NeuroNews

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Mechanical thrombectomy treatment: When does the clock run out?

Is there a time after symptom onset at which acute ischaemic stroke patients should no longer be eligible for mechanical thrombectomy? This has become one of the most important questions now that the safety and efficacy of mechanical thrombectomy has been established.

According to Tudor Jovin (University of Pittsburgh School of Medicine, Pittsburgh, USA) we should be asking the question, "Should there be a time window at all? And should we even be concerned about time in acute stroke interventions?" Jovin weighed in on the subject at the International Stroke Conference (ISC; 17–19 February, Los Angeles, USA). His main point was that there are two types of stroke patients to consider—"fast progressors" and "slow progressors"—and there is a need for fast workflows and fast recanalisation overall.

He pointed out that recent trials have shown that the purpose of intervention is to prevent infarct growth and to end up with a small infarct at the end of the procedure because there is a very strong correlation between infarct volume and good clinical outcomes. It was shown in IMS III and replicated in SWIFT PRIME that patients with small infarcts have a much higher chance of doing well than those patients with small infarcts.

"We know that when a vessel is occluded we are dealing with two compartments: core and penumbra (core being dead brain and penumbra tissue that is functionally impaired but structurally intact). We are all after penumbral salvage, but we need to understand that this is a time dependent process, and with time, the core grows and the penumbra shrinks until the entire territory that is supplied by the occluded vessel has infarcted and at that point, any attempts to recanalise the vessel are futile or even detrimental," Jovin explained.

What is perhaps less well understood, according to Jovin, is that this process occurs at different speeds in different individuals. This was illustrated with data from DEFUSE 2 (a study that required an MRI scan prior to endovascular therapy) where there was a range of patients who had similar infarct growth and widely different time points—"fast progressors" and "slow progressors". He explained that it is the collaterals that determine this rate of growth.

"Should there be a time window at all? And should we even be concerned about time in acute stroke interventions?"

"It was worked out after IMS III by Khatri *et al*, that every 30 minute delay in reperfusion is associated with a 10% relative reduction in probability of good clinical outcome (mRS 0–2). If we look at the modern endovascular trials, we need to revise the Khatri curve. I think we are dealing perhaps with different patient populations in the most recent trials. In MR CLEAN there is still a curve and it is significant, but it is only 5% relative reduction in probability of good clinical outcome. Why is that? Perhaps in MR CLEAN even though there were no requirements for eliminating patients with large infarcts, based on the fact that median ASPECTS score was 9, maybe MR CLEAN enrolled patients who had better collaterals than IMS III," he said. Similarly, in REVASCAT, the Khatri curve mirrors that seen in MR CLEAN—5% reduction for every 30-minute delay.

ESCAPE, Jovin went on, required inclusion only of patients who had good collaterals, and the Khatri curve in ESCAPE patients is almost flat, indicating that every 30-minute delay in reperfusion is associated with a 0.5% relative reduction in probability of good clinical outcome.

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Paraesthesia may increase attention to pain, study finds

A study recently published in the journal *Neuromodulation* has concluded that using spinal cord stimulation devices, paraesthesia are not necessary for pain relief and may actually increase attention to pain.

Until recently, paraesthesia and spinal cord stimulation have come hand-in-hand. That was until the development of paraesthesia-free spinal cord stimulation using high-density parameters. The study investigators, Jennifer Sweet (University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, USA) and others sought to evaluate the relative effectiveness of conventional, subthreshold high-density, and sham stimulation on pain intensity and quality of life.

To conduct the study, Sweet *et al* screened 15 patients with response to conventional stimulation (60Hz/350µsec) with a

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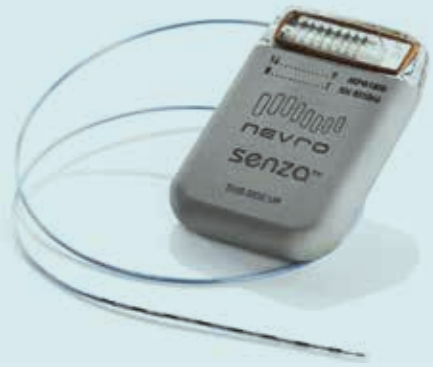

Mechanical thrombectomy treatment: When does the clock run out?

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Jovin reported a deeper analysis of the REVASCAT data, detailing all patients that were subjected to endovascular therapy, not only the ones who reperfused. He said that it was found that from symptom onset to reperfusion there was a 26% reduction in probability of good outcome with every 30-minute delay. But from symptom onset to imaging, there is no association with time; the curve is in fact driven by the imaging to reperfusion interval. When it comes to patients who had poor collaterals, ie. those with low ASPECTS scores, there is a very steep curve—that is where there is a strong relationship between time to reperfusion and good outcome. On the other hand, in patients who have good ASPECTS scores, ie. good collaterals, this association does not exist. He added that in DEFUSE 2, which enrolled patients with good collaterals evidenced by a median baseline infarct volume of 16cc, the Khatri curve is actually in the opposite direction and there is absolutely no association between time to symptom onset and good outcome.

"How do I make sense of all these data? I think we are looking at different patient populations here. In ESCAPE and in DEFUSE 2 we are looking at an enriched patient population with respect to good collateral status, we are looking at 'slow progressors', that is why this curve is much flatter or the association between time of stroke onset to reperfusion and outcome is very attenuated or not detectable, whereas if we take a less strictly selected segment of the acute stroke population such as those enrolled in IMS III and (to a lesser extent) MR CLEAN and REVASCAT we are going to deal with a higher percentage of 'fast progressors' and that is where we are going to encounter a steep curve," Jovin said.

As for what happens if these patients are treated, Jovin explained that data from DEFUSE 2 suggest that if there is mismatch and good collaterals, whether a patient is treated beyond six hours or within six hours what really counts is whether they reperfuse, and not the time window at which they are treated.

"What does this mean? Should we treat patients with large vessel occlusions and mismatch beyond six hours without any time limit in routine clinical practice? Not necessarily. Do we need any other proof? Yes, we do need proof because the problem is that we have absolutely no idea what the behaviour is of the patients who have mismatch and good collaterals but do not get treated with endovascular therapy. Because they have good collaterals it may be that their stroke will never grow and therefore they may do well without intervention. The challenge is to figure out who are those people with good collaterals who are going to experience growth of core with persistent vessel occlusion and devise strategies for the treatment of those patients," he maintained.

Tudor Jovin

To answer these questions, there are now two large randomised trials ongoing—DAWN and DEFUSE 3. DAWN is a single device trial (Trevo embolectomy device) sponsored by Stryker Neurovascular, with a time window of six to 24 hours, enrolling patients with proximal anterior circulation occlusions (M1, ICA T), with a core and clinical mismatch type selection paradigm where age is also a factor. Nearly 100 patients have been enrolled to date in this world-wide trial. DEFUSE 3 is an NIH-funded, prospective, randomised, multicentre, adaptive blinded endpoint trial that uses diffusion and perfusion mismatch as selection criteria. Mismatch on diffusion and perfusion is the same as the DEFUSE definition—core <70mL, mismatch ratio >1.8 and mismatch volume ≥15cc.

Concluding, Jovin stated, "Time dependency of favourable outcomes in patients with large vessel occlusion in the anterior circulation is most pronounced in those with poor collaterals—that does not mean that in patients who are 'slow progressors' (those with good collaterals) we have a justification to take our time. We need to have fast workflows and fast recanalisation even in the 'slow progressors' because there could be other benefits that current outcome measures are too insensitive to detect when we open up vessels very fast in these 'slow progressors'. A non-insignificant proportion of patient with large vessel occlusion stroke in the anterior circulation (estimated at about 20–30%) presenting in the beyond six-hour time window have substantial mismatch ('slow progressors'). Contrary to popular belief, it has been shown that whether they are wake-up or witnessed onset does not make a difference in terms of their response to endovascular therapy. In this patient population, endovascular treatment appears to be feasible and safe, but because we do not know anything about the natural history of these 'slow progressor' patients we need to complete a randomised trial to establish the clinical efficacy of this approach".

Data support "careful" use of mechanical thrombectomy in non-top tier evidence criteria ELVO patients

Investigators have found that with strict adherence to top tier evidence criteria, half of ischaemic stroke patients with emergent large vessel occlusion (ELVO) may not be considered for mechanical thrombectomy even though according to their data, there is no increased risk of symptomatic intracerebral haemorrhage (sICH) and higher mortality is largely linked to occlusions in the basilar artery and patients treated at an extended time window.

Rohini Bhole (Stroke Team, Methodist University Hospital, University of Tennessee Health Science Center, Memphis, Tennessee, USA) and others state in the *Journal of NeuroInterventional Surgery* that this study comes in response to the recent guidelines for endovascular management of ELVO which award top tier evidence to the selective criteria that was implemented in the five positive trials (MR CLEAN, EXTEND-IA, ESCAPE, SWIFT PRIME, REVASCAT) in favour of mechanical thrombectomy for the treatment of acute ischaemic stroke.

The study's aim then, was to understand how guideline adherence would have impacted treatment numbers and outcomes in a cohort of patients from a comprehensive stroke centre. The investigators compared disability and functional outcomes in patients that underwent mechanical thrombectomy at one comprehensive stroke centre, according to whether these patients met the top tier criteria for endovascular treatment set forth in the new guidelines (2015 AHA/ASA focused update of the 2013 guidelines for the early management of patients with acute ischaemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association).

The authors conducted a retrospective observational study of consecutive acute ischaemic stroke patients registered in their centre's database that were treated with mechanical thrombectomy between January 2012 and June 2015. All cases were coded as either meeting or not meeting top tier evidence recommendations based on their conformance to the following criteria presented in the new guidelines: pre-stroke modified Rankin Scale (mRS) score 0–1; acute ischaemic stroke with receipt of IV t-PA within 4.5 hours of symptom onset; causative occlusion of the internal carotid artery of proximal (M1) middle cerebral artery (MCA); age 18 years or older; National Institute of Health Stroke Scale (NIHSS) score of ≥6; Alberta Stroke Program Early CT (ASPECT) score of ≥6 and; treatment that can be initiated (groin puncture) within six hours of symptom onset.

Further, "Prospectively collected outcome and process data were used in this retrospective cohort study as the following dependent variables: neurological improvement during hospitalisation (defined as the difference between pretreatment and discharge NIHSS scores); sICH, defined as per the SITS-MOST definition; serious haemorrhage (defined as life-threatening systemic haemorrhage requiring transfusion); time from groin puncture to recanalisation; post-recanalisation TICI grade; endovascular procedural complications; and 90-day mortality and mRS score."

A total of 126 ELVO patients treated with mechanical thrombectomy were included in the analysis. Of them, 64 patients fulfilled top tier evidence criteria (mean age 64±15 years; 47% men; median pretreatment NIHSS score 16 (IQR 14–18)), and 62 patients did not meet top tier evidence criteria (mean age 62±13 years; 52% men; median pretreatment NIHSS score 14 (IQR 7–18)). The authors state: "Charateristics not meeting top tier evidence for mechanical thrombectomy in the comparision group included six (10%) patients with a pretreatment NIHSS score of <6, 4 (6.5%) patients with an ASPECT score <6, 17 (27%) patients with a premorbid mRS score ≥2, 6 (10%) patients with M2 occlusions, 20 (32%) patients with posterior circulation occlusions, and 36 (58%) patients with symptom to groin puncture time >6 hours. Twenty-six (42%) patients had two or more characteristics removing them from the top tier evidence group."

They report that IV t-PA was given to 92% of patients in the top tier group, versus 40% ($p<0.001$) in the non-top tier group, primarily due to late arrival after symptom onset. Similarly, patients in the top tier group had shorter symptom onset to groin puncture

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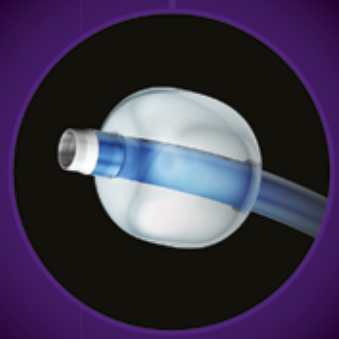

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There is a “place” for MR imaging in acute stroke

Magnetic resonance (MR) imaging may have advantages over other imaging modalities in later time windows when it comes to selecting patients for endovascular treatment of acute ischaemic stroke. That is according to Gregory Albers (Stanford University Medical Center, Stanford, USA). He made this assessment during a presentation at the International Stroke Conference (ISC; 17–19 February, Los Angeles, USA).

Making the case for MR imaging over computed tomography (CT), Albers explained that in the SWIFT PRIME trial, patients could be selected using either MR imaging or CT. While the majority of patients were selected using CT, of the patients selected using MR imaging in SWIFT PRIME, 63% had a good outcome in the endovascular arm selected by MR, and 33% in the control group, with a 30% difference.

Further, Albers reported, in the Rankin shift primary analysis of SWIFT PRIME, in the MR selected subgroup (34 patients) the control group had mRS (modified Rankin Scale) 4 at 90 days, and the thrombectomy group had mRS of 2 (p=0.022). Infarct volume at 27 hours was 61ml in the control group and 24ml in the thrombectomy group (p=0.052). There was no difference in CT perfusion versus MR group in age, NIHSS (National Institutes of Health Stroke Scale), or door to randomisation time (median 67 min vs. 68.5 min). The door to randomisation was only 90 seconds longer in these patients.

He explained that this can be attributed to the fact that many of these patients were “drip and ship” or transfer patients—therefore, the hospitals were aware of them and were able to have the MR ready upon their arrival.

“Why choose MR imaging over CT? Diffusion weighted imaging is the gold standard for estimating ischaemic core, it may have some greater advantages in later time windows: it always gives you full brain coverage and it detects smaller lesions. So if your patient comes in and their hemiplegia is because of a medial medullary infarct, which technique is going to show you that? Not the CT,” Albers maintained.

The caveat however, Albers said, is that MR imaging should not delay acute stroke therapy. He acknowledged that this is likely the reason most stroke teams do not use it because it would delay acute stroke therapies, but reiterated that if the hospital is prepared for the patient and has a system that can do the MR, the MR can be done very quickly.

Gregory Albers

In the recently initiated DEFUSE 3 (a prospective, randomised, multicentre trial of patients with an acute ischaemic stroke who can be treated between six and 16 hours of stroke onset) he explained, there is a six minute MR imaging protocol with 45 seconds of automated processing, “so if you have scanner availability, you should be able to get those images quickly”.

“CT perfusion has some limitations for core. If you had bad ischaemia a few hours ago and now it is resolved, you will not see the core on CT perfusion, but you will see it on diffusion weighted imaging. The reason is you are using cerebral blood volume or cerebral blood flow to determine your core on CT perfusion; your core is going to give you an answer for what the cerebral blood volume or the cerebral blood flow is at the moment of your scan, it gives you no history. So if you had critical ischaemia a couple hours ago, you will not see it—after reperfusion the cerebral blood flow is normal, after reperfusion the cerebral blood volume is normal, maybe even elevated, so we are still at the advantage with diffusion weighted imaging in that situation,” Albers argued.

At his own centre in Stanford, the acute stroke imaging protocol is rapid MR imaging for acute stroke transfers. If they are told that the patient is coming, the MR technician is pre-notified, the MR is then open by the time the patient arrives, and they are taken straight down to the MR, and with the six minute MR protocol, seven minutes after the patient gets onto the scanner, the team gets the results.

“But I must admit that we do not do that when they roll into the emergency room because if we have very little pre-notification, even at Stanford, we cannot get an instant MRI scan. We can get a CT much faster, so our CT/CTA/CT perfusion rapid processing is two minutes,” Albers conceded.

Another possible advantage for MR, he added, is the late time window.

“Time is brain, that is our mantra, and what it says is that when you reperfuse a patient at eight hours, the good outcome rate is not terrific. In the recent studies 30% of the patients had a good outcome if the reperfusion occurred at eight hours. Think about this, what if we had a way to identify that 30% and that was the only 30% that you took to your cath lab, what would your good outcome rate be at eight hours? It would be pretty good,” Albers pointed out.

As for the way forward, Albers maintained that, at least in the later time window, there is a need for sophisticated imaging. The following trials are currently using a combination of CT perfusion and/or MR perfusion and will help to determine if endovascular therapy improves functional outcome in stroke patients with favourable clinical and imaging characteristics: DEFUSE 3 (6–16 hours), DAWN (6–24 hours), POSITIVE (6–12 hours), EXTEND (4.5–9 hours) and ECASS 4 (4.5–9 hours) is using MR only.

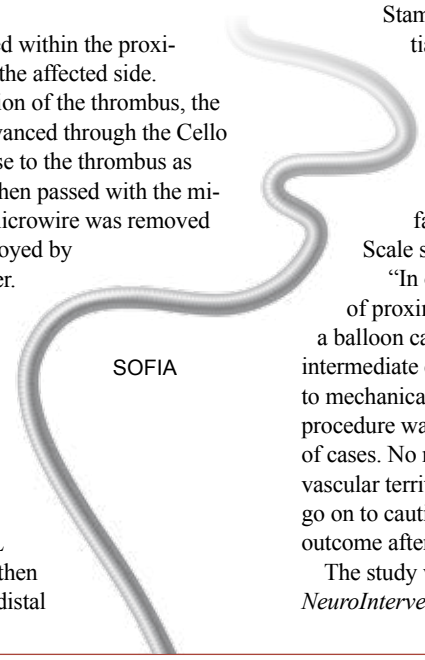
Novel combination technique prevents distal embolisation during thrombectomy

In a study evaluating the safety and feasibility of a combination of proximal internal carotid artery occlusion using a balloon catheter and distal aspiration through an intermediate catheter in stroke patients treated with mechanical thrombectomy with a stent retriever, the investigators report that there was no macroscopic thrombus migration to a new vascular territory.

The study, carried out by Sibylle Stampfl (Department of Neuroradiology, University Hospital Heidelberg, Heidelberg, Germany) and colleagues, included patients with an occlusion in the anterior circulation who were treated with thrombectomy using a balloon catheter for proximal flow arrest, and an intermediate catheter for distal aspiration. Pre- and post-interventional thrombolysis in cerebral infarction (TICI) scores were assessed. Clinical presentation at admission and discharge and after three months was evaluated and complications were recorded.

