
LINC
Review
2017

LINC Review

Publishing and Production
MediFore Limited

Course Director
Dierk Scheinert

Editor-in-Chief
Peter Stevenson

Editors
Ryszarda Burmicz
Becky McCall

Design
Peter Williams

Industry Liaison Manager
Amanda D'rojcas

Head Office
51 Fox Hill
London
SE19 2XE
United Kingdom
Telephone: +44 (0) 7506 345 283
editor@medifore.co.uk
www.medifore.co.uk

Introduction

Over 5,000 were in attendance at the 2017 Leipzig Interventional Course – held in January – making it the largest gathering in the meeting's history. Reflecting LINC's increasing size, the meeting moved into a new hall, and expanded into seven main rooms, allowing the programme to feature an even more comprehensive and expansive range of topics, stretching further into the many realms of interventional medicine.

As regular visitors to LINC will know, live cases are a central thread running throughout the programme, and this year was no exception. Over 90 cases were welcomed via satellite from Germany, Italy, Switzerland, Belgium, Ireland, France and the USA. With exemplary techniques, novel devices and challenging concepts all laid bare, the live cases served as a compelling forum for all to witness.

Collaboration, open discussion and the sharing of international perspectives were also key, perhaps best exemplified by the dedicated '@LINC' symposia – joint sessions with leading vascular courses from around the world, including: Vascular InterVentional Advances (VIVA), the Charing Cross (CX) Symposium, Complex Cardiovascular Therapeutics (CCT), the International Symposium on Endovascular Therapeutics (SITE), and the International Congress of Interventional Surgery (CICE).

Within these pages you will find just a snapshot of this year's roster of lectures, clinical trial reviews, controversial debates, pioneering techniques and technologies, live cases, and so on. Although the *LINC Review* offers a glimpse of the meeting as a whole, we also encourage you to visit the LINC website to catch up on the series of lectures, live cases and presentation slides that are hosted there.

The LINC 2017 organisers would like to thank all of our delegates and industry sponsors for their continued support, and we look forward to seeing you at LINC 2018, held between January 30 and February 2, 2018 at the Trade Fair Leipzig.

http://www.leipzig-interventional-course.com

Contents

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www.angioweb.ch

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Congress production
Provascular GmbH,
Sonnenleite 3
91336 Heroldsbach
Germany
E-mail: dr.hornung@provascular.de
Phone: +49 9190 994041
Fax: +49 9190 994039
www.provascular.de

Congress organisation
CongO GmbH
Congress Organisation & more
Ruffinistrasse 16
80637 Munich
Germany
E-mail: info@cong-o.de
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AV support
mediAVentures
St. Jozefstraat 18
9820 Merelbeke
Belgium
E-Mail: info@mediaventures.be
Phone: +32 9 239 0110
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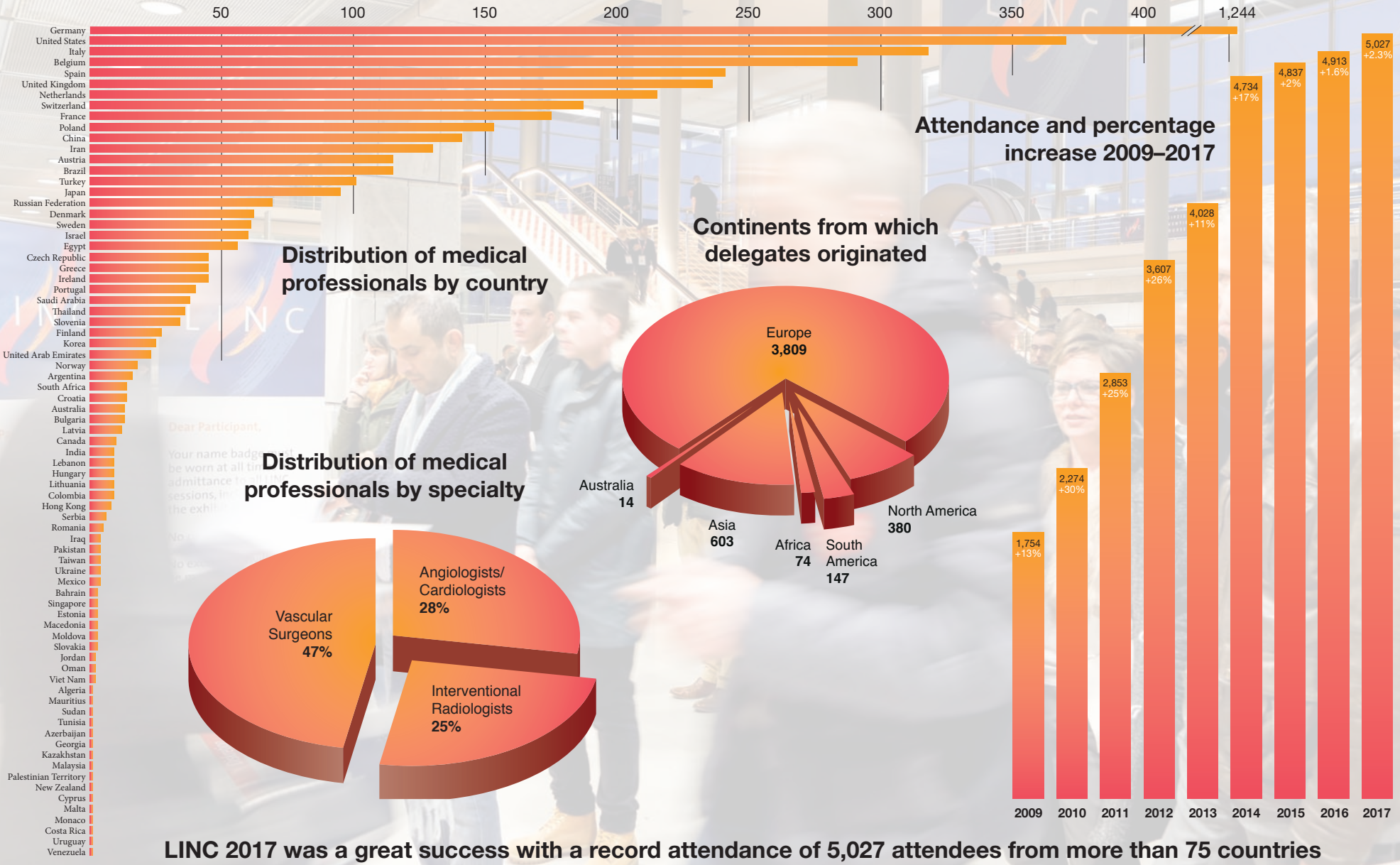
MediFore
51 Fox Hill
London
SE19 2XE
United Kingdom
Telephone: +44 (0) 7506 345 283
editor@medifore.co.uk
www.medifore.co.uk

LINC in numbers



Distribution of medical professionals by country

Continents from which delegates originated

Distribution of medical professionals by specialty

Attendance and percentage increase 2009–2017

LINC 2017 was a great success with a record attendance of 5,027 attendees from more than 75 countries

Percutaneous DETOUR around long complex lesions

DETOUR I is the prospective, multicentre, independently reviewed single arm trial to evaluate the safety and performance of the PQ Bypass DETOUR technology and technique (PQ Bypass, CA, USA) for percutaneous femoropopliteal bypass. The trial's six month results were presented at LINC 2017 by Dierk Scheinert (University Hospital Leipzig, Germany), and it was upon this basis that PQ Bypass gained CE Mark approval for DETOUR's use in TASC C and D femoropopliteal lesions.

"We all know that as we go for long, complex lesions, there are still limitations in terms of our technologies to achieve optimal patency," opened Professor Scheinert, noting that long-term patency has traditionally only been achievable with surgical bypass despite the significant maturing of endovascular techniques. However, recent technologies such as the DETOUR percutaneous bypass procedure offer a durable solution akin to that of open surgery, with the reduction in morbidity and mortality that endovascular techniques offer. "This is the where the primary promise of this new technology might be," suggested Professor Scheinert.

"The DETOUR percutaneous bypass is designed to achieve an end result with a similar construction as an open bypass. It is a revascularization via a modular stent graft system. The specific approach is that it uses the accompanying femoral vein as a conduit to get enough space to get the fully open bypass reconstruction beside a potentially heavily calcified artery."

This concept, explained Professor Scheinert, has already been around for some time, with proof of concept groundwork coming from groups such as James Joye's at El Camino Hospital in San Francisco, USA. The group used off-the-shelf devices to treat a series of 25 limbs in 25 patients with mostly TASC D lesions of mean length 31.2±9.7 cm. In this cohort a primary patency of 82% was achieved at one year, with secondary patency at four years of 91%, and no objective venous morbidity. "This was encouraging, and the starting point to develop a commercially-available toolkit to reliably achieves such a percutaneous bypass construction."

Professor Scheinert went on to described the three proprietary devices that comprise the DETOUR percutaneous bypass system: the Torus stent graft, a self-expanding nitinol frame encapsulated in ePTFE, with high radial force and elongated exposed end-rings to prevent edge stenosis; the PQ snare, designed to capture and extract guidewires through the tibial vein; and the PQ crossing device, a spring-loaded guidewire support and delivery system which creates tibial artery-vein-artery communication.

The DETOUR I trial sought to generate robust evidence in the treatment of specifically long femoropopliteal occlusive lesions (including those above 25 cm) using the DETOUR system. It is one of the largest prospective series evaluating the percutaneous treatment of SFA occlusions of ≥25 cm.

The trial assessed the safety and performance of the PQ Bypass DETOUR technology, with a primary safety endpoint of 30-day major adverse events (MAE; including death, target vessel revascularisation (TVR), and target limb amputation), and a primary efficacy endpoint of six-month primary patency (targeted upon an objective performance goal of 70%

"[DETOUR] uses the accompanying femoral vein as a conduit to get enough space to get the fully-open bypass reconstruction beside a potentially heavily calcified artery." Dierk Scheinert

patency). 60 patients were treated at seven international sites from January 2015 to May 2016, with additional clinical, lab, and digital ultrasound follow-up at one, three, six, 12, 18 and 24 months.

Inclusion criteria sought femoropopliteal lesions of ≥10 cm in length and included: chronic total occlusions (CTO); diffuse stenoses (with >50% stenosis) with moderate to heavy calcification; or in-stent restenoses (with >50% stenosis). Further stipulations included one or more patent tibial arteries to the foot, and a patent femoral vein of ≥10 mm in diameter.

Clinical characteristics at baseline conformed to expectations for such patient cohorts, with the overwhelming majority (96.6%) falling within Rutherford class 3, with mean ankle brachial index (ABI) of 0.65±0.19. Mean lesion length was 28.6±5.1 cm, ranging between 13.4 and 43.2 cm. 96.7% of lesions were CTOs, with calcification at landing zones occurring mildly in 56.7% of cases and moderately to severely in 43.3%. (Figure 1)

Discussing acute results, Professor Scheinert described that technical success – successful delivery of the device and removal of delivery system – was achieved in 59/60 total subjects (98.3%). Procedural success – technical success in the absence of in-hospital MAEs – was achieved in 58/60 cases (96.7%). Clinical success, defined as ≥1 grade improvement in the Rutherford class at six months, was achieved in 54/57 cases (94.7%).

Crucially, DETOUR's primary safety and efficacy endpoints were met, with a 30-day MAE rate of 3.4%, and a six-month primary patency rate of 84.7%. Detailing MAE events, Professor Scheinert noted that no deaths occurred throughout the six-month study period, with TVR occurring in 3.4% of cases (2/59 patients) at 30 days and 10.2% (6/59) at six months. No major amputation of the ipsilateral target limb occurred throughout the six-month period.

In terms of major adverse vascular events (MAVE), these comprised: acute limb ischemia, which occurred in a single patient out of the total of 59 (1.7%) at 30 days; stent thrombosis was present in two patients (3.4%) at 30 days, and in six patients at six months (10.2%).

There was no evidence of any DVTs at 30 days, noted Professor Scheinert, adding that the Venous Clinical Severity Scale (VCSS) and Villalta Scores both evidenced no relevant change over the time course of the observation. Baseline ABI increased significantly compared to baseline, and Rutherford classes shifted significantly with 94% of subjects fitting within class 0 at the six-month timepoint (Figure 2).

"The primary patency at six months of 84.7% in nearly-30-cm TASC D lesions is very encouraging," concluded Professor Scheinert. "The primary performance endpoint was met, without any impact on venous health.

"That really demonstrates that this technology has a good potential in very severe lesions – this is worthwhile to be investigated further."

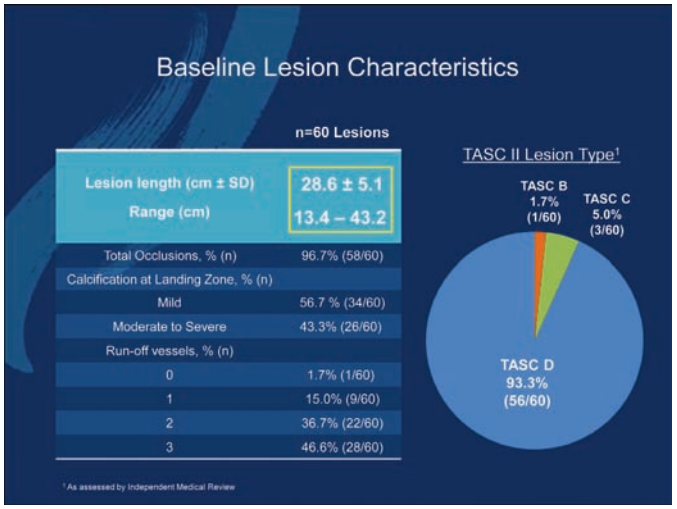
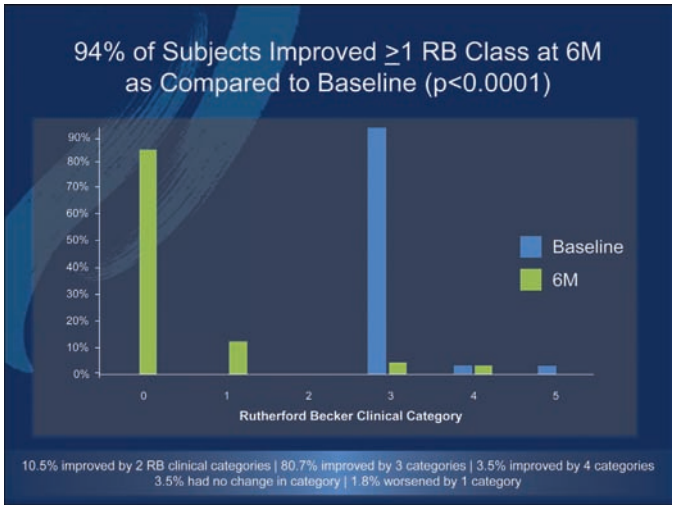


Figure 1. Baseline lesion characteristics, with lesions almost exclusively being CTOs, and falling into the TASC D category.



Source: LINC 2017 presentation archive (www.leipzig-interventional-course.com)

Figure 2. Rutherford classification at baseline and six months, demonstrating that 94% of subjects experienced a clinical improvement of at least one class at six months relative to baseline (p<0.0001). 10.5% improved by two clinical categories, 80.7% by three categories, 3.5% by four categories. 3.5% had no change in category, and 1.8% worsened by one category.

"This technology has a good potential in very severe lesions." Dierk Scheinert

ILLUMENATE Global sheds light on real world

Thomas Zeller (University Heart Centre Freiburg-Bad Krozingen, Germany) presented the latest on the Stellarex drug-coated balloon (DCB; Spectranetics, USA) with 12-month findings from the ILLUMENATE Global study[1], during a session focussing on DCB trial updates for the prevention of restenosis in claudicant patients with femoropopliteal disease.

"This is another study looking at real-world, global patients," introduced Professor Zeller. The prospective, multi-centre, single-arm study follows up patients for up to five years, with the same rigorous data collection process as randomised trials, including independent adjudication by angiographic core lab, duplex ultrasound core lab, clinical events committee and data safety monitoring board, with 100% source data verification.

The study's objective is to assess the safety and performance of the Stellarex DCB in the superficial femoral artery (SFA) and/or popliteal arteries with a primary safety endpoint of a composite of freedom from device and procedure-related death through 30 days and freedom from target limb major amputation and clinically-driven target lesion revascularisation (CD-TLR) through 12 months. The primary efficacy endpoint was primary patency at 12 months (defined as peak systolic velocity ratio of ≤2.5 and absence of CD-TLR).


Thomas Zeller

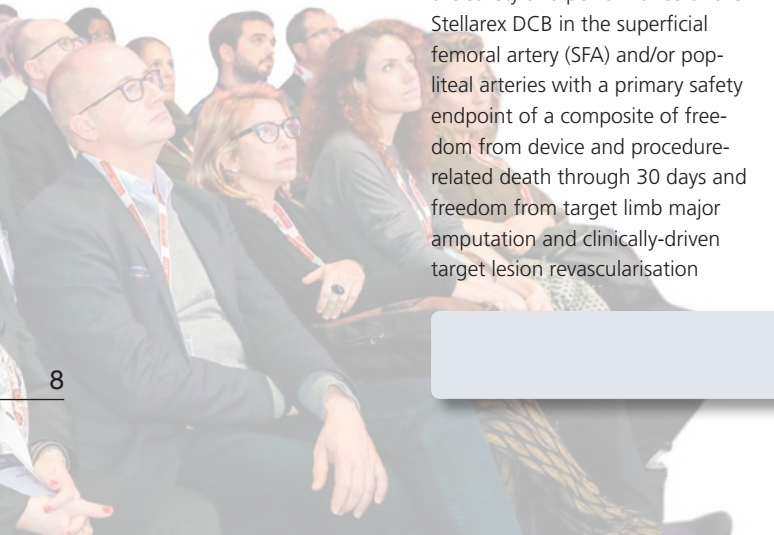
Describing the Stellarex design, Professor Zeller compared it to other DCBs on the market: "The Stellarex DCB is coated with 2 µg/mm^2 paclitaxel, and the coating is made from a hybrid crystalline formulation. It has been shown in pre-clinical animal studies that drug transfer and tissue residency is effective for longer than 28 days, so very comparable to the best-in-class DCB so far. And it is important to know the limited drug loss, which is lower than other DCBs."

ILLUMENATE Global included only patients of Rutherford class 2-4 with SFA and/or popliteal disease (including the P3 segment terminating at the trifurcation). These patients possessed at least one patent run-off vessel below the knee, with one or two target lesions of cumulative length ≤20 cm, and a target vessel reference diameter of 4-6 mm. Exclusion criteria included acute or sub-acute thrombus in the target vessel, significant in-flow disease not successfully treated, in-stent restenosis, severe calcification that precluded adequate percutaneous transluminal angioplasty treatment, or the use of adjunctive therapies (i.e. debulking or plaque incision).[1]

The majority of patients in the study (total n=371) had been suffering from Rutherford category 3 disease [57.7%] at time of intervention, with 33.4% Rutherford category 2. The rate of diabetes mellitus was comparable to analogous studies of similar patient populations (33.7%), as was renal insufficiency rate (7.0%), hypertension (79.5%), hyperlipidaemia (74.7%), and status as previous or current smoker (81.9%). Mean ankle brachial index (ABI) was 0.70±0.20 at the time of intervention.

Baseline angiographic results as per core lab assessment revealed a

"Drug transfer and tissue residency is effective for longer than 28 days, so very comparable to the best-in-class DCB so far." Thomas Zeller



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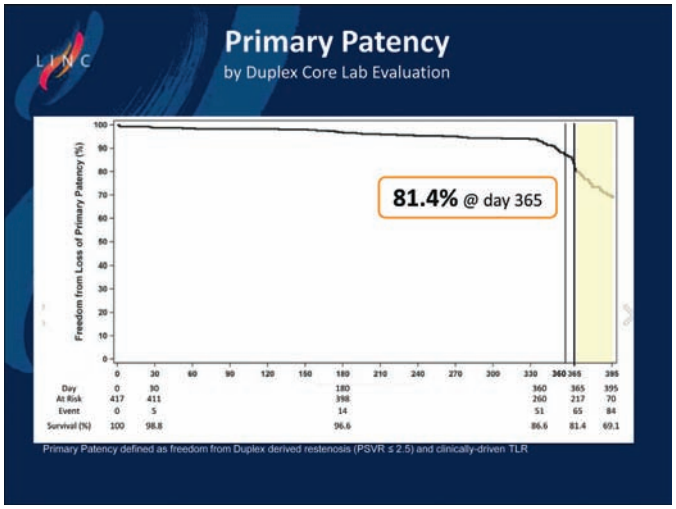

Figure 1. 12-month primary patency outcomes of the ILLUMENATE Global study, as evaluated by Duplex core lab.

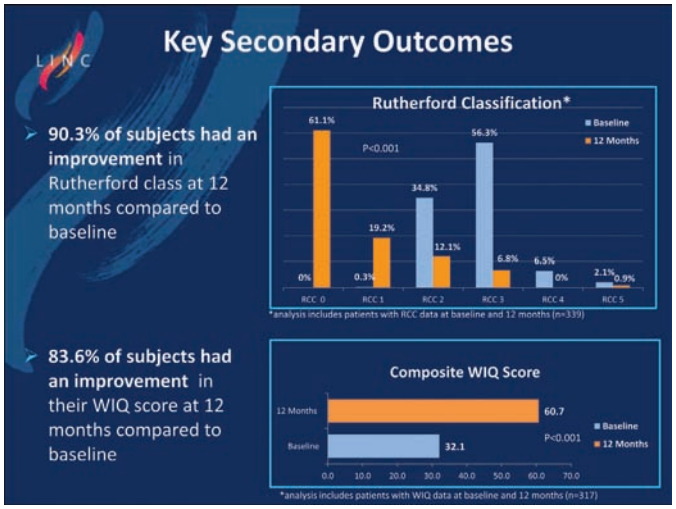

Figure 2. Secondary outcome measures at baseline and 12 months, including Rutherford classification (above) and Walking Impairment Questionnaire (WIQ) score (below).

31.3% rate of total occlusion, with a mean lesion length of 7.5±5.3 cm. Calcification was defined as severe in 40.8% of cases, moderate in 16.2% of cases, and mild or absent in 43.0%. 94.0% of lesions were de novo.

Predilatation was mandated by the study protocol, although carried out in 98.1% of cases. Post-dilatation was performed in 28.3% of cases. Provisional stenting was carried out in 17.3% of cases, of which 8.65% were due to dissection.

Primary safety endpoints were met in 94.8% of cases, continued Professor Zeller. "All-cause mortality was in two cases, not related to the procedure but due to cancer. There was one amputation which was in a patient with Rutherford class 5 (which was an exclusion criterion).

"CD-TLR was 94.8% at day 365, dropping slightly at the end of the follow-up period [of 395 days] to 91.2%, which is still is remarkably high. Primary patency at 365 days was 81.4% (Figure 1). If you compare that with outcomes in severe calcifications in other studies, it is very comparable with those studies including the IN.PACT SFA study[2] but also the other randomised controlled ILLUMENATE Pivotal[3] and EU[4] studies. On CD-TLR rates, again it is in line with the best so-far published data, and superior to what has been published for the LEVANT II study[5], considering that the percentage of severe calcification was higher in the ILLUMENATE studies. With regard to secondary outcomes, there was a 90.3% improvement in Rutherford class at 12 months and an 83.6% improvement in the walking impairment questionnaire score at 12 months (Figure 2)."

Indeed, Professor Zeller illustrated that out of three randomised studies with similar lesion characteristics (specifically, including severely calcified lesions), ILLUMENATE EU RCT fared best with regard to 12-month patency of 89.9%, as compared with 87.5% and 78.5% for IN.PACT SFA and LEVANT II, respectively. Regarding CD-TLR, comparing these same three RCTs pegged ILLUMENATE EU RCT at 5.9% at 12 months, IN.PACT SFA at 4.6%, and LEVANT II at 12.3%.

With his concluding remarks, Professor Zeller added: "ILLUMENATE Global demonstrated a 12-month primary patency rate of 81.4% and a CD-TLR of 6.2%. The data support and reinforce findings from the ILLUMENATE Pivotal trial and the European randomised trial. It builds on the robust ILLUMENATE program with four trials including more than 1,000 patients, and confirms that low dose, next-generation DCB can outperform within a wide range of patient complexities."

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CD-TLR was 94.8% at day 365, dropping slightly at the end of the follow-up period to 91.2%, which is still is remarkably high." Thomas Zeller

Crossing techniques for fem-pop CTOs

As part of a Scrub-in with the experts session on complex femoropopliteal lesions, Hiroyoshi Yokoi (Fukuoka Sanno Hospital Cardiovascular Center, Japan) joined others to describe his own approaches to these notoriously difficult and time-consuming recanalisations.

Within the realm of peripheral artery disease, around 60-70% of patients possess lesions in the femoropopliteal region. Short lesions bearing little or no calcium are reasonably well treatable using standard intraluminal techniques. Recanalisation of chronic total occlusions (CTO), however, is renowned to be technically challenging within this segment, with experience being one of the principle factors in determining procedural success along with lesion-related factors such as extent of calcification and lesion length. Standard guidewire and catheter techniques do not always meet the challenge of heavily calcified segments, being reported as failing in approximately 20% of cases. Yet specifically-tailored crossing devices as well as re-entry catheters may not be affordable for every institution and patient.

In the session, Professor Yokoi described how he tackles challenging femoropopliteal CTO. His recent work in the femoropopliteal region has included studies based on the ZEPHYR registry. The most recent sub-study compared subintimal with intraluminal drug-eluting stent (DES) implantation in femoropopliteal CTO, finding one- and two-year restenosis rates to be comparable.

Hiroyoshi Yokoi

As a cardiologist highly experienced in CTO crossing, *LINC Review* asked Professor Yokoi to describe his CTO population and some of the strategies he employs – strategies which contribute to the 90% or greater success rates seen in Japanese CTO work. Recently, he said, Duplex- and IVUS-guided guidewire manipulation is common in his practice. "I will treat TASC C-D lesions as well as TASC A-B lesions," he explained. "There is no upper limit on lesion length."

Turning to wires and support catheters, Professor Yokoi also spoke of some of his 'go-to' devices that have been useful in cracking the toughest cases: "I choose the 0.014-0.018 Treasure and Astato Wire (Asahi Intecc), with a 4F-CXI catheter (Cook Medical), or the 2.6F CXI Catheter (Cook Medical), or the Corsair micro-catheter (Asahi Intecc).

Asked what some of the key considerations must be when different crossing approaches are adopted, whether that is intraluminal, subintimal, or antegrade versus retrograde approaches, Professor Yokoi supported intraluminal passage via the antegrade approach in cases that permit it, with the qualification: "We will adopt the sub-intimal space for lesions with severe calcification.

"If the guidewire enters the sub-intimal space and it is difficult to return to the intraluminal space, then we will switch to the retrograde approach. We choose distal puncture (via the distal superficial femoral artery, the popliteal artery, or the tibial artery), or the trans-collateral approach using a retrograde approach."

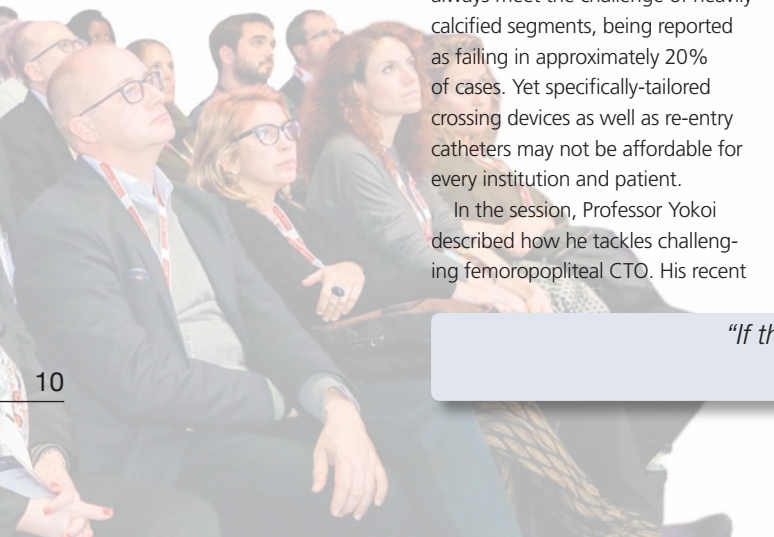
Endovascular CTO treatment is not the best option for all of his patients, noted Professor Yokoi, although this is far from common. "In less than 5% of cases, we will consider surgical revascularisation surgery," he said, adding other alternatives: "And there are times when you choose exercise therapy. I think a surgical operation is desirable for lesions with many thrombus and highly calcified lesions."

After crossing a CTO, IVUS investigation reveals key measures that will dictate further actions that may be required to secure patency, explained Professor Yokoi. "First I will observe the vessels – from the IVUS findings you can see the following information: (1) there is a high probability of capturing the true lumen; (2) you can identify proximal and distal reference segment landing zones and accurately select stent length; (3) you can accurately measure lumen size to maximize stent dimensions; and (4) you can determine when debulking should be considered."

Describing the decision-making process, he continued: "First, after a 3-5 minute inflation with a balloon, use a drug-coated balloon if there is no dissection, and drug-eluting stent if dissection has occurred. If the lesion is suitable, I will use a Viabahn [Gore]."

Addressing how his practice has evolved over recent years in terms of device choices, timing of interventions, and treatment aggression, Professor Yokoi first stressed that endovascular therapy has been an active field since extensive work has demonstrated its safety and efficacy. "Early treatment may be better for the short lesion," he added, "But long lesions experience more restenosis, so it still not recommended here."

Returning to the principle techniques that support successful CTO treatment, Professor Yokoi concluded with some of the questions he would like seen addressed in future research: "I would like to know if the use of IVUS will improve long-term results. And I would also like to consider whether or not there is a difference in the effect of drug-elution depending on the part of passage of the guide-wire (intraluminal or true lumen)."



"If the guidewire enters sub-intimal space and it is difficult to return to the intraluminal space, then we switch to the retrograde approach." Hiroyoshi Yokoi

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Optimising the use of EKOS™ in PE & DVT

Advances and approaches to the use of ultrasound-assisted thrombolysis for the treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT) was the order of business in the session 'Why EKOS™? A future of an effective and smart treatment of thrombosis'. Sponsored by BTG (UK), the symposium featured leading experts who shared their techniques and top tips for a packed audience.

First on the podium was Nils Kucher, Director of the Venous Thromboembolism Research Group at the University Hospital in Bern, Switzerland. He discussed the use of EKOS™ (EkoSonic™ Endovascular System Acoustic Pulse Thrombolysis™) in PE, focusing on the data supporting its use – relative to other interventions for PE – specifically touching upon the results of the ULTIMA study, a randomised, controlled trial (RCT) of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk PE patients.

Building the case for the use of EKOS™ in the treatment of PE, Professor Kucher expressed his enthusiasm for the technology. "Ultrasound-assisted catheter-directed PE thrombolysis rapidly reverses right ventricular (RV) dysfunction and haemodynamic instability whilst being associated with a low risk of bleeding and mortality," he said.

