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Clinical Review

A NEW PARADIGM SHIFT IN ACUTE ISCHEMIC STROKE, LARGE VESSEL OCCLUSIONS, AND ENDOVASCULAR THERAPY

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☐ **Abstract—Background: In the past three years, there have been several major studies published on the use of endovascular therapy (EVT) in large vessel occlusion (LVO) acute ischemic stroke. With multiple publications in such a short amount of time, it is difficult to keep up with the evolving landscape of ischemic stroke therapy. Objective: This narrative review discusses recent randomized controlled trials evaluating EVT and its effects on acute ischemic stroke management. Discussion: Ischemic stroke is the most common type of stroke overall, and recanalization is the predominant focus in stroke therapy to improve outcomes. Treatment first focused on systemic thrombolysis for ischemic stroke, followed by studies evaluating the use of thrombolysis with EVT. Early research did not find a benefit to EVT; however, recent studies using current devices and with narrow selection criteria demonstrate significant benefit to EVT in LVOs. In patients with LVOs and perfusion mismatches, reperfusion rates are higher with EVT compared with systemic thrombolysis alone. Recognition of patients with small infarct cores and large areas of ischemic but salvageable brain tissue up to 24 h after symptom onset stresses the need for advanced imaging to recognize the target group. Conclusions: EVT technology for acute ischemic stroke has now become more efficient, minimizing complications and improving the efficacy of EVT. Several viable interventions for a small subgroup of patients with ischemic stroke up to 24 h after symptoms onset can significantly improve patient outcomes. Published by Elsevier Inc.**

☐ **Keywords—stroke; large vessel; occlusion; thrombolysis; endovascular**

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INTRODUCTION

According to the American Heart Association/American Stroke Association, the majority of acute strokes are ischemic in origin; accounting for over 80% of all strokes (1,2). This burden of disease leads to significant morbidity and mortality worldwide. Stroke is the fifth leading cause of death in adults, and death and disability due to ischemic stroke, as well as costs, will likely increase as the population ages (3,4). In acute ischemic stroke, there is typically a core infarct and an ischemic penumbra, resulting in central nervous system cellular changes (5–7). Reperfusion therapy attempts to salvage the penumbra (1,2). Currently, systemic intravenous (i.v.) alteplase administered within 4.5 h after symptom onset is the mainstay of therapy (1,2,8–10). However, many question its risk/benefit ratio in ischemic stroke (10–12). Regardless of efficacy, 4.5 h is a narrow therapeutic time window, and many contraindications such as recent surgery, coagulation abnormalities, and history of

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intracranial hemorrhage prevent patients from receiving systemic thrombolysis (1,2,10).

Ischemic stroke can be divided into three subtypes: large vessel, small vessel (lacunar), and cardioembolic (2,13). Large-vessel occlusions (LVO), a subset of acute ischemic stroke defined by occlusion of the carotid terminus, middle, or anterior cerebral arteries, are associated with reduced revascularization and effectiveness of systemic thrombolytics, and these types of strokes are associated with poorer prognosis (2,13–15). Endovascular therapies (EVT) offer a unique therapy that may improve the rates of rapid revascularization and patient functional outcomes (2). This article serves as a narrative review of the studies evaluating LVOs and EVT.

Literature Review Methods

The objective of this narrative review is to discuss recent randomized controlled trials (RCTs) published on the topic of EVT in acute LVO ischemic stroke. A PubMed search was conducted with the terms "Endovascular Therapy" and "Ischemic Stroke." We found 2849 unique citations using this search strategy. We excluded studies that were retrospective, observational, not in the English language, and non-full text. We further limited our search to include only RCTs. Our final in-depth analysis of RCTs evaluating EVT for acute LVO ischemic stroke included 12 studies (Table 1). We did not pool data for meta-analysis.

Outcomes

Although the primary outcome varied among studies, all RCTs assessed the modified Rankin score (mRs) at 90 days (some as a secondary outcome). The mRs is a commonly used scale to measure the degree of disability or dependence in the activities of daily living. A score of 0 represents the best possible neurological outcome with no symptoms at all, and a score of 6 represents death (Table 2).

