing adjunctive neuroprotectants and neurorestorative therapies.

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Introduction

The central nervous system is the most energy-consuming organ in the body. Thus, it is extremely sensitive to glucose and oxygen deprivation and, consequently, to adenosine triphosphate deprivation. Tissue ischemia due to arterial occlusion, without timely reperfusion, results in acute ischemic stroke. Acute ischemic stroke is the principal cause of permanent disability and the second most common cause of mortality worldwide.

In 1995, the National Institute of Neurological Disorders and Stroke trial established the benefit of intravenous thrombolytic alteplase over placebo in patients who present with acute ischemic stroke within 3 hours of symptom onset, despite an increased incidence of symptomatic intracranial hemorrhage (sICH).[1] Three decades later, intravenous thrombolysis remains the only proven medical therapy to reduce disability after acute ischemic stroke. Clot retrieval or dissolution with intra-arterial therapy was also developed to achieve reperfusion in patients who were ineligible for or refractory to intravenous thrombolysis, but who presented with a clot accessible by a catheter. In 2016, a meta-analysis of five pivotal trials conducted from 2010 to 2014 established the benefit of endovascular therapy (EVT) with or without bridging intravenous thrombolysis therapy in patients with anterior circulation large-vessel occlusion (LVO) (i.e., the M1 segment of the middle cerebral artery or intracranial internal carotid artery).[2] Subsequent randomized controlled trials demonstrated benefits

in patients with anterior circulation occlusion who presented with up to 24 hours of symptoms as well as in patients with posterior circulation strokes from basilar artery occlusion.[3-5]

EVT trials have focused on patients with severe clinical deficits and a small established ischemic core on presentation because it has long been believed that reperfusion therapy for a large established ischemic injury is likely futile and potentially harmful. A series of recently completed randomized controlled trials of patients who presented with large infarcts challenged this principle and demonstrated improved functionality and reduced mortality with EVT. These trials have significant global implications for the continuum of stroke care, including prehospital triage, patient selection, imaging requirements, workforce needs, and postprocedural care as well as, long-term sequelae of stroke care, spanning from rehabilitation to poststroke epilepsy, headaches, depression, apathy, sleep disorders, movement disorders, cognitive impairment, and overall brain health.

Search strategy and selection criteria

We searched MEDLINE and Scopus for the period of January 1, 2020, through June 17, 2025, using the following terms in combination: "thrombolysis," "thrombolytic," "thrombectomy," "intra-arterial therapy," "endovascular therapy," "mechanical thrombectomy," "large vessel occlusion," "large core," "large stroke," "large infarct," and "ischemic stroke." We selected randomized and nonrandomized studies that evaluated the use of thrombolytic agents and endovascular therapy for the treatment of patients with acute ischemic stroke in the setting of large strokes. Case reports, case series, and retrospective cohort studies were excluded. The reference lists of all articles that met the inclusion and exclusion criteria were examined to identify studies that the initial database search may have missed.

Mapping the future of precision brain health

The specific clinical paradigm of acute ischemic stroke and the development of effective treatments over the past few decades have followed a traditional approach of selecting focused case scenarios or subsets of patients with acute ischemic stroke and implementing specific therapies, culminating in randomized controlled trials. These trials assumed that baseline and cohort imbalances in covariates were addressed and that the results overwhelmingly reflected the effect of only the investigational treatment. Against this backdrop, precision medicine for stroke and brain health has emerged as a novel conceptual and practical approach. Precision medicine can focus on imaging patterns of infarction and ischemia in patients with acute ischemic stroke in hospitals. These imaging patterns may represent the effect of ischemia from a specific cause or etiology, and a subset of large-vessel occlusions. However, each patient's imaging reflects differences in collateral circulation, brain health, resilience, and course of the ischemic cascade. Future precision medicine approaches to acute ischemic stroke should focus on linking specific imaging patterns to specific drug therapies (antithrombotic, thrombolytic, cytoprotective, and anti-edema therapies) or endovascular device therapies. Extensive infarction is a good example of the effectiveness of precision medicine.

Incomplete cerebral ischemia and recanalization

Cell death occurs within seconds to minutes, with complete cessation of energy to the neuronal tissue. However, immediate and complete cessation is rare during acute ischemic stroke because partial perfusion via collateral flow and variable thresholds of ischemic resilience allow threatened tissues to remain viable for some time. Early animal studies established cerebral blood flow thresholds at which electrical failure occurs with corresponding functional deficits but with a preserved ability to uphold membrane potential. A further decline in flow is necessary for the failure of energy metabolism. The brain region experiencing electrical failure without energy failure (electrical silence with an essentially normal concentration of extracellular potassium) is termed the penumbra, and it serves as the therapeutic target for reperfusion therapy in acute ischemic stroke patients.[6] Tissue that experiences complete energy and ion pump failure is irreversibly damaged (infarcted). However, the surrounding halo of at-risk penumbral tissue may be salvageable. Permissive hypertension and supine positioning can preserve the penumbra, and recanalization of the occluded vessel can prevent irreversible injuries. Ischemic core regions are increasingly being recognized as likely to contain islands of salvageable tissue. Thus, the penumbra may surround and intercalate with the ischemic core. Preclinical proof of the recanalization concept was demonstrated in a macaque model of transient middle cerebral artery occlusion.[7] Initially, microscopic infarcts grew from small (15–30 min) to moderate (2–3 h) to large (>6 h) depending on the duration of occlusion. Importantly, paralysis after a decrease in local cerebral blood flow (<23 mL/100 g/min) can be reversed by removing the vessel ligature. Hyperemia observed after restoration of blood flow was inversely related to the duration of occlusion, possibly indicating a higher intensity and duration of postrecanalization hyperemia in patients with prolonged ischemia. This association may form the basis for the higher rate of

hemorrhagic transformation in patients with delayed reperfusion.

