

Overview of Mechanical Thrombectomy Techniques

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The recently reported superiority of mechanical thrombectomy to intravenous thrombolytics has jettisoned endovascular intervention into the forefront of acute ischemic stroke (AIS) management. These successes have allowed a chance for recanalization for patients not meeting the strict eligibility criteria for intravenous thrombolytics. Stent retrieval and aspiration have emerged as two of the most popular and effective approaches for AIS thrombectomy. Since the beginning of mechanical thrombectomy with the Merci device (Stryker) and first-generation Penumbra aspiration system (Penumbra Inc), contemporary techniques have demonstrated reliable recanalization and improved clinical outcomes. Here, we review the use of stent retrieval and aspiration, as well as their synergy, in the management of AIS.

KEY WORDS: Acute ischemic stroke, Aspiration thrombectomy, M2 occlusion, Stent retrieval, Solumbra

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Until recently, the treatment for acute ischemic stroke (AIS) had focused on intravenous thrombolytic administration. In 2013, the publication of the Interventional Management of Stroke (IMS III),¹ Synthesis Expansion; A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS Expansion),² and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy³ trials reported no significant differences in functional outcome with endovascular therapy compared to standard therapy (ie, intravenous tissue plasminogen activator or tissue-type plasminogen activator [tPA]) alone. As a result, the 2013 American Heart Association (AHA)/American Stroke

Association guidelines for the early management of patients with acute ischemic stroke⁴ advised that the “ability to improve patient outcomes has not yet been established” for thrombectomy devices.

However, severe methodological flaws in these studies resulted in a design bias against endovascular therapy. In IMS III, 20% of patients randomized to receive endovascular treatment had no large-vessel occlusion. Furthermore, the thrombectomy devices used in the studies were antiquated and associated with unreliable recanalization rates. In SYNTHESIS Expansion, only 13% of patients underwent thrombectomy with a retrievable stent, which is a device that has been shown to result in recanalization rates up to 3 times greater than earlier devices.⁵

ABBREVIATIONS: ADAPT, a direct aspiration first pass technique; AHA, American Heart Association; AIS, acute ischemic stroke; COMPASS, Comparison of Direct Aspiration vs Stent Retriever as a First Approach; CRISP, CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project; CTP, computed tomography perfusion; DAWN, DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE 3, endovascular therapy following imaging evaluation for ischemic stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial; ICA, internal carotid artery; ICH, intracranial hemorrhage; IMS III, interventional management of stroke trial; MCA, middle cerebral artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; SWIFT PRIME, Solitaire with the Intention for Thrombectomy as PRiMary Endovascular Treatment; SYNTHESIS Expansion, Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke; THERAPY, the randomized, concurrent controlled trial to assess the penumbra system’s safety and effectiveness in the treatment of acute stroke; TICI, thrombolysis in cerebral infarction; tPA, tissue plasminogen activator or tissue-type plasminogen activator

TABLE. Successful recanalization, defined as Thrombolysis in Cerebral Infarction (TICI) 2b or 3, following endovascular procedures^a

Study	TICI 2b or 3 (%)	TICI 2b (%)	TICI 3 (%)
MR CLEAN ⁶	115/196 (58.7)	68/196 (34.7)	47/196 (24)
EXTEND-IA ⁸	25/29 (86)	11/29 (38)	14/29 (48)
ESCAPE ⁷	113/156 (72.4)	(data not available)	(data not available)
SWIFT PRIME ⁹	73/83 (88)	16/83 (19.3)	57/83 (68.7)
REVASCAT ⁴³	63/102 (65.7)	48/102 (47.1)	19/102 (18.6)

^aFrom Munich SA, Mokin M, Snyder KV, Siddiqui AH, Hopkins LN, Levy EI. Guest editorial: An update on stroke intervention. *Neurosurgery*. 2015;77(3):313-320,¹⁰ by permission of the Congress of Neurological Surgeons.

