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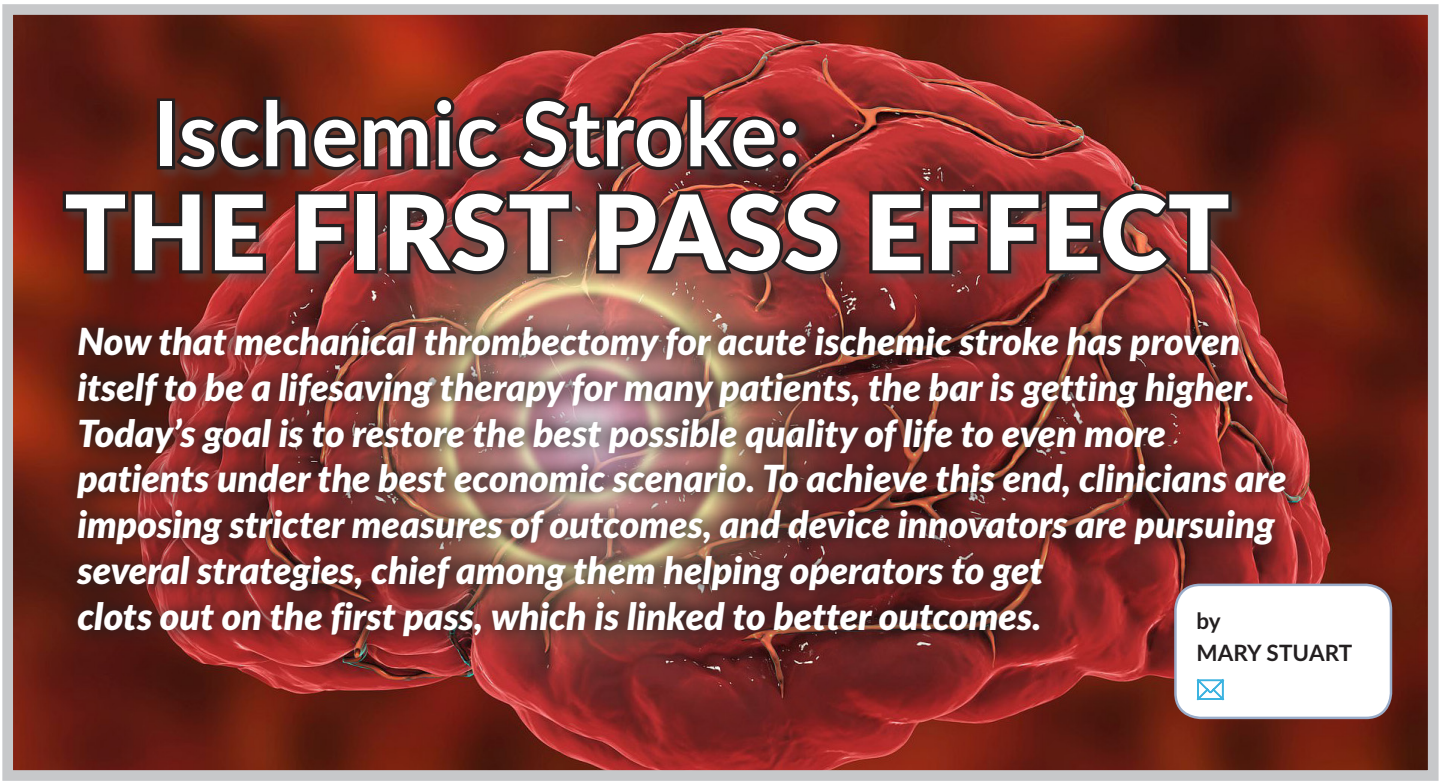


Ischemic Stroke: THE FIRST PASS EFFECT

Now that mechanical thrombectomy for acute ischemic stroke has proven itself to be a lifesaving therapy for many patients, the bar is getting higher. Today's goal is to restore the best possible quality of life to even more patients under the best economic scenario. To achieve this end, clinicians are imposing stricter measures of outcomes, and device innovators are pursuing several strategies, chief among them helping operators to get clots out on the first pass, which is linked to better outcomes.

by
MARY STUART

KEY POINTS

- The efficacy bar is being raised for mechanical thrombectomy devices for the treatment of acute ischemic stroke. Revascularization rates are 85-95%, but only after many passes with several devices.
- Companies and clinicians are working to increase first pass success rates because clinical trials suggest that outcomes are better when the occluded artery can be opened in one pass.
- Many are looking to aspiration devices to solve the problem, since this modality is less expensive, easier to use, offers shorter procedure times, and is likely to be more benign to vessels than stentrievers.
- The field of stroke care is exploding, and was the impetus for the founding of a new neurovascular strategic, Imperative Care, which will both build and buy advanced stroke technologies across the spectrum from intervention to post-stroke care.

