NeuroNews

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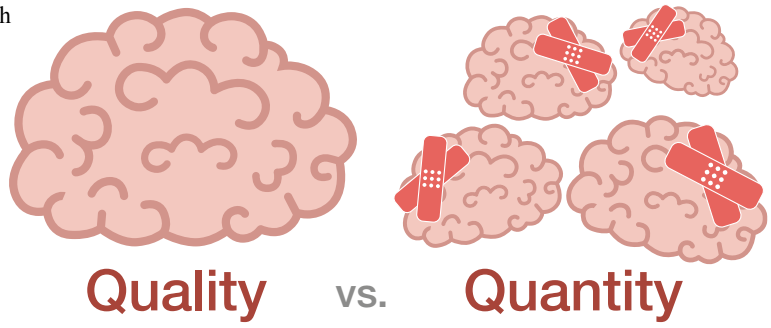
Quality over quantity: Consensus document outlines training guidelines for ischaemic stroke intervention

Twelve international societies have joined together to produce a consensus document to guide physicians seeking to treat acute ischaemic stroke patients with mechanical thrombectomy as to the required training and qualifications.

This consensus document comes after the results of five randomised controlled trials have changed the face of acute ischaemic stroke treatment, providing overwhelming evidence in favour of mechanical thrombectomy for patients with emergent large vessel occlusions. It comes partly in response to suggestions that physicians without prior experience or formal neuroendovascular training should consider attempting treatment to address some of the geographical limitations to rapid access to acute stroke centres providing mechanical thrombectomy. The multi-society consensus states however, "We believe that a neuroscience background, dedicated neurointerventional training, and stringent peer-review and quality assurance processes are critical to ensuring the best possible patient outcomes. Well-trained neurointerventionalists are a critical component of an organised and efficient team needed to deliver clinically effective mechanical thrombectomy for acute ischaemic stroke patients".



The new training guidelines were released simultaneously in eight journals including: *Interventional Neuroradiology*, *American Journal of Neuroradiology*, *Interventional Neurology Journal*, *European Journal of Minimally Invasive Neurological Therapy*, *Journal of Neuroendovascular Therapy*, *Journal of NeuroInterventional Surgery*, *Neuroradiology*, and *Neurosurgery*.

The document maintains that "it is important to recognise that modern endovascular stroke therapy focuses on direct clot removal with mechanical devices, as compared with previous paradigms where intra-arterial thrombolytic infusion was an acceptable treatment option for large vessel occlusions. The technical skills needed to safely deliver devices into the intracranial circulation are significantly more involved than simply placing a catheter for medication infusion. Catheter skills from other circulations do not replace the need for formal training in safe intracranial microcatheter navigation and device placement."

It has been established that both patient selection and procedural expertise are critical in achieving a good clinical outcome. Hence, the authors have found a clear rationale for formal training in both clinical neuroscience and interventional neuroradiology.

The purpose of this document, they write, "is 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

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LUMINA data demonstrate 70% greater low back pain relief with spinal cord stimulation system at 24 months

Final results evaluating the Precision Spectra spinal cord stimulation system (Boston Scientific) demonstrate that the device provides more than 70% greater low back pain relief than with the previous generation Precision Plus system.

The study showed a significant decrease in average pain scores sustained over a two-year period. Additionally, when the Precision Spectra was used with the CoverEdge Surgical Lead (Boston Scientific)—a 32-contact spinal cord stimulation lead—12-month data demonstrated further pain relief in patients with low back pain. The LUMINA study is one of the largest multicentre studies of spinal cord stimulation to date designed to characterise real-world outcomes of neural targeting spinal cord stimulation. The data show that the improved outcomes were achieved using the Precision Spectra proprietary Illumina 3D neural targeting algorithm that is designed to enable precise control with point-and-click targeting.

The new LUMINA data were presented at the 19th Annual Meeting of the North American Neuromodulation Society (10–13 December, Las Vegas, USA).

Commenting on the rationale for the study, Robert Frey (Pacific Pain Management, Ventura, USA) said that conventional stimulation to capture pain has been challenging. "Imagine if you could just take a mouse pointer and point somewhere along the dorsal columns and let the computer do the work and make

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Quality over quantity: Consensus document outlines training guidelines for ischaemic stroke intervention

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acute myocardial infarction, an analogous time sensitive disease".

According to the authors, this document represents an international consensus on adequate training to safely and effectively perform these procedures. The guidelines are divided into three main areas: baseline training and qualifications; maintenance of physician qualifications; and hospital requirements.

While acknowledging that specific training pathways may differ across nations, the consensus document maintains that adequate training to perform emergent endovascular stroke intervention is mandated. According to the document, new practitioners who are not currently performing acute stroke intervention with mechanical thrombectomy must undergo:

1 Residency training (in radiology, neurology or neurosurgery) which should include documented training in the diagnosis and management of acute stroke, the interpretation of cerebral arteriography and neuroimaging under the supervision of a board-certified neuroradiologist, neurologist or neurosurgeon with subsequent board eligibility or certification. The residency programme and supervising physicians should be accredited according to national standards as they pertain to the countries involved. Those physicians who did not have adequate such training during their residencies must spend an additional period (at least one year) training in clinical neurosciences and neuroimaging, focusing on the diagnosis and management of acute stroke, the interpretation of cerebral arteriography and neuroimaging prior to their fellowship in neuroendovascular interventions.

2 Dedicated training in interventional neuroradiology (also termed endovascular neurosurgery or interventional neurology) under the direction of a neurointerventionalist at a high-volume centre. It is preferred that this is a dedicated time (minimum one year), which occurs after graduating from residency. A training programme accredited by a national accrediting body is also strongly preferred but not required. Within these programmes, specific training for intra-arterial therapy for acute ischaemic stroke should be performed, including obtaining appropriate access even in challenging anatomy, microcatheter navigation in the cerebral circulation, knowledge and training of the use of stroke specific devices and complication avoidance and management.

Further, the document urges practitioners to meet their national minimum procedural and training standards, adding that fellowships that are not accredited by national credentialing bodies should still have adequate training to meet their local minimum procedure requirements.

In terms of maintenance of physician qualifications, the consensus is that it is vital that the physician have ongoing stroke-specific continuing medical education. It suggests a minimum of 16 hours of stroke specific education every two years. Additionally, it reads, "the physician should participate in an ongoing quality assurance and improvement programme. The goals of this quality assurance programme for stroke therapy would be to monitor outcomes both in the periprocedural period and at 90 days. The quality assurance programme must review all emergency interventional stroke therapy patients". In terms of threshold levels for recanalisation, complication rates, etc. the document suggests the following as a minimum: successful recanalisation (modified TICI 2b or 3) in at least 60% of cases; embolisation to new territory of less than 15%; and symptomatic intracranial haemorrhage rate less than 10%.

Finally, the consensus document outlines requirements for hospitals providing mechanical thrombectomy as treatment for acute ischaemic stroke, indicating that a centre must have 24/7 access to: "angiography suites suitably equipped to handle these patients, as well as equipment and capability to handle the complications; dedicated stroke and intensive care units, staffed by physicians with specific training in those fields; vascular neurology and neurocritical care experience; neurosurgery expertise, including vascular neurosurgery; and all relevant neuroimaging modalities, including 24/7 access to CT and MRI".

The consensus document is the cumulative work of the following societies: American Academy of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS); American Society of Neuroradiology (ASNR); Asian Australasian Federation of Interventional Therapeutic Neuroradiology (AAFITN); Australian and New Zealand Society of Neuroradiology—Conjoint Committee for Recognition of Training in Interventional Neuroradiology (CCINR) representing the RANZCR (ANZSNR), ANZAN and NSA; Canadian Interventional Neuro Group (CING); European Society of Neuroradiology (ESNR); European Society of Minimally Invasive Neurological Therapy (ESMINT); Japanese Society for Neuroendovascular Therapy (JSNET); Sociedad Ibero Latino Americana de Neuroradiologica (SILAN); Society of NeuroInterventional Surgery (SNIS); Society of Vascular and Interventional Neurology (SVIN); and World Federation of Interventional and Therapeutic Neuroradiology (WFITN).

NeuroNews spoke to Istvan Szikora (National Institute of Clinical Neurosciences, Budapest, Hungary), Raul Nogueira (Emory School of Medince, Atlanta, USA) and Donald Frei (Radiology Imaging Associates, Denver, USA), the respective presidents of ESMINT, SVIN and SNIS, to find out what these societies are doing to help implement adequate training opportunities for physicians who would like to treat acute ischaemic stroke with mechanical thrombectomy.

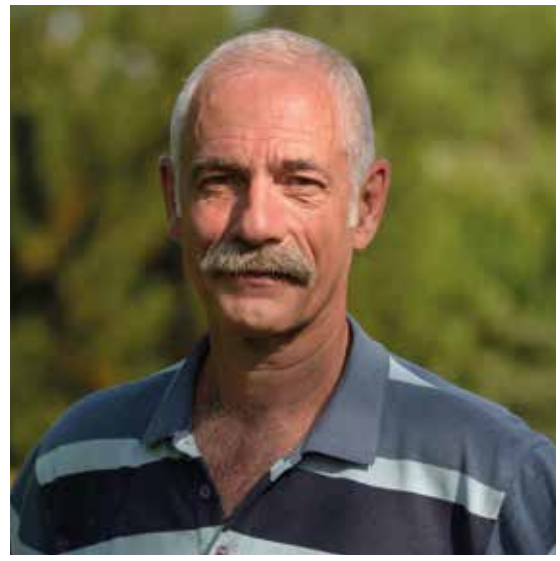
Considering the concept of quality *versus* quantity, do you think that implementing these guidelines, thus initially limiting the number of practising physicians, will be better for the treatment approach (and patients) in the long run?

Istvan Szikora: The concept is not to limit the number of physicians but to make sure the treatment is done appropriately. Any neuroendovascular procedure requires thorough knowledge of cerebrovascular anatomy and pathology as well as skills and proper understanding of the devices and technologies applied. Acute stroke thrombectomy is an emergency procedure. Such knowledge and skills are of critical importance under emergency conditions. These skills cannot be provided without training and experience by maintaining sufficient case volume. Implementing the guidelines is primarily important not to harm patients but also not to ruin the excellent results of the method.

Raul Nogueira: The idea is not to limit the number of practising physicians but to assure the proper quality of those delivering these highly complex treatments as we all know that in the wrong hands this therapy has higher chances of harming than helping patients.

Donald Frei: The excellent results found in the recently published clinical trials were achieved because the physicians performing the procedures were fellowship trained neurointerventional surgeons practicing in conjunction with other physicians (stroke neurologists and neurointesivists) in high volume centres, offering comprehensive care of the stroke patient. These results cannot be duplicated by physicians with no training in neurointerventional surgery, who in effect, would be practicing or experimenting on patients. We have over 1,000 fellowship trained neurointerventional surgeons in the USA. That is more than enough qualified, experienced physicians to take care of our patients with acute ischaemic stroke secondary to ELVO.

What steps can be taken to ensure that as many patients as possible get access to mechanical thrombectomy in the current environment where the majority of qualified physicians are at a relatively small numbers of centres?



Istvan Szikora

Raul Nogueira

Donald Frei

Istvan Szikora: Centralisation of stroke care is needed. Patients with large vessel occlusion strokes need to be transferred and treated in comprehensive stroke centres. This requires proper organisation involving stroke centres, ambulance services and fast teleradiology/teleconsulting systems. To assist this work, ESMINT, together with ESO

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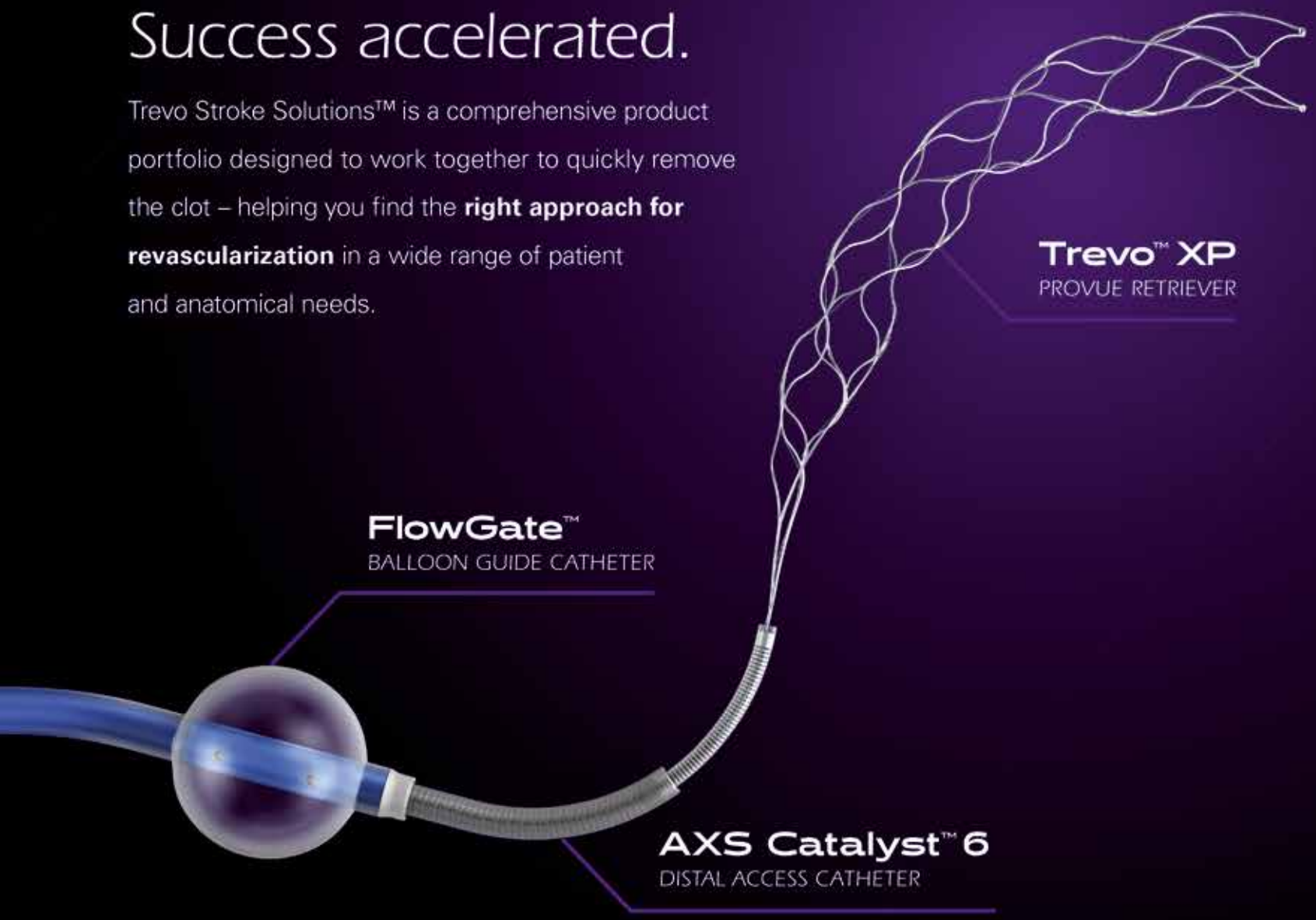

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Outcomes of UK stroke trial consistent with other published data

The results of the UK-based PISTE trial demonstrate that the outcomes are consistent with the published data from similar trials and closer to those trials that aimed for a rapid intervention approach.

PISTE (Pragmatic ischaemic stroke thrombectomy evaluation) co-principal investigator, Keith Muir (University of Glasgow, UK), presented the data for the first time at the International Stroke Conference (ISC; 17–19 February, Los Angeles, USA). The trial was funded by the UK Stroke Association, and in part by the National Institute for Health Research Health Technology Assessment programme.

Eleven centres across the UK participated in the PISTE trial which enrolled 65 patients on an intent-to-treat basis. Thirty-two patients were randomised to receive IV t-PA only and 33 were randomised to receive IV t-PA and additional intra-arterial therapy. Patients were selected using simple imaging.

"Where PISTE sits is a subtly different place within the ecosystem of acute thrombectomy trials in that we have had trials based on simple imaging, but these also had a policy of waiting to assess response to IV therapy—both MR CLEAN and REVASCAT either explicitly or implicitly waited for a response. The trials which used complex imaging (CT perfusion, multiphase collaterals or MRI) selected favourable profiles, and these were the trials which additionally had a policy of proceeding as fast as possible to intervention. PISTE occupied a small niche of proceeding as fast as possible to intervention on the basis of simple imaging of CT and CT angiography alone," Muir explained.

In the PISTE trial IV t-PA had to be started within 4.5 hours after symptom onset, and enrolment, randomisation and procedure commencement (groin puncture) had to be started within 90 minutes of the start of IV t-PA treatment (groin puncture had to be within 5.5 hours after symptom onset). The primary outcome was modified Rankin Scale score of 0–2 at 90 days.

Like many of the other thrombectomy trials, PISTE was discontinued prematurely, which resulted in a small sample size and some baseline imbalances. In the intra-arterial therapy arm there was by chance an older population, and also a higher proportion of patients with diabetes and a higher stroke severity with a median NIHSS score of 18 compared with 14 in the t-PA only group.

In both groups the median ASPECTS score was 9. It was predominantly M1 occlusions and there was a range of collateral scores across the two groups.

Investigators excluded patients who had protocol deviations, which included extensive ischaemia on baseline CT, allocation crossovers on both sides and those who were ineligible on the basis of having an incorrect occlusion site. They therefore had a per protocol population of 28 patients in the t-PA only group and 30 patients in the intra-arterial therapy group.