We have come a long way since the early days of endovascular mechanical thrombectomy using the Merci device (Stryker, Kalamazoo, Michigan). In 2015, the publication of the results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN),⁶ Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE),⁷ Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial (EXTEND-IA),⁸ and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME)⁹ demonstrated conclusively the superiority of endovascular therapy over intravenous tPA alone in patients with AIS due to large-vessel occlusion in the anterior circulation (Table).¹⁰ However, although these trials extended the time window past 4.5 h (the accepted window for intravenous tPA therapy), time constraints remain. It was not until the publication of the DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial¹¹ that patients with wake-up strokes (estimated to be 8%-50% of ischemic strokes^{12,13}) and those presenting beyond 8 h from symptom onset were routinely considered for revascularization therapy. The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial added to these data, including patients presenting between 6 and 16 h of symptom onset with a ratio of ischemic tissue (identified via computed tomography perfusion [CTP] or magnetic resonance perfusion imaging) to infarct volume of 1.8 or more.¹⁴ The investigators found that endovascular therapy plus standard medical therapy resulted in a higher percentage of functionally independent (modified Rankin Scale [mRS] score of 0-2) patients than standard medical therapy alone (45% vs 17%, $P < .001$).

The utility of perfusion imaging for the evaluation of stroke patients, particularly those presenting at times remote from their symptom onset, was evaluated in the CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project (CRISP).¹⁵ In this trial, CTP was used to differentiate patients with a small ischemic core and a large penumbra (ie, a target mismatch) from those without target mismatch. Patients with

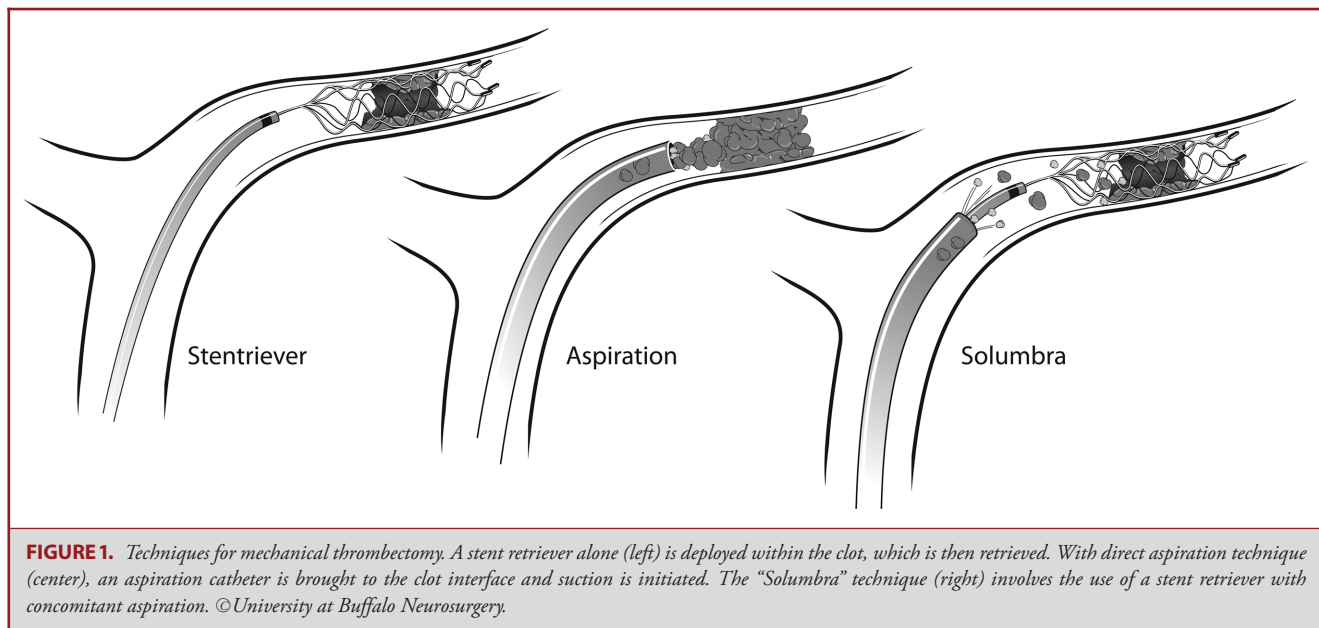
target mismatch were found to have a statistically significant higher rate of improvement on the National Institutes of Health Stroke Scale (NIHSS) of >8 points (83% vs 44% in those without target mismatch, $P = .002$). Importantly, this favorable rate of improvement remained regardless of whether patients were treated within or beyond 6 h. These findings not only highlight the utility of perfusion imaging in the evaluation of stroke but also add to the data of the DAWN and DEFUSE 3 trials demonstrating the efficacy of endovascular therapy beyond the traditional 6-h window.

