

The Current State of Stroke Therapy Endovascular Surgery for the Treatment of Intracranial and Extracranial Vascular Disease

A review of past and future topics in ischemic stroke care.

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The year 2019 has come to an end; the end of a decade and the beginning of one of the most fabled of futuristic years in cinema. For decades, the year 2020 has been portrayed as the pinnacle of human advancement and achievement, the age of artificial intelligence (AI), and more. This past decade saw both the rise (2010), the fall (2013–2014 with IMS-III,¹ SYNTHESIS Expansion,² and MR RESCUE³), and the resurgence (2015–present, starting with MR CLEAN⁴) of likely one of the greatest modern therapies medicine has to offer—mechanical thrombectomy.

The past year has seen its fair share of achievement both within medicine and beyond. The progress of the last year serves as a reminder of the triumph of human spirit over adversity. On October 12, 2019, Eliud Kipchoge advanced predictions for mankind by more than a decade by running the first sub-2-hour marathon (1 hours, 59 minutes, 40 seconds), a mark that modern statistical extrapolations gave a 10% chance of occurring in 2032.⁵ On his achievement, Kipchoge stated, “I can tell people that no human is limited.” The story of the sub-2-hour attempt best exemplifies how people, technology, and passion drive unthinkable outcomes. It took 41 elite pace runners, shoe technological advancements, and one failed attempt last year to bring about this feat. Speaking on passion, Kipchoge noted, “...only the disciplined ones in life are free; if

you are undisciplined, you are a slave to your moods and passions”—a point that registers not only within athletics but also within many occupations, including academic medicine.

INNOVATION CONTINUES IN ENDOVASCULAR STROKE THERAPY

This year in endovascular therapy for stroke, the field continued the momentum from the 2018 successes of the DAWN and DEFUSE 3 studies.^{6,7} As a field, it was recognized that the time window is no longer critical to successful patient outcomes but rather the individual patient tissue window, a unique characteristic born out of collateral supply.⁸ This year, there was a deep dive into techniques of thrombectomy by testing stent retrieval versus contact aspiration. COMPASS is a multicenter, randomized, noninferiority study that found that contact aspiration was a safe and efficacious alternative to stent retriever thrombectomy in a pool of 270 patients with large vessel occlusion (LVO).⁹ This will give practitioners alternative strategies that can be leveraged against difficult clots. Intravenous tissue plasminogen activator (alteplase) use up to 9 hours after symptom onset (the current standard is up to 3–4.5 hours after symptom onset) was tested in a randomized setting and was found to be beneficial, with modified Rankin Scale (mRS) scores of

0 to 1 reported in 35% of alteplase users and 29% of the placebo group. Advanced imaging was used for patient selection.¹⁰ Symptomatic intracranial hemorrhage occurred in 6.2% of patients receiving alteplase. Whether this finding will change the current guidelines remains to be seen. Although not completely new to 2019, the use of mobile applications such as Rapid AI (iSchemaView) and Viz LVO (Viz.ai) have revolutionized stroke triage, allowing practitioners immediate access to radiographic patient data for quick interventional decision-making.

There is a need for more nonrandomized, noncontrolled, real-world data to evaluate the generalizability of data gleaned from more rigorously selected, smaller cohorts in larger, more diverse populations. As such, more real-world experiences have been published. An investigator-initiated, industry-independent, prospective registry from 25 sites in Germany studied a cohort of 2,794 patients with LVO, revealing successful reperfusion 83% of the time,

with 37% of patients achieving a good outcome at 3 months.¹¹ The investigators concluded that high rates of success were possible on a country-wide scale but that mortality appeared slightly higher than that seen in randomized settings. This serves as a reminder regarding continued careful patient selection and meticulous training of future generations of neurointerventionalists.

There have been many recent technologic advancements not only in catheter technology and stent retriever design (eg, the PROST study currently underway comparing the Solitaire device [Medtronic] to the pRESET device [phenox GmbH] [NCT03994822]), but also in x-ray fluoroscopic technology with the addition of high-definition angiography,¹² which will likely revolutionize device design and future therapies.