European guidelines for treating VTE

Venous thromboembolism (VTE), which includes DVT and PE, is the third most common cardiovascular cause of death. Referring to the 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism, Professor Kucher discussed how to manage these patients, noting that clinical risk should be estimated according to the simplified PE Severity Index (sPESI). If a patient is zero risk based on the sPESI, it is unnecessary to assess biomarkers or right-sided heart size. "Anticoagulant treatment alone is sufficient, and patients may even be discharged as an outpatient."

However, he added that if the clinical risk is higher, a CT scan of the right heart for dilation is required as well as measurement of the patient's troponin level. "If both tests are positive then the ESC recommends the patient be considered as intermediate- to high-risk, and anticoagulant therapy is recommended, as is monitoring and timely initiation of rescue reperfusion therapy. The role of primary reperfusion is unclear in these patients, and evidence is not strong to support use in all patients," he said.

If the patient is high risk, Professor Kucher suggested not to wait for results of the troponin measurements or of the echocardiogram. "Treat immediately with primary reperfusion," he recommended, adding: "Unstable patients should get unfractionated heparin and the guidelines recommend systemic thrombolytic therapy. For patients who are intolerant of this approach, then surgical embolectomy or percutaneous catheter-directed treatment should be considered." (IIa)

He went on to note that for stable patients with PE, routine use of systemic thrombolysis is not recommended if they do not have shock or hypotension. "But these patients should be monitored even if they have normal blood pressure, because risk of death or haemodynamic collapse in the first 48 hours is quite high at 6%."

In patients with intermediate-high risk PE, and risk of haemodynamic decompensation, thrombolysis should be considered, according to Professor Kucher. But he noted that surgical embolectomy or percutaneous catheter-directed treatment should also be considered as the risk of bleeding with thrombolysis is high.

Evidence from clinical trials

Turning to the PEITHO (pulmonary embolism thrombolysis) trial, the largest RCT ever performed in patients with acute intermediate risk of PE, Professor Kucher said that tenecteplase (a thrombolytic agent), administered to 506 patients, was associated with 2.6% risk of all-cause mortality and haemodynamic collapse, versus 5.6% in patients who only received heparin. "However, safety was an issue with more bleeding and strokes associated with tenecteplase than with placebo/heparin. With haemorrhagic stroke, in particular, there were 10 patients on tenecteplase, versus one on heparin."

Referring to systematic reviews, he relayed their conclusions stating that, overall, there was a risk reduction in death in using thrombolysis to treat PE, but that results needed to be treated with caution due to

"We use EKOS™ in Bern for nearly all our patients." Nils Kucher

the heterogeneity of studies. "We do know that the odds ratio for major haemorrhage with thrombolysis is nearly three, and intracranial bleeding runs five times the risk as treating with heparin alone."

Interestingly, in clinical practice, figures show that three-quarters of patients with massive PE did not receive systemic thrombolysis, and use in unstable PE, in the US, had nearly halved from 40% to 23% between 1999 to 2008, according to Professor Kucher.[2]

He went on to discuss whether mechanical intervention was safe and effective in the pulmonary artery "The answer is we don't know. One meta-analysis found an 86% success rate, but most patients received thrombolytics at the same time."

Pharmaco-mechanical thrombolysis

Pharmaco-mechanical thrombolysis (local thrombolysis and mechanical intervention) is a new concept and currently "the best we have for PE," commented Professor Kucher. "There is the Angiojet system [Boston Scientific, USA] or EKOS™, which is ultrasound-assisted thrombolysis. We use EKOS™ in Bern for nearly all our patients."

Ultrasound per se does not treat thrombosis, but combined with thrombolytics, there are effects that dissolve the clot. For example, the fibrin mesh in the clot separates, and acoustic streaming actively delivers the drug.

Presenting the results of the ULTIMA study (Ultrasound-Accelerated Thrombolysis of Pulmonary Embolism) Professor Kucher, who was principal investigator, reported that the study confirmed a fixed-dose, ultrasound-assisted catheter-directed thrombolysis using EKOS™ regimen was superior to unfractionated heparin anticoagulation alone in improving RV dysfunction at 24 hours without an increase in bleeding complications.

The phase III trial compared EKOS™ (<20 mg of recombinant tissue plasminogen activator; rt-PA) directly into the occlusive pulmonary thrombus, plus unfractionated heparin versus unfractionated heparin alone, as per the guidelines. The primary outcome measures were reduction of RV/LV ratio over 24 hours, and change in the end-diastolic RV/LV ratio from baseline to 24 hours by echocardiography.

Patients who received EKOS™ plus heparin showed that the RV/LV ratio significantly improved at 24 hours from 1.28 to 0.99 ($p<0.001$). With heparin alone the RV/LV ratio reduced from 1.2 to 1.17 ($p=0.31$). Systolic RV dysfunction significantly improved with EKOS™, and there were no deaths or significant bleeding complications.

"The study was not powered to find a difference at 90 days but in this trial we did see a clear trend for benefit at three months with EKOS™ treatment," reported Professor Kucher.

He continued to discuss results of EKOS™ use by referring to a meta-analysis of 350 patients of whom 19% had massive PE. The total rt-PA dose (via EKOS™) had a mean of 24 mg, and thrombolysis duration had a mean of 18 hours. Major bleeding complications were found in 6.9% of patients, minor bleeding 10.7%, and deaths in 3.2% at the three-month time point. "Given 19% of patients were in shock these are impressive results," remarked Professor Kucher. "Importantly, to date there are no published data of patients with intracranial haemorrhage."

Towards the end of his comprehensive discussion, Professor Kucher described the PE Response Team (PERT) that they have in place at University Hospital Bern, the first place outside of the US to have such a setup, and founded in 2010. A PERT is a combination of the most relevant and important people to treat PE, including cardiovascular surgeons, cardiologists, vascular surgeons, angiologists, or whoever is responsible for use of the EKOS™ device.

"At Bern there is a 24-hour service where the clinicians look at the CT scan together and make a decision about treating with heparin alone or EKOS™ treatment," he said, also explaining the treatment approach taken by the Bern PERT, pointing out that if there is no RV dysfunction, the patient is considered low risk and they do not receive revascularisation. If the patient has RV dysfunction then they are intermediate risk and the decision needs to be made about whether they receive no revascularisation versus catheter therapy versus surgical embolectomy.

"There is no role for systemic thrombolysis anymore in our hospital," he pointed out, adding that "if the patient is high risk, they

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"Patients who do not have a coronary-related problem are treated with intravenous heparin, but they are not aggressively treated for their PE." Ralf Kolvenbach

Optimising the use of EKOS™ in PE & DVT

have an emergency echocardiogram, and if there is RV dysfunction they quickly receive surgical embolectomy or catheter-directed therapy."

Fast track treatment of PE

Next up to discuss use of EKOS™ was Professor Ralf Kolvenbach who presented data on the fast track treatment of PE. He believes that by minimising the risk of intracranial bleed with EKOS™, it represents a game-changer in treating high-risk PE. He also presented a modified protocol to the more widely recognised

Seattle II trial protocol, while results between the two protocols were comparable.

"Often after admission to an acute care centre, patients who do not have a coronary-related problem are treated with intravenous heparin, but they are not aggressively treated for their PE," said Professor Kolvenbach, "this is a problem today."

He pointed out that, ultimately, the aim of treatment was to reduce long term sequelae of treating PE, primarily RV heart failure. Professor Kolvenbach discussed whether it was possible to treat patients with PE in a non-intensive care unit, because many centres do not have beds available in this setting.

In answer to this question, Professor Kolvenbach and his team modified the protocol used in some EKOS™ studies that required patients to be treated in the intensive care unit (ICU) setting for 12-24 hours. "Many institutions will need to treat patients in a lower dependency unit."

The protocol that Professor Kolvenbach used for massive and sub-massive PE was modified such that 10 mg of rt-PA was given in each pulmonary artery (if both were affected) over two hours only. Heparin is given as a bolus (5000IE) at the start.

"If necessary, one catheter is placed in each artery, and we take care of the underlying DVT if diagnosed after the lysis procedure," he said.

To date, Professor Kolvenbach and his colleagues have treated 61 patients. Two patients died prior to start of lysis, some refused lysis. No major bleeding was seen," he reported.

"Only 16% patients were treated in the ICU setting and 84% in the intermediate care or recovery room. We saw a marked reduction in RV/LV ratio and pressure reduction in right ventricle, and more than 50% achieved thrombus resolution."

He related the advantages of the modified protocol: less logistical effort is required, fewer ICU resources are needed and a lower dependency unit is used. What is more, no further heparin is needed during ultrasound-assisted lysis, further reducing risk of bleeding complications and making faster hospital discharge possible. Importantly, he added, "results were comparable to the Seattle II trial protocol."

In conclusion, he pointed out that ultrasound-assisted low dose fibrinolysis for acute PE improves RV function and reduces pulmonary hypertension.

Marcus Treitl

EKOS in DVT treatment

Last to speak was Professor Marcus Treitl, who discussed his experience with EKOS™ in patients with DVT and peripheral arterial disease. He explained that the primary target is iliofemoral DVT, often caused by a compression syndrome of the iliac vein. These patients can experience acute symptomatic DVT, high burden of pain and development of post thrombotic syndrome.

After reviewing treatment options, he focused on pharmaco-mechanical thrombolysis e.g. EKOS™; rheolytic e.g. Angiojet; or isolated mechanical thrombectomy. "Ultimately we want reduction of the residual thrombosis," he said. "A study has shown that post-thrombotic morbidity correlates well with degree of thrombus removal, so we aim to remove the thrombus fast so pain is gone and valve destruction risk is low, minimising residual thrombosis."

After discussing some case histories, Professor Treitl summarised the available data on use of EKOS™. "If there is a mix of old and fresh thrombus then the technical success rate isn't always so good [approximately 85%]. One study showed that in acute symptoms that are less than 10 days old, the technical success rate was 100% with primary patency of 76-80%."

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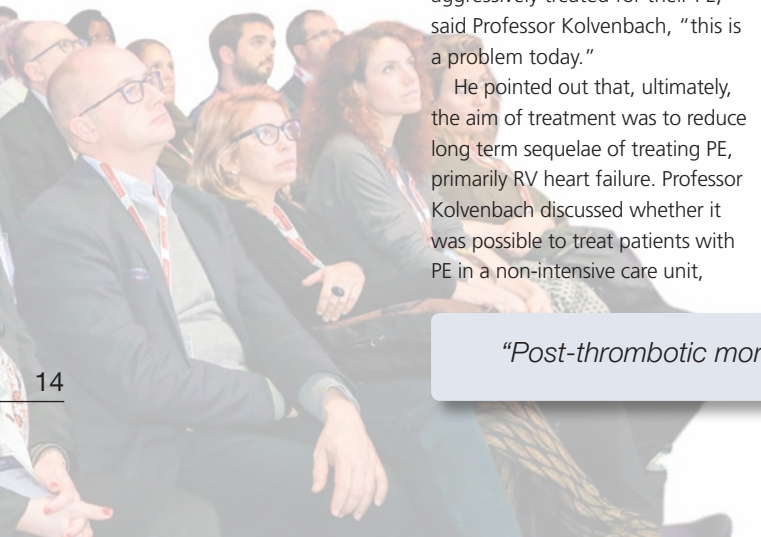

"Post-thrombotic morbidity correlates well with degree of thrombus removal, so we aim to remove the thrombus fast." Marcus Treitl

Cell therapy in peripheral artery disease

Sigrid Nikol is an angiologist at the Asklepios Klinik St Georg (Hamburg, Germany), whose current research centres upon the development of angiogenic therapies for the treatment of critical limb ischemia (CLI). Joining others in a session focussed upon patient-oriented approaches in severe CLI renal failure and beyond, she discussed cell therapy in peripheral artery disease (PAD).

Angiogenesis may be a promising solution for CLI patients who are at risk of major amputation – those who are deemed unsuitable for revascularisation, or whose revascularisation procedure has failed. While recanalisation techniques continue to improve, no medical therapy is available yet.

Angiogenesis offers an alternative strategy to increasing perfusion in areas of the leg and foot that req uire it, by creating new vascular structures. Gene therapy study has revolved around the delivery of angiogenic growth factor genes, including vascular endothelial growth factor (VEGF), fibroblast growth factor-1 (FGF-1), hepatocyte growth factor (HGF), amongst others. Cell therapy, on the other hand, seeks to bring a cocktail of growth factors into the vascular milieu by the administration of various types of stem cells. Both of these therapies seek to promote angiogenesis (and hence tissue survival) in an environment where endogenous remodelling is reduced leading to ischaemia.

Both gene and cell therapy have evolved immensely over the past decades, and Professor Nikol's research focus is currently on the latter of the two approaches. "The first cells that were used were autologous cells from the bone marrow," she explained, in conversation with *LINC Review*. "There were a large number of small trials, usually uncontrolled case reports or short series of five to ten patients, that all reported positive results. "But if you look at data from the few existing randomised controlled trials (RCT), and the meta-analysis of those RCTs, they don't look as good. This is especially the case for the placebo-controlled RCTs. Meta-analyses did not show any benefit for treatment with autologous cells."


Sigrid Nikol

Data are indeed controversial. A recent metaanalysis of placebo-controlled RCTs by Rigato *et al*. found that efficacy of cell therapy was insignificant for endpoints including major amputation-free survival and wound healing.[1]

The first prospective, randomised, double-blind, placebo-controlled multicentre trial was carried out by Powell *et al*., who in 2011 reported the results of RESTORE-CLI – which enrolled 86 patients, 46 of whom completed a six-month follow-up. While amputation-free survival and time to treatment failure were different, no relevant difference in rates of major amputation were found.[2]

More recently, the JUVENTAS study, results of which were published in 2015, found no significant reduction in rates of major amputation following the intra-arterial infusion of mononuclear cells from autologous bone marrow into the common femoral artery of patients with non-revascularisable CLI. Although secondary outcomes, including quality of life, rest pain and ankle-brachial index all improved during follow-up, no significant differences were found between treatment or placebo groups.[3]

Because of the negative findings for autologous cells, Professor Nikol became interested in studying cells from other sources: "Autologous cells are derived from the same sick PAD patient you are going to treat," she said. "Not only are the number of stem cells in these patients (being sick with cardiovascular disease including

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"Meta-analyses did not show any benefit for treatment with autologous cells." Sigrid Nikol

Cell therapy in peripheral artery disease

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PAD) lower than in the normal population, but also the quality of these cells is different."

This was demonstrated by the JUVENTAS investigators in 2013, in a study that found circulating endothelial progenitor cells reduced in CLI patients compared to controls. Moreover, they identified reduced matrix metalloproteinase-9 levels, and lower bone marrow CD34(+)-cell levels, indicating local inflammatory activity coupled with reduced progenitor cell recruitment.[4]

"We had to look for other cell sources," continued Professor Nikol. "Therefore, trials using placenta-derived stem cells as an alternative to autologous cells are promising. They are derived from placenta of young, healthy women who had just given birth. These cells are multiplied in reactors using advanced technology, controlled and checked, deep-frozen in liquid nitrogen, and then transported to us for use in the patients."

At present, only phase I studies have been completed using placenta-derived mesenchymal-like stem cells in CLI. Beyond that, one multinational phase II study in intermittent claudication has just completed its recruitment of 172 patients, with results expected in early 2018. One pivotal study in CLI involving 40 sites in Europe and the US will start in only few months, and an additional pre-marketing trial in CLI is planned to be initiated in Japan.

Commenting on evidence available today on this therapy, Professor Nikol said: "The efficacy data are still limited since only data from the phase I trials are available to date. But the safety profile has been good so far."

As well as being derived from healthy individuals, allogeneic cells such as placenta-derived stem cells confer considerable advantages over autologous cells. Allogeneic placenta cells are immediately available in unlimited quantity, with standardisation yielding consistent cell quality. Furthermore, the collection of the placental stem cells is non-invasive.

Asked what negative side-effects have been observed in patients treated with those cells in clinical trials, Professor Nikol replied: "Cell therapy with placenta-derived cells so far did not increase cancer, proliferative retinopathy or significant worsening of other biological functions, such as renal function. Thus, we have a good safety profile for these placenta-derived stem cells except for some inflammatory/allergic reactions, mostly at the site of injections.

"There were approximately 170 patients in the earlier trials. The side effects we saw were mostly transient local reactions at them injection site; in a few cases there were signs of systemic allergy (mostly mild and transient); and halitosis related to the excipient DMSO. So if there was a reaction it was local in most of the cases.

"In this regard, we are careful about patients who have comorbidities, as their situation may worsen of the situation (although this is just a suspicion)."

Interestingly, Professor Nikol and colleagues are not restricting their studies to the most severe CLI patients. Whereas pilot studies of placenta-derived stem cells were carried out in patients with ulcers, patients recruited to the phase II study have experienced intermittent claudication only – that is, they have walking difficulties, but no rest pain or ulcers. Some of these patients may be eligible for endovascular or surgical revascularisation procedures, explained Professor Nikol, but they chose to opt for this novel strategy. "Most claudication patients usually still have these endovascular or surgical options," she said, adding: "Some of them had very long occlusions that could have been treated with an intervention, but with a high re-occlusion rate. They chose to go for a less invasive approach using these cells."

"The unanswered question is, which cells are the best? Neuronal stem cells, or cells derived from adipose tissue are among others that are being investigated." Sigrid Nikol

As such, does she foresee that the therapy could apply to more than just 'no-option' patients, i.e. as something to be offered as a pre-emptive measure? "I can imagine three scenarios," she replied. "One is actually that the patient is no-option or poor-option (i.e. endovascular or operation are high risk options). High risk can mean either that the operation has a high risk of itself, or that it has a high risk of failure. The second scenario would be to use these cells in combination with endovascular or surgical therapy to improve their outcome. The third option could be a stand-alone therapy in earlier stages of PAD.

"Yet, the ideal stage for the treatment with angiogenic therapies needs to be defined – for some of the CLI patients it may be already too late. We just finished recruitment of claudication patients. During this year, 2017, we will start the CLI trial; we will have the study investigator meeting in March. We will include CLI patients with poor option, both endovascular or surgical. We need centres referring those CLI patients to the sites participating to the study and may need more active study centres."

This latest phase III CLI trial is a randomised, double-blind, multicentre, placebo-controlled, parallel-group study to evaluate the efficacy, tolerability and safety of intramuscular injections of placental-derived stem cells for the treatment of subjects with CLI with minor tissue loss who are unsuitable for revascularisation. Forty participating sites

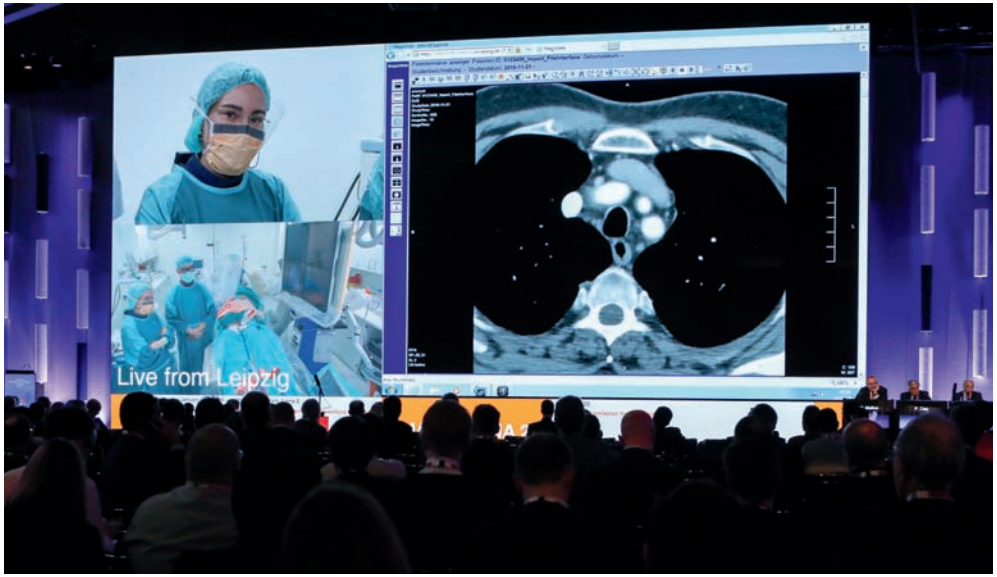
"Not only are the number of stem cells in these patients (being sick with cardiovascular disease including PAD) lower than in the normal population, but also the quality of these cells is different." Sigrid Nikol

are located in Germany, UK, US, Poland, Hungary, Czech Republic and Austria, and total recruitment is expected to be around 250. The intervention arm will receive doses in the affected leg intramuscularly, twice, at an eight-week interval. Follow-up will continue for 12 to 36 months, with a primary endpoint of time to occurrence of major amputation of the index leg or death and secondary endpoints of pain, wound healing, quality-of-life; and perfusion parameters (TcPO2).

One issue that pervades cell therapy is the survival time of the administered cells themselves, after finding themselves within the ischaemic environment. "Of course, these cells can only secrete growth factors as long as they remain alive," noted Professor Nikol. "They don't stay there forever. The less reaction you have against these cells, the longer they stay alive. But of course it is a matter of weeks and then they are probably faded. Some researchers have started to encapsulate cells for therapy in order to enhance their lifespan in the body. Apparently that does work. It may enhance the biological effect and extend the time interval between those intramuscular cell injections."

In previous decades, Professor Nikol was involved with gene therapy research for CLI – work that culminated in 2011 in the TAMARIS trial, the largest clinical trial of gene therapy for CLI patients with ischaemic skin lesions. "I was involved with gene therapy for more than 20 years," she recounted. "I started with animal experiments and then moved on to clinical trials. We really thought we might be successful with angiogenic gene therapy. Some of the animal experiments really looked good, and even some of the phase II trials confirmed those results, until we did the phase III TAMARIS trial. There, the good result we had in the phase II trial – of a significantly reduced risk for major amputation and death in 125 patients – could not be translated into phase III with 525 patients. This was extremely disappointing."

As a result, pharma companies pulled out of gene therapy altogether. Yet, it did provide valuable lessons in how to design those angiogenesis trials as well as the characterisation of no-option and poor option CLI patients. Deciphering why gene therapy angiogenesis might not have worked, Professor Nikol suggested: "Just one single growth factor was enhanced with gene therapy. But we know that angiogenesis is multifactorial process, a cascade of many factors. So maybe it is simply not enough to enhance one single growth factor. In contrast, cells tested here secrete a cocktail of growth factors, which is more likely to work."



Concluding with her thoughts on future directions, Professor Nikol noted that a broader range of cell sources needs to be investigated. "The unanswered question is, which cells are the best? Neuronal stem cells, or cells derived from adipose tissue are among others that are being investigated. Some may be genetically modified, such as neuronal stem cells genetically modified to overexpress certain growth factors. Embryonic stem cells have also been considered. They are not used for ethical reasons, but we do have other stem cells with similar characteristics, such as germ line stem cells derived from ovaries and testes." Regardless of the source, allogeneic cell therapies could be a central treatment option for large numbers of patients with PAD.

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"We had to look for other cell sources; therefore, trials using placenta-derived stem cells as an alternative to autologous cells are promising." Sigrid Nikol

Micro-infusion device puts best foot forward in trials

Updates from several studies using the Bullfrog Micro-Infusion Device from Mercator MedSystems (USA) were presented this year at LINC, hoping to demonstrate the therapeutic potential of injecting therapeutic agents directly, non-systemically and safely through blood vessel walls into adventitial tissues.[1]

The Bullfrog device has a microneedle tip, oriented perpendicularly to the length of a balloon, which is concealed and protected until required. Using two atmosphere inflation pressure (low enough to avoid trauma to the vessel wall), the injection needle is then unveiled at the appropriate vessel site.[1] "The Bullfrog device, and micro-infusion in general, appear to offer the next generation of therapy for peripheral artery disease and critical limb ischemia, above and beyond the first generation of drug therapy with drug-coated balloons and stents," noted Ian Cawich (Arkansas Heart Hospital, Little Rock, AR, USA).

"Since the device is not specifically tied to one drug, like paclitaxel-coated balloons, it can efficiently target tissue with medications that are intended to counteract the disease process more precisely. As an example, the DANCE and LIMBO trials have been designed, and are showing, that dexamethasone targeting of inflammation (the immediate consequence of mechanical revascularisation) is producing strong benefits over standard therapy without drug."

Dr Cawich focussed primarily on the TANGO trial – a prospective, multi-centre, randomised, dose escalation study of temsirolimus after revisualisation of BTK-CLI lesions. "The trial is designed to enrol 20 subjects in each of three groups: saline control, low-dose temsirolimus, and high-dose temsirolimus," he described.

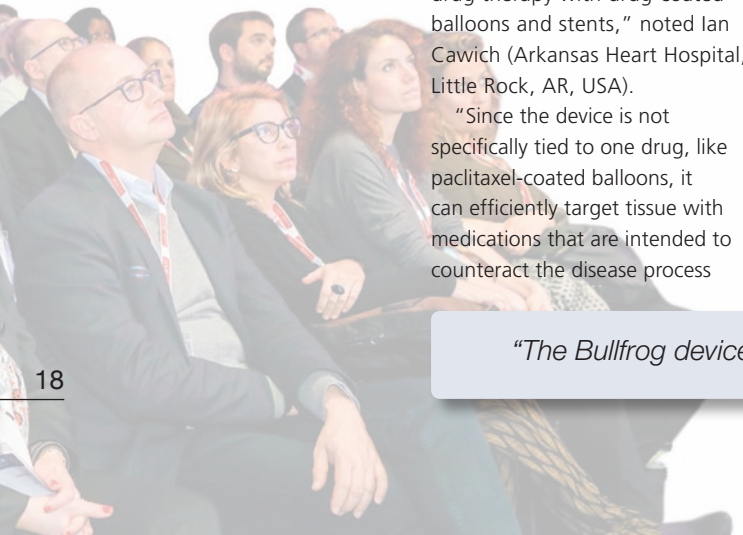
"Randomisation (2:1) of treatment to control will continue throughout the study, with a dose escalation decision to be made after the full enrolment of the low-dose group. The study will include Rutherford 3, 4, or 5 subjects, with atherectomy as needed, and will study up to 25 cm lesions in distal popliteal and tibial or peroneal arteries (below the knee joint space). The primary safety endpoint is 30-day safety by freedom from major adverse limb event or post-operative death and the primary efficacy endpoint will be determined by angiographic transverse-view vessel area loss (TVAL) at six months, or prior to six months in the case of any target lesion revascularsation. Since we are allowing up to 25 cm lesions and allowing the use of atherectomy, we expect a fairly real-world population of subjects enrolled in the trial."


Ian Cawich

Dr Cawich went on to note that the variety of therapeutic agents that can be delivered by the Bullfrog device is testament to why it is being featured in so much study. He expanded on this point: "In fact, ongoing clinical trials in the U.S. will now include the use of three different therapeutic agents (dexamethasone, temsirolimus, and vonapanitase) delivered by Bullfrog into the lower limb, and an ongoing clinical trial in the U.S. is utilizing a stem cell for improvement of outcomes in acute myocardial infarction."

Confident that the Bullfrog device could easily become integrated into the standard treatment regimen once data is published from the major trials, Dr Cawich noted that the potential for combination therapies with atherectomy or angioplasty is also intriguing: "It has been seen from the DANCE trial that there may be distinct benefits for some subjects to couple atherectomy techniques with Bullfrog, while Bullfrog with angioplasty alone appears to provide similar results to the current generation of drug-coated balloons (although the final analysis of those statistics is yet to be completed). Personally, I am looking forward to testing the device with temsirolimus, to

"The Bullfrog device, and micro-infusion in general, appear to offer the next generation of therapy for [PAD] and [CLI]." Ian Cawich



George Adams

see what the drug can do in two different doses."

Looking ahead, he commented on what we can expect: "In the future, we hope to study whether some patients may have a better result with an anti-proliferative agent, while other patients may do well with anti-inflammatories. That is all yet to be shown, but confirms for me that the future of this therapy is exciting."

Dr Cawich concluded: "The device is being studied extensively with dexamethasone in the LIMBO studies and in some planned registries for above the knee use. The Bullfrog has both a 510(k) and CE mark already, so we can already use it in cases outside of the clinical trials being performed. Further to that, the company is pursuing regulatory standing for the delivery of particular drugs and will surely be releasing the product for general use once the data has been presented.

"For now, dexamethasone appears to provide the necessary benefit to get it used in the clinical setting; temsirolimus may lead to positive outcomes given the efficiency in delivery offered by the Bullfrog; and then the use of other drugs, biologics or drug combinations are on the horizon as possible options for further

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"For now, dexamethasone appears to provide the necessary benefit to get it used in the clinical setting." Ian Cawich

Micro-infusion device puts best foot forward in trials

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improvement, if that is possible."

DANCE 12-month data unveiled

First-time data release from the DANCE trial,[2] which used the Bullfrog device in the SFA/popliteal arteries, was presented by George Adams (Rex Healthcare, Raleigh, NC, USA) during the session 'Drug-eluting devices for prevention of restenosis – the new standard for femoropopliteal interventions in claudicants'.

Dr Adams began by framing the need for such devices, saying: "Approximately 27-million people in Europe and North America have peripheral arterial disease, resulting in around 1-million endovascular lower extremity interventions every year. Studies have shown local luminal drug delivery with drug-coated balloons [DCBs] and stents [DES] have improved patency rates above the knee. However, when you look personalisation of care, there is a paucity of data especially looking at patients who have high inflammatory states, such as women and diabetics, as well as those with long lesions, heavy calcifications, chronic total occlusions, and then people treated with atherectomy."

Getting to the meat of Bullfrog's potential, he added: "Adventitial drug delivery of dexamethasone is proposed as a baseline therapy to treat these highly-inflammatory populations, and increase patency." As Dr Adams described, restenosis results from the inflammatory cascade – a sequence of events that begins with inflammatory mediators recruited after angioplasty or stenting. Recruitment of smooth muscle cells leads to proliferation to the intima, causing hyperplasia/narrowing of the vessel. "Dexamethasone is proposed to eliminate the upstream inflammatory process, thereby eliminating the downstream effect," he added.

Trials for Bullfrog include TANGO, the European LIMBO-PTA and US LIMBO-ATX studies (dexamethasone; below the knee [BTK]), PRT-201-115 (Proteon; vonapanitase BTK), and the upcoming TWIST combinationtherapy trial. Sitting in with these studies is the DANCE trial – a multicentre, open-label trial in two populations: primary atherectomy (ATX) and primary angioplasty (PTA).

Key eligibility criteria of the trial includes: Age >18 years, Rutherford 2-4 class, de novo or non-stented restenotic SFA or popliteal lesions (>70% stenosis, ≤15 cm length), with reference diameter 3-8 mm; no prior bypass, stenting or DCB of target lesion; no acute thrombus or acute limb ischaemia; and no concurrent use of drug-eluting products in the target limb.