It's been less than five years since, beginning with MR CLEAN, a series of landmark trials validated the role of clot-removing (thrombectomy) devices that can open up large vessel occlusions in the anterior circulation of patients experiencing acute ischemic stroke. But the field is moving fast. Mechanical thrombectomy devices known as stent retrievers (or stentrievers) and aspiration catheters are moving into the third generation.

The device market is growing rapidly too. According to Wells Fargo senior analyst Larry Biegelsen, in 2018, thrombectomy volume increased by 10,000 procedures to 38,000, driven by clinical trials that extend the treatment window for thrombectomy (according to a research note on **Penumbra Inc**. dated July 31, 2019). Looking forward, Biegelsen estimates that in 2019, the market will grow by more than 20% to 45,000 cases. By 2022, Wells Fargo models a treatment pool of 70,000. This is phenomenal growth for a medical device segment.

Until recently, the goal has been to get these effective treatments to as many patients as possible, largely by expanding the treatment window between stroke onset and the cut-off point beyond which mechanical recanalization of the occluded artery is deemed no longer effective (*see "Technologies to Watch in 2018: New Data and More Expansive Guidelines Give Ischemic Stroke a Push,"* MedTech Strategist, *April 20, 2018*). This has been accomplished by a series of clinical trials that have demonstrated the efficacy of the treatments for patients 6 hours post stroke onset, then 8 hours out, and finally,

24 hours after first stroke symptoms, based on brain tissue viability as determined by imaging studies (*see Figure 1*).

But now that mechanical thrombectomy devices have well and firmly demonstrated efficacy rates of up to 95% at removing clots and restoring blood flow in stroke victims (albeit after many passes, in most cases), the clinical bar is rising. Clinicians want to see ever higher reperfusion scores, and more importantly, higher measures of functional independence, that is, fewer stroke-related disabilities and symptoms.

In the past year, one strategy for achieving these goals has gained prominence: the first pass effect. Clinical trials of stroke thrombectomy devices suggest that when devices achieve complete recanalization of the occluded artery on a single pass of thrombectomy (rather than having to make multiple attempts to grab the clot with several devices) patient outcomes are better. This effect was further studied in the North American Solitaire Acute Stroke Registry database, and results were published in the journal *Stroke* in March 2018 (Osama O. Zaidat, MD was lead author).

Of 354 acute ischemic stroke patients in the study who underwent thrombectomy, 25.1% were treated successfully on the first pass. Median time to revascularization was faster for the first pass patients (34 minutes versus 60 minutes), and first pass success emerged as an independent predictor of a good clinical outcome indicated by a measure of functional independence known as the modified Rankin Score or mRS (where an mRS score of 0 means no symptoms at all, and higher scores mean greater levels of disability).

In the study, 61.3% of first pass patients got a good mrS score of 0-2, whereas only 35.3% of patients in the other cohort had such good results.

First pass success shortens procedure times, likely occasions less damage to blood vessels and also results in cost savings. For those reasons, consensus has developed that thrombectomy devices should be iterated or innovated from scratch to achieve the first pass effect. (*For a dissenting voice, see Box: "A Second Opinion: Neuroprotection Could Expand Patient Population."*) Thus, many companies are focusing on improving the ease-of-use and speed with which their mechanical thrombectomy devices can remove stroke occluding clots (*see, for example, "Vasotorq: Catching Clots Quicker,"* MedTech Strategist, *April 2019*).

As a therapy, mechanical thrombectomy leaves room for improvement; 20% of cases have proven to be resistant to mechanical thrombectomy, and in about 50% of cases, complete reperfusion isn't achieved. That's why the clinical community is looking to the first pass effect to boost efficacy. Today, first pass success rates are only 25-30%.

Aspiration Devices Pull Ahead

As noted, there are two categories of technologies for mechanical thrombectomy. Stentrievers were the first devices to gain clinical validation, regulatory clearance, and widespread adoption. Stent-like devices, these are advanced via guidewire across the occlusion to engage a clot in its struts and pull it out. **Stryker Corp.**, and **Medtronic plc** lead the market in this category, followed by Penumbra and the Cerenovus neurovascular division of **Johnson & Johnson**.