In terms of timing, Muir reported that in both groups there was a median of 120 minutes from symptom onset to IV t-PA start, and a median of 150 minutes from symptom onset to randomisation. In the intra-arterial group, the time from IV t-PA start to groin puncture was 82 minutes median; randomisation to groin puncture was 58 minutes median; groin puncture to device removal was 49 minutes median and the total time from symptom onset to procedure end was 256 minutes.

"It places us where we wanted to be in terms of early IV start with early reperfusion and no delay, more comparable to the SWIFT PRIME, EXTEND-IA and ESCAPE protocols compared with the other simple imaging-based trials," Muir explained.

Keith Muir

General anaesthesia was used in 31% of patients, the remainder being treated under conscious sedation or local anaesthesia only. Two-thirds of the patients in the intra-arterial therapy arm were treated using stent retrievers, and the rest using aspiration.

In terms of technical success, the PISTE trial had a mTICI 2b–3 rate of 87% (26/30 patients) at the end of the procedure. At 24 hours post-procedure however, CT angiography showed occlusion in six of 27 patients from the intra-arterial therapy arm that had the follow-up scanning. Muir explained that the investigators are looking more closely at this to see if they can speculate as to why there may have been reocclusion in this small number of cases.

In the per protocol population at 90 days post-procedure, there was significant outcome in both the primary and secondary outcome measures. Primary outcome: mRS 0–2: OR 4.92 (1.23, 19.69), p=0.021; and secondary outcome mRS 0–1: OR 14.6 (2.11, 101.5), p=0.005; and mRS distribution: OR 4.47 (1.45, 13.8), p=0.009.

"When we looked at all the primary and secondary clinical outcomes, we saw direction of effect clearly in favour of endovascular therapy across all of the efficacy outcomes. We saw no difference in safety measures, including mortality, symptomatic haemorrhage rates, PH 1/2 intracerebral haemorrhage rates, and favourable effect in terms of days spent in usual residence in favour of intra-arterial therapy," Muir said.

He added that the outcomes in PISTE are consistent with the published data from similar trials and closer to those trials that aimed for a rapid intervention approach.

"In conclusion, we did achieve the planned timelines for rapid intra-arterial therapy. We had a very high rate of modified TICI 2b–3. The primary endpoint was non-significant but there was a consistent odds ratio in the direction of the intra-arterial arm and the secondary endpoint showed significant benefit. All efficacy endpoints were consistent with intra-arterial benefit and we had primary and secondary endpoints significant in the per protocol population," Muir stated.

NeuroNews spoke to Muir about the uptake of mechanical thrombectomy in the UK since the PISTE trial.

What has been the uptake of thrombectomy procedures at your centre and in the UK generally since the PISTE trial?

The UK as a whole awaits the health economic review from NICE which will be important in determining whether or not thrombectomy becomes adopted widely. Our own centre has insufficient neurointerventional staff to offer this intervention at present, and many other stroke centres are in a similar position. A number of PISTE centres are offering treatment for limited hours, and only in one service in London is there an immediate plan to offer thrombectomy 24/7.

UK NICE concludes that use of mechanical clot retrieval is effective in treatment of ischaemic stroke

The UK National Institute for Health and Care Excellence (NICE) has published updated guidance for the UK National Health Service (NHS) on the use of mechanical clot retrieval to treat patients who have had an ischaemic stroke.

The guidance concludes that the use of mechanical clot retrieval for removing a blood clot from the blocked brain artery in people who have an acute ischaemic stroke is safe and effective.

The current mainstay of treatment for ischaemic stroke is the use of thrombolysis as soon as possible after the stroke. However, thrombolytic drugs must be given within 4.5 hours of the start of the stroke, and only benefit around one in seven people treated.

Mirella Marlow, programme director, Device and Diagnostics Systems, NICE, says, "When we originally looked at this in 2013 there was not enough evidence for us to advise that it worked well enough and was safe enough. At the time, we encouraged clinicians to collect more data to provide us with further evidence of the procedure's long-term safety and effectiveness. We are pleased that specialists took notice of our recommendation and recorded this information—this has contributed to NICE now being able to recommend this procedure with normal arrangements for clinical governance, consent and audit. We will also be exploring the potential for further NICE guidance on the devices used in the procedure."

The NICE guidance on mechanical clot retrieval for treating acute ischaemic stroke is now available on the NICE website. It does not make recommendations about whether or not the NHS should fund the procedure. NHS bodies will continue to decide locally if they want to offer the procedure to patients.

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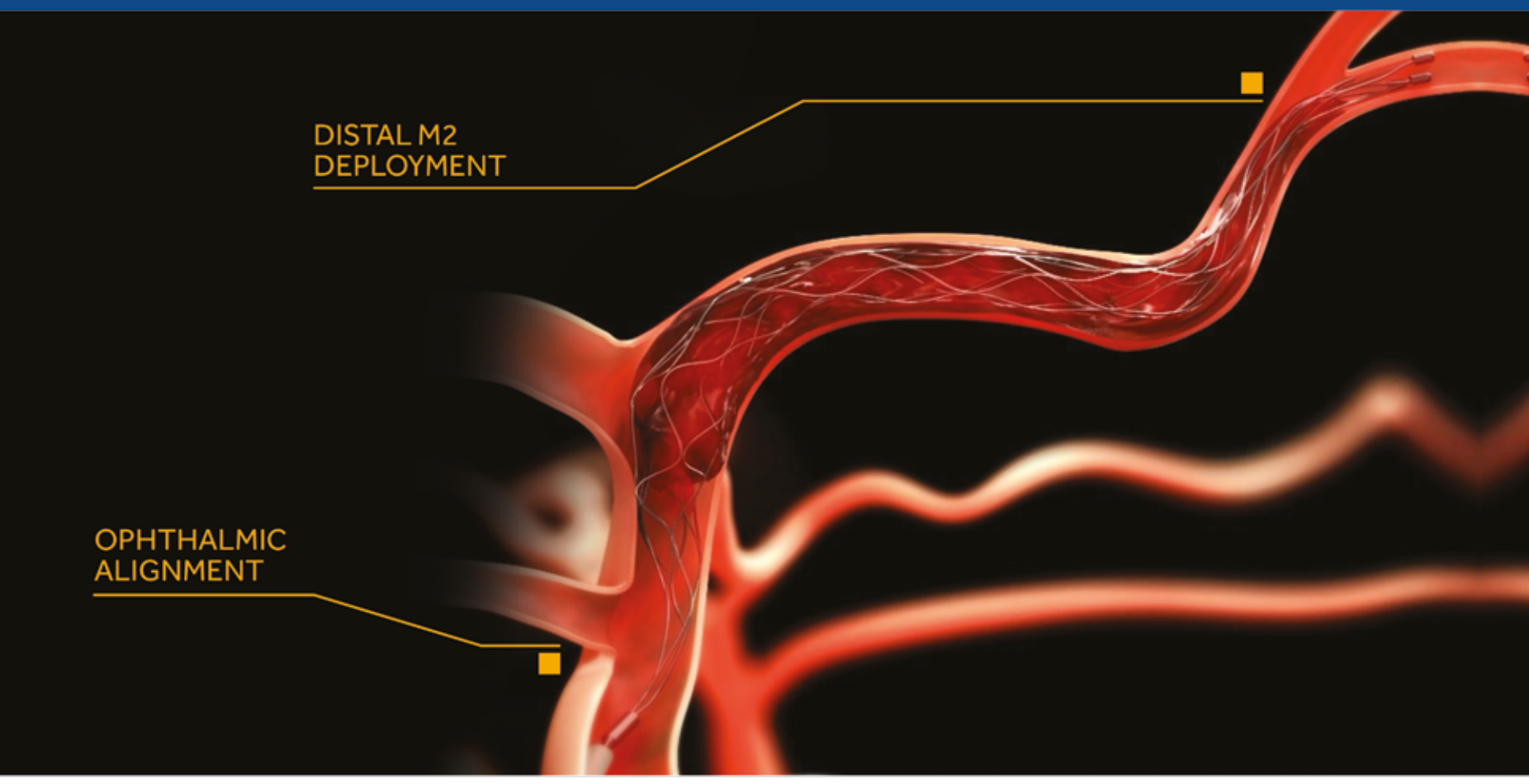

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Quality over quantity: Consensus document outlines training guidelines for ischaemic stroke intervention

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and ESNR will conduct a survey around Europe on the current situation of stroke care to help local organisations and governments. ESMINT is organising a European stroke registry collecting procedural and outcome data from as many European centres as possible.

Regarding human resources, I recommend ESMINT's "Standards of practice in interventional stroke treatment" document published in September 2015 as follows: "The increased demand for a round-the-clock interventional service creates a significant challenge for most neurointerventional sites. ESMINT recommends that sites without sufficient number of trained neurointerventionists may employ dedicated specialists without full training in neurointerventions as supervised members of the neurointerventional team. Such individuals need to be trained to collect the necessary knowledge and experience level."

Raul Nogueira: I believe the main issue is not a number of physicians or stroke centres but rather their distribution. I think we must develop the concept of a certification of need for endovascular capable stroke centres where a catchment radius would be defined based on population density and ground/air medical transport access. This would avoid redundancy and volume dilutions in certain areas and promote the need for the development of new centres in currently underserved areas.

Donald Frei: The concept of treating patients with ELVO only in a comprehensive stroke centre is not new. We have level 1 trauma centres that perform the same function for patients with severe trauma. Systems of care and EMS transport guidelines need to be developed and refined to get patients to a facility where comprehensive stroke care is available 24/7/365, including: rapid assessment by stroke neurologists, mechanical thrombectomy by stroke surgeons, and post procedure care in a neurointensive care unit by neurointensivists. These transport protocols will vary across the country depending on population density. What is needed in large cities will differ from what is needed in areas of lower population density. I practice in the western USA, where the population is dispersed across a wide area. In our region, we use air transport with helicopters and fixed wing aircraft to bring the patient from a five state area to our comprehensive stroke centre for treatment.

What plans does your society have in terms of training courses to help more physicians become qualified in treating acute stroke patients with mechanical thrombectomy?

Istvan Szikora: Again, I refer to the above document: "ESMINT offers didactic education and certified exams through its ECMINT training course (http://www.esmint.eu/training-education/teaching-course). The practical training needs to be provided by the clinical site."

Our ECMINT training course provides education in the entire neurointerventional field in four, four to five day courses in a two-year cycle. Treatment of acute ischaemic stroke represents a high priority among other neurointerventional topics.

Raul Nogueira: We do not believe training courses are an acceptable solution. There is no replacement for dedicated neuroscience-based fellowship training in a high-volume centre given the complexity of what is involved. What we have done as a society is to promote the need for proper certification of fellowship training in order to assure that high-quality treatment will be available to our patients.

Donald Frei: Neurointerventional surgery is a well-defined subspecialty with an accredited fellowship pathway to train physicians with expertise in the treatment of all neurovascular disease, which includes ELVO, brain aneurysms, arteriovenous malformations, etc. This multi-year fellowship training is available to any physician who has completed a residency in neuroradiology, neurosurgery or neurology. There is no weekend course or shortcut that would adequately prepare a physician to safely take care of these patients with the most dangerous form of stroke.

Mobile stroke unit with telemedicine proves feasible in Cleveland Clinic investigation

According to a study conducted by the Cleveland Pre-hospital Acute Stroke Treatment (PHAST) group and published in *JAMA Neurology*, mobile stroke treatment units can be made more resource efficient if the need for an on-site neurologist can be eliminated by relying solely on telemedicine for physician presence.

Ahmed Itrat and colleagues conducted a prospective observational study between July and November 2014 in the community-based setting of Cleveland, USA. The participants were the first 100 residents of Cleveland who had an acute onset of stroke-like symptoms between 8am and 8pm and were evaluated by the mobile stroke treatment unit after the implementation of the mobile stroke treatment unit programme at the Cleveland Clinic.

In the study, a vascular neurologist evaluated the first 100 patients via telemedicine, and a neuroradiologist remotely assessed images obtained by mobile computed tomography (CT). The data were then entered into the medical record and a prospective registry.

Investigators compared the evaluation and treatment of patients who used the mobile stroke treatment unit with a control group of patients who were taken to the emergency department via ambulance. The process times were measured from the time the patient entered the door of the mobile stroke treatment unit (for those in the mobile stroke treatment unit programme group) or from the time the patient entered the emergency department (for those in the control group), and any problems during evaluation were recorded.

Itrat *et al* report that 99 of 100 patients were evaluated successfully. They write, "the median duration of telemedicine evaluation was 20 minutes (interquartile range [IQR], 14–27 minutes). One connection failure was due to crew error, and the patient was transported to the nearest emergency department. There were six telemedicine disconnections, none of which lasted longer than 60 seconds or affected clinical care. Times from the door to CT completion (13 minutes [IQR, 24–47 minutes]) were significantly shorter in the mobile stroke treatment unit group compared with the control group (18 minutes [IQR, 12–26 minutes] and 58 minutes [IQR, 53–68 minutes], respectively). Times to CT interpretation did not differ significantly between the groups."

Based on those findings, the investigators conclude that a mobile stroke treatment unit using telemedicine is feasible, with a low rate of technical failure, and may provide an avenue for reducing the high cost of such systems.

NeuroNews spoke with lead author, Ken Uchino (Cerebrovascular Center, Cleveland Clinic, Cleveland, USA) about the mobile stroke treatment unit programme and whether it has the potential to be implemented in other cities.

Is the mobile stroke treatment unit programme using telemedicine still ongoing in Cleveland?

Yes, it is still ongoing. We started in July 2014 just covering the City of Cleveland from 8am to 8pm seven days a week. We have expanded to several adjacent municipalities. There are plans to recruit more on-board personnel and expand the hours of operation.

Cleveland Clinic mobile stroke treatment unit

Is this programme one that you think can be duplicated in other cities/countries?

Yes, I think it can be duplicated in other cities and countries where population density justifies the unit. Our programme is based on pioneering work in two cities in Germany and we have added the telemedicine component. Mobile stroke unit is being implemented in other cities in North America. University of Texas, Houston, started mobile stroke unit around the same time. University of Tennessee, Memphis, University of Colorado, Denver, and University of Alberta, Edmonton, are developing mobile stroke unit programmes. We hope to hear about their approaches and results in the future. We are organising a mobile stroke unit conference in May in Cleveland to hear about these.

What would be the steps towards implementation?

Aside from the obvious financial planning and building the physical unit, an important component in implementation are cooperation of mobile stroke unit operator (such as hospital, health system, university), area hospitals, and emergency medical service. Coordination of response from emergency medical service activation to communicating to personnel at receiving hospital are important. Another critical part of telemedicine in mobile stroke unit is having a good broadband internet coverage throughout the area.

To give or not to give IV t-PA: That is the question

JOSHUA
A HIRSCH

COMMENT & ANALYSIS

The year 2015 was a remarkable one for long-term proponents of endovascular therapy for strokes resultant from emergent large vessel occlusion (ELVO). The excitement of the current multiple positive trials was amplified by the failure in 2013 of Interventional Management of Stroke (IMS) III, Synthesis Expansion and MR RESCUE to demonstrate a benefit for endovascular therapy.

In January 2016, the *Journal of NeuroInterventional Surgery* featured a comment primarily authored by Ronil Chandra and Thabele Leslie-Mazwi (with a multi-disciplinary group of co-authors) that in its title posed the question, "Does the use of IV t-PA in the current era of rapid and predictable recanalisation by mechanical embolectomy represent good value?"

The authors concede upfront that the administration of IV t-PA is the current standard of care for eligible patients presenting with stroke up to 4.5 hours from symptom onset. They point out that IV t-PA may produce recanalisation and reperfusion on its own, thereby allowing the patient to avoid embolectomy. Further, IV t-PA may also help by preventing downstream microvascular thrombosis. Finally, they note that there might be patients that cannot be successfully approached with mechanical embolectomy. Conversely, they comment that t-PA is ineffective in the majority of patients with ELVO and might increase the risk of intracranial or systemic haemorrhage, and allergic reactions. In addition, in this era of time-critical reperfusion, t-PA could theoretically prolong the time interval from imaging to groin puncture.

The authors were focused on the point that embolectomy could be completed and reperfusion achieved prior to completion of the one-hour long t-PA infusion. This is not uncommon in comprehensive stroke centres where patients have rapid access to embolectomy. In that particular scenario, they query whether the money spent on t-PA a good investment. This, the authors believe, is an appropriate question in the present day healthcare milieu.

The authors point to the work of Michael Porter from Harvard Business School who defines healthcare value as outcome divided by cost. The trials make clear that marked improvement in patient outcomes and overall reduced post-acute care cost have improved the value proposition of performing mechanical embolectomy.

Thus, for patients who present directly to a comprehensive stroke centre who are able to access embolectomy rapidly, perhaps eliminating the additional cost and potential harms of t-PA will further enhance healthcare value. Groups treating stroke from around the world are actively engaged in a multitude of quality improvement initiatives with a focus on workflow optimisation for patients destined to receive intra-arterial therapy. As parallel processing opportunities continue to reduce treatment delay, they suggest that routine median door-to-groin puncture times at comprehensive stroke centres within 60 minutes are achievable. When one considers that a recent analysis of participating hospitals in the "Get With The Guidelines—Stroke" (GWTG) showed a median door-to-needle time for t-PA of 67 min (IQR 51–87 min), it is evident that patients might be mechanically reperfused while t-PA is still running.

