

# Neuroendovascular management of emergent large vessel occlusion: update on the technical aspects and standards of practice by the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery

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## INTRODUCTION

Acute ischemic stroke (AIS) is the fifth leading cause of death, and remains the leading cause of disability in the USA.<sup>1</sup> There are an estimated 680 000 new strokes per year in the USA, with a mortality rate of 53–94%, and with an even greater morbidity.<sup>2</sup> It is estimated that 3–22% of these patients are candidates for endovascular therapy.<sup>3–6</sup> In addition to baseline stroke severity, emergent large vessel occlusion (ELVO) has been shown to be an independent predictor of poor outcome at 6 months.<sup>3,4</sup> While intravenous recombinant tissue plasminogen activator (IV r-tPA) has proven efficacious predominantly for small cerebral vessel occlusions, endovascular therapies, including stent retriever based, aspiration based mechanical thrombectomy techniques, and intra-arterial administration of thrombolytic agents, have been shown to achieve higher rates of recanalization in patients with ELVO.<sup>7–10</sup> The purpose of this document is to provide an update and critical assessment of technical aspects of the mechanical thrombectomy procedure.

## MATERIALS AND METHODS

This document was prepared by the Standards and Guidelines Committee of the Society of NeuroInterventional Surgery (SNIS), a multidisciplinary society representing the leaders in the field of endovascular therapy for cerebrovascular disease. A review of the English language literature published between January 1998 and March 2016 was conducted using search terms that included: ‘stroke,’ ‘ischemic stroke,’ ‘large vessel occlusion,’ ‘thrombectomy,’ ‘mechanical thrombectomy,’ ‘neurointerventional,’ ‘tPA,’ and ‘technique.’ Additionally, we incorporated already existing guidelines published by the American Heart Association

(AHA) and the SNIS.<sup>11–15</sup> The strength of the evidence supporting each recommendation was summarized using a scale previously described by the AHA guideline panels, and by the University of Oxford, Centre for Evidence Based Medicine.<sup>13 15–18</sup>

## DISCUSSION AND RECOMMENDATIONS

Much of our current practice in mechanical thrombectomy derives from recent randomized controlled trials (RCTs) which provide a foundation for treatment goals. The online supplementary tables 1–3 provide details of these thrombectomy trials, and elucidate selection criteria, patient characteristics, and outcomes for them.<sup>7–10 19–25</sup> These summaries show the variances in eligibility, patient characteristics, and outcome. One of the most notable variations is significant technical heterogeneity (even within each trial), including use of concomitant r-tPA, type of anesthesia, methods of access, flow arrest, and thrombectomy methods. However, to understand the role of each of these technical aspects, one must view them in the context of the desired endpoint: rapid and complete recanalization.

## Degree of recanalization and outcome

Establishing a critical level of reperfusion is paramount to achieving significant improvements in functional outcomes.<sup>26–30</sup> SYNTHESIS Expansion, Interventional Management of Stroke III (IMS III), and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) were prospective, randomized, open, blinded, endpoint (PROBE) trials conducted using almost exclusively intra-arterial fibrinolysis or first generation mechanical embolectomy devices.<sup>20–22</sup> The failure of these trials to demonstrate clinical benefit



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was attributed, in part, to the relatively low rates of recanalization.<sup>31</sup> Patients enrolled in IMS III who achieved partial recanalization (Thrombolysis in Cerebral Infarction (TICI) grade 2a) did not do as well as those with nearly complete or complete recanalization (TICI grade 2b/3).<sup>32</sup> Of the patients with TICI grade 2b/3 recanalization, 41.0% were discharged home compared with 17.4% of the TICI grade 2a group. Furthermore, with regard to functional outcome at 90 days, 34% of patients with TICI 2a had a modified Rankin Scale (mRS) score of 0–2 at 90 days versus 49% with a TICI grade of 2b/3.<sup>21</sup> In contrast, Multi-center Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME), and Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) all showed clinical benefit in the endovascular group; in these studies, stent retriever utilization resulted in effective TICI 2b/3 recanalization rates of 59–88%.<sup>7–10 19</sup> Therefore, successful mechanical thrombectomy, as defined by TICI grade 2b/3 reperfusion, should be an angiographic goal to be achieved expeditiously and safely (ASA Class I; Level of Evidence B-R).

## TECHNICAL CONSIDERATIONS

To achieve the most rapid and complete recanalization, practitioners are currently faced with several technical and periprocedural decisions, with significant practice variations and standards.