The devices used were an 8F Cello balloon catheter (Covidien/Medtronic) and a SOFIA catheter (Soft torqueable catheter optimised for intracranial access; Microvention). The stent retrievers used were the Solitaire (Medtronic) and Trevo (Stryker Neurovascular).

The study authors retrospectively identified 31 patients from their prospectively collected stroke database who met the inclusion criteria. The procedure was carried out as follows: Using transfemoral access, the 8F Cello balloon guide catheter was placed within the proximal internal carotid artery of the affected side. After angiographic visualisation of the thrombus, the intermediate catheter was advanced through the Cello catheter and navigated as close to the thrombus as possible. The thrombus was then passed with the microwire/microcatheter. The microwire was removed and a stent retriever was deployed by withdrawing the microcatheter. Subsequently, the Cello balloon was inflated using a 2.5ml syringe filled with a mixture of contrast medium and normal saline. Prior to thrombectomy, aspiration was applied through the intermediate catheter lumen using a 20mL or 60mL syringe. Thrombectomy was then performed under continuous distal aspiration and balloon occlusion of the proximal internal carotid artery. After the thrombectomy the balloon was deflated and angiographic runs were performed to control flow restoration. In cases of persistent occlusion the procedure was repeated.



Stampfl *et al* report: “In all patients the initial TICI was 0. A TICI score of ≥2b was achieved in 96.8%. No new thromboembolic complications occurred. The median NIH Stroke Scale score was 19 at admission and 4.5 at discharge. After three months 51.6% of the patients had a favourable clinical outcome (modified Rankin Scale score 0–2) and 19.3% had died.

“In our study of 31 patients the combination of proximal internal carotid artery occlusion via a balloon catheter and distal aspiration through the intermediate catheter was a safe and efficient complement to mechanical thrombectomy with stent retrievers. The procedure was technically successful in a large number of cases. No macroscopic thrombus migration into a new vascular territory occurred,” the authors conclude. They go on to caution, however, that “the rate of favourable outcome after three months was not higher than 50%.”

The study was published in the *Journal of NeuroInterventional Surgery* (*JNIS*).

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Trial Funding Support	**Funded by Covidien INVESTIGATOR INITIATED**	**Funded by Covidien INVESTIGATOR INITIATED**	**Funded by Covidien**	**Funded by Covidien INVESTIGATOR INITIATED**
Number of Patients	**70**	**316**	**196**	**206**
Primary Device Studied	**Solitaire™** Revascularization Device*	**Solitaire™** Revascularization Device*	**Solitaire™** Revascularization Device**	**Solitaire™** Revascularization Device*
Study Conclusion	Improved outcomes vs. IV t-PA alone	Improved outcomes vs. IV t-PA alone or best medical therapy	Improved outcomes vs. IV t-PA alone	Improved outcomes vs. IV t-PA alone or best medical therapy

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Brain to Brain

IV thrombolysis in acute stroke treatment is dead

It has now been universally accepted that mechincal thrombectomy for the treatment of patients with acute ischaemic stroke with large vessel occlusions is the future. But what does that mean for long-time gold standard treatment of intravenous (IV) thrombolysis? In this *Brain to Brain* debate, Keith W Muir and Urs Fischer weigh in on whether stroke patients should still be receiving IV thrombolysis at all.

Is IV thrombolysis dead? Far from it

Keith W Muir

Endovascular mechanical thrombectomy is an important advance for those patients with large artery occlusive, anterior circulation stroke, but all that we know about this treatment modality is built on a foundation of highly efficient provision of intravenous thrombolysis—this applies equally to the 90% of participants in recent endovascular trials who had received IV thrombolytic drugs as part of standard care, but also to the 10% of trial participants who were considered ineligible for IV thrombolysis, since these patients benefitted from the same streamlined assessment process for selection. Median stroke onset to start of IV thrombolysis times in the recent trials were superior to all previously published data on routine thrombolytic treatment (as short as 85 minutes in the MR CLEAN trial,[1] and overall median 100 minutes across all five published trials[2]).

In order to justify omission of an established and effective treatment—IV thrombolysis—very robust evidence should be demanded. This presently is not available.

While individual patient data meta-analysis of the five trials included in the HERMES collaboration, including the 188 patients deemed ineligible for IV thrombolysis, yields a point estimate for effect very similar to those who received IV alteplase, the small sample means that confidence intervals are wide and encompass the possibility that the true effect may differ.[2] Randomised trial data that are now unfashionable—the SYNTHESIS expansion trial[3]—indicate that bypassing the established IV thrombolysis pathway in favour of a "more effective" endovascular approach may not be in the patient's interest: outcomes of endovascular treatment in SYNTHESIS were not different compared to IV thrombolysis alone, and a probable reason for this lies in the additional delay incurred in starting endovascular procedures. Devices and team organisation have improved since SYNTHESIS but "better" recanalisation may yet fail if it is not also "faster".

Contrary to a frequently repeated claim that "IV thrombolysis does not work" for some categories of patient, recent trials report higher rates of recanalisation with IV therapy alone, even for large vessel and high clot burdens,[4] than were documented in older studies. In EXTEND-IA, 11% of eligible patients had already largely recanalised prior to angiography.[5] The same proportion in SWIFT PRIME either could not have endovascular treatment (because of vascular access issues or imaging misinterpretation) or no longer needed it because recanalisation had occurred.[6] Intention to treat with endovascular approaches neither guarantees that this is feasible, or necessary. The rapidly declining benefit of IV thrombolysis over the first hours[7] does not concur with the time scale for loss of viable tissue on imaging,[8] and therefore may reflect modification of clot characteristics that make successful lysis less likely. Earlier delivery of IV therapy alters the landscape for IV therapy as well as for endovascular treatment, and it is wrong to assume that figures from studies conducted many years ago reflect today's reality as door to needle times shorten.

IV therapy itself does not stand still, but continues to evolve. Data already indicate both safety and efficacy of IV alteplase in many of the patient groups excluded from clinical trials and thus the current alteplase licence.[9,10] When faced with a patient who falls out of the licence criteria, the first question that a clinician ought to consider is whether the totality of evidence truly indicates a different risk:benefit balance in that individual compared with those who fall within licence. In a great many cases there is no evidence of greater risk or lower benefit, and IV thrombolysis should be considered. Trials investigating alternative doses of alteplase, alternative thrombolytic agents, and combination therapies, all promise to alter the landscape for IV therapy in the near future, with the prospect of safer and more effective IV therapy.[11]

Keith W Muir

Finally, and perhaps most importantly, endovascular treatment is currently inappropriate, inaccessible or unavailable for most stroke patients even in those high-income countries where pockets of expertise exist—worldwide it represents a tiny fraction of activity. IV thrombolysis can, in contrast, be delivered to a significant proportion of patients, and can even be brought to geographically remote areas with telemedicine.

In conclusion, IV thrombolysis is an effective treatment that should be initiated in all eligible patients as rapidly as possible, irrespective of whether subsequent eligibility for additional endovascular treatment is determined. Endovascular treatment in IV thrombolysis-ineligible patients appears to be a reasonable option based on a very limited amount of data, but grounds for ineligibility need to be considered carefully, and future evolution of IV thrombolytic treatments may well modify the risk:benefit balance. Is IV thrombolysis dead? Far from it: it is the basis for providing endovascular care for the small proportion of patients who require it, and ongoing trials are likely to reinvigorate it.

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Keith W Muir is SINAPSE professor of Clinical Imaging & consultant neurologist at the Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK

> ***Is IV thrombolysis dead? Far from it: it is the basis for providing endovascular care for the small proportion of patients who require it, and ongoing trials are likely to reinvigorate it.***
> *– Keith W Muir*

Acute endovascular stroke treatment: "To bridge or not to bridge, that is the question!"

IV treatment before mechanical thrombectomy is of no benefit

Urs Fischer

The unanswered question

In 1996 the US Food and Drug Administration approved intravenous thrombolysis with recombinant tissue plasminogen activator (IV rt-PA) for treatment of acute ischaemic stroke based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial.[1] In the meantime, IV rt-PA has become the "holy grail" of acute stroke treatment and is currently the standard treatment of care for all eligible stroke patients presenting within 4.5 hours after symptom onset.

However, the field of intravenous thrombolysis has been stagnant for the last 20 years. The major breakthrough in modern stroke treatment came in 2015, when five randomised controlled trials consistently showed that endovascular clot retrieval in addition to best medical treatment (± IV rt-PA) improves outcome in acute anterior circulation stroke patients with proximal vessel occlusion.[2,3,4,5,6] Interestingly enough, a meta-analysis of individual patient data from these five randomised trials did not show any difference in outcome in patients who received alteplase and those who were ineligible for IV rt-PA.

Whether treatment with IV rt-PA prior to mechanical thrombectomy is of any benefit has currently become an important unanswered question in acute stroke treatment.

Pros and cons of bridging therapy

There are several arguments for and against administering IV rt-PA in acute stroke patients with a proximal vessel occlusion in the anterior circulation:

- IV rt-PA can be started earlier than mechanical thrombectomy and may produce recanalisation and reperfusion, avoiding the need for embolectomy.[9] However, in the recent landmark trials, reperfusion prior to embolectomy occurred in only 5–10% of patients. Reperfusion rates depend on the site of vessel occlusion with very low rates in internal carotid artery (ICA) occlusions and with higher rates in occlusions in the M2 segment of the middle cerebral artery (MCA).
- IV rt-PA may facilitate embolectomy and may result in fewer stent retriever passes.[9]
- IV rt-PA may help to recanalise thrombi in small vessels and in the microvascular structure, inaccessible for endovascular devices.[8]

On the other hand, rt-PA has several important limitations:[9]

- IV rt-PA may increase the risk of intracerebral haemorrhage (ICH) and any other bleeding complications.[8] Kidwell *et al* found that intravenous or intra-arterial rt-PA resulted in a greater breakdown of the blood-brain barrier compared with embolectomy or no treatment.
- IV rt-PA is ineffective in the majority of patients with large thrombi and in patients with large vessel occlusions.
- IV rt-PA may result in migration of thrombi from proximal into distal vessels, where thrombectomy is no longer possible.
- Immediate administration of antiplatelet agents and heparin are contraindicated for 24 hours after IV rt-PA, but potentially beneficial after endovascular intervention and clearly indicated when stents have to be placed during the endovascular procedure.[8]
- The therapeutic window for IV rt-PA is narrow with a rapidly increasing number needed to treat.[8]
- IV rt-PA has a considerable impact on healthcare costs: IV rt-PA, which is eventually not beneficial in these patients would unnecessarily increase the cost of treatment in patients presenting with proximal vessel occlusion, if stent retriever thrombectomy alone is equally effective as IV rt-PA followed by stent retriever thrombectomy.[9]
- Many patients with severe strokes and large vessel occlusions have absolute or relative contraindications for IV rt-PA (ie. wake-up strokes, borderline coagulation status, high blood pressure and glucose levels, etc.) putting them at an increased risk of ICH.[8]
- IV rt-PA prior to endovascular clot retrieval might even delay endovascular therapy, especially in centres where patients can be quickly moved to the endovascular suite.
- Initial triage to a primary stroke centre for administration of IV rtPA may delay transfer to a comprehensive stroke centre for embolectomy.[9]
- IV rt-PA causes some rare side effects such as life-threatening orolingual angioedema.[8]

	Broeg-Morvay et al. (8)		Weber et al. (16)	
	MT and IVT (40)	MT alone without contraindications for IVT (40)	MT and IVT (105)	MT alone without contraindications for IVT (70)
TICI 2b-3, n (%)	31 (77.5%)	35 (87.5%)	76 (73.8%)	52 (74.3%)
sICH, n (%)	1 (2.5%)	1 (2.5%)	6 (5.9%)	2 (2.9%)
aICH, n (%)	14 (35%)	5 (12.5%)	12 (11.4%)	7 (10%)
Any ICH, n (%)	15 (37.5%)	6 (15%)	18 (17.6%)	9 (13.2%)
Systemic bleeding, n (%)	5 (12.5%)	0	n.a.	n.a.
Any bleeding, n (%)	19 (47.5%)	6 (15%)	n.a.	n.a.
mRS 0-2, n (%)	17 (42.5%)	17 (42.5%)	37 (35.2%)	34 (48.6%)
mRS 0-1, n (%)	11 (27.5%)	11 (27.5%)	n.a.	n.a.
Mortality	19 (47.5%)	8 (20%)	28 (26.7%)	18 (25.7%)

TICI: Thrombolysis in cerebral infarction; sICH: symptomatic intracerebral hemorrhage; aICH: asymptomatic intracerebral hemorrhage; Any ICH: sICH plus aICH; mRS: modified Rankin scale

Table 1 Outcome in bridging patients (mechanical thrombectomy and IV rt-PA) versus patients with mechanical thrombectomy alone without contraindications for IV rt-PA.

Current evidence

Several studies compared IV rt-PA eligible patients treated with mechanical thrombectomy with IV rt-PA ineligible patients: The proportion of functionally independent patients at 90 days were similar across studies ranging 48–68% in the IV rt-PA plus mechanical thrombectomy group and 42–59% in the mechanical thrombectomy alone group.[12,13,14,15] These data were confirmed in the above-mentioned meta-analysis of individual patient data from the five randomised trials.[7] However, in all these studies patients treated with mechanical thrombectomy alone had contraindications for IV rt-PA, which makes a direct comparison of these different patient groups difficult.

Only recently, two studies compared clinical and radiological outcomes of patients treated with IV rt-PA in combination with mechanical thrombectomy to IV rt-PA eligible patients treated with mechanical thrombectomy alone directly referred to comprehensive stroke centres.[8,16] In both studies, outcome in patients treated with bridging thrombolysis and those with mechanical thrombectomy alone did not differ, but rates of haemorrhages tended to be higher in bridging patients than in those, treated with mechanical thrombectomy alone.

Relevance

Critics argue that the proportion of patients treated with endovascular treatment is only relevant for a small minority of patients in advanced healthcare systems, and therefore the question whether patients should be treated with IV rt-PA is irrelevant.[17] However, recent positive trials have boosted the proportion of patients treated with thrombectomies in many countries. In well-established comprehensive stroke centres with a large network of stroke units, up to 20% of stroke patients referred to a comprehensive stroke centre are currently treated with mechanical thrombectomy (unpublished data from the Bernese stroke registry).

Outlook

IV rt-PA will remain the standard of care for all patients presenting within 4.5 hours after symptom onset with peripheral vessel occlusion. However, current evidence suggests that direct mechanical intervention may be equally effective compared to bridging thrombolysis in patients with large anterior circulation stroke and there is equipoise that calls for a randomised trial. A randomised trial comparing mechanical thrombectomy alone with bridging therapy in patients directly referred to a comprehensive stroke centre, where immediate reperfusion is possible could solve this question and is currently planned.

Therefore, one of the relevant unanswered questions in acute stroke treatment 400 years after the death of William Shakespeare is: "To bridge or not to bridge. That is the question!"

Urs Fischer

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Urs Fischer is professor for Acute Neurology and Stroke and co-director of the Clinical Trial Unit at the University of Bern, Switzerland

Inside the NIH StrokeNet

The National Institutes of Health (NIH) StrokeNet, which was initiated in 2013, currently involves 288 hospitals across the United States and is designed to serve as the infrastructure and pipeline for new potential treatments for patients with stroke and those at risk of stroke, according to the User's Guide published in the journal *Stroke*.

NeuroNews now speaks to Joseph Broderick (Department of Neurology and Rehabilitation Medicine, University of Cincinnati Neuroscience Institute, Cincinnati, USA), principal investigator of the National Coordinating Center for the NIH StrokeNet, about the ins and outs of the network and its progress thus far.

Joseph Broderick

Why was the NIH StrokeNet established?

The NIH StrokeNet was established primarily to facilitate Phase II and Phase III Trials of acute stroke treatment, stroke prevention, and recovery after stroke. Having an infrastructure already in place substantially decreases the time for new stroke trials to get started and the infrastructure can be immediately focused on other trials when a trial is completed or stopped early. A second goal of the NIH StrokeNet is to train the next generation of clinical researchers in stroke with at least one new fellow at every of the 25 regional stroke centres every year. Industry collaboration is encouraged.

What is its organisational structure?

The NIH StrokeNet is composed of 25 Regional Stroke Centers in the USA. Each regional centre includes a number of hospitals and/or additional academic hospitals. These Regional Centers include Rehabilitation Hospitals as well as Children's Hospitals. The National Coordinating Center is based at the University of Cincinnati and the National Data Management Center is based at the Medical University of South Carolina. The NIH StrokeNet represents a close collaboration with the NINDS who provide significant input and oversight to the activities of the network.

Since its initiation in 2013, how has StrokeNet been performing?

All parts of the network were not funded until mid-2014, and the first year and a half was focused on setting up the infrastructure and contracts, reliance agreements at each regional centre and participating hospitals with the central IRB at the University of Cincinnati, and the development and submission of new trials. The NIH StrokeNet centres currently participate in the CREST 2, MISTIE III, iDEF Trial, POINT, Rhapsody, and SHINE trials as well as other NIH funded stroke trials. Two trials which have come directly from the NIH StrokeNet investigators include the TeleRehab Trial (just started this autumn) and DEFUSE 3 which is just starting. A large number of trials have been submitted for review or will be submitted for review by June 2016.

What are the subgroups within the NIH StrokeNet and what roles do they play?

There are three working groups (Acute Treatment, Prevention, and Recovery/rehabilitation) who help investigators assess their trial design and feasibility. Some of the proposed trials have sprung out of these working groups. There are two major Cores: the Educational Core and the Imaging Core. The latter Core plays a major role in assessing the imaging components of proposed trials. There are also advisory groups (Minority Recruitment, Endovascular, Paediatric) who provide input as needed on proposed trials.

How would new hospitals go about joining StrokeNet and what are the key benefits of doing so?