Endovascular therapy for large core ischemia

After decades of negative and neutral trial results, the results of EVT trials using mostly stent retrievers have reignited confidence in recanalization. Several notable populations have been understudied and have become the subject of clinical trials (some are still ongoing), including trials on posterior circulation strokes (i.e., occlusion of the vertebrobasilar system), mild clinical deficits (National Institutes of Health Stroke Scale [NIHSS] <6), distal medium vessel occlusion, preexisting functional dependence, and large ischemic burden at presentation.

Of these populations, patients with large core ischemia offer a clinically significant treatment opportunity because they represent 15%–20% of patients ineligible under the American Heart Association and American Stroke Association guidelines.[8,9] An analysis of data from the population-based GCNKSS (Greater Cincinnati Northern Kentucky Stroke Study) extrapolated to the U.S. population estimated that 5,316–10,635 patients are considered ineligible annually for EVT because of a large infarct burden at presentation.[10]

In a meta-analysis of patient-level data for 1,278 patients in the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration, EVT benefit was observed for patients with either Alberta Stroke Program Early Computed Tomography Score (ASPECTS) 9–10 or ASPECTS 6–8.[11] Despite the HERMES focus on patients with small core infarcts, a subset of patients with ASPECTS 0–5 were enrolled and had encouraging but nonsignificant common odds ratios (ORs) of 1.24, favoring EVT.[2] However, EVT was associated with a higher risk of sICH in patients with ASPECTS 0–4 (19% in the EVT group vs. 5% in the control group).[11]

In a prospective, multicenter Chinese registry of 1,396 patients with anterior-circulation LVO who underwent EVT, 94 had baseline ASPECTS <6.[12] Good outcomes were lower for them than for those with ASPECTS ≥6 (34% vs. 46%), and their incidence of intracranial hemorrhage was higher (21% vs. 8%). In a prospective multicenter Japanese registry of 2,420 patients with LVO and pretreatment ASPECTS <6 based on computed tomography (CT) or diffusion-weighted imaging (DWI) (RESCUE–Japan Registry 2 [Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Registry 2]), good functional outcomes (modified Rankin Scale [mRS] score 0–2) were higher with EVT than without EVT (20% vs. 4%), but sICH was comparable (4% vs. 5%).[13]

Large core ischemia trials

Six randomized controlled trials have tested the efficacy of mechanical thrombectomy in patients with large core ischemia (Table 1).[14-19] Of these six trials, four (TENSION [Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window],[14] LASTE [Large Stroke Therapy Evaluation],[15] RESCUE-Japan LIMIT [Randomized Controlled Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core],[16] and TESLA [Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke])[17] used ASPECTS for patient selection. The remaining two (ANGEL-ASPECT [Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core][18] and SELECT2 [Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke][19]) used perfusion imaging. Figures 1 and 2 show two patients with large core infarcts: one treated with mechanical thrombectomy and the other untreated.

Aspects-based selection

To test the effect of EVT in patients with a large baseline infarct who presented with a proximal anterior-circulation LVO, the TENSION trial randomized patients with ASPECTS 3–5 (82% by CT, 18% by magnetic resonance imaging [MRI]) who presented within ≤11 hours of symptom onset or last known well-functioning for EVT (with expected completion by 12 h) plus medical management or medical management alone.[14] This prospective, multicenter, open-label, randomized trial was conducted across 40 European sites and 1 Canadian site, and it included 253 patients (125 EVT plus medical management vs. 128 with medical management alone). The study was halted after the first interim analysis because of better outcomes for the EVT plus medical management treatment arm (adjusted common OR, 2.58; 95% confidence interval [CI] 1.60–4.15) and lower mortality (hazard ratio, 0.67; 95% CI 0.46–0.98). The sICH rates were comparable (5% vs. 5%).

The LASTE trial investigated the role of EVT in patients with a baseline ASPECTS 0–5 or ASPECTS 4–5 for patients older than 80 years of age (16% by CT, 84% by MRI).[15] Three hundred thirty-three patients across 24 centers in France and 6 centers in Spain who presented within 6.5 hours of symptom onset or within 24 hours since last known to be well with no infarction on initial fluid-attenuation inversion recovery (FLAIR) imaging, with an anterior-circulation LVO, were randomized to EVT plus medical management or medical management alone. The trial was halted after the publication of data from other trials that

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Table 1. Six randomized controlled trials on the efficacy and safety of endovascular therapy vs. medical management in treating patients with anterior circulation, large vessel occlusion, and large core ischemia