Aspiration thrombectomy for acute ischemic stroke is a relatively new category that Penumbra has had to itself since it gained the first FDA approval in 2007. An aspiration catheter is advanced to the proximal side of a clot where it applies suction to pull it into the guide catheter and out of the body. Now, many generations later, the leader in aspiration thrombectomy recently introduced its most advanced product, the *Jet 7* aspiration catheter, with *XTRA Flex* technology, at the 2019 meeting of the Society of NeuroInterventional Surgery in July.

Figure 1

A Wider Treatment Window Gets More Stroke Patients Treated

Thrombectomy Trial/ Publication Date	Description
MR CLEAN (12/2014), EXTEND-IA (3/2015), and SWIFT PRIME (6/2015)	Proved the value of thrombectomy in anterior circulation within the first 6 hours of stroke symptom onset
ESCAPE (3/2015) REVASCAT (6/2015)	Provided initial evidence for the benefits of thrombectomy in patients with anterior circulation AIS up to 8 hours of symptom onset
DEFUSE 3 (2/2018)	Value of thrombectomy up to 16 hours (endovascular therapy following imaging evaluation)
DAWN (1/2018)	*Trevo* device only; endovascular therapy is safe and effective in patients selected according to imaging criteria for up to 24 hours post stroke onset

Source: Various studies published in the *New England Journal of Medicine*

But today, Penumbra is far from alone. Several aspiration thrombectomy devices for acute ischemic stroke have been introduced recently, including, from Medtronic, the *React* line of catheters with an aspiration system called *Riptide;* and from Stryker**,** the *AXS Vecta.* Terumo Microvention (a division of **Terumo Group**), sells the *SOFIA* aspiration catheter line, and **MIVI Neuroscience Inc.** sells its R4Q revascularization catheter in Europe.

Aspiration thrombectomy devices for acute ischemic stroke are gaining in popularity because of clinical trials that demonstrate that they deliver functional outcomes on par with stentrievers while offering procedural and economic advantages over the stent-like devices. Aspiration catheters are easier to use, and are potentially safer, because they don't require manipulation of the clot, and operators aren't required to pass them through the occlusion, risking the fragmentation of the clot and embolization to distal regions. Working at the proximal end of the clot also avoids the situation where operators are blindly navigating beyond the clot, where fragile aneurysms could lurk.

The most recent and perhaps most compelling study to come out in support of aspiration is COMPASS, a prospective, multicenter, randomized, open label, blinded outcome, core lab-adjudicated non-inferiority trial, which was published in *The Lancet* in March 2019. While demonstrating that functional outcomes are similar between stentrievers

A Second Opinion: Neuroprotection Could Expand Patient Population

Aaron L. Berez, MD, founded interventional neuroradiology device company **Palmera Medical Inc.**, which is focused on improving outcomes for acute ischemic stroke. Its first product is an improved aspiration thrombectomy device.

Berez is a neuroradiologist and a cofounder of Chestnut Medical, which, at a time when manufacturers were tweaking coils for the treatment of cerebral aneurysms, developed a completely new approach, the *Pipeline Embolization Device* (now sold by Medtronic), a stent-like device implanted in the parent vessel across the neck of a cerebral aneurysm to treat the aneurysm by re-forming the vessel.

He looks at mechanical thrombectomy the same way. Supposing that opening the vessel would not be the whole solution, he felt that the way expand the number of patients who experience good outcomes after stroke intervention lay in another direction.

"There's a lot of talk about the 'first pass effect' but people are confusing causation with correlation. Perhaps patients experiencing the best outcomes are those that are having first pass success because they are easier to treat. In other words, the first pass effect might select for patients who are easier to treat."

Berez points out that current mechanical thrombectomy devices are doing a pretty good job. "People are getting good angiographic results about 85% of the time, and the 15% that don't are probably clots that are hard to remove with current devices, or are due to other pathologies like atherosclerosis." If one regards stroke as a plumbing problem, he says, we've gotten really good at treating it in the cath lab. But of course it's more than a plumbing problem; it's an issue of brain health.

Palmera is thus focusing on an endovascular way to provide regional neuroprotection, while the patient is in the cath lab. The company is at an early stage and is in stealth mode. "I do think we have the potential to have an important impact on improving the outcomes for patients treated today, potentially enlarging the treatment population to help more people," Berez says.