However, recognition of the limitation of perfusion imaging in the posterior circulation and/or brainstem is essential. The criteria for patient selection for revascularization of posterior circulation stroke are less clear than those for anterior circulation stroke. Consequently, physician experience and judgment play an increasingly important role in patients with posterior circulation ischemic strokes. In the Registry on Revascularization in Ischemic Stroke Patients trial, time from onset to visualization of the occlusion and time from onset to mechanical thrombectomy were longer for posterior circulation stroke compared to anterior circulation stroke.¹⁶ This is likely due, at least in part, to the often vague and nonlocalizing symptoms of posterior circulation ischemia, which demand a high index of suspicion for stroke. Given the poor natural history of basilar artery occlusions, the threshold for intervention generally is accepted to be low and, therefore, intervention is favored in most cases.

The positive functional impact of endovascular revascularization reported in these trials has paved the way for further development in the field. The development and refinement of retrievable stents, utilization of and improvement in aspiration catheters, and use of techniques combining these strategies (Figure 1) are the subjects of intense investigation. Here, we review these technologies and therapies for the treatment of AIS.

RETRIEVABLE STENTS

The introduction of retrievable stents into the ischemic stroke mechanical thrombectomy treatment paradigm enabled stroke physicians to achieve reliable recanalization rates similar to those seen by cardiologists in the treatment of myocardial



infarction.⁵ The development of these devices was a significant improvement on the first-generation device (Merci retriever), with which unreliable recanalization resulted in unpredictable clinical outcomes.

Since the Food and Drug Administration’s approval of the first two retrievable stents—Solitaire (Medtronic, Dublin, Ireland) and Trevo (Stryker)—additional devices are rapidly being brought to market. Although they have minor variations in design with resultant purported benefits, they function similarly. First, the clot is crossed with a microcatheter. As the retrievable stent is unsheathed from the microcatheter, it deploys, integrating into the clot and providing immediate reperfusion. After a short time (typically 2–4 min) of allowing the stent to integrate into the clot, the stent and microcatheter are retrieved (hopefully), pulling out the clot.

With more than 80% of patients enrolled in MR CLEAN, EXTEND-IA, ESCAPE, and SWIFT PRIME undergoing thrombectomy with retrievable stents, these studies demonstrated the efficacy of this technique. Effective recanalization (thrombolysis in cerebral infarction [TICI] grade 2b or 3) was achieved in 58%–88% of patients in these studies. This resulted in rates of functional independence (mRS scores of 0–2) in 53% to 71%, a significant increase compared to the rates in those being treated with intravenous thrombolysis alone (mRS scores of 0–2 in 19%–40% of patients). These outcomes in the stent-retriever group were achieved safely, with symptomatic intracranial hemorrhage (ICH) rates ranging from 0% to 7.7% and not significantly different from the group receiving intravenous tPA alone. These results led to the application of mechanical thrombectomy with retrievable stents outside the inclusion criteria of randomized trials.

The successes of these early trials galvanized the development of “next-generation” retrievable stents. Although the Solitaire and Trevo devices remain widely used, the development of novel retrievable stent designs is demonstrating promising results. Use of the Penumbra 3D revascularization device (Penumbra Inc, Alameda, California) resulted in TICI 2b or 3 recanalization in 84% of patients when used in conjunction with the Penumbra aspiration system.¹⁷ The efficacy of the EmboTrap retrievable stent (Cerenovus/Johnson & Johnson, New Brunswick, New Jersey) was evaluated in the Analysis of Revascularization in Ischemic Stroke with EmboTrap trial.¹⁸ TICI 2b or 3 recanalization was achieved in 92.5% of patients with a first-pass TICI 2b or 3 recanalization in 51.5%.

Posterior Circulation

Stent retrievers have been used successfully for revascularization of the posterior circulation. Sonig et al¹⁹ reported a series of 12 basilar occlusions treated with retrievable stent mechanical thrombectomy. Effective recanalization (TICI 2b or 3) was achieved in 11 patients (91.7%). The median mRS scores were 2 at discharge and 1 at last follow-up.

Similarly, Kang et al²⁰ demonstrated successful reperfusion in 90.3% of patients with acute basilar artery occlusion who underwent thrombectomy with retrievable stents. Favorable functional outcome (mRS 0–2) was achieved in 46.9%. Gory et al²¹ achieved TICI 2b or 3 reperfusion in 72.2% and favorable functional outcome (mRS scores 0–2) in 34%. In these studies, the risk of hemorrhage was 2% to 5%.