"This is a unique trial design," continued Dr Adams, "we had two parallel groups: one atherectomy in which we in enrolled 157 patients, and one angioplasty group which was 124 patients. In both cases we added dexamethasone treatment after endovascular intervention. This was compared to historical, matched drug-coated balloon patients. We did blood draws for changes in biomarkers at 24-hours and four weeks, and there was clinical and haemodynamic duplex ultrasound at 6, 12, 18 and 24 months."

As Dr Adams detailed, primary safety endpoints for the trial were a composite of freedom from all cause peri-operative (30 day) death, and freedom at one year in the index limb from major amputation BTK or ATK (above the knee), bypass surgery or thrombolysis. Primary efficacy was set as primary patency of the target lesion at one year, tested with core lab-adjudicated absence of binary restenosis (DUS PSVR > 2.4 or angiographic narrowing >50%) and freedom from clinically-driven target lesion revascularisation (CD-TLR).

Looking at the demographics, Dr Adams highlighted a few points, one being the presence of a 'sicker' population in the atherectomy group, as observed by a higher proportions of Rutherford 4 or TASC B/C/D lesions.

Jumping into the results, Dr Adams relayed the findings: "With regards to the 12-month safety endpoints, there were no device-related or drug-related serious adverse events, and the major adverse limb events were extremely low, as well as death from either a cardiovascular or non-cardiovascular means also being low."

Moving on to primary efficacy endpoints at 12- and 13-months, Dr Adams focused on the latter, noting: "Looking at the Kaplan-Meier estimate, freedom from TLR in the atherectomy group was 88.7%, compared to the balloon angioplasty of 89.1%. In terms of primary patency in the atherectomy group, it was 80% compared to 78.2% in the angioplasty group. Not much different than that we've seen in the drug-coated balloon trials."

Harking back to the notion that women and diabetics may have a higher inflammatory state, Dr Adams shared that the DANCE results showed no apparent difference between men and women, as well as diabetics and non-diabetics at the 13-month endpoint. He continued: "Looking at the stented versus the non-stented group … there was no significant difference in primary patency, which suggests that adding dexamethasone may enhance unstented patency, and stented patency alike."

Dr Adams offered his conclusions: "In summary, the addition of dexamethasone in DANCE has produced positive results in both primary atherectomy (in a challenging patient population) and primary angioplasty intervention. The paradigm shift [is] direct targeting of the adventitia with efficient delivery – using this Bullfrog device, and an anti-inflammatory drug (dexamethasone) – quells inflammation to improve patency after revascularisation."

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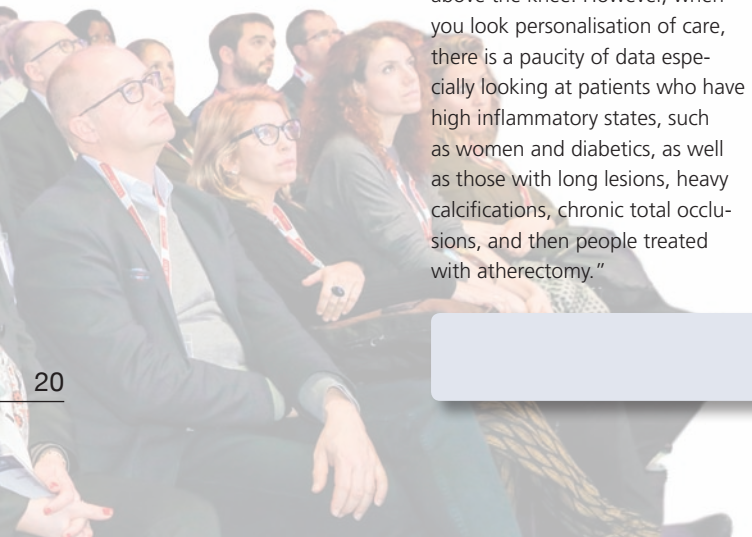

"…using this Bullfrog device, and an anti-inflammatory drug (dexamethasone) – quells inflammation to improve patency after revascularisation." George Adams

Acute DVT: Live from Galway

An acute iliofemoral deep vein thrombosis (DVT) case in a 74-year-old female patient was presented during a dedicated DVT session at LINC 2017, with Gerard O'Sullivan and his team at Galway University Hospital, Ireland, joining a packed audience in Main Arena 2. "This is an interesting one," he said, adding: "She presented with leg swelling just around the new year. She went to the hospital, had an ultrasound, was reassured and sent home. She came back five days later and it was positive.

"Assuming that the person doing the ultrasound the first time knew what they were doing, this implies that this is a descending deep vein thrombosis. And I have come to realise over the years that I am seeing more and more of these, and that is because there is a proximal stenotic lesion – a crossing point – as many of these patients have."

The patient's CTPA was clear, and the CTV showed lots of thrombus in the IVC, with occluded common and external iliac veins, and quite a lot of inflammation around the groin.

"The reason the thrombus in the internal iliac is important is because for years this patient has had a near occlusion of the common iliac, and she has been draining through her internal iliac to the contralateral side. So when the internal iliac thromboses, that is when she becomes symptomatic."


Gerard O'Sullivan

Dr O'Sullivan noted that, interestingly, over the previous two-to-three weeks before the case, the patient had low molecular weight heparin, and things had improved substantially. There was little if any thrombus in the thigh, and a narrowed segment in the external iliac. There were some filling defects in the common femoral, and then a longstanding occlusion.

She had a "rather typical" thrombus along the wall of the external iliac vein, and then good cross-pelvic filing. "Indeed her leg symptoms have gone down considerably in the past three weeks because she has reopened her collateral pathways. The common iliac has been occluded for a long time," said Dr O'Sullivan.

At that time, session co-moderator Iris Baumgartner (Switzerland) posed a question: "What made you step out of the 'filter business'… I saw that you have no filter placed?"

Dr O'Sullivan responded: "That is a good point. I think early in one's experience, using a filter is quite a good idea."

He added: "But my rules for using filters now are right ventricular strain, large-volume pulmonary embolus, considerable IVC thrombus – not just a tongue projecting into the IVC. And then the last one is a bit more difficult: if there is no proximal stenosing segment. In this patient clearly there is a longstanding stenosis of the common iliac vein… we know that there has not been a pulmonary embolus

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"I now balloon dilate to the nominal diameter of the stent straight off. I don't do sequential dilatation anymore because I don't think it is of any benefit." Gerard O'Sullivan

Acute DVT: Live from Galway

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based on CTPA, and therefore from my point of view this is a safe case to not use a filter."

Describing the plan ahead, Dr O'Sullivan and his team planned to puncture the popliteal vein under ultrasound guidance, insert a 10F sheath, and 5000u of IV heparin. "Because the lesion is very well defined I will probably not use IVUS in this particular instance; we will use large-bore stents," he said.

For removal of the thrombus, the Penumbra (USA) Indigo Mechanical Thrombectomy System (8F) was selected. Touching upon the selective nature of the device's aspiration, Dr O'Sullivan continued: "What this device does differently, is it has a separator, so when it hits thrombus, it sucks it out, but when you are in blood, you get an indication that you should not be sucking.

"But it is much more sophisticated than that. It has got fantastic results in the cerebral circulation, pretty impressive results in the arterial circulation, and now they are moving into the venous sphere. So I think this is an interesting device."

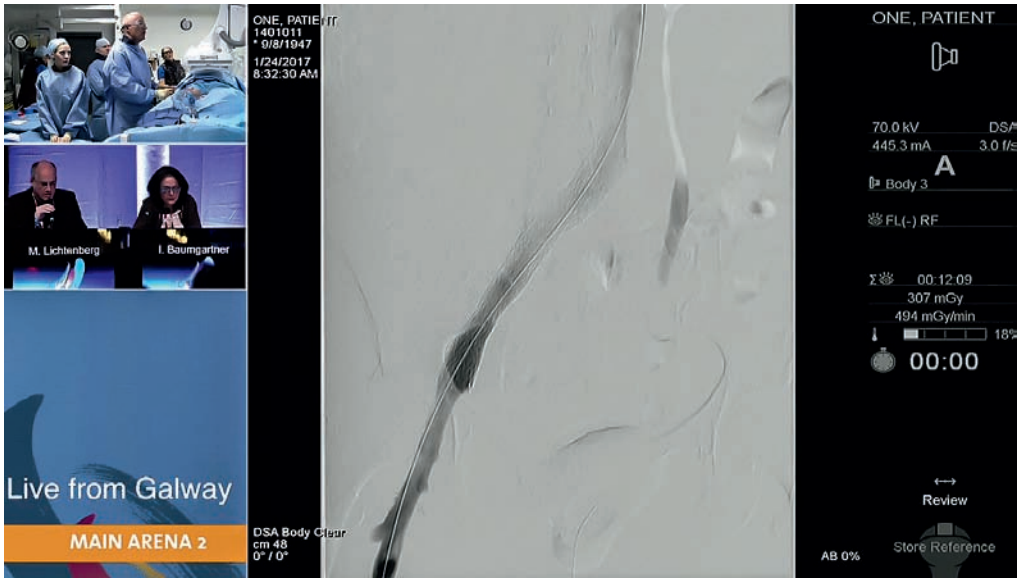
Following use of the Indigo, the team planned to use a Bard (USA) VENOVO stent. "It's a one-handed deployment device, and comes in a wide variety of lengths and diameters," Dr O'Sullivan described, adding: "It has got a slightly flared end with markers, so it maybe a little easier to see that some of the other stents."

After a short break to let them work, Main Arena 2 re-joined the Galway team for an update on the procedure. At that time, thrombus removal had been completed using the Indigo device, the chronic occlusion crossed, and balloon pre-dilatation was initiated.

Commenting on his dilatation technique, Dr O'Sullivan noted: "One of the things that I have done differently over the last few years is I now balloon dilate to the nominal diameter of the stent straight off. I don't do sequential dilatation anymore because I don't think it is of any benefit."

He added: "You should dilate the lesion first, up to the diameter of the stent that you wish to put In, rather than expecting the stent to do the work afterwards. Because quite honestly, it won't."

As the balloon was deflated, co-moderator Michael Lichtenberg (Germany) jumped in to pose a question: "You just showed us a very good tip/trick with the deflating balloon that you pulled back,



Angiogram after placement of the VENOVO stent

which shows you there is still an underlying problem. Is that your usual approach to find out if there is still a high-grade stenosis?"

Dr O'Sullivan replied: "It proves to you that it is there … I think the thing I have learned over the last couple of years is that although we call this an 'acute DVT', there is always an underlying chronic lesion, and that is important to recognise, because if you don't address that lesion, the patient will re-thrombose. That is why patients treated with anticoagulation alone do very poorly."

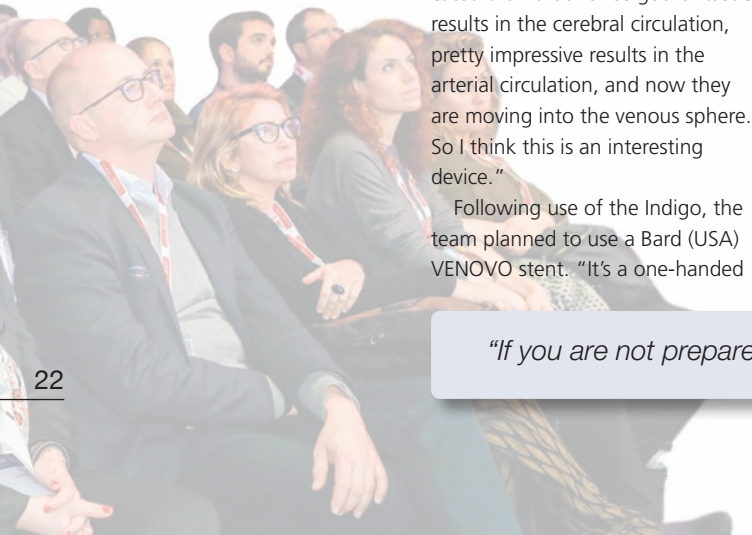
He added: "In a way, if you are not prepared to stent, then in the majority of cases – certainly after thrombectomy – you are going to fail."

Before stenting began, Dr O'Sullivan estimated he would need to go as far as the femoral head. Indeed, the size of the collaterals suggested that the lesion had been there for quite some time.

"I'm stenting up a little bit higher because there was a little 'nubbin' of thrombus into the IVC, and while I thought that would have gone away, but in fact it felt quite resistant with the catheter," he said.

As he introduced the VENOVO stent, Dr O'Sullivan noted its straightforward deployment, with very little foreshortening. In addition, Dr Lichtenberg highlighted the advantageous full-lesion coverage of the stent due its longer design.

As the team began the final post-dilatation, the panel commented on a very slick case: "A perfect result," said Dr Lichtenberg.



"If you are not prepared to stent, then in the majority of cases – certainly after thrombectomy – you are going to fail." Gerard O'Sullivan

Mechanical debulking for arterial & venous occlusions

Live surgery, the sharing of clinical experiences, and expert talks on the mechanical debulking of occluded vessels provided the subject matter for this year's Straub Medical symposium on 'The therapeutic benefit of effective debulking in arteries and veins'.

Moderating the session was expert angiologist, Thomas Zeller (Department of Angiology, University Heart-Center Freiburg, Bad Krozingen, Germany), who also gave a talk on 'Why do I use mechanical debulking for the treatment of arterial occlusions?' He was joined by fellow speakers Marcus Treitl (Institute for Clinical Radiology, University Hospitals of Munich, Germany), and Sven Bräunlich (Park Hospital Leipzig, Germany). Live surgery was also transmitted from Sankt-Gertrauden-Hospital, Berlin, and St. Franziskus Hospital, Munster, Germany.


Thomas Zeller


Marcus Treitl

Straub Medical's endovascular rotational catheter systems, Rotarex®S and Aspirex®S were discussed for their ability to restore blood flow in occluded blood vessels by mechanically breaking up thrombi then aspirating and transporting the debris via the catheter into a collecting bag outside of a patient's body. As a strong and rapid mechanical debulker, Rotarex S is used in arteries, for occluded stents and grafts, and the less aggressive Aspirex S offers the same effective solution for acute occlusions in both arterial and venous systems. The debulking occurs at a rate of up to 1 cm per second, depending on the consistency of the occlusion material.

Professor Zeller highlighted cases where mechanical debulking in the arterial system played an important part in improving outcomes in the case of 'hostile' lesions. These tend to be heavily calcified, and include in-stent restenoses, in-stent reocclusions, chronic total occlusions, and lesions containing soft plaque and thrombi. The procedural goals for medical debulking in these clinical challenges are the avoidance of stenting, as well as improving drug elution, and modifying vessel compliance.

Regarding drug elution, Professor Zeller suggested that, "removing thrombus or modifying its presence may be a promising approach in enhancing drug eluting stent or drug coated balloon effectiveness". He went on to explain that paclitaxel diffusivity is significantly diminished when clots are fresh and have a high level of red blood cells, due to the red blood cells cross-linking with fibrin in the thrombus. For this reason, the removal of fresh clots is particularly important before using a drug-coated balloon.

Turning to the prevention of distal embolisation, which can happen with many types of femoropopliteal intervention, and can be associated with devastating sequalae, Professor Zeller stated the risk posed to patients was not only present when treating occlusions in the native artery, but also when treating in-stent restenosis or re-occluded lesions.

He gave an account of a fresh occlusion of the superficial femoral artery that had been successfully treated with aspiration thrombectomy and balloon angioplasty. Despite this treatment, "it is not uncommon to see an embolic particle located at the bifurcation of the anterior tibial artery and the tibial peroneal trunk, and this needs to be removed otherwise the patient will be harmed," said Professor

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"If you don't remove the thrombus it can go downstream, and the best preventive measure of avoiding embolic events with recanalisation of fresh total occlusions is to use Rotarex." Thomas Zeller

Mechanical debulking for arterial & venous occlusions

Continued from page 23

Zeller. He added: "If you don't remove the thrombus it can go downstream, and the best preventive measure of avoiding embolic events with recanalisation of fresh total occlusions is to use Rotarex."

Economic benefits with mechanical debulking

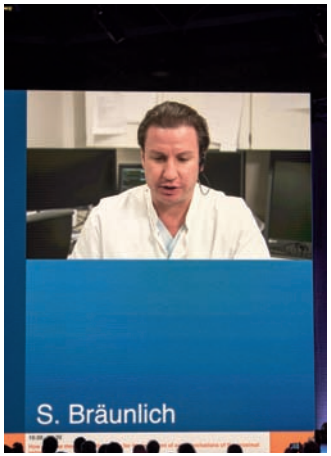
From a health economic point of view, studies on femoropopliteal arteries have shown that the use of mechanical thrombectomy (versus lytics) can reduce the length of a patient's stay in the hospital and as well as catheter intervention time. One study (Wissgott, 2008[1]) showed that conducting mechanical thrombectomy with Rotarex can reduce mean hospital stay to 2.3 days compared to lytics where the mean stay was 8.5 days. Referring to the potential benefits of using mechanical thrombectomy, Professor Zeller pointed out that, "you have 'no stay' in the intermediate care unit, and no lytics, so there's no increased risk of bleeding, and potentially you need fewer balloons and stents."

Professor Zeller drew his presentation to a close by taking the audience through a treatment algorithm in managing thrombotic femoropopliteal occlusions that he uses at University Heart-Center Freiburg. He explained that fresh occlusions are treated by mechanical debulking as a first choice, while second choice would be use of rotational aspiration atherectomy followed by drug-coated balloon. If, after rotational aspiration atherectomy, there is residual thrombus, lysis is given followed by use of a drug-coated balloon.

In the case of in-stent lesions, the choice of whether mechanical debulking is required upfront, depends on whether the case in question is an occlusion or stenosis. If it is an occlusion, then mechanical debulking is used first; a stenosis is treated directly with drug-coated balloon.

Mechanical debulking and acute occlusions of proximal veins

The treatment of acute occlusions of the proximal veins with mechanical debulking was the subject of Professor Treitl's presentation. After an overview of the available treatment options, ranging from conservative approaches such as low molecular weight heparin followed with long-term anticoagulation, he went on to discuss invasive treatments, namely, pharmaco-mechanical thrombolysis and



mechanical thrombectomy.

The benefits of using mechanical debulking were highlighted, these included:

- Fast relief of acute symptoms
- Salvage of valve function
- Greater prevention of post-thrombotic syndrome
- Immediate restoration of blood flow
- No systemic complications such as bleeding
- No intensive care unit stay

Turning to which rotational debulking device to use and when to use it, Professor Treitl pointed out that he uses Aspirex for fresh thrombi (up to two weeks old) and Rotarex for chronic, organised occlusions (between two weeks to six months old). He continued by providing his tips for using the devices in relation to particular clinical indications. These included that the Rotarex can handle older thrombi, but due to its sharpness is primarily used in the arterial system; Aspirex, a "softer" device, handles fresh thrombi and is the choice for the venous system. He pointed out that during the run of the catheter it was important to bear in mind that because the blood flow cooled the catheter, if the device warmed up then it could indicate insufficient flow. In this case sodium chloride infusion should be considered in occluded venous segments.

Professor Treitl gave an account of the clinical experience of his team with Aspirex in treating proximal vein occlusions. Together they had treated 37 patients with iliofemoral or upper extremity deep vein thrombosis but had not seen any pulmonary embolisms during treatment. They had used a mean of five passages and had achieved a technical success rate of 81%. In seven cases, they had switched to pharmaco-mechanical thrombolysis due to the older age of the thrombus. Overall, their work had achieved a primary patency rate of 89.2% after eight months of follow-up.

After showing a treatment algorithm for managing proximal vein occlusions, Professor Treitl concluded that Aspirex is the system of choice for the venous arena. "[Mechanical thrombectomy] is a very safe and feasible procedure. It is especially valuable in patients with contraindications for thrombolysis. The key to success is the age of the thrombus with less than 14 days being optimal."

Mechanical debulking of arterial occlusions

Discussing his experience with the Rotarex catheter in Leipzig, Dr Bräunlich pointed out that it resulted in a high procedural success rate of 94.7%. "The Rotarex is safe and effective in a broad range of lesions," he said.

He also emphasised that the 12-month target lesion revascularisation (TLR) rate of 10.6%, together with a marked improvement of the clinical status, demonstrates the clinical effectiveness of Rotarex mechanical debulking in arteries.

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"[Mechanical thrombectomy] is a very safe and feasible procedure. It is especially valuable in patients with contraindications for thrombolysis. The key to success is the age of the thrombus". Marcus Treitl

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CCT@LINC demonstrates the Japanese approach

CCT (Complex Cardiovascular Therapies) has been held annually in Japan since 2001, founded with the motto of 'Challenge and innovation'. The live demonstration course is the biggest live course in Asia at present, with over 4,500 participants, drawing increasing participation from overseas in the learning experience that spans cardiovascular and endovascular diseases.

CCT merged with LINC in a joint session that explored the Japanese perspectives for endovascular treatment. The session delivered a number of case presentations, a pre-recorded live case, and a discussion of strategies in chronic total occlusion (CTO) crossing and aggressive treatment for below-the-ankle CLI interventions.

Hiroshi Ando (Kasukabe Chuo General Hospital, Japan) was on the panel of peripheral course directors for last year's meeting. He explained to *LINC Review*: "The peripheral course was newly organised in 2013. CCT peripheral shares the spirit of CCT, with challenges and severe cases in the live course.

"In the last live course, Professor Giancarlo Biamino participated as special guest. He also gave valuable comments as a cath-lab commentator. CCT peripheral is and will be closely connected to the major meetings, such as LINC and VIVA.

"We will try to make the [upcoming] CCT meeting more splendid. I expect many participants will attend CCT 2017, which will be held in Kobe, Japan from 26 to 28 October."

During the CCT@LINC session, Dr Ando spoke on the role of distal puncture in crossing the 'uncrossable' CTO, as well as presenting a clinical case and participation in panel discussion.

Reasons for failure of CTO crossing are understood to include factors such as device buckling during initial puncture (due to the presence of tough fibrous CTO cap), inadequate visualisation, as well as the inability to actively navigate through the CTO (due to the presence of calcification or tortuosity).[1]

"The common reason for failure in passing CTO lesion in endovascular therapy is the same as that in percutaneous coronary intervention," noted Dr Ando. "However, in coronary cases, if we succeed in passing the wire and externalisation, we can almost certainly pass the next device.

"In endovascular therapy on the other hand, as there are many dialysis patients in Japan, it often happens that in lesions with severe calcification, we can cross the guidewire, but no other device can pass thorough."

Atherectomy devices present one option in such cases, although they are not currently available in Japan. Continued innovation has led Japan down a unique path, with various methods being invented to cross devices through challenging CTO, explained Dr Ando: "Some of these methods are the 'Needle cracking technique', and the 'BAD FORM technique', which I presented at LINC last year."

In thinking about procedural success in CTO treatment, operator skill is important – the difference between highly-skilled operators (who typically achieve a CTO success rate of 90-95%) compared to those with less experience (where procedural success varies but can be as low as 50%), demands an emphasis on teaching and demonstration, noted Dr Ando. "For the improvement of beginners' treatment results, the most important thing is, after all, to increase specialists' treatments and views. The role of the live demonstration course is meaningful. It is also significant to simulate the treatment

"CCT peripheral is and will be closely connected to the major meetings, such as LINC and VIVA." Hiroshi Ando

before doing it practically."

The session included case presentations demonstrating CTO decision-making strategies in a number of clinical scenarios. Describing his experience of CTO treatment, Dr Ando outlined his basic step-wise strategy: "I basically use 0.014 inch guidewires, because I have conducted PCI as a cardiologist for many years. CTO cases are no exception."

A variety of these are on the market, including Terumo's Run-through Ph, Asahi Intecc's Cruise, Lifeline's Wizard PV, and Kaneka's Athlete Ruby.

"I choose a hydrophilic guidewire with 3g tip load as a first wire, supported by a microcatheter. When the wire cannot advance in this way, if there seems to be a micro channel, I change it with a soft tapered one, and select a stiffer one for abruptly severe occlusion.

"We can choose a suitable guidewire according to lesion, because there are various 0.014 inch wires in Japan. When the antegrade approach is unsuccessful, we conduct a distal puncture early. In such a case, we use the 0.014 inch guidewire only with the back-up support of a micro-catheter. This is called the 'sheathless approach'. Sometimes we prick on the metatarsal artery or planter artery.

"One key to success in CTO is the bidirectional approach, therefore it is very important to be familiar with distal puncture. In endovascular therapy, it is also important to estimate lesion size and the deployment position of the stent by IVUS and contrast."

The continued development of devices and technique has meant that CTO can now be opened up with a high probability, noted Dr Ando. The newest challenge, he explained, lies in keeping the treated vessel patent in the mid- and longer-term.

"I don't think we succeed in keeping it open, as in PCI," he said, concluding: "In the future, the main point will change from 'how to open' to 'how to keep it open'. To be honest, I don't have an obvious solution for that."

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"For the improvement of beginners' treatment results… the role of the live demonstration course is meaningful." Hiroshi Ando

Bern: Thoracic inlet syndrome/in-stent thrombosis

University Hospital Bern's Heart and Vascular Center (Switzerland) was the scene of a live case carried out by Nils Kucher, Torsten Fuß and team, during a session dedicated to the topic of central venous stenosis of the chest.

A 46-year-old female patient had suffered a spontaneous upper extremity deep vein thrombosis in mid-2015 (due to Paget-Schroetter syndrome), undergoing lysis and anticoagulation therapy. Case work-up at the time identified a bony exostosis of the first rib and clavicular, demanding resection of the first rib in order for stenting of the subclavian vein to be performed (this occurring in late 2015). Following cessation of anticoagulation, recurrent swelling of the right arm occurred and was treated by thrombus aspiration in a tertiary care hospital in late 2016.

Presently, she had been suffered swelling of the right arm for several weeks. CT imaging evidenced regrowth of the first rib stump of around 1.5 cm, advancement which may have been compromising the integrity of the previously placed stent – a relatively low radial force Sinus SuperFlex 12 mm. Duplex ultrasound demonstrated in-stent flow acceleration as an indicator of in-stent stenosis.

The team gained access to the subclavian vein via the femoral vein, placing a 10 French sheath and crossing the stent with a 0.035" stiff angled Terumo wire (Terumo, Tokyo, Japan). Angiographic imaging was carried out in the 'arm-up' and 'arm-down' positions, with arm-up clearly indicating the stenotic region (Figure 1).

Asked how the team arrived at the conclusion that the regrown rib stump was the cause of the stenosis, Professor Kucher responded: "We looked carefully at the CT; what we saw was that the first rib – the stump – is in close proximity to the stent. It doesn't look like the stent is really compressed by the first rib. But we have to say that it is not really a dedicated venous stent. It is a Sinus SuperFlex, which is known to have basically no radial force, but is highly flexible.

"After the first rib was resected, because of the poor flow we put the stent in to keep the vein open. Anticoagulation was fine for six months but then she re-thrombosed. So we believe that the main problem now is the radial force of the stent. We can still go for re-surgery to take the stump out, but we thought we would place a stent-in-stent with a high radial force, and then we should be okay."

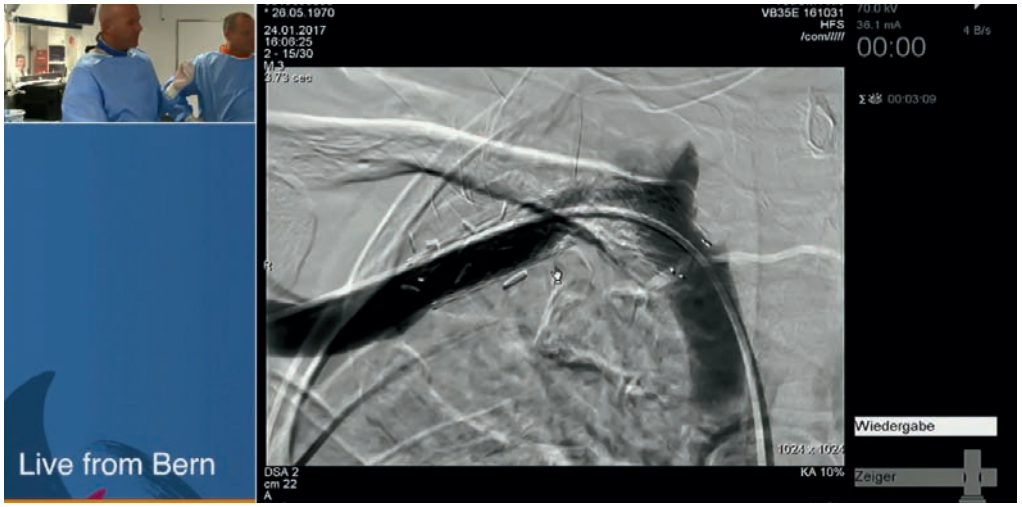


Figure 1. Angiographic image with arm in abducted position, illustrating stent narrowing.

With arm down, IVUS showed the stent to be heavily compressed, and then confirmed the near-collapsed state of the stent during arm-up positioning. The team opted for a Vici Venous stent (Veniti, USA), a dedicated venous stent with high radial stiffness yet remaining relatively flexible.

The Vici stent was advanced through the previously-placed stent over the curve of the subclavian vein and released. Professor Kucher commented: "One thing I don't like about the Vici stent, because of its closed-cell design with flexible interconnections, is that it foreshortens. You see the stent is only 6 cm long, but in the sheath it is 20% longer. It will foreshorten at the final stage of releasing the stent."

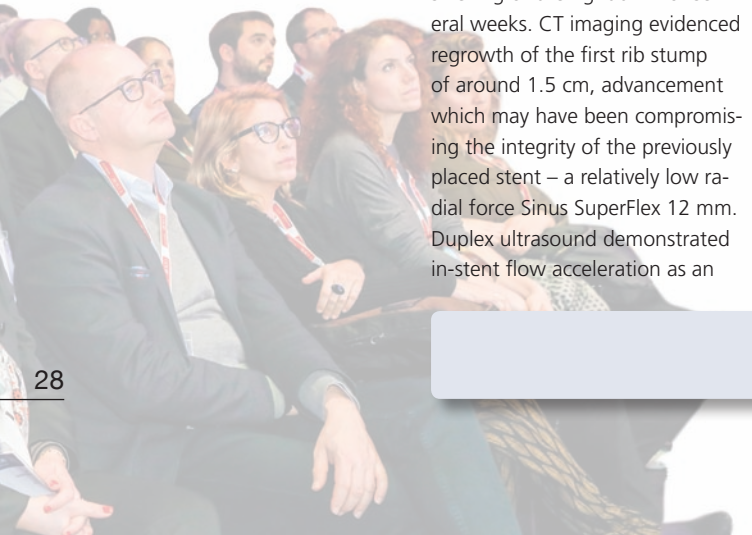
Session co-moderator Andrew Holden (Auckland, New Zealand) posed the question: "How often do you use a groin approach as opposed to an upper limb approach – is there any particular advantage to the groin approach?"