Hospitals can contact one of the Regional Center principal investigators (this information can be found on NIH StrokeNet website) to see if they would qualify as a satellite site. However, it is up to the Regional Center to decide whether this is possible. Hospitals can also participate in future NIH Stroke Trials even if they are not part of the network, if there is a need for centres beyond the NIH StrokeNet and they can demonstrate the ability to recruit into a specific type of clinical trial.

Can you explain the education platform provided by StrokeNet? What are its benefits?

The platform provides a year of support for trainees to learn about stroke research. These trainees (including neurologists, as well as physicians from other specialties, pharmacists and physical therapists among others) have access to an extensive series of scientific and professional educational presentations, the opportunity to present their research at national meetings, local and national mentorship for trainees, and interaction with their peers and stroke leadership across the USA.

Are there any plans to link this network with national stroke networks in other countries? If so, what would the implications of that be?

Yes. Our leadership has been meeting with newly developing stroke networks in other countries for the past 12+ months. These other networks may decide to participate in some of our ongoing trials. They may be able to support their local stroke infrastructure and thus help facilitate quicker completion of trials. Networking also can allow for planning of similar trials in other countries which facilitates pooling of data when the trials are completed.

Thrombectomy in clinical practice: what we can expect

It must be accepted that mechanical thrombectomy for the treatment of acute ischaemic stroke in clinical routine will not have the same "excellent" results as in the trial environment. That being said, the use of mechanical thrombectomy in clinical routine will give patients who could not meet trial inclusion criteria a chance at an improved outcome.

That is according to Werner Hacke (University Hospital of Heidelberg, Heidelberg, Germany) who spoke at the International Stroke Conference (ISC; 17–19 February, Los Angeles, USA).

In the recent thrombectomy trials there were many common features: These were mostly moderate to severe strokes, in mostly proximal occlusions (ICA, M1); predominant use of modern stent retriever devices; and the majority of patients were treated on top of t-PA. The differences among the trials were seen in the time to recanalisation and in the type of imaging selection (imaging almost exclusively CT-based; CT-selection varied from plain CT over ASPECTS, estimation of collaterals to automatic analysis of tissue at risk or RAPID).

Hacke pointed out that the factors influencing the treatment effects are time to recanalisation (or, more frequently assessed, time to groin) and level of recanalisation. "But the level of imaging requirements for patient selection also varied between the trials. In MR CLEAN (plain CT, ASPECTS post hoc) there was 14% absolute difference between the endovascular treatment group and the control group; in REVASCAT (plain CT and ASPECTS) there was 16% absolute difference; in ESCAPE (all ASPECTS >5) there was 24% absolute difference; in SWIFT PRIME (ASPECTS, some RAPID) there was a 21% absolute difference; and finally, in EXTEND-IA (all RAPID), which had the best treatment effect and the largest response rate also had the best placebo response, there was a 31% absolute difference," he reported.

As for how that will compare with clinical routine, Hacke explained that the broader the inclusion criteria are and the less complex the imaging criteria are (plain CT, exclusion of very large early infarct and bleed only), the more patients will qualify for thrombectomy. As a result, more patients with a lower likelihood to show superiority to standard treatment will be treated, including M2 occlusion, milder stroke (NIHSS <10), long time windows and extended early infarcts.

With very broad inclusion, as will be the case in clinical routine, he added, it is unrealistic for stroke teams to expect to generate outcomes like in SWIFT PRIME or even EXTEND-IA. Rather, he said, the mRS 0–2 outcome will probably be closer to that in ESCAPE and hopefully a little better than in MR CLEAN or REVASCAT.

"But let us accept that in clinical routine we will treat patients who would not have made it into a clinical trial. For example, think of someone who has Parkinson's disease, and because of his Parkinson's he has a mRS of 2. He can never get into a stroke trial, but saving him to remain with the mRS 2 instead of going down to a mRS 4 because now he had a stroke, that is what medicine is about, but it is not reflected in clinical trials. So let us not be disappointed when our local registries show higher mortality rates and lesser percentages of excellent outcome because this reflects clinical reality with broad inclusion. So let us accept that there will be a higher number of treatment failures with broad inclusion.

"We will treat patients that we know are probably not the best candidates (very old, more than eight hours after onset, tandem occlusions) because we know we will give them a chance with the treatment, and as long as we do not hurt them with giving them a chance this is absolutely appropriate. In some the miracle will work, in most it will not," Hacke stated.

Werner Hacke

Giving advice for how patients should be designated in registries from now on, Hacke suggested that patients should be classified as ideal candidates and last chance candidates prospectively, and then the results can be benchmarked for the ideal patients and operators must accept that the non-ideal patients will dilute the results.

"Even if we get very broad with the inclusion, we may include patients who will not benefit and may have a risk, but independently of that we will never lose the good ones, they will always qualify, the broader the inclusion may be," Hacke concluded.

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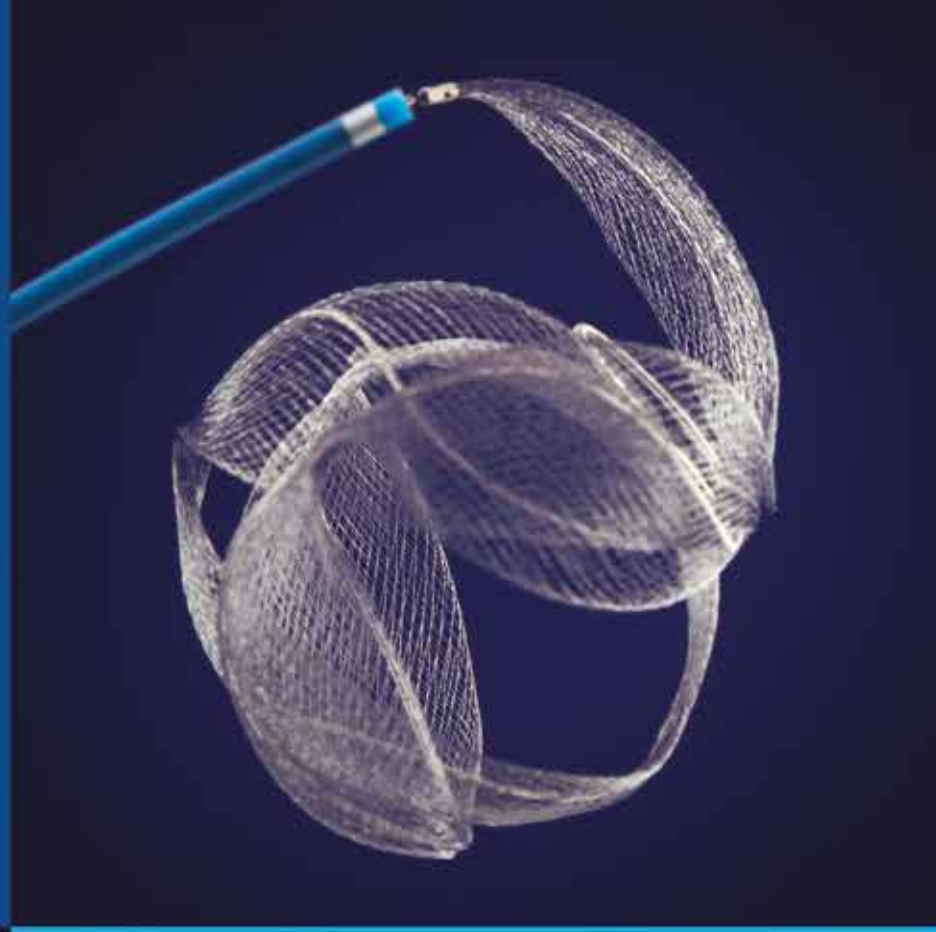

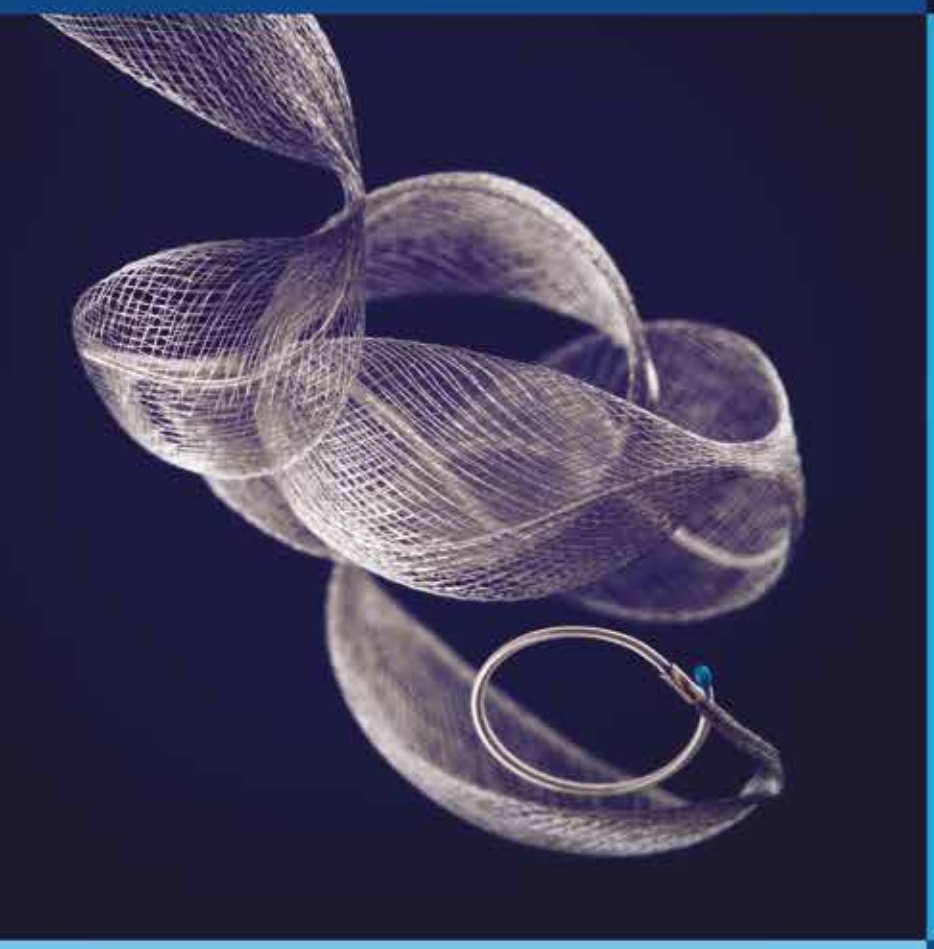

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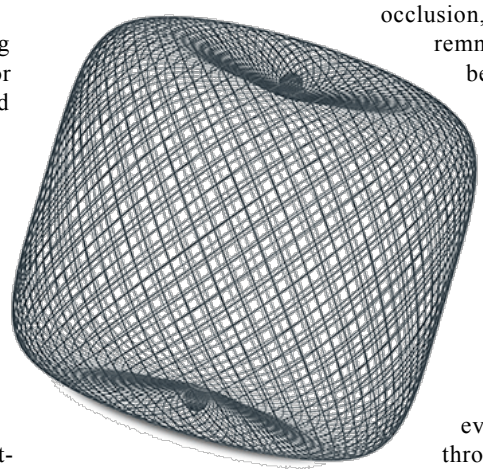
Real-world experience confirms safety and efficacy of WEB in wide-necked aneurysms

The real-world experience of a centre in Germany has confirmed the overall promising results in feasibility, safety and effectiveness of the WEB device (Woven Endobridge; Sequent Medical) reported in other studies.

In the largest single-centre experience published to date, Christin Clajus (Helios General Hospital Erfurt, Erfurt, Germany) and others analysed an all-inclusive cerebrovascular database of patients treated with the WEB device between October 2010 and May 2015. The database included 108 patients with 114 saccular aneurysms treated with the WEB.

The WEB is a self-expanding intra-aneurysmal flow disruptor consisting of compliant braided nitinol mesh. The device is currently available in Europe.

In terms of procedure in their series, the authors report that following WEB placement, post-interventional control angiography was performed to evaluate the degree of initial aneurysm occlusion. Clinical status was assessed immediately post-procedure, at discharge, and at the time of follow-up using the modified Rankin Scale (mRS). According to the WEBCAST trial, morbidity was defined as an mRS >2. Follow-up imaging and clinical examinations have been performed—and will continue to be—at six months, 12 months and five years post-intervention. Aneurysm occlusion was graded as either "adequate" (complete occlusion, neck remnant) or "aneurysm remnant" (if filling of the aneurysm beyond the neck was noted).



WEB

Of the 114 aneurysms treated, 47 aneurysms were ruptured (41.2%). After a mean of 13.4 months, 86 patients received angiographic and clinical follow-up. One hundred and ten of the 114 WEB devices (96.5%) were deployed successfully.

As it relates to adverse events, the authors report that thromboembolic complications occurred in 11 of 110 interventions (10%), with a new permanent deficit in one patient. Re-rupture after WEB treatment was detected in two aneurysms (4.3%), which had both initially presented with subarachnoid haemorrhage. Overall, angiographic follow-up revealed adequate occlusion in 68 of 90 aneurysms (75.6%), with complete occlusion in 52 aneurysms (57.8%) and a neck remnant in 16 aneurysms (17.8%). In 22 aneurysms (24.4%) residual aneurysm filling was noted. Fifteen aneurysms (16.7%) required retreatment. Finally, the study authors write, permanent morbidity and mortality in all patients who received a WEB device and follow-up angiography were 5.3% and 8.5% (five and eight patients of 94 patients involved), respectively.

The authors conclude, "Intra-aneurysmal flow disruptors represent an emerging endovascular treatment strategy for wide-necked bifurcation aneurysms, with the main advantages of not requiring permanent anti-platelet therapy and allowing the treatment of many of these aneurysms during a technically straightforward, efficient, single-step procedure. From the results of the WEBCAST, the French Observatory and our series, we think that the WEB device can become the treatment of choice for many cerebral aneurysms."

The study was publishing the *Journal of NeuroInterventional Surgery*.

New aneurysm device acts as both flow disruptor and diverter

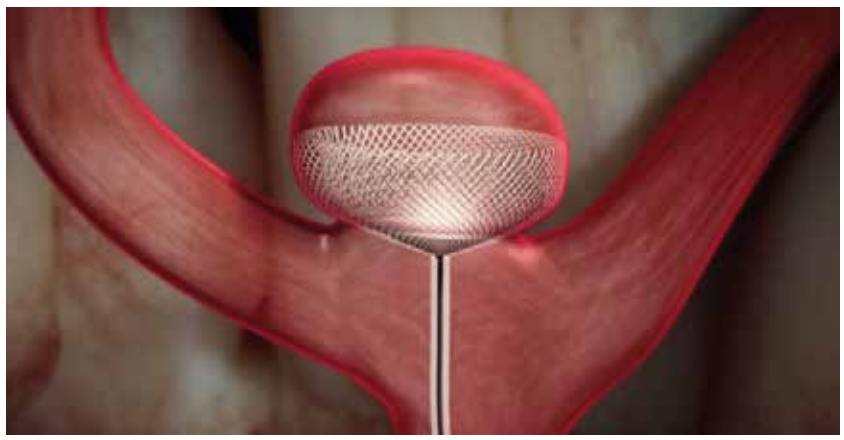
The Contour Neurovascular System (Cerus Endovascular) will offer a new option for treating intracranial aneurysms. According to Kyriakos Lobotesis, Principle Clinical Advisor at Cerus, "the objective of the device is to treat the neck of the aneurysm, thus avoiding protracted manoeuvres and manipulation within the aneurysm, which can be experienced while using other available devices".

Can you describe the Contour Neurovascular System?

The Contour Neurovascular System is an innovative, intrasaccular, self-anchoring, embolisation device targeting the aneurysm neck.

How is it different from existing devices for the treatment of intracranialaneurysms, such as coils, intrasaccular flow disruptors and flow diverters?

The device, due to its unique placement across the neck of the aneurysm, acts as both a flow disrupter and diverter. Unlike other intrasaccular devices the Contour Neurovascular System is not as limited by aneurysm size or shape. Its unique stabilising design architecture prevents it from migrating or compacting into an aneurysm post-deployment. The device mesh provides a uniform scaffold distributed across the neck of the aneurysm for the establishment of neointimal development and unlike devices placed in the parent vessel, is not dependent on the use of dual antiplatelet therapy. Hence it can be used for the treatment of both ruptured and unruptured intracranial aneurysms.



Contour Neurovascular System

How does the device work and what are the objectives?

The objective of the device is to treat the neck of the aneurysm, thus avoiding protracted manoeuvres and manipulation within the aneurysm, which can be experienced while using other available devices. The aim is to offer consistent neck coverage and stability to reduce the risk of compaction/recanalisation/retreatment. The device works by a combination of diversion and disruption of flow in the aneurysm sac.

What were the results of the animal studies?

Over a number of animal studies, the device has consistently demonstrated high rates of complete occlusion of the aneurysm, which were sustained over a period of time. Thrombosis and neointimal growth across the neck were repeatedly confirmed histopathologically. Deliverability, positioning and device stability were also excellent throughout. These results, and other testing performed, provided the confidence to move forward into first human use.

What types of intracranial aneurysms can the Contour device be used to treat?

Because the Contour System addresses the neck of the aneurysm, it is not limited to specific aneurysm location or morphology, therefore it can be used to treat a wide range of intracranial aneurysms. Its ease of deliverability and accurate positioning allow it to address even difficult to treat wide-necked bifurcation aneurysms and aneurysms with branches arising from their side wall. As mentioned above, being intrasaccular, its use does not necessitate dual antiplatelet therapy. It hence can be used for the treatment of both ruptured and unruptured intracranial aneurysms.

What were the results of the first-in-man study?

First-in-man studies have confirmed device stability at six months and steady aneurysm occlusion during this period. The patients all maintained their pre-treatment status and most importantly there were no adverse events. The patients will of course continue to be followed-up.

What is planned in terms of future trials?

The first trial has been approved and is already recruiting patients. A second multicentre trial is currently seeking approval and will start enrolling patients shortly.

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Long-term experience confirms ADAPT as effective treatment for stroke

A study of the long-term use of the ADAPT technique for the treatment of acute ischaemic stroke has confirmed that it is an efficient method to achieve good clinical and angiographic outcomes, with 82.2% of patients achieving TICI 2C or better recanalisation and 90-day mRS scores of 0–2 in 54.4%.