DISCUSSION

Prior to delving into the specific trials, it is worth mentioning that the mRs is not an objective score. It is a clinician-reported measure of global disability, which is widely accepted in evaluating stroke patient outcomes. However, studies have shown a poor inter-rater reliability of the mRs due to its subjectivity (16,17).

The initial set of trials evaluating EVT in combination with systemic thrombolysis used the first-generation MERCI™ (Concentric Medical, Inc., Mountain View, CA) (Mechanical Embolus Removal in Cerebral Ischemia) retriever system (Table 1 details study characteristics, and Table 3 provides a summary of study results). The first EVT trial published was IMS-III (Interventional Management of Stroke) in 2013 (18). This was a phase 3, randomized, open-label clinical trial with a blinded outcome. There were 656 patients eligible to receive systemic thrombolysis within 3 h after stroke symptom onset. Patients then underwent a 2:1 randomization scheme to EVT plus standard care or standard care alone. The primary outcome in this trial was the proportion of patients with mRs of ≤ 2 at 90 days. There was no statistical difference in this outcome (EVT 40.8% vs. systemic i.v. thrombolysis 38.7%; absolute adjusted difference 1.5%; 95% confidence interval [CI] −6.1–9.1), and investigators stopped the study early due to futility (18).

The next EVT trial was MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy), also published in 2013 (19). This study was a phase 2b, randomized controlled, open-label, clinical trial assigning patients within 8 h after onset of large-vessel, anterior circulation strokes to receive EVT plus standard care or standard care alone. Investigators randomized 118 patients to mechanical embolectomy vs. standard care based on imaging demonstrating a favorable vs. nonfavorable penumbral pattern. The primary outcome was mean 90-day mRs. Again, there was no statistical difference in the primary outcome (embolectomy

Table 1. Study Characteristics

Study	Year	Patients n	Primary Outcome	Hours to Intervention
IMS – III	2013	658	Proportion of patients with mRs < 2 at 90 days	3
MR RESCUE	2013	118	Mean 90 days mRs	8
SYNTHESIS	2013	181	Survival free of disability (mRs 0–1)	6
MR CLEAN	2015	500	mRs at 90 days	6
ESCAPE	2015	316	mRs at 90 days	12
EXTEND IA	2015	70	Reperfusion at 24 h and early neurologic improvement	4.5
SWIFT PRIME	2015	196	mRs at 90 days	6
REVASCAT	2015	206	mRs at 90 days	8
THRACE	2016	414	mRs at 90 days	5
THERAPY	2016	108	mRs at 90 days	4.5
DAWN	2017	206	mRs at 90 days	24
DEFUSE 3	2018	182	mRs at 90 days	16

mRs = modified Rankin score.

Table 2. Modified Rankin Score

Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

3.9 vs. standard care 3.9; $p = 0.99$), and the study also demonstrated no difference in mortality or intracerebral hemorrhage between groups (19).

The final study published in 2013 was the SYNTHESIS trial (Endovascular Treatment for Acute Ischemic Stroke) (20). This was a pragmatic, multicenter, open-treatment, randomized clinical trial of 362 patients with acute ischemic stroke, presenting within 4.5 h of symptom onset. Patients were randomized again to EVT vs. systemic i.v. thrombolysis. The primary outcome was survival free of disability, which was defined as a mRs of ≤ 1 at 3 months. Once again, the results were not statistically significantly different (EVT 30.4% vs. systemic i.v. thrombolysis 34.8%; absolute difference 4.4%; 95% CI 0.53–1.27; $p = 0.37$) (20).