Variables	Randomized Controlled Clinical Trials					
	TENSION	LASTE	RESCUE-Japan LIMIT	TESLA	ANGEL-ASPECT	SELECT2
Trial registration	NCT03094715	NCT03811769	NCT03702413	NCT03805308	NCT04551664	NCT03876457
Country	Europe, Canada	Europe	Japan	U.S.	China	U.S., Canada, Europe, Australia, New Zealand
Planned sample size, No.	714*	450*	200	300	502*	560*
Patients recruited, No.	253*	333*	203	300	456*	352*
Inclusion criteria						
Age (yr)	≥18	≥18	≥18	18–85	18–80	18–85
Premorbid mRS	0–2	0–1	0–1	0–1	0–1	0–1
NIHSS	<26	≥6	≥6	≥6	6–30	≥6
Large core ischemia	ASPECTS 3–5 on NCCT (82%) or DWI (18%)	ASPECTS 0–5 or 4–5 if age >80 years, on NCCT (16%) or DWI (84%)	ASPECTS 3–5 on NCCT (14%) or DWI (86%)	ASPECTS 2–5 on NCCT	0–24 h: ASPECTS 3–5 on NCCT, or ASPECTS 0–2 on NCCT & infarct core 70–100 mL on CTP or DWI; 6–24 h: ASPECTS 6–10 on NCCT & infarct core 70–100 mL on CTP or DWI	ASPECTS 3–5 on NCCT; or infarct core ≥50 mL on CTP (98%) or DWI (2%)
Time window	<12 h	<6.5 h of known onset time or <24 h LSW with FLAIR (-)	< 6 h LSW or 6–24 h LSW with FLAIR (-)	0–24 h	0–24 h	0–24 h
Baseline characteristics						
Age (yr)	74 (65–80)	74	76 (mean)	67	68 (60–73)	67 (58–75)
Male sex (%)	51	53	46	54	61	59
NIHSS	19 (16–22) vs. 18 (15–22)	21 (18–24) vs. 21 (18–24)	22 (18–26) vs. 22 (17–26)	19 (15–23) vs. 18 (14.5–21)	16 (13–20) vs. 15 (12–19)	19 (15–23) vs. 19 (15–22)
ASPECTS	Not provided	2 (1–3) vs. 2 (1–3)	3 (3–4) vs. 4 (3–4)	2–3: 36% vs. 35%; 4–5: 65% vs. 66%	3 (3–4) vs. 3 (3–4)	4 (3–5) vs. 4 (4–5)
Infarct core volume (mL)	Not provided	132 (104–185) vs. 137 (106–187)	94 (66–152) vs. 110 (74–140)	Not provided	61 (29–86) vs. 63 (31–86)	74 (50–112) vs. 77 (50–105)
Onset-to-randomization interval (h)	2.0 (1.2–3.5) vs. 2.1 (1.2–3.6)	4.5 (3.3–5.9) vs. 4.5 (3.5–5.6)	3.8 (2.4–7.7) vs. 4.0 (2.4–6.3)	10.9 (5.6–15.7) vs. 12.6 (5.6–17.1)	7.6 (5.0–11.9) vs. 7.7 (5.1–13.0)	9.1 (5.3–15.3) vs. 9.8 (5.8–15.3)
Onset-to-groin puncture interval (h)	4.2 (3.4–5.9)	5.1 (3.9–6.3)	4.2 (2.8–8.0)	11.1 (6.0–15.8)	7.9 (5.4–13.0)	Not provided
Intravenous thrombolysis	39% vs. 34%	35% vs. 35%	27% vs. 28%	20% vs. 20%	29% vs. 28%	21% vs. 17%
Primary outcome	90-day mRS	90-day mRS	90-day mRS 0–3	90-day UW-mRS	90-day mRS	90-day mRS

Table 1. Continued

Variables	Randomized Controlled Clinical Trials					
	TENSION	LASTE	RESCUE-Japan LIMIT	TESLA	ANGEL-ASPECT	SELECT2
Outcome data & treatment effects						
90-day mRS or UW-mRS						
Median (IQR) or mean (SD)	4 (3–6) vs. 6 (4–6)	4 (3–6) vs. 6 (4–6)	4 (3–5) vs. 5 (4–5)	2.93±3.39 vs. 2.27±2.98	4 (2–5) vs. 4 (3–5)	4 (3–6) vs. 5 (4–6)
OR (95% CI)	2.58 (1.60–4.15)†	1.63 (1.29–2.06)†	2.42 (1.46–4.01)†	Adjusted difference: 0.63 (-0.09–1.34)	1.37 (1.11–1.69)†	1.51 (1.20–1.89)†
90-day mRS 0–1	Not provided	Not provided	5% vs. 3%	Not provided	Not provided	Not provided
90-day mRS 0–2	17% vs. 2%†	13% vs. 5%†	14% vs. 8%	15% vs. 9%	30% vs. 12%†	20% vs. 7%†
90-day mRS 0–3	31% vs. 13%†	34% vs. 12%†	31% vs. 13%†	30% vs. 20%†	47% vs. 33%†	38% vs. 19%†
Symptomatic ICH	5% vs. 5%	10% vs. 6%	9% vs. 5%	4% vs. 1%	6% vs. 3%	1% vs. 1%
90-day mortality	40% vs. 51%†	36% vs. 56%†	18% vs. 24%	35% vs. 33%	22% vs. 20%	38% vs. 42%

Values are presented as median (IQR) unless otherwise indicated.
TENSION, Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window; LASTE, Large Stroke Therapy Evaluation; RESCUE-Japan LIMIT, Randomized Controlled Trial of Endovascular Therapy for Acute Large Vessel Occlusion With Large Ischemic Core; TESLA, Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; ANGEL-ASPECT, Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core; SELECT2, Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; NCCT, non-contrast computed tomography; DWI, diffusion-weighted imaging; CTP, computed tomography perfusion; LSW, last seen well; FLAIR (-), fluid-attenuated inversion recovery negative/no fluid-attenuated inversion recovery changes; UW, utility-weighted; IQR, interquartile range; SD, standard deviation; OR, odds ratio; CI, confidence interval; ICH, intracranial hemorrhage.
*Trial was halted early after an interim analysis; †P<0.05 for the treatment effect, in favor of endovascular therapy plus medical management vs. medical management alone.

showed the benefits of EVT in patients with large core infarcts. The results showed a statistically significant shift toward better outcomes in the EVT plus medical management arm (adjusted common OR, 1.63; 95% CI 1.29–2.06) and lower mortality (adjusted relative risk, 0.65; 95% CI 0.50–0.84). The sICH rates were comparable (10% vs. 6%). Most patients (56%) had an ASPECTS of 0–2 at baseline and benefited from EVT (common OR, 1.77).