### Usage of r-tPA before and during thrombectomy

#### Intravenous thrombolysis

The two part National Institute of Neurological Disorders and Stroke (NINDS) stroke trial showed clinical benefit after early administration of IV r-tPA to eligible stroke patients within 3 hours of symptom onset.<sup>33</sup> This resulted in FDA approval for intravenous administration of r-tPA within 3 hours of stroke onset. Subsequently, the European Cooperative Acute Stroke Study III (ECASS III) expanded the window for IV r-tPA for a selected subgroup of AIS patients to 4.5 hours from stroke onset. While this has not resulted in an expanded FDA indication, administration between 3 and 4.5 hours after symptom onset has become a community standard, and national guidelines have endorsed fibrinolysis with IV r-tPA for up to 4.5 hours from symptom onset.<sup>34–38</sup>

Several trials and meta-analyses have shown that ELVO patients are unlikely to achieve recanalization with IV r-tPA alone, but it is important to note that there is no evidence for harm from IV tPA administration. Because of the possibility of benefit and the lack of clear evidence of harm, candidacy for thrombectomy should not preclude patients from receiving full dose IV tPA. However, the emphasis must be placed on rapidly proceeding to mechanical thrombectomy given the association between earlier treatments and better clinical outcomes.<sup>11 12 39–41</sup> Further, there should be no delay to assess the effect of IV tPA following administration. In agreement with AHA guidelines, patients who meet the criteria for on label use of IV tPA should receive IV tPA, irrespective of whether endovascular treatments are being considered (ASA Class I; Level of Evidence A).

#### Intra-arterial thrombolysis

Intra-arterial (IA) administration of r-tPA for stroke patients remains off label, reflecting an unapproved use of an approved drug. Usage of IA thrombolysis has varied among recent RCTs. EXTEND-IA and REVASCAT did not permit IA thrombolysis. In contrast, MR CLEAN, ESCAPE, and SWIFT PRIME allowed it as a 'salvage' measure. There are no outcome data comparing the use of IA r-tPA with mechanical thrombectomy using stent retrievers. Consequently, endovascular therapy with stent retrievers is recommended over IA fibrinolysis as firstline therapy (ASA Class I; Level of Evidence C-EO).

The Prolyse in Acute Cerebral Thromboembolism Trial I (PROACT-I) and PROACT II trials, the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) trial, and several meta-analyses, demonstrated the safety and efficacy of IA fibrinolysis when compared with placebo.<sup>42–45</sup> These IA therapies were not randomized against contemporary medical management, and so findings should be interpreted with caution. Thus IA fibrinolysis remains a reasonable option for patients who have contraindications to systemic use of intravenous thrombolysis, and in whom anatomy restricts the use of mechanical devices. Therefore, IA fibrinolysis has been demonstrated to be of benefit in carefully selected patients with major ischemic strokes of less than 6 hours' duration secondary to middle cerebral artery (MCA) occlusion (ASA Class I; Level of Evidence B-R). In those who have contraindications to IV r-tPA, however, the consequences are not well studied and caution is recommended (ASA Class IIb; Level of Evidence C-EO).

Variations exist in the literature regarding dosage of IA administration. In MR CLEAN, the maximal total dose of alteplase (r-tPA; Genentech, South San Francisco, California, USA) was 90 mg. In Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke (THRACE), a mean dose of 8.8 mg was administered to 11% of patients undergoing neuroendovascular therapy, with no impact on outcome.<sup>23</sup> Currently, a clinically beneficial dose of IA tPA is not well established, and should be individualized per patient.

#### Conscious sedation versus general anesthesia

There is significant controversy about the type of anesthesia used during thrombectomy. Indirect evidence in several trials raised concerns about the possibly deleterious effect of general anesthesia on clinical outcome, but earlier studies did not perform predetermined outcome analyses on this point. Among RCTs evaluating thrombectomy, general anesthesia has been used to varying degrees (see online supplementary table 2).<sup>8–10 20 23</sup> A recent meta-analysis pooled the results from nine studies enrolling 1956 patients (814 with general anesthesia and 1142 with conscious sedation), and found that patients undergoing general anesthesia had higher odds of death (OR=2.59; 95% CI 1.87 to 3.58) and respiratory complications (OR=2.09; 95% CI 1.36 to 3.23), and lower odds of good functional outcome (OR=0.43; 95% CI 0.35 to 0.53) and successful angiographic outcome (OR=0.54; 95% CI 0.37 to 0.80) compared with patients treated under conscious sedation.<sup>46</sup> However, the impact of selection bias in this meta-analysis limits its value for decision making in clinical practice. Subsequently, an RCT (Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA)) directly compared general anesthesia versus conscious sedation during endovascular stroke thrombectomy. Despite increased procedural complications with general anesthesia, there was no significant clinical outcome advantage to conscious sedation, as previously suggested.<sup>47</sup> Another recent RCT (Anesthesia During Stroke (AnStroke)) also found no difference in the rate of good

