Indications for Mechanical Thrombectomy for Acute Ischemic Stroke
Current Guidelines and Beyond

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Neurology® 2021;97:S126-S136. doi:10.1212/WNL.0000000000012801

Abstract

Purpose of the Review
This article reviews recent breakthroughs in the treatment of acute ischemic stroke, mainly focusing on the evolution of endovascular thrombectomy, its impact on guidelines, and the need for and implications of next-generation randomized controlled trials.

Recent Findings
Endovascular thrombectomy is a powerful tool to treat large vessel occlusion strokes and multiple trials over the past 5 years have established its safety and efficacy in the treatment of anterior circulation large vessel occlusion strokes up to 24 hours from stroke onset.

Summary
In 2015, multiple landmark trials (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, and EXTEND IA) established the superiority of endovascular thrombectomy over medical management for the treatment of anterior circulation large vessel occlusion strokes. Endovascular thrombectomy has a strong treatment effect with a number needed to treat ranging from 3 to 10. These trials selected patients based on occlusion location (proximal anterior occlusion: internal carotid or middle cerebral artery), time from stroke onset (early window: up to 6–12 hours), and acceptable infarct burden (Alberta Stroke Program Early CT Score [ASPECTS] ≥6 or infarct volume <50 mL). In 2017, the DAWN and DEFUSE-3 trials successfully extended the time window up to 24 hours in appropriately selected patients. Societal and national thrombectomy guidelines have incorporated these findings and offer Class 1A recommendation to a subset of well-selected patients. Thrombectomy ineligible stroke subpopulations are being studied in ongoing randomized controlled trials. These trials, built on encouraging data from pooled analysis of early trials (HERMES collaboration) and emerging retrospective data, are studying large vessel occlusion strokes with mild deficits (National Institutes of Health Stroke Scale <6) and large infarct burden (core volume >70 mL).
Reperfusion Hypothesis

Cerebral ischemia occurs when a blood vessel hypoperfuses the target tissue. The target tissue subsequently undergoes irreversible damage in a time dependent fashion with dead tissue referred to as “core” and at-risk tissue referred to as “penumbra.” The reperfusion hypothesis posits that the penumbra is salvageable tissue that can be rescued with expeditious and complete restoration of blood flow. Conversely, failure to restore blood flow inevitably results in the surrender of penumbral tissue to irreversible damage and expansion of the core. Early attempts to both intravenously and intra-arterially reinstate perfusion established proof of concept but safety and efficacy required further refinement. After numerous negative thrombolysis trials, the results of the NINDS tPA trial in 1995 demonstrated the superiority of IV tPA over placebo in patients presenting within 3 hours of symptoms.1 This prompted the Food and Drug Administration (FDA) to approve the use of IV tPA up to 3 hours in 1996. While subsequent studies such as the ECASS3 trial in 2008 further demonstrated the benefit of IV tPA over placebo in patients presenting within 3–4.5 hours of symptoms,2 the FDA did not find this data sufficient to grant supplemental biological license and the current on-label indication for IV tPA remains restricted to 3 hours.3

While the intravenous approach is more easily administrable and therefore more broadly available, the limited therapeutic time window as well as low efficacy13 for large vessel occlusions prompted interest in an endovascular approach. The Prolyse in Acute Cerebral Thromboembolism (PROACT I) trial enrolled patients presenting with a middle cerebral artery (MCA) occlusion within 6 hours of symptoms onset. Patients were randomized to local intra-arterial infusion of thrombolysis (r-proUK) vs saline. The trial was halted early due to the approval of IV tPA, however analysis revealed higher rates of recanalization with r-proUK (57.7%) vs placebo (14.3%). This landmark study was the first randomized controlled trial investigating the benefit of an intra-arterial approach for acute ischemic stroke and laid the groundwork for future investigations.14

Based on the encouraging results of PROACT I, the PROACT II study randomized a larger set of patients with MCA occlusions presenting within 6 hours of symptoms onset to receive a local infusion of r-proUK vs placebo over a 2-hour period.15 Both groups received low dose intravenous heparin (in PROACT I and II). Once again, higher rates of recanalization were noted in the lytic cohort and while there were higher rates of symptomatic hemorrhage in the treatment population, there was improved outcomes in the r-proUK group (40%) compared to the placebo group (25%). Despite the positive primary outcome, the FDA ultimately did not approve the use of r-proUK due to the small study sample size. In the first AHA/ASA acute ischemic stroke guidelines in 199416 intra-arterial therapy was considered investigational with level E evidence but in 200317 the results of PROACT II were extrapolated to alteplase based on consensus as supported by case series data.