With time window criteria similar to those of the LASTE trial, the RESCUE-Japan LIMIT trial enrolled patients who presented within 6 hours of last known to be well or within 24 hours of last known to be well with no infarction on initial FLAIR.[16] This open-label, parallel-group, randomized, controlled trial was conducted in 45 Japanese hospitals and enrolled 203 patients with an NIHSS ≥6 who had an anterior-circulation LVO and large core ischemia. Large core ischemia was defined as an ASPECTS 3–5 on CT or MRI in patients presenting within ≤6 hours of last known to be well or an MRI ASPECTS 3–5 with no FLAIR changes in patients who presented 6 to 24 hours of last known to be well (14% CT, 86% MRI). Patients who underwent EVT plus medical management had higher rates of the primary endpoint (mRS 0–3 at 90 days: 31% vs. 13%, P=0.002). The proportion of patients with sICH within 48 hours of EVT was 9%, whereas the proportion of sICH in the control group was 5% (P=0.25).

Most patients in the RESCUE-Japan LIMIT were enrolled on the basis of MRI ASPECTS. However, MRI availability might be limited at many centers, which could make the universal implementation of such a paradigm impractical. In contrast, the TESLA trial investigated a CT ASPECTS-based approach (ASPECTS 2–5) in patients presenting within ≤24 hours of symptom onset with an anterior-circulation LVO.[17] This multicenter, open-label, blinded-endpoint, randomized, controlled trial enrolled 300 patients at 47 hospitals in the U.S. The mean (standard deviation) 90-day utility-weighted mRS score was 2.93 (3.39) in the intervention group and 2.27 (2.98) in the control group (adjusted difference, 0.63; 95% CI -0.09–1.34). No significant differences were found in the 90-day mortality (35% vs. 33%) or 24-hour sICH rates (4% vs. 1%). The difference in functional outcomes was also not statistically significant, with the trial reaching a posterior probability of superiority of 0.957 (P=0.04) compared with the planned endpoint of 0.975 (P=0.92).

Perfusion-based selection

Although ASPECTS on CT and MRI serve as semiquantitative measures of infarct burden, multiple efforts have been made to achieve a more sensitive and quantitative assessment of core infarct size. CT perfusion parameters, such as mean transit time, measure the tissue at risk or the penumbra. At the same time,

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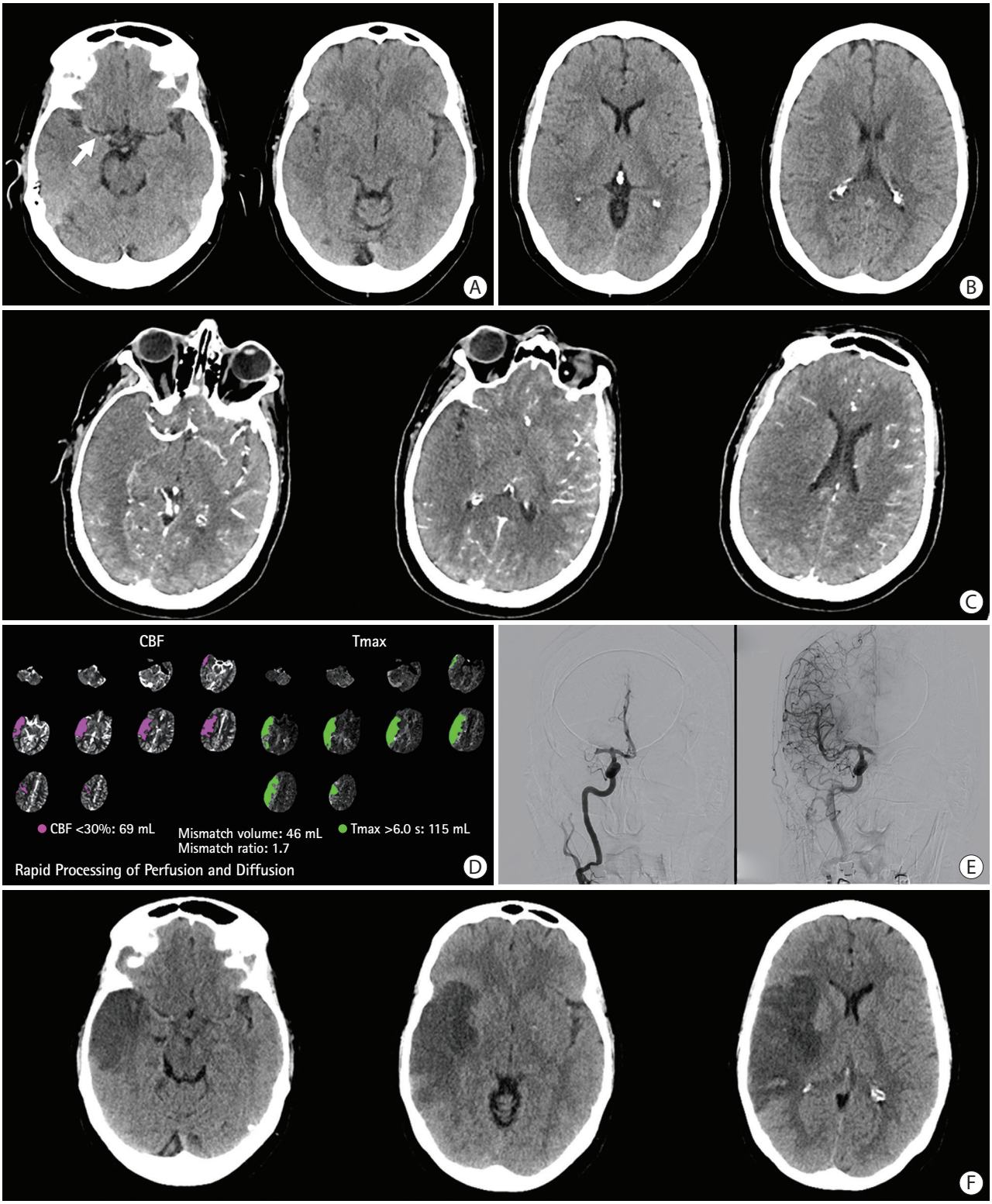