(mRS  $\leq 2$ ) outcomes at 90 days after thrombectomy in patients treated under conscious sedation (n=45) or under general anesthesia (n=45).<sup>48</sup> Hence, the choice of anesthetic technique during endovascular therapy should be individualized on the basis of anesthesia availability, patient risk factors, tolerance of the procedure, and other clinical characteristics. The superiority of conscious sedation over general anesthesia remains unclear (ASA Class IIb; Level of Evidence C-LD).

### Methods of access

Mechanical thrombectomy for acute ischemic stroke is most commonly performed through transfemoral access. However, difficult anatomy can lead to delays or even inability to reach the target vessel. Difficult catheter access, which may contribute to delays in revascularization, has been associated with lower recanalization rates and worse clinical outcomes.<sup>49</sup> In instances where the occluded vessel cannot be accessed quickly via a transfemoral approach, alternative approaches should be considered.<sup>50 51</sup> The most common alternative access routes in the setting of mechanical thrombectomy for acute ischemic stroke include transradial,<sup>52–54</sup> transbrachial,<sup>53–55</sup> transcervical–carotid,<sup>56–58</sup> and transcervical vertebral.<sup>59</sup> Overall, there is a low rate of groin complications in endovascular mechanical thrombectomy, even with the usage of large bore balloon guide catheters.<sup>60</sup> Reasons for choosing a non-femoral route may include vessel occlusion proximal to the target vessel (ie, femoral or aortic occlusion), tortuous aortic arch, brachiocephalic and carotid anatomy, and carotid ostial stenosis. One study identified hypertension, age >75 years, dyslipidemia, and left anterior circulation stroke as risk factors associated with difficult access.<sup>49</sup> The decision to attempt a transfemoral approach and convert to an alternative access route if necessary versus proceeding initially with an alternative access route may be aided by CT angiography or MR angiography of the head and neck to assess the vascular anatomy prior to intervention.

Several small series and case reports describe transcervical carotid access in the setting of acute ischemic stroke, with direct percutaneous puncture or a surgical cut down to access the carotid followed by cannulation with a 5–8 F sheath.<sup>56–58 61</sup> Ultrasound can be used when performing direct puncture. Closure of the artery may be performed with manual compression or various closure devices. The principal benefit of direct carotid access is avoiding any occluded, stenotic, or tortuous proximal anatomy. However, formation of a neck hematoma can result in life threatening airway compromise, and availability of prophylactic or rapid intubation is a necessity when performing this approach, particularly for patients who have received tPA or have other reasons for coagulopathy.

Transradial and transbrachial approaches have also been recently described for both anterior and posterior circulation strokes.<sup>52–55 62 63</sup> The radial artery is relatively superficial, easy to cannulate, and convenient for hemostasis compared with the more challenging transbrachial route. The ease of hemostasis is particularly attractive in the setting of tPA or other coagulopathies, and transradial has been described as a firstline approach in acute ischemic stroke.<sup>52</sup> The transbrachial approach offers similar access as the transradial approach in a larger caliber vessel which can then accommodate larger catheters, although hemostasis may be more difficult to achieve. The transradial or transbrachial approach is particularly useful for the ipsilateral posterior circulation, although both routes have been demonstrated to be appropriate for the anterior circulation as well.<sup>52 55</sup> Therefore, while transfemoral access remains the most widely used method, alternate routes, including transradial, transbrachial,

and direct carotid puncture, are technically feasible and should be employed if necessary to obtain recanalization (ASA Class IIb; Level of Evidence B-NR).