When compared to the favorable functional outcome rates achieved in the anterior circulation, those reported after thrombectomy in the posterior circulation are lower. However,

this should not be interpreted as the retrievable stent being less effective. Rather, the comparison should be made to outcomes achieved after intravenous tPA alone for acute basilar occlusion, because the natural history of basilar artery occlusion is worse than that for anterior circulation occlusion. The rate of recanalization of basilar artery occlusions with intravenous tPA has been reported as low as 4%,²² and the rates of death or major disability range from 50% to 85%.²³⁻²⁶ When viewed in this context, it is clear that mechanical thrombectomy using retrievable stents provides improved outcomes.

Distal Occlusions

Mechanical thrombectomy with retrievable stents has been reported beyond the internal carotid artery (ICA) terminus and M1 segment of the middle cerebral artery (MCA). In a series of 52 patients with M2 occlusions, 30 were treated with retrievable stents.²⁷ The median National Institutes of Health Stroke Scale (NIHSS) score at discharge was 2, and there were no symptomatic ICH. A posthoc analysis of the Solitaire Flow Restoration Thrombectomy for Acute Revascularization, SWIFT, and SWIFT PRIME included 50 patients with M2 occlusions.²⁸ Successful reperfusion was achieved in 85%, and favorable outcome (mRS score 0-2) was achieved in 60%. The rate of symptomatic ICH was 2%.

Although stent retrievers are produced in smaller sizes, theoretically allowing their deployment in more distal MCA territories, the anatomy of the MCA complicates its delivery and retrieval. As the MCA transitions from the M2 to the M3 segment within the circular sulcus, an acute angle is formed. This angle provides an obstacle to pushing the stent retriever distally for deployment in the M3. Similarly, the location of the M3 segment in the sulcus, with limited anchoring to surrounding parenchyma, may complicate retrieval because the vessel may undergo extraordinary manipulation and/or torque. Therefore, with current technology and devices, the use of retrievable stents likely is limited to locations no further distal than the proximal M3 segment.

Expanding the Time Window

The resounding positive results of the DAWN trial¹¹ solidified the use of a stent retriever for thrombectomy in patients with favorable functional or perfusion imaging characteristics (indicating salvageable brain) who present beyond the traditional 6-h time window. This randomized, controlled trial included 206 patients with ICA or M1 occlusion who had last been known well 6 to 24 h earlier and who had infarct cores <51 mL. Recanalization at 24 h was achieved in 77% of patients who underwent thrombectomy (compared to 36% treated medically). Functional independence at 90 d was achieved in 49% of patients who underwent thrombectomy (compared to 13% treated medically). The rate of symptomatic ICH was 6%. These findings resulted in a modification of the AHA stroke guidelines to consider mechanical thrombectomy for patients presenting up to 24 h from symptom onset.²⁹

ASPIRATION

Most patients in MR CLEAN, EXTEND IA, ESCAPE, and SWIFT PRIME underwent mechanical thrombectomy using retrievable stents. Consequently, most subsequent series and/or trials used this method of thrombectomy. However, recent data suggest that aspiration provides an efficient and effective means of recanalization in patients with large vessel occlusions.

Historically, the use of direct (or contact) aspiration in the setting of acute intracranial occlusion was limited by the lack of catheters large enough to provide enough aspiration, yet flexible and atraumatic enough to navigate the tortuous intracranial vasculature. With newer aspiration catheters, these obstacles have been overcome, prompting the inclusion of aspiration alone in the armamentarium of stroke physicians.

In The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY),³⁰ 108 patients were randomized to receive thrombectomy via aspiration after intravenous tPA or intravenous thrombolytics alone. The study was halted after the publication of the results of the aforementioned trials in 2015. TICI 2b or 3 recanalization was achieved in 70% of patients. However, the study did not reach its primary endpoint because it was underpowered due to early termination.