Although the first three trials that were published in 2013 found no statistical or clinical differences in the primary outcome based on mRs, it is worth mentioning that subsequent trials had two key differences. First, patients had to have radiographically proven intracranial proximal occlusion with either computed tomography angiography or magnetic resonance angiography. Second, newer retrievable stents were used, as opposed to the first-generation MERCI devices. The MERCI retriever system was the first system to be used and was originally designed for foreign body removal, comprised of a wire covered with platinum coil to improve visibility, which is inserted through a braided microcatheter to a position distal to the thrombus (21). It takes the shape of a corkscrew and is slowly pulled back under continuous aspiration. The Solitaire™ (Medtronic, Dublin, Ireland) and Trevo™ (Stryker, Kalamazoo, MI) retrievers, on the other hand, are a self-expanding stent-like mesh of wires delivered through a microcatheter within the thrombus, entrapping the clot and withdrawing it back into a delivery catheter (stent retrievers) (21).

The first study demonstrating benefit for EVT in acute ischemic stroke was MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for acute Ischemic Stroke in the Netherlands), published in 2015 (22). This was a pragmatic, phase 3, multicenter, randomized clinical trial of intra-arterial treatment plus usual care or usual care alone. Investigators enrolled 500 patients from 16 medical centers with proximal arterial occlusion in the anterior cerebral circulation confirmed on imaging that could be treated within 6 h of symptom onset. The primary outcome was mRS at 90 days. There was a statistically significant difference in median mRs at 90 days (intervention mRs 3 vs. control mRs 4; adjusted common odds ratio [OR] 1.67; 95% CI 1.21–2.30). One of the secondary outcomes of this study was also the mRs of ≤ 2, which favored the EVT arm (intervention 32.6% vs. control 19.1%; adjusted OR 2.16; 95% CI 1.39–3.38; number needed to treat [NNT] = 7) (22).

The ESCAPE trial (Endovascular Treatment for Small core and Anterior Circulation Proximal Occlusion with emphasis on Minimizing CT to Recanalization Times), also published in 2015, was a multicenter, prospective, randomized, open-label, controlled trial of patients with acute ischemic stroke with small infarct cores, proximal intracranial arterial occlusions, and good collateral circulation, diagnosed on neuroimaging up to 12 h after

Table 3. Study Outcome Summary

Study	Year	Patients n	Hours to Intervention	Disability Benefit	Number Needed to Treat
IMS – III	2013	658	3	No difference	–
MR RESCUE	2013	118	8	No difference	–
SYNTHESIS	2013	181	6	No difference	–
MR CLEAN	2015	500	6	13.5% benefit	7
ESCAPE	2015	316	12	23.7% benefit	4
EXTEND IA	2015	70	4.5	31% benefit	3
SWIFT PRIME	2015	196	6	25% benefit	12
REVASCAT	2015	206	8	15.5% benefit	7
THRACE	2016	414	5	11% benefit	9
THERAPY	2016	108	4.5	No difference	–*
DAWN	2017	206	24	36% benefit	3
DEFUSE 3	2018	182	16	28% benefit	4

mRs = modified Rankin score; NNT = number needed to treat.
* The THERAPY trial did not have statistically significant difference in disability benefit between treatment arms.

Table 4. Vision, Aphasia, Neglect (VAN) Emergent Large Vessel Occlusion Screening Tool

Assessment	Criteria
How weak is the patient? Raise both arms up	- Mild (minor drift) - Moderate (severe drift, touches or nearly touches ground) - Severe (flaccid or no antigravity function) - Patient shows no weakness (VAN Negative)
Exceptions to this first component include confused/comatose patients with dizziness, focal findings, or no reason for altered mental status, then consider basilar artery thrombus and obtain CTA	
Visual disturbance	- Field cut (which side) (4 quadrants) - Double vision (ask patient to look to right then left; evaluate for uneven eyes) - New-onset blindness - None
Aphasia	- Expressive (inability to speak or paraphasic errors); do not count slurring of words (repeat and name 2 objects) - Receptive (not understanding or following commands; close eyes, make fist) - Mixed - None
Neglect	- Forced gaze or inability to track to one side - Unable to feel both sides at the same time, or unable to identify own arm - Ignoring one side - None
Patients must have weakness and one or all of the VAN criteria present to be VAN positive for LVO. - VAN positive patients demonstrated 100% sensitivity and 90% specificity for large vessel occlusion.	