Lee Schwamm, one of the architects of the GWTG programme, thinks that the issue may be more nuanced. "While we know that patients with LVO receive great benefit from embolectomy, most of the data have been in patients who first received t-PA and those who did not were not eligible for t-PA. Additionally, at the high performing centres that were included in the embolectomy trials, median door-to-needle times are very fast and it is, nonetheless, still quite unusual for the t-PA to still be dripping when the groin is punctured". Schwamm continues that "since the patients undergoing embolectomy after t-PA have very low haemorrhage rates, t-PA is not adding risk as a first line agent. It may be helpful in promoting successful TIC 2b3 reperfusion, and it avoids the need for endovascular treatment in ~5–15% of cases enrolled in the major trials. Lastly, 25% of all t-PA in GWTG hospitals is given in a drip and ship paradigm". His greatest concern would be limiting access to t-PA and believes the only way forward would be in developing a thoughtfully constructed trial.

Chandra, Leslie-Mazwi *et al* argue that all of this sets the stage for a randomised controlled trial comparing t-PA and embolectomy against embolectomy alone for patients with ELVO presenting directly within 4.5 hours of last known well to neuroendovacular equipped centres of excellence. We believe that this would be an exciting trial indeed.

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

Implementing endovascular treatment for acute ischaemic stroke as the standard of care: The Madrid Stroke Network experience

María Alonso de Leciñana, Exuperio Díez-Tejedor and Blanca Fuentes

Recent evidence demonstrating the effectiveness of endovascular treatment with mechanical thrombectomy for acute ischaemic stroke due to proximal large vessel occlusion in the anterior circulation, and its superiority over standard therapy including intravenous thrombolysis, has completely changed the approach to this disease in the acute setting. As mechanical thrombectomy has become the standard of care for these patients, health providers must face new challenges for its implementation. First, it is mandatory to make it available and to ensure equality of access for all eligible patients. Second, the process to correctly diagnose, select patients and provide treatment, should be fast enough to achieve success.

Considering the complexity and expense of endovascular procedures, effectively organised systems of care are necessary for an efficient implementation within the community, which is of particular relevance for public health systems that must deal with budget issues. Networking between all the different stages in the care chain for health provision is essential for this purpose. The Madrid Stroke Network is a good example of a collaborative system of care at a regional level, aimed to provide the optimal specialised treatment for any patient suffering from an acute ischaemic stroke, including prompt access to a stroke unit facility, to IV thrombolysis and to endovascular procedures if necessary.

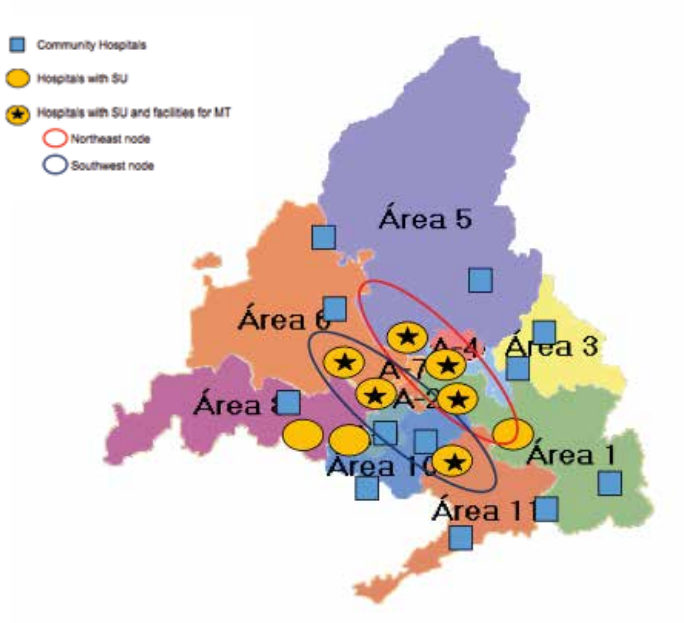
The Autonomous Community of Madrid is a region of Spain with a population of around 6.5 million inhabitants. The metropolitan area of the city of Madrid is surrounded by a rural area, the longest distance from the centre being 100 km. Madrid has a public Health System comprising of 15 community hospitals and nine hospitals with stroke units that have a neurologist available 24h/7d. Six of the hospitals with stroke units are equipped with all the resources and technical support to perform mechanical thrombectomy. Each hospital has its own catchment area, but the network has been organised to ensure rapid transfer of patients with the suspicion of an acute stroke directly to the nearest hospital with a stroke unit for prompt, specific treatment (ie. intravenous thrombolysis), thus avoiding delays due to initial attention in small community hospital not equipped with the necessary resources. Secondary transfers from the community hospital to the stroke unit are also possible if necessary, and specialised support by a neurologist via telestroke systems has been implemented between one of the stroke units and one community hospital in order to be able to initiate treatment as soon as possible with ulterior transfer to the stroke unit (drip-and-ship paradigm). Once in a stroke unit, protocols for rapid diagnosis—including neurovascular imaging—and treatment of patients are applied. For provision of endovascular treatment 24h/7d in the whole area of Madrid, six of the qualified hospitals have been organised in two collaborative nodes (Northeast and Southwest), consisting of three hospitals each, that are grouped based on proximity and catchment area, one of which is on-call in a weekly rotating shift. Thus, everyday there are two centres in Madrid capable of providing mechanical thrombectomy for suitable patients, each one covering half the geographic area and the population of the region. Every patient meeting criteria is transferred to the corresponding on-duty hospital for mechanical thrombectomy from the first-attending stroke unit after initial evaluation and treatment. Occasionally, patients can be transferred directly to the on-duty hospital for mechanical thrombectomy based on clinical data from the forewarning made by the emergency medical systems, provided agreement between the stroke unit and the hospital on-duty for mechanical thrombectomy. After treatment, once the patient is stable they are transferred back to the referral stroke unit, thus avoiding overload of the treating hospital during the period that it is on-call.

This collaborative networking permits the sharing of resources and costs thus making implementation of mechanical thrombectomy in the clinical routine affordable (shared-care model). The system has demonstrated not only efficiency, but also efficacy, since it has extended the treatment opportunity to a greater number of candidate patients with results regarding procedural times, recanalisation rates, and outcomes that are similar to those from clinical trials and that are continuously improving.

Some key factors have been essential for accomplishing this achievement. First, a close collaboration between stroke neurologists and the public health authorities to make an adequate plan based on estimation of needs for an adjusted setting up of resources. Second, involvement of all professionals that participate in acute stroke care, including emergency services, community hospitals, hospitals with stroke units, and referral hospitals for mechanical thrombectomy, in elaboration of and compliance with protocols for diagnosis, treatment and transfer of patients, that ensure a rapid and efficient workflow. Third, registration of all cases, procedures, outcomes and complications in a shared database is crucial for continuous monitoring of performance that helps to identify pitfalls and failures and to enable continuous improvement of the process.

Actually, monitoring of our performance has allowed us to identify some opportunities of improvement, mainly to reduce onset-to-treatment times and futile secondary transfers. One important issue is repetition of diagnostic tests, mainly neuroimaging, when a patient is transferred for mechanical thrombectomy. Rapid transmission of clinical data and neurovascular imaging, as well as a fluent communication between the treating physicians are crucial to avoid repetition of tests that could be unnecessary and that may add unacceptable delays in initiation of treatment. Also, we have verified that one of the major sources of delay in treatment is the time taken in secondary transfers. This is really difficult to reduce even in an organised network in which collaborating hospitals are quite close one from the other. Routing patients directly to the hospital on call for mechanical thrombectomy would result in shorter times to treatment at the cost of an overload of the emergency room with patients that might not be eligible once evaluated. Accurate selection of patients that are very likely to be suitable for mechanical thrombectomy by the emergency services would be desirable, and efforts should be made to develop reliable tools that could be used for pre-hospital patient selection.

In summary, the Madrid Stroke Network experience could serve as an example for development of collaborative networks for provision of endovascular treatment in other cities. The particular characteristics of the area should be taken into account to ensure feasibility and efficacy.



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Time is brain: The Calgary approach for endovascular thrombectomy

The Calgary Stroke Program has been focused on increasing efficiency of acute stroke treatment for over a decade. They implemented their learnings and strategies across Canada and other centres across the world during the running of the ESCAPE trial—the trial has by far the fastest workflow among all the recently completed trials; start of imaging to groin puncture of 51 minutes; start of imaging to first reperfusion of 84 minutes (median times). The team described their workflow as they followed one patient through the system. This was recently published in the *American Journal of Neuroradiology*.

Now, Mayank Goyal (University of Calgary, Canada), who has been at the forefront of pushing for speed and efficiency in acute stroke, tells *NeuroNews* about what factors contributed to the success of the stroke workflow in the Calgary Stroke Program.

I attribute the success of the stroke workflow at the Calgary Stroke Program primarily to the following factors:

1 Pre-notification: for over a decade, the Calgary Stroke Program set up a system of pre-notification by the paramedics. The message comes through the paging system and gives key simple information: age, last seen normal time, key deficit and expected time of arrival to the emergency room (ER). As a consequence the stroke team is able to meet the patient at the entrance of the ER.

2 Simple, decision-oriented imaging: Multiphase computed tomography angiography (CTA) based collateral imaging came out of the Calgary Stroke Program and was implemented in the ESCAPE trial. I firmly believe that at two million neurons per minute, all that I am willing to spend on all the imaging, post processing and decision-making is five minutes or 10 million neurons. As such, we do not do any magnetic resonance (MR) imaging or even CT perfusion imaging. In fact, we have found that decision-making based on head CT (ASPECTS score, which, by the way, also came out of the Calgary Stroke Program) and multiphase CTA is better than using CT perfusion for decision-making and of course takes significantly less time.

3 Parallel processing: The Calgary Stroke Program believes in and practises a team approach where different parts of the team have their clear tasks and responsibilities. Each member takes care of what their role is without waiting for another part of the team to finish their part. Typically, all members of the team converge at the CT scanner, imaging is viewed in real time, a decision is made and then the team splits up based on what each person needs to do.

4 Pre-organisation of the angio suite: I call this BRISK (Brisk Recanalisation Ischaemic Stroke Kit). I set this up in Calgary many years ago and it was implemented across most ESCAPE sites. There is already a stroke tray ready to go with everything available so that even if a stroke patient came at 2 o'clock in the morning, there is hardly any time spent on opening packets and getting organised. I feel that this saves over 30 minutes for cases done after working hours.

Mayank Goyal

Overall, it is critical, especially in light of the recent evidence for the efficacy of endovascular thrombectomy and "time is brain" that we focus on opening the vessel fast and safe.

Stenting as effective as carotid endarterectomy for prevention of strokes in asymptomatic patients

A clinical trial has found no significant differences between the use of carotid-artery stenting and carotid endarterectomy over a period of five years for the prevention of strokes in asymptomatic patients with serious narrowing of the carotid artery.

The results of the study have been published online in the *New England Journal of Medicine* (*NEJM*) to coincide with their presentation at the International Stroke Conference (ISC; 17–19 February, Los Angeles, USA).

"Our study showed that carotid artery stenting is just as safe and just as effective in treating asymptomatic patients as carotid endarterectomy, which has been the standard treatment approach for patients who are not at high risk for open surgery," says Kenneth Rosenfield, head of Vascular Medicine and Intervention at the Massachusetts General Hospital Division of Cardiology, Boston, USA, lead and corresponding author of the *NEJM* report. "While a previous, major trial also found equivalent results for the two procedures, it was not able to determine whether that result applied to patients with asymptomatic carotid stenosis."

A 2010 study (the Carotid Revascularization Endarterectomy versus Stenting Trial; CREST) found that both procedures had similar outcomes, although in the period immediately after the procedures there was a slightly higher risk of minor stroke with carotid-artery stenting and of heart attack with carotid endarterectomy. But, CREST examined patients both with and without prior symptoms of stroke and did not enrol enough asymptomatic participants to determine whether the results applied independently to those patients. The current study, called Asymptomatic Carotid Trial (ACT) I, was designed to investigate that specific question.

Kenneth Rosenfield

Conducted from 2005 to 2013 at 97 US centres, ACT I enrolled 1,453 participants aged 79 or less, all of whom had no stroke-related symptoms, despite having narrowing of from 70–99% of one carotid artery. Their diagnoses were confirmed by either ultrasound or angiogram, often after their physician had detected a bruit while listening to the carotid area with a stethoscope. Participants were randomly assigned to either carotid endarterectomy or carotid artery stenting, and received a complete neurological assessment before and after the procedure; one, six and 12 months later; and then annually for up to five years.

A total of 1,089 patients received carotid stents, while 364 had carotid endarterectomy. In terms of the incidence of stroke, death or heart attack in the 30 days after the procedure, overall rates were very low—around 3.5% for each—and with no significant difference between the two groups. The long-term results also were very similar, with 97.3% of those in the stenting group and 97.8% in the endarterectomy group remaining free of stroke involving the treated side.

The authors note that treatment of carotid stenosis with medications only—platelet-blocking agents, statins and drugs to reduce blood pressure—has become more accepted in recent years. However, whether medical treatment alone outweighs the benefit of eliminating the blockage in asymptomatic patients has yet to be investigated. "We really do not know if patients with severe asymptomatic carotid-artery stenosis can be safely treated with medications only," says study co-author Michael R Jaff, medical director of the Massachusetts General Hospital Fireman Vascular Center, Boston, USA. "That is the outstanding remaining critical question."

A follow-up to the CREST trial—called CREST 2—has been designed to investigate the role of stenting or endarterectomy versus intensive medical treatment alone in asymptomatic patients with severe carotid stenosis. Also important to investigate, adds Jaff, will be methods of determining which procedure is best for a specific individual patient.

Computed tomography perfusion may determine best candidates for clot retrieval

The identification of patients likely to benefit from stroke clot retrieval may be made more accurate with the use of brain imaging, rather than relying on the amount of time since symptoms began, according to research presented at the American Stroke Association's (ASA) International Stroke Conference (ISC; 17–19 February, Los Angeles, USA).

Evaluating data on 102 patients who have had endovascular therapy up to 18 hours after the start of their stroke, and had a computed tomography (CT) perfusion imaging scan before treatment, showed where a large area of brain tissue may be safely salvaged.

Good recovery—defined as little to no disability—was achieved in 71.4% of the patients treated within six hours and 61.7% of patients treated beyond six hours of stroke onset. There was no significant association between time to treatment and good outcomes when CT perfusion imaging showed salvageable brain tissue.

"Using this image-based selection, we would be able to look at any patient who comes through the door to identify the ones likely to benefit from these therapies, regardless of what the clock shows," said Jenny Tsai, study author and neuroimaging and vascular neurology fellow at the Stanford Stroke Center, Palo Alto, USA. The facility is part of the University of Stanford's School of Medicine.

Image courtesy of ASA

"This is important because we want to offer the best treatments to every patient who suffers stroke and who may benefit from them. One of the best ways to do this is to have an objective imaging tool to evaluate every single patient," Tsai says.

Researchers analysed patient data from the clinical study CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project (CRISP). The two-year study focused on adults 18 and older and finished in 2014. It was funded by the NIH and conducted at six US medical sites with the goal of developing a practical tool to identify acute stroke patients likely to benefit from endovascular therapy.

"We now have a very effective treatment for the large and disabling acute strokes," Tsai said. "And we know that there are patients likely to benefit from interventional treatments who are not being captured using basic imaging and time criteria alone. We need to do better."

> ***"We want to offer the best treatments to every patient who suffers stroke and who may benefit from them. One of the best ways to do this is to have an objective imaging tool to evaluate every single patient."***

Cost-utility analysis of mechanical thrombectomy in the United Kingdom

KYRIAKOS LOBOTESIS

COMMENT & ANALYSIS

To date, five randomised controlled trials have demonstrated the clinical benefit of endovascular therapy compared with intravenous (IV) tissue-type plasminogen activator (t-PA) in acute stroke. However, the economic evidence evaluating stent retrievers is limited. Kyriakos Lobotesis and others therefore set out to compare the cost-effectiveness of IV t-PA alone *versus* mechanical thrombectomy and IV t-PA in the context of the UK National Health Service.

The study, recently published in the journal *Stroke*, demonstrated that although the upfront costs for thrombectomy are high, the potential gains in quality-adjusted life years make the procedure cost-effective. This is a very central factor to consider when deciding whether to commission this clearly beneficial for acute stroke patients interventional service.

The decisions to implement new medical technologies and healthcare services are increasingly being made while taking into account economic considerations, such as cost, affordability and budget impact for which a health economic study is usually needed. Recently, five randomised controlled trials demonstrated the clinical superiority of adjunctive mechanical thrombectomy versus IV t-PA alone in acute ischaemic stroke. Previous economic evaluations of mechanical thrombectomy have been undertaken but have been based in the USA and on a range of outdated mechanical devices, all now superseded by stent retrievers. This new generation of thrombectomy devices has demonstrated a higher recanalisation rate and a better clinical outcome. More importantly, this is in patients with a stroke secondary to a large vessel occlusion who are known to have very poor outcomes.

Ischaemic stroke is the third highest cause of death and the leading cause of disability in the United Kingdom. Its overall incidence is postulated to increase and the economic burden of stroke is estimated to be £9 billion per year in the UK (it is US$38 billion in the USA). Stroke itself is an expensive disease in terms of its personal, healthcare and societal impact. The clinical value and effectiveness of thrombectomy is guided by the benefits, risks and costs associated. It has been suggested that although the upfront costs of thrombectomy are high, the potential reduction in morbidity can result in savings downstream, resulting in a significant reduction in the overall economic burden from stroke. The purpose of this study was to investigate the cost-effectiveness of mechanical thrombectomy in hyper acute stroke in the UK, based on a meta-analysis of the data recently published five randomised control trials.