"Groin approach is much easier when you have a stent in place," responded Professor Kucher. "For the acute cases, we always use cubital access at the arm (also to have proper venograms). But for reinterventions, we always go for femoral.

"For chronic occlusions it is different. We also use arm access, and we have access in the groin as well to have basically the pull-through technique, because sometimes it is very difficult to advance the material. You see that even the Vici stent has a problem to open up after the first predilation."

To address this, a high pressure (20 atm) balloon was used to post-dilate the stent, with the patient under remifentanil analgesia.

"Anticoagulation was fine for six months but then she re-thrombosed. So we believe that the main problem now is the radial force of the stent." Nils Kucher



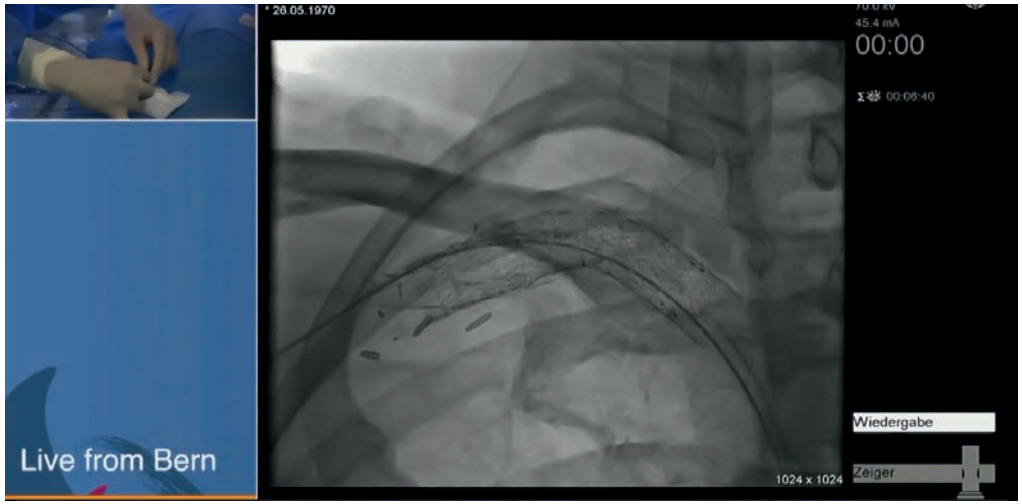


Figure 2. The post-dilated Vici stent.


Nils Kucher

"This is an acceptable result," confirmed Professor Kucher, concluding the case with a final venogram. (Figure 2)

"Do you have any feel for the long-term result of stenting in the upper limb?" Asked Session co-moderator Stephen Black (London, UK). "This looks lovely – it has opened up nicely – but we have all been nervous over the years about stenting in the upper limb.

"I would never place a venous stent in a patient with thoracic outlet syndrome where the first rib is still in place. I would only consider stenting if the first rib was resected. For patients with other pathologies (e.g. catheter-associated deep vein thrombosis (DVT) with post-thrombotic syndrome (PTS)) I am not afraid of using stents. But there is only very sparse data on the patency rates. The only few papers with 10-20 patients report patency rates up to one year which are close to 80%.

"An important take-home message for us all, particularly behind the clavicle, is that you are not prepared to put a stent in there unless that first rib anteriorly is resected," summarised Dr Holden. "And of course we now how stents such as the Vici that are likely to perform more favourably. So maybe there has been a paradigm shift with our new stent devices."

The question of rib resection in venous thoracic outlet syndrome was addressed in a study of 23 patients carried out by Professor Kucher and colleagues, with the aim of ascertaining whether or not the surgical procedure is required in all patients with upper extremity DVT. The study found excellent results (freedom from PTS >90% at one year) when performing surgical decompression only in symptomatic patients with rethrombosis or restenosis.[1]

Commenting on this study, Dr Holden said: "I've seen a couple of other publications similar to this excellent study, where they have done the thrombolysis, thrombectomy, anticoagulated the patient, and then restudied them at about three months, only considering rib resection where there is a persistent stenosis. Your protocol

Continued on page 30

"I would never place a venous stent in a patient with thoracic outlet syndrome where the first rib is still in place." Nils Kucher

Continued from page 29

suggests that you don't even need to do that."

Professor Kucher responded: "Our study is different, because we don't treat asymptomatic patients. We don't do repetitive venograms at three months if the patient is asymptomatic. In the old studies, if there was a restenosis in the venogram, regardless of if there were symptoms or not, they did first rib resection. We show that a minority of patients require first rib resection because of symptoms."

He further highlighted: "Of course this is only 12-month data. The majority of patients have stopped anticoagulation, so it is still possible that in two or three years they might suffer a recurrence. So these data from Bern can only be considered to be preliminary. What we will do is see what happens with these patients in the next couple of years and we will publish long-term results of this approach, to find out if this holds in the long term."

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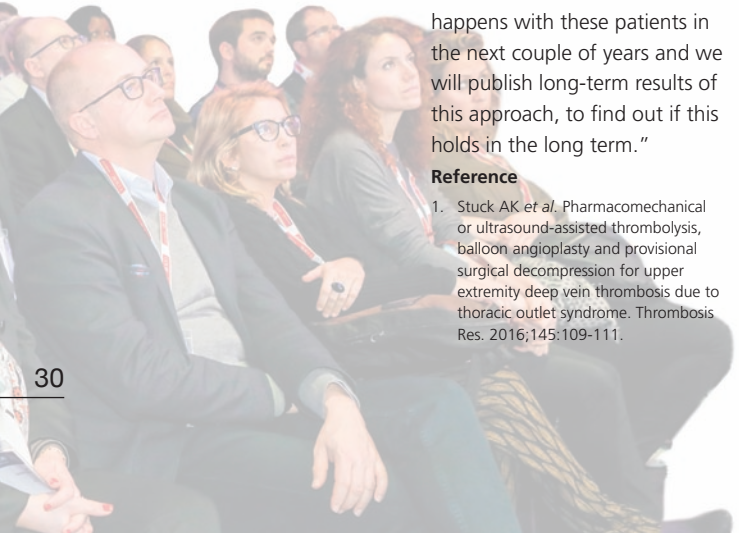

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April 26, 2017, Olympia Grand,
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LINC New York @ Mount Sinai
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VIVA@LINC

2017's Vascular Intervention Advances (VIVA)@LINC sessions included a frank exploration of a number of topics, as well as 'strategies on the frontline' discussion sessions in a more informal atmosphere. VIVA, dedicated to vascular care and education, convenes each autumn in Las Vegas, USA, and is a longstanding collaborator of LINC.

REALITY check for DCBs in the SFA: Is it time for more 'real-world' thinking?

In a session dedicated to drug-coated balloons (DCBs) Krishna Rocha-Singh (Prairie Vascular Institute, Springfield, IL, USA) delved into the best means of evaluating the potential of DCBs in the SFA while avoiding the traps that some trials have fallen into with restrictive designs and exclusion criteria.

Indeed, his opening comments to *LINC Review* made a clear statement: DCB trials in the SFA are simply not indicative of real-world patients. Building on this, he argued that lesion length, lesion calcification and other exclusion criteria would, in practice, negate enrolment of many of the patients he sees through his door. "And this really restricts the generalisability of the clinical results," he said.

"We want trials to go for the 'nasty players', if you will – the challenging cases. I think most devices can do well in the TASC A and B lesions, but we badly need data that explores complex calcified lesions, longer stenoses, and chronic total occlusions."

To that end, Dr Rocha-Singh went on to highlight the importance of real-world registries, along with stringent adjudication by independent parties, to first assess if a clinical event was associated with a device, and secondly, ensure that the results were not site-reported. "I.e. that they are in fact adjudicated by an independent angiographic core lab, with primary patency determined by a combination of clinical and ultrasound endpoints," he said.

As such, Dr Rocha-Singh is adamant that company-led trials should be transparent, and doctors should be ready to constructively critique any results, thus leading to better, collaborative understanding and advancement. "This way we can come to standardising therapies and definitions, which in turn means we can more adequately compare these trials, and better

compare these devices against each other," he added.

For real-world DCB outcomes to be better reflected, one such improvement that Dr Rocha-Singh underlined is the importance of improved definition and assessment of calcium. Specifically, while calcium is a primary driver in the decision to use adjunctive therapy (atherectomy, for example), the angiographically-defined severity of calcium build-up is inconsistent.

"I am going to request that companies promote transparency and disclose how severe calcium is defined in their trials, as well to avoid the temptation to make veiled marketing claims regarding their superiority in treating severely-calcified arteries," he said, "But at the same time, conceding that there is no accepted standardised angiographic definition at the moment.

"This leads us on to a second consideration: how do we actually treat these patients? As we start treating more complex patients with femoropopliteal disease – and as diabetics become more prevalent – the degree of calcification in these vessels becomes more severe. And then because this calcium is being treated by a balloon alone, it causes a 'failure mode', per se, during the procedure, and in turn ends up with the need for adjunctive therapies such as bare-metal stents."

Remaining on the issue of vessel preparation, Dr Rocha-Singh recounted that in the US at least, the term 'vessel preparation' itself has become a sort of mystic, nebulous term that, in the eyes of regulatory agencies such as the FDA, stretches to many approved technologies, including scoring balloons, cutting balloons, atherectomy, etc.

While the utilisation of vessel preparation devices would hope to reduce recoil and dissections prior to the application of a DCB, and therefore reduce stent use, Dr Rocha-Singh argued that the problem would be that in so doing, a lot of cost is injected into the procedure. Crucially, without solid data behind this decision, some of these costs may not have been necessarily warranted.

REALITY

To better assess the indications and costs for combination therapies using DCBs and adjunctive devices, Dr Rocha-Singh and colleagues from VIVA Physicians are collaborating with Medtronic (USA) in an international study, REALITY[1]. Specifically, the study will assess outcomes for patients with significantly-calcified and symptomatic femoropopliteal peripheral artery disease, following adjunctive use of their HawkOne or TurboHawk directional atherectomy devices, and their IN.PACT Admiral DCB.[1]

"We really want to know what the truth is," said Dr Rocha-Singh. "It is unfortunately not a randomised trial, because obviously the sponsor of the study owns both the DCB and atherectomy catheters, but it is an international registry of up to 250 patients, with sites in Germany and the

"We badly need data that explores complex calcified lesions, longer stenoses, and chronic total occlusions." Krishna Rocha-Singh

US. We are prospectively evaluating the use of the HawkOne and TurboHawk in complex lesions of up to 25 cm that only have moderate or severe calcium – so these are the 'bad players'. We are also including chronic total occlusions up to 12 cm, i.e. the sorts of patients that drive provisional stent use up. The hypothesis is that this pre-treatment regimen will reduce provisional stent rate, and give us acceptable results out to two-years."

A key facet of the study that Dr Rocha-Singh is keen to emphasise is the incorporation of four independent core labs. The first, an angiographic core lab, will assess the procedural results, specifically after atherectomy, and the final result after DCB. "We are looking at vessel recoil and dissection grades, at distal embolisation, and of course we are looking at complications – all with intravascular ultrasound [IVUS]," he said.

He went on to underline that, because IVUS use in the extremities has never truly been fully evaluated, a second independent IVUS core lab is also included in REALITY, to examine plaque volumes, and the amount of atheroma that will be removed. "Of note, the operator is blinded to all IVUS images, so they cannot make any therapeutic care decisions based on the IVUS results," he said. "The IVUS core lab will be assessing several essential metrics (lumen diameter, cross sectional area, plaque burden) at pre- and post-atherectomy, and then pre- and post-DCB images, residual vessel wall calcium, dissections, and will make a comparison to angiography.

"The last two core labs are a duplex Doppler core lab, which will assess binary restenosis at 12 months, and then interestingly – and never having been done before – a pathology/ histology core lab that will analyse all atheroma that is removed. That is very interesting, because we are actually seeing dysplastic bone in severely calcified lesion in the REALITY Study. This reinforces the simple point that I think a lot of doctors don't fully appreciate: calcium is a very biologically active material. In the angiographic core lab, when we independently assess the degree of calcium, we make that assessment before atherectomy, and then after, with the question being 'does atherectomy actually remove calcium from the vessel wall?'. Now we can assess that both angiographically, and with IVUS."

Vascular Career Advancement Award

VIVA and LINC have bolstered their collaboration even further with the development of the Vascular Career Advancement Award – an initiative that recognises young physicians who show promise as potential leaders in the vascular field. Open to those practicing for 10 years or less, winners are selected for their dedication to a philosophy of multidisciplinary vascular care, and the improvement of patient outcomes.

Congratulations to this year's recipients
Saher Sabri, MD and Antonio Micari, MD, PHD

More information about the Award, and its winners, can be found at:
vivaphysicians.org/annual-conference/awards/vcaa/

Dierk Scheinert (left) and Sean Lyden announce the winners of the 2016-2017 Vascular Career Advancement Award

He added: "So although REALITY is not a randomised controlled trial, it will provide us with a lot of independently-adjudicated imaging, histologic and clinical data, exploring a wide range of important issues that I think doctors will want to know about."

Harking back to the topic of vessel preparation costs, Dr Rocha-Singh stressed that it is important to undertake randomised evaluation of the cost-efficacy of these two treatment paradigms, commenting: "When you start looking at procedural costs, and costs extended out over two-year follow-up, some of these patients may need to come back because of clinically-driven restenosis. That becomes very important too, i.e. understanding that these are claudicants: they are not going to die from their SFA disease within the next three to five years, typically.

"We have to continue to build the clinical science in a meaningful way, because I do think drug-eluting balloons are an important modality – if not the most important modality, as far as I am concerned. Looking at drug-eluting stents, although there are more costly upfront, could their primary effectiveness, when observed over a two- to three-year period of time, actually become more cost effective, because it reduces the return of that patient for the treatment of that extremity? These are the hypotheses that I think we have to continue to challenge ourselves with."

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"I am going to request that companies promote transparency and disclose how severe calcium is defined in their trials." Krishna Rocha-Singh

The case builds for endovascular CFA treatment

Final two-year results of the TECCO trial[1] were presented by Yann Gouëffic (University Hospital of Nantes, France), providing evidence that endovascular treatment of the common femoral artery (CFA) atherosclerotic lesions is not only feasible but preferable to open surgery.

TECCO, the randomised, controlled, investigator-initiated study, was carried out in 17 French centres, and was independently funded by Nantes University Hospital. Prior to this, a prospective pilot study carried out in 36 patients at the University of Nantes between 2006 and 2008 demonstrated the feasibility of endovascular repair within the CFA region, with acceptable clinical outcomes out to five years.[2,3]

The purpose of the study, explained Professor Gouëffic to *LINC Review*, was to question both the premise that open repair is the best response to lesions of the CFA, and that the putative risk of stent fracture is a justified reason to avoid an endovascular approach.

"When you talk about the CFA with radiologists and angiologists, they don't want to do endovascular treatment. Because the CFA is so close to the hip joint, and because of its mobility, they are afraid of stent fracture. And also, in this region, you tend to have huge calcification. When I discuss with interventionalists or vascular surgeons, they think I am completely crazy. But in fact, like a surgeon, we know that if you fall we can fix it. Vascular surgeons talk about how easy surgery is in the CFA – with 100% technical and clinical success. But we have few results of surgery of the CFA."

A 2015 study by Bao Ngoc Nguyen *et al*, in which the US National Surgical Quality Improvement Program database was queried for common femoral endarterectomy between 2005 and 2010, placed peri-procedural mortality at 3.4%, and reintervention at a rate of 10%.[4] More recently, Siracuse *et al*. (2016) queried the Vascular Quality Initiative for all endovascular interventions of the CFA and deep femoral artery, finding peri-procedural mortality to be 1.6%.[5]

"We have less peri-procedural morbidity and mortality with endo," said Professor Gouëffic. "But another concern is the mid-term outcomes. My hypothesis in TECCO was that we have less morbidity and mortality in the peri-operative period, and that we have similar results at two years."

TECCO included clinical follow-up at 1, 6, 12 and 24 months, with stent x-ray at 1, 12 and 24 months, Duplex ultrasound core laboratory and data safety monitoring board adjudication. 120 patients were randomly assigned 1:1 to either open or endovascular repair (n = 61 vs. 56, respectively). Patients comprised classic claudicants, with de novo CFA stenoses of Rutherford class 3 to 6. Mean age in both groups was around 68 years, with a 30-40% incidence of diabetes mellitus, and around a 10% incidence of renal insufficiency. Exclusion criteria included restenosis, thrombosis, asymptomatic lesions, or life expectancy of <1 year.

Lesions were classified by type: in type I, lesions were located at the iliac external artery and extended into the CFA; in type II, lesions were limited to the CFA; and in type III, lesions were located at the CFA and its bifurcation. Type I and II were treated with nitinol stent, while balloon-expandable stents were used for type III lesions. No specifications were made with respect to stent type.

The procedural specifications were relatively loose; open repair was performed at the discretion of the physician, and in endovascular repair the only specification was of primary stenting. Anaesthesia,

"Although it is just at the hip joint, vessel movement is above and below – but not at – the common femoral artery." Yann Gouëffic

approach, and antiplatelet treatment were discretionary within the stenting group.

"We treat mostly complex type III lesions, which is not so easy to deal with in surgery," explained Professor Gouëffic. "It is actually very interesting, because we [previously] didn't know which open techniques were used to treat the CFA; most centres used endarterectomy plus [prosthetic] patch, in 64% of cases. But stenting was mainly carried out with cross-over technique [78%]."

Both modified intention to treat analysis (three patients having been removed due to death) and per-protocol analysis (excluding those that crossed over from surgery to stenting or vice versa) were found to be significantly different in favour of endovascular stenting (p=0.05 and 0.005, respectively) – findings that closely matched the original hypothesis.

Perioperative complications included a single incident of stroke (1.8%) at 30 days in the endovascular group, and delayed wound healing in the surgical group (n=16, 26%). Local infection and vascular perforation each occurred in one patient (1.8%) in the stenting group. In terms of survival, patency, target lesion revascularisation (TLR), and ankle brachial index (ABI), no significant differences were found.

The results provide a clear message, noted Professor Gouëffic. Interestingly, a single stent fracture was identified as part of the five-year follow-up in the prospective cohort – although it was not located at the CFA but at the external iliac level.

One of the justifications of surgical treatment has been the putative risk of stent fracture due to the vessel compression, torsion and stretch associated with flexion and extension of the hip. In an anatomical cadaveric study, Professor Gouëffic examined the effect of hip flexion on the major vessels of this region, finding the CFA itself to remain relatively unaffected. This, he said, provides a basis for the low incidence of stent fracture found in TECCO: "Although it is just at the hip joint, vessel movement is above and below – but not at – the common femoral artery. This is why I am not surprised when I see the long-term results, with no fractures."

How does Professor Gouëffic see treatment trends changing in the era of drug elution? "Restenosis is not a main concern at this level," he said, "And TLR related to restenosis is not so important (compared to the SFA, for example). The main problem at this location is to deal with huge calcification. We need a stent with good chronic outward force, and good resistance to crush. For example, the Supera stent [Abbott Vascular] could be an option to deal with compression resistance, but this is just a hypothesis."

Professor Gouëffic noted the importance of work such as this in bringing the evidence base up to scratch at a time when endovascular interventions in the CFA are becoming more common. "We have less peri-operative morbidity and mortality in the endo group, with comparable results at two years. This makes endo stenting perhaps the first line of treatment for CFA treatment."

"I am not surprised when I see the long-term results, with no fractures." Yann Gouëffic

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CX@LINC: ‘Life after EVAR’

The Charing Cross (CX) @ LINC symposium offered up stimulating and engaging insights into ‘life after EVAR’, with invited experts sharing their perspectives for the audience. Held in London, UK since 1978, the Charing Cross Symposium is now the longest running vascular and endovascular symposium in Europe, and one of the largest in the world.

Kicking off the session was Ian Loftus (St George’s Vascular Institute, London, UK), who relayed the age-dependent benefits of EVAR, touching upon large-scale registry data from the UK.

Framing his thoughts, Professor Loftus told *LINC Review* that randomised trials, large-scale registries and single-centre series have all made the early benefit of EVAR clear, including peri-procedural mortality, morbidity, length of stay and return to normal activity. Crucially, however, he added that there is mounting evidence that the advantage is not maintained in the long term. “This is partly, but not entirely, down to re-interventions, device failures and a late rupture risk following EVAR,” he noted.

“Of course, many aspects of our aortic interventions are changing. This is especially true for endovascular repair, but also open surgery to a lesser extent. Our peri-procedural care has improved, our case planning and imaging is better, along with our knowledge of when and how to reintervene, and of course the device technology continues to evolve. However, the literature to support the net gain in terms of benefit of EVAR over OR [open repair] over the last 10 years is lacking, apart from data from some large company-sponsored trials, which may not reflect real-world practice.”

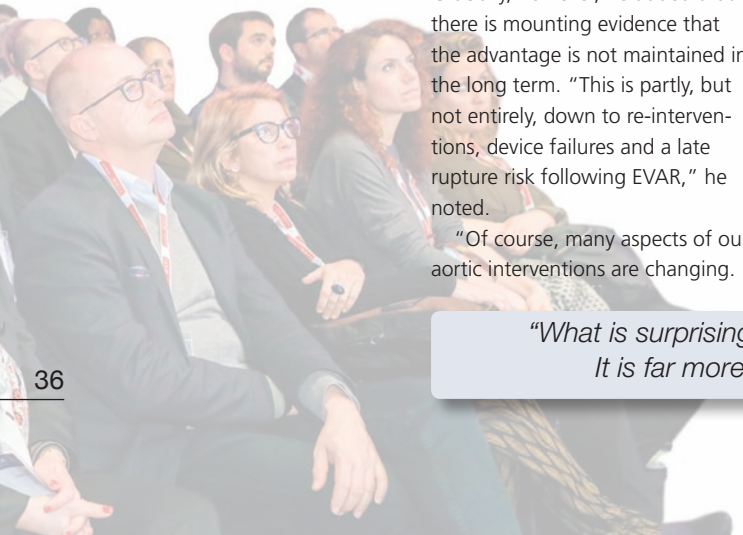
Ian Loftus

Diving into the main question at hand, Professor Loftus tackled the broad effect that age has on EVAR indication and outcomes, noting results from his large-scale Registry in the UK. “The registry suggests that the short-term benefit is most dramatic in the older and sicker age group,” he said. “This of course is not surprising, but what *is* surprising is that the extent of net gain – in terms of survival – diminishes quickest in the older and more frail cohorts. It is far more than age though, and we should never set thresholds for intervention based purely on age.

“Far more work is required to assess which groups are likely to benefit from which approach, including the option of a conservative strategy for those unlikely to gain quality life years. We should be working harder to develop algorithms with all relevant factors, including age, comorbidity aneurysm size and aortic morphology, to help us to determine the correct intervention for an individual patient.”

For younger patients, as Professor Loftus described, there is very little difference in the short- or long-term outcomes of EVAR versus OR. However, while this would lead some to argue that in such cases an open repair approach would therefore be preferential

“What is surprising is that the extent of net gain – in terms of survival – diminishes quickest in the older and more frail cohorts. It is far more than age though, and we should never set thresholds for intervention based purely on age.” Ian Loftus



(to release patients from life-long surveillance), Professor Loftus cautions such a simplistic view: "In the absence of a significant difference in mortality … one could argue the opposite approach in good anatomy," he said.

"Also, patient preference is essential and most would still choose an endovascular approach if given the choice. It is not the surveillance and risk of reintervention that influences patient choice – it's largely a short-term gain, in terms of complications and return to normal activity. Open repair will always have a role, but may become limited to fewer vascular/aortic centres providing the broad range of aortic interventions to large cohorts of patients."

Summing up his main messages for the audience, Professor Loftus reiterated that the outcomes from EVAR and OR are good for younger, fitter patients, both in the short- and long-term, adding: "The early gain in terms of survival is most stark for the older, less-fit age groups, but the long-term outcomes for these patients following EVAR are much worse than those who survive OR."

Follow-up takes centre stage in Q&A

At the end of the session, the panel opened up the floor for questions from the audience – one of the most prominent topics being follow-up, i.e: How long should we follow-up patients after EVAR; is there a time we should stop doing so; and what tools should we use to facilitate it?

"Well my opinion on this is actually the other way around," said Hence Verhagen (Rotterdam, the Netherlands). "I think we should look very hard for patient categories that do not need any follow-up during the first five years – just like open surgery. And then just because of further degeneration of the aorta, after five years it becomes more important to do follow-up. And, unfortunately, a lot of follow-up: yearly at least."

Frank Vermassen (Gent, Belgium) weighed in: "I think you can never, ever stop follow-up, because there always remains a risk for degradation. All of these prostheses have been tested for 10 years, but a considerable number of patients survive longer than that."

In terms of what tools are best-suited to pursue follow-up, Dittmar Böckler (Heidelberg, Germany) added his thoughts, saying: "I'm not really sure if MR is the way to go, because of the compliance of patients, time and other issues make it unpractical … so I think ultrasound is the way to go."

"I think we should look very hard for patient categories that do not need any follow-up during the first five years." Hence Verhagen

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‘CLI trials should be evaluated earlier!’

Current studies of critical limb ischaemia (CLI) should shift their endpoint evaluations from one year to six months, delegates heard at LINC 2017 in a session that focussed on optimising outcomes in below-the-knee interventions and CLI.

In the current era, many would argue that there is still a lack of consensus at to what constitutes a ‘successful’ intervention for CLI patients, with outcome measures such as limb salvage and wound healing all tipping the scales. As Jihad Mustapha (Metro Health Hospital, Wyoming, MI, USA) described in an interview with *LINC Review*, part of the issue is significant variability in the definitions used: “One might think the procedure is successful based on an angiogram showing great flow to the target vessel,” he said, “Whereas others consider that just the beginning of the long trail of events to follow, such as the input of the other multidisciplinary professionals, until the wound is healed.

“That leads us to the other school of operators who believe that a successful intervention has now been achieved. In summary, successful intervention of the CLI patient should always include successful revascularisation followed with wound healing.”

A common criticism of randomised trials focussed on CLI is that their cohorts do not mirror real-world patients. Indeed, many patients seen in daily practice would be excluded from certain trials. “We need to really face the inevitable, and design trials to treat true CLI patients who, in reality, need the most care,” continued Dr Mustapha.

“In order to have a successful trial outcome that can be implemented to the masses in the real world – and thereby resolve the epidemic of CLI disease – we must include mild, moderate and severe forms of CLI in our trials. This is absolutely necessary to isolate the proper medications and devices that can actually bring sustainable patency in all forms of the disease, so we can achieve successful interventions.”

Procedural experience should not be overlooked either, noted Dr Mustapha, as although operators will tend to use devices they are most comfortable with – and in most cases all the better for success – modern CLI presents variation in the disease stage, which means thinking outside of the box. “We must adapt and learn to operate outside our comfort zone, learning new methods of therapy which can include new devices and tools that we weren’t initially comfortable with,” said Dr Mustapha. “The current status quo is not an option. Change is inevitable.”

“It is more scientifically sound to focus on a six-month endpoint for the CLI patient instead of the current one-year standard.”
Jihad Mustapha

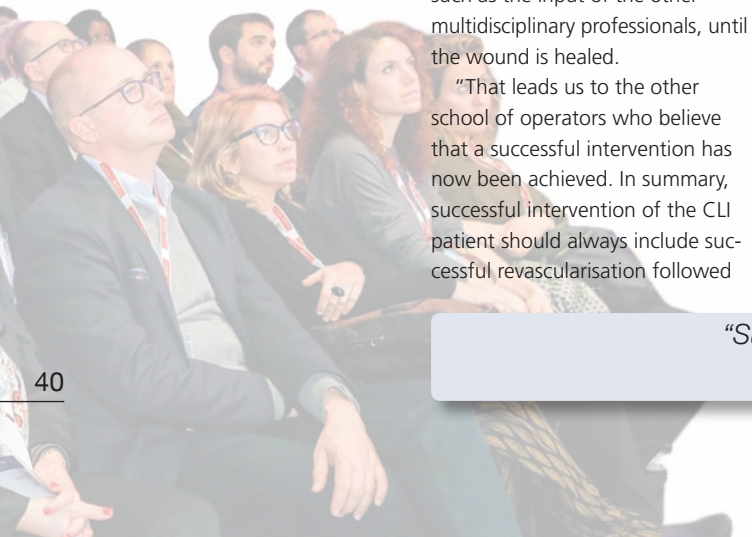
Settling on the main crux of his presentation, Dr Mustapha outlined his thoughts on why a shift to six-month endpoints should be pursued in CLI trials: “CLI disease is, in a way, a separate entity of the generalised term of PAD. When patients present with CLI, the cascade of events leading to an end-stage outcome or resolution of the illness usually presents itself within a period of six months. Because of that, it is more scientifically sound to focus on a six-month endpoint for the CLI patient instead of the current one-year standard, which is well known to be borrowed from general PAD trials.”

With a perspective rooted in the thousands of patients he has encountered over the last decade, Dr Mustapha is passionate that waiting for endpoints longer than six months will usually mean the outcome is catastrophic, rife with major amputations and increased rates of mortality.

“The implications and potential for trial designs is a great opportunity for us to change the current rigid peripheral vascular disease patient follow-up regime and create a new flexible CLI follow-up regime,” he continued. “As you all know, your CLI patients tends to come back with recurrent symptoms anywhere between 6-12 weeks in most cases, and 12-24 weeks in the rest of the cases. Doing the math, we find that there are multiple gaps in the six-month period. So not only do we need to reduce our endpoint to six months – to catch the progression of the CLI disease – but also we must change the follow-up protocol so that adequate patient surveillance occurs during this critical period of predictable CLI disease.

“Hence, in future trial design for device approvals we hope to see study evaluation and follow-up that is more rigorous and frequent in the first six months following revascularisation. To some this might seem to be aggressive, but in reality this is what happens every day in clinical practice.”

He concluded: “It’s time for us to accept this is a deadly disease that kills more people than colon cancer, prostate cancer and breast cancer. CLI does not receive the attention and awareness it deserves, despite its potential mortality factor.”



“Successful intervention of the CLI patient should always include successful revascularisation followed with wound healing.” Jihad Mustapha

Diving into carotid revascularisation

A 'Deep dive' session on carotid revascularization saw Martin Storck (Department of Vascular and Thoracic Surgery, Klinikum Karlsruhe, Germany) presenting his perspectives as to whether guidelines and clinical practice regarding asymptomatic carotid stenosis will change in the near future.

Speaking to *LINC Review* ahead of the session, Professor Storck began by underlining a key message: guidelines for asymptomatic carotid stenosis haven't changed much in recent years, because there has been little data to bump the changes into place. "No randomised studies have been completed, so we still have the wait until some of the ongoing studies such as CREST 2[1] or ACST-2[2] are finished, which may take some time," he said.