What can we learn from previous years? Saber et al recently examined all neurointerventional clinical trials registered between 2007 and 2018 and found that among 206 trials across 1,691 medical centers, acute

TOP HEADLINES OF 2019 IN STROKE

► Aspiration Therapy Alone Is Noninferior to Stent Retriever Thrombectomy

Studies comparing a direct aspiration first-pass technique with stent retriever thrombectomy are limited. Benefits of direct aspiration include reduced procedural time and costs. With the COMPASS trial showing noninferiority of direct aspiration alone versus stent retriever thrombectomy, this opens the door for alternative thrombectomy strategies in patients presenting with acute ischemic stroke.

► High-Definition Angiography Shows Promise; Could Dramatically Change Device Design and Visualization

In a blinded-rater clinical utility study of images obtained during deployment of flow diversion devices for treatment of internal carotid artery aneurysms, high-definition-mode images were chosen at a frequency of at least 95% by two raters, and images were rated as much better than flat panel detector images with a frequency of 73% on average (60 image pairs). With continued advancements in imaging quality, device design enhancements can be expected, which in turn could lead to improved neurointerventional procedural outcomes.

► The Deep Dive Into Low ASPECTS, High NIHSS Score LVOs Continues

Recent studies have shown less malignant transformation of low ASPECTS, high NIHSS score strokes with

recanalization. This is possibly related to a reduction in edema in recanalized patients.¹³ Mortality benefit has also been noted. These findings have set the stage for randomized trials, including TESLA.

► Mobile AI Applications Help Facilitate Interventional Decision-Making

The use of mobile applications has revolutionized stroke triage, providing immediate access to radiographic patient data for quick interventional decision-making.

► Stenting for ICAD Revolutionized by Advances in Catheter and Stent Design and Improved Protocols

Learning from previous studies and implementing careful patient selection, a watchful waiting protocol prior to stenting, and utilization of newer-generation devices, patients with symptomatic ICAD have experienced positive results and a low complication rate.

► Neuroprotection Is the Next Frontier to Be Explored in Endovascular Therapy

Studies of neuroprotective strategies for small vessel occlusions and LVOs in animal models have not clearly translated into a standard of care for clinical use. Studies evaluating high-flow normobaric oxygen and use of a N-methyl-D-aspartate inhibitor are underway.

TOP ARTICLES OF 2019

- **Aspiration Thrombectomy Versus Stent Retriever Thrombectomy as First-Line Approach for Large Vessel Occlusion (COMPASS): A Multicentre, Randomised, Open Label, Blinded Outcome, Non-Inferiority Trial.**

Turk AS 3rd, Siddiqui A, Fifi JT, et al. Lancet. 2019;393:998–1008.

In 270 patients with LVO, contact aspiration was found to be a safe and efficacious alternative to stent retriever thrombectomy, giving practitioners another strategy to manage difficult clots.

- **WEAVE Trial: Final Results in 152 On-Label Patients.**

Alexander MJ, Zauner A, Chaloupka JC, et al. Stroke. 2019;50:889–894.

This postmarket surveillance study of patients with symptomatic ICAD who met FDA on-label usage

criteria and underwent angioplasty and stenting demonstrated a low periprocedural complication rate and excellent safety profile.

- **Clinical Benefit of Thrombectomy in Stroke Patients With Low ASPECTS Is Mediated by Oedema Reduction.**

Broocks G, Hanning U, Flottmann F, et al. Brain. 2019;142:1399–1407.

Reducing brain edema after thrombectomy for patients with LVO and low ASPECTS has been suggested to improve outcomes and decrease malignant syndrome transformation. Malignant transformation of infarcts was noted in 44% of persistent occlusions compared with 26% of recanalized vessels.

stroke was the most studied condition and was included in 33% of trials, followed by aneurysms at 31%.¹⁴ As we look back on the year and into the future, does this finding support or stand in contrast to the success of the past years? Those authors also noted low dispersion rates and high rates of study noncompletion as challenges to trial medicine.