A cost-utility analysis was carried out with outcomes measured in terms of quality adjusted life years (QALYs). The number of deaths averted was also looked into as an additional outcome measure. A short term model was used to analyse the data on costs and clinical outcomes within three months with patients falling into one of three possible health states (see Figure A). A long-run Markov model was then used to estimate the expected costs and outcomes over a life-time horizon of 20 years (see Figure B). Two treatment options were considered, IV t-PA alone versus mechanical thrombectomy and IV t-PA. For both strategies, outcomes were based on modified Rankin Scale (mRS) scores measured at 90 days after stroke, which were assumed to be affected by recanalisation rates and symptomatic haemorrhage rates. The analysis was undertaken from the perspective of the UK National Health Service and Personal Social Services. Costs were calculated in 2013–2014 UK£ and are presented in US$.

The cost of the mechanical thrombectomy was estimated to be US$13,803 (£8,365), including the cost of the stent, the materials, and the procedure. The cost of IV t-PA was estimated to be US$2,953 (£1,214). The costs for the acute management of patients in the first three months after stroke and the following ongoing annual costs were taken from published reports. Acute and ongoing costs differed according to the level of disability, measured by mRS score. Acute costs include the length of stay in the Hyper Acute Stroke Unit, in the Acute High Dependence Unit, and in the rehabilitation ward, as well as the supported discharge cost and community care costs. The cost of a recurrent stroke was also assessed. Because it is not possible to predict the type and severity of a recurrent stroke, the cost to treat a recurrent stroke was calculated as the mean expected cost to treat an average stroke that may not need thrombolysis or thrombectomy.

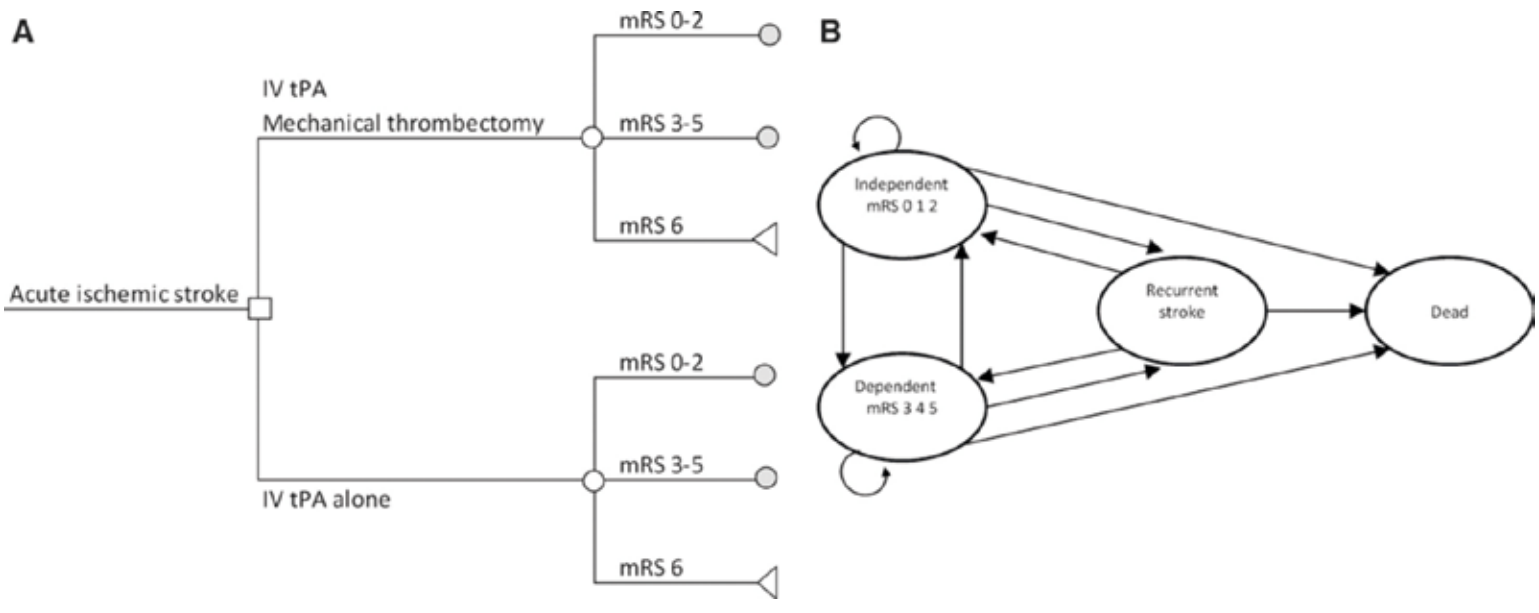
The study demonstrated that mechanical thrombectomy following IV t-PA was associated with an incremental cost of US$12,262 (£7,431) and a gain of 1.05 QALYs per patient over 20 years. The additional costs were due to the cost of the procedure and device. QALYs were higher for mechanical thrombectomy because in the clinical trials used in the analysis, patients were more likely to have a better outcome and be independent (mRS 0,1,2). Assuming a cohort of 1,000 patients, the number of deaths over 20 years was 787 in patients treated with IV t-PA alone and 716 in patients treated with thrombectomy. Therefore, mechanical thrombectomy averted 71 deaths over 20 years. The incremental cost-effectiveness ratio of mechanical thrombectomy compared with IV t-PA was US$11,651(£7,061) per QALY gained. The results of a sensitivity analysis also showed that thrombectomy was cost-effective up to the cost to US$33,000 (£20,000).

Although the cost of thrombectomy is higher than that of IV t-PA initially, it leads to savings downstream in the stroke care pathway because of better outcomes. The difference between mRS scores can have a huge impact on the long-term healthcare costs, including societal costs. Obviously the cost effectiveness of thrombectomy is greatest in patients that improve clinically the most at three months. Between January and March 2014, 19,638 new cases of stroke were registered in the United Kingdom; 87.3% were ischaemic strokes and 11.5% had thrombolysis. Fifteen per cent of ischaemic strokes registered an acute large vessel stroke with an NIHSS score >16; therefore, thrombectomy could potentially be performed in 20% of patients who had thrombolysis. This means that in one year, around 1,800 patients could have had a thrombectomy, for an incremental cost (budgetary impact) of US$22 million (£13.4 million).

Summary

The principle finding of the study was that mechanical thrombectomy following IV t-PA, for acute large-vessel ischaemic stroke, saves one life for every 14 thrombectomies performed. It also significantly reduces disability and hence is cost-effective when compared with IV t-PA alone. We hope that this study will supplement the recently published randomised controlled trials but more importantly, will assist healthcare commissioners regarding purchasing and investing in this new but essential aspect of acute stroke services.

Kyriakos Lobotesis is at Imperial College London, UK



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Penumbra Coil 400 safe and effective in small aneurysms

The results of a multicentre study have shown that catherisation with the larger profile coil delivery microcatheter and aneurysm occlusion with large volume coils is feasible and safe for aneurysms <10mm. Zsolt Kulcsàr and others report in the *Journal of NeuroInterventional Surgery* that with the Penumbra Coil 400, they achieved a high packing density of 45%, with a low average number of coils. Further, they write that aneurysm occlusion grades improved during the seven-month follow-up period, achieving 91% sufficient occlusion.

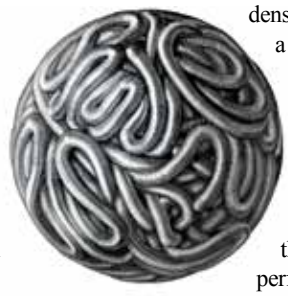
A retrospective analysis of prospective data collected at three different centres was performed on consecutive aneurysms <10mm treated with the Penumbra Coil 400 system. A total of 92 aneurysms were included in the study. Feasibility, procedure safety, angiographic and clinical results, and follow-up results were evaluated.

The Penumbra Coil 400 system consists of 0.02 inch primary diameter coils constructed of 92% platinum/8% tungsten round wire filament with a diameter of 0.00125 inch or 0.0015 inch. The nominal outer primary diameter is 0.02 inch and the inner core comprises a second open-pitch coil made with nitinol and an additional thin nitinol wire which is heat-shaped to confer either a complex or helical coil shape. The coil is delivered through a microcatheter with a minimum inner lumen of 0.025 inch. Since January 2013 the original coil delivery microcatheter was replaced by a redesigned version (PX Slim). The PX Slim has a reduced and smoother profile of 2.6F outer diameter at the tip and 2.95F outer diameter (in comparison with the original PX 400 with a distal outer diameter of 2.8F and a proximal outer diameter of 3.4F).

The study authors report the results of 92 patients (mean age 60±12 years). Twenty-three aneurysms (25%) were acutely ruptured. The mean value of maximal aneurysm diameter was 5.8±2mm and the mean neck size was 3.2±1.3mm. Forty-one aneurysms (45%) were ≤5mm and an adjunctive device (balloon, stent or flow diverter) was used in 21% of cases.

"Sufficient occlusion rates (grades 1 and 2) were achieved in 66% of cases (grade 1: 38%, grade 2: 28%). The average number of coils used per aneurysm was 2.5±1.3. The mean length of coils introduced per aneurysm was 18±16cm and the mean packing density of the aneurysms was 45.6±14.4%. Treatment-related thromboembolic events were observed in three cases (3.3%), all in patients with acute subarachnoid haemorrhage (only one of these patients suffered a procedure-related infarct). No procedural aneurysmal rupture was observed," Kulcsàr *et al* write.

In terms of follow-up, 79 patients (86%) have had follow-up imaging with a mean time of 7.4±4.6 months. The authors report that aneurysm occlusion grades at the last imaging follow-up have shown a major improvement (sufficient occlusions of 91% vs. 66%). The follow-up results of 44 aneurysms (65%) did not change over time, and 33 aneurysms (42%) have shown progressive occlusion. Only two aneurysms (3%) demonstrated a worsening compared with the initial result. Out of 27 aneurysms with a primary grade 3 occlusion, 67% showed progressive occlusion and 30% remained unchanged. Only one aneurysm from this group worsened in occlusion grade. Of the aneurysms with complete primary occlusion, none demonstrated recanalisation during the follow-up, and none of the aneurysms were retreated during the follow-up period.



Penumbra Coil 400

As relates to the outcome of aneurysms treated with stent or flow diverter assistance (12/92 aneurysms, 13%), and those treated without parent artery reconstruction (80 aneurysms), the authors write that there was no difference in the immediate occlusion grades (66.7% vs. 66.2% grade 1 and grade 2 occlusions). "At the last follow-up, however, there was a tendency for higher occlusion grades of aneurysms with adjunctive stent or flow diverter implants (83.3% vs. 75.5% grade 1 and 2 occlusions)," they say.

Commenting on the Penumbra Coil 400 system, Kulcsàr *et al* state that the device "has increased softness and flexibility due to the construction of the 0.02 inch primary coil diameter from a thin primary core wire. These features translate into increased compaction and quicker filling of the aneurysm volume. Compared with conventional coil delivery microcatheters which have a smaller inner diameter, the PX Slim microcatheter has improved stability inside the aneurysm during coil delivery. These coil and microcatheter qualities allow high densities to be achieved with a lower number of coils."

Finally, they report that the safety of the Penumbra Coil 400 system was demonstrated "by the low thromboembolic event rate of 3.3% and by the fact that no aneurysm perforations were observed during catheterisation of coil delivery."

On what lessons were learned about the Penumbra Coil 400 system during this study, Kulcsàr *et al* state:

1 There is the need to accurately estimate the packing density that will be achieved with the coil selected prior to insertion. Small aneurysms may be quickly overfilled by selecting a coil that is too long. The entire coil may require removal due to the inability to introduce the last few millimetres of the coil into the aneurysm.

2 It is important to try and prevent expulsion of the microcatheter tip from the aneurysm during coil insertion. In general, it was found to be more difficult to re-access the aneurysm (this is probably related to the larger microcatheter outer diameter not fitting into the smaller interstices between the large diameter coils). Furthermore, distally located small aneurysms may not be ideal for treatment with the Penumbra Coil 400 system, mostly due to the limitations of accessing these aneurysms with the higher profile microcatheter.

Oxford developing new flow diverter

An Oxford University spinout is developing a new flow diverter device invented by engineers and clinicians at the University to treat intracranial aneurysms. Oxford Endovascular has raised £2 million from investment company Oxford Sciences Innovation PLC, Parkwalk Advisors and other private investors to take the device through clinical trials, and ultimately aims to treat thousands of patients worldwide.

Now, *NeuroNews* speaks to Oxford Endovascular chief executive officer, Mike Karim, about the new device and how they think it will address the limitations currently encountered using the existing devices of its kind.

What inspired the invention of this device?

The challenges of making an interventional implant that has the following characteristics:

1 Flexible enough to conform to twists and turns of blood vessels in the brain;

2 Provides sufficient coverage to isolate the aneurysm;

3 Provides sufficient radial force so that it will not collapse when placed inside the blood vessel;

4 Can be folded into a very small diameter for delivery.

Professor James Byrne collaborates with professor Zhong You of Oxford University's Engineering Department who he alerted to the challenges of dealing with brain aneurysms with existing technologies. Prof Byrne felt that it was necessary to develop a new one to meet the challenges listed above.

What separates your flow diverter from other similar devices already on the market?

Our flow diverter is still undergoing further development much of which is top secret; however we plan to have a technology that will be more efficacious and will be easier and more accurate to place in the patient.

Mike Karim

What limitations do you think this device will address?

Existing devices are limited by the time it takes to place them accurately into the patient and with certain complications that may arise. We hope to develop a product that is easier to place and that reduces complications.

Which aneurysm types/patient types will this device be used to treat?

This device will be used to treat large and giant necked aneurysms as well as hopefully others that are too small or deep in the brain for existing treatments.

What are your plans for the future in terms of the development of the device and clinical trials?

We are working on refining the stent design to fit into as small a catheter as possible as well as developing the delivery system that is compatible with it. We have found many partners willing to collaborate with us. Of course we will have to carry out the necessary clinical work to meet the regulatory requirements; we are confident we have a next generation device that will bring great value to patients and physicians alike.

According to a release, the University's technology commercialisation company, Isis Innovation, supported the team by filing patents, profiling the business plan to marketing the opportunity to potential investors. The device was developed with support from the Wellcome Trust, Technikos and the University. Oxford Endovascular aims to complete development and begin manufacturing the device before moving into clinical trials and applying for regulatory approval in major markets.

Profile Guido Guglielmi

World-renowned as the inventor of the Guglielmi Detachable Coil (GDC), Guido Guglielmi speaks to *NeuroNews* about what inspired him to pursue that invention and gives his advice for aspiring inventors. Now retired, he talks about how he spends his time and addresses the three main questions in the field of endovascular neurosurgery that remain unanswered.

What drew you to medicine and to endovascular neurosurgery in particular?

My father was a physician and probably that is what drew me to medicine. At first I wanted to enrol in electronic engineering, but at the last minute I changed my mind and enrolled in medicine. During my course in medicine I was quite enthusiastic about the brain because it is constituted by millions of relays and millions of wires that transmit electricity and are connected to one another (I have been very interested in electronics since I was 10 years old). This is the reason why later on I wanted to become a neurosurgeon.

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

During the preparation of my thesis and during my four years of fellowship in neurosurgery I learned the theory and the practical application of neurosurgery from professor Beniamino Guidetti who was the chairman of the Institute of Neurosurgery. He was very interested in vascular neurosurgery (mainly aneurysms and arteriovenous malformations). I learned from him the base of the discipline of neurosurgery. In particular, his motto was: "it is enough to look at an aneurysm to provoke its rupture"! I utilised this motto later on when I designed GDC coils soft enough not to rupture the aneurysmal wall.

What has been your most memorable case, and why?

Strangely enough, my most memorable case was not related to the GDC coils. In fact, I succeeded in reopening thrombosed brain vessels in a lady who had a stroke. I utilised t-PA to reopen the left internal carotid artery and the left middle cerebral artery. With this procedure I literally saved the life of the young lady. She was left with a minor neurological deficit only (minor signs of dysphasia), but she started again to work, to drive her car, and to lead a normal life. I consider this case memorable because it was performed at the beginning of the era of the endovascular treatment of stroke. So, it was a sort of pioneering work.

You are responsible for one of the most important inventions in the field of neurointerventional surgery, the Guglielmi Detachable Coil. How did you come up with the idea?

As you say, I am responsible for my invention: actually I feel responsible all the time, especially when I hear of clinical complications with the GDCs. The creation of the GDCs took place because of the following reasons: I am a neurosurgeon, I am an interventional neuroradiologist-endovascular neurosurgeon, I have a diploma in electronics, and I am very interested in applied mechanics. All these four components were in one single mind. Further, I learned that it was possible to navigate microcatheters into the arteries of the brain, and that it was possible to perform electrothrombosis of pathologic arteries applying a direct electric current. Being a surgeon and an endovascular neurosurgeon, it was possible for me to create experimental aneurysms onto the common carotid of swine and embolise them with the GDC (this happened at the University of California-Los Angeles, USA). The background in electronics and mechanics was important because I was able to construct an electrically detachable junction and to make the platinum portion of the GDC very soft. I came up with the idea of GDCs in the first half of 1989 after several *in vitro* and *in vivo* experiments.