Crucially, Professor Storck emphasised that the guidelines are very much under discussion as to whether they should take precedence in decision-making. After all, the alternative – a personalised medicine kind of approach – puts the decisions in the hand of the physicians to a more significant degree. "If you compare carotid stenosis treatment to other treatments, carotid stenosis treatment has always come down to conservative, endovascular or open," he continued.

"We have to find the best therapy for each patient, and the guidelines can only help us by giving us some evidence from randomised trials. But today it depends also on the localised experience from each centre."

Another key topic up for discussion, Professor Storck noted, is the perspective that asymptomatic stenosis may never actually become symptomatic. "This has been discussed extensively at recent meetings, and I think we should really think about whether the patient needs treatment at all," he said.

But how does Professor Storck envisage stratifying patients to better assess who needs treatment? "Silent embolisation might be a risk factor," he remarked, adding: "Patients that are clinically considered asymptomatic might still be high-risk patients if they have recurrent silent emboli. [Furthermore], the issue of plaque morphology has not been really solved of course. Soft plaque with embolic material, or thrombotic material, is a good indication to pursue treatment. Or really progressive stenosis, i.e. despite medical treatment, there is progression … higher than 70%.

Martin Storck

"And gender is not completely answered. I think some of the longer-term data from the ACST-1 study[3] showed that female patients also benefit from complication-free revascularisation regarding long-term stroke-free survival."

Professor Storck went on to note the central point that, if the patient receives carotid revascularisation, there is definitely a need for control of risk factors which are responsible for the progression of atherosclerosis. "I think if someone has had a carotid endarterectomy, they still need surveillance of their risk factors, which will determine general risk. This means best medical therapy [BMT] is necessary in all of these patients.

"The guidelines argue BMT alone is enough, but we argue to do BMT plus revascularisation, which is even more safe… but there is no information about the effectiveness of BMT because there are no controlled studies about BMT alone in carotid stenosis. This is a big problem."

Turning to areas within the guidelines that are due an update, Professor Storck noted that what is very new is that, because patients on haemodialysis or renal transplantation have a very short life expectancy, it is not recommended to revascularise an asymptomatic patient with renal insufficiency who is on dialysis. To emphasise this point, he spoke of US registry data, not-yet published, from the Unites States Renal Data System. "They had 4268 patients analysed, and they had a very high stroke rates," he said. "Asymptomatic stroke was 2.7%, and symptomatic 5.2%, which is very high, and with no difference in myocardial infarction or death."

Similarly, he touched on renal implantations. "They had the first study ever, with 462 patients… treated for asymptomatic stenosis,

Continued on page 42

"Guidelines can only help us by giving us some evidence from randomised trials. But today it depends also on the localised experience from each centre Martin Storck

Diving into carotid revascularisation

Continued from page 41

and it didn't really have a benefit, because of their life expectancy. So in these patients it probably doesn't make sense to do carotid reconstruction, if you are asymptomatic."

Summing up the way guidelines may shift in the near future, he commented: "It might be that the role of best medical treatment is more eminent in the future – it could become more important – but in general in the near future nothing will change."

Concluding with the message that, because data are limited, guidelines will likely have to wait a while for trials such as CREST 2 or ACST-2 to surface, he said: "We have different healthcare systems and different [opinions] as to how studies can be interpreted. We have large registries, but the problem is that in evidence-based medicine they don't accept registries, even if it is 28,000 patients."

Alison Halliday

ACST-2 trial updated

Also speaking during the session was Alison Halliday from the University of Oxford, UK, who offered up an update on the ACST-2 carotid trial[2]. Setting the scene in her introduction, she commented: "The randomised trials obviously only cover those that have tighter stenosis, and it is not clear from this whether the average annual rate of strokes has actually dropped in the way it has been claimed, because the other studies tend to have many patients with around 50% stenosis," she said.

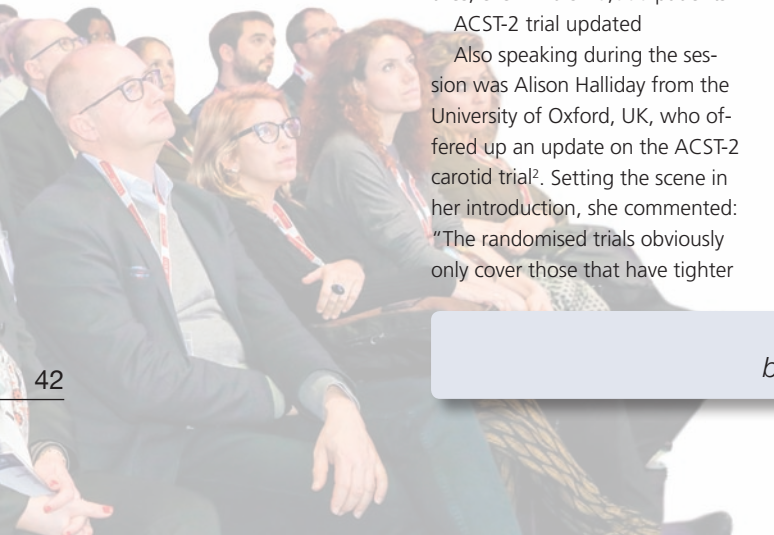
"Asymptomatic carotid stenosis even on anti-thrombotic, blood pressure lowering and lipid-lowering therapy – which I refer to as 'triple' therapy – from our recent IPD analysis of more than 5,000 patients, shows successful CEA will halve the stroke rate over the next five to ten years."

She added that analysis, comprising the VACS[4], ACAS[5] and ACST-1[3] studies, covers the period from May 1991 to May 2008: "So although lipid-lowering therapy has certainly reduced stroke risk, endarterectomy will still halve the remaining stroke risk."

The ACST-2 trial, as Dr Halliday noted, will directly compare CEA and CAS in patients, providing that a CT or an MRI of the arch demonstrates that the patient is suitable for both procedures, at which time they can be randomised. Noting that CAS is thought to be more hazardous than CEA, Dr Halliday said that the two main hazards are crossing the lesion, and navigating the aortic arch. "With endarterectomy, you have an open removal of the atheroma, under direct control, so our question is can stenting be as safe, but yet much less invasive?"

She continued, noting the patients thus far: "We have 70% men, median age 69, just over a third with ischaemic heart disease, and almost a third are diabetic. That is much higher than in ACST-1. Renal impairment is fairly uncommon [8%], and atrial fibrillation was 6%. A quarter of our patients are over the age of 75, and 40% of them have had previous stroke symptoms or infarcts. However, none have had symptoms for the last six months in the artery under consideration."

"The guidelines argue best medical therapy [BMT] alone is enough, but we argue to do BMT plus revascularisation, which is even more safe." Martin Storck



Apart from 4% of patients lying in the 50-69% ipsilateral stenosis range, the majority of patients in the study are either 70-89% stenosed (73% of patients), or 90-99% (23% of patients). Contralateral stenosis of 50-99% was seen in 30% of patients, with occlusions in 7%.

"A definite plaque echolucency was present in about 30% of patients," said Dr Halliday, adding: "The mean cholesterol is certainly lower than when we did the first trial [5.6 mm/L] – it is now 4.7 mm/L, and HDL is 1.3 mm/L."

Drugs at trial entry were as follows: 80% of patients were on lipid-lowering medications; 85% anti-hypertensives; and 95% anti-thrombotics. "One month after the procedure, we still have high levels of these [medications], and as you would expect there are quite a lot of people on aspirin and clopidogrel," said Dr Halliday.

In terms of randomisation, and follow-up, CEA patients underwent their procedure an average of 24 days from randomisation, whereas CAS stretched to 27 days. Follow-up is currently at 2.9 person-years for both CEA and CAS as of January 2017. Noting the drug-specific follow-up, Dr Halliday continued: "[In 2015] you have very high rates of good medical therapy. We're looking particularly at statins, and you will see that in 2016… it was just over 50% for atorvastatin. We will have very good follow-up of our annual medicines for these patients.

"Compliance with allocated treatment [2015] is excellent: about 4% of patients have crossed over. You find with this that some procedures have not been done, but when we have completed enrolment, that will move more towards 95%. In the surgery arm, about 29% of people require shunting under general anaesthetic, and about a quarter of that if they are under local."

Dr Halliday stressed that the stents and devices have changed a lot since the earlier trials, with flow reversal capabilities, membrane-covered stents, and 'surgically-approached' stenting (avoiding aortic arch atheroma). Looking at the choices of stents used in the 1020 patients thus far, Dr Halliday highlighted that 43% of patients received closed-cell stents, 34% open-cell, 18% hybrid, and 5% membrane-covered. Hybrid and open-cell stents can be seen to be decreasing in recent times, she added, being largely replaced by membrane stents. Similarly, in terms of embolic protection, 67% of patients received a filter, 18% a proximal occlusion, <1% a distal balloon, and 15% no embolic protection.

"The disabling and fatal stroke rate for both procedures so far is 1%, which is lower than ACST-1's result just for endarterectomy [1.7%]," said Dr Halliday.

In her concluding statement, Dr Halliday underlined that of the total patients being studied in CAS versus CEA studies, ACST-2 will provide up to 60% of the evidence base, so it is sure to be a hotly-anticipated part of the CAS versus CEA puzzle.

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"It is not clear…whether the average annual rate of strokes has actually dropped in the way it has been claimed." Alison Halliday

First-time REAL-PTX data unveiled at LINC 2017

Two-year results of the REAL-PTX randomised clinical trial comparing the Zilver PTX drug-eluting peripheral stent (Cook Medical, USA) versus DCB treatment in femoropopliteal lesions were presented by the study's principle Investigator Dierk Scheinert (University Hospital Leipzig, Germany).

A total of 150 patients were prospectively studied at five European sites with a 1:1 randomisation (n=75) in both groups. Stratification for lesion length for both groups was 1:1:1 and included short (≤10 cm), mid-length (>10 cm and ≤20 cm) and long (>20 cm and ≤30 cm) lesions. Mean lesion length was 152.6±88.2 mm.

"All endpoints were independently assessed by core labs, both for the angiographic and duplex endpoints," said Professor Scheinert. "Follow-up is carried out through to three years, and primary endpoints are primary patency (based on duplex at 12 months), and then of course we now report on these endpoints also at later time points."

He added that the lesion characteristics indicated really challenging lesion cohorts. Some patients had critical limb ischaemia, with target lesion lengths over 14 cm in the DCB arm and almost 16 cm in the Zilver PTX arm. Moderate to severe calcification was also high in both groups. Looking at the clinical outcomes, Professor Scheinert commented: "Outcomes showed good improvement in Rutherford class in both groups, and also in terms of ABI [ankle brachial index] improvements there really are no differences.

"What is interesting now is of course to look at the primary endpoints at one year: I think we can say essentially no difference, with 76% primary patency in both groups… but interestingly beyond the one-year time point we are starting to see a certain separation of the curves. The primary patency in the DES arm is 58% versus 49% in the DCB group, so it is going to be interesting to see what the three-year follow-up looks like."

Examining the different treatment methods specifically, drug-coated balloon lesions showed "very good results" for short lesions, but a decline in patency down to even 33% at two years in the long-lesion group. With a similar trend noted in the DES group at 24 months, Professor Scheinert highlighted an interesting observation in the first year – that of a relatively high proportion

of restenosis – noting that it was "probably higher than expected".

He explored further: "We looked a bit deeper into these early events with the Zilver PTX stent, and what we saw was that there were actually 16 early failures up to 12 months, most of them in long lesions, in restenotic lesions, and in patients with severe or moderate calcification. What was important was that there was only one case where we actually had a stent thrombosis documented. There were four other occlusions where we suspected maybe a partial thrombotic component. Eleven lesions were actually stenotic, so not occluded, and interestingly seven out of sixteen patients which were reported as patency failures never really needed a TLR."

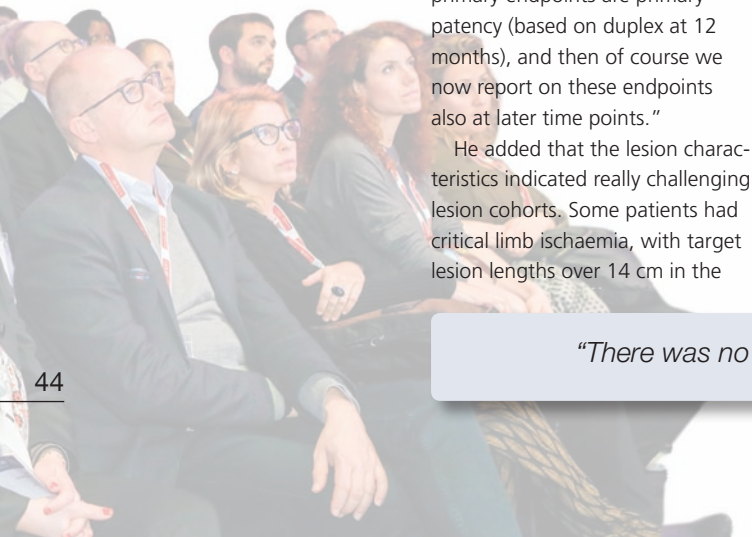
Professor Scheinert went on to note with interest that 40% of patients in the Zilver PTX arm had more than 30% residual stenosis (according to the core lab) – a greater proportion than that of the DCB arm: "That surprised us a bit, and probably calls out for a better vessel preparation, potentially leading to better results," he said.

Summing up the 24-month data in terms of lesion-length strata, Professor Scheinert stressed that for short lesions, there is essentially no difference in performance between DCB and DES out to two years. For longer lesions, he added, there may be a somewhat better outcome with the Zilver PTX stent, and for longer lesions – and probably because of some issues early on – there is no real difference again.

"In conclusion I think we can say that there was no significant difference between DCB and DES in terms of primary patency at 12 months, which was the primary endpoint," said Professor Scheinert, adding: "There was a trend showing better durability of DES at two years, particularly in mid- and longer lesions; there were significantly better outcomes for short lesions in both groups. There was increased benefit of DES in longer lesions in comparison to DCB-only treatment; and vessel preparation is really key both for DCB and DES, particularly in complex lesions.

"It is clearly a small pilot trial – not powered to show statistical significance, but it is hypothesis-generating, and three-year results will be available next year [at LINC 2018]."

"There was no significant difference between DCB and DES in terms of primary patency at 12 months." Dierk Scheinert



JOTEC's E-xtra DESIGN ENGINEERING grafts shine

During the 'Critical issues and pioneering solutions in aortic endografting' session, held on the last day of LINC 2017, Andrej Schmidt and Daniela Branzan joined via satellite from the Department of Angiology at University Hospital Leipzig for a live case of branched/fenestrated EVAR (B/FEVAR) for a type IV thoracoabdominal aneurysm (TAAA)

The patient was a 61-year-old male who had an incidental finding of the suprarenal TAAA, progressing to 61 mm maximum diameter. Due to several risk factors, including CAD, PTCA heart failure in 2012, an ejection fraction of 40%, and thyroidectomy in January 2017, the patient was selected for endovascular treatment with a percutaneous stent graft.

Drs Schmidt and Branzan explained the steps taken before the audience joined them live, including: Coiling of the intercostal and lumbar arteries prior to B/FEVAR to reduce the risk of spinal ischaemia; bilateral femoral and left axillar percutaneous accesses, with preloading of ProGlide Suture-Mediated Closure Systems (Abbott Vascular, USA) for all three access sites; coiling of the right upper accessory renal artery; and implantation of a custom-made device (CMD) thoracoabdominal stent graft from JOTEC (Germany).

Describing the CMD stent graft, Dr Branzan introduced the hybrid graft – hybrid because of fenestrations and branches, with two retrograde inner branches for the left and right renal arteries. "We have chosen three fenestrations: the first one in the celiac trunk, the second for the superior mesenteric artery, and the third for the left upper accessory renal artery," she said.

She also commented on the device's circular positioning markers, noting their effective design: "For the large fenestration of the visceral artery you have four markers: a circle that points exactly to the midpart of the fenestration, for the renal fenestration … and then you can see the inner branches, which are also adapted to our needs."

Dr Schmidt also shared his thoughts on the CMD's lettered markers (e.g. 'E') which help align the fenestrations: "The orientation is very nicely done … in AP the 'E's should be at 12 o'clock."

Showing a video of the initial implantation they performed earlier, he added: "You can see that the 'E' was going a little bit too far to the right side, so we were able to twist the graft a little to the left."

Dr Schmidt reasoned that because patient had four renal arteries, and due to the design of the CMD graft, they had to close the fourth (and smallest) right accessory renal artery using two Amplatzer Vascular Plugs (St. Jude Medical, USA). He also noted that because the lower left renal artery had a difficult angulation, it was more important to keep the upper left accessory renal open in his opinion.

However, he posed a question to the panel as to whether they concur with the decision to close the upper accessory renal artery, or whether they might have gone with a five-vessel fenestrated or branched graft?

"That is an interesting question," said session moderator Marc van Sambeek (the Netherlands). "My perspective is how close they are together, and if it is feasible to have all of these fenestrations."

Co-moderator Piotr Kasprzak (Germany) commented: "Yes we do go for access in the renals if they are bigger than 3 mm, because I think it is important to have some diameter for the target vessel stent grafts."

Along with the three fenestrations and the two inner branches of the CMD device, the team planned to implant two E-ventus BX balloon-expandable covered stents (JOTEC) into the visceral arteries. The E-ventus BX has a unique design comprising an ePTFE layer and a biocompatible cobalt chromium stent, aiming to set new standards in terms of flexibility and radial strength combined.[1] "The stent graft is encapsulated in the ePTFE membrane," noted Dr Branzan.

Additional benefits of the most recent iteration of the E-ventus BX design, as the operators noted, include the implementation of wider connecting stent struts for increased longitudinal stiffness, low foreshortening, high trackability and a low catheter profile.

The fenestration work began

After leaving Drs Schmidt and Branzan to work (in the meantime exhibiting flash presentations for the audience), the session linked back to University Hospital for an update of their progress. At that time, the mesenteric and celiac trunk branches of the CMD device had been successfully finished, opening the hepatic and splenic arteries. "You see that the lumbar artery is coming retrogradely due to our coiling … that is what we have done here to prevent spinal ischaemia, and it seems to have been effective," said Dr Schmidt.

Before tackling the left upper accessory renal artery, the operators opened the tip capture and took the tip out, slowly pulling down the tip across the mesenteric artery. "The reason we have done this now is first of course to give flow to the right hypogastric artery, and to avoid going with the tip past the trunk stent and the mesenteric stent," said Dr Schmidt. "Now we just go past one stent, so the risk of deforming anything is diminished."

He went on to note that while they had hoped to access the upper renal from above, it was too difficult, thus they switched to a femoral approach. With this decision, treatment of left upper accessory renal artery could be finished quickly. "We still have [two (left and right renal artery with inner branches)] arteries to take the grafts in," commented Dr Schmidt, "so still some work!"

Continued on page 46

"For the large fenestration of the visceral artery you have four markers: a circle that points exactly to the midpart of the fenestration, for the renal fenestration … and then you can see the inner branches." Daniela Branzan

JOTEC's E-xtra DESIGN ENGINEERING grafts shine

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Left and right renal arteries

After another short break for scheduled presentations, we dived back in just as the team were planning implantation of the first E-ventus BX into the right renal artery. However, at that time they had encountered a problem in accessing the inner branch with a sheath. While it was the left renal artery that they had earlier predicted to be difficult, due to its angulation, the discovery of a tricky "edge" on this right access site led Dr Schmidt to caution that the road ahead could be quite challenging.

While he – and the panel for that matter – noted that it was very unusual to have any problems in this scenario, it was nevertheless true that it served as a useful lesson to expect the unexpected in any procedure. "We are witnessing some of the most skilled people here operating, and there are moments in the procedure when they struggle," said panellist Martin Malina (UK). "And I have to admit I struggle also when I do these cases."

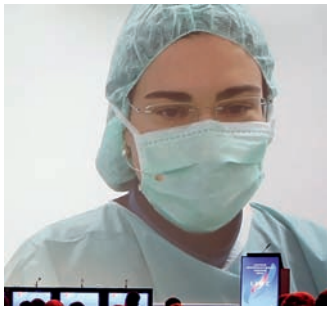
Dr van Sambeek added: "As you said, we are watching one of the most – if not the most – skilled interventionalists in the world, and as you can see, if you are trying to advance your catheter, and you hit a ridge, sometimes you don't know why it is, and whatever you try, it can be difficult to pass."

To resolve the access problem, Dr Schmidt and Dr Branzan used a V-18 ControlWire from Boston Scientific (USA): "The tip is 'semi-aggressive'," said Dr Schmidt, before successfully crossing. However, with sufficient reach lacking with the wire choice, they needed to go back to "square zero" with a Supra Core wire from Abbott: "We already had a Supra Core wire in, and we had a 7F sheath in, but let's try once again!" he said.

Using a self-expanding stent to "smooth out" the edge, the E-ventus BX device was then positioned successfully. "I think we are now fine with this here, and we can now turn our attention to the 'really difficult' renal" said Dr Schmidt.

Despite worries that left renal artery would indeed be the hardest, the team were able to implant an 8 mm diameter E-ventus BX stent in place with comparable ease, reinforcing the notion that one cannot always predict where challenges will arise.

"The angio looks good," said Dr Schmidt, adding: "So now we have all five fenestrations and branches in place."



Final steps

For the final part of the procedure, a graft was still required for the bifurcation, but with the session overrunning, moderator Dr van Sambeek brought the session to a close while the operators were undertaking the final steps. He concluded: "Thank you very much for this live case. You showed us that even the best interventionalists sometimes have struggles, and sometimes it is not easy to overcome these hurdles. But you and your team did an excellent operation, and I think the end result will be very good."

Indeed, the final result from Leipzig has proven to be very good after 30 days follow-up.

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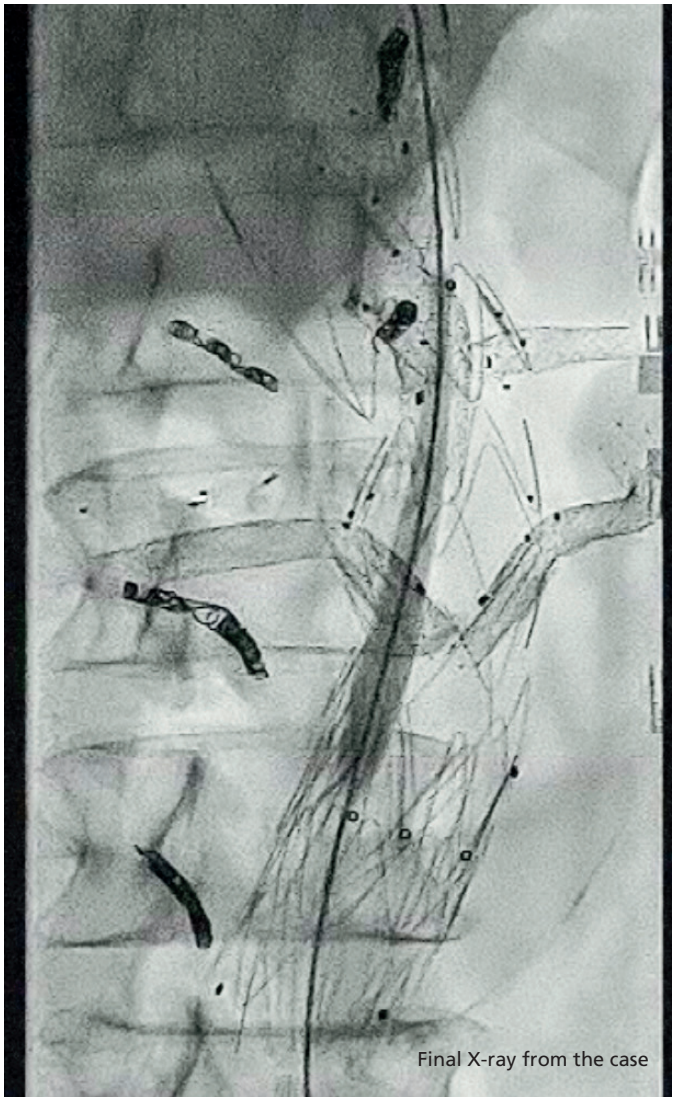
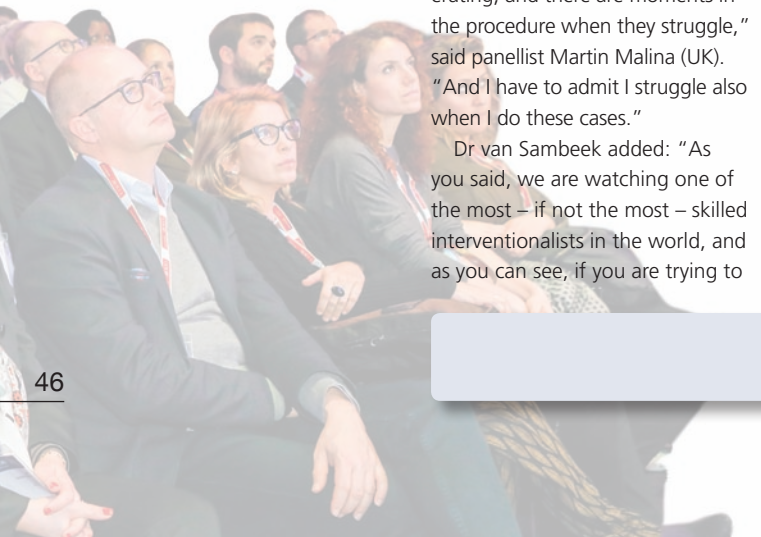


Final X-ray from the case

"You showed us that even the best interventionalists sometimes have struggles, and sometimes it is not easy to overcome these hurdles." Marc van Sambeek



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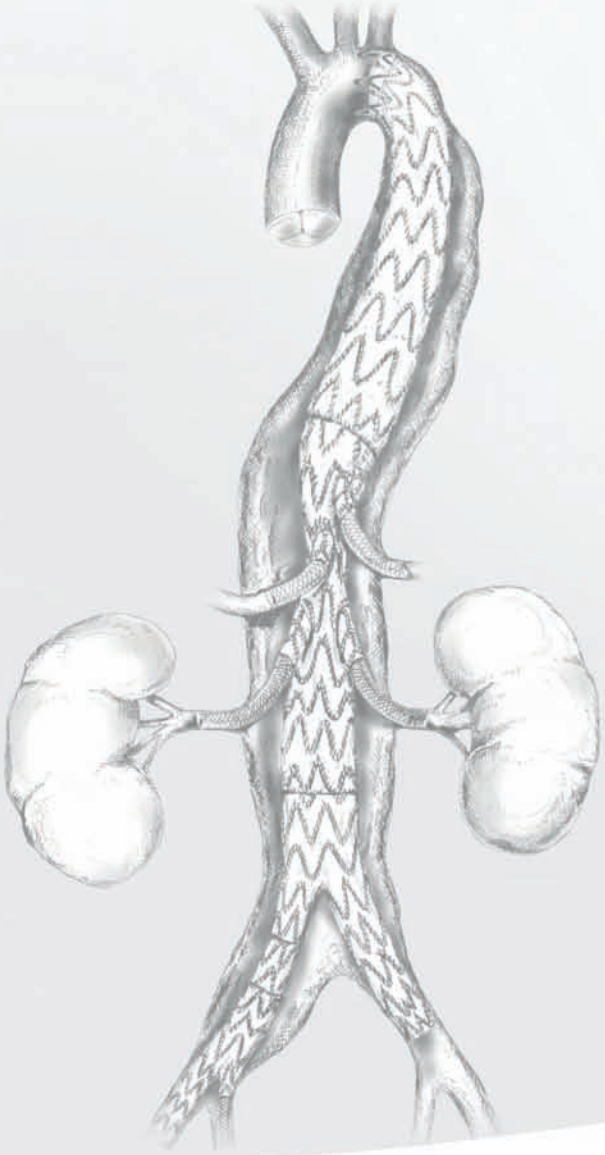

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CICE@LINC: Venous occlusive disease

Continuing LINC 2017's globe-spanning collaborations, the CICE@LINC session explored acute venous occlusive disease, with particular focus on the use of mechanical debulking as the first therapeutic option. CICE, the international Congress on Endovascular Surgery, took place this year between 5 and 8 April in Sao Paulo, Brazil.

During the CICE@LINC session, CICE course director Armando C Lobato (Sao Paulo Vascular & Endovascular Surgery Institute, Brazil) gave a step-by-step of mechanical thrombectomy in venous occlusive disease. Deep-vein thrombosis (DVT) remains an under-diagnosed phenomenon, explained Professor Lobato to *LINC Review* ahead of the meeting. Literature suggests that most episodes of DVT are asymptomatic, confined to the deep veins of the calf. 20-30% of these untreated thrombi extend proximally into the thigh over time, posing a 40-50% risk for pulmonary embolism (PE).[1]

There is evidence also that approximately 10-15% of PE are diagnosed only at autopsy. This is also true for upper extremity DVT (UEDVT), as patients are either asymptomatic or present with unspecific clinical symptoms.[2] "New treatment modalities for DVT and UEDVT are a whole new world and deserve a lot of thinking, researching and discussion. Therefore, we set dedicated sessions in our meeting."

He added: "In the last few years, interest in the treatment of DVT has skyrocketed. Compared to arterial re-interventions, the treatment of re-occlusions of veins is much more complex, sometimes even impossible, and always calls for a very experienced physician."

The various venous forums around the world are helping to initiate the differentiation between different types of DVT, he noted, which will in turn improve the outcomes for patients. "In many hospitals, we already find multidisciplinary units approaching the pathology from several points of view, following the patient from the emergency room to the interventional procedure, and later follow up."

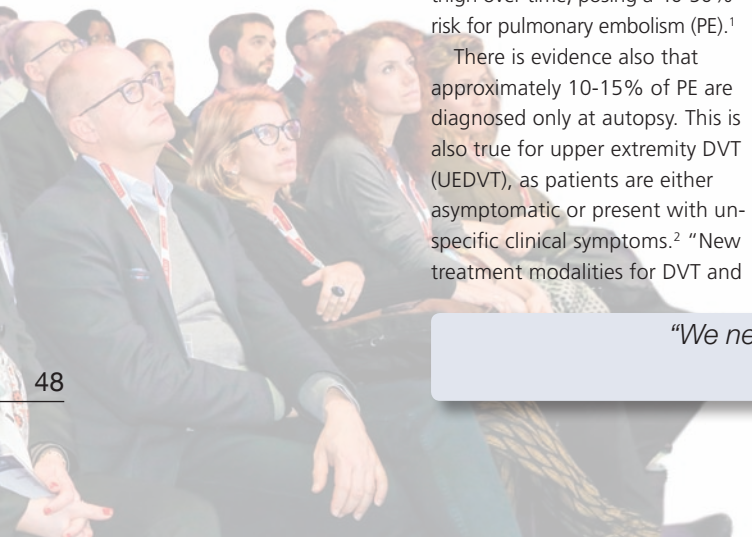

Armando C Lobato

Physicians need to be more aware and more alert to asymptomatic DVT and UEDVT, as well as to new treatment modalities, continued Professor Lobato. "Suspicion leads to investigation and to early diagnosis, which can prompt immediate treatment, which in its turn is the key to better results, reduced morbidity and better quality of life. Four items are determinative for success in these cases. The first is detailed diagnosis and patient assessment (of underlying diseases, life expectancy, contraindications); the second is the timeline to treatment institution; the third is physician expertise, and the fourth is availability of new devices."