An additional study conducted in Japan from 2002 to 2005 compared the efficacy of intra-arterial urokinase vs placebo for patients presenting within 6 hours of symptoms. This study was halted after the approval of IV tPA in Japan. Good outcomes were more frequent in the treatment arm; however, the results did not reach statistical significance due to limited sample size.18 In clinical practice terms, the results of these studies were extrapolated to tPA and this led to increased use of intra-arterial therapy, particularly in patients who did not respond to or qualify for IV tpa.

First Generation Technique Trials

To some extent, the promising experience with PROACT II and MELT likely led to some loss of equipoise among practitioners and thereby created barriers to conducting further randomized controlled trials. Nonetheless, the PROACT II introduced several important concepts relevant to future study design including the utilization of dichotomized modified Rankin Scale (mRS) of 0–2 as a primary endpoint for an acute ischemic stroke trial as well as expanding the treatment time window from 3 hours to 6 hours.15

Given lingering concerns of hemorrhagic complications associated with lytics, the development of mechanical devices for clot disruption and retrieval became of high interest. Several classes of devices were developed including lasers, ultrasonography, angioplasty and micro-snare. In 2004, FDA cleared the Merci retriever which consisted of a memory-shaped nitinol wire with helical loops that was delivered to the thrombus via microcatheter navigation. Approval was based on a single arm, prospective study of patients who presented within 8 hours of symptoms onset and were ineligible for IV tpa. Recanalization was achieved in 46% of patients and good outcomes were more frequent in the patients who experienced successful recanalization (46% vs 10%, p < 0.0001).17 Since the data was not a randomized comparison to a medical therapy, the FDA granted the 510K-pathway for clearance as a device for clot removal in acute ischemic stroke, however not for a clinical indication for reduced disability. Modelled after the reimbursement for craniectomy, the device company was successfully able to negotiate a diagnosis-related group reimbursement through the Centers for Medicare & Medicaid Services. The 510-k pathway was successfully pursued in 2007 for a second class of devices: reperfusion catheters with aspiration pump. This was based on the results of the single arm prospective pivotal Penumbra trial which enrolled patients who were ineligible or refractory to IV tpa presenting within 8 hours of symptoms onset.20 The use of mechanical thrombectomy was supported by a class II level B recommendation by the AHA/ASA.21

While intra-arterial therapy became increasingly available, there was no high-quality data to suggest that this approach...
was any more efficacious than medical therapy. Given the associated cost and variable availability, EVT was offered sporadically and the use of mechanical thrombectomy as of 2013 was only supported by a class II level B recommendation by the AHA/ASA. Three randomized controlled trials (IMS III, SYNTHESIS, MR RESCUE) were conducted to address the question of whether EVT as stand-alone or adjunctive therapy would lead to superior outcomes over IVT in patients presenting with acute ischemic stroke. While all the studies had slightly different trial designs, a majority of patients were treated with first generation technology (intrarotal alteplase, Merci retriever, Penumbra reperfusion catheter) with resultant low rates of recanalization. Additional trial limitations included: inclusion of patients without proven occlusion (lack of surgical target lesion in approximately 8% of patients) and established infarct (minimal salvageable tissue) as well as slow work flow. Furthermore, there was often failure to randomize all consecutive eligible patients, likely reflecting provider lack of equipoise. While the results were disappointing, the lessons learned galvanized efforts to design a second wave of trials focused primarily on more efficacious devices, appropriate patient selection and streamlined workflow.