Figure 1. Large core ischemia treated with mechanical thrombectomy. A 57-year-old man initially presented to an emergency department 2.5 hours after the onset of left hemiparesis. The initial NIHSS score was 17. (A) CT showed a hyperdense right middle cerebral artery sign (arrow) and an ASPECTS of 8. The patient received intravenous thrombolysis and was transferred to a comprehensive stroke center. One hour after arrival at this center, (B) repeat CT showed an ASPECTS of 5, (C) CT angiography confirmed a right M1 middle cerebral artery occlusion with poor collaterals. (D) CT perfusion revealed a core of almost 70 mL and extensive penumbra. (E) Mechanical thrombectomy achieved first-pass recanalization with full reperfusion (thrombolysis in cerebral infarction score of 3). (F) Despite a sizable final infarct, the patient had an excellent recovery (NIHSS 5 and modified Rankin Scale score 2 at the 1-month follow-up). CBF, cerebral blood flow; Tmax, time to maximum delay (seconds); NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ASPECTS, Alberta Stroke Program Early Computed Tomography Score. Used with permission from Barrow Neurological Institute, Phoenix, AZ, USA.

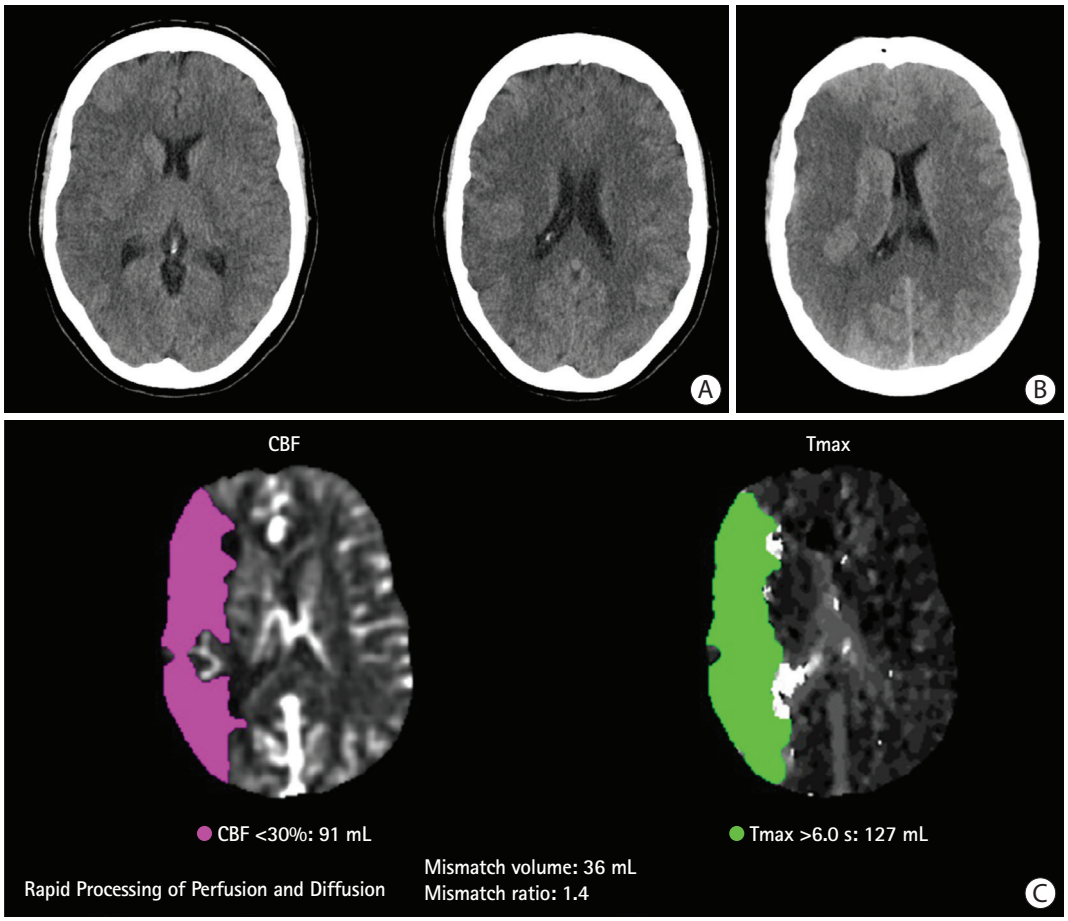

Figure 2. Large core infarct not treated with mechanical thrombectomy. A 66-year-old woman presented to an emergency department 6 hours after her last known well-functioning. The initial NIHSS score was 18. (A) CT of the brain showed extensive changes in the right anterior circulation with an ASPECTS of 4. The patient was transferred to a comprehensive stroke center. (B) Repeat CT upon arrival showed progression of hypoattenuation. (C) CT perfusion displayed a core of approximately 90 mL with limited penumbra. The patient did not undergo thrombectomy. Her clinical evolution was unfavorable, and she was eventually transitioned to palliative care. CBF, cerebral blood flow; Tmax, time to maximum delay (seconds); NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ASPECTS, Alberta Stroke Program Early Computed Tomography Score. Used with permission from Barrow Neurological Institute, Phoenix, AZ, USA.

various thresholds of decreased cerebral blood volume and cerebral blood flow are highly correlated with irreversible injury and are thus valuable in defining the ischemic core.