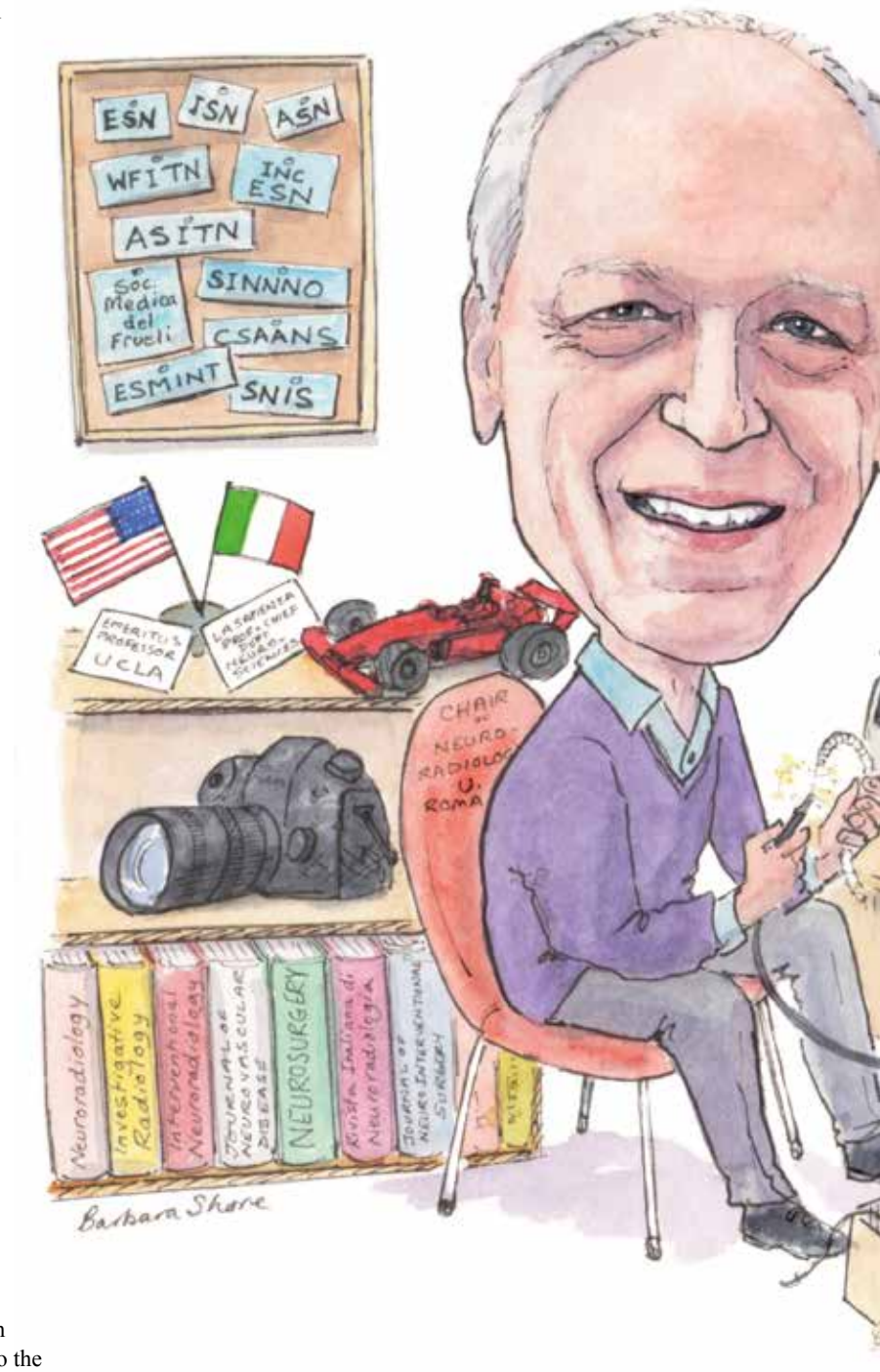
The idea of applying an electric current to thrombose an experimental aneurysm was conceived in the early eighties. At the experimental laboratory of the Institute of Neurosurgery, University of Rome, Italy, *in vitro* and *in vivo* studies were conducted. Experimental saccular aneurysms were created on the carotid artery of 10 rabbits. A 3F catheter was navigated into the aneurysm, via transfemoral approach. Through the catheter, a 0.2mm stainless steel wire-electrode was introduced into the aneurysm. A 10mA positive current was then applied to the wire for 10 minutes, eliciting electrothrombosis. Minimal occlusion of the aneurysms was achieved. This led to the temporary abandonment of the research. Nevertheless, a "rat tail" erosion of the intra-aneurysmal stainless steel electrode was noticed, due to the passage of the electric current. This phenomenon, of inducing electrolysis of an endovascular intra-aneurysmal stainless steel guidewire was applied, almost 10 years later, for the detachment mechanism of the detachable coils.

In the mid-eighties, a new concept was tested *in vitro*. Glass models of saccular aneurysms were utilised, using an artificial circulation of saline made of silastic tubings. A pump was used to circulate the fluid into the silastic tubings and in the glass aneurysm. A 1mm cylindrical micromagnet was glued to the tip of a stainless steel wire. The magnet was introduced "endovascularly" into the aneurysm sac. Iron microspheres (less than 8 microns in diameter) were then injected into the circulation. The microspheres became attracted to the magnet, increased its size, and partially occluded the glass aneurysm. No electric current was applied.

This concept was tested *in vivo* in 1989 at the Leo G Rigler Research Center, University of California at Los Angeles. Experimental aneurysms were created on the common carotid of swine. A micromagnet-tipped stainless steel wire was introduced into the aneurysm via a then new microcatheter: the Tracker. Iron microspheres were injected into the aneurysm via the intra-aneurysmal microcatheter, and, as a result, the magnet attracted the microspheres and "enlarged". This enlargement was not enough to occlude the aneurysm. We had the idea of further increasing the occlusive mass by eliciting an electrothrombotic phenomenon around the magnet. A 4mA positive electric current was applied to the stainless steel wire which produced an erosion of the wire next to the magnet and subsequently detached the magnet in the aneurysm by electrolysis. A reliable detachment mechanism had been discovered!

The substantial failure of the ferromagnetic technique led to find an alternative endovascular method. Now that the detachment mechanism had been found, the question was: what do we detach? This was the key, crucial moment of the discovery of the detachable coils.

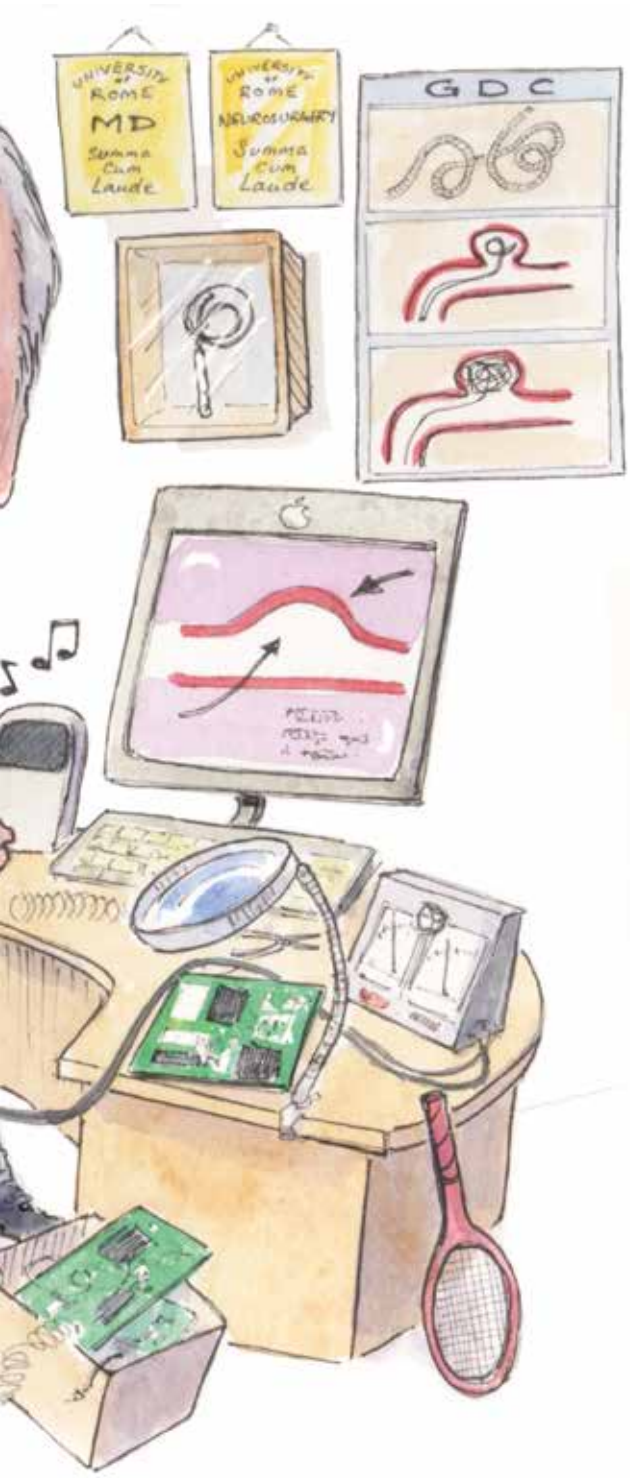
Modifying an existing stainless steel, platinum tipped micro-guidewire, I created a



1cm long detachable platinum tip. It became possible to enter an aneurysm, fill it with a platinum tip, and detach the tip with a 4mA positive electric current. This current, in fact, dissolves the stainless steel wire, next to the platinum tip, by electrolysis (ie. migration of ferrous ions from the anode to the cathode). Platinum is radiopaque, biocompatible, and, being a noble metal, is not affected by electrolysis. It became also clear that a tip was not enough to fill the entire aneurysm. Therefore a platinum coil was soldered to the stainless steel delivery wire. The detachable coil was born! Looking at the facts, I must say that the GDC was a true revolution in the field of neurosurgery. The GDC was a game changer. Before GDC, interventional neuroradiologists would perform only a few cases per week. After GDC, the clinical work substantially increased. Nowadays endovascular neurosurgeons treat many patients per week. Nowadays about 90% of brain aneurysms are treated with the endovascular approach using coils. Before the GDC, 99% of brain aneurysms were surgically clipped.

In your opinion, how has the Guglielmi Detachable Coil changed the face of neurointerventional surgery?

As I said, the Guglielmi Detachable Coil constituted a revolution in the field of neurointerventional surgery. Brain aneurysms are now predominantly treated with the GDCs. GDCs paved the way for many new devices like microcatheters, microguidewires, endovascular stents (which, for instance, allow treatment of difficult aneurysms and enable an improved treatment of stroke), etc.



What advice would you give to aspiring inventors?

To aspiring inventors I would say: First, do not become discouraged if at a certain point the research does not give the expected results. Sometimes a change of technique may lead to success. Second, do not become discouraged if the work you believe is important is not fully appreciated by the academia. As an example, in 1990 I sent an abstract on the first few cases treated with GDCs to AANS, for possible acceptance. They did not accept my abstract saying that "it is not relevant enough"!

Other than GDC, what are the three most important innovations in endovascular neurosurgery in the last 20 years?

The most important innovations in endovascular neurosurgery in the last 20 years have been: the endovascular treatment of stroke, the creation of a new glue for the treatment of brain arteriovenous malformations and arteriovenous fistulas, and the creation of endovascular stents suited for the treatment of wide-necked brain aneurysms. It goes without saying that MRI, MRA, CT, AngioCT underwent major changes with noteworthy and fundamental improvements that helped us in providing the best possible treatment of vascular diseases of the brain and spinal cord. Digital Biplane Rotational Angiography with Road-Mapping capability constituted a revolution in the diagnosis and therapy of vascular diseases.

From your research and experience, what motivates you?

I believe that motivation to perform research comes from inside and cannot be taught: it is in the DNA of a person. I would say that, in my experience, the goal of a good researcher should not be to obtain an economic reward. Instead, the goal should be to have pleasure in what he/she is doing. It is also very important to have a mentor that can "inject" enthusiasm in the negative, frustrating and difficult times of research, where the enthusiasm of the researcher may fade.

What do you believe are the three main questions in the field of endovascular neurosurgery that remain unanswered?

The three main questions that remain unanswered in endovascular neurosurgery are: 1) an ideal treatment of brain arteriovenous malformations; 2) an ideal treatment of wide-necked aneurysms (mostly large or giant aneurysms); 3) sometimes embolising materials and delivery systems that are not ideal are produced and sold by the manufacturing companies.

What are your interests and hobbies outside of medicine?

My hobbies and interests outside of medicine are:
1) Electronics (I build radios and all sort of electronic circuits)
2) Informatic (using the Apple Macintosh)
3) Contemporary art (I make Installations)
4) Photography (I use a Canon 6D)
5) Psychology-Psychiatry (Freud, Adler, etc)
6) Philosophy (hellenistic and existentialism)
7) Music (contemporary, pop, rock and classic)
8) Tennis, Soccer, and Formula 1
9) Films (mostly, I like German movies)

Fact File

Appointments

- Chair of Neuroradiology, Full Professor and Chief, Department of Neurosciences, University of Roma "La Sapienza", Rome, Italy (recruited as Full Professor for "Chiara Fama")
- Full Professor in Residence, Emeritus Professor, Department of Interventional Neuroradiology, University of California at Los Angeles (UCLA), Los Angeles, USA

Research projects

Principal investigator for the following:

- National Council for Research Grant Award (Italy) on Study of Embolizing treatment of tumors and vascular malformations of head and neck: embolizing substances and technique of embolization
- Ministry of Public Education Grant Award (Italy) on: Embolizing treatment of brain arteriovvenous malformations via endovascular approach
- Ministry of Public education Grant Award (Italy) on: Angioplasty of brachiocephalic vessels via endovascular approach
- National Institute of Health Grant Awaed (USA) RO1 HL46286-01 on: Endovascular Occlusion of Aneurysms by Electrothrombosis
- National Institute of Health Grant Award (USA) 2 RO1 HL46286-03A1 on: Endovascular Treatment of Wide-Necked Aneurysms

Publications

- Over 90 articles published in peer-viewed journals
- Twelve chapters and articles in books
- Over 120 abstracts and proceedings
- Co-author of the book: Endovascular Treatment of Intracranial Aneurysms. Springer Verlag, Berlin-Heidelberg, James V Byrne, Guido Guglielmi (Eds.), 1998

Honours and awards (selected)

1995	Food and Drug Administration approval of the Guglielmi Detachable Coil (GDC) for clinical use
1995	Nomination for the Lemelson-Massachusetts Institute of Technology Prize for exceptional inventiveness and creativity
2005	Honorary President of the 2005 World Federation of Interventional and Therapeutic Neuroradiology, Venice, October 19-22, 2005
2006	Honorary Member of the European Society of Neuroradiology
2012	Honorary Member of the European Society of Minimally Invasive Neuro Intervention

PRECISION SPECTRA™
Spinal Cord Stimulator System

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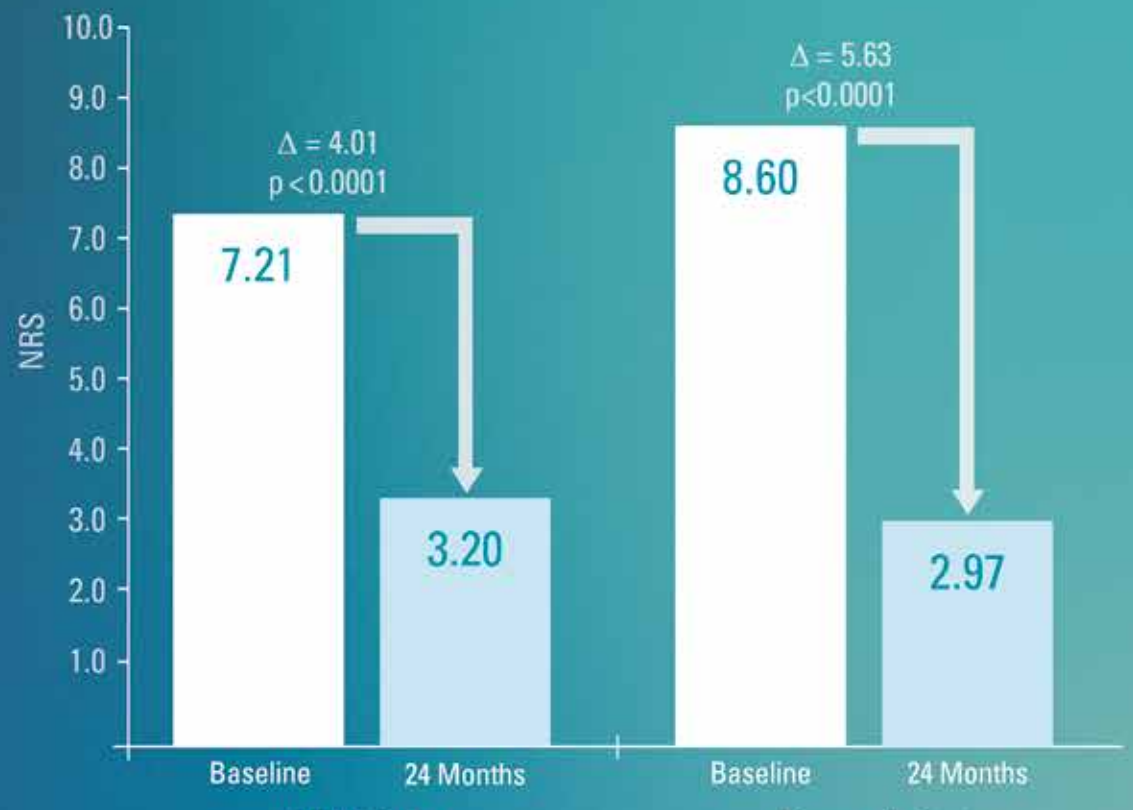


Long-Term Clinical Outcomes with Advanced SCS Using Anatomically-Guided Neural Targeting

Hayek et al. Multi-center, observational study of consecutive Precision Spectra patients across 13 sites. Presented at the International Neuromodulation Society 12th World Congress, Montreal, Canada, 2015

*Not all patients have reached 24 months post implant. Remaining data will be presented at NANS 2015.