### Flow arrest/flow reversal and balloon guide catheter

Balloon tip guide catheters are meant to provide antegrade flow arrest, and possibly flow reversal, in the proximal artery during thrombectomy. MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, and REVASCAT did not require the use of a proximal balloon guide catheter for flow arrest in conjunction with stent retrievers.<sup>7–10 19</sup> However, the efficacy of flow reversal to prevent distal embolization during stent retrieval of the thrombus has been examined in a case series. A prospectively maintained registry identified 338 patients where balloon guide catheters were utilized. In patients undergoing stent retriever thrombectomy, procedure times were shorter, there was less need for adjunctive therapy, and the rate of TICI 3 score was higher.<sup>64</sup> However, since the patients were not randomized according to the use of a balloon guide catheter, and ‘use of balloon guide catheter’ was a secondary post hoc endpoint of the registry, selection bias and operator experience may have played a significant role in determining the results.<sup>64</sup> Recently, a comparison of balloon versus non-occlusive guide catheters was performed using the STRATIS (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) registry, and presented at the International Stroke Conference Annual Meeting.<sup>65</sup> Among 936 subjects in the registry undergoing thrombectomy, 54% had procedures utilizing a balloon guide catheter, while 32% of patients’ procedures included a distal large bore catheter, and 8% had a conventional guide catheter. The rates of first pass TICI 2B/3 were 68%, 55%, and 43% ( $P < 0.001$ ), respectively. Furthermore, the mean number of passes were  $1.7 \pm 1.1$ ,  $2.0 \pm 1.3$ , and  $2.2 \pm 1.6$  ( $P < 0.001$ ), respectively. Finally, while the overall rates of recanalization at the procedure conclusion were not significantly different, the rates of good clinical outcome (mRS 0–2) were 62%, 50%, and 45%, respectively ( $P = 0.001$ ). Hence, current evidence suggests that the use of balloon guide catheters is safe, effective, and may result in faster procedure times when used with distal access/aspiration catheters and stent retrievers (ASA Class IIa; Level of Evidence C-LD).

### Thrombectomy device choices and techniques

Based on multiple trials, the data suggest that the efficacy of stent retriever mediated mechanical thrombectomy has been established. Stent retrievers were utilized in approximately 80% of subjects in MR CLEAN and ESCAPE, as well as in all subjects in EXTEND-IA, SWIFT-PRIME, and REVASCAT. As a result, the AHA guidelines recommend the use of stent retrievers for prespecified endovascular candidates with AIS secondary to occlusion of the internal carotid artery or proximal MCA (M1) (AHA Class I; Level of Evidence A) and M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries (AHA Class IIb; Level of Evidence C).<sup>12</sup> However, these RCTs were not designed to evaluate differences among stent retrievers, or to evaluate additional techniques, such as pure thromboaspiration. Additional data now exist to further elucidate the role of thrombectomy tools and techniques.

A subgroup analysis of patients enrolled in MR CLEAN examined the effect on functional outcome of patients based on the choice of mechanical thrombectomy device used. Of the 233 patients allocated to the interventional arm of the trial, 124 (53%) were first treated with Trevo, 31 (13%) with Solitaire,

and 40 (17%) with other retrievable stents or mechanical devices. There was no association between device and treatment effect on functional outcome and all other secondary and safety outcomes.<sup>66</sup>

The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) was an international, multicenter, PROBE design superiority trial of aspiration thrombectomy for AIS in conjunction with a separator device. A stent retriever device was used to facilitate thrombus removal in approximately one third of patients. None of the patients in this trial were treated using modern thromboaspiration devices or techniques. The trial evaluated ELVOs with thrombi measuring  $\geq 8$  mm in length on thin section CT brain scans, randomizing to suction thrombectomy after IV r-tPA versus IV r-tPA alone. THERAPY was terminated prematurely after the publication of MR CLEAN and, with enrollment at 108 patients, did not achieve its primary endpoint of increased functional independence at 90 days.