New Year's resolutions are important this time of year, and as a field, we should resolve to study what we do, publish what we study, and ensure that what we publish has far-reaching impact, not only locally but also internationally. Topics that will need further study include distal occlusions associated with middle cerebral artery-M3 segment, anterior cerebral artery and posterior cerebral artery medium-size vessel occlusions, low National Institutes of Health Stroke Scale (NIHSS) score LVOs, and large-core low Alberta Stroke Program Early CT Score (ASPECTS) LVOs. With respect to LVOs with a low NIHSS score, the available data appear promising, with Pandhi et al noting mRS scores of 0 to 1 at 3 months for 65% of patients with LVO and an NIHSS score < 6 (mean NIHSS score, 3.6) undergoing mechanical thrombectomy.¹⁵ However, no firm conclusions can be definitively drawn at this time.¹⁴ Brain edema reduction after successful thrombectomy for low ASPECTS LVO strokes has been one purported mechanism of improved outcomes and decreased malignant syndrome transformation. Broocks et al noted malignant transformation of infarcts in 44% of persistent occlusions versus 26% of recanalized

vessels.¹³ The TESLA study (NCT03805308) will further examine interventional versus medical therapy for low ASPECTS (score of 2–5) LVO. The TENSION study (NCT03094715) is also evaluating patients with low ASPECTS (score of 3–5) up to 12 hours last known well and comparing thrombectomy to medical management. The IN EXTREMIS study was designed to assess thrombectomy in patients who are “automatically ruled out for thrombectomy”; the two groups included are those with low NIHSS score LVOs and those with large-core infarcts (ASPECTS 0–5). The purpose of IN EXTREMIS is to study the undertreatment of LVOs in present-day care and determine whether other patient populations will benefit from mechanical thrombectomy.

REVASCLARIZATION FOR ATHEROSCLEROTIC DISEASE

Rescue stenting will also likely come to the forefront of topics in conjunction with the recent positive results for symptomatic intracranial atherosclerotic disease (ICAD) stenting with the Wingspan device (Stryker) (4% periprocedural stroke rate, 97.4% event freedom at 72 hours) from the WEAVE trial¹⁶ and previous positive results from submaximal angioplasty series.¹⁷ CREST-2 (NCT02240862) is still enrolling patients and will examine which patients will benefit from endarterectomy and stenting among those with asymptomatic carotid stenosis.

As “asymptomatic” continues to be defined, studies will continue to evolve. Is asymptomatic defined

as a lack of diffusion-weighted imaging changes, fluid-attenuated inversion recovery changes, or symptoms? Is cognition or cognitive decline related to carotid stenosis, and if so, is it reversible? These questions will need further answers and will be studied in CREST-H (NCT03121209). The cognition question can also be asked of intracranial steno-occlusive disease; unfortunately, no definitive answers currently exist. Kolb et al performed a systematic review of revascularization for steno-occlusive disease and its effect on cognition.¹⁸ Nine studies were identified that included extracranial-to-intracranial (EC-IC) bypass and angioplasty and/or stenting procedures. Mixed results were noted, with no firm conclusions drawn from the available published data. Lastly, transcarotid artery revascularization (TCAR) has become a viable option for carotid revascularization, especially in older patients. One study found lower rates of adverse outcomes for patients aged > 77 years with TCAR versus transfemoral carotid artery stenting in those at high surgical risk.¹⁹

LESSONS LEARNED FOR MOVING FORWARD

If there are any lessons to be learned from the aforementioned studies or headlines from the past year, it is that reexamining past failed attempts can help identify a new way to successfully move forward. Thrombectomy could have been written off after 2013 had the aforementioned few failures been taken as the truth. The positive results of the WEAVE trial stand in stark contrast to the SAMMPRIS trial.^{16,20} The success of the WEAVE trial was built on the premise that medical therapy does work for many patients, but some patients will have recurrent events despite dual antiplatelet therapy. The study investigators identified the highest at-risk population (patients experiencing ischemic events while placed on aspirin and clopidogrel) and then exercised caution and waited 7 days to proceed with stenting. Along these lines, the VERITAS study revealed the extreme risk of stroke caused by hypoperfusion in patients with vertebrobasilar stenosis.²¹ Among patients with $\geq 50\%$ stenosis, a systemic blood pressure < 140 mm Hg was associated with a 20% risk of stroke compared to a 6.2% risk with a systemic blood pressure ≥ 140 mm Hg (hazard ratio, 4.5; $P = .02$). More recently, the VERITAS group noted that hypoperfusion symptoms alone do not correlate well with stroke risk, and quantitative flow monitoring is needed for more accurate risk assessment.²² The VERITAS study reminds us that plaque rupture and embolism can cause events, but hypoperfusion alone can also confer a high risk of stroke. ICAD therapy, including angioplasty and stenting, will be an area for progress in the coming years.