Indeed, neuroprotection for stroke patients has been investigated for years, but due to the failure of many neuroprotective drugs, that strategy fell by the wayside. One of the road blocks was the occlusion itself; how to get neuroprotection to the brain when a clot is blocking the way.

The success of mechanical thrombectomy has revived the concept of neuroprotection. At the international stroke conference in February 2019, Michael Hill, MD (of the Department of Clinical Sciences at the University of Calgary), gave a talk titled "Expanding the Time Window for Thrombectomy: Neuroprotection in the Era of Endovascular Treatment." Hill pointed out that although thrombectomy has impactful efficacy for large vessel occlusion strokes, 37% of patients treated are still disabled and 10% still die, and went on to discuss an ongoing Phase III trial (ESCAPE-NA1), which is investigating a neuroprotective drug developed by **NONO Inc.**, which will be used in patients undergoing endovascular treatment for acute ischemic stroke.

The development of neuroprotective drugs is a complicated undertaking; different agents are probably required to counter destructive processes at different points in the development of a brain infarct. But Palmera's endovascular device concept promises to be broadly neuroprotective. Synergy Ventures and private investors have provided seed funding.

and aspiration, the study found aspiration procedures to be shorter, and less expensive.

COMPASS, which was funded by Penumbra, enrolled, between June 2015 and July 2017, 270 patients within six hours of stroke onset (according to certain stroke scores), and these were randomized one-to-one to either stentriever thrombectomy with any FDA-approved device or aspiration thrombectomy with the Penumbra system.

There were 134 patients in the "aspiration first" arm and 136 patients received stentrievers as a first-line treatment. Operators could use adjunctive devices as needed (i.e. the stentriever or aspiration) to complete the procedure. The primary endpoint was the achievement of a good functional outcome at 90 days, indicated by mRS 0-2.

The study outlined several secondary efficacy endpoints, starting with the amount of time from the groin puncture to a reperfusion level of TICI 2b or better (on the Thrombolysis in Cerebral Infarction Scale, TICI 2b indicates almost complete perfusion and TICI 3 means complete perfusion).

Other secondary endpoints looked at the rate with which procedures achieved TICI 2c or better within 45 minutes, and the percentage of procedures in which TICI 3 was reached within 45 minutes. A secondary outcomes endpoint evaluated the number of times TICI 2b or greater was achieved on the first pass (*see Figure 2*).

The investigators (led by Aquilla S. Turk, DO, Greenville Health System, SC) found that 52% of patients in the aspiration group met the functional endpoint of an mRS of 0-2 at 90 days as did 50% patients in the stentriever group. Rates of intracranial hemorrhages were comparable between the two groups.

In the aspiration group, clinicians bailed out to stentrievers in 21% of cases. Distal aspiration was used in 85% of the stentriever cases. While TICI 2b reperfusion rates were at about 80% with the primary modality, results were boosted to about 90% when the other modality was mixed in.

Aspiration came out ahead on measures of cost-effectiveness both in terms of procedure speed and total device cost. Median time to reperfusion of TICI 2b or greater was 11 minutes faster in the aspiration first pass group, and median time from groin puncture to the time the final thrombectomy pass was done was 10 minutes faster in the aspiration group.

In terms of the cost of devices used, the aspiration devices were $5,074 less (mean reduction per case) than stentrievers. In the conclusion to the *Lancet* article, the study's authors note that COMPASS, in demonstrating a non-inferior outcome at 90 days that was achieved with significantly lower device costs, "supports the use of the aspiration first pass approach for stroke thrombectomy and the findings might directly affect current stroke treatment guideline recommendations."

Perfuze: Third Generation Aspirations

Today there is no consensus about whether it's better to choose aspiration or stentriever thrombectomy first for a particular patient. Most companies operating in the neurovascular industry offer both stent retrievers and aspiration

Figure 2

Selected Highlights from the COMPASS Trial

	Aspiration First	Stentriever First
Primary efficacy endpoint of mRS 0-2 at 90 days	52%	50%
Median time to TICI 2b or greater	22 minutes	33 minutes
TICI 2b or greater within 45 minutes of access	76%	68%
TICI 2c or greater within 45 minutes	50%	44%
TICI 3 within 45 minutes	34%	23%
TICI 2b or greater on first pass	57%	51%
Distal aspiration	100%	85%
At least one stentriever	21%	98%
More than one stentriever	6%	13%
Time between cath lab arrival and TICI 2b or greater	40 minutes	46 minutes
Time from groin puncture to final revascularization	25 minutes	35 minutes

Source: Lancet 2019; 393;998-1008

catheters with the goal of bundling together an offering that achieves the best clinical outcomes in acute ischemic stroke.