Jan Vargas (Medical University of South Carolina, Charleston, USA) and colleagues sought to report their centre's ongoing experience with the ADAPT technique, which has been used as the primary revascularisation technique at that institution since 2012.

A retrospective analysis of a prospectively maintained database was performed to identify all patients undergoing thrombectomy for large vessel occlusion with ADAPT at that institution using an institutional review board approved protocol. Patients undergoing thrombectomy between December 2012 and April 2015 were included. Specific parameters captured included age, gender, National Institutes of Health Stroke Scale (NIHSS) score at presentation, and time to presentation from last normal. Of significance, angiograms were blindly graded by an independent neurointerventionalist to assess pre- and post-revascularisation using both the Thrombolysis in Cerebral Ischaemia (TICI; with scores of 0, 1, 2A, 2B, and 3) flow post procedure and the modified 2C TICI grading scale (including scores of 0, 1, 2A, 2B, 2C, and 3).

According to the data, from December 2012 to June 2015, 191 consecutive patients who suffered an acute ischaemic stroke were treated with ADAPT by four operators. Ninety-one patients were women (47.6%), and the average age was 67 (range 27–93 years, ±14 years). A total of 171 (89.5%) ischaemic strokes occurred in the anterior circulation and 20 (10.5%) in the posterior circulation. Patients presented with a mean NIHSS score of 15.4 (range 0–36, ±7), and 71 (37.2%) patients received IV t-PA. The average time from onset to puncture was 7.8 hours (range 20min to >36 hours, ±6.1 hours). Twenty-three patients (12%) presented as wake up strokes. The average length of stay was 9.3 days (range 0–193, ±16.9 days). Twelve (6.3%) patients had tandem lesions noted during treatment. In 10 cases, the occlusion was in the internal carotid artery, with tandem distal lesions in ipsilateral branches of the middle cerebral artery. There were no cases of emboli to new territory following aspiration thrombectomy. In two cases of basilar artery occlusion, the patients had additional occlusion of left sided middle cerebral artery branches, one of which was felt to be a chronic thrombus and was not aspirated.

The authors report, "The average time for recanalisation was 37.3min (range 7–160min, ±29.6) across all cases. There were no differences among operators. Independent adjudicated angiographic outcomes of TICI 2B or better recanalisation was achieved in 180 (94.2%) patients, TICI 2C or better was achieved in 157 (82.2%) patients, and TICI 3 was achieved in 85 patients (44.5%). Recanalisation was unsuccessful in two cases. In one patient who suffered a basilar occlusion from extensive atherosclerotic plaque, recanalisation was not achieved (TICI 0) due to abortion of the procedure secondary to intraprocedural basilar artery rupture. In a second patient, multiple attempts were made to recanalise a completely occluded right internal carotid artery, ultimately resulting in partial revascularisation. The ACE 64 catheter (Penumbra) was used in seven cases, all of which achieved a TICI score of 2C or better (100%). The 5 MAX ACE (Penumbra) was used in 101 cases, of whom 78 (77.2%) achieved TICI 2C or better. The 5 MAX catheter (Penumbra) was used in 33 cases, of whom 30 (90.2%) achieved TICI 2C or better. The likelihood of achieving TICI 2C or better recanalisation was not significant for the ACE 64 (p=0.35), 5 MAX ACE (p=0.087), or 5 MAX (p=0.21) catheters."

As it relates to complications, they write that there were four intraprocedural complications. Further, 13 (6.8%) patients suffered clinically significant post-procedural parenchymal haematomas; one patient (0.57%) had a retroperitoneal haematoma; and seven patients (3.7%) suffered post-procedural gastrointestinal bleeds.

In terms of outcome, Vargas *et al* report that the average time from onset to puncture was 7.8 hours and the average time for recanalisation was 37.3min. TICI 2B or better recanalisation was achieved in 180 (94.2%) patients. Ninety-eight patients (54.1%) had an mRS of 0–2 at 90 days.

Of note, ADAPT was successful in achieving final recanalisation in 145 of cases, and 43 cases required the additional use of a stent retriever. Eight direct aspiration only cases had lesions in more than one vessel, compared with four in the direct aspiration with adjunctive devices. In two cases, recanalisation was not achieved. Additionally, the authors highlight, "Mean time to recanalisation was significantly faster for direct aspiration only cases, with revascularisation achieved in 30.12min (range 7–150min, ±29.56) compared with 61.4min (range 8–160min, ±35.85) (p=0.00000201). There were no significant differences in likelihood of achieving a 90-day mRS of 0–2 (57.7% for direct aspiration only vs. 43.2%; p=0.12) or mortality rates among the two groups (13.9% for direct aspiration only vs. 18.2%; p=0.47)."

Vargas *et al* conclude that in their long-term experience, "ADAPT is an efficient method to achieve good clinical and angiographic outcomes, with 82.2% of patients achieving TICI 2C or better recanalisation and 90-day mRS scores of 0–2 in 54.4%. These results are comparable with recent randomized trials that demonstrate the benefit of intra-arterial thrombectomy." They add that ADAPT as a first line strategy for achieving revascularisation in the setting of acute large vessel occlusion should be further studied in a randomised trial.

The double-edged sword of clinical data sharing

JOSHUA A HIRSCH

COMMENT & ANALYSIS

The *Journal of NeuroInterventional Surgery* (*JNIS*) recently featured a point/counterpoint regarding sharing clinical trial data. In fact, the participants were two of the journal's founding editors.

At the heart of the discussion was a proposal from the International Committee of Medical Journal Editors (ICMJE) that was published in multiple lead journals entitled "Sharing Clinical Trial Data—A Proposal from the International Committee of Medical Journal Editors. "

The ICMJE describes itself as a "small working group of general medical journal editors, whose participants meet annually and fund their own work on the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals". The premise of this proposal is that the editors believe there is an ethical responsibility, indeed, "obligation", to share clinical trial data, because trial participants in a tangible way have been placed in potential harm's way.

The proposal is that investigators would be required to share de-identified individual-patient data (IPD), underlying the results presented in an article published in a member journal. This requirement would include tables, figures, and appendices or supplementary material and be required to happen no later than six months after publication. The data underlying the results are defined as the IPD required to reproduce the article's findings, including necessary metadata. Notably, the ICMJE proposal will require a specific indication of the author's plan for data sharing as a component of clinical trial registration. This plan would include where the researchers will house the data and how other interested parties will be provided access to the data. The ICMJE proposes a one-year delay in implementing the proposal to minimise disruption to current efforts.

The editors of the *New England Journal of Medicine* (*NEJM*) have written a contemporaneous commentary that has received quite a bit of attention. Drs Dan Longo and Jeffrey Drazen raise concerns that people who were not involved in the generation and collection of the data may not understand the choices made in defining the parameters. Doubling down, they raise the notion that a new class of research person could emerge; people they termed "research parasites."

Dr Joshua Hirsch supported the proposal and took aim at the notion of "research parasites". He noted that Longo and Drazen use of this inherently negative term to make a point. Hirsch thought it would be helpful to remember that remora, oxpeckers and orchids have been, at times inaccurately described as parasites as well when in fact they provide commensal or symbiotic relationships to their hosts. He believes the metaphor is helpful in thinking through clinical data sharing.

Hirsch goes on to further argue that there are more ideas within each data set than can be explored by the people that are collecting it. Moreover, there are many more practitioners in the field of medicine with ideas than there are with the ability to generate large, randomised datasets. He points to potential research partners in private practice, who lack a strong research infrastructure. So-called "research parasites" might allow greater realisation of this academic potential through broader collaboration.

Hirsch's final argument related to the moral imperative at work in clinical trials as exemplified by ischaemic stroke. Neurointerventional practitioners asked their vulnerable patients and families suffering from strokes caused by large vessel occlusion to participate in endovascular trials despite the fact that many lacked "personal" equipoise and believed that randomisation away from treatment put patients in harm's way. In fact, the trials proved that this is the case. Going against our own beliefs we withheld what might have been life saving treatment by promoting participation in the trials. In the article, Hirsch states that neurointerventional scientists and clinicians honour that sacrifice by publicly sharing trial data to facilitate further study and commentary.

Dr David Fiorella takes a different point of view with respect to the ICMJE proposal. He asks, "Is clinical data sharing the future of clinical trials?" Reading through his response, it is fair to say that Fiorella believes the answer to be a firm and resounding no.

With brilliant flair, Fiorella turns the question back on the journals and editors that make up the ICMJE. He points out that the cost of open access publication is high and passed on to authors. If authors do not accept this cost, readers often need to pay a high fee in order to read the article. Fiorella posits that a moral obligation to study participants might include allowing the papers to be more broadly studied than the present model allows for. He thus calls for universal open access from publishing houses.

Fiorella goes on to point out that the ICMJE is creating an unfunded mandate for clinical researchers to create the mechanisms by which this data sharing occurs. He points out that the ICMJE does not offer any insight or suggestions in how to fund these requests.

Fiorella's final argument relates to industry sponsorship of clinical trials in neurointervention. He imagines a situation in which industry sponsors would choose not to allow the publication of medical research in peer-reviewed journals, but simply submit to regulatory bodies and then use the data as they see fit to construct marketing materials. In these cases, such studies would then never be subject to the scrutiny of peer review and publication for public consumption. This IPD sharing mandate, he thus argues, could also provide a powerful overarching disincentive to industry to enter into collaborative clinical research initiatives with physicians.

Both authors recognise the legitimacy of each other's point of view and are delighted that the *JNIS* provides a forum for robust discussion. We are hopeful that however this ICMJE proposal plays out, remora, oxpecker's and orchids are made to feel welcome.

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Joshua A Hirsch is at Massachusetts General Hospital, Boston, USA

Data support "careful" use of mechanical thrombectomy in non-top tier evidence criteria ELVO patients

Continued from page 2

times (234 min (IQR 177–291) vs. 381 min (IQR 268–454) p<0.001), but the median door to puncture times between the two groups were not significantly different (151 min (IQR 115–190) vs. 149 min (IQR 115–237), p=0.628).

Further, they write that median ASPECT scores were also higher in patients meeting top tier criteria compared with those not meeting top tier criteria (10 (IQR 10–10) vs. 9 (IQR 8–10), p=0.001). Additionally, cases not meeting top tier evidence included 20 (32%) basilar artery occlusions, and of these, 11 (55%) died, while five (25%) achieved mRS ≤2 at the three-month follow-up.

Finally, the investigators report that rates for sICH were 8% in each group, and serious haemorrhage rates were similar at 8% in the top tier group, compared with 10% in the non-top tier group (p=0.731). Patients in the top tier group also achieved greater neurological improvement during hospitalisation (10 points (IQR 6–14)) compared with the patients in the non-top tier group (5 points (IQR 1–10); p=0.006) in initial univariate analyses. Mortality was significantly lower in the top tier evidence group at 26% compared with 45% in other cases (p=0.044), whereas favourable outcome (mRS ≤2) at three months was similar at 46% in the top tier evidence group versus 33% non-top tier evidence group (p=0.158).

They explain, "After adjusting for potential imbalances between the two groups, including baseline ASPECT score, IV t-PA pretreatment, intubation and time elapsed from symptom onset to groin puncture, associations between endovascular mechanical thrombectomy in top tier evidence cases and others did not reach statistical significance in multivariate analysis."

Trevo-XP ProVue Retriever (Stryker Neurovascular)

Overall, the study showed that despite lacking top tier evidence for mechanical thrombectomy, "33% of cases treated outside these recommendations attained an mRS score of ≤2 by three months, and that nearly half of the mechanical thrombectomy cases would have been denied mechanical thrombectomy if top tier evidence criteria were upheld in clinical practice. Additionally, the data indicated no increased risk of sICH or serious haemorrhagic complications in the group that lacked top tier evidence for mechanical thrombectomy, demonstrating that a sizeable percentage of patients not meeting top tier criteria may still have a good outcome with mechanical thrombectomy."

Finally, commenting on the devices used for mechanical thrombectomy, the authors add, "Despite guidelines endorsing stent retrievers as the technology of choice for thrombectomy, our data showed that in clinical practice, aspiration and a combination of technologies (aspiration and stent retrievers) played a greater role in the treatment of ELVO."

Profile Jacques Moret

As the course director of the Live Interventional Neuroradiology and Neurosurgery Course (LINNC; 23–25 May, Paris, France) Jacques Moret talks about the importance of a live course and about the highlights of the 2016 meeting. He also shares the advice that he hopes his mentees will always follow and addresses three questions in interventional neuroradiology that are still in need of an answer.

What drew you to medicine and neuroradiology in particular?

I wanted to be a doctor since I was in college. I moved to Interventional Neuroradiology (INR) because I had the "vision" that doing surgical procedures without opening the body could be the future. The beginning of Interventional Neuroradiology, which was promoted by Professor Réné Djindjan in France, for spinal cord arteriovenous malformations treatment was the spark!

Who were your mentors and what wisdom did they impart to you?

My mentors were Dr Jacqueline Vignaud and Professor Dominique Doyon. They brought me a very important parameter for my career, which is more than a parameter, it is a real gift; they gave me their confidence and a full freedom. I remember one very important sentence: "Jacques, maybe you are right or maybe you are wrong, but if this is what you want to develop, do it".

Which innovations in interventional neuroradiology have shaped your career?

Innovations are steps of development and will never stop, but it is not a "shaping tool", at least for me. The shaping tool is the concept of the so-called "minimally invasive surgery". The innovations are just the consequences of new therapeutic concepts. However, over the last 35 years, I recognise three major technological innovations: the coils, the flow diverter stents and the phenomenal peri-operative imaging improvement. As far as the concept is the way to progress, I recognise that clearance of cerebral artery using mechanical thrombectomy is the most important evolution for the quality of life of stroke patients over the last ten years.

What was one of your most memorable cases?

One of my most memorable cases is of a one and a half year old baby I treated in 1990 in Beijing for a mural type of Vein of Galen malformation. The procedure went ok and after it, I requested to keep the baby quiet, with control of the blood pressure and heparin treatment. When I came back the next morning, the baby was playing with some other children outside of his room, in a garden of the hospital, with no control at all and no heparin treatment. Last year I got a picture of the baby who is now a strong man in very good shape!

As the course director of LINNC for many years, what do you think is the importance of a live course?

Medicine is an imprecise science where being utterly convinced is frequently perceived as a medical truth, despite the fact that there is no scientific basis! In medicine one can say anything and everything! During live courses lying is not possible! Having said that, live courses must respect the patient and give them the best chance of success, that is the reason why during the LINNC course, the operator has no direct link with the audience, he cannot speak and answer questions at the time of the treatment. A doctor, from the operator's team in the conference room, speaks and answers in the name of the operator. These are our ethics and I stick to it, without any exception.

At LINNC, a lot of focus is placed on delegate participation and interaction, why is this important?

Interventional neuroradiology has four components: the knowledge of the disease, the knowledge of the vascular anatomy, the practical training (as any surgical procedures) and how to manage a complication. The discussion is open all along, and the sessions are organised as a live forum, which is fed by the flow of questions from the audience, through the "app" of the course. It is a fantastic way to learn and an incredible source of progress for everybody, just because an imprecise science needs gathering of multiple experiences to become more and more reliable.

What are the highlights of LINNC Paris 2016?

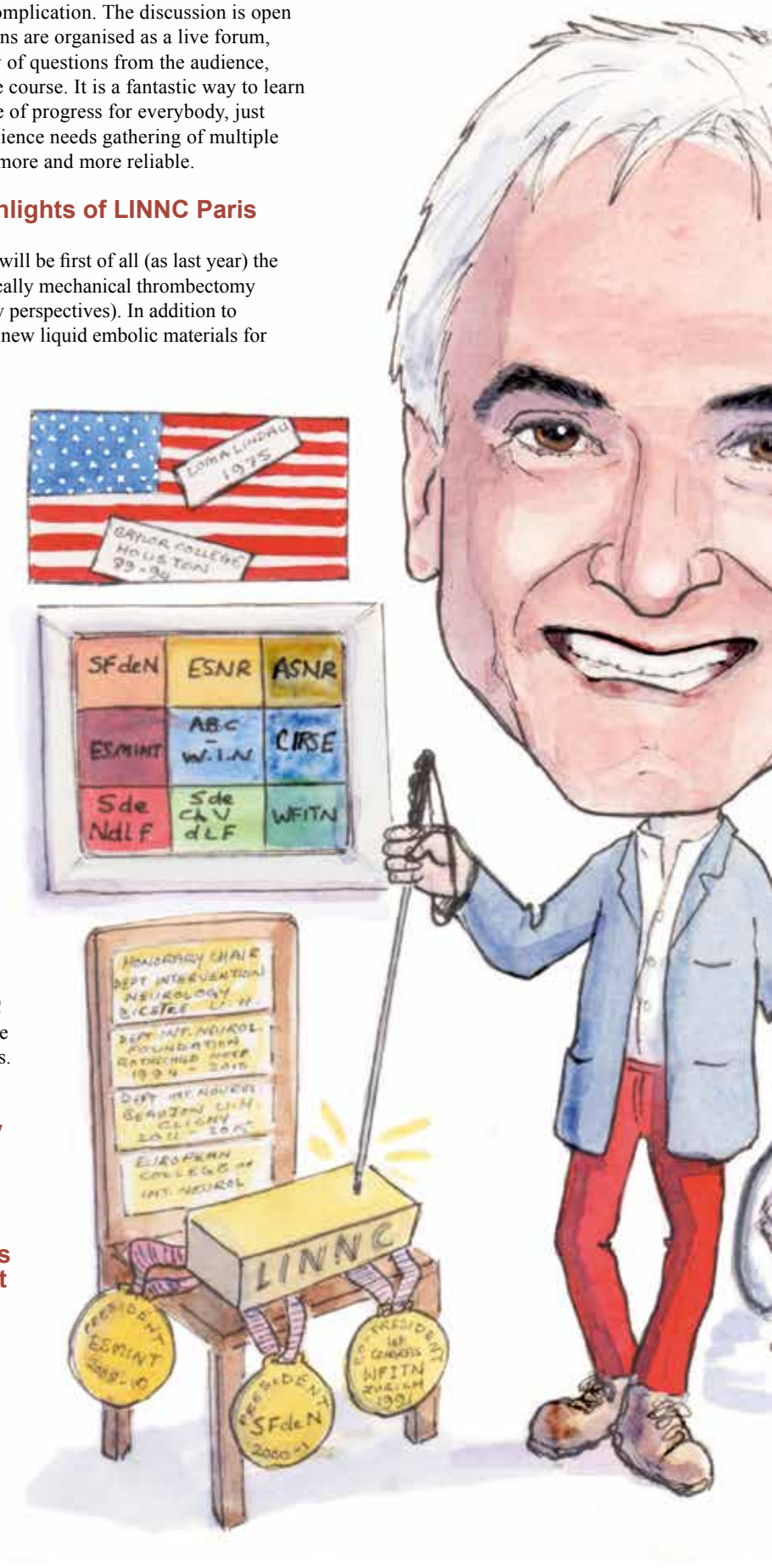
This year the highlights will be first of all (as last year) the "stroke treatment": basically mechanical thrombectomy (results, indications, new perspectives). In addition to stroke, we will focus on new liquid embolic materials for brain arteriovenous malformations treatment, as well as flow study, computerised virtual tools for aneurysm treatment mimicking real practice and "live micro-vascular anatomy" which is the future for the coming five years.