PRECISION SPECTRA SCS SYSTEM

Innovation Focused on Pain Relief™

Indications for Use: The Precision Spectra™ Spinal Cord Stimulator System (Precision Spectra System) is 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, warnings, precautions, side effects: The Precision Spectra System is contraindicated for patients who: are unable to operate the Precision Spectra System, have failed trial stimulation by failing to receive effective pain relief, are poor surgical risks, or are pregnant. Refer to the Instructions for Use provided with the Precision Spectra System or ControlYourPain.com for potential adverse effects, warnings, and precautions prior to using this product. Caution: Federal (U.S.) law restricts this device to sale by or on the order of a physician. Note: Clinical study results may not necessarily be indicative of clinical performance. Results in other studies may vary.

Neuromodulation

Long-term data confirm positive pain relief results for dorsal root ganglion stimulation

Long-term data from the ACCURATE study have confirmed dorsal root ganglion (DRG) stimulation with the Axium neurostimulator system (St Jude Medical) provides sustained and superior pain relief over traditional spinal cord stimulation in patients with complex regional pain syndrome (CRPS) or peripheral causalgia. In addition, patients receiving DRG stimulation reported better therapeutic targeting and a reduction in paraesthesia compared to traditional tonic spinal cord stimulation.

The data were presented at the 19th annual meeting of the North American Neuromodulation Society (NANS; 10–13 December, Las Vegas, USA) and confirm three-month primary endpoint data originally presented at the International Neuromodulation Society annual meeting (INS; 27 May–1 June 2015; Montreal, Canada) and reported in Issue 19 of *NeuroNews*.

Giving a background into dorsal root ganglion stimulation, Timothy Deer (chief executive officer and president of the Center for Pain Relief, Charleston, USA and co-principal investigator of the ACCURATE study) said, "Epidural spinal cord stimulation is an established technique in the treatment of chronic pain in the lower limbs, and we are finding that there are limitations in the current spinal cord stimulation therapies which provide an opportunity to improve upon treatment outcomes. The role of DRG in the development and maintenance of chronic pain makes it an attractive target in neuromoulation."

He added, "The DRG is the Grand Central Station of the nervous system, so it is very complex organ. The ACCURATE study is the largest randomised, controlled trial ever conducted in CRPS/causalgia that was undertaken to provide evidence of safety and efficacy for market approval in the USA."

One hundred and fifty-two patients were randomised in a 1:1 ratio to DRG stimulation or control (a commercially available spinal cord stimulation device) at 22 investigational sites. Enrolled patients had chronic, intractable pain of the lower limbs for at least six months, either complex regional pain syndrome or peripheral causalgia, and a minimum VAS ≥60mm in the area of the greatest pain in the lower limbs.

The study was statistically powered for non-inferiority and superiority. A patient was considered a primary endpoint success if they met the following three criteria: ≥50% pain relief in their primary area of pain at the end of the trial phase, ≥50% pain relief in their primary area of pain at the three month visit post implant, and freedom from stimulation-induced neurological deficit through three months. Secondary endpoints were positional effects on paraesthesia intensity in the control group *versus* the DRG group (statistically powered) and paraesthesia intensity (post-hoc). Tertiary endpoints were stimulation specificity, HR-QoL (SF-36), psychological disposition, functional status and patient satisfaction.

The analysis populations were three groups: the intention-to-treat which included all randomised patients; the modified intention-to-treat which included all patients who received a trial stimulator; and implant only which included patients who received a fully implantable system.

In terms of safety, Robert Levy (director of the Marcus Neuroscience Institute in Boca Raton, USA, and co-principal investigator of the ACCURATE study), reported that there were no stimulation-induced side effects or deficits, in either the traditional neurostimulation arm or the DRG stimulation arm. "The number of significant adverse events was within the range of what you would expect in a device-related study, and there were no significant differences between either of the two arms. Similarly, the number of device-related adverse events were equivalent in both groups and were within the range you would expect in a device-related trial and there were no unanticipated device-related adverse events in either of the two groups," he said.

Long-term, 12-month data from the ACCURATE study showed DRG stimulation includes:

- Pain relief: after 12 months, the ACCURATE study demonstrated a statistically significant number of patients receiving DRG stimulation achieved meaningful pain relief and greater treatment success when compared to patients receiving traditional spinal cord stimulation (74.2% vs. 53%).
- Improved therapeutic targeting: Nearly all patients receiving DRG stimulation reported better stimulation targeting in their area of pain without extraneous paraesthesia than patients receiving traditional spinal cord stimulation (94.5% vs. 61.2%).
- Reduced paraesthesia: After 12 months, more than a third of patients who received DRG stimulation were experiencing greater than 80% pain relief with no paraesthesia.

Levy summarised the results stating: "This study demonstrated that the DRG group was statistically non-inferior and superior in the composite endpoint of safety and efficacy at the three and 12-month visits compared to the control traditional spinal cord stimulation group." DRG stimulation, Levy said, "Showed a greater percentage of patients that responded to therapy versus commercially available spinal cord stimulation at three months (81.2% vs. 55.7%) and at 12 months (74.2% vs. 53%). There were greater improvement in quality of life measures, psychological disposition and physical activity levels. There were clearly less positional effects on paraesthesia intensity when compared to traditional spinal cord stimulation. I believe that this has led to significant data to suggest that for patients with CRPS or peripheral causalgia, the primary treatment modality for consideration should be dorsal root ganglion stimulation as opposed to traditional spinal cord stimulation, and this is prospective, randomised controlled data that demonstrates that not only at three but also at 12 months."

The Axium system was approved by the US Food and Drug Administration in February 2016. The Axium Neurostimulator system has been available in Europe since 2011.

LUMINA data demonstrate 70% greater low back pain relief with spinal cord stimulation system at 24 months

Continued from page 1

a cocktail of anodes and cathodes such that you stimulate only where you want to stimulate and nothing else. This is known as anatomically guided neural targeting. So we thought we would take a hypothesis of low back pain and see if we could not only capture low back pain, but capture it over time," Frey noted. He added that the LUMINA cohort was an all-comers population; "We did not exclude the type of challenging patients that physicians see every day," he said.

The LUMINA cohort includes four patient groups: 213 consecutive patients treated with the Precision Spectra system for up to 24 months post-implant (LUMINA Spectra group); 213 consecutive patients treated with the previous generation system, Precision Plus, in a statistically matched comparison with the Precision Spectra system (LUMINA Precision Plus group); 50 consecutive patients treated with the Precision Spectra system and CoverEdge 32 Surgical Lead for 12 months post-implant (LUMINA Surgical group); and 100 consecutive patients treated with the Precision Spectra system where disability was measured out to 12 months (LUMINA Physical Function group). Key findings of the study include:

LUMINA Spectra group

- Sustained and highly significant reduction in overall pain from an average baseline score of 7.17 to 2.94 at 24 months post-implant (n=169), as measured on the 0–10 numeric rating scale.
- In a subset of severe patients (8 or greater baseline pain score) with only low back pain (n=38), a sustained and highly significant reduction from an average baseline score of 8.6 to 2.98 at 24 months post-implant.

Comparison between the Precision Spectra and Precision Plus groups

- Responder rates (≥50% pain reduction) at 24 months post-implant for the Precision Spectra system were 74% for overall pain, 81% in leg pain only patients and 71% in low back pain only patients. For low back pain, the improvement with Spectra was more than 70% compared to that of the previous generation group (Precision Plus).

LUMINA Surgical group

- Highly significant reduction in overall pain from an average baseline score of 7.8 to 2.6 at 12 months post-implant (n=46).
- In a subset of patients with only low back pain (n=25), 83.1% responder rate and a highly significant reduction from an average baseline score of 8.3 to 2.2 at 12 months post-implant.

LUMINA Physical Function group

- Clinically significant reduction of greater than 20 points in disability (n=100), maintained out to 12 months, as measured by the Oswestry Disability Index.

Finally, Frey reported that there is further research ongoing to confirm the low back pain results of neural targeting spinal cord stimulation in relation to disability and when coupled with a 32-contact surgical paddle.

SUNBURST data demonstrate superior pain relief results for Burst stimulation over traditional spinal cord stimulation

Burst stimulation can relieve chronic pain more effectively than traditional tonic spinal cord stimulation, according to data from the SUNBURST (Success using neuromodulation with Burst) study. The study also showed that patients generally preferred Burst stimulation to traditional spinal cord stimulation. Additionally, most patients experienced a reduction in paraesthesia, or experienced no paraesthesia at all.

The results of the prospective, randomised study—which is intended to support US Food and Drug Administration approval of Burst stimulation therapy—were presented at the 19th annual meeting of the North American Neuromodulation Society (NANS; 10–13 December, Las Vegas, USA).

The SUNBURST study was designed to assess the effects of Burst stimulation, and enrolled 100 patients from 18 centres across the United States randomised to either receive tonic stimulation prior to Burst stimulation, or to receive Burst stimulation prior to tonic stimulation. Each patient had a device that could deliver both tonic and Burst stimulation.

To be included in the study, patients had to have a successful tonic spinal cord stimulation trial evaluation (>50% pain relief), have chronic intractable pain of trunk and/or limb, and an average seven day visual analogue scale (VAS) score of 60mm or higher prior to the tonic spinal cord stimulation trial.

The patients included in the trial were 59.1 (±13.5) years; had 12.8 (±10.9) years of pain and 60% of the patients were female. In terms of conditions, 42% of patients had failed back surgery syndrome and 37% had radiculopathies. The overall baseline VAS was 75.1mm. As it relates to mental health, the mean Beck Depression Inventory was 10.1 (±6) with 75% having no depression. There was no clinically meaningful catastrophising; and the mean pain catastrophising scale (PCS) was 20.2 (±11.8).

The primary efficacy endpoint was non-inferiority of Burst compared to tonic stimulation. Secondary endpoints included superiority of overall VAS, superiority of trunk VAS, superiority of limb VAS, paraesthesia coverage, and preference of stimulation type.

After six months, an analysis of the first 85 patients to complete their 24 week visit showed Burst stimulation delivered:

- Pain relief: The study met its primary endpoint of non-inferiority and achieved statistical significance for its pre-specified secondary endpoint of superiority demonstrating that Burst stimulation achieved superior pain relief and greater treatment success when compared to traditional spinal cord stimulation.
- Patient preference: A statistically significant majority of patients (69.4%; n=59) in the SUNBURST study preferred Burst stimulation to tonic spinal cord stimulation for the treatment of chronic pain. Tonic stimulation was the preference of 21.2% (n=18), and eight patients (9.4%) had no preference.
- Reduced paraesthesia: The vast majority (91%) of patients reported a decrease in paraesthesia during treatment with Burst stimulation relative to tonic spinal cord stimulation. In addition, 65% of SUNBURST patients were paraesthesia free while using Burst stimulation and 20% experienced reduced paraesthesia.

Commenting on the reasons given for patient preference, Timothy Deer (chief executive officer and president of the Center for Pain Relief, Charleston, USA and chairman of the SUNBURST study), reported that the number one reason patients preferred Burst was superior pain relief. On the other hand, he added, 10.3% of patients said that they liked to have the paraesthesia with the tonic stimulation. "I think that is important. Without the paraesthesia that patient group may not have done well," Deer said.

Timothy Deer

In summary, Deer noted, "We achieved improved pain relief for Burst over tonic for overall pain, as well as trunk and limb pain; we achieved preference to a superior degree with the Burst waveform 69% of the time; we achieved reduction of paraesthesia 91% of the time and elimination in 65% of those patients. So we achieved all the endpoints we wanted and in addition there were no adverse events."

Finally, commenting on the fact that all the patients in the study experienced both Burst and tonic spinal cord stimulation, Deer said, "The ability to offer different waveforms, different modes of stimulation to the same patient with the same device is very critical because we do not want patients to fall out of either group for failure."

Medtronic and Samsung to collaborate on telehealth solutions for neuromodulation patients

Medtronic and Samsung Electronics America are to begin a broad-based strategic alliance aiming to speed up the development of digital health solutions for those who could benefit from neuromodulation therapy. According to Medtronic, convenient access to mobile technology will help these people—and their healthcare providers—to better manage their health.

This partnership was announced at the North American Neuromodulation Society (NANS) annual meeting (10–13 Dec; Las Vegas, USA). It is intended to leverage Samsung's understanding of consumer technology to develop advanced tools aimed at improving how patients and physicians interact with Medtronic's neuromodulation systems. Medtronic is seeking to deliver real-time health data to patients and physicians, from its devices.

"Through this alliance we intend to create efficiencies by developing digital solutions that connect patients and healthcare providers in real time," says Tom Tefft, senior vice president and president of Neuromodulation, which is part of the Restorative Therapies Group at Medtronic. "Medtronic has a track record of developing meaningful patient innovations, and this collaboration is the first step to providing more personalised patient care and arming patients and physicians with the best consumer-relevant technologies."

In the future, this alliance between Medtronic and Samsung is intended to focus on enabling patients implanted with neuromodulation therapies to use consumer electronics, such as smartphones, wearables or tablets, to securely and wirelessly transmit real-time data from their device to their physicians. Connecting patients and physicians in this manner could provide many potential benefits, including allowing physicians to more quickly make informed, data-driven treatment decisions.

Dave Rhew, chief medical officer and head of healthcare and fitness for Samsung Electronics America, says, "These future solutions will help better manage the health of patients by providing them with advanced, easy-to-use tools that securely deliver real-time data to their physicians."

Product News

StimRelieve receives FDA IDE approval for a wireless stimulator system for the treatment of chronic migraines

Investigational Device Exemption (IDE) approval to launch a clinical trial comparing the StimRelieve Halo Migraine System to more conservative options has been granted by the US Food and Drug Administration. According to StimRelieve, this is the smallest percutaneously implantable device for the treatment of chronic migraine available in the world. The product uses wirelessly-powered neurostimulators leveraging nanotechnology for the treatment of chronic migraines.

"To date, treatments for chronic migraines have had limited and inconsistent results," says Konstantin Slavin, professor of neurosurgery at the University of Illinois, Chicago. "Chronic migraine headache pain is a crippling condition, disabling millions of Americans every year. If determined safe and effective, StimRelieve's wireless neuromodulation device offers a promising option for alleviating and controlling this type of condition so that those living with this pain can better function and go on with their lives."

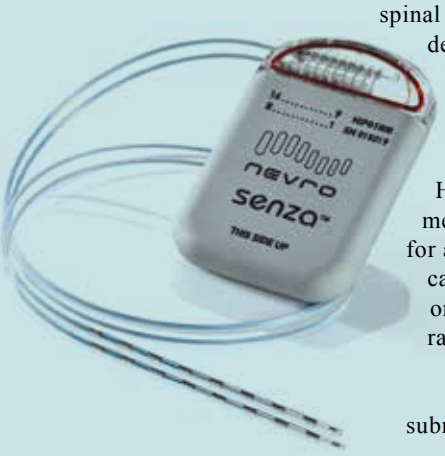
This clinical trial will assess the safety and effectiveness of occipital and supraorbital nerve stimulation using the StimRelieve Halo Migraine System for the treatment of chronic migraines. The StimRelieve Halo Migraine System is based on wireless neuromodulation technology. It is among the world's smallest devices—95% smaller than other implanted options—and, according to StimRelieve, is implantable with a standard gauge needle, thus eliminating the need for extensive surgery to the face, head and neck.

There is no implanted battery pack placed in the patient. Instead, a discreetly-worn external transmitter worn on the ear provides energy and therapy to the implanted device. The goal of the study is to achieve a 30% reduction in headaches with no increase in medication at three months as compared to the control group that will have no active treatment during the same period.

CMS approves transitional pass-through payment for outpatient use of Nevro's Senza spinal cord stimulation system

Nevro has announced that the Centers for Medicare & Medicaid Services (CMS) have approved a transitional pass-through payment for High Frequency Stimulation under the Medicare hospital outpatient prospective payment system effective beginning 1 January, 2016.

This pass-through payment for HF10 therapy will be in addition to the established reimbursement for spinal cord stimulation devices. CMS determined the Senza SCS System delivering HF10 therapy met the criteria for a new device category based on the published randomised control trial (RCT) evidence submitted.



The Healthcare Common Procedure Coding System (HCPCS) code for this new device category is C1822.

FDA approves deep brain stimulation for people with Parkinson's disease with recent onset of motor complications

Medtronic plc has announced US Food and Drug Administration (FDA) approval of Medtronic deep brain stimulation (DBS) therapy for use in people with Parkinson's disease of at least four years duration and with recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication.

In 2002, the FDA initially approved Medtronic DBS therapy for use in patients with advanced Parkinson's disease. Medtronic DBS has demonstrated improvement in motor complications, quality of life, activities of daily living and reduction in medication usage in individuals with Parkinson's disease.