Clinical practice varies from one hospital to another, and a multiplicity of acronyms has arisen to describe techniques for using these devices in combination with each other and other technologies like balloon guide catheters. There is Solumbra (retraction of the *Solitaire* stent retriever within the Penumbra aspiration catheter); GUARD (guide sheath advancement and aspiration in the distal petrocavernous internal carotid artery technique during thrombectomy); ADAPT (a direct aspiration first technique); ARTS (aspiration-retriever technique for stroke, to bail out failed ADAPT attempts) and SAVE (distally placed stent retriever and proximally placed aspiration devices), among others.

"Currently there are more than 12 techniques in use, combining various technologies in order to get the best results," says Wayne Allen, co-founder and CEO of start-up **Perfuze Ltd.** (Galway, Ireland), "and this is a clear indication of a space in flux. The physician shouldn't have to combine multiple devices in an attempt to get an optimized result. We would interpret this as a sign of poor ease of use."

After selling their peripheral vascular disease start-up Embo Medical to **CR Bard Inc.** in 2015, Allen and co-founder Liam Mullins began looking for a new, important clinical need to solve and found the ischemic stroke opportunity to be very timely.

"The stroke market is evolving rapidly, and that's not unexpected because mechanical thrombectomy only gained clinical acceptance in 2015," he says. "There are a number of pieces of evidence that suggest we haven't yet reached optimal clinical performance with existing technologies."

The first is the clinical data on mechanical thrombectomy for acute ischemic stroke. "The latest randomized controlled trials imply that about 50% of patients who undergo mechanical thrombectomy don't receive a positive result, by which I mean an mRS score of 0-2."

Another indicator: "The bail-out rates are still very high. You use an aspiration device and bail-out to a stentriever and vice versa about 30-40% of the time. That adds significantly to the time and cost of these procedures."

Allen and Mullins set out to design new technology that would be able to surpass current clinical results, and improve upon the ease of use of current devices and procedures. Founding Perfuze in 2018 with a €3 million seed round led by Earlybird Venture Capital (Berlin) and HBM-MedFocus (Irvine, CA), the founders bent their heads to the task of devising a third-generation mechanical revascularization device that would meet ever higher hurdles for efficacy and ease of use. "More and more, clinicians want to redefine success as TICI 3 after a single thrombectomy pass, which is a known predictor of better outcomes. They are demanding a technology that increases the First Pass Effect." That's the foundation for the Perfuze *Millipede Clot Ingestion System* (CIS), he says.

It's very early for Perfuze, which is still in pre-human development and filing IP, so Allen is reluctant to discuss some details of his company's technology. He says it is an aspiration-focused product that has the ability to completely ingest a clot in any large vessel at the point of occlusion "without manipulating, dragging, or inducing fragmentation of the clot, which is what you have today. All of these unnecessary procedural steps are not conducive to optimal clinical outcomes."

Allen says the company's bench data suggest that the *Millipede* can increase the percentage of first pass success, and it improves ease of use. "We don't require device exchange or any elaborate technique for clot management."

In August 2019, the FDA granted Perfuze a Breakthrough Device Designation for the *Millipede CIS*, a validation of a promising therapy for a life-threatening condition, which helps device developers interact with the FDA to gain timely feedback that speeds development and approval. "It sets us up nicely to get some clarity from the FDA on how we are going to execute our clinical trials and get some early and precise feedback," Allen says. He anticipates that the *Millipede* will enter into first-in-human studies next year.

Early this year, the company was the beneficiary of a €2.5 million Horizon 2020 grant from the European Innovation Council.

Clot Composition Influences First Pass Rates

The blood clot is *the* (one and only) therapeutic target in ischemic stroke; it's what the lytic drug tPA is trying to dissolve and what mechanical thrombectomy devices are trying to pull out of the body.

Because the blood clots that cause ischemic stroke are heterogeneous, one might surmise that if the first pass success rate today is only about 30%, perhaps we don't understand which therapy is best for which clot; or further, perhaps we don't yet have the devices that can retrieve certain types of clots.