In a matched case-control, single-center study of 56 patients who presented with a large penumbra (maximum delay >6 s), despite large core ischemia at presentation (relative cerebral blood flow <30% of the opposite hemisphere; large core >50 mL), EVT had a higher likelihood of better outcomes than medical management (mRS 0–2 at 90 days of 25% vs. 0%).[20] Rates of sICH, hemicraniectomy, and mortality were lower in the EVT group. Most patients were treated early, with a median time of 262 minutes from the last known normal functioning to puncture. A subgroup analysis of the prospective, multicenter SELECT (Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) registry that focused on patients with a large ischemic core (CT ASPECTS 0–5 or CT perfusion ischemic core volume ≥50 mL) demonstrated higher rates of mRS 0–2 at 90 days in the EVT group versus medical management alone (31% vs. 14%).[21]

To test the effect of EVT in patients with extensive infarct at baseline selected on the basis of CT ASPECTS or CT perfusion, the ANGEL-ASPECT trial randomized 456 patients across 46 sites in China.[18] This multicenter, prospective, open-label, randomized trial was halted early after the second interim analysis because of its efficacy in the treatment arm. Trial eligibility was based on CT ASPECTS 3–5 ≤24 hours of symptom onset or CT ASPECTS 0–2 ≤24 hours of symptom onset and a core volume of 70–100 mL (by CT perfusion or MRI) or CT ASPECTS 6–10 within 6 to 24 hours of symptom onset and a core volume of 70–100 mL (by CT perfusion or MRI). Only 38 patients were selected using MRI, while the remainder were selected using CT. In this trial, 63% of enrolled patients were treated >6 hours after symptom onset, and 37% of patients were treated ≤6 hours after symptom onset. The primary outcome analysis identified a shift in

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mRS score distribution at 90 days toward better outcomes for EVT versus medical management alone (generalized OR, 1.37; 95% CI 1.11–1.69; *P*=0.004). The intracranial hemorrhage rates were higher in the EVT group (49% vs. 17%); however, the rates of sICH were not significantly different (6% vs. 3%).

The SELECT2 trial used a similar CT-based approach in patients presenting ≤24 hours from their last known well-functioning.[19] This prospective, randomized, open-label, adaptive, international trial was conducted across 31 countries. The trial underwent early analysis after 352 patients were enrolled because of positive results in the RESCUE-Japan LIMIT trial. Patients presenting within 24 hours of symptom onset with an anterior-circulation LVO were randomized by CT ASPECTS 3–5 or ≥50 mL ischemic core volume by CT perfusion (e.g., relative cerebral blood flow <30% of the opposite hemisphere) or MRI (only three enrolled patients met the MRI criteria). Consistent with the results of other trials, EVT was superior to medical management alone (generalized OR, 1.51 for a shift in mRS distribution at 90 days). One patient who underwent EVT and two who underwent medical management developed sICH.

Clinical endpoints after extensive infarction

All trials used the 90-day mRS score as the primary efficacy endpoint. However, they variably used dichotomized mRS scores (mRS 0–3 in RESCUE-Japan LIMIT),[16] mean utility-weighted mRS scores (TESLA),[17] or median mRS scores (TENSION, ANGEL-ASPECT, SELECT2, LASTE).[15,18,19,22] The TENSION, ANGEL-ASPECT, SELECT2, and LASTE trials all showed significantly higher rates of functional independence (mRS score 0–2), whereas the endpoints of the RESCUE-Japan LIMIT and TESLA trials lacked significance in the same direction (Table 1). Significant mortality benefits were observed in the TENSION and LASTE trials (Table 1). The benefit of thrombectomy persisted at 1 year follow-up in the SELECT2 and TENSION trials.[22,23]

Across trials, EVT had a good safety profile, with low rates of sICH (1%–10%), which were not significantly different from the noninterventional groups (Table 1). However, parenchymal hemorrhage frequently occurs after reperfusion (30%–70%), and an NIHSS ceiling effect may have resulted in sizable hemorrhages not being considered symptomatic.

These recently completed large-core ischemia trials have greatly expanded the proportion of patients who would benefit from EVT. However, many questions remain unanswered, and several subgroups remain untested.

Imaging criteria and infarct size

These large-core trials suggest that several imaging paradigms may be sufficient to identify patients who are likely to benefit from EVT. Within the early time window, CT ASPECTS 0–5 (LASTE), CT ASPECTS 3–5 (TENSION, SELECT2, ANGEL-ASPECT), and MRI ASPECTS 3–5 (RESCUE-Japan LIMIT) identified eligible patients, whereas in the late time window, a large ischemic core was defined as 70–100 mL in ANGEL-ASPECT[18] and ≥50 mL in SELECT2[19] trials on the basis of MRI or CT perfusion. Although the TESLA trial did not meet its primary endpoint, outcomes were numerically better in patients selected by CT ASPECTS 2–5 ≤24 hours from symptom onset.[17] Core-adjudicated patient-level meta-analysis will help tailor simplified imaging selection criteria across time windows.