### Stent Retriever Devices

In order to appropriately test the reperfusion hypothesis, a basic prerequisite is that vessel recanalization is achieved with complete (TICI3) or near complete recanalization (TICI2b). A major limitation of the first-generation devices was low efficacy with recanalization. For example, successful recanalization after thrombectomy in the IMS3 trial was only 44% and even less in the MR RESCUE trial (27%). The rates of recanalization in the SYNTHESIS trial were not reported. Given the relatively low efficacy of intra-arterial thrombolysis with LVO, the MERCI retriever and first-generation Penumbra aspiration catheters, continued interest remained in further refining the mechanical thrombectomy approach. In cases where vessels could not be recanalized with available technologies, practitioners began resorting to angioplasty and intra-cranial stent placement as salvage methods. While there was technical success in opening the vessel, the need for subsequent dual anti-platelets to preserve implant patency complicates routine use of this approach given concerns for hemorrhagic complications. Nonetheless, the general principle of radially displacing the whole length of thrombus against the vessel wall while simultaneously incorporating the clot in the stent struts prompted the development of a new class of stent-like devices termed stent retrievers. Importantly, stent retrievers are subsequently withdrawn from the intra-cranial vasculature after clot engagement without significant vessel disruption and abrogate the need for dual antiplatelets.

The Solitaire Flow Restoration device is a self-expanding stent retriever that was compared to the predicate Merci retriever device in the SWIFT study. Rates of recanalization (TIMI 2 or 3) were significantly higher with the Solitaire device (61% vs 24%). A second stent retriever device, the Trevo retriever, was similarly compared against the Merci retriever device. Rates of recanalization (TICI 2 or higher) were significantly higher with the Trevo device (86% vs 60%). Superior clinical outcomes were observed in the stent retriever arm of both studies. The use of stent retriever devices over the Merci retriever for clot retrieval were supported by a class I level A recommendation by the 2013 AHA/ASA guidelines. Given the results of the SWIFT study and the TREVO2 study, both devices were cleared by the FDA in 2014. Similar to the Merci and Penumbra devices, the stent retriever devices were initially cleared for clot removal but not for reducing clinical disability.

### Early Time Window Trials

Given the improved recanalization rates, a new set of trials, predominantly employing the Solitaire and Trevo devices, studied the benefit of EVT therapy over medical therapy alone. MR CLEAN was a randomized controlled trial performed in the Netherlands that studied 500 patients presenting within 6 hours of symptoms onset related to an intra-cranial anterior circulation occlusion. Patients were randomized to receive...

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline mRS, mRS 0–2</th>
<th>Stroke burden</th>
<th>Occlusion location, % ICA/MCA-M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>95.8</td>
<td>ASPECTS ≥5: 94.4</td>
<td>91.6</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>N/A</td>
<td>ASPECTS ≥6: 97.2</td>
<td>97.2</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>N/A</td>
<td>N/A</td>
<td>91.2</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>mRS 0–1: 98.4</td>
<td>ASPECTS ≥8: 76.7</td>
<td>90.3</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>N/A</td>
<td>N/A</td>
<td>85.7</td>
</tr>
<tr>
<td>HERMES</td>
<td>N/A</td>
<td>ASPECTS ≥6: 90.5</td>
<td>90.8</td>
</tr>
<tr>
<td>DAWN</td>
<td>mRS 0–1: 100</td>
<td>Core ≤51 mL: 100</td>
<td>97.6</td>
</tr>
<tr>
<td>DEFUSE-3</td>
<td>mRS 0–2: 100</td>
<td>Core ≤70 mL: 100</td>
<td>99.5</td>
</tr>
</tbody>
</table>

Table 1: Frequency of Baseline mRS, ASPECT, and Site of Occlusion by Trial

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standard medical management (including IV tpa) alone vs adjunctive EVT. At 24 hours, 75.4% of the patients in the intervention had absence of residual occlusion as compared to 32.9% of the patients in the control group. Importantly, the primary end-point of mRS 0–2a at 90 days was higher in the treatment group (32.6% vs 19.1%) and the follow up infarct volume was smaller by 19 cc on average. This study was the first to demonstrate the benefit of EVT over usual care (including IV tpa).

The favorable results of MR CLEAN compared to IMS III have been attributed to several important study design considerations. In terms of patient selection, MR CLEAN required the documentation of an intra-cranial occlusion whereas initially the use of CTA was not routine during the enrollment of IMS III and vessel status was unknown in 47% of the patients.22 Of patients that underwent mechanical thrombectomy, nearly all cases (190 out of 195) used stent retrievers. In addition, a major concern of IMS III had been the slow enrollment (1–2 patients per center per year) which was attributed in part to treatments being offered outside the context of a clinical trial. This enrollment bias was minimized in MR CLEAN as all centers offering EVT participated in the trial and after policy changes in 2013, insurance reimbursement was only provided for patients being treated in the context of the clinical trial.