Within the category of iliofemoral DVT in particular, the ACCP 2012 guidance considers mechanical thrombectomy an option only when certain conditions apply – symptom presence for <7 days, good functional status, life expectancy of ≥1 year, as well as the availability of both resources and expertise. Consensus literature has already extended this timeframe to 14 days, explained Professor Lobato, adding that even now the limit is unclear. "Our experience shows success in treatment of iliofemoral DVT in patients at 14/21 days from symptoms with the use of the effective thrombectomy devices available today such as the Aspirex S [Straub Medical AG, Switzerland].

"I guess we will need to wait for the results of ongoing randomised clinical trials of percutaneous mechanical thrombectomy compared with standard anticoagulation. Four ongoing studies have not published

"We need to be fast and effective since we know that otherwise, conservatively, 50% of these patients will develop post-thrombotic syndrome." Armando C Lobato



their results to date: the CAVA trial, the Sonic 1 Safety and Efficacy trial, the PEARL registry, and most importantly the ATTRACT study."

The aim of these trials is to assess whether more aggressive alternatives to anticoagulation can reduce the rate of development of complications such as post-thrombotic syndrome and recurrent venous thromboembolism (VTE). The Dutch Catheter Versus Anticoagulation trial (CAVA) is a multicentre randomised controlled trial comparing catheter directed thrombolytic therapy with anticoagulation in IFDVT.

The study population includes all consecutive patients with IFDVT presenting at the emergency or outpatient departments of the participating centres, with thrombus no older than 14 days at randomisation.[3]

Sonic 1 is a prospective, multicentre single arm registry assessing the use of the OmniWave Endovascular System (OmniSonics Medical Technologies, Inc., USA) in subjects presenting with either lower or upper extremity acute DVT (symptoms have been present for greater than or equal to 14 days).[4] The Pearl registry collects observational data about the clinical usage of mid-length AngioJet catheters (Boston Scientific, USA).[5]

The phase III, multicentre, randomised, open-label, assessor-blinded, parallel two-arm, controlled ATTRACT study commenced in 2008, and studies the use of pharmacomechanical catheter-directed thrombolysis for the prevention of post-thrombotic syndrome and the improvement of quality of life. The study recruited 692 patients with acute proximal DVT involving the femoral, common femoral, and/or iliac vein arm, and is expected to complete early this year.[6]

Turning to his own experience, Professor Lobato underscored the reasoning supporting the use of thrombectomy: "I perceive the value of more effective thrombus-removal treatments such as mechanical thrombectomy. Complete thrombus removal will create a better vessel situation and avoid fast re-occlusion. In quite a lot of old patients, we will find acute and chronic thrombus. The chronic thrombus has very wall-adherent, organised material, which currently cannot be removed. But the acute inner thrombus should be completely removed – so offering a channel for stenting with the new dedicated venous stents with high radial force.

"It is also well established that patients with iliofemoral DVT have a poor prognosis when treated with late thrombus removal strategies. We need to be fast and effective since we know that otherwise, conservatively, 50% of these patients will develop post-thrombotic syndrome within two years, and as many as 79% at 3-5 years. DVT is potentially a severe disease. Acutely, the situation can become life threatening due to the highly increased risk for PE. Post-thrombotic syndrome, as a result of an untreated or insufficiently treated proximal DVT, is a further threat to the quality of life of the patient as well as to their mortality."

Expertise and resources are fundamental to successful treatment of these patients, stressed Professor Lobato, with access to adequate devices forming just the tip of the preparatory iceberg. "IVUS would be very helpful to judge immediately after the intervention," he explained. "We also need dedicated venous stents and guide wires with good pushability (stiff and strong).

"Last but not least, we need a team with good knowledge of MRI, CT-V, venography and venous sonography, who are trained in the management of VTE patients from recovery to discharge. Understand-

"New treatment modalities for DVT and UEDVT are a whole new world and deserve a lot of thinking, researching and discussion." Armando C Lobato

CICE@LINC: Venous occlusive disease

Continued from page 49

ing the underlying pathology is vital to ensuring the correct treatment plan for the patient."

Planning, therefore, is crucial in the successful treatment of DVT patients. Rapid diagnosis in the emergency room with Well's Score evaluation, lays out the shortest path from diagnosis to treatment. IVC filters also play an important role, noted Professor Lobato, for the removal of thrombus in the IVC or iliac vein, as well as peri-procedural dedicated filters that can be positioned before the intervention, cleaned in case of embolisation and immediately and easily removed after the procedure.

"Performing our procedures with Aspirex, we also infuse saline and contrast in the vein to better visualise the procedure, and how the catheter is aspirating the thrombus during the back and forth movements of the catheter head," he added.

"Follow up at 1, 6, 12, 24, and 36 months is also essential for evaluating the results and ensuring the patients are given adequate post-procedure anticoagulation. Looking at the long-term results will help us all learn about the best treatment modalities for different patient sub-groups."

Why is mechanical debulking the logical treatment option?

Also speaking during the CICE@LINC session was Michael Lichtenberg (Vascular Centre Arnsberg, Germany), who discussed the evidence for mechanical thrombectomy followed by stenting for improving DVT outcomes.

Dr Lichtenberg began by underlining that when patients with iliac- and iliofemoral DVT are treated conservatively, the literature evidences a propensity for post-thrombotic syndrome (PTS) after a couple of years, which could be as high as 70%, with 'severe' being possibly as high as 23%. "So there is a clear need to treat patients with acute DVT of the proximal iliac and femoral system with an endovascular approach to help avoid post-thrombotic syndrome."

Building on the clinical implications, Dr Lichtenberg also spoke of the economic burden of PTS. Quoting a 2006 paper on annualised resource utilisation and costs for patients with PTS,[7] he noted that PTS patients had a clearly-increased cost ($20,569) versus non-PTS patients ($15,834).

Similarly, quality of life for patients suffering from PTS is very low, especially if they have a proximal DVT, Dr Lichtenberg added.[8] "But what do we know about the pathophysiology of acute DVT?" he continued. "We know that especially acute descending DVTs of the iliac system are associated with an underlying reason." He added that the seminal paper from Oguzkurt *et al*. did indeed find that significant stenosis could be found in many acute DVT patients.[9]

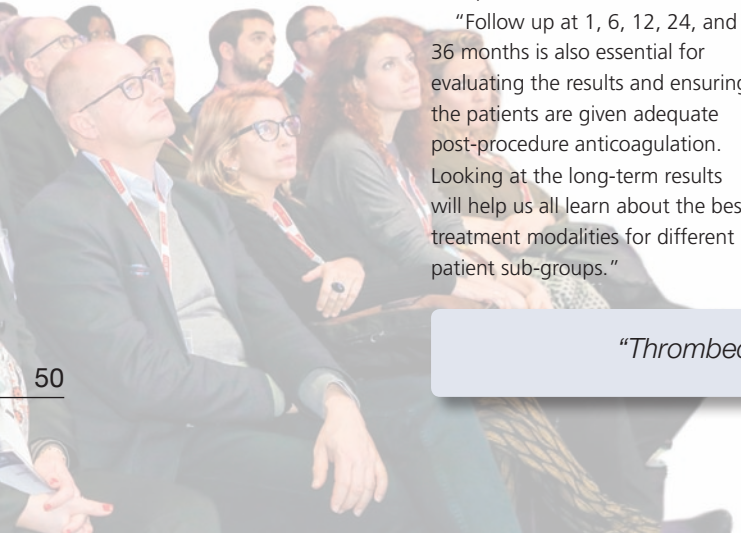
"Therefore the American Venous Forum, and the Society for Clinical Vascular Surgery in the United States said, in their guidelines, that '80% of iliofemoral DVTs, DVTs that involve the iliocaval segment in addition to the veins below the inguinal ligament, have an underlying iliac vein compression."

It is therefore paramount to treat the underlying cause of the DVT, Dr Lichtenberg stressed, adding that stenting can be a powerful way to achieve this for chronic iliocaval compressive or obstructive lesions that are uncovered by any thrombus-removing strategy.

Michael Lichtenberg

Turning to early clot removal strategies, Dr Lichtenberg said that he would not recommend the pharmacomechanical route, preferring purely mechanical devices instead. "You don't need any kind of additional lytic therapy … it is a safe and effective," he said. He went on to note that mechanical thrombectomy is also very effective for in-stent restenosis.

"Thrombectomy is effective in venous thrombus removal – even in more organised thrombi." Michael Lichtenberg



Concluding, he focussed mainly on the Aspirex mechanical thrombectomy device, commenting: "Thrombectomy is effective in venous thrombus removal – even in more organised thrombi. The Aspirex device is quite safe from my perspective, and restores vein patency in upper and lower limbs, and has a low risk, with fewer side effects.

"We do not have to send the patient to the ICU: we can 'end it in the angiolab' with a single-session approach. I personally believe that the pure mechanical thrombectomy approach will be a standard treatment, but do not forget to treat the underlying reason with a dedicated iliac vein stent."

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"I personally believe that the pure mechanical thrombectomy approach will be a standard treatment, but do not forget to treat the underlying reason with a dedicated iliac vein stent." Michael Lichtenberg

Budget impact model supports DCBs and DESs

This year's Boston Scientific symposium, 'Redefining SFA treatment in a drug eluting world' took the audience on a tour of the most recent data from their impressive portfolio of drug eluting technologies, with a much-needed focus on the increasingly important health economic data to support market access in Europe.

Dr Konstantinos Katsanos, Assistant Professor of Interventional Radiology (Patras University Hospital, Greece), presented the health economic data behind the use of drug-based technologies versus non-drug based ones, including data on Eluvia, Boston Scientific's drug-eluting vascular stent system.

"New drug-based technologies, whether drug-coated balloons or drug-eluting stents, have been shown to significantly reduce the need for repeat procedures, and in this way they reduce the associated healthcare costs for health systems, and at the same time improve clinical outcomes for patients," said Dr Katsanos.

"There was a lot of heterogeneity in studies driving the results, so although the balloons came out as the preference in some studies, and the stents were the preferred option in others, overall it is fair to say that drug-based technologies come out on top and are both equally effective," he remarked.


Konstantinos Katsanos

Plain balloon angioplasty often fails because of restenosis but this might be resolved by the use of drug-coated balloons and stents, he said. "Post-angioplasty stenosis has often been considered a benign process but it is not," he said, adding that the BASIL study (Bradbury AW, *et al*. J Vasc Surg. 2010 May;51(5 Suppl):18S-31S) provides evidence that a failed angioplasty can actually result in more amputations that can negatively impact patient survival and carry significant costs for the healthcare system."

Evidence shows that plain balloon angioplasty and bare metal stents rank as the least-effective treatments, and that the paclitaxel-coated balloons and stents rank as the top performers in terms of restenosis, and this minimises the need for a repeat procedure, added Dr Katsanos.

Whilst working in the UK at Guy's and St Thomas' Hospitals, London, Dr Katsanos developed a Budget Impact Model for payers based on a systematic review and meta-analysis of 28 randomised and pragmatic clinical studies comprised of 5,167 patients receiving femoropopliteal interventions. The model was designed to estimate 24 month costs to payers for four superficial femoral artery (SFA) index procedure modalities: percutaneous transluminal angioplasty (PTA, or plain balloon angioplasty), bare metal stents (BMS), drug-coated balloons (DCB), or drug-eluting stents (DES). Therapy-specific target lesion revascularisation (TLR) rates were factored into the calculation based on weighted pooling, as well as index procedure-specific repeat revascularisation strategies.

"This analysis confirmed that in comparison to the reference treatment, which was plain balloon angioplasty, the need for TLR can be significantly reduced on average from 36.2% to 19.4% with DES (including COOK Zilver PTX), 17.6% with DCB and ~10% with Eluvia. The latter is based on the most recently released data from the MAJESTIC study that investigated the treatment of femoropopliteal artery lesions with Eluvia.

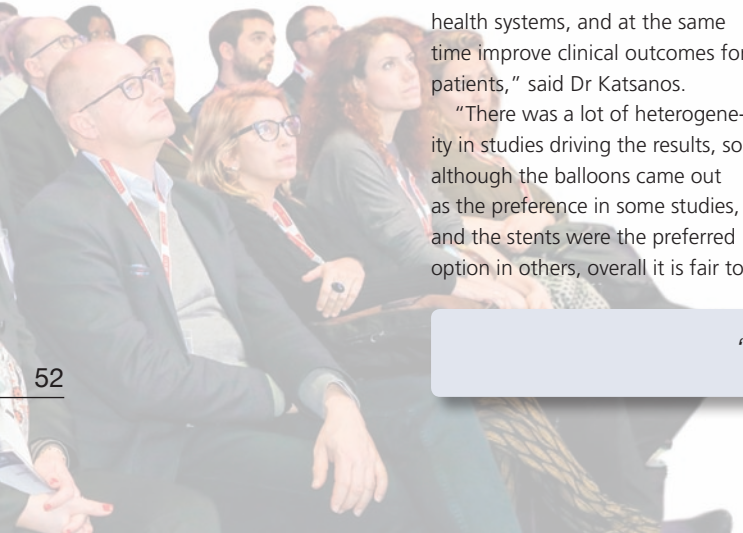
"This significant reduction in TLR translates into a number needed to treat [NNT] which is single digit in all cases of drug-based technologies. NNT was 5.4 for DCBs, 6 for DESs (not including Eluvia) and 3.8 for Eluvia," reported Dr Katsanos.

"With use of drug-coated technologies, we found that the cumulative cost adds up to being the same as the reference treatment at 24 months," he said. These UK payer costs, that incorporated both the device and the re-intervention costs, were £2,863 for PTA; £2,975 for BMSs; £2,906 for DCBs; £2,907 for DESs (not including Eluvia) and £2,710 for Eluvia.

"Not only does a patient have significantly improved clinical outcomes with the significant reduction of TLR, but it is cost neutral," said Dr Katsanos. "It is a no-brainer that drug-eluting technologies need to be adopted."

These results were replicated when use of the four modalities was assessed in Germany. Because the market dynamics are different from the UK, the results show that drug-eluting technologies actually reduce costs. Drug-eluting technologies were associated with improved clinical outcomes and represented cost-savings of between 10–14% compared to PTA at 24 months. "Germany shows the lowest re-intervention cost for DCBs.

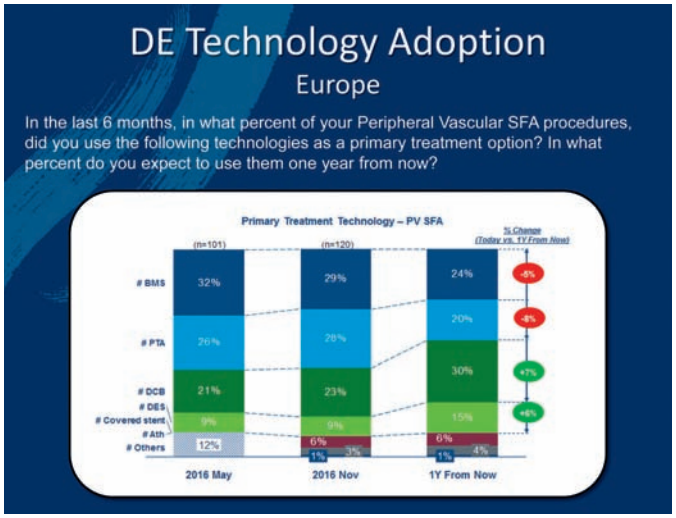
"With the projection for the Eluvia stent which is slightly more effective still [compared to other DESs], the cumulative cost for the UK is less, and in the future there



"It is a no-brainer that drug-eluting technologies need to be adopted." Konstantinos Katsanos

would be cost savings with Eluvia use," emphasised Dr Katsanos. "Overall, the better the stent the less the TLR and the lower the budget impact."

In terms of the incremental cost-effectiveness ratio (ICER), bare metal stents were found to have an ICER of around £20,000/QALY; drug-coated balloons around £4,000/QALY; DES was £4,500/QALY; and Eluvia was £2,300/QALY, reported Dr Katsanos.



Slide courtesy of Boston Scientific

Eluvia – Drug-Eluting Stent

Turning to Eluvia in more detail, Giovanni Torsello, Professor and Chief of the Department of Vascular Surgery, St. Franziskus-Hospital, and Chair and Head of the Center of Vascular and Endovascular Surgery, Münster University Hospital, Germany provided a data overview of the paclitaxel-eluting vascular stent system, which obtained its CE Mark in Europe last year.

Eluvia, which is built on the company's Innova stent system, restores blood flow in the peripheral arteries above the knee specifically in the superficial femoral artery (SFA) and proximal popliteal artery. It features a drug-polymer combination designed to provide sustained release of paclitaxel to prevent restenosis of the vessel. It is designed to optimise flexibility and have greater fracture resistance.

Timing of SFA restenosis is around 6-12 months. "This presents two unmet medical needs: firstly a need for a flexible stent that is resistant to fracture, but secondly a stent that is resistant to restenosis at the right time," said Professor Torsello, and referring to Eluvia, he added that, "In Europe for the past year, we have had a stent that meets these needs in femoropopliteal disease."

Drawing attention to the role of the polymer in sustained timing of the drug release that lasts for more than one year, Professor Torsello referred to the results from a recent preclinical study (Kaluza G, LINC 2016) saying: "In this case the drug release co-exists with restenosis. Results compare Eluvia with the Zilver PTX and the Innova stents after one and three months. It shows that the Zilver PTX and Eluvia reduce the neo-intima thickness at 90 days. Also, after three months with Eluvia the results are better than with the other products."

Professor Torsello commented on the findings from the MAJESTIC study, pointing out that the results were very impressive with freedom from TLR by Kaplan-Meier estimate at one year of 96.4% and after two years, 91.3%, without any fracture or amputations. These findings also applied in patients at high risk of restenosis.

These results correspond very well to the improved sustained outcome of the patients, according to Professor Torsello. "Up to two years, it was found that 91% of patients had no symptoms [wRutherford Category 0–1]. These are really good results."

Boston Scientific's ongoing randomized controlled trial (IMPERIAL) is evaluating the safety and efficacy of Eluvia compared to the Zilver PTX stent. The company has also begun enrolling in the EMINENT trial in Europe that aims to confirm the superior effectiveness of Eluvia to self-expanding bare metal stents in femoropopliteal lesions.

Ranger DCB uptake lags behind in Europe

Gunnar Tepe, Professor of Radiology (Klinikum Rosenheim, Rosenheim, Germany) gave a talk entitled Drug coated balloons: for all or some? Amongst others, he discussed Boston Scientific's Ranger DCB in both above-the-knee and below-the-knee lesions.

Combining the Sterling balloon

Continued on page 54

"After three months with Eluvia the results are better than with the other products." Giovanni Torsello

Continued from page 53

platform with the long-established drug paclitaxel, the Ranger DCB is designed for maximum delivery of the drug to the vessel wall, by minimizing drug loss from the balloon coating. Drug loss may impact the efficacy of other DCBs.

In deciding whether to use a DCB or a DES, Professor Tepe said it depended on the lesion. "With severe calcium, drug coated balloons and stents might have limitations so I consider adjunctive atherectomy or lithoplasty. Secondly, during the intervention, I pre-dilate the vessel and if this looks fine I then move on with a DCB straight away. If it doesn't look good then a stent is considered, and a DES should be used for its anti-proliferative properties."

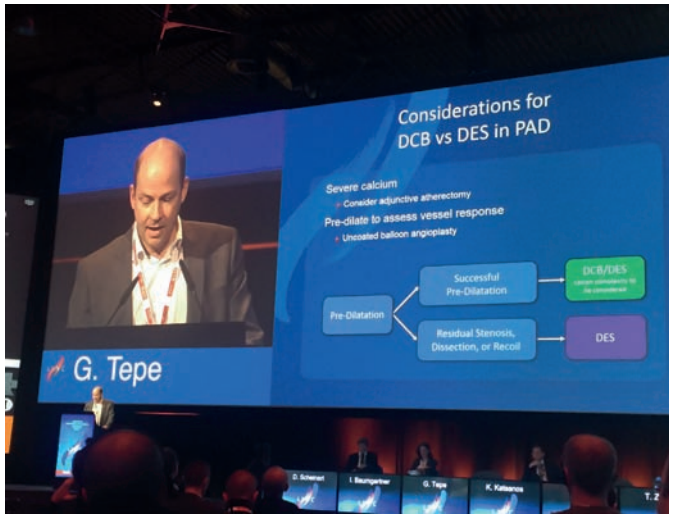
Lesion length is also a consideration, he added. "With short lesions, a DCB is fine but with longer lesions a DES might be superior."

Professor Tepe referred to the six-month results of the Ranger–SFA trial during his talk. In this first-in-human trial, the Ranger DCB was investigated in lesions of the SFA and popliteal artery in 105 patients. Late lumen loss at six-months post-procedure was the primary endpoint.

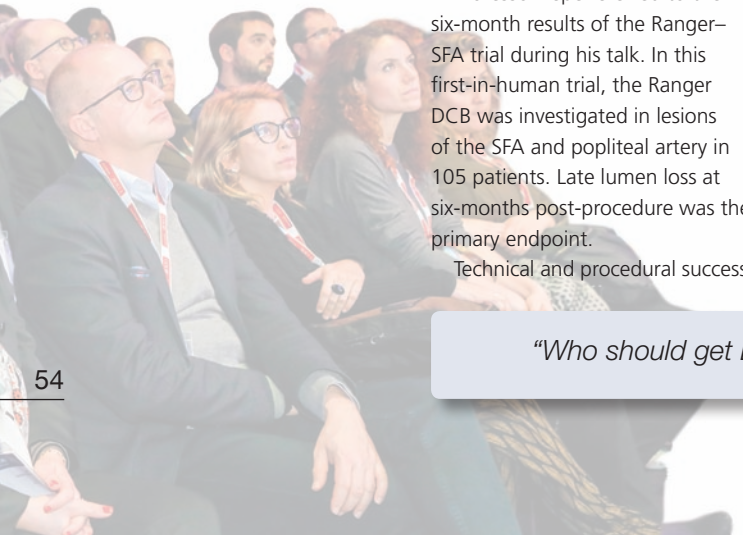
Technical and procedural success rates were similar between active and control groups. Patients treated with the Ranger DCB demonstrated significantly less late lumen loss at six months compared to those in the control group. Late lumen loss was +0.76 mm versus -0.16 mm (p=0.0017) in the control versus Ranger DCB groups respectively.

TLR rate was halved at 12% in uncoated balloons versus 5.6% for Ranger. Clinical findings included 81% of Ranger DCB patients who presented with no or mild symptoms at six months, and according to ankle brachial index (ABI), both groups showed significant improvement at six months, said Professor Tepe.

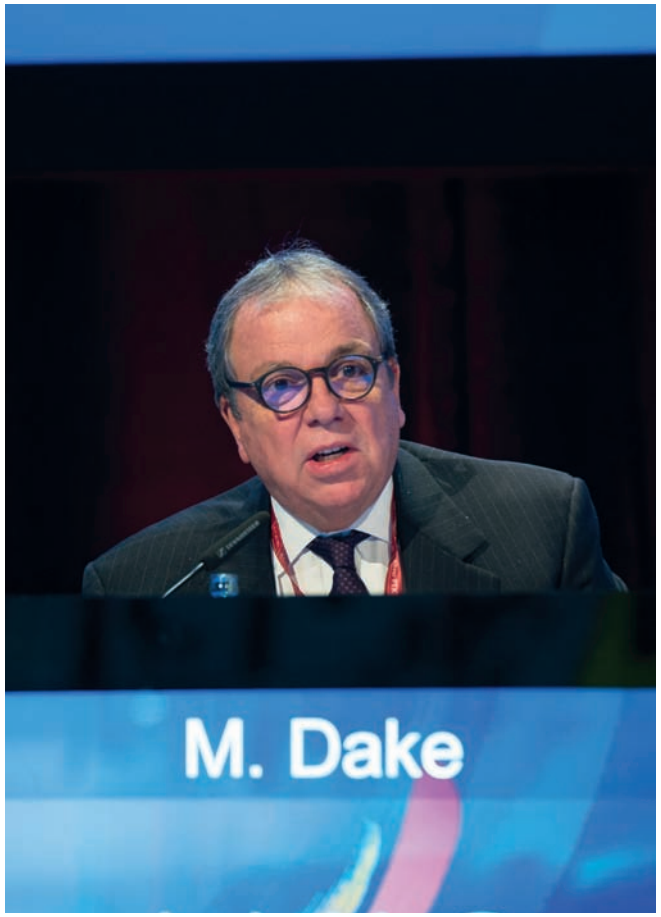
The expert in DCBs concluded his talk by referring to uptake rates of drug-eluting technologies. "Who should get DCBs or DES? All or some patients?" he asked. Showing figures from Europe, he said the current percentage of patients that get drug-eluting technology is 32% "In the US, which started much later with this technology, the adoption rate is much higher. This is an issue, but I don't know why it is the case. I believe far more patients in Europe could have drug-eluting technologies."



"Who should get DCBs or DES? All or some patients?" Gunnar Tepe



The Great Debate:



On the Thursday of LINC 2017, Boston Scientific sponsored the 'The Great Debate: Meet the venous experts' session, designed to address the burning issues on venous interventions.

Chairing the session was Thelma and Henry Doelger Professor

"In reality there's a huge patient population that can benefit from these [venous] therapies." Michael Dake

‘Meet the venous experts’

of Cardiovascular Surgery, Michael Dake, from Stanford University School of Medicine, CA, US.

He spoke to *LINC Review* after the session and summarised his overall impression of the discussion around venous disease today. “These venous sessions have been absolutely standing-room only,” he stressed. “There’s clearly huge interest in this venous area, but I think we saw that there is still an unmet need for physicians and delegates. I was pleasantly surprised that the subject was so embraced, and this session, like every session on venous work, was just packed.”

The four speakers were Stephen Black (‘Clinical work-up of the venous patient – what is essential?’, Consultant Vascular Surgeon at Guy’s and St Thomas’ NHS Foundation Trust, London, UK); Gerard O’Sullivan (‘What is the optimal technique for thrombus removal in acute DVT?’, Consultant Interventional Radiologist at Galway University Hospitals, Ireland); Nils Kucher (‘How to best approach chronic venous occlusions?’, Vascular Surgeon, University Hospital Bern, Switzerland); and Rick de Graaf (‘What are the features of the ideal venous stent?’, Interventional Radiologist in the Department of Radiology at Maastricht University Medical Centre, the Netherlands).

“I think the four panellists, who are the experts in Europe, are testament to the excitement around treating venous disease. It’s getting a lot more exposure, a lot more face-time. Europe has kicked it up a notch,” Dr Dake pointed out. He went on to explain that interest in treating venous disease started in the US, back in 1992, when he and his colleagues published their first paper on the subject. Following this, in the US, there was a surge in interest, but in Europe the fear of lytic-related cerebral bleeds outweighed any research agenda and interest lay low for years. “But now it’s going stronger than in the US, which has shown a much more gradual interest.”

Dr O’Sullivan commented, “Thanks to the work of our colleagues, a lot of exciting work is happening now. I think we now have access to medical devices quickly, so we have the newest and the best stents, and thrombectomy devices quicker. We are seeing the benefits of technological development.”

Dr Dake drew attention to the fact that in the near future data from the ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial from the US National Institutes of Health (NIH) would be released. The trial will determine if the use of pharmacomechanical catheter-directed thrombolysis in patients with acute proximal DVT prevents post-thrombotic syndrome and improves quality of life.

“We are only just seeing the tip of the iceberg, because as opposed to arterial disease, venous disease is the stepchild,” noted Dr Dake. “In reality there’s a huge patient population that can benefit from these therapies, but who are being told by their family physicians to just live with it. Now we are exposing not only physicians but patient groups to the fact that there are new ways to treat this.”

With this, there have been new technologies that recognise that this is an opportunity, and equipment is custom designed for venous disease. This is despite limited understanding of all the factors that would make a venous stent different from an arterial stent. “Now people are seriously looking at it and researching. Before they would just take a stent designed for an artery and put them in a vein, and these are very different,” added Dr Dake.

He highlighted that there was not a “single way to do this [treat venous disease], it is more art than science but it is starting to coalesce into some key considerations that everyone is starting to embrace as standard of care.”

Asked to summarise some key points from the discussion, Dr Dake noted:

- Most interest is in treating patients with ilio-femoral DVT with pelvic involvement. There is less interest in exclusively infrainguinal or femoral DVT. “The real benefits come from improving the proximal or more central involvement in the iliac – the trunk of the tree, not the branch,” he said.
- The value of stents is critical. Previously, there has been doubt about whether a stent would remain patent or if there would be restenosis. “In light of this, physicians were not using stents aggressively. Now, the treatment rate with stents is around 80-90%,” said Dr Dake.
- Anticoagulation: Dr Dake explained that it was necessary to protect a stented fragment by anticoagulating and there was agreement that three months was the right length time.

Among the many aspects of venous disease discussed, one area highlighted by Professor Kucher was the lack of standardised lysis regimen for DVT patients. “Some centres still use lysis for two to three days and we know that prolonged thrombolysis causes systemic bleeding complications, so we need to standardize lysis. In Bern, we use a fixed dose regimen of 20 mg TPA for 15 hours and nobody gets more than that. If we do not achieve flow then we use adjunctive treatments including mechanical thrombectomy or stenting. If there is no lysis after a day it is unlikely to lyse thereafter.”

Dr de Graaf questioned whether the stent should be as flexible as possible or as rigid as possible. “I don’t know,” he said. “I can talk about what not to do and this includes not stenting into the vena cava across to the other side. That would not be wise.

“I would like a stent that is foolproof, a stent that does not cause stent related patency loss, does not cause additional complications including contralateral DVT and pain in the groin or upper leg and this can happen if the stent is too stiff,” he pointed out.

“We are only just seeing the tip of the iceberg, because as opposed to arterial disease, venous disease is the stepchild.” Michael Dake

Acute DVT: ready for a paradigm shift?

A discussion of the data surrounding acute deep vein thrombosis (aDVT) was given by Iris Baumgartner (University Hospital, Bern, Switzerland), whose central focus was to address an important question in the field: Are we ready for a paradigm shift in treating aDVT?

"At the bottom of my heart, I would say 'yes' and then end my talk! But I will be a little bit more critical," she began. "Venous thromboembolism (VTE) is a major health problem that I think we are all aware about. There is a pulmonary embolism (PE) related increase in mortality. We have a 30% recurrence rate over time, particularly in the proximal ones. And we have complications, in particular post-thrombotic syndrome (PTS), but also pulmonary arterial hypertension and venous claudication. If we give that in numbers, there is a five-year cumulative severe PTS incidence that is 10%.