The results of these large-core trials challenge our understanding of the imaging findings that identify reversible ischemia versus irreversible infarction. Is the ischemic core truly infarcted? However, this issue remains to be resolved. In clinical practice, CT without contrast, CT with contrast (perfusion parameters), and DWI or apparent diffusion coefficient mapping can delineate tissue viability. However, the reliability of the current standards for imaging interpretation is suboptimal and could overestimate the extent of brain injury (e.g., ghost core on CT or CT perfusion and reversibility on DWI). All commonly used imaging modalities provide probabilistic estimates of ischemia and the risk of progression to infarction; however, these measurements are prone to technical failures and limitations. Additionally, although infarct volume is a critical determinant of functional outcomes, only 43% of the clinical recovery appears to be attributable to infarct size, suggesting that other factors play key roles in patient outcomes. Recent studies have suggested that reperfusion therapy can mitigate secondary injury due to cerebral edema and minimize infarct growth.[24]

Management of edema and neuroprotection

In the HERMES meta-analysis, which included data from five early-window EVT trials, thrombectomy and reperfusion in patients with large hemispheric infarctions were not associated with an increase in midline shift, except in those with a large core volume (>130 mL). However, in this subgroup, thrombectomy was indeed associated with a greater midline shift because of space-occupying ischemic edema.[25] Addressing cerebral edema and minimizing secondary injury in patients with large infarcts could potentially enhance the outcomes after reperfusion therapy.

Decompressive hemicraniectomy is considered a lifesaving procedure for patients with extensive tissue damage and early midline shift. The procedure reduces the risk of mortality and severe disability (mRS score >3), but it is also linked to a clinically significant rate of moderate to severe disability (mRS score 4–5) in survivors.[26] The American Heart Association and American Stroke Association guidelines suggest that a decompressive hemicraniectomy is a reasonable option for patients ≤60 years old who have large hemispheric infarctions and neurological worsening within 48 hours of symptom onset despite medical intervention. For patients in whom cerebral edema develops after an infarction, nonsurgical management options (notably osmotic agents such as hypertonic saline or mannitol) are considered safe; however, scant evidence from large prospective randomized controlled trials has confirmed their efficacy.[27] Given the limited treatment options for cerebral edema, there is an urgent need for new therapies that target the mechanisms underlying edema development and aim to prevent rather than treat life-threatening edema. No medical approach has been proven to prevent severe cerebral edema before the appearance of neuroimaging signs or clinical symptoms.

Emerging therapies for preventing cerebral edema focus on key mediators of water movement within the brain, such as aquaporin-4 and the SUR1-TRPM4 (sulfonylurea receptor 1–transient receptor potential melastin 4) channel. Aquaporin-4 plays a key role in the development of cytotoxic edema and in clearing excess fluid caused by vasogenic edema. Currently, several compounds that affect aquaporin-4 are in the early stages of development. Similarly, the SUR1-TRPM4 channel has been identified as a critical player in the formation and persistence of cerebral edema, which has led to the investigation of glibenclamide (intravenous glyburide)—a SUR1-TRPM4 channel blocker—as a potential treatment.[28] In the randomized phase 2 study GAMES-RP (Glyburide Advantage in Malignant Edema and Stroke), no significant differences in the primary outcome (mRS score 0–4 without decompressive hemicraniectomy at 90 days) were observed between treatment groups.[29] However, a significant reduction in 30-day mortality was observed in patients treated with glibenclamide compared with those receiving placebo. Despite these findings, the subsequent phase 3 trial CHARM (Glibenclamide for Large Hemispheric Infarction Analyzing mRS and Mortality) failed to demonstrate any significant benefit from glibenclamide on functional outcomes for patients with severe cerebral edema after a large hemispheric infarction.[24] This trial was stopped prematurely; however, hypothesis-generating subgroup analyses suggested that patients with an infarct volume <125 mL could benefit from the study drug. Whether additional research should be conducted on glibenclamide to mitigate edema after large hemisphere infarction remains uncertain.

Cytoprotection in patients with stroke aims to preserve brain tissue during the acute phase of ischemic injury to minimize the damage caused by reduced blood flow and oxygen supply. Many neuroprotective therapies have shown favorable effects in experimental models; however, their benefits have not been translated into successful clinical trials. However, recent studies have renewed interest in this research topic.[30,31]

Procedural considerations

No large core trials were prescriptive for specific procedural techniques, and all used a combination of approaches, including stent retrievers, aspiration catheters, and balloon guide catheters. The treatment providers determined the use of general anesthesia or conscious sedation. Future patient-level meta-analyses should investigate whether certain procedural techniques are associated with better outcomes. A few patients who presented with tandem lesions underwent angioplasty or stent placement. The optimal approach for tandem lesions (i.e., whether acute stenting leads to better outcomes despite the potential for hemorrhagic complications) remains unanswered and is the subject of ongoing randomized controlled trials.

Untested populations

As in previous EVT trials, trial enrollment was limited to patients with a good functional status at baseline. The TENSION trial enrolled patients with baseline mRS scores of 0–2.[22] The other five trials had more restrictive eligibility criteria (mRS scores of 0–1) (Table 1). The benefit of EVT in patients with preexisting disabilities is an area of active research that remains tailored to individual considerations. Because age was an exclusion criterion across multiple trial designs (SELECT2 included ages 18–85 years; TESLA included ages 18–85; ANGEL-ASPECT included ages 18–80; and LASTE included ages 18–80 for ASPECTS 0–3), very elderly patients were underrepresented. The role of EVT in the pediatric population has not been evaluated in any randomized controlled trial; however, several non-randomized studies have suggested its benefits, even in patients with large core infarcts.