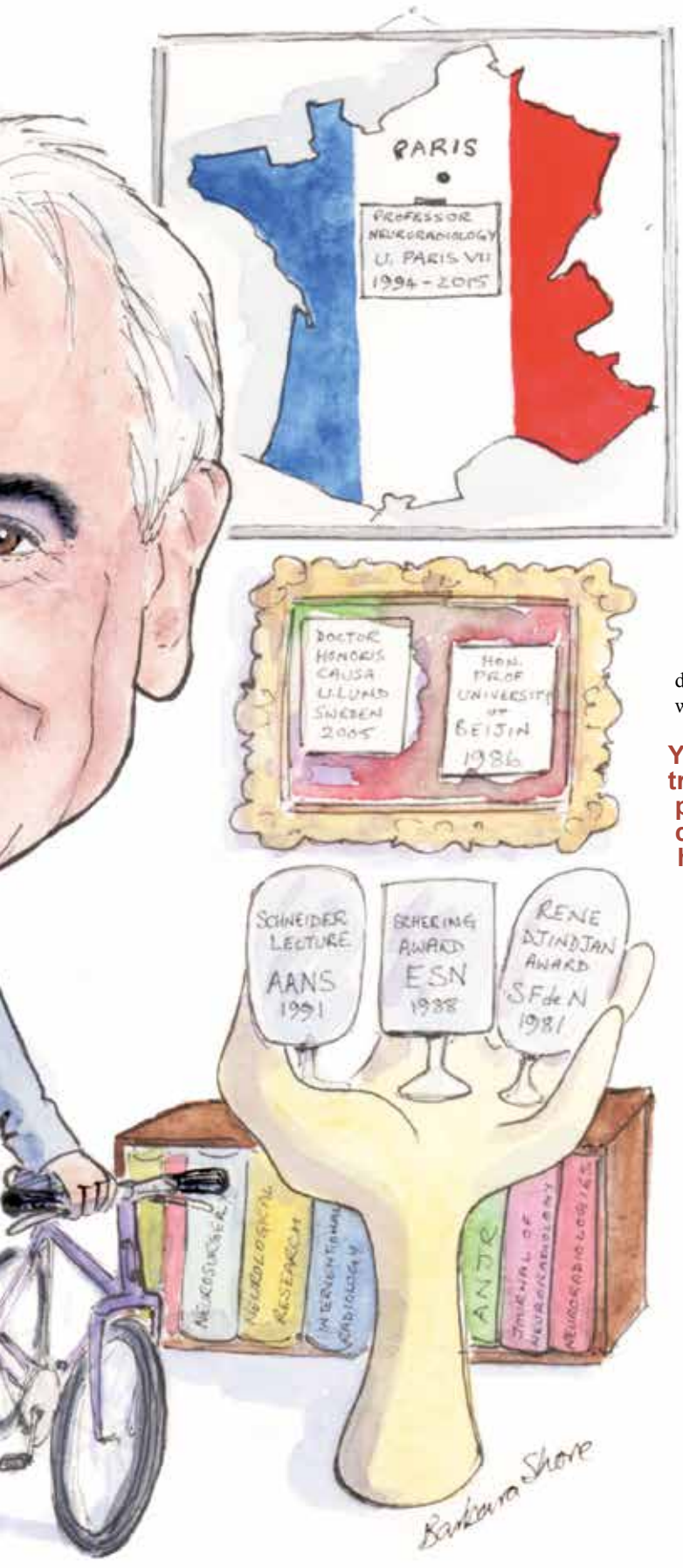
What are your current research interests?

Current research is going towards the screening of the structure of the arterial wall and the structure of the clot. "Live micro-vascular anatomy" is one of the highlights of the LINNC 2016 course, but also one of the research directions.

You have been involved in many studies into new neuro devices throughout your career. In your opinion, what has been the greatest advancement, and how do you see the field of interventional neuroradiology developing in the future?

The answer to this question is a kind of melting pot of the above reported items. I have no doubt that the





greatest advancement comes from the five stroke studies that have been published in 2015. It is absolutely unique in the medical literature to have, over a one year period, five randomised studies, which all demonstrate the incredible positive result of mechanical thrombectomy versus thrombolysis. How do I see the field of interventional neuroradiology developing in the future? This is a difficult question because there are parameters that I do not master. What I clearly master is the tremendous potential of development of interventional neuroradiology in terms of concept evolution, and technological innovations. What I do not master at all is the way this fast growing field will be organised by the doctors and the healthcare authority. Interventional neuroradiology is a tremendously attractive "cake" and it arouses a lot of keen interests. I am afraid that those interests push the discipline in a direction where the patients will not be the full beneficiary!

You have mentored and trained a number of physicians throughout your career. What advice do you hope they will always follow?

I hope they will follow and feel my enthusiasm in doing and developing interventional neuroradiology, I hope they will share my happiness teaching them and by the way I hope they will reproduce it when teaching their own pupils. I hope they will behave as scientists being true and good medical doctors and becoming true "medical leaders" instead of becoming "key opinion leaders" which is a pure industrial concept and a hidden way to say "best customers".

What three questions in interventional neuroradiology are still in need of an answer?

1. How to make the guidelines of the WFITN a reality in the medical education and medical organisation.
2. How to change the process of the healthcare authority in the analysis of the services rendered to the patients regarding the new devices in order to get the reimbursement in due time.
3. How to regulate the distribution of the interventional neuroradiology centres in big cities such as Paris, in order to serve a better medical quality for the patients, understanding that this quality is for a large part related to a large practice.

Fact File

Current position

Professor and honorary chairman of Interventional Neuroradiology, NEURI, the Brain Vascular Center, Bicetre University Hospital, Paris, France

Professional career:

- Medical Doctor, (Thesis 1975)
- Fellowship in Radiology 1974–1977
- Fellow Department of Neuroradiology, Loma Linda University USA (1975)
- Board of Radiology (1977) University René Descartes, Paris, France
- Full Professor of Radiology, Baylor College of Medicine, Houston, USA (1989–1994)
- Former chairman, Department of Interventional Neuroradiology, Foundation Rothschild Hospital, Paris, France (1994–2010)
- Former chairman, Department Of Interventional Neuroradiology, Beaujon University, Hospital Clichy, Paris, France (2011–2015)
- Honorary chairman, Department of Interventional Neuroradiology at Bicetre University Hospital Le Kremlin Bicetre, Paris (2015–)
- Professor of Neuroradiology, University Paris Vii, Faculty of Medicine "Bichat-Beaujon", Paris, France (1994–2015)

Medical Societies

- Member of the Societe Francaise de Neuroradiologie
- Member of the European Society of Neuroradiology
- Member of the American Society of Neuroradiology
- Member of European Society of Minimally Invasive Neurological Therapy (ESMINT)
- Founding Member of ABC-W.I.N. (Working Group In Interventional Neuroradiology)

Distinctions

- President of ESMINT (2008–2010)
- Doctor Honoris Causa of the University of Lund, Sweden (2005)
- President of the Societe Francaise de Neuroradiologie (2000–2001)
- Co-president of the first congress of the World Federation of Interventional and Therapeutic Neuroradiology, Zurich (1991)
- Winner of the "Schneider Lecture" of the American Association of Neurological Surgeons (Cushing Society) (1991)
- Winner of the "Schering" Award of the European Society of Neuroradiology (1988)
- Honorary Professor of the University Of Beijing (1986)

SVIN releases consensus criteria for standardising stroke infrastructure

The Society for Vascular and Interventional Neurology (SVIN) has developed Stroke Interventional Laboratory Consensus (SILC) criteria to standardise stroke interventional laboratories for safe, effective, and timely stroke care worldwide.

"Brain attack care is now exploding with new devices and options, just as heart attack care grew rapidly in the 1990s," says Tanzila Shams, and lead author of a report on the criteria published *Interventional Neurology*.

"There is an unmet need to establish a new national standard to provide optimal, timely stroke care to all patients suffering from acute ischaemic strokes."

The SILC criteria reflect the need to clearly distinguish stroke interventional lab capabilities at a time of rapid advancements in stroke treatment, including the use of stent retrieval devices, vacuum suction devices, and clot-busting drugs to save lives and reduce long-term damage to the brain.

"Our hope is that these consensus criteria will provide the roadmap for growth of high quality stroke intervention labs worldwide similar to the growth of cardiac catheterisation labs," says SVIN past-president Tudor Jovin, co-author of the report.

To advance this goal, SVIN developed a "7M" management approach for standardising stroke infrastructure and includes:

- Manpower: personnel including roles of medical and administrative directors, interventional technologists, interventional nurses, physician extenders, and all the key stakeholders in the stroke chain of survival;
- Machines: resources needed in terms of physical facilities, and angiography equipment;
- Materials: medical device inventory, medications, and angiography supplies;
- Methods: standardised protocols for stroke workflow optimisation;
- Metrics (volume): existing credentialing criteria for facilities and stroke interventionalists;
- Metrics (quality): benchmarks for quality assurance; and
- Metrics (safety): radiation and procedural safety practices;

"National efforts in the uniform organisation, accreditation, and certification of stroke intervention practices are more important than ever," says Vallabh Janardhan, and senior author of the report. "For effective stroke therapy to reach millions of people, we need to have the right infrastructure in place."

"Standardising stroke interventional labs will increase treatment rates and help achieve SVIN's Mission 2020 goal of 200,000 clot retrieval procedures worldwide by the year 2020," says Dileep Yavagal, SVIN past-president, and co-author of the report.

"We now have exciting new therapies for brain attacks, such as retrievable stents and vacuum suction devices that are similar to balloons and stents for heart attacks," says Janardhan. "But these technology innovations need to be supported by the appropriate stroke interventional lab infrastructure so that patients receive timely care."

Currently, there are 1,476 primary stroke centres in the USA that can provide clot-busting medications, and more than 170 comprehensive stroke centres whose capabilities include neurosurgical and catheter interventional treatments as well as medications.

"Although this tiered system of stroke centres has improved outcomes in the treatment of strokes, more emphasis is needed on the development and operations of the stroke intervention lab within a stroke centre," says Janardhan. For instance, standardisation is needed on emergency triage procedures for stroke patients, stroke interventional protocols and equipping, staffing and managing a stroke interventional lab.

"As we enter a new era of stroke care, national standards are needed to direct patients, families and EMS to the right centre," said Raul Nogueira, SVIN president. "We believe SVIN's report on consensus criteria can provide a framework for developing those standards, leading to a higher level of care and better patient outcomes."

Majority of Charing Cross audience disagrees that endovascular acute stroke treatment should be done only by neuroradiologists

During the inaugural Acute Stroke Challenges session at the Charing Cross Symposium (CX; 26–29 April, London, UK), 68.8% of the audience disagreed that neuroradiologists should be the only operators that perform intra-arterial treatment of acute ischaemic stroke. The issue has been a topic of contention since the results of five randomised controlled trials published in 2015 changed the face of acute ischaemic stroke treatment, providing overwhelming evidence in favour of mechanical thrombectomy for patients with emergent large vessel occlusions.

As is customary at the Charing Cross Symposium, the issue became a subject for debate ("Only neuroradiologists should undertake intra-arterial thrombectomy") between two experts—in this case, a neuroradiologist and an interventional radiologist. Andrew Clifton (consultant neuroradiologist, St George's University Hospitals NHS Foundation Trust, London, UK) spoke for the motion, facing off against Jos van den Berg (interventional radiologist, Ospedale Regionale di Lugano, sede Civico Lugano, Switzerland) who spoke against the motion.

Starting his argument, Clifton acknowledged that there is growing pressure from patient groups and the stroke community to roll out this therapy as soon as possible, but maintained that delivering it with inexperienced operators may discredit the technique. While the results of the published trials are convincing, he said, those excellent results were achieved because the procedures were performed by fellowship-trained neurointerventionalists practising in conjunction with stroke neurologists/physicians and neurointensivists at high volume centres. These results, Clifton cautioned, cannot be duplicated by physicians with no training in interventional neuroradiology.

The ideal person to perform mechanical thrombectomy, he argued, is someone with adequate knowledge, experience and training, who is part of a high volume centre and therefore performs a great number of interventional neuroradiology procedures. Further, he added, the stroke patients must be treated at a centre that can provide good post-procedure care and stroke care.

To support his argument, Clifton quoted from the National Institute of Health and Care Excellence (NICE) recommendations: "Current evidence on the safety and efficacy of mechanical clot retrieval for treating acute ischaemic stroke is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. Selection of patients for mechanical clot retrieval for treating acute ischaemic stroke should be done by clinicians experienced in the use of thrombolysis for stroke and interpretation of relevant imaging. The procedure should only be carried out by appropriately trained specialists with regular experience in intracranial endovascular intervention with appropriate facilities and neuroscience support".

Finally, Clifton referred to the recently published "Training Guidelines for Endovascular Ischaemic Stroke Intervention: An International Multi-Society Consensus Document", which according to the document "seeks to define what constitutes adequate training for physicians who can provide endovascular treatment for acute ischaemic stroke patients. These training guidelines are modelled after prior standards of training documents such as the training, competency and credentialing standards for diagnostic cerebral angiography, carotid stenting and cerebrovascular intervention and the performance and training standards for endovascular ischaemic stroke treatment, written and endorsed by multispecialty groups. In addition, the importance of organ specific training, rigorous quality improvement benchmarks, and minimum volume requirements needed to maintain high quality care has been extensively described for acute myocardial infarction, an analogous time sensitive disease".

Summarising his points, Clifton conceded that in his opinion, mechanical thrombectomy in acute stroke should be performed by a trained neuro-interventionalist who can be a neuroradiologist, neurosurgeon, neurologist, cardiologist, or interventional radiologist, but a person who has had proper training.

"Training leads to appropriate patient selection, faster and safer procedures with fewer complications. Many will have read the misguided *BMJ* article which suggested teams of cardiologists in DGH settings were best placed to take on mechanical thrombectomy, however, such teams will need to acquire the necessary diagnostic interventional and clinical decision making skills which will require a significant period of training to gather the adequate knowledge and experience," Clifton stated.

Charing Cross Symposium

Posing the other side of the debate, Jos van den Berg maintained that there is sufficient evidence from the literature that acute stroke treatment can be performed safely and successfully by a large range of specialists, including, interventional neuroradiologists, interventional radiologists, interventional neurologists, vascular surgeons, neurosurgeons.

Van den Berg quoted from a study in journal *Cardiovascular Interventional Radiology*, which concludes that "a treatment strategy with general interventional radiologists performing neurointerventional procedures in acute stroke patients with large vessel occlusions can be achieved to the benefit of patients". Further, he referred to a study in the *Journal of Vascular and Interventional Radiology* which concludes "peripheral interventional radiologists who use CT perfusion imaging for patient triage can have good neurological outcomes and provide sustainable, safe and complete around-the-clock coverage for endovascular stroke treatment".

A common factor in the existing literature, van den Berg pointed out, is that there was always a close collaboration with diagnostic neuroradiologists and stroke neurologists.

The key issue, he said, was that the mechanical thrombectomy operator should have adequate training, as is made clear in the CIRSE guidelines: "Intra-arterial stroke therapy requires imaging, clinical, cognitive, and extensive technical skills. It is our belief that there is a direct correlation between skill level and outcome for intra-arterial stroke therapy. The unskilled must undergo rigorous curriculum-based training in approved training institutions associated with an assessment of competence before performing these procedures. Reaccreditation must be earned on a frequent basis. Patients deserve appropriately trained expert endovascular specialists".

Similarly, the Society for Interventional Radiology has outlined three components of adequate training:
1. Formal training that imparts an adequate depth of cognitive knowledge of the brain and its associated pathophysiologic vascular processes, clinical syndromes, and the full array of ischaemic stroke presentations;
2. Procedural skill, including management of complications secondary to these endovascular/surgical procedures, that is achieved by repetitive supervised training in an approved clinical setting by a qualified instructor;
3. Diagnostic and therapeutic acumen, including the ability to recognise procedural/angiographic complications.

Weighing in on the debate, panellist Tommy Andersson (AZ Groeninge Kortrijk, Belgium and Karolinska University Hospital, Stockholm, Sweden) said that when it comes down to it, it does not matter the specialty, as long as the individual possesses the adequate training.

"It is not the background, but the training that counts. Why should we accept that untrained people do mechanical thrombectomy when we would not accept it for anything else?" he questioned.

At the end of the debate, the consensus was clear from all sides that mechanical thrombectomy operators do not necessarily have to be neuroradiologists, but they must have the proper knowledge, experience and training as outlined in the respective guidelines.