CTA = computed tomography angiography; LVO = large-vessel occlusions; VAN = vision, aphasia, neglect assessment.

symptom onset (23). Investigators randomized 316 patients to standard care vs. standard care plus EVT up to 12 h after symptom onset. This study was stopped early due to efficacy. The primary outcome was functional independence at 90 days, which was statistically significant in this study (adjusted common odds ratio 3.1; 95% CI 2.0–4.7). One of the secondary outcomes was mRs $\leq$ 2 at 90 days, which favored the intervention arm (EVT 53% vs. standard care 29.3%; adjusted rate ratio 1.7; 95% CI 1.3–2.2; NNT = 4) (23).

The EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial) trial was also published in 2015 (24). This was another multicenter, prospective, randomized, open-label, blinded-endpoint, controlled trial. Investigators randomized 70 patients to 0.9 mg/kg of alteplase <4.5 h after onset of ischemic stroke plus EVT with the Solitaire FR stent retriever or systemic thrombolysis alone. The study was stopped early due to efficacy. The primary outcome was median percentage of ischemic territory undergoing reperfusion at 24 h and early neurologic improvement (>8-point reduction on the National Institutes of Health Stroke Scale, or a score of 0–1 at day 3). Patients receiving EVT demonstrated improved outcomes for imaging reperfusion (EVT 100% vs. alteplase 37%; adjusted OR 4.7; $p < 0.001$) and for symptom improvement (EVT 80% vs. alteplase 37%; adjusted OR 6.0; $p = 0.002$). This also correlated with their secondary outcome of functional independence at 90 days (EVT 71% vs. alteplase 40%; $p = 0.01$; NNT = 3) (24).

SWIFT PRIME (Solitaire With the Intention for Thrombectomy as PRIMary Endovascular Treatment) was the next trial published in 2015 (25). This was an international, multicenter, prospective, randomized open controlled trial. Investigators randomized 196 patients to systemic i.v. alteplase or EVT within 6 h after stroke symptom onset, but the study was stopped early due to efficacy. The primary outcome was median mRs at 90 days, which was statistically significantly different (EVT 2 vs. control 3; $p < 0.001$). Again, one of the secondary outcomes of this trial was rate of functional independence at 90 days, which was defined as an mRs $\leq$ 2 and favored EVT (EVT 60% vs. control 35%; $p < 0.001$; NNT = 12) (25).

REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device vs. Best medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset) was the final randomized trial published in 2015 (26). This was a multicenter, sequential, open-label, phase 3 randomized controlled trial with blinded evaluation of patients with stroke symptoms within 8 h, with confirmed proximal anterior circulation occlusion and absence of large infarct on neuroimaging. Investigators randomized 206 patients to medical therapy (systemic i.v. alteplase when eligible) vs. EVT with the Solitaire stent retriever. The primary outcome was mRs at 90 days, which favored patients receiving EVT (EVT 43.7% vs. medical therapy 28.2%; adjusted OR 2.1; 95% CI 1.1–4.0; NNT = 7). Investigators stopped the trial early due to loss of equipoise (26).

THRACE (THRombectomie des Arteres CErebrales) was the first of two trials published in 2016 (27). This was an RCT consisting of patients aged 18–80 years with acute ischemic stroke and proximal cerebral artery occlusion. Investigators randomized 414 patients to i.v. thrombolysis alone vs. i.v. thrombolysis plus mechanical thrombectomy. The primary outcome was functional independence at 90 days, which, as in previous studies, was defined as an mRS $\leq$ 2. There was a statistically significant difference favoring EVT (53% vs. 42%; OR 1.55; 95% CI 1.05–2.30; NNT = 9) (27).