The Contact Aspiration vs Stent Retriever for Successful Revascularization study³¹ was designed to test the efficacy of thrombectomy via aspiration compared to that performed with retrievable stents. The study included 381 patients. Recanalization (TICI 2b or 3) was achieved in 85.4% of patients in the aspiration group, which was not statistically different than that in the retrievable-stent group (86.2%). Functional independence (mRS score <3) was realized in 45.3% of patients undergoing aspiration—again, not significantly different from that in the retrievable-stent group (50.0%). Similarly, there was no difference in symptomatic ICH or procedure-related adverse events between groups. The similar outcomes of retrievable-stent and aspiration thrombectomy have been confirmed in other series that evaluated large-vessel anterior circulation occlusion.³²

These potential benefits prompted the development of a direct aspiration first pass technique (ADAPT) in which aspiration is attempted as the initial thrombectomy strategy. If unsuccessful, rescue therapy, which may include the use of a retrievable stent, is initiated. Using this strategy, effective recanalization and good neurological outcomes have been reported.^{33,34}

The efficacy of direct aspiration was confirmed in the recently completed Comparison of Direct Aspiration vs Stent Retriever as a First Approach (COMPASS) trial (Mocco J, Oral Presentation LB4, International Stroke Conference, January 25, 2018, Los Angeles, California). In this randomized controlled trial comparing Penumbra's aspiration system with first-line retrievable stent thrombectomy, the investigators found no difference in mRS scores at 90 d (90-d mRS score 0-2 occurred in 52% of patient treated with aspiration vs 49% of those treated with retrievable stents) or TICI 2b or 3 recanalization (92% aspiration

vs 89% retrievable stents). Additionally, there were no differences in secondary safety endpoints, such as distal embolization or symptomatic hemorrhage.

Proponents of contact aspiration thrombectomy cite decreased procedure time³⁴ and cost savings.³⁵ The COMPASS trial investigators found a nonsignificant trend toward faster revascularization (on average, 10 min faster) with aspiration compared to retrievable stent thrombectomy (Mocco J, Oral Presentation LB4, International Stroke Conference, January 25, 2018, Los Angeles, California).

Distal Occlusions

Contact aspiration thrombectomy may be ideally suited for distal occlusions. Because the microwire and microcatheter are navigable to distal vessels, delivery of the thrombectomy device is not as problematic as with retrievable stents. Additionally, no stent is deployed, so much less torque is applied to the target vessel when the catheter is retrieved.

Altenbernd et al³⁶ reported a series of 58 patients with M2 or M3 occlusions treated using ADAPT. Aspiration alone resulted in revascularization (TICI 2b or 3) in 83.9% with no symptomatic ICH. At 90 d, functional independence (mRS score <3) was achieved in 96.8%. In 2 smaller series including distal MCA, anterior cerebral artery, and posterior circulation (P1, P2, and P3) occlusions, recanalization (TICI 2b or 3) was achieved in 60% to 100% and favorable outcome (mRS score <3) occurred in 50% to 80%.^{37,38}

COMBINATION THERAPY

With the addition of the ADAPT thrombectomy techniques, significant research has gone into the need for salvage therapies. Although stent-retriever thrombectomy and direct-aspiration thrombectomy remain the 2 most dominant forms of thrombectomy, attempts to enhance rates of successful recanalization with combined therapy have shown recent success. This technique, known as “Solumbra,” involves the use of large-bore aspiration catheters and stent-retriever techniques simultaneously. Initial stroke trials including MR CLEAN, EXTEND-IA, ESCAPE, and SWIFT PRIME tended to use a switching strategy of either ADAPT or stent-retriever thrombectomy followed by stent-retriever thrombectomy as a salvage maneuver. Kang et al³⁹ demonstrated improved recanalization rates with the switching strategy with 85.1% of patients achieving TICI 2b or 3 recanalization vs 73.8% without the switching strategy. In addition, 3-mo functional outcomes were statistically significantly improved in patients treated with the switching strategy compared to those without.