Stroke-inducing clots come from multiple sources in the body, originating from both venous and arterial sources, and they differ as to their physical properties (stiff, soft, solid, breakable) and composition. Some are largely made of red blood cells (in the argot of the community, these are referred to as "red") while others are predominantly composed of platelets or fibrin ("white"). Some are solid and will easily come out in one piece, and others have a

tendency to break up and send fragments downstream.

These characteristics ought to influence the choice of therapy. However, today, clinicians don't have cost-effective and time sensitive tools to know, in most cases, what kinds of clots they're dealing with. So today's stroke therapies really aren't patient-specific; rather they're strategies aimed at restoring perfusion by removing clots with aspiration, stentrievers and combinations of the two, the order of devices used being up to physician or hospital preference.

In recent years, the widespread use of mechanical thrombectomy devices has allowed researchers to analyze thrombus removed from the body, and clot science is advancing. The Irish start-up Neuravi, which developed *EMBOTRAP*, a stentriever providing distal protection and capable of retaining a clot in an inner chamber, was perhaps the first to push for the influence of clot composition.

In 2016, Neuravi published its first data showing the importance of understanding clot composition, and in March 2017 formalized that effort by launching a registry called STRIP (Stroke Thrombembolism Registry of Imaging and Pathology) in conjunction with the Mayo Clinic and CURAM, the center for medical device research located at the National University of Ireland, Galway.

Johnson & Johnson, which purchased Neuravi in 2017 for its Cerenovus division, is further seeking to develop an understanding of the role that certain clots play in treatment success rates. In 2018 the company launched the EXCELLENT registry, to collect and analyze stroke-inducing clots collected by the next generation *EMBOTRAP II* and *Geometric Clot Extractor* (GCE) revascularization devices. (The GCE was designed to retrieve both hard and soft thrombus types and gained CE mark approval in December 2018). EXCELLENT has a goal of enrolling 1,000 patients at 50 clinical sites in the US and Europe to collect real-world evidence on how clot composition relates to co-morbidities, clinical outcomes, and revascularization rates.

Other research groups have similar aims. COMPO-CLOT (Thrombus Composition in Ischemic Stroke: Analysis of the Correlation with Plasma Biomarkers, Efficacy of Treatment, Etiology and Prognosis), which is sponsored by the Fondation Ophtalmologique Adolphe de Rothschild, was launched in 2017 to collect thrombus from 1200 patients treated by thrombectomy (at six sites in France).

Sensome Wants to Provide Real-Time Clot Assessment

These are *in vitro* studies; designed to create a general understanding of stroke treatments after the fact. But in 2016, having in hand a minimally invasive technology for the real-time assessment of tissues in the body, Franz Bozsak, PhD, wondered, "Wouldn't it be great if clinicians had a tool that they could use during a thrombectomy intervention to see what kind of animal they were dealing with?"

In 2014, Bozsak had founded Instent with Abdul Barakat, PhD, an expert in biomedical engineering. Barakat advised Bozsak on his thesis on the optimization of stent design, leading to his PhD in biomedical engineering from France's École polytechnique.

> ***Increasingly, clinicians want to redefine success as TICI 3 after a single thrombectomy pass, which is a known predictor of better outcomes.***

Instent's goal was to commercialize a sensor-equipped coronary stent, which, using electrical impedance technology, could help clinicians identify patients developing late-thrombosis, a rare but serious problem associated with drug-eluting stents.

After spending two years developing and validating the accuracy and reliability of the sensor, ischemic stroke emerged as a larger and even more compelling problem in which the sensor could play a role. The founding team pivoted to that application in 2016, renaming the start-up **Sensome**. To date the company has raised €9.2 million from an investor group that includes lead investor Kurma Partners, Paris-Saclay Seed Fund, Idinvest Partners, and BNP Paribas Développement.

Sensome's solution combines an electrical impedance sensor with artificial intelligence. While some advanced imaging modalities can reveal information about clots (MRI can identify clots rich with red blood cells, for example), Sensome's founders thought it crucial to develop a product that would fit into the existing, time-constrained workflow.

Sensome's thin film electrical impedance sensor, which, at 10 microns thick, is a tenth of the size of a human hair, is placed on the distal part of the guidewire that is the first step of every interventional thrombectomy procedure (*see Figure 3*). When the *Clotild Smart Stroke Guidewire* passes through the occlusion, the sensor will capture an impedance signal from the clot and artificial intelligence will determine what type of clot it is. The company is preparing for its first clinical trial next year.