The second RCT published in 2016 was THERAPY (The Randomized, Concurrent Controlled Trial to Assess

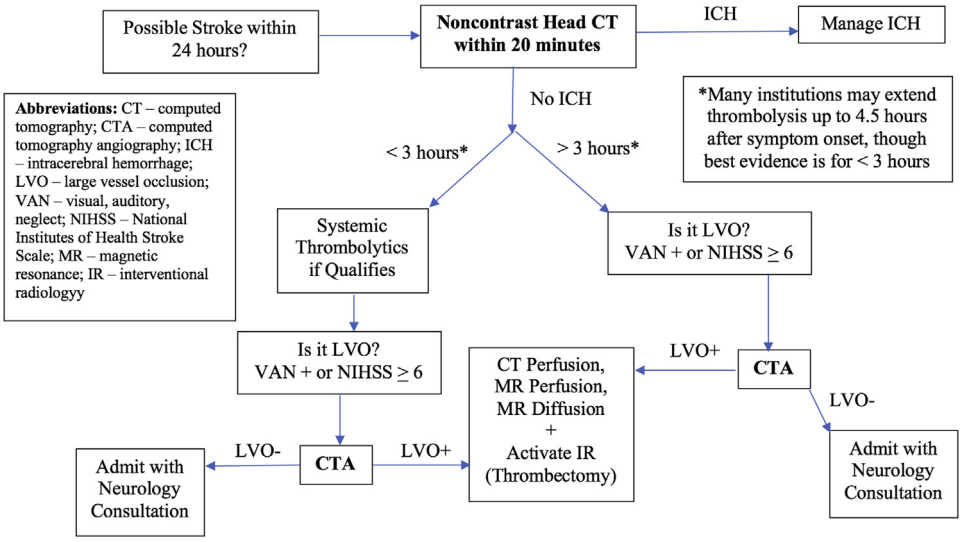

Figure 1. Ischemic stroke algorithm incorporating assessment for large vessel occlusion.

the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke) (28). This was an international, multicenter, prospective, randomized, open-label, blinded-endpoint, controlled clinical trial. Investigators randomized 108 patients to aspiration thrombectomy after i.v. alteplase vs. i.v. alteplase alone. The primary outcome was percentage of patients achieving functional independence at 90 days. After a string of statistically significant studies, this was the first to not show statistically significant benefit of EVT (38% vs. 30%; $p = 0.52$). However, investigators halted the study early due to external evidence of EVT benefit (28).

The DAWN Trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo), published in 2017, was the first trial looking at extended time windows for EVT (29). This was a multicenter, prospective, randomized, open-label clinical trial. Investigators randomized 206 patients to thrombectomy plus standard care vs. standard care alone. There were multiple primary outcomes, but the primary outcome of interest was rate of functional independence (mRs $\leq$ 2) at 90 days. Patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery, last known to be well between 6 and 24 h, with mismatch in clinical deficit and infarct volume, comprised the patient population studied. The rate of functional independence (mRs $\leq$ 2) was statistically significant and favored thrombectomy (49% vs. 13%; absolute difference 36; adjusted difference 33; 95% credible interval 21–44; NNT = 3) (29).

The final trial published was the DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) in 2018 (30). This was a multicenter, randomized, open-label trial with blinded outcome assessment. Investigators randomized 182 patients to thrombectomy plus medical therapy vs. medical therapy alone if they arrived 6–16 h after stroke symptom onset and had ischemic brain tissue with initial infarct size <70 mL and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8. The primary outcome was mRS score at 90 days, but one of the secondary outcomes was functional independence (mRs $\leq$ 2) at 90 days. There was again a statistically significant difference favoring EVT for functional independence at 90 days (45% vs. 17%; $p < 0.001$; NNT = 4) (30).

Analysis

It is important to note that successful reperfusion (whether by systemic thrombolytics alone or via EVT) does not guarantee improved outcomes. Revascularization will not benefit the patient if there is no or minimal viable tissue (2). This is similar to placing a stent in a coronary artery when the myocardium is already dead.

