Welcome to Leipzig…

It is with great pleasure that I welcome you to the 2016 Leipzig Interventional Course. Spanning four days, the LINC programme returns with its most comprehensive edition to date, packed with educational lectures, great debates, live cases, novel devices and trial updates, to name a few. To facilitate all of these sessions, this year we expand our total arenas to six, adding ‘Speaker’s Corner’ to the roster, in which more informal, smaller presentations on original research topics, challenging cases and complications will be showcased.

As always, live cases will be a central component running throughout the programme, with over 90 scheduled satellite links that will serve up the latest and greatest techniques, tips and tricks from experienced operators the world over. With audience and panel discussion encouraged throughout, these live cases offer real talking points in terms of technical nuances, device usage and regional approaches to vascular disease.

This sentiment is mirrored in our collaborative sessions, in which we invite a number of esteemed partners to step up to the podium and share their wealth of expertise with us. This year we welcome the Charing Cross (CX) Symposium, Vascular InterVentional Advances (VIVA), the International Congress of Interventional Surgery (CICE), the International Symposium on Endovascular Therapeutics (SITE) and Complex Cardiovascular Therapeutics (CCT).

Due to the success in previous years, this year will also play host to a Nurse and technician session, the content of which is developed in cooperation with cath lab personnel in order to provide maximum correlation with daily routine. Symposia will focus on basic techniques and advanced technologies in peripheral interventions, critical limb ischaemia, and a more general ‘miscellaneous’ session spanning a range of topics.

We also extend a special welcome to our industry partners, whose yearly attendance ensures that novel and clinically-relevant technologies are given the spotlight they deserve, ensuring an continuing bond between clinician and technology.

On behalf of the organisers and faculty, I wish you a stimulating experience at this year’s LINC meeting, and a safe journey home.

Dierk Scheinert
Live ‘LINC-ups’ bolstered with new transatlantic site

This year LINC will expand its impressive roster of live case venues with a link-up to New York, USA. Led by Prakash Krishnan (Mount Sinai Hospital, New York, USA), the intercontinental collaboration will see two cases streamed live via satellite to the eagerly-awaiting audience.

“I would like to congratulate Dierk Scheinert and the entire LINC team for putting together the leading endovascular conference in the entire world,” Dr Krishnan told LINC Today. “I think LINC, with the fact it has now branched [to all of its other world-wide meetings] has really influenced the teaching and the appropriate vascular care for all of our patients with advanced vascular disease.”

“[LINC] has really influenced the teaching and the appropriate vascular care for all of our patients with advanced vascular disease.”

Prakash Krishnan

Think LINC, with the fact it has now branched [to all of its other world-wide meetings] has really influenced the teaching and the appropriate vascular care for all of our patients with advanced vascular disease.

Diving straight into an overview of the two cases he will be leading during the LINC proceedings – both of which will be taking place this afternoon – Dr Krishnan commented:

“One case, in Main Arena 1 [at 16:44], is an example of calcific superficial femoral artery lesions – multiple lesions which are very heavily calcified – and I think it brings about multiple challenges in the treatment of these particular lesions. We’d like to demonstrate our approach to the calcific lesions, in terms of mechanical debulking, but also in the use of ancillary devices, which I think are very important.”

As he detailed, an important consideration when undertaking mechanical debulking is what...
to do with the debris. While he pointed out the use of a filter to capture the debris and hopefully prevent embolisation is no longer a novel technique, the way in which one proceeds when emboli do present in an important issue. “In this kind of case, you really are predicting that you are going to have large embolic episodes occurring in your filter,” he said. “The question is how to manage that filter, in order to be able to treat these patients properly, and not have any embolic complications?

“We’re predicting that we are going to have emboli … and we’re going to really be ready for that, by using some new aspiration technology.”

The aspiration technology he speaks of, available from Penumbra, Inc. (USA), has seen a great deal of use in the hands of Dr Krishnan and colleagues. “This is an aspiration-type device that has been used phenomendally in the brain in embolic stroke, but the company has developed a larger bore catheter along with a mechanical aspiration suction that we’ll use to clear out the filter, and be able to capture the filter and bring it back,” he said.

Following debulking, the question will then become whether to use a mimetic stent, or a drug-coated balloon (DCB). “The Europeans have a lot more experience with them, but our experience is growing rapidly,” he added.

The other case streamed from New York, held even earlier this afternoon in the Technical Forum (13:30), will form part of a Scrub in with the experts session on challenging femoro-popliteal lesions. “This is going be a long case,” said Dr Krishnan. “It features a patient who had a recent SFA stent … who basically thrombosed in the stent, had it opened, and now I believe is re-closing, thus is coming to us for intervention. The patient had a prior stent placed in the past, which had multiple fractures, and has really poor run-off.”