"Strong clinical evidence demonstrates that, when compared to the best medical treatment alone, Medtronic DBS Therapy offers Parkinson's patients with recent onset of motor fluctuations and dyskinesias not adequately controlled with medication a higher likelihood of symptom improvement. Historically, the therapy has often not been considered until symptoms have had a significant impact on quality of life," said Mahlon DeLong, the W P Timmie professor of neurology at Emory University School of Medicine, USA. "This decision by the FDA is significant in that Medtronic DBS Therapy may be considered before the symptoms and complications of disease become severe. Parkinson's patients should be referred to an experienced DBS multidisciplinary centre for a comprehensive evaluation of possible Medtronic DBS therapy. For patients who are still functioning socially and able to work, this may translate into improved quality of life and an overall reduction of the burden of disease."

This recent approval by the FDA was based on data from the EARLYSTIM clinical study, published in the *New England Journal of Medicine* in 2013, which found that patients treated with Medtronic DBS therapy and best medical therapy (BMT) reported a mean improvement of 26% in their disease-related quality of life at two years, compared to a 1% decline in patients treated with BMT alone. In a study of patients with longer-standing motor complications, DBS patients' quality of life improved 20% from baseline to six months compared to no improvement in the patients treated with BMT alone.

"Parkinson's disease is progressive, and as a result a patient's quality of life will deteriorate over time. This approval is important because it expands the therapeutic window when patients can benefit from DBS," said Lothar Krinke, vice president and general manager of the Brain Modulation business, which is part of the Restorative Therapies Group at Medtronic. "Medtronic's goal is to advance medical care and deliver the best possible patient outcomes. DBS is proven to provide long-term benefits and it can now be used sooner in the care continuum, giving patients with recent onset motor complications another option to maintain or restore quality of life."

Impaired motor complications are associated with decreased quality of life, and the impact is similar for patients with recent onset or longer-standing motor complications. In the EARLYSTIM study, 85% of patients who received DBS along with BMT had a clinically meaningful improvement compared to only 36% in the BMT alone group over 24 months. Thirty per cent of patients that remained on BMT alone got worse over 24 months compared to only 2% in the DBS group. The study also found a 61% improvement in levodopa-induced complications, including dyskinesias and motor fluctuations, in participants receiving Medtronic DBS therapy at two years, compared to a 13% worsening in those only receiving BMT. Additionally, a long-term study of people with advanced Parkinson's disease who received DBS therapy show benefits at 10 years, despite potential surgical and device-related complications.

FDA approves Axium Neurostimulator System for dorsal root ganglion stimulation

St Jude Medical has announced FDA approval of the St Jude Medical Axium Neurostimulator System for dorsal root ganglion (DRG) stimulation. The approval of DRG stimulation in the USA will ensure access to a superior therapeutic approach for treating moderate to severe chronic intractable pain of the lower limbs in adult patients with complex regional pain syndrome (CRPS I and II).

The chronic pain disorder known as CRPS often affects the extremities. St Jude Medical expects that DRG stimulation will be available to physicians and patients in the coming months.

By stimulating the DRG, a spinal structure densely populated with sensory nerves that transmit information to the brain via the spinal cord, the Axium system delivers a form of spinal stimulation that gives physicians the ability to treat the specific areas of the body where pain occurs. As a result, DRG stimulation is a first-of-its-kind therapeutic approach that provides pain relief to patients with neuropathic conditions underserved by traditional SCS who have tried multiple treatment options without receiving adequate pain relief.

"The approval of St Jude Medical's DRG neurostimulation system represents an exciting new option for me to deploy in the fight against the focal and intractable chronic pain syndromes facing my patients every day," said Timothy Deer, an interventional pain physician, president and chief executive officer of the Center for Pain Relief in Charleston, USA. "For the large and growing numbers of under-treated patients suffering from complex regional pain syndromes—like those resulting from total knee arthroscopy, foot surgery or hernia surgery—DRG stimulation can offer improved, long-lasting relief."

Approval of DRG stimulation with the St Jude Medical Axium system was based in part on the results of 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. Patients in the study were randomised to receive either DRG stimulation delivered by the Axium Neurostimulator System or traditional tonic SCS therapy delivered

Product News

by a competitor's system. At both three-month and 12-month intervals, results from the ACCURATE study showed DRG stimulation provided patients with superior pain relief over traditional tonic SCS.

The Axium system originally received CE Mark approval in November 2011 for the management of chronic intractable pain. The Axium system is also approved for use in Australia.

Medtronic offer first complete portfolio of full-body MR conditional neurostimulation systems

The US Food and Drug Administration (FDA) has approved Medtronic's Specify SureScan MRI surgical leads, which are indicated for use as part of Medtronic implanted neurostimulation systems for chronic pain.

According to a company release, physicians can now offer a Medtronic full-body MR (magnetic resonance) conditional SCS (spinal cord stimulation) system best suited for their patients regardless of the type of neurostimulator (rechargeable or non-rechargeable) or lead type (percutaneous or surgical).

"All patients with a spinal cord stimulation system should have the ability to be offered the same imaging options as those without one," says Steven Falowski, neurosurgeon at St Luke's University Health Network in Bethlehem, Pennsylvania, USA. "Now more than ever, patients and other health care providers are concerned about access to MRI when considering an implantable device. This approval means I can offer a neurostimulation system that helps manage my patients' pain and gives them access to the diagnostic benefits of MRI."

The Medtronic release also lists the following as additional benefits of the Medtronic spinal cord stimulation therapy:

- The opportunity for patients to "test drive" spinal cord stimulation with an external stimulator for a three to 10 day trial period.
- AdaptiveStim technology, which adjusts stimulation automatically.
- Personalisation to empower patients to manage their own pain therapy by adjusting their stimulation within pre-set limits.

Stimwave receives CE mark approval for Freedom-8A spinal cord stimulation system

Stimwave Neuro LP has announced CE mark approval for a wireless programmable neuromodulation device with up to eight electrodes that can be introduced through a needle without surgery for relief of chronic back and leg pain. This is the first of its kind on the global market.

According to Stimwave, its CE marked Freedom-8A spinal cord stimulation (SCS) System can provide European patients with up to 64 electrode contacts, offer traditional programming options, as well as other programming options including frequencies up to 10,000Hz or waveform customisation. The Freedom-8A SCS System with eight electrodes continues to utilize the Apple iPad programmer, leveraging Bluetooth protocols for ease of use in programming the variety of options.

"A wireless system that enables clinicians to actually have the full programming capabilities of IPGs, all in a device that can be injected, represents a paradigm shift in the field of options to provide the best of breed in customisation for patients to manage their pain profile," says Jean-Pierre Van Buyten, director of the Multidisciplinary Pain Centre, AZ Nikolaas of Belgium. "The ability of the CE Marked Freedom-8A SCS System to offer a variety of stimulation programmes, advance algorithm options, as well as 1.5 or 3T MRI scans, gives clinicians all the options they need without having to switch manufacturers."

According to a press release, the system eliminates the long wires painfully tunnelled through the body and connected to the implantable pulse generator (IPG), offered by traditional products. With the Stimwave technology, only a small device with electrode contacts and an embedded chip is placed within the body through a needle, shortening the time required for the minimally-invasive, outpatient procedure, and enabling a potentially lower-cost option for the European market. The Freedom-8A SCS System allows the European patient to have a whole body 3T or 1.5T MRI without removing the implant. With other systems, the patient is limited to certain body parts and cannot have a 3T scan.

"Now people in pain will be able to use one system, with all features, that we can inject easily in a minimally-invasive procedure and allows them to have an MRI anytime," says Frank de Loos, head of the Pain Department at Amphia Hospital and chief excutive officer and Founder of StimClinics. "Previously, we had to remove systems to give an MRI and also replace systems for IPGs that fail often. This system will make long-term patient care better. In Europe, we also eliminate the trial phase, because the full system is implanted in one visit."

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Dear Colleagues,

Once again it is our great pleasure to present this year's program for the **world's premiere course in Interventional Neuroradiology & Neurosurgery, LINNC Paris 2016!**

With each new edition of our pioneering course we face the challenge of how to renew this historic meeting while keeping the continuity and reputation that has made LINNC Paris so valuable to all of us. And each year, faced with the ongoing and rapid evolution in our specialty – and guided by your interaction with us – we find ourselves once again inspired by our discipline whose future is more promising than ever before.

In order to advance together, we have developed the current program through three critical axes – **Live Centers, New Technologies and Education.** The aim, as in previous LINNC Paris courses, is **to provide a forum for the exchange of ideas and the sharing of experience with world-renown experts** while, at the same time, offering a series of quality "take-home" messages that will have an immediate impact on your practice. To create a program of this level is a constant work in progress, and occurs from one LINNC Paris to the next, reflecting the expertise of the Editorial Board and Course Directors as well as your own invaluable input when you participate in LINNC online or at one of the other meetings of the LINNC family of courses (such as the increasingly successful LINNC NYC Seminar – US Edition).

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This program represents more than the few days we will spend together in Paris, it encapsulates the heart of the LINNC philosophy itself, **a philosophy founded on coming together to share what we know for the overall improved treatment and benefit of our patients.** It is at meetings such as these that we can dedicate ourselves once again to the excellence our profession demands, to the evolution in our knowledge and the quality of care we provide. We are proud to offer you this opportunity and look forward to your participation in LINNC Paris 2016.

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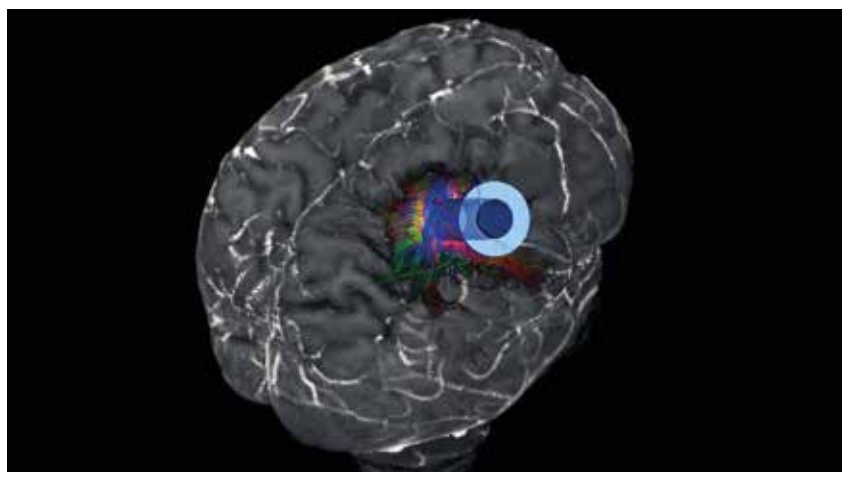
NICO announces BrainPath haemmorhagic stroke trial

Two US stroke centres, associated with Emory University School of Medicine, Atlanta, USA, have joined NICO (Neurosurgical Intervention Company) to perform a randomised controlled trial evaluating the clinical effectiveness of early surgical intervention using BrainPath following spontaneous intracerebral haemorrhage (ICH).

The Emory Stroke Center of Emory University hospitals and the Marcus Stroke & Neuroscience Center of Grady Memorial Hospital will lead the trial, ultimately comparing the outcomes between early intervention using atraumatic access with BrainPath for fluid evacuation and a medically managed cohort.

This trial will build on current peer-reviewed clinical data on the BrainPath Approach including the results of a multicentre pilot study presented at the 2015 International Stroke Conference 17–19 February, Los Angeles, USA). The study was on the safety and efficacy of haematoma evacuation using a trans-sulcal surgical approach with BrainPath and showed "statistically significant" improvement in patients' neurological state associated with early intervention. This improvement was reported in 35 patients at 10 centres with outcomes showing 89% clot evacuation and no new surgical deficits or deaths and was cited as a breakthrough in the treatment of haemorrhagic stroke by the National Stroke Association.



BrainPath

"This randomised trial will allow us to produce prospective data documenting the best course of action for patients we treat with this very deadly form of stroke," says Dan Barrow, chairman of neurosurgery, Emory University. "It underlines our commitment to partnering with other institutions in establishing a standardised minimally invasive approach and contributing to establishing a new standard of care for ICH patients."

The BrainPath device is used to access the haemorrhage site by navigating through the delicate folds and fibre tracks of the brain, displacing brain tissue as it creates a corridor to the haemorrhage site and evacuate the clot, all through an opening the size of a US dime. More than 300 neurosurgeons, residents and fellows have been trained on BrainPath and more than 2,500 BrainPath procedures have been completed at over 60 institutions throughout the United States since the device became commercially available three years ago.

"I have performed over 50 procedures using the BrainPath to access these bleeds," says Gustavo Pradilla, chief of neurosurgery, Grady Memorial Hospital. "My early experience is encouraging and I am hopeful the results of this trial, in addition to the growing body of clinical evidence, will provide a new standard for better outcomes for these patients."

The trial will include up to 10 centres and will begin this year, with approximately one year for patient enrolment and six months of patient follow-up. Ideal trial candidates are spontaneous supratentorial ICH patients with a good clinical chance of benefiting from the surgical treatment based on well-defined criteria for study enrolment.

"It is encouraging that recent ischaemic stroke trials have shown clinical success with mechanical technology for the removal of clots. We want to provide the same level of research and validation for treatment protocols for our ICH patients," says Michael Frankel, chief of neurology, Grady Memorial Hospital, and professor of neurology at Emory. "This study could contribute to revolutionising the standard of care for this high-risk patient population."

Product News

Tigertriever

First stroke patient treated with Rapid Medical's Tigertriever

Rapid Medical's Tigertriever has been used to treat its first patient. Using Rapid Medical's proprietary technology, this stent retriever is designed to be fully visible and controllable. The device can be adjusted by physicians to fit the dimensions of blood vessels causing acute ischaemic stroke, and is the first of its kind, according to the company.

"I am very pleased with the results and performance of the device," says René Chapot, head of the Neuroradiology Department at Alfried Krupp Hospital in Essen, Germany. "The Tigertriever's unique braiding and adjustability allowed me to safely secure the blood clot during its retrieval and achieve complete recanalisation in one attempt. The Tigertriever has vast clinical potential and I am very happy to be the first physician using this breakthrough device."

The Tigertriever uses Rapid Medical's proprietary technology platform, which is based on seven years' experience in controllable and visible advanced braided stent design. It is intended to accomplish both continuous adjustability and high radial force.

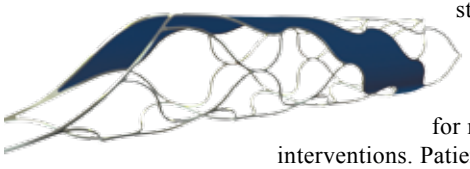
Rapid Medical plans to launch the Tigertriever in Europe during Q2 2016.

SITS Open stroke trial includes phenox pREset thrombectomy device

The phenox pREset and pREset LITE thrombectomy devices have been included in the study portfolio of the SITS Open clinical trial. Two other devices are included in the trial.

A company release states that the positive outcomes of recent randomised clinical trials for mechanical thrombectomy such as MR CLEAN, ESCAPE, EXTEND IA and SWIFT PRIME have renewed interest in studies enrolling a large number of patients—studies such as SITS Open. The SITS Open protocol is designed to provide a higher level of evidence for mechanical thrombectomy through a direct comparison between mechanical thrombectomy and a concurrent control of medical management alone.

According to the Department of Neuroscience at Karolinska Institute (Stockholm, Sweden), sponsors of the trial, 194 patients have been enrolled in the open, prospective, international, multicentre, controlled clinical trial as of 8 March 2016. The protocol calls for enrolling 600 patients in total, 300 in each arm. Patients enrolled in the treatment arm will be done so at centres that currently perform thrombectomy for stroke and fulfil the quality and training criteria for neuro-interventions. Patients in the control arm will be enrolled by clinics which offer IV thrombolysis and neither practice thrombectomy nor refer patients with ischemic stroke to other clinics where thrombectomy is offered.



phenox' Managing Director,–Ing Hermann Monstadt says, "Given the growing evidence regarding the effectiveness of mechanical thrombectomy, it is very important that pREset and pREset LT are a part of the tools available to physicians in treating ischaemic stroke."

IDE study for the WEB system completes enrolment

Sequent Medical has announced that it has completed patient enrolment in its Investigational Device Exemption (IDE) pivotal trial to evaluate the safety and effectiveness of the WEB Aneurysm Embolisation System.

The WEB Intrasaccular Therapy Study (WEB-IT) enrolled 150 patients at 31 participating sites in the USA, Canada and Europe. Data from the study will be used to evaluate the WEB for the treatment of both ruptured and unruptured intracranial bifurcation aneurysms.

The WEB consists of a dense mesh constructed from a large number of extremely fine Nitinol wires, and functions as an intrasaccular flow disruptor, bridging the neck of the aneurysm and providing rapid, peri-procedural stasis.

"The WEB is a valuable tool for the treatment of wide-necked bifurcation aneurysms," states Adam Arthur, professor, University of Tennessee Department of Neurosurgery/Semmes-Murphey Clinic and principal investigator of the WEB-IT study. "Completion of enrolment is the result of strong collaboration between a talented group of physician investigators. Their dedication and expertise means we are a step closer to making this treatment available to US patients. We look forward to reporting long-term results."

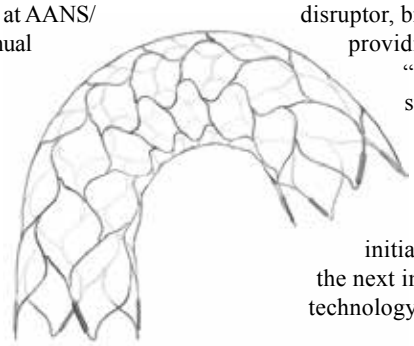
"The WEB-IT study is the first-ever pivotal study of an intrasaccular flow disruptor," says Tom Wilder, president and chief executive officer of Sequent Medical. "Completing enrolment ahead of schedule represents another major milestone for Sequent. We are highly encouraged by the physician investigators' enthusiasm for the WEB device and commitment to enrolling the study so proficiently and we are pleased with our continued progress towards our objective of US regulatory approval."