Many of the trials were stopped early during planned and unplanned interim analysis. As a result, the magnitude of benefit for EVT may be over-inflated in many of these trials. Despite this limitation, there seems to be a specific patient population that benefits from EVT. Recruitment into each of the studies reviewed averaged approximately 1–2 patients per month per center; the vast majority of stroke patients will not fit these inclusion parameters. Only patients with an LVO (occlusion of the middle cerebral artery, anterior cerebral artery, or distal intracranial internal carotid artery) with a small core infarct and large penumbra may benefit from EVT.

Based on the overwhelming number of positive studies, the American Heart Association/American Stroke Association released new guidelines for the treatment of acute ischemic stroke at the beginning of 2018 (2). These recommendations concerning EVT are as follows (2):

"Patients eligible for i.v. alteplase should receive i.v. alteplase even if EVTs are being considered." – Level IA

"In patients under consideration for mechanical thrombectomy, observation after i.v. alteplase to assess for clinical response should not be performed." – Level III: Harm

"Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: 1) prestroke mRS score of 0 to 1; 2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); 3) age ≥ 18 years; 4) NIHSS [National Institutes of Health Stroke Scale] score of ≥ 6; (5) ASPECTS [Alberta Stroke Program Early CT Score] of ≥ 6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset." – Level IA

"Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS [acute ischemic stroke] in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs." – Level IIb

"Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries." – Level IIb

"Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score > 1, ASPECTS < 6, or NIHSS score < 6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed." – Level IIb

"In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended." – Level IA

"In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable." – Level IIa

"The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 angiographic result to maximize the probability of a good functional clinical outcome." – Level IA

"As with i.v. alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible within the therapeutic window." – Level IA

"Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device." – Level IA

"The use of mechanical thrombectomy devices other than stent retrievers as first-line devices for mechanical thrombectomy may be reasonable in some circumstances, but stent retrievers remain the first choice." – Level IIb

"The use of a proximal balloon guide catheter or a large-bore distal-access catheter, rather than a cervical guide catheter alone, in conjunction with stent retrievers, may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization." – Level IIa

"Use of salvage technical adjuncts including intra-arterial thrombolysis may be reasonable to achieve mTICI 2b/3 angiographic results." – Level IIb

"EVT of tandem occlusions (both extracranial and intracranial occlusions) at the time of thrombectomy may be reasonable." – Level IIb

"It is reasonable to select an anesthetic technique during endovascular therapy for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics. Further randomized trial data are needed." – Level IIa

"In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP [blood pressure] ≤180/105 mm Hg during and for 24 hours after the procedure." – Level IIa

"In patients who undergo mechanical thrombectomy with successful reperfusion, it might be reasonable to maintain BP at a level < 180/105 mm Hg." – Level IIb

"For patients who otherwise meet criteria for EVT, a noninvasive intracranial vascular study is recommended during the initial imaging evaluation of the acute stroke patient, but should not delay i.v. alteplase if indicated. For patients who qualify for i.v. alteplase according to guidelines from professional medical

societies, initiating i.v. alteplase before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible." – Level IA

"In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, is reasonable to provide useful information on patient eligibility and endovascular procedural planning." – Level IIa

"In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP [computed tomography perfusion], DW-MRI [diffusion-weighted magnetic resonance imaging], or MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy." – Level IA

"It may be reasonable to incorporate collateral flow status into clinical decision making in some candidates to determine eligibility for mechanical thrombectomy." – Level IIb

The updated guidelines also discuss regional systems of stroke care with centers capable of performing EVT (Level IA), use of telestroke networks for triaging patients with ischemic stroke who may be eligible for EVT (Level IIb), and need for primary stroke centers to develop the capability to perform noninvasive vascular imaging to select those patients eligible for EVT (Level IIb) (2).