"In numbers, if we go to Europe we have about 760,000 DVTs per year. That is counting in 370,000 associated mortalities, mainly due to thromboembolism in the pulmonaries. These are quite [big] numbers. But if we go back to the initial question [are we ready for a paradigm shift in interventional treatment?] then we have to look a bit deeper into the anatomical location of the DVTs.

"The recent analysis published by De Maeseneer *et al* (2016)[1] of 1,338 patients with acute DVT, spoke to this issue. 38% of the total cohort had a proximal iliofemoral thrombosis involving at least the common femoral vein and/or the iliac veins, with or without inferior vena cava involvement. The remaining 62% femoropopliteal lesions occurred below the level of the groin (at least occurring in the popliteal and/or femoral vein). 28% of the total cohort had DVT isolated to the calf veins."

Professor Baumgartner noted the "We are focusing on this one-third of [iliofemoral] patients," adding her thoughts on the "ideal" candidate for interventional treatment: "Potentially, all patients with iliofemoral DVT are candidates for early clot removal. Of these patients, those with no calf and popliteal vein thrombosis have better outcomes following invasive treatment, and in the present study[1] this is about 12%, which counts as about 80,000 candidates for clot removal annually in Europe."

With real-world data, a recently published US study of proximate aDVT treated invasively compared catheter-directed thrombolysis (CDT) plus anticoagulation with anticoagulation alone. This was a propensity-matched observational study with a primary outcome was in-hospital mortality. Out of a total of 90,618 patients hospitalised for DVT (generating a national estimate of 449,200 hospitalisations), 3,649 (4.1%) underwent CDT. The CDT utilisation rates increased from 2.3% in 2005 to 5.9% in 2010.[2] "If we go with the defined 'ideal candidate', 6% [CDT utilisation] is about 50% of the ideal candidates, so there does not seem to be a question of interventional resources – quite a bit of the patients are already being treated invasively in the US," said Professor Baumgartner.

However, no difference in in-hospital mortality was found between the CDT and anticoagulation-alone groups (1.2% vs 0.9%; OR, 1.40 [95% CI, 0.88-2.25]; p = 0.15). The rate of PE was significantly higher in the CDT group (17.9% vs 11.4%; OR, 1.69 [95% CI, 1.49-1.94]; p < 0.001), and this difference was also found for complications such as blood transfusion and intracranial haemorrhage.[2] "The conclusion from that registry was that therapy really should be offered to patients with a low bleeding risk, because this is already increased with this kind of treatment," said Professor Baumgartner. Another important insight, she said, is the learning curve demonstrated in the year-on-year decrease of mortality rate (from

"I think that the way we go today is adding stenting to the crucial compression in the iliacs or residual thrombosis in the iliofemoral after lysis." Iris Baumgartner

1.3% in 2005 to 1.0% in 2010 (p<0.005)). This learning curve was shown in both arms, due, explained Professor Baumgartner, to the implementation of new pharmacomechanical therapies and improving expertise. However, bleeding complications including intracranial haemorrhage and blood transfusion rates continued to be higher in the CDT group.[2]

Turning to the issue of bleeding, Professor Baumgartner described the CaVenT trial, which looked at additional CDT versus standard treatment for iliofemoral aDVT.[3] The trial demonstrated a statistically significant improvement in PTS over a 42-month time period, with incidence at 41% versus 56% in the CDT group and the control group, respectively (p=0.047). Iliofemoral patency after six months was 65.9% for CDT versus 47.4% for controls (p=0.012). "There was a mean thrombolysis duration of 2.4 days and a daily dose of 20 mg rtPA per day, and a stenting rate of 17%," she said.

"There were 20 bleeding complications related to CDT, included three major and five clinically relevant bleeds [out of 90 CDT subjects at 24 months completion]. Together, this resulted in an efficacy endpoint of the absolute risk protection of PTS over 24 months of 14.4%. "I think that the way we go today is adding stenting to the crucial compression in the iliacs or residual thrombosis in the iliofemoral after lysis."

During the same period of 2010-2014, the BERN registry recorded a stenting rate of 80%, concluding that a fixed-dose USAT regimen followed by routine stenting of underlying venous stenosis in patients with ilio-femoral DVT was associated with a low bleeding rate, high patency rates, and a low incidence of PTS.[4] "If we compare that with the CaVenT results of primary patency and secondary sustained clinical outcome, this means no PTS by adding stenting to lysis. We can considerably improve clinical outcomes for these patients.

"Also in the BERN registry, we had complications in 11% of patients. There was no symptomatic PE during the hospital stay, 1% major bleeding, and clinically-relevant minor bleeding in 7%. I think this is the road we have to take." Returning to her original question regarding a paradigm shift in the treatment of acute DVT, Professor Baumgartner concluded: "I would say yes. It is an improvement for the patient, regarding PTS, quality of life and patency of the iliofemoral lengths. However, the acceptance overall is related to a treatment that might reduce incidence of PTS, but at the cost of bleeding complications, as I have shown.

"Right now, there is no effect on PE-related mortality. It has not been shown yet. There was even a higher rate in the real-world data from the US registry. There is no reduction in recurrence rate shown yet, but this might be related to power. And it is dependent on technical refinement as I have shown it. There is still a learning curve, an evolution in devices being available, and in techniques being adapted to these patients."

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"If we go to Europe, we have about 760,000 DVTs per year." Iris Baumgartner

Re-entry catheters for challenging CTOs

Challenging femoropopliteal lesions were the topic of a Scrub-in with the experts session on Tuesday at LINC 2017. The session mingled live cases from Leipzig and Cotignola with discussion of CTO crossing techniques, retrograde femoral access, and re-entry devices.

The development of the subintimal passage technique made treatment possible for certain tough CTO cases where true lumen passage is found to be unyielding. Procedural success revolves around operator experience as well as lesion complexity. While the highly-experienced operator might simply require a wire and catheter, the last decades have also seen the development of new devices and techniques designed to overcome technical failures – thereby improving success rates for the less experienced, as well as reducing procedural time, and limiting radiation exposure. A 2008 systematic review by Met *et al*. concluded that, despite moderate patency rates at one year, and technical success in 80-90% of cases, subintimal angioplasty could serve as a 'temporary bypass' to facilitate wound healing.[1] More recently, last year's Cochrane review of subintimal angioplasty for lower limb arterial CTO noted that quality of evidence supporting its use over other techniques is low overall at present. Nevertheless, the review included studies demonstrating the success of subintimal angioplasty in TASC-II D SFA CTO patients[2]. In 2016 the ZEPHYR investigators demonstrated no significant difference in restenosis rates between true lumen and subintimal passage using a propensity-matched comparison.[3]

In conversation with *LINC Review*, Matthias Ulrich (University Hospital Leipzig, Germany) described when and why he turns to subintimal passage: "If possible, I try to pass through the lesions in the lumen (especially in stenoses), but this is often not possible with occlusions. For long and calcified arterial occlusions, subintimal recanalisation is quicker and often simpler than intraluminal recanalisation. And this does not seem to influence the therapy success."

Commenting on the ZEPHYR subanalysis, which only included patients treated with the Zilver PTX drug-eluting stent (Cook Medical, USA), he added: "It is probably, but not known for sure, whether this result also applies to uncoated stents and/or drug-eluting balloon."

Re-entry forms one of the most challenging elements affecting technical success in subintimal passage, with the possibility of its failure as well as extension of dissection. In a study of subintimal angioplasty of 506 infrainguinal artery occlusions, Scott *et al*. examined feasibility, patency, and clinical outcomes; out of a total of 67 unsuccessful cases, failure to re-enter the true lumen accounted for 73% (n=49).[4]

Re-entry catheters were designed to ameliorate this issue, explained Dr Ulrich, who co-authored a 2011 paper investigating mid- and long-term outcomes with the Outback re-entry catheter (Cordis, USA). The study included patients with claudication or CLI whose procedure demanded the use of re-entry device due to wire re-entry failure, achieving re-entry in 108 out of 118 cases.[5]

"A core problem of subintimal recanalisation is distal re-entry, so re-entry devices are very helpful – the success rate is indeed very good," said Dr Ulrich. "Of course, success is also dependent on the experience of the interventionist, but also on the choice of the appropriate device. The popularity of the different currently-marketed re-entry catheters has changed since their invention, due to a combination of factors including technical refinement, alternative access, and the development of new crossing tools. Explaining how this has evolved in his centre, Dr Ulrich noted: "A few years ago we used a lot of re-entry devices – the

Matthias Ulrich

"A core problem of subintimal recanalisation is distal re-entry, so re-entry devices are very helpful." Matthias Ulrich

Outback, the Pioneer (Volcano Corporation, USA), and the OfFRoad (Boston Scientific, USA). The re-entry device is usually used only after the less costly options have been tried – for example, different CTO wire, stiff Terumo wire, wire loop technology, PTA, dedicated support catheters, etc.

"Most re-entry devices are used at the SFA and popliteal level, rarely in the lower leg, and even more rarely in the pelvis. But since we have specialised in retrograde puncture in Leipzig, our consumption of re-entry devices has declined slightly."

Adding advice drawn from his own lengthy experience with re-entry devices, Dr Ulrich continued: "The success of the procedure depends on the correct application of the re-entry device. First, subintimal recanalisation should take place. Distally, look for a less calcified segment with not too many collaterals for the puncture. The distance from the device to the true lumen should be as short as possible.

"If, in particularly difficult cases, the re-entry device is combined with a retrograde puncture, some more options are available – for example, the puncture of a retrograde balloon with the re-entry device. With this, the success rate is even higher.

"Distal collaterals can make success more difficult. One other limitation for all devices is massive calcification. Occasionally, it is necessary to make a subintimal predilatation in order to control the device."

Depending on the particular system, orientation is guided by IVUS, as is the case with the Pioneer. The Outback can be used without IVUS, as it possesses markers at its tip to indicate orientation and angulation. "It is very important to know that the puncture needle is not located directly at the tip of the device," concluded Dr Ulrich.

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"If, in particularly difficult cases, the re-entry device is combined with a retrograde puncture, some more options are available – for example, the puncture of a retrograde balloon." Matthias Ulrich

Viabahn rises to two-year challenge in Japan IDE trial

The national principle investigator of the Viabahn Japan investigational device exemption (IDE) trial for complex superficial femoral artery (SFA) lesions presented the trial's two-year results during a session focussed upon new concepts in complex femoropopliteal lesions. Takao Okhi (Jikei University, Tokyo, Japan) emphasised the importance of going beyond 12 months of follow-up, as well as making comparisons with similar studies to expose some of the factors that contributed to the Japan IDE study's success.

The Viabahn endoprosthesis (WL Gore & Associates, DE, USA) gained approval in Japan in February 2016 on the basis of this trial's 12-month data on complex SFA disease. The device is composed of an ePTFE tube bonded to a nitinol support structure, with contoured proximal edge and CBAS heparin surface. It comes in lengths of 2.5, 5, 10, 15 and 25 cm with diameters of 5-13 mm. The latest 2016 model – 0.018" compatible – was adopted in the Japan IDE trial.

The single-arm prospective study was set in 15 Japanese sites, and recruited 103 patients who were generally otherwise indicated for bypass. Primary endpoints included primary assisted patency, with secondary endpoints of safety defined as freedom from death, target vessel revascularisation (TVR) and major amputation of the treated limb through 30 days post-procedure. Primary patency was defined as haemodynamic blood flow through the device that had not required a TVR to maintain or restore blood flow, while secondary patency was defined as no performance of bypass surgery and no occlusion at the target site.

Follow-up was carried out at one, three, six, 12 and 24 months with duplex ultrasound. Annual visits continue through to five years, in order to ascertain fracture occurrences and adverse events.

Inclusion criteria allowed the recruitment of patients within Rutherford class 2-5, with ankle brachial index (ABI) ≤ 0.9 or tibial brachial index (TBI) ≤ 0.5. Angiographically, only lesion lengths longer than 10 cm were included, with no upper limit. Patients who had had previous stenting or surgical interventions in the target vessel were excluded, as were those with active infection in class Rutherford 5, and those on dialysis at the time of recruitment.

Dr Okhi noted the lessons from previous trials that guided the Viabahn trial's protocol development: "When we looked at the Viper trial[1], it was obvious that proper sizing was crucial in obtaining long-term patency. Keeping that in mind, in this trial we incorporated these rules to do a quantitative angiography to measure the vessel size and if possible to use intravascular ultrasound."

Demographics data show the majority of patients to be male

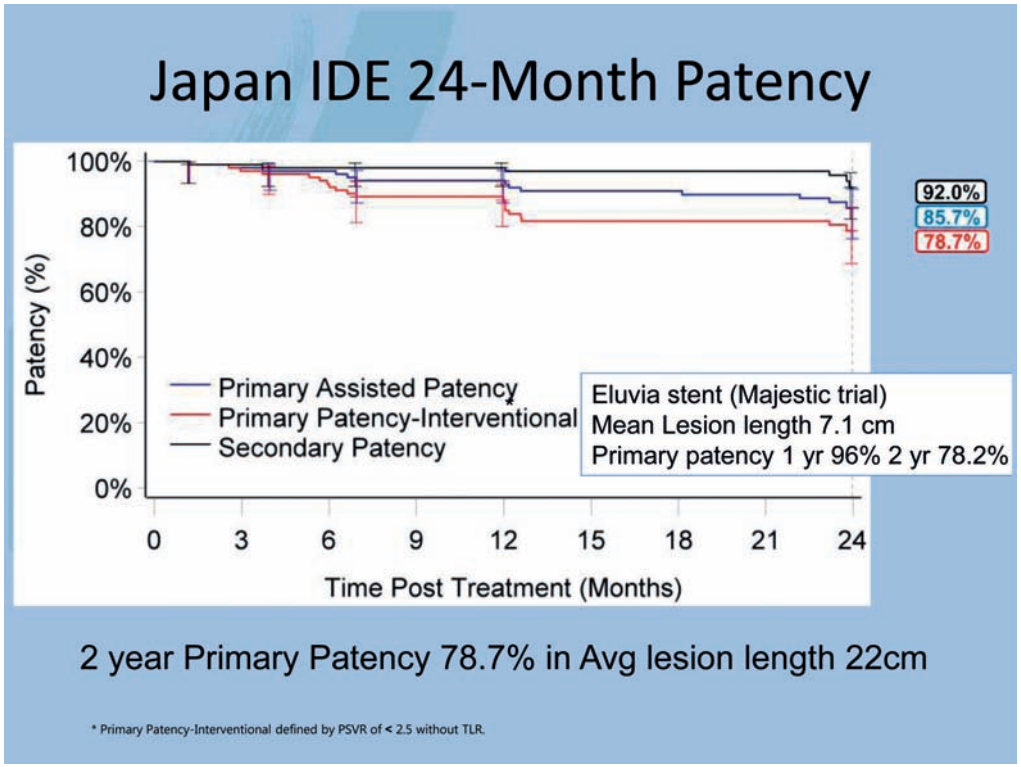

Figure 1. Two-year patency rates of the Viabahn Japan IDE trial, which were comparable to the Majestic trial's[2] patencies despite significantly longer mean lesion length in the Viabahn trial (22 cm vs. 7.1 cm).

"We were pretty happy to see that these patency rates were pretty flat beyond the 12-months point." Takao Okhi

(82.5%) of mean age 74.2 years, with a high prevalence of current or former smokers (78.7%). 60.2% were diabetes, and most were claudicants (97.1%). Mean lesion length was 22 cm, and 65.7% of lesions were totally occluded. 84.5% of lesions were either TASC C or D.

12-month data is shortly to be published. Primary patency at 12 months was placed at 88.1%, freedom from TLR 93%, and secondary patency 98.0% – encouraging, especially given the make-up of the cohort. "It was very respectful data," commented Dr Ohki.

"We learned [earlier at LINC] that one-year success does not guarantee long term success: the Eluvia stent [Majestic trial[2]; Boston Scientific, MA, USA] showed one-year patency of 96% in fairly short [7.1 cm] lesions, but the two-year patency was a pretty disappointing 78.2% (losing 18 points in one year).

"We were very keen to look at the Viabahn data and we were pretty happy to see that these patency rates were pretty flat beyond the 12-months point [out to two years] – 78.7% primary patency, and 85.7% primary assisted patency (Figure 1). We did not see the significant drop-off that we saw in the Eluvia trial. Freedom from TLR – a respectful 87% at two years."

Subanalyses of two-year results by lesion length compared those ≤ 20 cm (mean 16.2 cm, n=43) with those >20 cm (mean 25.7 cm, n=60), with the finding that shorter lesions fared better over this timeframe (85.0% patency vs. 73.9% at two years). "But even those longer than 20 cm had primary patency of 73% and were above our expectation," stressed Dr Ohki.

Subanalysis by device size indicated that greater device diameter was associated with superior primary patency over the two-year period; however, it was unclear whether this was simply a function of the diameter of the vessel itself. "You have to take this with caution, because we correctly sized the stent sizes based either on quantitative angiogram or IVUS," said Dr Ohki. "In the VIPER trial, the 6 mm stent group did not do so well, and that is probably because they were placing 6 mm in a vessel that really required a 5 mm. So if it is correctly sized, then bigger is better."

Interestingly, despite primary patencies (defined as peak systolic velocity ratio (PSVR) <2.5) significantly differing between device diameters, freedom from TVR did not. This, explained Dr Ohki, was due to the fact that PSVR failure often did not result in TVR in patients with 5 mm-diameter devices.

Further addressing the reluctance of some operators to cover collaterals with devices such as the Viabahn, Dr Ohki continued: "In our trial, we followed a 'complete lesion coverage' policy – from healthy to healthy vessel. We observed 13 patients with occlusions, but there were no patients that showed up with acute limb ischemia. Limb salvage was 100%; no death, and no major amputation despite going from healthy to healthy.

"As long as we follow best practice rules, excellent results can be achieved."

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"As long as we follow best practice rules, excellent results can be achieved." Takao Okhi

SITE@LINC: Unmet needs in EVAR and TEVAR


Vicente Riambau

The 12th International Symposium on Endovascular Therapeutics (SITE), which took place between 29 and 31 March this year at the University of Barcelona's School of Medicine in Spain, joined LINC 2017 in a collaborative session that provided updates on the current evidence, unmet needs, clinical questions and technological conundrums, as well as exploring the future directions in vascular diagnosis and advanced endovascular therapies.

SITE@LINC focused on key areas, namely: the major limitations for endovascular repair of para- and supra-renal aneurysms; whether TEVAR needs to be considered in all type B dissections; the major limitations for endovascular repair of para and supra-renal aneurysms; and the need for centralisation in EVAR and TEVAR.

The SITE symposium is held every other year, while the SITE Update meeting runs during each non-symposium year and is more focussed towards an expert audience. In comparison, SITE is more of a traditional congress meeting with free paper sessions, posters, workshops, and a lot of discussion.

SITE chairman Vicente Riambau (University of Barcelona, Spain) described the new features of this year's symposium, in conversation with *LINC Review*. "The congress has moved to the medical school this year, because it has new facilities. We [aim] to create a more academic environment too – to escape a little bit the formulas that are more commercially-driven.

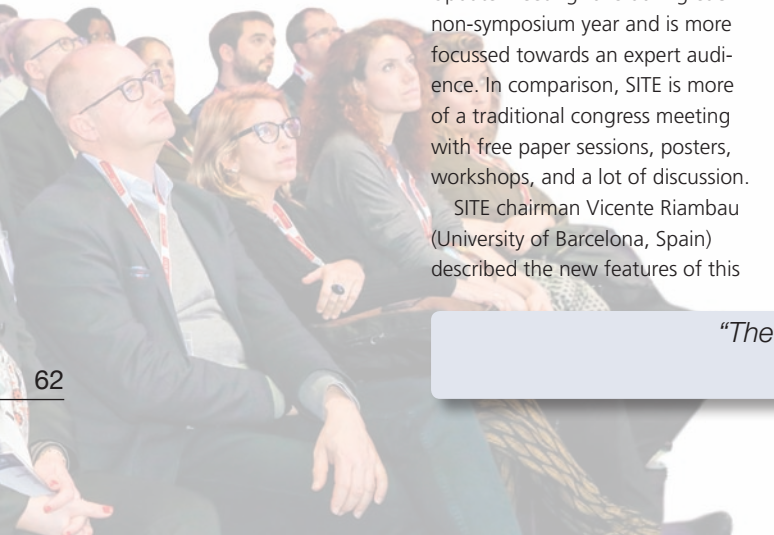
"We also tried to perform a lot of discussion in terms of more practical tips and tricks; we have more 'top secret' sessions, where we hear tips from the experts about facing specific procedures."

With only a small exhibition area, emphasis is given to its two main rooms running parallel sessions across three full days beginning at 8am and concluding at around 7pm. "It is non-stop, really," noted Dr Riambau. "Although there are lunches, they are also working lunches. And there are lunchtime symposia.

"Both rooms run in parallel but with very different topics, so that, for example, thoracic endografting runs in parallel with venous disease. This is because it is quite common, when you are at a meeting with lots of rooms running in parallel, that it is difficult to follow [your topics of interest]. Even if you have the opportunity later to catch up (via online recordings or some kind of tutorial) you don't always have the time to do this."

Even so, for those who do have time, SITE has and continues to publicly publish a large body of recorded sessions via endovascular.tv, and discussions are ongoing on the possibility of real-time streaming of sessions.

Each symposium day emphasises different themes; for example, abdominal aortic aneurysm (AAA) on the first day, in combination with a selection of miscellaneous topics in the second room. Thursday is more focussed on the lower limbs in the main auditorium, with the secondary room (Aula Magna) covers miscellaneous topics including malformations, vascular access issues, and carotid stenting. Finally, Friday exam-



"The National Health system, and also the administration are looking for the best health-value, and the only way to get the best health value is to centralise." Vicente Riambau

ines thoracic and thoracoabdominal endografting, paralleled by a venous forum in the Aula Magna.

While publishing free symposium content is a keen step towards the democratisation of the latest knowledge in endovascular therapy, it is hard meanwhile to ignore the growing body of cutting-edge technology that support and elucidated once-obscured diagnoses: "The technology is very appealing, but it is expensive," agreed Dr Riambau. "When you talk about the technology involved in the diagnostics process we are starting, as a vascular community, to apply much more than just CT.

"We are playing with 4D-CT functional imaging, and dynamic imaging with MRI or CT. These are involved in a regular way in some centres but they are not yet popularised, because they require specific software and also the investment of time to do all of the post-processing work. You also need staff from the imaging department to be willing to invest this kind of time. But this is part of our job – to convince that there is something beyond (for instance) just the diameter of an AAA necessary in order to perform some kind of prognosis or even an indication.

"In the next decade, these diagnostics could be more widely implemented, with softwares that are perhaps not so expensive, that could be available for everyone involved in this particular pathology. It takes some time for sure, but the technology is evolving very quickly."

Such technology is of interest to the academic as well as to the clinical community, because it can be used to determine aetiologies and pathophysiological pathways involved in different clinical phenomena.

Yet it is the technical as well as the technological expertise that at present sets clinics apart as centres of excellence in the care of particular pathologies. This 'centralisation' is one of the themes of today's SITE@LINC discussion this afternoon, and Dr Riambau explained why it makes sense: "It is well-known that volume is a very important factor in getting the best results.

"In other worlds, the best outcome is directly proportional to the volume of experience. So if you don't have this kind of centralisation – if you have atomisation of procedures around one single country – then this kind of huge experience is quite difficult to get. And the results are poorer if you compare with centralised countries.

"In my country, Catalonia, we started a vascular surgery centralisation project two years ago. It is running well. The most important drawback [involved] the personal 'emotional status' when small centres were forbidden to perform EVAR in small centres, because some young vascular surgeons working in these small centres prefer to perform everything, even if that is only once a year. But the results of this, and even the cost-effectiveness, are not so good. The National Health system, and also the payers (the administration) are looking for the best health-value, and the only way to get the best health value is to centralise."

The topic is sensitive – and as such one important to air in a forum within the endovascular community like today's. Centralisation requires new infrastructure, too, including a referral system whereby small centres can refer complex cases to more specialist centres. The specialist centre also invites interested vascular surgeons to participate in complex cases to accelerate their learning.

"But it is curious," said Dr Riambau, "You would be surprised to hear that these small centres, who were at first against the centralisation process, refuse when you invite them to be involved with complex cases because they are happy treating less complex pathologies. They are very busy with their own work. So this kind of interest is relative."

SITE@LINC follows a loose format that aims to draw the audience in with the discussion by its panel of five experts, moderated by Dr Riambau. "We need to capture this particular feedback from the audience, especially in areas where there is little evidence," he noted. "We are very poor in evidence when talking about EVAR and TEVAR at the moment. So to get some consensus, we need to have different inputs. Probably there are also geographical differences. Putting all of this together with the panel – it will be very attractive for the audience."

Clinical dilemmas present themselves whether there is sufficient evidence addressing them or not. Thus, reason, born out of broad discussion and expert consensus, is an important means of forging resolution. "When there is not so much evidence, you have to go to expert opinion. Expert opinion is formed in ways like at [SITE@LINC], in written consensus documents, or even in some kinds of clinical guidances.

"We need to work to get more and more evidence, but still there is a lot of room in order to maintain this consensus among experts, and to give this opinion to the rest of the population involved with these particular pathologies."

Dr Riambau concluded with a look forward to an as-yet undefined but changing future of medical meetings: "This year, 2017 is a little bit critical, because there are some changes in the regulation of behaviours between industry and physicians. In 2017, it will be mandatory to follow the Eucomed guidelines, which are restrictive over the direct relationship between industry and the physicians – and this is strictly and strongly related to the congress performance.

"Everybody here in attendance is invited by the companies. Next year, that is forbidden. So it is a funny year, 2017. We need to find a way to give education with, or without, industry involvement. We need to be altogether in the same boat. We even need to involve adminstrations more, and even patients. The patient is very important. Ultimately we are all tied together – each of us is not independent, we are dependent on each other."

"We are very poor in evidence when talking about EVAR and TEVAR at the moment. So to get some consensus, we need to have different inputs." Vicente Riambau

Belgian IN.PACT & Austrian budget analysis

Results and insights from the IN.PACT Global Study were presented at LINC 2017, including a budget analysis which has led to a positive reimbursement decision in Austria, based in large part on the IN.PACT study results. Koen Deloose, Head of Vascular Surgery at Sint-Blasius Dendermonde, Belgium, presented results of the IN.PACT Global Belgian cohort at one year. Following on from his presentation, and reporting data on the budget impact and reimbursement analysis conducted in Austria, angiologist Marianne Brodmann (Medical University of Graz, Austria) took to the podium to report findings that illustrate how trial results can be used to good effect in reimbursement situations.


Marianne Brodmann

The real world IN.PACT Global Study is a multicentre, single-arm study designed to increase the evidence base for the IN.PACT Admiral drug-coated balloon (DCB) from Medtronic (USA). Patients who entered the study required treatment for femoropopliteal lesions, including long lesions, in-stent restenosis (ISR), and chronic total occlusion (CTO). More than 1,500 patients were enrolled at 64 sites in 25 countries worldwide, and these formed the clinical cohort. A subset of these patients underwent an imaging study at 12 months to assess patency.

"The data were independently and rigorously adjudicated by a Clinical Events Committee," noted Dr Deloose of a feature of the study that was a particular strength. In Belgium, 305 patients formed the cohort, and Dr Deloose reported the findings on this latter group.

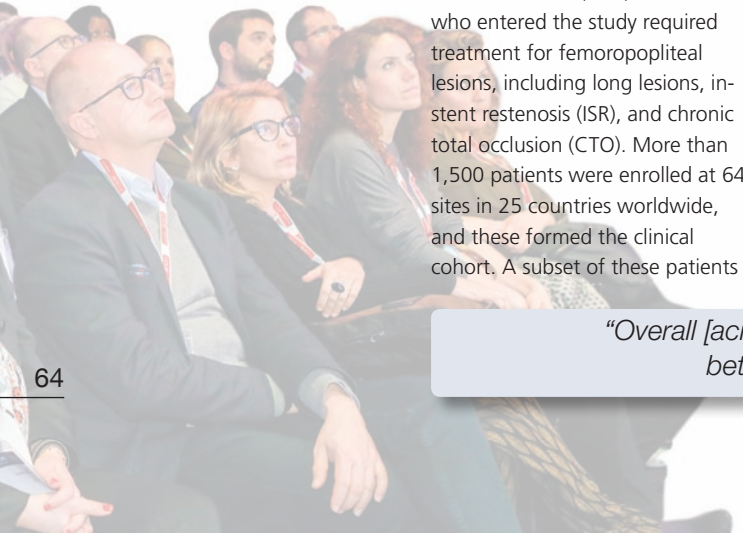
Patients included had lesions of Rutherford class 2, 3 and 4, located in the SFA and/or the popliteal artery. Single or multiple stenosis or occlusions of any length over 2 cm were included, both de novo and restenotic. Patients were also required to have at least one infrapopliteal run-off vessel. Primary endpoints comprised efficacy of the clinical cohort as measured by 12-month freedom from clinically-driven target lesion revascularisation (CD-TLR) and 12-month primary patency. Safety endpoints included a composite of 30-day freedom from device and procedure-related mortality, and 12-month freedom from major target limb amputation and CD-TLR.

"In the Belgian cohort, 30% of patients were diabetic," reported Dr Deloose. "They were quite a sick population with 58% having had previous peripheral revascularisation and a third having concomitant below-the-knee disease."

Mean lesion length was 9.54 cm, which was less than in the Asian cohort (results of which were presented earlier in the same session), and the provisional stent rate was 20.7%. Results showed that freedom from CD-TLR in the Belgian cohort was 92.5%, and safety outcomes showed CD-TLR rate of 7.6% of participants. Major adverse events were seen in 12.8% of patients, and the composite primary safety endpoint was met by 90.6%.

"It's interesting to see that it is not only more or less comparable

"Overall [across the subgroups] we see primary safety endpoints between 88-96% and clinically driven TLR rates between 2.4% and 11.3%, and in all lesion types we see almost the same results." Koen Deloose



Koen Deloose

with the Asian cohort, but it is completely in line with the consistency of data in the RCTs [randomised controlled trials], the global clinical cohorts and sub-cohorts of imaging, long lesions, ISR lesions, and chronic total occlusions," remarked Dr Deloose. "Overall [across the subgroups] we see primary safety endpoints between 88-96% and clinically driven TLR rates between 2.4% and 11.3%, and in all lesion types we see almost the same results," he stressed.

In her presentation, Professor Brodmann pointed out that they had put a lot of effort into obtaining reimbursement for DCB use in the lower extremities in Austria, but were pleased to have been granted reimbursement from January 1, 2017. The evidence upon which the decision was made indicates that DCB for patients with peripheral artery disease (PAD; Rutherford ≥ 3) in femoropoliteal arteries is more effective and not less safe that percutaneous transluminal angioplasty (PTA) with uncoated balloons.