Bozsak notes that in the years that Sensome has been focusing on the stroke problem, the market has moved in the

company's direction as clinical studies demonstrate the clinical and economic advantages of the first pass effect.

Also, as the revascularization success rates are already high—80-95% success at restoring perfusion (again, sometimes after many passes)—Bozsak notes "It is getting increasingly difficult for a company to have a competitive advantage, unless they can say their device is better for this type of clot. They will have to get down to the clot level to differentiate themselves." Today's approach of choosing either aspiration or stentriever first, then switching among devices during multiple passes to get the job done, will no longer hold.

The Power of AI

Bozsak notes that Sensome has placed research versions of the electrical impedance sensor (printer-sized equipment for *ex-vivo* analysis) in a number of hospitals across the world. Whenever hospitals retrieve a clot, Sensome's study partners use the system to analyze it and capture its composition, along with information about the procedure that was done, and outcomes data. "We are studying how clot composition is associated with retrieval method, to confirm today's theories about the best device to use for each type of clot."

In the future, through artificial intelligence, "our device will not only be able to tell you whether this clot is red or white, but the probability of first-pass success for this type of clot with this type of device. We want to give clinicians the highest odds of success. That's where we are headed," says Bozsak.

The market is now ready for the company's first application, Bozsak believes. But there is another unmet clinical need in ischemic stroke, and the company has already begun to create the research infrastructure to address it.

Once the acute phase of stroke has been addressed successfully, patients are still at risk of having strokes. Recurrent stroke risk is about 13% within the first year, and 30% by five years. It's important for clinicians to understand the etiology of a clot so they can determine the best stroke prevention strategy. If the clot originated from the heart, say in the case of atrial fibrillation, patients might be put on anti-coagulation; if from another source, anti-thrombotics might be the best treatment. However, in about 35% of cases, even after imaging studies and other aspects of the workup, the etiology remains unknown, a case known as a cryptogenic stroke. "We aim to not only tell you what you should do acutely, but also what you should do next based on the origin of the clot. That's our moonshot," says Bozsak.

Meet the Newest Strategic in Stroke

Imperative Care Inc. (Campbell, CA) was founded just four years ago, but it is both a start-up and a strategic in the neurovascular industry. It has a five-year pipeline of neurointerventional products developed in-house, and it will also acquire innovation from start-ups and other inventors as it goes along, to further its goal of "Elevating Stroke Care," the company's motto. The company has disclosed a $25 million funding round lead by Ascension Ventures (St. Louis, MO) and Delos Capital (Hong Kong), along with 3H Capital (Hong Kong) and Rock Springs Capital (Baltimore, MD).

The young company was co-founded by neurointerventionalist L. Nelson ["Nick"] Hopkins and Fred Khosravi, a serial medtech entrepreneur and medical device executive many times over, having co-founded 23 companies, some within the Incept LLC incubator, of which he is a managing director. Imperative Care is Incept's 21st portfolio company.

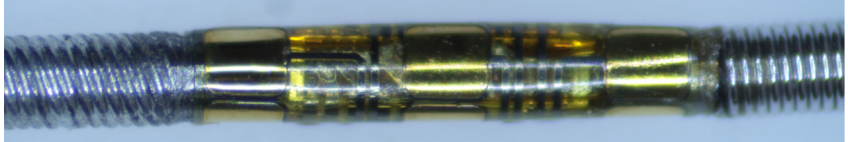
Over a long and productive career Khosravi has founded or co-founded companies in embolic filters (EPI and Claret Medical, both acquired by **Boston Scientific Corp.**); vascular access closure (AccessClosure, which was acquired by **Cardinal Health**); transcatheter heart valves (Sadra Medical, bought by Boston Scientific); vascular intervention (HotSpur Technologies, now under the wings of **Teleflex Inc.**), and many other diverse clinically focused companies.

Dr. Hopkins is the founder and chief scientific officer of the Jacobs Institute in Buffalo, New York, former Chairman and current SUNY Distinguished Professor, Department of Neurosurgery at University at Buffalo, and a pioneer in the field of neurointerventional medicine who served in leadership roles for the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the Academy of Neurosurgery and American Heart Stroke Council.

This time around, Khosravi is out to bring stroke care to the approximately 80% of people who suffer an acute ischemic stroke who don't get treated. "Our focus is on elevating the clinical standards, the clinical

Figure 3

The *Clotild Smart Stroke Guidewire*



Source: Sensome

data, and innovations in this space, to make these innovative therapies available to more patients," says Khosravi.