After the results of MR CLEAN were presented at the World Stroke Conference in the October of 2014, several ongoing EVT trials were either halted due to lack of equipoise or examined at a pre-specified interim analysis. In short order, the results of EXTEND-IA, ESCAPE, SWIFT PRIME and REVASCAT similarly confirmed the benefit of EVT over medical therapy.4-7 These trials were all published in 2015 and based on these cumulative results, the AHA/ASA guidelines were revised and supported a class I level A recommendation for patients with baseline good functional status (mRS 0–1) and treatment initiation within 6 hours of disabling stroke (NIHSS≥6) due to anterior circulation proximal occlusion (internal carotid artery, MCA segment 1) and small infarct (Alberta Stroke Program Early CT Score [ASPECTS] of 6 or better) should receive IV tpa and undergo stent retriever thrombectomy.27 In addition, the FDA expanded clearance for stent retrievers from simply clot removal to also reducing disability. The stent retrievers are the first and only class of neurothrombectomy devices cleared for clinical indication.

The rationale for these specific criteria was based on the AHA/ASA Level of Evidence grading algorithm requiring more than one positive trial specifying the various criteria to warrant a level A recommendation: baseline mRS 0–1 (SWIFT PRIME, REVASCAT), treatment within 6 hours (SWIFT PRIME, EXTEND-IA), ASPECTS 6 or better (SWIFT PRIME, ESCAPE) and NIHSS 6 or higher (ESCAPE, REVASCAT). Furthermore, a majority of the trials either excluded or minimally included occlusions involving or distal to the MCA segment 2 (MCA-M2). Table 1 provides trial specific inclusion criteria and Figure 1 provides a figure including the rates of recanalization and rates of functional independence in the intervention arm of early window thrombectomy trials.

Late Time Window Trials

While the ESCAPE trial randomized patients up to 12 hours and the REVASCAT trial enrolled patients treatable within 8 hours of time last seen well, very few patients were available from the 2015 clinical trials to determine the benefit of EVT in patients presenting beyond 6 hours of symptoms onset. Indeed, in the MR CLEAN study, benefit was no longer statistically significant if reperfusion occurred after 6 hours and 19 minutes of symptoms onset. A meta-analyses of the 5 trials was conducted as part of the HERMES collaboration (MR...
Beyond 6 hours, the physiologic basis for this approach has top-tier recommendation and of those, 58% were treated. 126 patients were treated outside of the AHA/ASA guidelines. Analyses of patients treated with EVT between 2012 to 2015, time-based paradigm has been increasingly adopted in favor of a purely tissue-based paradigm.33,34

Indeed, time has become well recognized as a treatment effect modifier for both IV and IA therapy and much of the stroke systems of care have evolved around the principle of streamlining workflow and reducing time delays. Nonetheless, it has also been long recognized that a subset of patients benefits from perfusion therapy even at late time windows and EVT has been offered off label routinely. In a single center analyses of patients treated with EVT between 2012 to 2015, 126 patients were treated outside of the AHA/ASA guidelines. Top tier recommendation and of those, 58% were treated beyond 6 hours.30 The physiologic basis for this approach has been predicated on the clinical observation that patients presenting after similar duration of symptoms onset will have variable established infarct31,32 and therefore a tissue-based paradigm has been increasingly adopted in favor of a purely time-based paradigm.33,34

In 2011, a multi-center study of 237 patients presenting with an anterior circulation occlusion treated beyond 8 hours of symptoms onset and selected based on perfusion imaging revealed rates of good outcomes comparable to those treated in the early time window with comparable safety profile.34 This “pre-DAWN” cohort of patients served as the rationale for a prospective trial comparing the benefit of EVT vs usual care in patients presenting between 6-24 hours. The DAWN trial was a multi-center study specifically comparing the benefit of Trevo thrombectomy to medical management in late time window patients.10,35 Patients were selected based on severe clinical deficit (high NIHSS) in the setting of a small established infarct (small core). This clinical-core mismatch paradigm successfully identified patients who benefited from EVT in the late time window and the trial was halted after a pre-specified interim analysis. Rate of functional independence at 90 days was 49% in the EVT group as compared with 13% in the control group.10