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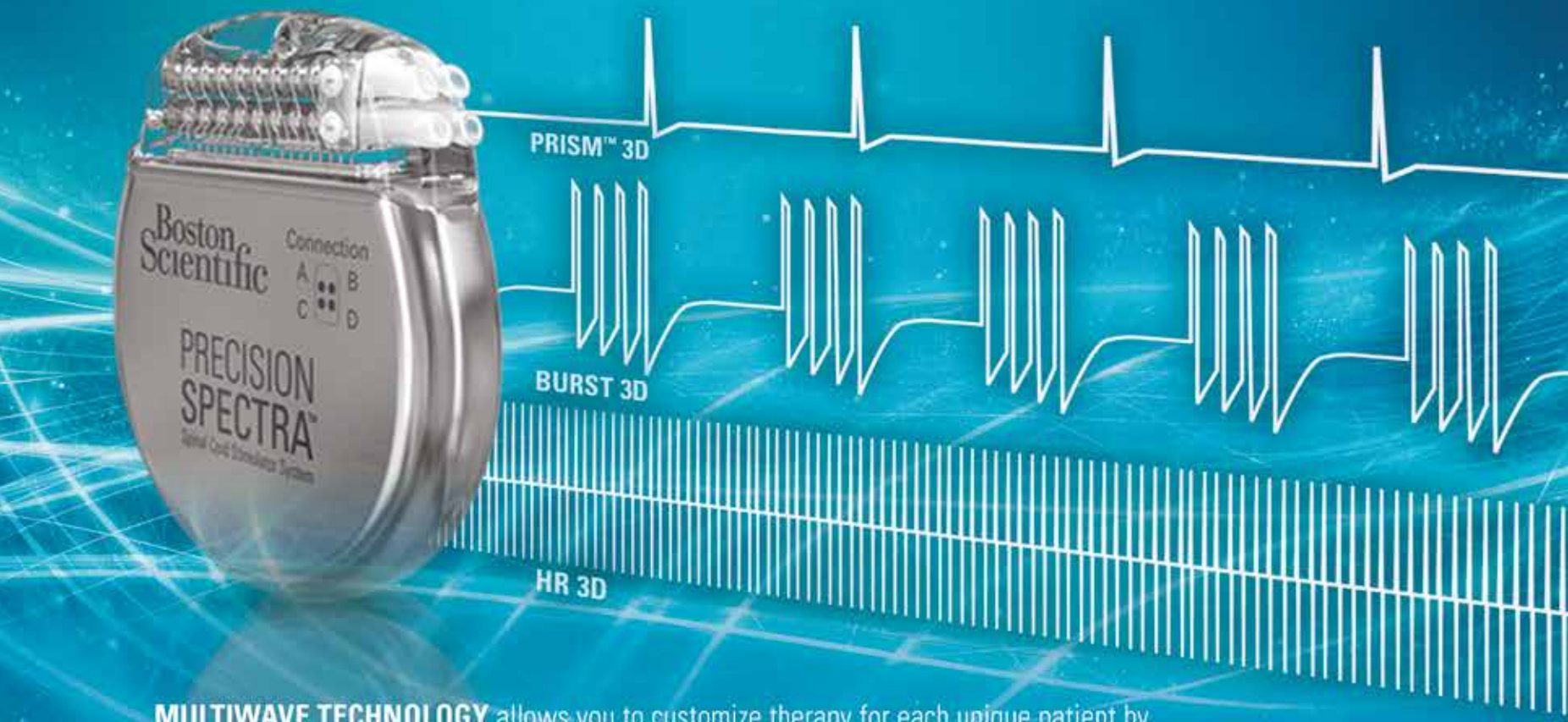


MULTIWAVE TECHNOLOGY allows you to customize therapy for each unique patient by offering a broad spectrum of waveform options. In a registry of 800 SCS patients 72% used multiple waveforms to customize pain relief.

Indications for Use: Boston Scientific's Spinal Cord Stimulator Systems are indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain and leg pain. Contraindications: Spinal Cord Stimulation Systems are not for patients who are unable to operate the system, have failed trial stimulation by failing to receive effective pain relief, are pacemaker dependent, or are pregnant. Patients implanted with Spinal Cord Stimulator Systems with ImageReady MRI Technology are "MR Conditional" only when exposed to the MR environment under the specific conditions defined in the ImageReady MRI Guidelines for Spinal Cord Stimulator Systems manuals. Warnings: Patients implanted with Spinal Cord Stimulator Systems without ImageReady MR Technology should not be exposed to Magnetic Resonance Imaging (MRI). Exposure to MRI may result in dislodgement of the stimulator or leads, heating of the stimulator, severe damage to the stimulator electronics and an uncomfortable or jolting sensation. As a Spinal Cord Stimulation patient, you should not have diathermy as either a treatment for a medical condition or as part of a surgical procedure. Strong electromagnetic fields, such as power generators or theft detection systems, can potentially turn the stimulator off, or cause uncomfortable jolting stimulation. The system should not be charged while sleeping. Spinal Cord Stimulator Systems may interfere with the operation of implanted sensing stimulators such as pacemakers or implanted cardiac defibrillators. Advise your physician that you have a Spinal Cord Stimulator before going through with other implantable device therapies so that medical decisions can be made and appropriate safety measures taken. Patients should not operate motorized vehicles or potentially dangerous machinery with therapeutic stimulation switched "on." Your doctor may be able to provide additional information on Spinal Cord Stimulator Systems. For a copy of Spinal Cord Stimulator Systems Patient Handbooks, including the indications for use, contraindications, warnings, precautions, and side effects, call 866.360.4747. Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician.

Outside the US indications for Use: For further information refer to the product labeling and instructions for use provided with each product which includes indications, contraindications, warnings and precautions. Not for distribution in France.

Neuromodulation

Burst stimulation "generally" more effective than tonic stimulation

A new study has concluded that burst spinal cord stimulation is "in general" more effective than tonic stimulation in patients already familiar with spinal cord stimulation.

Marleen C Tjepkema-Cloostermans (Department of Clinical Neurophysiology, Medisch Spectrum Twente Hospital, Enschede, The Netherlands) and others state in the journal *Neuromodulation* that it has been suggested that burst spinal cord stimulation (five pulses at 500 Hz, delivered 40 times per second) suppresses neuropathic pain at least as well as conventional tonic spinal cord stimulation, but without evoking paraesthesia. The aim of this study, therefore, was to evaluate the efficacy of paraesthesia-free high and low amplitude burst spinal cord stimulation for the treatment of neuropathic pain in patients who are already familiar with tonic spinal cord stimulation.

The study included 40 patients receiving conventional (30–120 Hz) tonic spinal cord stimulation for at least six months. The authors report that all patients received high and low amplitude burst spinal cord stimulation, for a two-week period in a double blind randomised crossover design, with a two-week period of tonic stimulation in between. The investigators evaluated the average visual analogue scale (VAS) scores for pain during the last three days of each stimulation period, as well as quality of life (QoL) scores, and patient's preferences.

They report that the "average VAS score for pain were lower during high (40, p=0.013) and low amplitude burst stimulation (42, p=0.053) compared with tonic stimulation (52). QoL scores did not differ significantly. At the individual level, 58% of the patients experienced significant additional pain reduction (>30% decrease in VAS for pain) during high and/or low amplitude burst stimulation. Eleven patients preferred tonic stimulation, 15 high amplitude burst stimulation, and fourteen low amplitude burst stimulation".

The authors conclude that "burst stimulation is in general more effective than tonic stimulation" and that "individual patients can highly benefit from burst stimulation"; but caution however, that "the therapeutic range of burst stimulation amplitudes requires individual assessment".

The study, Effect of burst stimulation evaluated in patients familiar with spinal cord stimulation, was published online ahead of print in April 2016.

Image courtesy of St Jude Medical

Paraesthesia may increase attention to pain, study finds

Continued from page 1

one-week trial of subthreshold high-density stimulation (1200Hz/200µsec/ amplitude 90% paraesthesia threshold) and enrolled them if there was at least a 50% reduction on visual analogue scale (VAS) for pain. Patients were randomised into two groups and treated with four two-week periods of conventional, subthreshold high-density, and sham stimulation in a randomised crossover design.

The study authors report that four of 15 patients responded to subthreshold high-density stimulation. "Mean VAS during conventional, subthreshold high-density, and sham stimulation was 5.32±0.63, 2.29±0.41, and 6.31±1.22, respectively. There was a significant difference in pain scores during the blinded crossover study of subthreshold high-density stimulation versus sham stimulation ($p<0.05$, Student's t-test)," they state.

Further, a post hoc analysis revealed that patients reported significantly greater attention to pain during conventional stimulation compared with subthreshold high-density stimulation ($p<0.05$, Student's t-test). Sweet *et al* explain, "All subjects reported a positive impression of change for subthreshold high-density stimulation compared with conventional stimulation, and there was a trend toward greater likelihood for response to subthreshold high-density stimulation in comparison with sham stimulation ($p=0.07$, Fisher's exact test)."

Notably, Sweet and colleagues further report that at the end of the trial, all of the patients enrolled elected to continue to receive subthreshold high-density stimulation rather than conventional stimulation.

The study therefore concluded that in fact, "Paraesthesia are not necessary for pain relief using commercially available spinal cord stimulation devices, and may actually increase attention to pain. Subthreshold high-density stimulation represents a viable alternative to conventional stimulation among patients who are confirmed to have a clinical response to it."

Higher spinal cord stimulation frequency may reduce epileptic seizure

The ability of spinal cord stimulation to affect spike-and-wave discharges has been suggested as a means to mitigate epileptic seizures in recent literature. In an attempt to map the relationship between spinal cord stimulation frequency and spike-and-wave discharges, researchers from Aalborg University (Aalborg, Denmark) measured their effects in rats.

Pentylenetetrazole was used in nine rats to induce spike-and-wave discharges. Four frequencies (30, 80, 130 and 180Hz) of spinal cord stimulation were delivered by means of a cervical-level epidural electrode. Electrocorticographic and intracortical signals were analysed to derive normalised spike-and-wave discharges and frequency—data which were used to project the severity of seizures. These results were measured against control intervals without stimulation.

The researchers observed significant increases in normalised spike-and-wave spike power and frequency when spinal cord stimulation was conducted at 30Hz, whilst no significant changes were noted at 80Hz stimulation. Conversely, decreases in both normalised spike-and-wave spike power and frequency were induced by 130 and 180Hz stimulation frequencies.

The authors noted that the observed reductions "may indicate an anticonvulsive effect of these spinal cord stimulation frequencies, whereas 30Hz spinal cord stimulation induced the opposite effects and, therefore, may be proconvulsive.

The study was published in the journal *Neuromodulation*.

Pulse frequency is "vital parameter" for successful spinal cord stimulation therapy

The importance of pulse frequency as a parameter in neurostimulation is well-known. Data published in *Neuromodulation: Technology at the Neural Interface* offer an analysis of the effects of pulse frequency alteration on stimulation thresholds, paraesthesia site coverage and patient sensation and satisfaction associated with spinal cord stimulation.

Measuring changes in perception threshold, therapeutic perception and discomfort threshold, researchers stimulated fifty patients at 26 pulse frequency rates between 40 and 1200Hz. Sustaining a pulse width of 300µsec, the researchers also observed the paraesthesia coverage of the painful area, as well as patient satisfaction and sensation.

The researchers found a statistically significant ($p<0.05$) inversely proportional relationship between pulse frequency and stimulation threshold, with the mean threshold decreasing for all three measures as the pulse frequency increased. "As pulse frequency increased from 40 to 1200Hz, the mean threshold decreases from 7.25 to 1.38 (perception threshold), 8.17 to 1.63 (therapeutic perception) and 9.2 to 1.85 (discomfort threshold)", the authors noted. Differences became significant at 750Hz for perception threshold and therapeutic perception, and at 650Hz for discomfort threshold. Paraesthesia coverage was not observed to be significantly influenced by pulse frequency. Unsurprisingly, the authors noted that pulse frequency significantly "affects patient sensation and satisfaction."

Given the inverse relationship between pulse frequencies, stimulation thresholds and therapeutic perception, the authors recognise that pulse frequency is a "vital parameter" to the achievement of therapeutic success. According to these data, the quality of paraesthesia and patients' individual sensory experience can be modified by pulse frequency.

Considering the implications of their research, the authors suggest that "higher pulse frequency may need to be set up at subthreshold amplitude to achieve positive response."

The study was carried out by David Abejón (Hospital Universitario Quirón Madrid, Spain) and colleagues.

Electrical brain stimulation could support stroke recovery

Applying an electric current to the brain can help recovery from stroke, Oxford University researchers have found. Their research is published in *Science Translational Medicine*.

A team from Oxford's Nuffield Department of Clinical Neurosciences, led by Heidi Johansen-Berg and Charlotte Stagg, studied the use of transcranial direct current stimulation (tDCS) to support rehabilitation training.

In this case, the team used a variant called ipsilesional anodal tDCS. Anodal stimulation has previously been shown to increase the learning of motor skills in healthy people. The hope was that this effect could also be demonstrated in stroke patients, using tDCS to reinforce training that helps patients relearn how to use their body.

Heidi Johansen-Berg says, "For stroke patients, longer and more intensive training leads to greater recovery. However, cost and staff availability limit what can be provided. That means that there is increasing interest in therapies that can be used to boost the effects of training."

The study included twenty-four volunteers who had had a stroke affecting their hand and arm function, split into two groups. Both groups were given nine days of motor training. One group had tDCS during the training sessions, while the other group acted as a control.

Before, and at various times up to three months after the training, the volunteers' motor skills were assessed using established clinical measures to see how much they had improved.

Johansen-Berg says, "The assessments before the training were used to establish a baseline score for motor skills. Further assessments could then be used to determine what improvement there was above that baseline.

"Three months after training, the group that had received tDCS had improved more on our clinical measures than those in the control group. This showed that the patients who had received tDCS were better able to use their hands and arms for movements such as lifting, reaching and grasping objects."

Magnetic resonance imaging scans also showed that those who had had tDCS had more activity in the relevant brain areas for motor skills than the control group.

The research team conclude that there is positive evidence for the use of tDCS to aid stroke recovery but caution that the technique must be proved to have long term benefits not only in clinical measurements but also in the ability to carry out tasks important to daily life. Larger studies, they say, will be needed before this approach could enter routine clinical care.

Transcranial direct current stimulation can boost language comprehension, Penn study finds

How the human brain processes the words we hear and constructs complex concepts is still somewhat of a mystery to the neuroscience community. Transcranial direct current stimulation (tDCS) can alter our language processing, allowing for faster comprehension of meaningful word combinations, according to new research from the department of Neurology the Perelman School of Medicine at the University of Pennsylvania, USA. The work is published in the *Journal of Neuroscience*.

"Integrating conceptual knowledge is one of the neural functions fundamental to human intelligence," says the study's first author Amy Price, a neuroscience graduate student at Penn. "For example, when we read or listen to a sentence, we need to combine, or integrate, the meaning of the words to understand the full idea of the sentence. We perform this process effortlessly on a daily basis but it is quite a complex process and little is known about the brain regions that support this ability."

Semantic memory is our stored knowledge about the world, such as the meaning of words and objects. "We sought to understand how and in what part of the brain semantic representations are integrated into more complex ideas," says senior author Roy Hamilton, an assistant professor in the departments of Neurology and Physical Medicine & Rehabilitation, and director of the Laboratory for Cognition and Neural Stimulation at Penn. Recent findings from functional MRI scans (fMRI) and magnetoencephalography (MEG) have suggested the angular gyrus, a region of the brain known to be involved in language, number processing and spatial cognition, memory retrieval and attention, as a potential hub for semantic memory integration, specifically the left angular gyrus.

Hamilton and team, which also included Jonathan Peelle, an assistant professor in the Department of Otolaryngology at the Washington University School of Medicine; Michael Bonner, a postdoctoral fellow in the Department of Psychology at Penn; and Murray Grossman, professor of Neurology and director of the Penn Frontotemporal Dementia Center, looked at the role of the left angular gyrus in semantic memory by applying high definition tDCS in healthy adults to modulate neural activity and determine its effect on semantic integration. This was done using three separate brain stimulation sessions in 18 healthy adults. Subjects donned the tDCS stimulation cap equipped with electrodes that stimulated the left angular gyrus or the right angular gyrus, as well as applied a fake form of stimulation known as sham stimulation as a control. After each stimulation session, subjects were presented with word pairs that could to be semantically integrated into coherent, or meaningful, combinations—such as "plaid jacket" and another set of word pairs that formed non-coherent, or non-meaningful combinations—such as "fast blueberry."

This was followed by a letter task that served as a control for brain stimulation effects on vision and attention, in which subjects looked at non-pronounceable strings of letters—such as vsbsl vsbql—and were asked to indicate whether or not the letter strings matched.

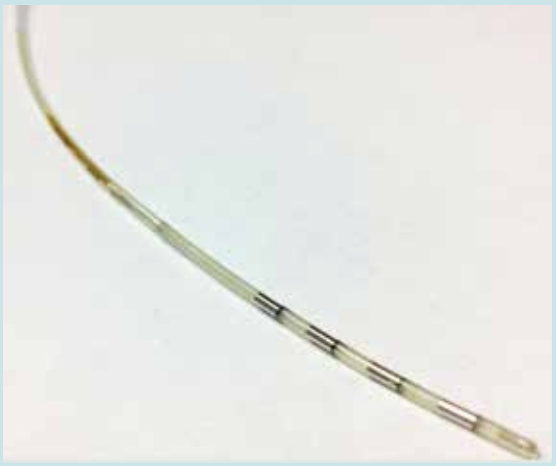
Results showed that stimulation to the left angular gyrus resulted in a faster comprehension of meaningful relative to non-meaningful word pairs when compared with both sham and right angular gyrus stimulation. This same effect was not produced in the letter-string task, showing that these findings cannot be easily attributed to non-specific effects on attention, motor control or low-level visual processing.

"Our findings extend our knowledge about the angular gyrus as a centre wherein the brain constructs higher-level meaning from individual words during semantic comprehension and plays an important role in the fluent composition of meaning in language," Hamilton says. "They are also consistent with the broader claim that the angular gyrus is a cortical semantic hub."

This work was supported by the National Institutes of Health (AG017586, AG032953, AG038490, NS044266, NS053488, AG00255), the Wyncote Foundation, and the Jameson-Hurvich fund.