The WEB-IT study is a prospective, multicentre, single-arm study evaluating the WEB in 150 patients with ruptured or unruptured wide neck intracranial bifurcation aneurysms. More information on the WEB-IT study can be found at www.clinicaltrials.gov under NCT# 02191618.

Codman Neuro launches Enterprise 2 in the USA

Codman Neuro has launched the Enterprise 2 Vascular Reconstruction Device, the latest generation of the company's self-expanding stent and delivery system used to treat wide-necked intracranial aneurysms and to help maintain the position of endovascular coils during and after the procedure.

The new device was featured at AANS/CNS Joint Cerebrovascular Annual Meeting in Los Angeles, USA, held in conjunction with the Society for Neurointerventional Surgeons (SNIS).



The new Enterprise 2 System is designed to improve vessel wall conformability, while maintaining a stable structure at the neck of an aneurysm. The device helps secure the placement of endovascular coils and maintains blood flow through the artery. In addition, the stent is more visible under fluoroscopy than the previous device and has a self-flushing introducer to facilitate ease of use.

"The precision, conformability and occlusion that can be achieved when treating wide-necked aneurysms with the Enterprise 2 System are excellent. It was easy to use and deploy, and m*et al*l expectations for treatment. This is truly a next generation stent that helps overcome the clinical challenges of treating wide-necked aneurysms," said Donald Frei, a neurointerventional radiologist at Radiology Imaging Associates in Denver, USA, and one of the first physicians to use the technology.

According to the American Stroke Association, about three to five million people in the United States have some form of brain aneurysm, though most do not produce any symptoms. However, between 0.5 and 3% of people with a brain aneurysm may suffer from bleeding and rupture and require treatment. If an aneurysm has not ruptured, the treatment decision depends on its size, location and shape, and the patient's symptoms.

"We have made important design improvements to the Enterprise 2 System so that it better fits vascular anatomy, is more visible on X-ray, and is more easily deployed," says P Laxmin Laxminarain, worldwide president of Codman Neuro. "This technology is specifically designed to enhance the way physicians repair wide-necked aneurysms, which can be life-threatening and very difficult to treat."

The Enterprise Vascular Reconstruction Device and the Enterprise 2 Vascular Reconstruction Device are Humanitarian Use Devices approved by the FDA under a Humanitarian Device Exemption (HDE) in the United States Only, where it is authorised by Federal Law for use with embolic coils for the treatment of wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with a diameter of ≥2.5mm and ≤4mm. Wide-neck is defined as having a neck width ≥4mm or a dome-to-neck ration <2.

Sequent Medical initiates study of WEB aneurysm embolisation system for ruptured aneurysms

Sequent Medical has begun enrolling patients in a study which will evaluate the safety and effectiveness of the WEB (woven endobridge) aneurysm embolisation system for the treatment of ruptured intracranial aneurysms.

The first patient was enrolled by Laurent Spelle, head of Neuroradiology, Bicetre University Hospital, Paris, France, who is the study's principal investigator.

Fifty patients with ruptured aneurysms are to be enrolled in the "Clinical Assessment of WEB device in Ruptured Aneurysms" (CLARYS) study, which will take place at up to 15 sites in France and Germany.

CLARYS will be the first prospective, multicentre study focused only on gathering data on the WEB device in this particular patient population. The primary endpoint of the study will be the rate of aneurysm re-bleeding at 30 days. An independent core lab will review all study data and CLARYS will also feature independent clinical event adjudication.

The WEB device consists of a dense mesh constructed from a large number of extremely fine nitinol wires, and functions as an intrasaccular flow disruptor, bridging the neck of the aneurysm and providing rapid, peri-procedural stasis.

"The combination of rapid and durable stasis, a safe, fast procedure and the avoidance of long-term dual antiplatelet therapy makes the WEB an ideal treatment option for ruptured aneurysms," states Spelle. "The initiation of the CLARYS study represents the next important milestone for this exciting technology platform, and a critical step towards

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Product News

Elekta Leksell Gamma Knife Icon

improving outcomes in a large patient population with significant unmet needs."

First US patient treated with Elekta's Leksell Gamma Knife Icon

The Elekta Leksell Gamma Knife Icon stereotactic radiosurgery (SRS) system has been used for the first time in the USA, on 1 March 2016 at the Sutter Medical Center, Sacramento, USA.

The patient, a 52-year-old male, from El Dorado Hills, USA, had previously undergone successful treatment for primary melanoma and for melanoma metastases to his lung. He was treated for a metastatic brain tumour. The patient's treatment was planned and guided using a frameless approach. The frameless mask solution is one of several new features of Icon and is integrated with a novel high definition motion management. According to a company release, the system provides accuracy similar to that of frame-based SRS systems while minimising dose to normal tissue.

"Increasing the precision of frameless cranial SRS is essential for effectively targeting tumour tissue while protecting healthy brain tissue from damage," says Samuel Ciricillo, medical director of Adult and Pediatric Neurosurgery at the Sutter Neuroscience Institute. "The new Gamma Knife system, Icon, now provides the most accurate motion tracking during treatment. Additionally, with Gamma Knife there is a two- to four-fold improvement in sparing normal brain tissue compared to other linear accelerator platforms. These features allow for greater potential to protect patient quality of life both during treatment and after recovery."

The Icon system will make cranial SRS available to more patients and to improve the efficacy of cranial SRS with fewer side-effects, according to a company release. Icon also provides the flexibility for single dose administration or multiple treatment sessions over time, which enables treatment of larger tumour volumes, targets close to critical brain structures and new or recurring brain metastases.

At the time of SRS, pre-treatment magnetic resonance images and cone beam computed tomography (CT) images are aligned to identify precise coordinates for radiation targeting within the brain. This technology is especially important for patients who undergo multiple treatment sessions. Because the cone beam CT images are based on fixed structures within the brain, they ensure that dosage and delivery area are calculated correctly for each session, even if the patient's head is in a slightly different position from one treatment session to another.

Ciricillo worked with Sutter Medical Center radiation oncologist Harvey Wolkov and physicist Stanley Skubic, on the procedure. They are founding members of the team that started the Sutter Gamma Knife program in 1998.

Bill Yaeger, Elekta's executive vice president of Region North America, says, "We are excited to be working with other leading centres across the US to install additional Gamma Knife Icon systems over the coming months."

Jan Medical secures US$7.5 million in series C funding from Brainlab

Jan Medical has secured US$7.5 million in series C funding from Brainlab. This funding will be used to complete ongoing clinical trials and filing of product de novo with the FDA, as well as funding CE mark registration in the EU, for BrainPulse.

This product is a new diagnostic tool designed to rapidly and reliably help detect abnormal neurological conditions including concussion and stroke.

"With growing public awareness and concern about concussions, Brainlab is excited to invest in a partner that will provide medical professionals and athletic trainers with the tools to help accurately diagnose concussions," states Joseph Doyle, chief financial officer, Brainlab. "This is an important and innovative product that allows us to expand our expertise in neurological diagnostic tools."

The BrainPulse device is designed to capture a novel, non-invasive, physiological signal that utilises the cardiac output to measure vasculature and brain tissue conditions. The BrainPulse data has the potential to significantly impact non-invasive neurodiagnostics and provide a clinically relevant 'aid to diagnoses' for a range of indications, including concussion and stroke.

The BrainPulse data has been shown to detect and longitudinally observe sports-related concussion in a clinical trial at Stanford University, reported in the Clinical Journal of Sport Medicine. In another early trial published by Neurocritical Care, the device detected vasospasm with clinically meaningful accuracy at the University of California San Francisco (UCSF). Additional clinical trials in concussion detection and vasospasm are ongoing.

"This series C funding further validates the potential of the BrainPulse device, as we accelerate our regulatory clearances and prepare for market launch," adds Paul Lovoi, president and chief executive officer of Jan Medical. "We are fortunate to collaborate with such an exciting, passionate team from a leading neuroscience company."

In addition to the series C funding, Brainlab will provide resources to assist in ongoing clinical research, regulatory filing and commercialisation activities for Jan Medical, as well as expertise in research and development. Ken Bruener, Vice President of Marketing and Business Development, Brainlab, will become the Brainlab representative on the Jan Medical Board of Directors.

InSightec secures US$22 million and appoints Maurice R Ferré as chief executive officer

InSightec has secured a US$22 million as part of its round D investment. This investment has been led by its current shareholders. In addition, InSightec has appointed Maurice R Ferré, a medical device executive, as chief executive officer. Kobi Vortman, InSightec's former chief executive officer and founder, will take a board seat, and will drive strategy, as well as the product road map.

InSightec was founded by Vortman in 1999. According to a press release, his intention was to create a next-generation operating room by developing magnetic resonance guided focused ultrasound (MRgFUS) technology as an effective, non-invasive form of therapy. MRgFUS technology received its first FDA approval in 2004, and has been adopted globally.

Ferré, who has been serving as InSightec's chairman of the board, brings over 20 years of experience in the medical device industry. Before InSightec, Ferré served as chairman of the board and chief executive officer of MAKO Surgical, a robotic surgical company that he co-founded in 2004. The company was IPO'd in 2008 and recently sold to Stryker for US$1.65 billion in 2013.

"InSightec is at the forefront of the global shift towards non-invasive procedures. These procedures have the potential to improve patient outcomes, reduce morbidity and trauma while reducing costs," says Ferré. "My goal is to lead the company on its path to commercial success," he concludes.

Vortman says, "We started with proving our concept then continued to develop our first application for the treatment of uterine fibroids. Today the company offers clinical applications in three clinical areas: Women's Health, Oncology and Neurosurgery, and has over 90 patents and many regulatory approvals," he emphasises. "I will continue to support the company as a member of the board and have no doubt that Ferré will continue to lead the company to its success," Vortman concludes.

InspireMD receives EU regulatory approval for additional supplier of CGuard delivery catheters

InspireMD has received a DEKRA medical device certification for the manufacture and commercialisation of its CGuard delivery catheter.

According to a press release, the catheter incorporates some design enhancements and a lower cost manufacturing structure. The certification also allows the company to add-on facilities for seamless manufacturing work flow. DEKRA is a notified body for global certification of products, combining CE marking with ISO 13485 Quality Management Systems in the testing of medical devices for sale in the European Union (EU).

Alan Milinazzo, chief executive officer of InspireMD comments, "We are pleased to receive DEKRA certification for our enhanced CGuard delivery catheter. Our CGuard system continues to be well received during our initial product launch in key markets around Europe and our recent positive 12 month CARENET data should bolster our commercial efforts going forward."

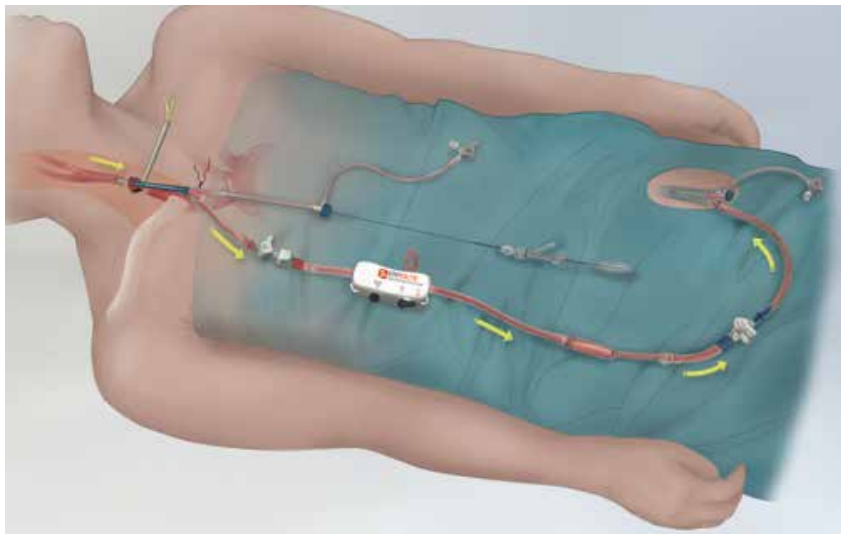
Twelve month CGuard CARENET (Carotid embolic protection study using micronet) trial results demonstrated zero strokes or stroke-related deaths. Further, duplex ultrasound analysis confirmed no changes in the in-stent velocities between 6 and 12 months. This indicates no sign of vessel narrowing and is consistent with the durability of carotid artery treatment seen using CGuard. In addition, the all-comer single centre PARADIGM trial continue to show favourable angiographic and clinical outcomes in using the CGuard system in treating patients with carotid artery disease. PARADIGM is an investigator-initiated prospective evaluation of all-comer percutaneous carotid revascularisation in symptomatic and increased-risk asymptomatic carotid artery stenosis using CGuard Mesh-covered embolic prevention stent system.

Silk Road Medical receives CE mark for next-generation Enroute transcarotid neuroprotection system

Silk Road Medical has been granted CE approval for its Enroute transcarotid neuroprotection system (NPS). The company has also reported the first patients have been treated with the system. The Enroute NPS is specifically designed and indicated for transcarotid artery revascularisation (TCAR).

Silk Road Medical developed the next-generation system in partnership with treating physicians. Based on feedback from over 700 TCAR procedures, the Enroute NPS was upgraded to provide physicians with a more dependable and easy-to-use system to treat their patients as safely as possible. The Enroute NPS allows the physician to directly access the common carotid

Product News



artery in the neck and initiate high rate temporary blood flow reversal to protect the brain from stroke while delivering and implanting Silk Road's Enroute transcarotid stent. The first TCAR procedures with the new Enroute NPS were recently performed in European hospitals including the Virgen de la Salud Hospital in Toledo, Spain, Klinikum rechts der Isar (Technische Universität München) in Munich, Germany, Augusta Krankenhaus in Dusseldorf Germany, John Paull II Hospital in Krakow, Poland and Gent University Hospital in Gent, Belgium.

"We have been working to improve the safety profile of carotid revascularisation through the development of the TCAR procedure, and this latest design of the Enroute NPS for TCAR is state-of-the-art," says Antonio Orgaz, chief of Vascular Surgery from Virgen de la Salud Hospital. "We were extremely impressed with the smooth, atraumatic entry of the sheath into the carotid artery and the more ergonomic design of the overall system. It is easy to use and inspires confidence."

The first generation Enroue NPS was clinically proven in the ROADSTER clinical trial, and the data were published in the November 2015 issue of the *Journal of Vascular Surgery* where the authors conclude, "The overall stroke rate of 1.4% is the lowest reported to date for any prospective, multicentre clinical trial of carotid angioplasty and stenting." The next generation Enroute NPS has been designed with the same flow rate specifications to maintain the neuroprotection seen in the ROADSTER trial, according to a company release.

"Whereas elsewhere in the body we routinely use minimally invasive endovascular techniques to treat vascular disorders, carotid artery disease is one of the last frontiers that is still treated primarily by an invasive surgical approach," says Ralf Kolvenbach, director, Department of Vascular Surgery and Endovascular Therapy at Augusta Krankenhaus. "This is because techniques used during carotid surgery are very good at protecting the brain during the procedure. With the Enroute NPS we can leverage surgical principles of neuroprotection like avoiding unprotected manoeuvres, maintaining exquisite control of the carotid bifurcation and blood flow, and removing embolic fragments of any size. But we can now do it in a less invasive manner that mitigates the risks of surgical complications like cranial nerve injury and wound complications while providing the patient with an aesthetic result and a quicker recovery."

Calendar of events

13–15 April
ESC: European Stroke Conference
Venice, Italy
W: www.eurostroke.org/news.html

30 April–4 May
AANS: American Association of Neurological Surgeons Annual Scientific Meeting
Chicago, USA
W: www.aans.org

10–12 May
ESOC: European Stroke Organisation Conference
Barcelona, Spain
W: www.esoc2016.com

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

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

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- Intracranial clot retrieval
- Use of techniques for urgent stroke treatment
- Current role of urgent carotid endarterectomy
- Current role of urgent carotid stenting

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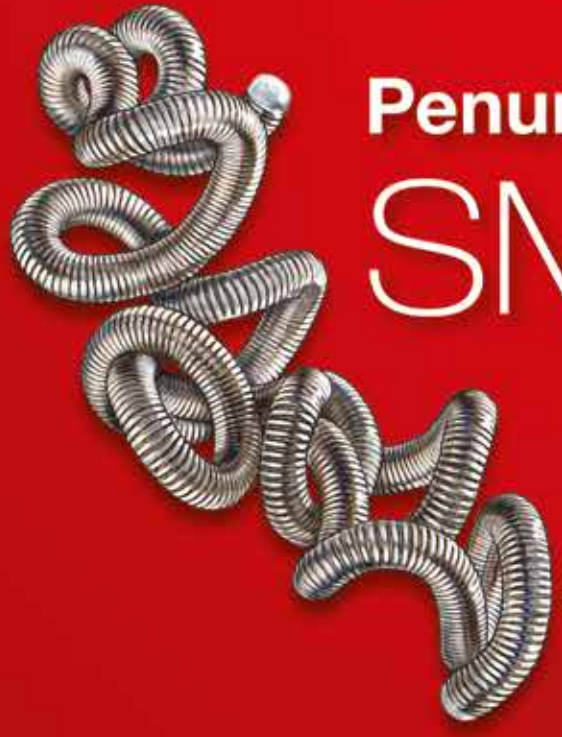

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