In 2012, the results of the DEFUSE-2 study demonstrated comparable rates of good outcomes after EVT in patients presenting within 6 hours vs beyond 6 hours as long as a target mismatch was identified on perfusion imaging.36 The target mismatch paradigm served as the basis for patient selection in the DEFUSE-3 trial.11 Similar to the DAWN trial, the DEFUSE-3 trial enrolled patients in the late time window (6–16 hours) with stent retrievers used in a majority of the cases (75%). After the DAWN trial results were presented in the May of 2017, the DEFUSE-3 trial was halted due to lack of equipoise and an early interim analysis at the time confirmed benefit of EVT over medical therapy in patients selected based on a tissue paradigm. Good outcomes in the treatment arm were 45% compared to 17% in the medical arm.11

Together, the results of the DAWN and DEFUSE-3 trials significantly expanded the time window in which acute stroke therapy could be offered. In 2018, the AHA/ASA guidelines were revised and supported a Class I level A recommendation for patients presenting in the 6–16 hours time window and class IIA level B-R recommendation for patients presenting in the 16–24 hours time window with baseline good functional status and disabling stroke (NIHSS≥6) due to an anterior circulation proximal occlusion (internal carotid artery, middle cerebral artery segment 1) and tissue at risk (as defined by trial

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Recommendation</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al. (1994)16</td>
<td>IA STK or UKN</td>
<td>Level V</td>
<td>Case series</td>
</tr>
<tr>
<td>Adams et al. (1996)49</td>
<td>IA STK or UKN</td>
<td>Level V</td>
<td>Case series</td>
</tr>
<tr>
<td>Adams et al. (2003)17</td>
<td>IA thrombolysis</td>
<td>Grade IB (0-6h)</td>
<td>PROACT2</td>
</tr>
<tr>
<td>Adams et al. (2005)20</td>
<td>IA thrombolysis</td>
<td>Grade IB (0-6h)</td>
<td>PROACT2</td>
</tr>
<tr>
<td>Adams et al. (2007)51</td>
<td>IA thrombolysis</td>
<td>Grade IB (0-6h)</td>
<td>PROACT2</td>
</tr>
<tr>
<td>Jauch et al. (2013)21</td>
<td>IA thrombolysis</td>
<td>Grade IB (0-6h)</td>
<td>PROACT2, MELT</td>
</tr>
<tr>
<td>Mechanical thrombectomy</td>
<td>Grade IIB</td>
<td>Merci, Penumbra</td>
<td></td>
</tr>
<tr>
<td>Mechanical thrombectomy</td>
<td>Grade IA (0-6h, M1/ICA)</td>
<td>MR CLEAN, REVASCAT, ESCAPE, SWIFT PRIME, EXTEND IA</td>
<td></td>
</tr>
<tr>
<td>Mechanical thrombectomy</td>
<td>Grade IA (0-6h, M1/ICA)</td>
<td>MR CLEAN, REVASCAT, ESCAPE, SWIFT PRIME, EXTEND IA</td>
<td></td>
</tr>
<tr>
<td>Mechanical thrombectomy</td>
<td>Grade IA (6-24h, M1/ICA)</td>
<td>DAWN, DEFUSE 3</td>
<td></td>
</tr>
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</table>

IA-Intraarterial.
criteria) to undergo stent retriever thrombectomy. While the treatment time window studied in trials has been limited to 24 hours, it appears that even patients presenting beyond 24 hours who otherwise meet DAWN criteria may be safely treated with comparable clinical outcomes to those treated within 24 hours.