Product News

FDA clears Stimwave's miniature StimQ peripheral nerve stimulator



Stimwave

Stimwave has begun to market the StimQ peripheral nerve stimulator (PNS) system for the relief of severe intractable chronic pain of peripheral origin.

The system is designed to provide relief to peripheral nerves with an implantable device that can be optionally placed through a needle-sized cannula to next to peripheral nerve locations where the pain is originating.

The StimQ PNS system, the world's first wireless, fully-programmable PNS (peripheral nerve stimulator) neuromodulation device, also received US Food and Drug Administration (FDA) 510k clearance this month.

"By providing an alternative to opioids, our Freedom spinal cord stimulation (SCS) system helps minimise back and leg pain, and now our new StimQ PNS System expands the treatment field by pinpointing stimulation directly to the affected peripheral nerves," says Stimwave chairman and chief executive officer, Laura Tyler Perryman. "The StimQ PNS System can be placed directly at the site of pain at many peripheral nerve locations without wires and bulky battery implants."

The StimQ PNS System can be implanted through a standard needle size insert or small incision. According to a company release, this wireless neuromodulation approach is expected to significantly reduce the lifetime cost of care for chronic pain patients and offer a safe, viable and effective alternative to pain medications.

Sanjay Gupta, president of the American Pain Association and principal clinician at Atlantic Pain and Wellness Institute, says "Our country is facing a horrible epidemic of drug overdose deaths, which has led the American Pain Association to launch an awareness campaign. These wireless products provide an alternative to opioids, which is much needed in the armamentarium for effective pain control."

This new indication will allow the use of wirelessly powered, micro-technology neurostimulators to be used for the treatment of various pain syndromes including, but not limited to: shoulder, upper extremity neuropathies, mid and low back pain, chest wall pain, abdominal wall pain, hernia pain, pelvic pain, as well as lower extremity neuropathies at the knee, tibial, ankle, and foot.

"The major issue with peripheral nerve stimulators in the past has always been the bulk and length of cables, connectors and pulse generators needed to stimulate a small target that is often 'out on a limb,'" says Richard North, consultant and retired professor of Neurosurgery at John Hopkins University School of Medicine, Baltimore, USA. "A miniature wireless peripheral nerve stimulator will minimise the need for surgery in patients who already are suffering from pain. It has long been needed and now is finally a reality."

The technology uses a miniature device—which is less than 5% of the size of other standard implanted options—that delivers small pulses of energy, in a fully-selectable manner, to electrodes placed at a peripheral nerve. The implant is powered by a small, flexible and comfortable wearable external fabric patch unit.

The company previously received FDA clearance for the Freedom-8A/4A spinal cord stimulation (SCS) system, which utilises the same technology specifically for back and leg pain based on placements only in the spinal column region for the device.

Neuros Medical completes interim analysis of pivotal study for post-amputation pain

Neuros Medical has announced that it has successfully completed a planned interim analysis of its pivotal study. The study is designed to evaluate the Altius System High Frequency Nerve Block technology for the management of post-amputation pain.

As part of the interim analysis, an independent data monitoring committee conducted a statistical probability analysis focused on safety as well as efficacy factors for the first 20 patients enrolled. Based on the results, the committee recommended continuation of the study.

"The interim analysis provides hope for this promising therapy and for a successful pivotal study. The Neuros High Frequency Nerve Block therapy is truly a paradigm shift in treating chronic pain, especially post-amputation pain, due to its on-demand blocking effect," says Leonardo Kapural, the study's principal investigator, from the Carolinas Pain Institute in Winston-Salem, USA.

"The successful completion of the interim analysis marks an important step in our goal of providing a proven, safe, and effective therapy for patients suffering from chronic pain," states Jon J Snyder, president and chief executive officer of Neuros Medical, "And is a testament to the commitment of our pivotal study principal investigators and clinical research coordinators, as well as the team at Neuros."

The prospective, randomised, controlled pivotal clinical trial will consist of up to 130 patients at 15 institutions to evaluate the safety and efficacy of Neuros Medical's Altius System. When completed, the results will support a PreMarket Approval Application to the FDA in order to market the device. The pivotal study builds off of Neuros' long-term pilot study, in which patients are nearing four years of device use and over 4,300 uses to date, and patients continue to report significant pain reduction. In addition, more than half of the responders discontinued their pain medication use during the pilot study.

First US commercial implants of Axium DRG system announced

St Jude Medical has announced the US launch and first post-approval implants of the St Jude Medical Axium Neurostimulator System for dorsal root ganglion (DRG) stimulation to treat patients with chronic pain that has been hard to control with traditional spinal cord stimulation (SCS). First commercial implants of the device were performed at the Center for Pain Relief in Charleston, USA by Timothy Deer, and at the Sutter Santa Rosa Surgery and Endoscopy Center in Santa Rosa, USA, by Jason Pope.

In the coming weeks, DRG implants will occur in half the states in the United States. St Jude Medical has already partnered with implanting chronic pain specialists who will conduct more than 100 procedures in 59 centres nationwide in the first month after launch. Over the course of the year, the company expects to have more than 300 physicians across the country trained to effectively deliver DRG therapy to patients in immediate need of targeted stimulation to alleviate chronic pain resulting from moderate to severe chronic intractable pain of the lower limbs in adult patients with Complex Regional Pain Syndrome (CRPS) types I and II.

"Although many chronic pain patients can find relief from a traditional spinal cord stimulation device, many patients suffering from focal chronic pain including CRPS I and II do not receive adequate pain relief from spinal cord stimulation," Deer says. "Adding dorsal root ganglion stimulation with the Axium neurostimulator system to my therapeutic arsenal is an exciting step in the treatment of chronic intractable pain of the groin, knee and foot. I am impressed with the speed in which I am able to reach and stimulate the dorsal root ganglion, something I was unable to do before the Axium neurostimulator system. For the first time, I now have a device designed specifically for the large and growing number of under-treated chronic pain patients I could not previously serve."

Stimulation of the DRG, a spinal structure densely populated with sensory nerves that transmit information to the brain via the spinal cord, allows physicians to treat the specific areas of the body where pain occurs. The St Jude Medical Axium neurostimulator system is the only therapeutic approach of its kind designed to treat moderate to severe chronic intractable pain of the lower limbs in adult patients with CRPS. Patients with CRPS are often underserved by conventional medical management and many interventional pain procedures. Many patients have tried multiple treatment options without receiving adequate pain relief.

"Stimulation of the dorsal root ganglion is the

Product News

first therapy option designed specifically for patients suffering from complex regional pain syndromes. This serious and traditionally challenging to treat chronic pain condition can occur from complications to recovery from surgeries such as knee arthroscopy, foot surgery or hernia surgery," Pope says. "Having a treatment option rooted in clinical evidence fundamentally changes our approach to treating patients. I am thrilled to be among the first in the United States to offer previously underserved patients this revolutionary technology."

According to the Institute of Medicine, chronic pain affects more than 100 million Americans, an incidence rate which outpaces heart disease, cancer and diabetes combined. Neuropathic pain represents one of the most prevalent yet under-treated forms of chronic pain in the United States, with an estimated one in every 10 adults over the age of 30 suffering from the condition.

"Since the approval of dorsal root ganglion stimulation with the Axium system in February 2016, we have focused on a strategic rollout with a disciplined training program for physicians across the country. We believe this approach ensures patient access to this highly effective new therapy to help manage their chronic pain," says Allen Burton, medical director of Neuromodulation and vice president of Medical Affairs at St Jude Medical. "The first Axium system implants in the United States reflect our ongoing commitment to working with our physician partners to deliver on our promise to transform the treatment of chronic pain."

Initial results from the ACCURATE IDE study, the largest study to date evaluating patients suffering from neuropathic chronic intractable pain associated with CRPS I and II or peripheral causalgia (PC), showed DRG stimulation provided patients with superior pain relief over traditional tonic SCS. Approval of DRG stimulation with the Axium Neurostimulator System was based in part on the results of this study in which patients were randomised to receive either DRG stimulation delivered by the Axium neurostimulator system or traditional tonic SCS therapy delivered by a competitor's system.

Monteris Medical receives IDE approval from FDA to evaluate NeuroBlate in patients with medically refractory epilepsy

Monteris Medical has announced that the US Food and Drug Administration (FDA) has approved the Investigational Device Exemption (IDE) to evaluate the NeuroBlate System in medically refractory epilepsy. With this approval, Monteris will initiate the Feasibility study on laser interstitial thermal ablation for the treatment of medically refractory epilepsy (FLARE). This multicentre, open-label prospective study is expected to enrol up to 45 patients at as many as eight clinical sites in the USA, with the goal of evaluating approximately 30 patients using laser interstitial thermal therapy (LITT) for neurosurgical applications.

Since obtaining initial FDA clearance in 2013, the NeuroBlate System has been used by surgeons to destroy and coagulate neurosurgical soft tissue lesions.

The Centers for Disease Control and Prevention estimate that there are about 2.9 million people in the USA with active epilepsy and that about one third of these patients continue to experience seizures despite treatment with one or more anti-epileptic drugs.

"Many refractory epilepsy patients in the USA are eligible for resection surgery treatment, but the vast majority of patients and their doctors choose not to undertake such an invasive procedure due to the underlying risks associated with traditional open brain surgery," says Dennis Spencer, chair of the Department of Neurosurgery at Yale University School of Medicine and principal investigator of the study. "The FLARE study will help to determine whether patients may benefit from a minimally invasive procedure, such as LITT. FLARE is designed to provide important insight into the safety and efficacy of this approach and its potential impact on neurocognition and seizures. This study is an important step forward in evaluating a new modality designed for medically refractory epilepsy."

FLARE is designed to evaluate the performance of LITT using the Monteris NeuroBlate System for the treatment of drug-refractory medial temporal lobe epilepsy in appropriate candidates. The primary endpoint of the study is to characterise the safety of laser ablation surgery with the NeuroBlate System in this patient population, including evaluation of adverse events and neuropsychological changes. Seizure outcome and quality of life will be evaluated as secondary endpoints. Patients enrolled in the study will undergo laser ablation surgery and will then be followed for 24 months. Monteris Medical expects to initiate FLARE in the second half of 2016 and estimates that it will take approximately 3.5 years to complete the study.

"Refractory epilepsy represents a significant unmet medical need. The FLARE study will help increase our understanding of the potential benefit the NeuroBlate System may have on the quality of life of patients living with this serious and debilitating disease," says Daryle Petersen, vice president, Clinical Affairs at Monteris Medical.

FDA approves new surgical leads for Senza SCS System

Nevro has announced that it has received US Food and Drug Administration (FDA) approval for its surgical leads, which are specifically designed for use with the Senza Spinal Cord Stimulation (SCS) System delivering HF10 therapy.

"Placement of surgical SCS leads is an important clinical option for many surgeons and their patients," says Michael DeMane, chairman and chief executive officer of Nevro. "With the approval of Nevro surgical leads, we can now enable more surgeons to deliver on the promise of HF10 therapy. Consistent with the US launch of HF10 therapy, the Nevro organisation is prepared to initiate a responsible and staged rollout to US surgeons and the patients they serve to ensure we deliver the clinical outcomes that are the foundation of our therapy and company."

"My fellow surgeons and I have eagerly awaited the approval of this lead for the Senza SCS system," says Ashwini D Sharan, professor and program director of Neurosurgery at Thomas Jefferson University, USA. "In my practice, I have already witnessed the significant advantages of HF10 therapy, which provides superior pain relief for chronic back and leg pain patients. Now, with the ability to use surgical leads with the Senza SCS system, I look forward to providing Nevro's therapy to a broader set of patients."

The Senza system is the only SCS system that delivers Nevro's proprietary HF10 therapy, an SCS therapy that provides electrical pulses to the spinal cord to alleviate pain. The electrical pulses are delivered by small electrodes on leads that are placed near the spinal cord and are connected to a compact, battery-powered generator implanted under the skin.

HF10 therapy is the only SCS therapy indicated to provide pain relief without paraesthesia (a stimulation-induced sensation, such as tingling or buzzing, which is the basis of traditional SCS) and is also the first SCS therapy to demonstrate superiority to traditional SCS for back and leg pain in a comparative pivotal study.

Nevro leads

Abbott to acquire St Jude Medical

Abbott is set to acquire St Jude Medical, expanding its portfolio to cover cardiovascular markets such as atrial fibrillation, structural heart and heart failure as well as neuromodulation. The combined company will thus produce devices across cardiovascular, diabetes, vision and neuromodulation markets.

Miles D White, chairman and chief executive officer, Abbott, says, "The combined business will have a powerful pipeline ready to deliver next-generation medical technologies, and offer improved efficiencies for health care systems around the world."

Michael T Rousseau, St Jude Medical president and chief executive officer, says, "Our combined scale will expand the global reach, competitiveness and impact of our medical device innovation for physicians and hospitals."

New medical devices planned for release across diverse markets by the combined company include:

- St Jude Medical's EnSite Precision next-generation cardiac mapping system, designed to allow physicians to visualise and navigate catheters in the heart during ablation procedures;
- MultiPoint pacing technology using quadripolar technology, which is designed to provide additional options for cardiac resynchronisation therapy patients who are not responsive to other pacing options;
- Proclaim Elite recharge-free spinal cord stimulation system; and
- Prodigy chronic pain system—a device used for treating chronic pain which is MRI safe, upgradeable, featuring St Jude Medical's proprietary Burst technology.
- Abbott's FreeStyle Libre, a sensor-based glucose monitoring system;
- Tecnis Symfony, a continuous range of vision intraocular lens for the treatment of people with cataracts; and
- Absorb, a bioresorbable coronary stent.

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Product News

NICE provides positive guidance on gammaCore treatment for the prevention and acute treatment of migraine and cluster headache

The UK's National Institute of Health and Care Excellence (NICE) has published guidance that electroCore's non-invasive vagus nerve stimulation treatment (gammaCore) for the prevention and acute treatment of migraine and cluster headache is safe and can now be used in the NHS.

The guidance issued by NICE showed that among the five separate clinical trials of gammaCore they reviewed, many patients experienced substantial and meaningful benefit from the therapy.

Among cluster headache patients, this benefit included significantly fewer headache attacks, complete headache relief in some patients within minutes of using the device, supplementary headache treatments were needed on fewer occasions, and there was an improved quality of life.

In the migraine trials reviewed, NICE found that there was pain relief in about half the patients and complete pain relief in around 20% of patients within two hours of using gammaCore. They also found that there was relief from sickness, sensitivity to light and noise in up to 50% of patients, recovery from disability in about 30% of patient within two hours and additional migraine treatments were only needed in about half the patients two hours after treatment.

JP Errico, chief executive officer and founder of electroCore commented, "We are very pleased that with this guidance gammaCore can now be used across the NHS which will open up this treatment to more patients suffering from these very debilitating conditions. While these five studies represent a significant number of patients, we have conducted and continue to conduct a number of additional clinical trials that will be used to update NICE to advance the guidance available to patients and providers throughout the UK."

The gammaCore device, which is CE marked, is widely used across the world and is available across the UK at specialist headache clinics and through neurologists.

The treatment is easily self-administered by patients, by placing the gammaCore on the side of the neck, over the vagus nerve (where the pulse is felt), and stimulating for two minutes. Multiple doses can be administered, with a typical treatment lasting between four and six minutes. The number of treatments per day is dependent on the type of headache and treatment regimen advised by the treating clinician.

According to electroCore, two of the benefits of gammaCore are, first, that there are no serious side effects, particularly compared to other headache treatments (a few patients experienced a local skin irritation at the site of stimulation, but that was mild and transient), and second, that patients can take existing medications without any known drug interaction side effects. This allows the patient to decrease the use of some of their existing medications or to use combination treatments with minimal risk.

Nicholas Silver, consultant neurologist at the Walton Centre for Neurology and Neurosurgery said: "We as specialists very much welcome the emergence of new therapies such as gammaCore that may potentially provide safe, effective and reliable treatment, both to prevent attacks of headache and also to treat attacks when they occur. In my view, electroCore are to be congratulated on their innovation and the development of a high quality worldwide research program to find better treatments in these conditions."

First mobile stroke unit with advanced CT imaging capabilities launched in Memphis, USA

Mobile stroke unit

The University of Tennessee College of Medicine in Memphis, USA has introduced the world's most comprehensive mobile stroke unit, designed to conduct and produce advanced quality imaging for stroke diagnosis and noninvasive computed tomography (CT) angiography with a Siemens Somatom Scope CT scanner.

According to a press release, this is the first time CT capabilities of this magnitude have been available in a mobile setting. This is intended to create the ability to diagnose and launch treatments, including tissue plasminogen activator (tPA) treatment and nicardipine within the first hour, and select patients for endovascular interventions, neurosurgery and neuro-critical care directly from the prehospital arena.

This unit is designed to prep a patient straight for the catheterisation laboratory, neuro intensive care unit or hospital stroke unit, bypassing a stop in the emergency department entirely.

"We are thrilled to have this medical first in Memphis. I want to stress that the mobile stroke unit is a product of worldwide industry leaders," said David Stern, the Robert Kaplan Executive Dean and Vice-Chancellor for Clinical Affairs for The University of Tennessee College of Medicine and The University of Tennessee Health Science Center. "The vehicle framework is from Canada…the scanner was developed by a German company, the custom assembly took place in New York, with the oversight and direction coming from University of Tennessee College of Medicine in Memphis."

The Mobile Stroke Unit, weighing in at more than 14 tons, includes features and capabilities such as:

- A hospital-quality CT scanner with advanced imaging capabilities to not only allow brain imaging, but also imaging of blood vessels in the brain.
- A dedicated gantry automatically moves the patient to obtain images, providing the same number of slices in high resolution as obtained and expected in the hospital setting.
- The unit is to be staffed with stroke fellowship-trained, doctorally-prepared nurses certified as advanced neurovascular practitioners.
- It is the largest mobile stroke unit in the world, complete with an internal power source designed to match regular electrical outlet access.
- The unit should transport trainees and researchers interested in the science of early stroke management.

"We have a tremendous burden of stroke in Shelby County, with a stroke rate per 100,000 population that is 37% higher than the national average," says Stern. "The goal of the mobile stroke unit is to minimise morbidity and mortality, to have more patients walk out of the hospital fully functional."