Future Directions

There are many questions regarding EVT in ischemic stroke that require further investigation. In most of the studies, systemic thrombolytics were given to patients presenting within a prespecified time window (3 or 4.5 h) prior to EVT (1,2,10). However, it is unclear if systemic thrombolytics are beneficial given their low rate of recanalization, or, if they simply add to the potential for harm (31). Limited studies evaluating this question have not shown benefit to systemic thrombolytics plus EVT vs. EVT alone, but further research is needed (32–34). The clear benefit of adding CT perfusion or MR diffusion/perfusion imaging to identify patients with small infarcts and large penumbra is apparent in the later EVT studies. The utility of such imaging for all stroke patients is unclear, but should be investigated further. This may lead to a shift from the "time is brain" paradigm to a perfusion-based paradigm.

Finally, given the apparent benefit of EVT for LVOs, improving physician's ability to recognize LVOs is crucial. The current EVT RCTs utilized variable NIHSS cutoffs of 2, 6, 8, or 10 as the initial entry criteria for LVO consideration (19,22,23,25–30). More refined tools that can be quickly and accurately deployed are necessary. One potential tool is the vision, aphasia, neglect (VAN) assessment (Table 4). In a pilot study, the VAN assessment was found to be equally sensitive to an NIHSS $\geq$ 6, but with increased specificity (32). Additionally, the VAN score allowed rapid exclusion of 30% of patients in the cohort by a simple assessment of weakness (32). Further prospective, multicenter studies are necessary prior to system-wide institution of this approach, as well as patient groups requiring transfer to comprehensive stroke centers.

Potential Endovascular Therapy and Ischemic Stroke Workflow

With this potential benefit for EVT in LVO, two of the authors (SR, AS) created a potential workflow in consultation with Evie Marcolini, MD, to simplify how to achieve fast recanalization and potentially improve reperfusion rates (Figure 1). This will be dependent on the system in which a clinician works, but is generalizable to most emergency departments. This algorithm is most beneficial when utilized in combination with other specialties, including neurology, neurosurgery/neurointerventionalist, radiology, interventional radiology, and radiology technicians. The algorithm uses a positive VAN screening tool or NIHSS $\geq$ 6 as suggestive of LVO requiring further management.

CONCLUSIONS

Ischemic stroke is the most common form of stroke. Prior therapies focused on systemic thrombolysis within a specific time window of symptom onset. Patients suffering a large-vessel occlusion typically have poor outcomes, and recanalization may play a significant role in improving outcomes. Systemic i.v. thrombolysis has limited efficacy in recanalizing large thrombi in the central circulation, a narrow time window for administration, and significant risk of cerebral and systemic hemorrhage. Prior endovascular devices did not provide benefit, but more modern devices can significantly improve outcomes in patients with LVO. Therefore, EVT for acute LVO ischemic stroke is suitable for patients with ischemic stroke within 24 h of symptom onset (this includes "wake-up" strokes), evidence of proximal intracranial vessel occlusion on imaging, and advanced imaging (CT perfusion or MR perfusion diffusion) demonstrating a small infarcted core with a large at-risk penumbra. An efficient workflow should be

incorporated into clinical care to improve identification of this select group and improve access to EVT.

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ARTICLE SUMMARY

1. Why is this topic important?

Large-vessel occlusion acute ischemic stroke can result in significant patient morbidity and mortality, and new treatment options including endovascular therapy (EVT) demonstrate promise in improving patient outcomes.

2. What does this review attempt to show?

This review provides a focused update of the recent literature evaluating EVT in acute ischemic stroke management.

3. What are the key findings?

Acute ischemic stroke is the most common type of stroke overall, with recanalization the predominant focus in treatment. Though prior literature evaluating EVT did not find a benefit with older devices, recent literature using current devices with narrow patient selection criteria suggest benefit to EVT in large-vessel occlusion acute ischemic stroke. Reperfusion rates are higher with EVT, with improved patient outcomes. Recognition of patients with small infarct cores and large areas of ischemic but salvageable brain tissue up to 24 h after symptom onset stresses the need for advanced imaging to recognize patients who will benefit from this therapy.

4. How is patient care impacted?

EVT for large-vessel occlusion ischemic stroke in specific patient populations up to 24 h after symptom onset may significantly improve patient outcomes. Further evaluation is required defining time windows and transfer criteria.