### Treatment Eligibility Based on Current Guidelines

Given the time-sensitive nature of stroke intervention along with the complex infrastructure required to triage, treat and manage large vessel occlusions, the landscape of acute stroke has evolved dramatically with the eventual goal of offering all eligible patients this ground-breaking advancement. Paramount to allocating the appropriate resources involves understanding the number of patients that harbor large vessel occlusions and furthermore, how many of those would qualify for class IA treatment. Estimating the frequency of large vessel occlusions is primarily complicated by the definition that is applied as well as the population mix examined. In a recent meta-analysis of 16 studies examining the incidence of large vessel occlusions, the authors identified 9 different classification schemes. The prevalence ranged from 7.3% to 60.6% with a mean prevalence of 31.1% across all studies. While all definitions include ICA and MCA-M1 occlusions, there was variable inclusion of basilar occlusions or distal occlusions (MCA-M2, MCA-M3, ACA-A1, ACA-A2, PCA-P1, PCA-P2). Nonetheless, such data provides some estimate for the burden of disease that must now be considered as systems of care are being re-aligned and optimized.

The number of patients eligible for thrombectomy based on current guidelines has been addressed in several studies. In one analysis of 318 patients presenting with acute ischemic stroke over a one-year period, 7% of patients were eligible for EVT based on guideline criteria within the early time window. At a population level, this was estimated to be 11 potential EVT cases per 100,000 person-years. A single comprehensive stroke center analysis of 2,667 patients presenting with acute stroke revealed that 2.7% of all patients were EVT eligible based on DAWN or DEFUSE3 criteria. Importantly, 42% of all patients presenting in the 6–24 hours time window with anterior circulation large vessel occlusion were EVT eligible. In a nutshell, 93 in 100 acute ischemic strokes and 1 in 2 acute ischemic strokes with anterior LVO currently do not meet top tier criteria for thrombectomy. Given the disproportionate impact of LVO strokes on morbidity and mortality, thrombectomy should be offered to all eligible patients and reasons for ineligibility must be addressed.

### Table 3: Estimated Endovascular Thrombectomy Eligibility per Current and Projected Thrombectomy Eligibility Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligibility per AHA/ASA</th>
<th>Comprehensive stroke center eligibility(^{13,44}) (among all acute ischemic stroke), %</th>
<th>Population based eligibility (per 100,000 person years)</th>
<th>Total numbers in United States (extrapolation based on 680,000 acute strokes in US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6-hour AHA/ASA criteria</td>
<td>Yes. Eligible per AHA/ASA</td>
<td>12</td>
<td>18</td>
<td>81,600</td>
</tr>
<tr>
<td>6-24-hour AHA/ASA criteria</td>
<td>4</td>
<td>6</td>
<td>27,200</td>
<td></td>
</tr>
<tr>
<td>0-24 hours AHA/ASA criteria</td>
<td>7</td>
<td>11</td>
<td>108,800</td>
<td></td>
</tr>
<tr>
<td>0-6 Applying 0-6-hour criteria to 6-24-hour criteria (0-24 hours)</td>
<td>No. Potentially Eligible per meta-analyses and/or retrospective data but pending RCT confirmation</td>
<td>11</td>
<td>17</td>
<td>74,800</td>
</tr>
<tr>
<td>Including MCA-M2 occlusions (0-24 hours)</td>
<td>4</td>
<td>6</td>
<td>27,200</td>
<td></td>
</tr>
<tr>
<td>Including Basilar artery occlusion</td>
<td>4</td>
<td>6</td>
<td>27,200</td>
<td></td>
</tr>
<tr>
<td>Including Large Core Strokes (0-24 hours)</td>
<td>3.5</td>
<td>5</td>
<td>23,800</td>
<td></td>
</tr>
<tr>
<td>Including Low NIHSS stroke patients (0-24 hours)</td>
<td>3.5</td>
<td>5</td>
<td>23,800</td>
<td></td>
</tr>
<tr>
<td>Including all above (0-24 hours and beyond 24 hours)</td>
<td>21.3</td>
<td>33</td>
<td>144,840</td>
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</table>
large stroke burden in 21% of patients, poor baseline in 20% of patients, MCA-M2 site of occlusion in 23% of patients and vertebrobasilar site of occlusion in 24% of patients. Table 2 provides a concise tabulation of evolution of AHA/ASA guidelines over last 25 years. Certain population subgroups have not been tested in clinical trials and are currently under investigation, hence an analysis of potential need for thrombectomy is required. Based on the study conducted by Desai et al., Table 3 provides approximate estimation of current and projected thrombectomy eligible patients at a comprehensive stroke center in the United States and overall in the United States.