"If we eliminate the treatment delay getting to and through the emergency room, we can save up to 90 minutes… Our hypothesis is that we will deliver hospital-level standard of stroke care faster, equally safe, but with better outcomes due to the ability to intervene much earlier," says Alexandrov. "Our 'time to treatment' target is less than one hour."

The mobile stroke unit is funded through a public-private collaboration for which more than US$3 million has been raised, which will enable operation for up to three years. The unit will operate 12 hours a day, one week on and one week off beginning late April 2016.

"The mobile stroke unit will be based in the heart of a 10-mile, most critical needs areas of Memphis with the highest incidence of stroke, but can be deployed within the entire metro region. We estimate that 300 patients will need to be treated by the Mobile Stroke Unit to prove its effectiveness over the course of three years," says Alexandrov. "We believe this study will help establish a baseline of results that medical communities worldwide can use to develop and deploy similar programs to affect stroke outcomes."

Toshiba partners with UC Irvine for study of cerebral microbleeds in high school football players

As chronic traumatic encephalopathy stands in the national spotlight for high impact sports, the University of California, Irvine has partnered with Toshiba America Medical Systems for a first-of-its-kind study of cerebral microbleeds in high school football players as a potential precursor to chronic traumatic encephalopathy. The study will utilise Toshiba's Vantage Titan 3T MR system as the key diagnostic tool, taking advantage of its non-invasive capabilities.

The study will investigate the use of non-contrast MRI as a safe and noninvasive way to examine youth athletes and other patients for early signs of chronic traumatic encephalopathy, a degenerative disease found in those who suffer head trauma and a well-documented consequence of sub-concussive head injury. This will include evaluations of local high school student volunteers, including 100 test subjects (football players) and 50 control subjects (non-football players). Toshiba will provide application training to UCI researchers concerning the use of Toshiba's MRI equipment.

"There have not been extensive studies of chronic traumatic encephalopathy in younger populations to date, so we see this as an important opportunity to examine if there are precursors or early signs that can lead to better diagnosis and treatment," says Mark Fisher, UCI professor of Neurology and study lead researcher. "Using Toshiba's Titan 3T MR system, we may have an effective way to examine how playing football is affecting these patients, and we hope to break new ground in diagnosing and treating head trauma before it can potentially cause problems for these athletes in the future."

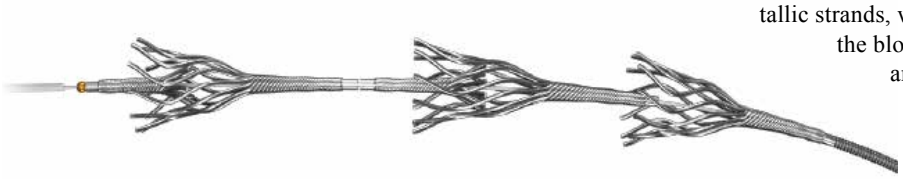
The Vantage Titan 3T MR was chosen for its ability to provide non-contrast neuro imaging. This includes elements such as a suite of advanced neuro-imaging sequences and Pianissimo noise-reduction technology, and in particular its ability to determine the prevalence of cerebral microbleeds using the Flow Sensitive Black Blood sequence.

Vantage Titan 3T

Product News

"This study presents an opportunity to determine how Toshiba's MRI equipment can be used by healthcare providers to safely and effectively diagnose serious brain trauma or chronic traumatic encephalopathy earlier than ever before, which could ultimately impact a patient's quality of life in the future," says Eugene Mensah, director, Clinical Collaborations, Toshiba. "We are proud to have the researchers using Toshiba's Vantage Titan 3T MR system to establish these potential markers of chronic traumatic encephalopathy, which speaks to Toshiba's commitment to partnering with healthcare providers to identify the right imaging solutions to complex clinical situations."

Golden Retriever safe and effective in pre-clinical trials



Golden Retriever

Amnis Therapeutics has announced successful results in its pre-clinical trials, which tested the safety and efficacy of the Golden Retriever neuro thrombectomy device. The safety trial was conducted in Israel, while the efficacy trial was conducted in a US lab.

According to a company press release, the safety trial comprised catheterisations in two animals. The effect of the product on the functioning of six blood vessels in which it was operated was tested and compared to a competing product.

In the trial, both angiographic parameters (radiographic visualisation of blood vessels during the catheterisation) and histologic parameters (microscopic blood vessel structure) were tested.

The results of the trial showed the Golden Retriever not to have any significant side effects during the catheterisation and the blood vessels to be altogether undamaged and fully functional following a 30-day follow-up period. On the other hand, the release states, the competing product demonstrated significant pathological findings in the blood vessels walls after 30 days (including trauma to artery layers and emboli) in two of the six treated vessels. Overall, this pre-clinical trial demonstrated the high safety profile of the Golden Retriever compared to the competitor in the tested animal model.

The efficacy trial comprised of 16 catheterisations, each including the extraction of blood clots from various arteries. The blood clots were similar in their qualities and size to those typically found in stroke cases. The interventionalists succeeded in extracting 15 of the 16 blood clots, with 13 clots extracted at first attempt, one at the second attempt and one at the third attempt. One catheterisation was deemed a failure.

Overall, the Golden Retriever achieved a score of 93.8% in the efficacy trial, as well as very positive feedback regarding its effectiveness and ease of use (an accumulated score of 30 of 30), the company release states.

The catheterisations were performed by the company's consultants, Professor Ronit Agid, from Toronto Western Hospital in Canada and Professor Adnan Siddiqui, director of the Neurosurgical Stroke Service, Kaleida Health in Buffalo, New York, USA. Agid noted that, "The ease of using the device, its small size, which enables the fast and relatively easy access to the clot, as well as its flexibility and effective grasp and grip of the clot, distinguish it and provide a substantial advantage over its competitors."

Aviv Lotan, chief executive officer of Amnis Therapeutics, noted: "The results of the recent trials prove that the product is safe and effective in thrombectomy in an animal model. Moreover, the results significantly support the company's belief of the Golden Retriever's superiority over its competitors, and our ability to offer the market a product which was designed for neuro thrombectomy and is better, safer, more effective and easier for use. Neuro thrombectomy is a large market, growing impressively each year, so an effective solution is sure to be very attractive to target audiences and potential strategic partners alike."

The company intends to continue the validation process towards a clinical trial estimated in Q4 2016.

The Golden Retriever is made of minuscule metallic strands, which open/deploy inside the blood clot and grip it strongly and it is expected to be the smallest in the market compared to current competition. Its size and flexibility enable quick and easy access to blood clots, usually located in middle cerebral artery in the brain. In addition, the device is capable of extracting large, long complex blood clots in a single procedure.

Amnis Therapeutics will present the positive results at the Advanced Treatment in Neuro Therapeutics Meeting on 2 May in Tel Aviv, Israel.

National Stereotactic Radiosurgery (SRS) patient registry gains momentum

Brainlab has enrolled 11, to date, of the expected 30 hospitals and healthcare systems in the national Stereotactic Radiosurgery (SRS) Patient Registry.

Launched in partnership with The American Association of Neurological Surgeons (AANS) and the American Society for Radiation Oncology (ASTRO), the patient registry will gather important patient data, aiming to define national patterns of care in radiosurgery, with an eye to improving health care outcomes, supporting informed decision-making and potentially lowering the cost of care for patients.

To date, the SRS Patient Registry is gathering de-identified data on almost 400 patients at the diverse, high-volume enrolled facilities. The registry logs the de-identified SRS treatment information of patients affected by brain metastases, benign brain tumours and arteriovenous malformations (AVMs). The SRS patient registry is set to prospectively collect data from 30 of the best hospitals in the USA over a three-year period, and under the banner of quality, generate a large clinical database, unlike any other.

"This level of detailed patient data analysis can change the way we look at methods and patterns of care from a both a population database and personalized medicine perspective," says Brian Kavanagh, Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, USA. "The more patients we upload into the registry, the closer we can approach our ultimate goal of thoroughly understanding SRS best practices so that we can help improve patient outcomes."

Brainlab transfers treatment and outcome information to the database through Quentry, a web-based image sharing service, which employs advanced encryption and access-control technologies to ensure that all sensitive medical information is secure.

"Over the next two years, all 30 hospitals in the registry are expected to upload thousands more patients," says Jason Sheehan, Harrison Distinguished Teaching Professor & Vice Chair, Department of Neurological Surgery, University of Virginia Health System (Charlottesville, USA). "In an era of evidence-based medicine, this SRS Registry offers the potential to provide concrete guidelines and process benchmarks that could change patient outcomes on a global scale."

Current US sites providing patient data via Brainlab Quentry:

- University of Colorado Hospital, Aurora
- University of Virginia Health System, Charlottesville
- University of Southern California Norris Comprehensive Cancer Center, Los Angeles
- Mayfield Clinic—University of Cincinnati, Cincinnati
- Jefferson Hospital for Neuroscience, Philadelphia
- Norton Cancer Institute, Louisville
- Carolina Neurosurgery and Spine, Charlotte
- Ronald Reagan UCLA Medical Center, Los Angeles
- Penn State Hershey Medical Center, Hershey
- Northwell Health, Great Neck (formerly North Shore LIJ)

By the end of the summer, five additional facilities in the USA are set to begin uploading data to the SRS Patient Registry:

- Huntsman Cancer Institute, University of Utah, Salt Lake City
- Yale New Haven Health System, New Haven
- University of Rochester Medical Center, Strong Memorial Hospital, Rochester

ASTRO and AANS lead the Scientific Advisory Committee charged with providing strategic oversight for the registry. Analysis of the de-identified patient data will be scientifically published, and the fully de-identified data elements will subsequently be made available in the public domain.

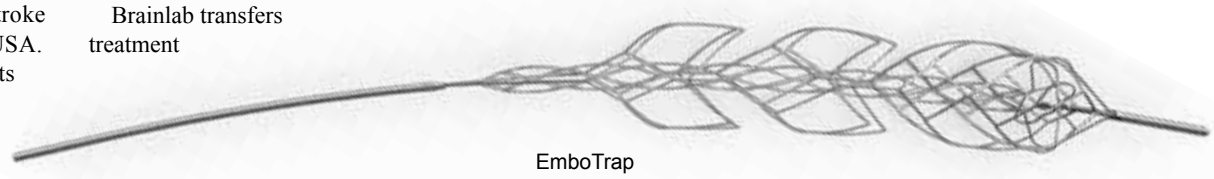
Neuravi stent retriever platform receives new US patent

The US Patent and Trademark Office (USPTO) has approved a patent providing additional coverage of Neuravi's therapeutic stent-retriever platform for the endovascular treatment of acute ischaemic stroke. Earlier this year, Neuravi also received a European patent grant for this platform.

The Neuravi intellectual property estate now extends to 63 US filings, 34 granted patents, one notice of allowance, and 28 pending applications. Outside the USA, Neuravi has multiple pending applications with the European Patent Office, in China and Japan, and internationally under the Patent Cooperation Treaty.

The design of Neuravi's EmboTrap Revascularisation device was informed by research on the wide range of different clot types that can cause ischaemic stroke. Insights from this research led to the enhancement of the proprietary design of both the EmboTrap and future Neuravi devices in development, according to a company release.

The EmboTrap Revascularisation Device is available in Europe to treat patients with acute ischaemic stroke. The EmboTrap is not currently approved in the USA, where it is available for investigational use only in the ARISE II clinical trial.



EmboTrap

Society News

American Association of Neurological Surgeons names Frederick A Boop president

Frederick A Boop has been named president of the American Association of Neurological Surgeons (AANS). His appointment was announced during the 84th AANS Annual Scientific Meeting (30 April–4 May, Chicago).

Named one of America's top doctors by US News and World Report in 2012, Boop is currently the JT Robertson professor and chairman of the department of neurosurgery at the University of Tennessee Health Science Center in Memphis, USA. Additionally, he works as the co-director of the LeBonheur Neuroscience Institute (Memphis, USA). Aside from his leadership role within the AANS, Boop's professional memberships include the American Board of Neurological Surgery (ABNS), the American Board of Pediatric Neurological Surgery (ABPNS), the International Society of Pediatric Neurosurgeons (ISPN) and NeurosurgeryPAC, where he served as president. In 2010, he received the Endowed Chair of Pediatric Neurosurgery at St Jude's Children's Research Hospital (Memphis, USA).

"The AANS has been fortunate to have a succession of vibrant, innovative leaders over the past years, and I've enjoyed the time I've served on the Executive Committee. I spent three years as secretary and this past year as president-elect learning the organisation and its major initiatives, which has helped prepare me for my new role. The AANS continues to do amazing things for its membership, and I will keep the momentum going during my tenure. From the NeurosurgeryPAC in Washington, DC (USA), working key legislation; to our own, neurosurgeon-designed-and-defined data collection group, NeuroPoint Alliance; to our efforts to provide and fund top-notch educational opportunities for the best medical candidates through the Neurosurgery Research and Education Foundation; the AANS is the voice of neurosurgery, and I'm proud to be part of its legacy," states Boop.

Boop received a Bachelor of Arts degree from the University of Arkansas in 1978 and his medical degree from the University of Arkansas for Medical Sciences in 1983 (both Fayetteville, USA). He completed his internship at The University of Texas Health Science Center (Austin, USA); his residency at The University of Texas Health Science Center; his neurology rotation at the Institute of Neurology, The National Hospital, Queen's Square, in London, UK; his paediatric neurosurgery rotation at The Hospital for Sick Children, Toronto, Canada; his epilepsy and functional neurosurgery fellowship at the University of Minnesota (Minneapolis, USA); and his paediatric neurosurgery fellowship at the University of Arkansas for Medical Sciences. He received his American Board of Neurological Surgery certification in 1993, his American Board of Pediatric Neurological Surgery certification in 1996 and his Gamma Knife certification in 2000.

AANS has also announced the appointment of Alex B Valadka as president elect of the society.

In addition to Virginia Commonwealth University's (VCU) professor and chair of the Department of Neurosurgery, Valadka is also a director of the American Board of Neurological Surgery (ABNS) and, most recently, served as the AANS Treasurer. He has also served as chair of the Washington Committee for Neurosurgery. Prior to joining VCU, he served as chairman and chief executive officer of the Seton Brain and Spine Institute in Austin, Texas; the largest and most comprehensive neuroscience program in Central Texas.

Valadka has a strong clinical and research interest in neurotrauma and critical care, as evidenced by his research funding and publications. He has been an investigator and co-investigator on 18 research grants, including serving as initiating investigator on a US$33.7-million Department of Defense research consortium on mild traumatic brain injury. He is author or co-author on more than a hundred scientific papers, as well as dozens of book chapters. He co-edited the textbook *Neurotrauma: Evidence-based Answers to Common Questions*.

Calendar of events

2016

20–23 May
WIP: World Institute of Pain Congress
New York, USA
W: www.wip2016.kenes.com

23–25 May
LINNC: Live Interventional Neuroradiology and Neurosurgery Course
Paris, France
W: www.linnc.com

27–29 May
WLNC: World Live Neurovascular Conference
Shanghai, China
W: www.wlnc.net

25–29 July
SNIS: Society of NeuroInterventional Surgery 13th Annual Meeting & Fellows Course
Boston, USA
W: www.snisonline.org

4–8 September
EANS: European Association of Neurosurgical Societies Annual Meeting
Athens, Greece
W: www.eans2016.com

8–10 September
ESMINT: European Society of Minimally Invasive Neurological Therapy Annual Meeting
Nice, France
W: www.esmint.com

3–5 October
SLICE: Stroke Live Course
Nice, France
W: www.slice-online.com

16–19 November
SVIN: Society of Vascular and Interventional Neurology Annual Meeting
Brooklyn, USA
W: www.svin.org

28–30 November
UK Stroke Forum Conference
Liverpool, UK
W: www.stroke.org.uk

2017

19–22 January
NANS: North American Neuromodulation Society Annual Meeting
Las Vegas, USA
W: www.neuromodulation.org

22–24 February
ISC: International Stroke Conference
Houston, USA
W: www.heart.org

27 May–1 June
INS: International Neuromodulation Society World Congress
Edinburgh, UK
W: www.neuromodulation.com

NeuroNews team

Editor-in-chief:
Prof Philip M Meyers

Publisher:
Roger Greenhalgh

Head of Publishing:
Marcio Brito

Editor:
Amanda Nieves
amanda@bibamedical.com

Editorial contribution:
Katherine Hignett

Design:
David Reekie

Layout:
Naomi Amorra

Advertising:
Shilpa Suthar
shilpa@bibamedical.com

Subscriptions:
Sue Couch
subscriptions@bibamedical.com

Please contact the NeuroNews team with news or advertising queries
Tel: +44 (0)20 7736 8788

Published by:
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Tel: +44 (0) 20 7736 8788
Fax: +44 (0) 20 7736 8283

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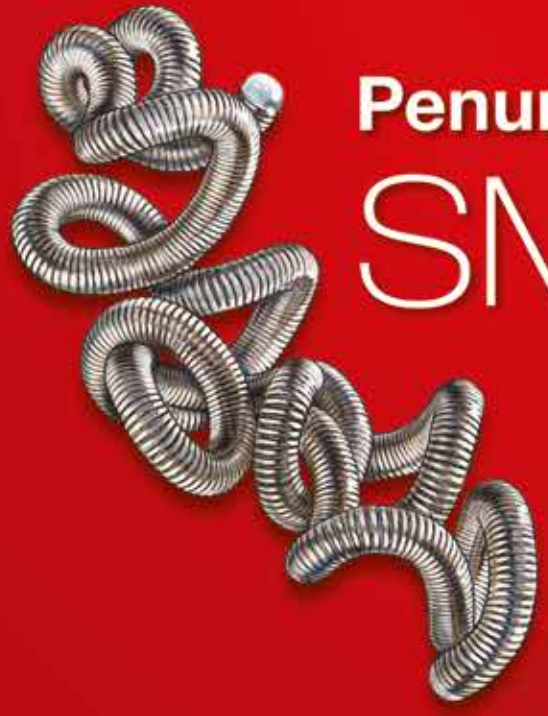

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