He added that this is another very difficult case in the sense that there are again numerous complications that have to be predicted as best as possible. In particular, his team suspect that subacute thrombosis will be present, meaning emboli could be a major, major issue. “So the question here is going to relate to the use of distal protection with an embolic filter, but also the decision to go ahead with mechanical thrombectomy – whether it is with an Angiojet device [Boston Scientific, USA], or maybe with the Penumbra device, as we talked about, using the aspiration section of the Penumbra to actually suck out the clot prior to it intervening,” said Dr Krishnan.

Stent fractures will also be a talking point, with the choice of covered stents, balloons, vascular mimetic stents etc. all having to be factored in. “I’m not sure, so I think I am going to rely on the panel for their judgment and their expertise,” said Dr Krishnan.

Expanding more on the great to and fro that audience and panel commentary facilitates during the live cases, Dr Krishnan was keen to point out that this is very important in order to tease out the technical and case-based approaches that different centres, personal preferences or regional device availabilities dictate. “This is our plan, but as with anything you are always going to learn from others and their experiences,” he said.

“It is going to be a wonderful opportunity for us here at Mount Sinai to demonstrate how we handle these cases, but also, more importantly, for us to learn from the expertise of other operators, and indeed the audience.”

Prakash Krishnan

Continued on page 4

Continued from page 2
Today, Dr Krishnan also offered a more general account of the Mount Sinai experience, its historical underpinnings, and the kinds of initiatives they have in place today. “We started programmes here at the cardiac cath lab in 2004, and then we have slowly grown this programme to be one of the leading ones in the country,” he said.

Indeed, the use of cases as teaching tools is somewhat of a speciality for Mount Sinai, which has an active schedule of live peripheral interventions that are transmitted every month.1 “It doesn’t have to be the hardest case, nor a case that nobody else can do – but more importantly it has to have some teaching points behind every single edition,” he said.

“We have now done almost four years of these cases, and believe it or not, if you look at the metrics from Google, we are attracting about 4000-5000 views of these cases per month, from all over the world. We impact, on the last count, 191 different countries... so it is a tremendous outreach to physicians and caregivers.”

In addition, another string to the Mount Sinai bow is the hosting of the Complex Coronary Valvular and Vascular Cases (CCVVC) symposium every year. “Last year we were very fortunate to have Dierk Scheinert here with us, and Andrej Schmidt performed two cases from Leipzig,” said Dr Krishnan.

He added: “This is also another regional conference, obviously nowhere near the scale of LINC, but we attract around 900-1000 people for a one-day vascular seminar, where we do about 6-8 live cases. Last year we had two from Germany as I said, two from Kingsport Tennessee [USA] with Chris Metzger, and four from Mount Sinai itself.

“So we are trying to do our part in reaching out to the community, and teaching via the internet as well as within our own conference.”

Dr Krishnan and his team will transmit two live cases from New York during this afternoon’s programme. The first will take place during the Scrub in with experts session ‘Challenging femoro-popliteal lesions’ (13:30–15:00, Technical Forum), and the second is scheduled at 16:44 during the ‘The last frontiers: Calcified lesions’ session (16:30–18:00, Main Arena 1).

References
The influence of revolutionary devices and technologies is a powerful component in driving change in interventional practice. With that in mind, a special session dedicated to the IN.PACT Admiral (Medtronic, USA) drug-eluting balloon (DEB) will be showcased this afternoon at LINC, with a straightforward question being laid bare from the outset: is the collective evidence for the device now changing the SFA treatment paradigm?

The IN.PACT DEB is a paclitaxel-eluting (3.5 μg/mm²) balloon with a naturally-occurring, non-toxic urea excipient that allows rapid drug transfer.1 To establish the device, its associated clinical trial programme consists of two central studies, the IN.PACT SFA2 and IN.PACT Global3 trials. Both trials are prospective and multicentre in their design.

The SFA trial is a level 1 clinical evidence study that has been tasked with evaluating the safety and efficacy of the IN.PACT Admiral balloon when compared to other standard (non drug-coated) PTA balloons in the superficial femoral artery (SFA) and proximal popliteal artery.2 Primary endpoints were set as primary patency at 12-months (efficacy; defined as freedom from clinically-driven target lesion revascularisation (TLR) and duplex ultrasound-derived restenosis) and composite 30-day freedom from device- and procedure-related mortality and 12-month freedom from major target limb amputation and clinically-driven target vessel revascularisation (safety endpoints).1,2

The Global clinical study has focused on the device in the treatment of atherosclerotic disease in the superficial femoral and/or popliteal arteries in a “real world” patient population.3 Primary safety endpoints were the same as in the SFA trial, with the primary efficacy endpoint in this study being freedom from clinically-driven target lesion revascularisation.1,3

Describing how IN.PACT evidence has changed his SFA treatment algorithm during the session will be Fabrizio Fanelli (“Sapienza’ University of Rome, Italy), who spoke to LINC Today to offer an inside look as to what he may be touching upon, starting with the data from the IN.PACT SFA trial in particular. “The one-year results were pretty important and impressive, and the two-year results are even more impressive,” he said.