The analysis lead by Professor Brodmann aimed to study the economic impact of the four main endovascular treatment strategies for femoropopliteal arterial disease in Austria, using the latest clinical evidence and 2016 reimbursement rates and device costs. The analysis estimated clinical performance of PTA, bare metal stent (BMS), DCB, and drug-eluting stent (DES) using information from a recent systematic search of studies of femoropopliteal lesions reporting TLR as an endpoint. The budget impact to payers was calculated considering up to one re-intervention. Figures were adapted to the Austrian setting.

The clinical model results showed that pooled findings of freedom from TLR over 24 months included 28 studies of over 5,000 patients with primarily de novo TASC A or B lesions. "Pooled freedom from TLR findings were 82.4% in DCB, 80.6% in DES, 73.1% in BMS, and 61.5% in PTA," Professor Brodmann relayed. "A subset analysis of urea excipient based DCB [IN.PACT] versus other DCBs yielded freedom from TLRs of 88.8% [in the IN.PACT study], and 78.1% in other DCBs."

Over 24-months, DCBs had the lowest budget impact to payers of €4,100, followed by PTA of €5,010, DES of €5,478, and BMS of €5,747. "Considering only the urea excipient based DCB, the budget impact was further reduced to €3,839 due to lower TLR costs," said Professor Brodmann.

Comparing DCB to the least effective therapy (PTA), she continued: "We also calculated that it would take 1.5 times as many patients treated with another DCB to avoid one TLR compared to the IN.PACT DCB."

The number needed to treat (NNT) with the IN.PACT DCB compared to PTA was 3.7, and the NNT of all other DCBs to PTA was 6.0. She concluded that reimbursement in Austria was in large part supported by the equality of the IN.PACT DCB clinical results.

"[We] calculated that it would take 1.5 times as many patients treated with another DCB to avoid one TLR compared to the IN.PACT DCB." Marianne Brodmann

Preventing air-emboli in TEVAR using CO_2-flushing

The pathomechanism of stroke risk in TEVAR is not sufficiently recognised, but air emboli could be a significant contributor – so heard delegates in a session that tackled the last remaining challenges in thoracoabdominal aortic aneurysm treatment.

"It is well recognised that TEVAR involves a significant risk for stroke," Tilo Kölbel (University Clinic Hamburg-Eppendorf, Germany) told *LINC Review*. "Stroke is the major drawback of this technique – in more complex endovascular procedures of aortic arch pathologies, stroke-rates have been reported to be up to 16%."

While embolisation of thrombotic and atherosclerotic material from the vessel wall has been a 'traditional' perspective on stroke risk, hard evidence is lacking.[1] With this in mind, another culprit – air emboli – has been identified as a potent stroke risk[1], thus opening up the necessity for treatment regimens that can tackle the complication at its source.

"There is evidence that more than 60% of patients treated by TEVAR have silent strokes,[2] and I believe a significant source for these are air emboli," said Dr Kölbel. "Although these strokes are clinically silent, without major functional deficit, no sound testing has been used so far to study cognitive function after this type of repair. I have seen air embolism to the innominate artery during our early experience with branched arch endo-grafting resulting in a stroke (Figure 1).


Tilo Kölbel

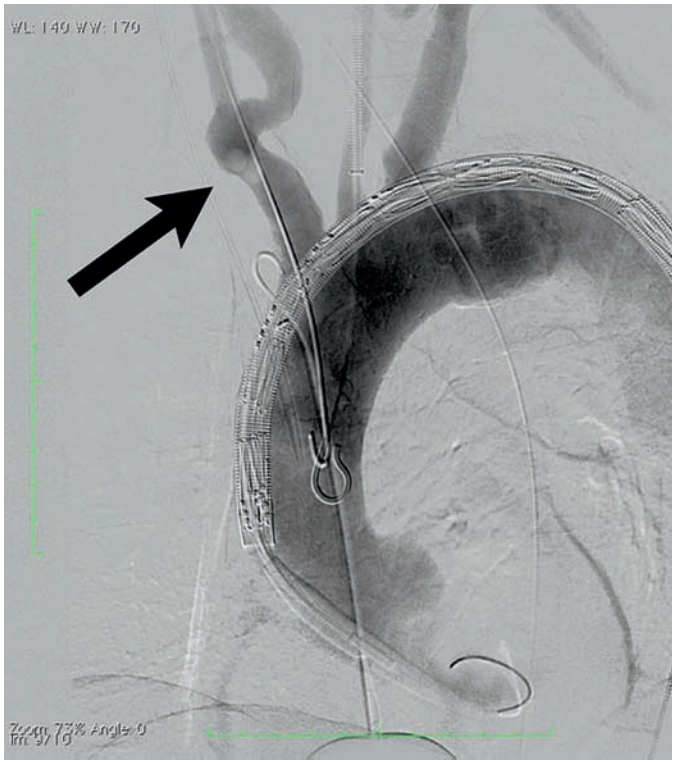


Figure 1. Air embolism in the innominate artery during branched arch endo-grafting.[3]

"We all know that air is released during EVAR procedures, because air bubbles are a very common finding on early postoperative CT scans in the aneurysm sac. However, this finding has not been studied any further to my knowledge, although it clearly demonstrates that we release potentially harmful substances during EVAR into our patients' bodies."

Looking into just how air emboli occur, Dr Kölbel described how stent-grafts used in EVAR and TEVAR are produced, constrained, packed and sterilised under 'room air' conditions, meaning that spaces within the constraining sleeve or delivery-sheath that are not filled by the stent-graft itself and the introducing catheter assembly contain room-air. For the sterilisation process, the assemblies are

"There is evidence that more than 60% of patients treated by TEVAR have silent strokes, and I believe a significant source for these are air emboli." Tilo Kölbel

packed in gas-permeable packaging and sterilised typically using an ethylene oxide (EtO) gas mixture removed by repeated vacuum and room-air ventilation.[1]

"As a result, the sterilised devices are delivered filled with room-air," he added. "According to instructions for use [IFUs] of current devices, room air is removed prior to introduction into the arteries by flushing the sheath in which it is loaded with an isotonic solution such as a 0.9% saline. The degree to which the air is removed by this NaCl flushing technique, and the amount of air that is released into the vasculature, is not well known yet."

He continued: "We have recently published our bench-top tests on standard tubular TEVAR devices showing that about 0.5-1.0 ml of air is released during stent-graft deployment in a water-filled model.[4] This amount of air may be even higher in more complex stent-grafts with side branches, etc."

With this in mind, CO_2 flushing has emerged as a potential solution to the purported air emboli problem. As Dr Kölbel detailed, CO_2 has a 22-fold higher solubility in blood compared to room air, and its composition makes it a preferred trapped gas for the vasculature when compared to room air. "It resolves faster than the nitrogen-rich room-air in the blood, potentially causing less harm," continued Dr Kölbel.

Taking this characteristic to heart, Dr Kölbel hypothesised that by using CO_2 flushing to reduce the amount of room air present in the stent-graft during deployment could in turn reduce the incidence of stroke during TEVAR. Expanding on the intrinsic aspects of his developed technique, he continued: "The endovascular graft is unpacked and prepared in the usual manner except from the flushing steps. Specifically, before flushing the graft with saline solution (according to the IFU recommendations), the flushing port is connected to a CO_2 gas cylinder with a reduction valve providing a pressure of 1.2 bar.

"The endovascular graft is then flushed for two minutes, before further flushing with saline according to the IFU. Dripping saline on the top of the sheath and dilator tip confirms the flushing of CO_2."

Describing the clinical impact of the flushing procedure thus far, Dr Kölbel underlined that, after introduction of the technique in 2013 in his practice, very low rates (<4%) of clinically-apparent stroke in complex aortic arch procedures have been observed, marking a stark difference to rates of >10% typical in this type of TEVAR.[1]

Dr Kölbel added his concluding remarks on this intriguing concept: "Every physician who uses endovascular materials should be aware of the potential harms of EVAR and TEVAR. The knowledge of air embolism shall be used to further study its incidence and effects on our patients. I am convinced that we will find techniques to reduce these potentially harmful side-effects of TEVAR, which itself offers so many advantages as a minimally-invasive therapy to our patients.

"Device companies need to follow their responsibility in providing products and techniques free from avoidable harms."

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"I am convinced that we will find techniques to reduce these potentially harmful side-effects of TEVAR." Tilo Kölbel

Luminor DCB finds encouraging 12-month results

During a Deep Dive session on lower limb interventions, operators Matthias Ulrich and Johannes Schuster at University Hospital Leipzig's Division of Interventional Angiology treated a long, moderately calcified right superficial femoral artery (SFA) occlusion using a combination of Luminor drug-coated balloon (DCB; iVascular, Spain) and a series of Multiloc Vascuflex stents (B.Braun, Germany).

The 71-year-old patient presented with severe claudication of the right leg, with walking capacity reduced to 100 m. With risk factors including arterial hypertension and smoking, she had previously undergone percutaneous transluminal angioplasty (PTA) and stenting of the left leg in late 2016, and PTA of the left iliac in late 2015.

A pre-procedural angiogram indicated an atypically high bifurcation, with disease at the origin of the SFA extending to its distal portion; below-the-knee (BTK) run-off was adequate, occurring via the anterior tibial as well as the peroneal artery (Figure 1). On this basis, the team opted for a cross-over recanalisation from the left groin.

Commenting on their choice of balloon, Dr Ulrich said: "We wanted to use the Luminor balloon, a paclitaxel balloon. The special thing is its multi-layered coating, which is very homogeneous for better drug transfer."

Matthias Ulrich

A 6F sheath was placed, and initial crossing was attempted with a Terumo Glidewire Advantage (Terumo, Japan): "This is very helpful," said Dr Ulrich. "You can do a lot with one wire, supported by a 5 French Judkins catheter."

Difficulties with intraluminal crossing attempts led the team to opt to track subintimally, with Dr Ulrich reasoning that, at present, there is no definitive data supporting better outcomes with intraluminal versus subintimal crossing. Re-entry into the true lumen provided yet additional challenges; dissections were created in attempts to re-enter the SFA, and a number of entries were also made into neighbouring collateral vessels. As such, the team carried out a short retrograde puncture at the distal SFA, whereby crossing was successfully achieved with the help of the Quick-Cross support catheter (Spectranetics, USA).

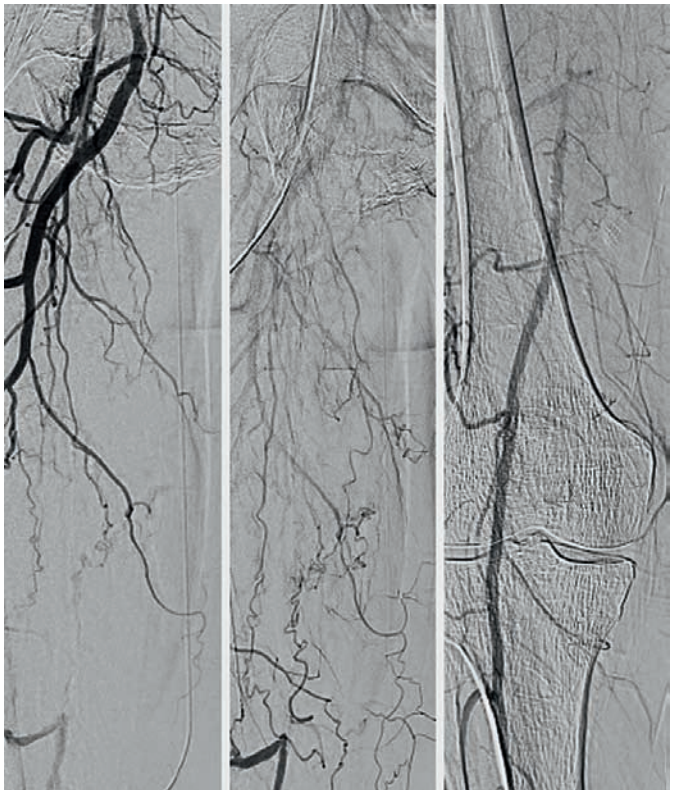


Figure 1. Pre-procedural angiogram reveals a high bifurcation, with a diseased origin of the SFA (left) a long occlusion (mid), extending to the distal portion (right).

After crossing, predilatation of the occluded segment was carried out using a 4 mm Pacific balloon (Medtronic, USA). This is usually necessary, explained Dr Ulrich, in order to ensure DCB efficacy: "You may lose some coating where you don't predilate."

A 5x200 mm Luminor DCB was then inflated in the distal segment, while in the larger-diameter

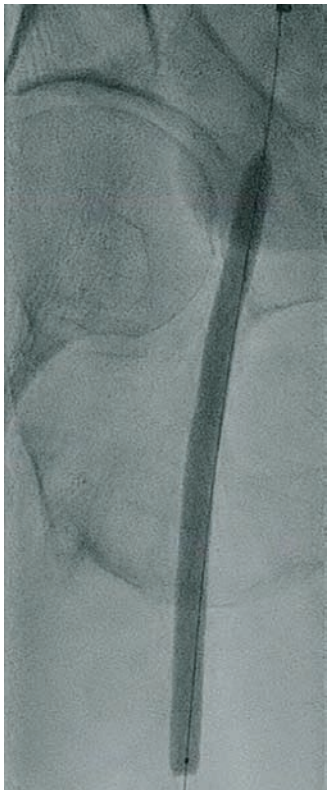


Figure 2. Inflating the Luminor balloon.

"We wanted to use the Luminor balloon…The special thing is its multi-layered coating, which is very homogeneous for better drug transfer." Matthias Ulrich

proximal segment a 6 mm Luminor was used (Figure 2). Asked how long DCB inflation ought to be, Dr Ulrich responded: "Normally, 2 to 3 minutes. But with this special balloon, because of the coating you have a quick drug transfer – 90% should be transferred into the vessel within 30 seconds. So with this, you can shorten the time a little bit. But as you can see, I always try to have at least 1 to 2 minutes."

Panellists Jos van den Berg and Koen Deloose pointed out the significance of a long inflation time, noting its role in reducing stenting rates. "There is not only the chemical aspect," said Dr Deloose, "You have this mechanical aspect as well. There are several studies (mainly in the coronaries but also in the peripheral area) saying that higher-grade dissections occur more often in short dilatations than prolonged dilatations of more than 180 seconds."

The present dissections, explained Dr Ulrich, may possibly have been avoided had the retrograde crossing approach been adopted sooner. Nevertheless this issue, coupled with the presence of calcification in the distal SFA and vessel recoil, demanded short-segment stenting, which was achieved using a series of 7x30 mm self-expanding Multiloc Vascuflex stents, followed by post-dilatation to complete their expansion using a single, long balloon. A final angiogram demonstrated excellent flow. Despite persistent proximal dissection, vessel recoil was resolved by stenting, and the operators concluded the case.

The Luminor registry

This was one of two cases at LINC 2017 of SFA occlusion treated using the Luminor DCB. Earlier on, Vicente Riambau (University of Barcelona, Spain) presented data on the Luminor registry, the observational, prospective, multicentre study with single-arm treatment for stenotic or occlusive lesions or in-stent restenosis of the femoropopliteal and BTK lesions.[1]

The study's aim, explained Dr Riambau, is to assess the Luminor 14 or 35 in terms of primary patency (defined as freedom from >50% restenosis) and safety (defined as freedom from serious adverse events, i.e. death, amputation, and target lesion revascularisation) during a minimum follow-up period of 12 months.

The study commenced in May 2014 and recruited, over a 15-month period, a total of 219 patients with validated Rutherford stage 2-5 clinical symptoms on an intention-to-treat basis. 60% of patients were classed as Rutherford stage 5. 140 out of the total of 219 patients were diabetic, 136 were smokers, 175 had arterial hypertension, and 124 had hyperlipidaemia. Primary stenting or atherectomy cases were excluded from the cohort.

Vicente Riambau

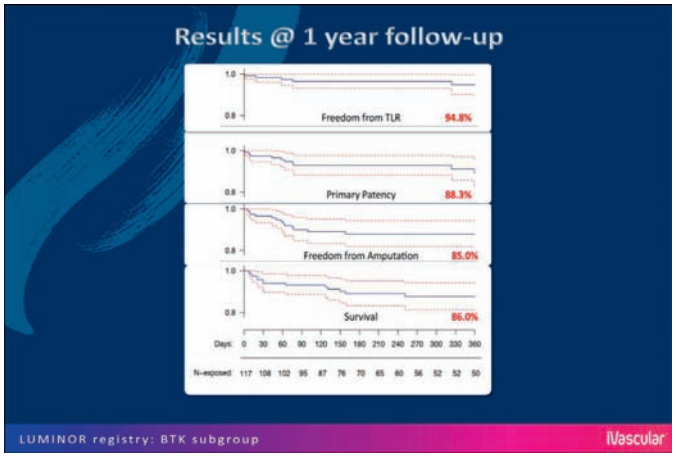


Figure 3. Luminor registry BTK analysis at one year follow-up.

Source: LINC 2017 presentation archive (www.leipzig-interventional-course.com)

A total of 252 lesions were included in the study. Mean lesion length was 77.8 (20-200) mm, 48.0% of lesions were chronic total occlusions (CTO). 61.2% of lesions occurred in the femoropopliteal segment, 34.2% BTK, and 4.6% in combined segments. Technical success was achieved in 91.4% of cases, with bailout stenting required in 6.8% of cases. At 30 days, all-cause mortality was 1.9%, with major amputation 1.9%. At one year, survival was 90.4%, with freedom from amputation 89.8%. Primary patency was 94.0%, and freedom from TLR 96.2%.

BTK analysis included 98 patients (84 of whom were Rutherford class 5, and 73 diabetic), and 116 lesions. Mean BTK lesion length was 77.9 (20-200) mm, with 61.2% of lesions CTOs. 30-day all-cause mortality was 7.1%, major amputation was 5.1%, and no TLR was observed. At one year, survival was 86.0%, freedom from amputation was 85.0%, primary patency was 88.3%, and freedom from TLR was 94.8% (Figure 3).

"That is an important point for us," commented Dr Riambau. "Initial primary outcomes are encouraging, taking into account the ischemic status severity of this cohort of patients.

"BTK results are especially positive, and reopen the door for DCB technology in this challenging field. The Luminor Spanish registry will complete the final results by the middle of this year. Interim and final results will be published in future reports."

Further data on the Luminor DCB can be expected from the Eff-Pac trial[2], with 12-months results emerging later this year.

"BTK results are especially positive, and reopen the door for DCB technology in this challenging field." Vicente Riambau

iVolution outstripping its predecessors?

The iVolution self-expanding nitinol stent (iVascular) was also discussed at LINC 2017, with Marc Bosiers (St. Blasius Hospital in Dendermonde, Belgium) presenting the first six-month results of the Evolution study in femoropopliteal lesions, of which he is principle investigator[3]. Referring to data from randomised trials of older generation stents in the SFA, Dr Bosiers noted that average patency rates have been around 78%, with patency rates falling in longer lesions.

Perhaps one of the reasons that results with these stents are not as good as have been achieved with some DCB, he explained, is that chronic outward forces of stents have been poorly estimated to date. He described the implications this might have: "If you have a stent with a chronic outward force that is too low, it is impossible to scaffold the lesion and you will have a residual stenosis. On the other hand, if you have a stent with a chronic outward force that is too high, it will be a continuous vessel irritation and this will induce intimal hyperplasia and secondary loss of patency."

Zhao *et al*. (2009) demonstrated the effects of stent oversizing with respect to the kinetics of late stent

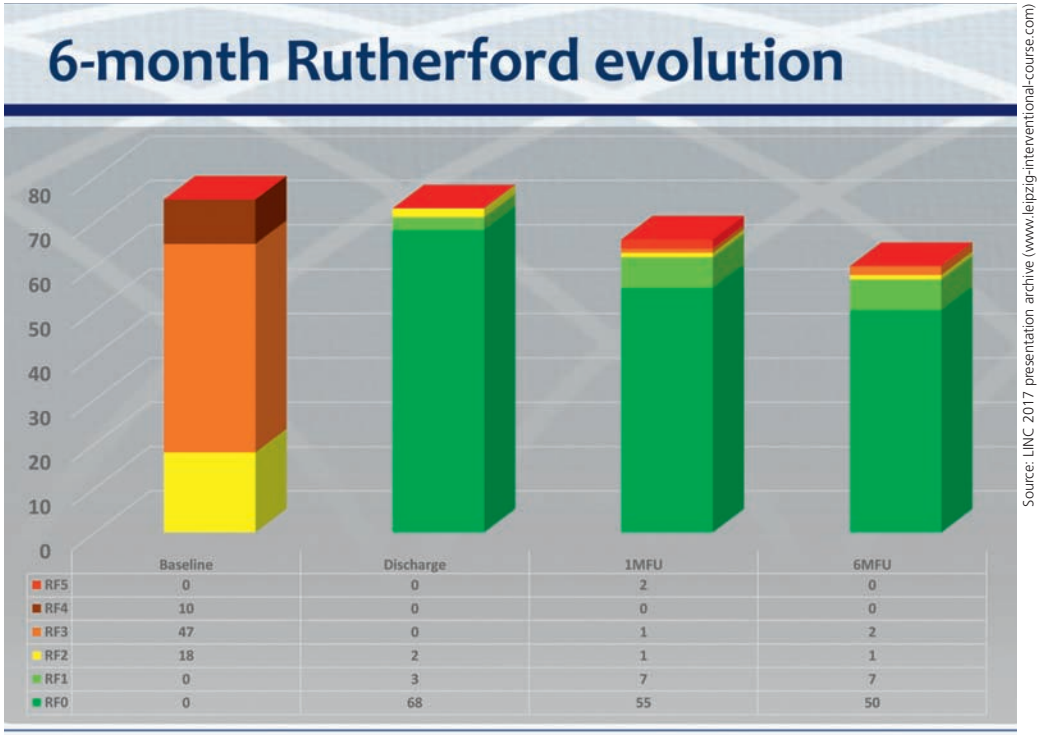
Marc Bosiers

expansion. While stent oversizing may ensure good apposition and reduce migration, it also leads to neointimal hyperplasia, even when implanted in healthy vessels.[4]

These findings, said Dr Bosiers, suggest that we should examine a particular stent's expansion curve in order to understand how to approach its sizing. "If you have a 6-mm stent with a steep expansion force curve and you put it in a bent vessel anatomy with diameters of between 5 mm and 3 mm, when you bend the knee this stent will induce up to 100 N of force at several points in the artery; whereas if you use a stent with a flat expansion curve, this stent will induce lesser outward forces and so [create] less intimal hyperplasia. This is why stent design is of utmost importance when you look at new stents hitting the market.

"One of the new stents is the iVascular stent, with not only a flat expansion curve but also a good radial force, very nice flexibility, fracture-resistance, and anti-kinking. This is a new tool in our armamentarium to maybe give us better results than with the old stents."

The prospective, non-randomised multicentre Evolution trial studies the 12-month safety and efficacy of the iVolution stent in 120 symptomatic (Rutherford class 2-4) patients with stenotic or occlusive de novo lesions of the femoropopliteal segment of ≤150 mm in length. Its primary endpoint is defined as freedom from >50% restenosis at 12 months as indicated by inde-



Source: LINC 2017 presentation archive (www.leipzig-interventional-course.com)

Figure 4. 6-month Rutherford evaluation of the Evolution study, demonstrating sustained clinical improvement.

"Six-month data suggest that the iVolution stent is a valid and effective alternative to treat femoropopliteal TASC A and B lesions." Marc Bosiers

pendent core lab verified duplex ultrasound. Four Belgian centres are participating in the trial.

Dr Bosiers presented six-month follow-up results, which was available for 75 of the study's total patient cohort. Mean lesion length was 86.64 ± 45.24 (range 9.0-150.0) mm, with 41.3% of lesions occluded, and 64.0% calcified. 89.3% of lesions received a single stent, while 10.7% received two stents.

At six months, primary patency was found to be 95.6%, and freedom from TLR 98.5%. Clinical improvements, as measured by Rutherford classification, were sustained out to six months (Figure 4). "Six-month data suggest that the iVolution stent is a valid and effective alternative to treat femoropopliteal TASC A and B lesions," summarised Dr Bosiers.

Comparing this iVolution data to six-month primary patency data of other stents, he concluded: "This new stent design gives you best-in-class results. We need to wait for the 12 month results, not only to compare with other stents on the market, but also to compare them with DCB."

On Wednesday at LINC 2017, Peter Goverde (Vascular Clinic ZNA, Antwerp, Belgium) presented an

Peter Goverde

in-depth look at the technical design features of the iVolution stent, which were evaluated in comparative bench tests in collaboration with ParisTech (Paris Institute of Technology, France). The group investigated design and manufacturing features that contribute to incidences of restenosis, stent fracture, and thrombus generation.

Restenosis was addressed by exploring inflammatory processes that occur when chronic outward force is too high, explained Dr Goverde. "There is a balance between radial force and chronic outward force. Lowering the chronic outward force will lower the inflammatory response and thus prevent restenosis."

A second contributing factor to inflammation, he added, is stent surface corrosion. "After every stent is produced, a very thin layer of titanium dioxide is put on the stent surface to smooth it out. But it can also be damaged; the more damage you have on this ultra-thin layer, the more problems with corrosion you can have.

"So ParisTech also did some investigation about the effect of this ultra-thin layer. What we saw was that there were differences between the different stent producers. The importance of stent design is something we already know from the study of Müller-Hülsbeck *et al*. (2010), that this has an effect on outcome[5]."

Stent fractures were investigated by examining stent design and materials. Dr Goverde explained that different kinds of inclusions in the nitinol tube material can lead to different manifestations of weakness: the inclusion of oxygen during the manufacturing process can lead to tunnel formation during tube extrusion; carbides can also be incorporated, leading to fracture-prone weaknesses. Thus, the absence of inclusions is key to ensuring stent quality and avoiding fractures. ParisTech bench tests of six different stent brands found the iVolution to possess the lowest inclusion rate, noted Dr Goverde.

On the topic of thrombus risk, further bench tests examined flexibility (both in terms of vessel adaptation, and of shape memory), kinking, and resistance to bending, favouring the iVolution stent over other stent models. Optimal design features, said Dr Goverde, can hence improve haemodynamic flow and reduce thrombus generation.

Surface finishing, he continued, can also enhance blood flow following implantation. A 2015 comparative study of the corrosion behaviour of peripheral stents in an accelerated corrosion model carried out in vitro in 28 metallic prostheses by Paprottka *et al*., provided evidence supporting the notion that corrosion might play a role in fracture generation.[6] Hence, said Dr Goverde, electropolishing can serve to diminish fracture risk.

"Can we actually improve the stent outcomes? Yes we can," he concluded. "Finding a balanced radial force, and lowering inflammatory reaction, can prevent restenosis. Stent design and quality of materials can avoid stent rupture or stent fracture. Enhancing flow dynamics and perfecting surface finish can limit thrombus formation.

"We [can] add optimal post-production control, and this is done by the Q-six device (Sensofar), a laser-driven microscope that can control every stent to eliminate error. So yes, we can influence this. In this sort of production line, every produced stent is inspected."

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"Finding a balanced radial force, and lowering inflammatory reaction, can prevent restenosis. Stent design and quality of materials can avoid stent rupture or stent fracture." Peter Goverde

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We would like to thank sincerely the outstanding faculty for their collaboration and commitment.

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Andrea Kahlberg Vascular Surgeon *Milan Italy*
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Narayan Karunanithy London *UK*
Piotr Kasprzak Vascular Surgeon *Regensburg Germany*
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Piotr Musialek Cardiologist, Angiologist *Krakow Poland*
Jihad Mustapha Interventional Cardiologist *Wyoming US*
Patrice Mwipatayi Vascular Surgeon *Perth Australia*
Tatsuya Nakama Cardiologist *Miyazaki Japan*
Giovanni Nano Vascular Surgeon *San Donato Milanese Italy*
Christoph Nienaber Cardiologist *London UK*
Sigrid Nikol Cardiologist, Angiologist *Hamburg Germany*
Thomas Noppeney Vascular Surgeon *Nuremberg Germany*
Gerard O'Sullivan Interventional Radiologist *Galway Ireland*
Gustavo Oderich Vascular Surgeon *Rochester US*
Takao Ohki Vascular Surgeon *Tokyo Japan*
Luis Mariano Palena Interventional Radiologist *Abano Terme Italy*
Ricardo Palmeiro Rodrigues Corelab Clinical Analyst *Isnes Belgium*
Patrick Peeters Vascular Surgeon *Bonheiden Belgium*
Tim Ole Petersen Interventional Radiologist *Leipzig Germany*
Ivo Petrov Cardiologist, Angiologist *Sofia Bulgaria*
Anna Pietersma Consultant *Amsterdam Netherlands*
Rupert Portugaller Vascular and Interventional Radiologist *Graz Austria*
Giovanni Pratesi Vascular Surgeon *Rome Italy*
Thomas Proebstle Dermatologist *Mannheim/Mainz Germany*
Daniele Psacharopulo Vascular Surgeon *Turin Italy*
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Venkatesh Ramaiah Vascular Surgeon *Phoenix US*
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Maria Antonella Ruffino Interventional Radiologist *Turin Italy*
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Bertrand Saint-Lèbes Vascular Surgeon *Toulouse France*
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Peter Schneider Vascular Surgeon *Honolulu US*
Maria Schoder Interventional Radiologist *Vienna Austria*

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Johannes Schuster Angiologist *Leipzig Germany*
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Sven Seifert Vascular Surgeon *Chemnitz Germany*
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Arne Stachmann Research associate *Munster Germany*
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Gunnar Tepe Interventional Radiologist *Rosenheim Germany*
Marcus Thieme Angiologist *Sonneberg Germany*
Matt Thompson Vascular Surgeon *London UK*
Jonel Trebicka Gastroenterologist *Hepatologist Bonn Germany*
Marcus Treitl Interventional Radiologist *Munich Germany*
Scott O. Trerotola Interventional Radiologist *Philadelphia US*
Santi Trimarchi Vascular Surgeon *San Donato Milanese Italy*
Andreas Ulbrich Angiologist *Dresden Germany*
Matthias Ulrich Angiologist *Leipzig Germany*
Kazushi Urasawa Cardiologist *Sapporo Japan*
Jos van den Berg Interventional Radiologist *Lugano Switzerland*
Joost A. van Herwaarden Vascular Surgeon *Utrecht Netherlands*
Marc van Sambeek Vascular Surgeon *Eindhoven Netherlands*
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Steve Williams Cardiologist *Baltimore US*
Christian Wissgott Interventional Radiologist *Heide Germany*
Adam Witkowski Cardiologist *Warsaw Poland*
Weiwei Wu Vascular Surgeon *Beijing China*
Zhidong Ye Vascular Surgeon *Beijing China*
Hiroyoshi Yokoi Cardiologist *Fukuoka Japan*
Baixi Zhuang Vascular Surgeon *Beijing China*

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Hammad Amer Vascular Surgeon *Boston US*
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Michael Klyachkin Vascular Surgeon *Macon US*
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Industry support

We would like to sincerely thank the following companies for their generous support of LINC 2017…

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