As expected, patients were enrolled on the basis of severe clinical deficit (NIHSS ≥6), and the average NIHSS in the large core trials was high (mid-teens or higher). Mild clinical deficits are likely rare in patients with large core ischemia. The role of EVT in distal medium-vessel occlusion across core sizes is another area of interest. Results from three distal medium-vessel occlusion trials indicate no additional benefit of thrombectomy over medical therapy alone (DISTAL [Endovascular Therapy Plus Best

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Medical Treatment Versus Best Medical Treatment Alone for Medium Vessel Occlusion Stroke], ESCAPE-MeVO [Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions], and DISCOUNT [Evaluation of Mechanical Thrombectomy in Acute Ischemic Stroke Related to a Distal Arterial Occlusion]).[32-34] Two other trials are ongoing: DISTALS (Distal Ischemic Stroke Treatment with Adjustable Low-profile Stentriever)[35] and ORIENTAL-MeVO (Endovascular Treatment in Acute Intracranial Distal Medium Vessel Occlusion Stroke).[36] Depending on their results, the role of EVT in patients with large core infarct from distal medium vessel occlusion could require additional investigation.

Although EVT has proven beneficial for patients with basilar artery occlusion[5] and small core ischemia (posterior circulation ASPECTS ≥6, or ≥8 in patients aged 80 years or older), the benefit in larger core posterior circulation remains uncertain. However, infarct size is less related to prognosis in the posterior circulation than in the anterior circulation. For example, a patient with a large cerebellar or occipital lobe infarct may have a better outcome than a patient with a smaller infarct that affects the brainstem. The relevance of specific topologies for the posterior and anterior circulation remains unexplored.

A pooled patient-level meta-analysis from trials (ATTENTION [Endovascular Treatment for Acute Basilar-Artery Occlusion], BAOCHE [Basilar Artery Occlusion Chinese Endovascular Trial], BASICS [Basilar Artery International Cooperation Study], and BEST [Acute Basilar Artery Occlusion: Endovascular Interventions vs. Standard Medical Treatment]) that recruited patients with vertebrobasilar ischemic stroke who were randomly assigned to treatment with either endovascular therapy or standard medical treatment alone was performed in the VERITAS (Endovascular Therapy for Acute Vertebrobasilar Occlusion) study. Given the enrollment criteria, nearly all enrolled patients had a baseline pc-ASPECTS (posterior circulation Acute Stroke Prognosis Early CT Score) of 6–10. Only 13 (1%) of the 970 patients presented with a pc-ASPECTS of 4–5.[37] Recently, Chang and colleagues reported the efficacy of EVT on functional outcomes in patients with acute basilar artery occlusion and low pc-ASPECTS (6 or less) presenting within 24 hours. Patients who underwent thrombectomy had higher rates of favorable outcomes (34%) than those in the conservative group (22%). EVT was associated with reduced mortality without an increase in the risk of sICH.[38] These data support the benefit of EVT in select populations of patients with basilar artery occlusions, particularly in those with pc-ASPECTS of 4–6 and NIHSS of 10 or greater.

Implications for systems of care

The proven benefit of EVT in patients with large core ischemia has practical implications for current triage paradigms. A shift toward a more simplified imaging approach might be justified to reduce treatment delays because time is the only proven modifiable predictor of improved outcomes, apart from reperfusion. The reduced need for detailed delineation of pretreatment ischemic parameters may allow for improved triage of patients in the field and the use of a mobile stroke unit or a referral facility to direct the patient to the angiography suite, particularly within an early time window. With an anticipated increase in the use of thrombectomy, there will be a commensurate increase in the need for thrombectomy-capable centers and qualified neurosurgeons, which has repercussions on the allocation of hospital resources.

Conclusions

Remarkable advances have been made in the past decade, from neutral to resoundingly positive thrombectomy trials, resulting in an ever-expanding number of eligible patients, including those with early to late therapeutic time windows, posterior circulation occlusion, and large core ischemia. Still, a substantial percentage of patients do not regain functional independence and experience long-term complications. The recanalization hypothesis has advanced significantly with chemical and mechanical approaches for opening thrombosed blood vessels. Large-core trials have significant implications in terms of expansion of indications for EVT. The Society of Vascular and Interventional Neurology recently provided a class 1A recommendation for endovascular therapy in patients with anterior circulation stroke presenting within 6 hours from symptom onset, baseline mRS score 0–1, age 18–80 years, occlusion of the internal carotid artery or the M1 segment of the middle cerebral artery, and ASPECTS of 0–5 on non-contrast CT or MRI.[39] The Chinese Stroke Association provided a class 1A recommendation for EVT in patients with acute ischemic stroke who present with NIHSS ≥6 and ASPECTS ≥3, with occlusions in the internal carotid artery or M1 segment of the middle cerebral artery within 24 hours of last known normal functioning.[40]

The next era of advancing stroke care must focus on bridging the gap between successful recanalization and recovery. Efforts must target the acute, subacute, and chronic phases of stroke recovery, with treatments directed at impaired microcirculation, postischemic excitotoxicity, inflammation, immune dysregulation, edema, and gliosis using pharmaceuticals, biologicals, and stem cells. This exciting new phase in stroke therapy has broad implications for the development of novel treatments across the spectrum of neurological diseases.

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Author contribution

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