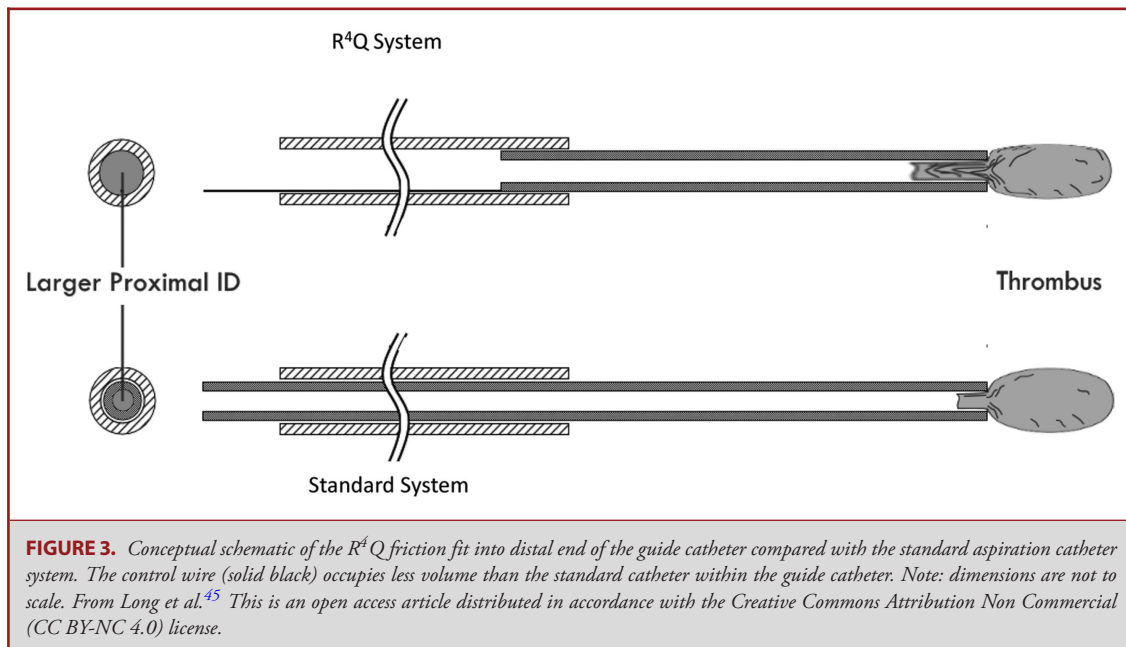
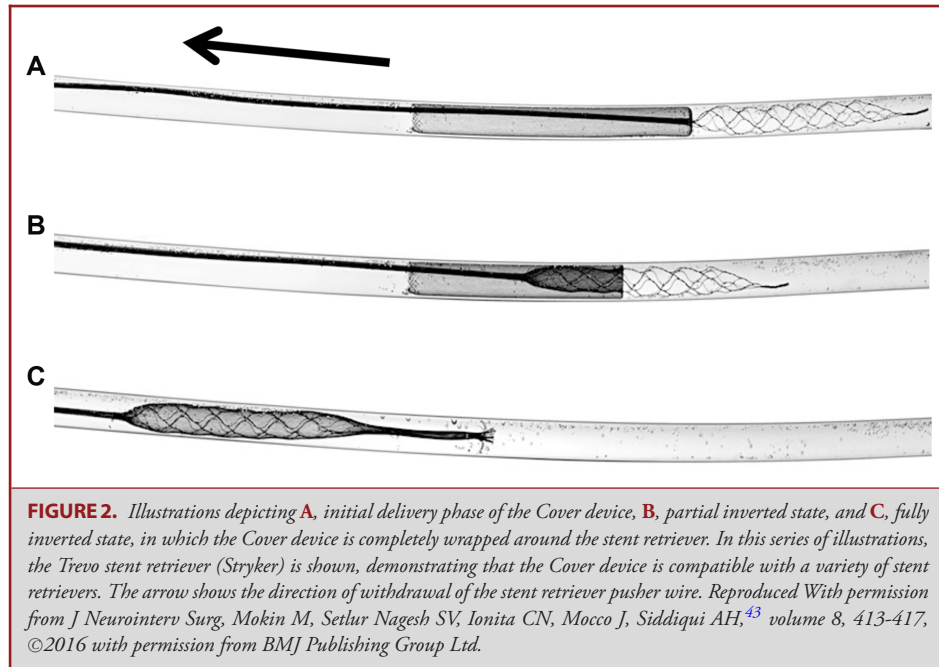
Since the advent of the switching strategy, the Solumbra technique has been more widely adopted. Lee et al⁴⁰ in 2013 demonstrated improved recanalization of ICA terminus occlusions with combined therapies, which was further supported by Humphries et al⁴¹ in 2015 to include combined therapies from 6 high-volume centers. Humphries et al supported the use of the

Solumbra technique, achieving 88% TICI 2b or 3 recanalization and 44% favorable mRS outcomes at 90 d. In 2016, Wong et al⁴² added to this group of patients in a retrospective analysis of 85 patients that demonstrated favorable recanalization in 88% of patients with an average of 1.9 passes of the retriever and favorable outcomes on discharge in 44% of patients.