Recent advances in thromboaspiration catheter technology and technique have led to major improvements in the efficacy and speed of cerebral aspiration thrombectomy.<sup>67</sup> Another observational study compared endovascular therapy with stent retrievers versus A Direct Aspiration First Pass Technique for the Endovascular Treatment of Stroke (ADAPT).<sup>24</sup> The study evaluated two groups with isolated internal carotid artery (ICA)/proximal MCA occlusion treated within 6 hours: stent retriever (n=119) versus an ADAPT direct aspiration first pass technique (n=124) with or without tPA. The primary outcome was defined as the total rate of TIC1 2b/3 recanalization. In the ADAPT treatment group, the rate of recanalization was 82.3% whereas in the Solitaire stent retrieval group the rate of recanalization was 68.9% (comparison 1.19 (CI 1.03 to 1.38),  $P=0.015$ ). Symptomatic intracerebral hemorrhage was 2.4% in the ADAPT group and 5.9% in the stent retrieval group. Equivocal clinical outcomes were observed, with 53% of ADAPT group patients having an mRS score of 0–2 at 90 days versus 54.8% of the stent retrieval patients (comparison 0.97 (CI 0.76 to 1.23),  $P=0.79$ ). Mortality at 90 days was not statistically different, with 22.6% in the ADAPT group and 17.4% in the stent retrieval group (comparison 1.30 (CI 0.77 to 2.19)  $p=0.32$ ). Another RCT, ASTER (Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke), was designed to compare the ADAPT technique with the stent retriever technique. While the final results are not yet published, preliminary results of completed enrollment were presented at the International Stroke Conference, and demonstrated no difference in the rates of TIC1 2B/3 recanalization (85.4% with ADAPT vs 83.1% with stent retriever,  $P=0.53$ ).<sup>68</sup> Furthermore, secondary endpoints, including embolization in a new territory and symptomatic intracranial hemorrhage, were not statistically different. Complicating this debate, there may be a difference in the efficacy of different devices with certain types of clot composition, although there are few data in this regard. Additional technical variations and standardized approaches have been reported in the literature noting particular retrieval techniques and/or combinations of reperfusion catheters and stent retrievers.<sup>69–73</sup> Whichever techniques are used, standardized approaches can minimize the risk and maximize speedy recanalization.<sup>74</sup> Therefore, in comparing currently available techniques, the superiority of stent retrievers versus thromboaspiration alone, versus combinational techniques, has not been clearly established. Given the published evidence, individualized choice of technique should optimize speed, high extent

of recanalization, and safety (ASA Class IIa; Level of Evidence B-NR).

### Emergent carotid stenting

In many of the multicenter, randomized controlled trials, data on emergent carotid stenting are lacking. In fact, critical cervical carotid artery occlusion was an exclusion criterion in several studies (MR RESCUE, THRACE, ADAPT vs Stent Retriever).<sup>22–24</sup> None of these studies recorded cervical stenting as a subgroup for outcome analysis. MR CLEAN reported a tandem (M1 and the ICA) occlusion rate of 27%, and an emergent carotid stenting rate of 12.9% in the intervention group when stent retrieval was utilized (n=233). Although emergent carotid stenting was not a subgroup for outcome analysis in MR CLEAN, extracranial ICA occlusion was: the OR favoring stent retrieval was 1.85 (CI 1.26 to 2.72) without extracranial ICA occlusion (n=354) while the OR favoring stent retrieval was only 1.43 (CI 0.78 to 2.64) with extracranial ICA occlusion (n=146). The ESCAPE trial did not record the percentage of patients who underwent emergent carotid stenting, but did use a cervical carotid occlusion subgroup for analysis: OR favoring stent retrieval of 9.6 (CI 2.6 to 35.5) in the carotid occlusion group versus OR of 2.2 (CI 1.4 to 3.3) if a carotid occlusion was not present.<sup>9</sup> EXTEND-IA reported an ICA occlusion rate of 31%, and an acute carotid stent rate of 8.6% in its thrombectomy treatment group (n=35).<sup>7</sup> REVASCAT reported an emergent carotid stent rate of 8.7% in its thrombectomy treatment group (n=103).<sup>19</sup> REVASCAT did not record cervical carotid stenting as a subgroup for outcome analysis, but did report a subgroup incorporating patients with both cervical ICA occlusion and intracranial ICA or M1 occlusion, favoring thrombectomy with an OR of 4.3 (CI 1.5 to 12.5) ( $P=0.82$ ). Based on these data, angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered, but the clinical utility is as yet not well established (AHA Class IIb; Level of Evidence C-LD). As importantly, tandem occlusion should not be considered a contraindication to mechanical thrombectomy. However, these data suggest that tandem extracranial cervical carotid occlusion is a common occurrence in AIS with ELVO, and those performing thrombectomy will be faced with decisions regarding emergent angioplasty/stenting. As such, future controlled studies, or at least additional registry data, are needed to assess safety and efficacy.

### CONCLUSION

The superiority of mechanical thrombectomy combined with medical therapy over medical therapy alone for ELVO is now well established. In order to achieve and improve on clinical outcomes noted in multiple randomized, multicenter prospective trials, neuroendovascular procedures must be performed with high standards of procedural as well as postprocedural care, minimal complications, and in the setting of highly organized systems for stroke care. Current research provides a platform for standards of practice in techniques of thrombectomy and its periprocedural care. To maintain quality of care in these techniques, thrombectomy should be performed by experienced neurointerventionists trained in formal practice standards. These techniques can and will be augmented with future research, which should be directed at improving preprocedural systems of care to further decrease treatment times, developing neuroprotective strategies and advanced imaging metrics for tissue selection to expand interventional time windows, and optimizing periprocedural care to augment thrombectomy with adjunctive therapies.

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