### Treatment for Medium Vessel Occlusions

Given the efficacy of IV tpa for smaller clot burden and hence more distal occlusions, a majority of the EVT trials either under-sampled or excluded MCA-M2 occlusions. An important consideration in this population is the anatomical variability of how much territory the occluded vessel supplies, particularly as it pertains to whether the occlusion is in the proximal or distal MCA-M2 or in a dominant or non-dominant MCA-M2 as well as what topographic regions the MCA-M2 supplies and how many MCA-M2 branches are present. Such heterogeneity has important implications for determining the risk/benefit profile of EVT. Given the paucity of high-quality data, the 2019 AHA/ASA guidelines have issued a class IIB recommendation for EVT in patients with a causative occlusion of the M2 or M3 portion of the MCAs. However, numerous single arm studies, non-randomized case-controlled studies and pooled meta-analyses of the EVT trials support the safety and efficacy of EVT for MCA-M2 occlusions.

In a meta-analysis of 12 studies with 1,080 patients undergoing MCA-M2 thrombectomy, good outcomes were noted in 59% of patients with 16% mortality and 10% sICH rates. A patient level meta-analysis of the early time window trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, THRACE, EXTEND IA, and PISTE) identified 130 patients with MCA-M2 occlusions. A majority were in the proximal location (proximal n = 116 vs distal n = 14). There were higher rates of good outcomes in the EVT group (58.2% vs 39.7%), particularly in those with proximal occlusions. The 2019 Society for Neuro-interventional Surgery guidelines have issued a class IA recommendation for thrombectomy in the MCA-M2 location. Furthermore, the feasibility of a randomized controlled trial in this population may be limited by lack of clinical equipoise by practitioners.

The issue of occlusions even more distal than the M2 location including the M3 location or occlusions in the anterior and posterior cerebral artery is even less studied. Figure 2 demonstrates a digital subtraction angiogram of 76 years old woman presenting with an acute ischemic stroke (NIHSS score of 9) and harboring a right MCA-M3 occlusion. Several case series have demonstrated the safety and feasibility of clot retrieval in both the anterior and posterior medium sized vessels however the benefit of this approach over the medical arm is poorly understood. With the development of small stent retrievers (“baby” Trevo, Tiger-13), larger size microcatheters (3 MAX, Headway-27) as well as adjunctive local intra-arterial thrombolytic infusion, there is increasing interest in testing the benefit EVT in this population.

### Treatment for Mildly Disabling Strokes

It has long been recognized that while stroke severity is a strong predictor of clinical outcome, a subset of patients with low NIHSS can do poorly with approximately of 30%–35% of patients having poor clinical outcome at 90 days. A majority of patients treated in the EVT trials had an NIHSS of 6 or higher and so there is limited data on this low NIHSS population. In a patient-level pooled analysis of the early time window trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA), the direction of effect favored EVT for the 177 patients with an NIHSS of 0–10, however the result was not significant and specific results on patients with an NIHSS of
0–5 were not reported. Several single center case series have demonstrated the safety and feasibility of EVT for patients with an NIHSS <6, however a recent multi-center study of 251 patients with large vessel occlusion in the setting of a low NIHSS managed with EVT vs medical therapy revealed no significant difference between the 2 groups. Likely the low NIHSS population is a heterogeneous group in which additional testing may be necessary to identify the higher risk population. Parameters such as elevated blood pressures, position dependent clinical stability, large perfusion deficit, and presence of motor or language symptoms may help identify the particularly vulnerable population. The benefit of EVT vs medical therapy will be investigated in the ENDO-LOW and MOSTE trials.