KEY UPCOMING TRIALS

- **IN EXTREMIS:** A multicenter, international study evaluating the effectiveness of mechanical thrombectomy on mRS score at 90 and 180 days in patients with LVO and a low NIHSS score and those with large-core infarcts (ASPECTS 0–5) within 7 hours of symptom onset
- **TENSION (NCT03094715):** A European, prospective, open-label, blinded-endpoint, two-arm, randomized, controlled, postmarket study comparing the safety and effectiveness of endovascular thrombectomy as compared with best medical care alone in acute ischemic stroke patients (ASPECTS 3–5) in an extended time window
- **TESLA (NCT03805308):** A prospective, randomized, open-label, blinded-endpoint study to establish the effectiveness of intra-arterial therapy with mechanical thrombectomy and best medical management versus medical management alone in patients with moderate-large infarcts (ASPECTS 2–5)

Recent advances in endovascular therapy were learned from past experiences. Technologic advancement and practitioner expertise have contributed, but the idea of revisiting past failures shows both passion and discipline. As physicians, we must also know when to stop, and the lines are often blurred just before some of the biggest breakthroughs, so we need to exercise caution. The failure of the COSS study²³ shows us that EC-IC bypass surgery is another technique with academically unproven benefit. In the era of stroke therapy, it would make sense that flow augmentation works, but this may need revisiting down the road.

Neuroprotection strategies for acute ischemic stroke in the age of revascularization are likely the next frontier. Numerous studies have assessed neuroprotective strategies for small vessel occlusions and LVOs in animal models with varying degrees of success; however, no animal study has clearly translated into a standard of care for clinical use. Savitz et al asked researchers to review their previous neuroprotection failures and reexamine them, considering the high revascularization rates achieved today with mechanical thrombectomy.²⁴ Can we diminish reperfusion injury? Is penumbral freezing possible? High-flow normobaric oxygen postthrombectomy is just one of many therapies that has been tested recently.²⁵ ESCAPE NA-1 (NCT02930018) is currently underway to assess the administration of an N-methyl-D-aspartate inhibitor after an ischemic event. This inhibitor showed promising imaging and behavioral results in animal models and is now being studied in patients undergoing mechanical thrombectomy.²⁶

Our best data on the incidence of acute ischemic stroke due to LVO estimate that 24 per 100,000 people in the United States will have an LVO.²⁷ The annual incidence of thrombectomy was noted to be only 3 per 100,000 patients, affording a significant opportunity for an expansion in the use of this therapy.²⁷ Racial and ethnic disparities,²⁸ as well as geographic disparities, have also been noted in thrombectomy utilization, with Stein et al showing that endovascular therapy remains predominately offered at large metropolitan teaching hospitals.²⁹ Social media has exploded with hashtags in recent years, and #leavenoLVObehind has become a popular hashtag for stroke therapy. Word of mouth is important, and educational campaigns will be paramount in ensuring this therapy is available for all patients. Decreasing the geographic disparity of this therapy will be as essential as primary prevention of stroke in the coming years. Primary prevention of stroke will continue to be important. Sur et al recently noted that 21% of patients who underwent mechanical thrombectomy at one center had been inadequately treated with anticoagulation therapy for known atrial fibrillation.³⁰ Those authors concluded that primary management of disease can help prevent LVOs.

Kipchoge, who accomplished the impossible in 2019, said, “The best time to plant a tree was 25 years ago; the second-best time to plant a tree is today.” For all of us involved in stroke care, this means that we should start building for the future today. Prevention, research, and expanding clinical use are all key to treating any disease, especially stroke. It is easy to focus on results, studies, and publications, but we must not lose track of what is most important in this field: our patients. ■

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