Although Solumbra has proven to be a safe and effective means of recanalization, studies focusing on long-term outcomes in comparison to ADAPT and stent-retriever techniques are still needed. Using univariate analysis of the pooled data from SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT, several factors were thought to be predictors of poor long-term outcomes including age, initial NIHSS score, 24-h NIHSS score, and rates of successful revascularization (TICI 2b or 3). Such outcomes suggest that Solumbra may serve as a workhorse methodology for approaching thrombectomy. Further efforts are needed to identify modifiable risk factors for long-term morbidity in AIS patients. Delgado et al performed a retrospective analysis of 100 patients who had undergone Solumbra or ADAPT and found that the ADAPT group had statistically significant improved mRS scores at 90 d. This study included a cohort of patients who underwent ADAPT thrombectomy with a higher baseline NIHSS score and a higher proportion of ICA terminus occlusions. Successful recanalization was comparable between the 2 groups with an mRS score of 0 to 2 in the ADAPT group at 90 d being 55.6% compared to 30.9% with Solumbra. Although technique was an independent risk factor upon analysis, 29% of ADAPT thrombectomies required conversion to Solumbra to achieve successful revascularization.

FUTURE OF INTRA-ARTERIAL STROKE THERAPY

New aspiration catheters and retrievable stents are being developed at a rapid pace. Although an expansive, in-depth discussion of novel devices is beyond the scope of this manuscript, some novel device concepts are highlighted: The Lazarus Effect Cover (Medtronic) is designed to provide a protective sheath around retrievable stents to protect against distal embolization (Figure 2).⁴³ In an in Vitro model, no embolization to new territories occurred when the Lazarus Effect Cover was used.⁴³ A recent report of its use in 20 patients similarly demonstrated effective recanalization (TICI 2b or 3 in 95%) with no evidence of embolization in new territories.⁴⁴ The R⁴Q aspiration catheter (MIVI Neuroscience Inc, Eden Prairie, Minnesota) can be thought of as “a catheter on a stick.” The proximal three-quarters of the catheter shaft are eliminated and instead consist of a 0.018-inch control wire. The distal one-quarter of the catheter functions as an extension of the guide catheter, allowing the full guide catheter to be used to deliver suction (Figure 3).⁴⁵ Initial testing of this catheter demonstrated increases in flow rates by 21.9%, 24.7%, 61.9%, and 244.7% for 6F, 5F, 4F, and 3F designs, respectively, compared to size-matched traditional aspiration catheters.⁴⁵



Even though the results of the DAWN trial were published recently (initially January 4, 2018), investigators are already looking ahead. In patients who otherwise met DAWN inclusion criteria but were >24 h beyond the time last known well (the mean time from last known well to time of groin puncture was 48 h), TICI 2b or 3 recanalization was achieved in 81% and good neurological outcome (mRS score 0-2) was achieved in 43%.⁴⁶ The rate of symptomatic ICH was 5%. Comparing these results

to those of the DAWN trial, there was no significant difference in any of these parameters.

With the resounding positive results of numerous clinical trials evaluating the efficiency safety, and efficacy of mechanical thrombectomy, the standard of care for the treatment of patients with anterior circulation large-vessel occlusion is clear. However, this benefit should not be limited to these select patients. As we have discussed, although not in the form of randomized

controlled trials, patients with occlusions of the posterior circulation and distal vessels have been shown to benefit from mechanical thrombectomy. The future of the field is bright and we should continue to explore the uncharted waters of endovascular recanalization, to thoughtfully and systematically push the boundaries of current therapies. Considering that constraints of intravenous tPA administration resulted in its use in only 2.4% of stroke patients in 1 study assessing its utilization,⁴⁷ the expansion of stroke treatment lies not in the realm of systemic thrombolytics, but rather in the purview of the endovascular intervention.

Disclosures

Dr Levy discloses the following: shareholder/ownership interests—Intratech Medical Ltd, NeXtGen Biologics. Principal investigator: Medtronic US SWIFT PRIME Trials. Honoraria: Medtronic. Consultant: Pulsar Vascular. Advisory Board: Stryker, NeXtGen Biologics, MEDX, Cognition Medical. Other financial support: Abbott Vascular for carotid training sessions. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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