Imperative Care is built for purpose and the long haul, he says, and will create solutions for the entire continuum of stroke care, from detection in the home and hospital, to acute intervention, to the post-stroke setting.

The company's initial development thesis for stroke intervention very much centers on "the first pass effect," says Khosravi. "We are focused on enabling better outcomes through faster, simpler procedures that achieve greater rates of first pass success."

Imperative Care believes that a direct approach to aspiration/removal of the offending blood clot will be the standard of care for the future. "Stentrievers will certainly be a meaningful part of the cases, but we believe that from a standpoint of safety, cost, simplicity, and effectiveness, aspiration will end up being the dominant technology."

Aspiration is also likely more benign to vessels, notes Khosravi. "It's proximal to the clot. You don't have to move an intrusive metallic device back and forth in the artery, which would be completely unacceptable in the coronary space but today is the standard of care in the neuro space. We have built our business on the assumption that aspiration is a gentler, easier modality for clot removal."

To realize Hopkins' vision of achieving higher rates of first pass efficiency, the Imperative Care team determined that "getting the largest possible device to go farther into the distal internal carotid artery could significantly improve the existing standard of care." Imperative Care's solution to this problem has two parts. First is the *ZOOM Aspiration System*, which has a beveled tip called *TRX* that, for the same diameter of catheter, provides a larger cross-sectional area for thrombus collection. *ZOOM* gained FDA clearance in April 2019 and is available in four sizes (.071, .055, .045 and .035 inches in diameter).

Again with an eye to first pass efficiency, the second part of the solution is a novel access system—the first step of every neurointerventional procedure—which will become a fundamental platform for many neurovascular interventions that facilitate the treatment of acute ischemic stroke by aspiration and stentriever thrombectomy as well as the treatment of cerebral aneurysms. This platform, called LDP (for "Large Distal Platform"), combines the need for a more solid proximal end for support with flexibility at the distal end, which is designed to navigate far into the distal internal carotid artery. "Access is the foundation for a streamlined procedure. You need to get close to the target of stroke, whether you are aspirating a clot or filling an aneurysm. To impact outcomes positively, you need a procedure that's simpler and faster."

Khosravi believes that over time, his company's products have the potential to improve the cost-effectiveness of acute stroke care by accomplishing revascularization with fewer devices. "With today's 'Tower of Power' procedures, there are anywhere between four to six expensive devices used. We believe these procedures should be done with no more than two or three devices. We want to be able to get to the clot and evacuate it on the first pass."

(*Editor's Note: This section was updated post-publication.*)

Addressing the Continuum of Stroke Care

While revascularization is Imperative Care's beachhead, the company's vision, which Khosravi says it owes to Dr. Hopkins, is to go upstream and downstream of stroke in the continuum of care, with the possibility of veering into digital health, electro-mechanical devices, artificial intelligence and machine learning. "We will look at the entire continuum and see where the application of technology can facilitate better stroke care, when strokes start, get treated, and post-stroke care."

To execute on such a large mandate, the company has created a business development team with broad and deep experience, including, to name just a few members, Kirsten Carroll, VP Strategic Development, the former Senior Director of Strategic Development for Stryker Neurovascular, Phillip Nalbone, VP, Corporate Development, a former Wall Street Analyst who became the VP of Corporate Development and Investor Relations for Vascular Solutions Inc., and Mike Strasser, VP and General Manager, Advanced Exploration, the founder and former CEO of Motiv, which developed the smallest wearable fitness tracking device.

Indeed, Imperative Care is not a start-up looking to exit by acquisition; it intends to be, itself, an acquirer of start-ups with solutions along the continuum of stroke care. "Our sign doesn't say 'For Sale'" says Khosravi; "It says 'Open for Business.'"

In speaking with *MedTech Strategist*, Imperative Care is breaking its silence, but Khosravi isn't quite ready to lay all the cards on the table. He does say the company is about to start "a landmark pivotal trial to look at aspiration outcomes focusing on the modified Rankin Scale," which, again, is a functional measurement that's more clinically relevant than the reperfusion score of TICI 2b or greater. The company will also look at first-pass efficiency, procedure time, and the correlation of procedure time to outcomes.

"This space has done some meaningful clinical studies, but a lot more needs to be done," says Khosravi. "We predict that in coordination with the FDA, more and more companies will do randomized trials. Much more economic and functional information will become available."