**Treatment for Large Core Patients**

Similar to stroke severity on presentation, infarct burden is a strong predictor of clinical outcomes in the acute ischemic stroke. Early data suggested that at a threshold of 70 cc, there was no benefit appreciated after EVT and a majority of the trials set an upper threshold of 50–70cc or ASPECTS of 6. In a patient level meta-analysis of the early time window trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and others),
THRACE, EXTEND IA, and PISTE), benefit after EVT was appreciated in patients with an ASPECTS of 6–10 as well as ASPECTS of 3–5 but not in patients with an ASPECTS of 0–2.28,55 Sample size was small in the low ASPECTS groups but importantly no signal of harm was noted in the large core populations. However, risks of reperfusion injury following recanalization of large stroke are important and several studies identify an increased incidence of post thrombectomy parenchymal hemorrhage amongst large burden strokes. Figure 3 demonstrates a non-contrast CT head-based ASPECTS score of 4 for a 56 years old woman presenting as an acute ischemic stroke with a NIHSS score of 24, time from stroke onset approximately 3 hours, and occlusion of the left internal carotid artery. Multiple additional retrospective and prospective studies of non-randomized have similarly confirmed the safety and feasibility of treating patients with large baseline infarct. The benefit of EVT is likely higher in younger patients, who are able to achieve functional recovery at larger infarct thresholds. The benefit of EVT vs medical therapy, amongst patients with large baseline infarct core and presence of substantial mismatch, will be investigated in the TENSION,56 TESLA57 and LASTE53 trials. Figure 4 demonstrates a CT perfusion map of an acute ischemic stroke patient harboring an acute left MCA-M1 occlusion with a NIHSS score of 22 and time from last known well of 6 hours. Baseline infarct volume is 101 mL (CBF <30%) and Tmax >6 seconds volume is 157 mL.

**Treatment in Advanced Age and Poor Baseline Patients**

While advanced age is a treatment effect modifier for outcomes after acute ischemic stroke, age per se is not considered a contra-indication for EVT. In multiple trials (MR CLEAN, EXTEND-IA, ESCAPE, DEFUSE-3), there was no upper age cutoff for trial inclusion. In a patient level meta-analysis of the early time window trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, THRACE, EXTEND IA, and PISTE53) of outcomes by age, the adjusted treatment effect was highest in patients with age 80 and higher. This likely reflects the particularly poor natural history of untreated large vessel occlusion in the advanced age population. A single center study of 30 nonagenarians undergoing thrombectomy demonstrated that a final infarct volume of <10 cc is a strong predictor of “return to home.”59

While age per se should not be considered a contra-indication for EVT, patients with poor baseline functional status and cognitive impairment were categorically excluded from all the EVT trials. Registry or single center studies of patients with pre-stroke disability have demonstrated that 20%–27% of patients will return to their baseline disability.60 Depending on individual patient and patient family preferences, treatment in these populations may be considered outside of guideline criteria.

### Special Populations

Although numerous trials have now demonstrated the benefit of EVT across numerous sub-groups, a majority of the trials excluded patients based on features related to demographics (age <18, pregnant), features that may compromise life expectancy (active cancer) or features that may increase the procedural risks (history of aortic dissection, intra-cranial aneurysm, endocarditis, thrombocytopenia, coagulopathy or underlying non-atherosclerotic vasculopathy). Multiple case series have demonstrated the safety and feasibility of EVT in these populations61–63 however efficacy will be difficult to demonstrate in the setting of a high quality randomized controlled trial given the rarity of these populations. This challenge highlights the importance of maintaining prospective multicenter registries of both treated and untreated large vessel occlusions irrespective of treatment eligibility.

### Conclusion

Acute ischemic stroke care has evolved dramatically as this year marks the 26th anniversary of the NINDS tpa trial and the 6th anniversary of the early time window trials. While the general concept of flow restoration is intuitive, the generation of high-quality data proving the benefit of IV therapy and subsequently EVT has been less straightforward and has required attention to appropriate patient selection, rapid work flow and effective treatments. High quality science ultimately informs societal guidelines and tilts organizations and policies to appropriate resources to maximize treatment opportunities. In the absence of high-quality data, treatments will continue to be offered off-label with provider and institutional variability. Irrespective of practice patterns, it is critical to maintain prospective registries and enroll patients in high quality clinical trials when possible.

### Study Funding

No targeted funding reported.

### Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

### Publication History

Received by Neurology May 21, 2020. Accepted in final form March 5, 2021.

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Indications for Mechanical Thrombectomy for Acute Ischemic Stroke: Current Guidelines and Beyond
Ashutosh P. Jadhav, Shashvat M. Desai and Tudor G. Jovin
*Neurology* 2021;97;S126-S136
DOI 10.1212/WNL.0000000000012801

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