Following on from the 12-month results, in

Continued on page 6
which freedom from clinically-driven TLR was significantly higher in the group receiving the IN.PACT device,\textsuperscript{4} indeed the two-year results, recently published in JACC,\textsuperscript{5} showed a demonstrable ‘durable and superior treatment effect’ of the IN.PACT versus PTA with significantly higher primary patency, lower CD-TLR, and similar functional status improvement with fewer repeat interventions. As the authors commented,\textsuperscript{5} the sustained clinical benefit of a local delivery of paclitaxel means that the IN.PACT device has the potential to change the SFA treatment paradigm – just as today’s session mirrors.

Obviously, comparisons with other devices are inevitable, with the Lutonix (C. R. Bard, USA) DEB, and its associated LEVANT 2 trial,\textsuperscript{6} being the natural choice. For Professor Fanelli, the biggest comparative point between the Lutonix and IN.PACT results is the magnitude difference of patency rates and freedom from TLR between each study’s DEB and standard balloon group.

“We know there are several technical differences between the two devices, but according to the numbers, it seems that IN.PACT is working a little bit better that the Lutonix,” he said.

He added: “We don’t know if it is connected to patient selection, or it is correlated to the efficacy of the balloon … and without a head-to-head comparison it is quite difficult, and ambitious, to say that one is much better than the other.”

When asked which device he uses more in his day-to-day practice, Professor Fanelli commented: “Honestly we use both, but IN.PACT is more present because, according to the studies that have been published, there is more evidence that it is working to improve results… so this is the reason that we use it relatively more.”

Professor Fanelli also stressed that the durable results from the IN.PACT device are a particular boon when treating the types of relatively young patients that present with SFA disease, especially when considering quality of life. “We don’t want to have something that is working for one, two, three months,” he said. “We are more in favour of something that can provide patients with very good results for a longer period.”

Looking to the future, LINC Today asked if there were aspects that Professor Fanelli would like to see emphasised in greater detail – perhaps data collection, or particular anatomies where DEBs such as IN.PACT can be applied?

“There is a big discussion regarding very heavily calcified lesions, because right now we know that in the case of completely calcified lesions, we have problems where the device is not working correctly, so maybe the combination of atherectomy plus use of the DEB can improve results, but we have to consider the economic problem,” he said.
“When you are using atherectomy plus maybe a filter, plus the DEB, you can imagine how expensive the procedure will be. So one option, and we are going to start a new trial very soon, is to combine the use of a scoring balloon and a drug-coated balloon.”

For more information surrounding the IN.PACT Admiral device, its associated trials, and what this might mean for the SFA treatment space in particular, head to Main Arena 1 at 13:30–15:00 today for the dedicated IN.PACT session.

References
2. Randomized Trial of IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease (INPACT SFA I; Available at https://clinicaltrials.gov/ct2/show/NCT01175850)
3. IN.PACT Global Clinical Study (Available at https://clinicaltrials.gov/ct2/show/NCT01609296)
Join the experts in their field in working through complex cases from a variety of clinical centres around the world. Showcasing innovative techniques, devices and technologies, these sessions provide a first-hand view of the cutting edge in a real-world setting. While this of course can throw up some interesting surprises, it also gives the audience a chance to gain insight into the kinds of approaches and decisions that expert interventionalists take under pressure.

There will be seven sessions this year, featuring a variety of cases that will be accompanied by lively discussion of approaches and techniques by the moderating panel in Leipzig, all of which will be punctuated by flash presentations highlighting novel insights, challenges and clinical experience in these areas.

**Tuesday**

**11:45–12:30: Current approaches to treating complex SFA disease. SMART Flex – practical application in the treatment of challenging SFA lesions (Technical Forum)**

Ralf Langhoff will discuss the current indications for SFA stenting live from Berlin’s Sankt-Gertrauden Hospital, as well as taking viewers through a case of bilateral chronic total occlusion of the SFA, with cross-over recanalisation of the left SFA, using a transfemoral retrograde approach and the insertion of two Smart Flex stents (Cordis,
Continued from page 8
Cardinal Health). Andrej Schmidt will also speak about the place of self-expanding stents and DCBs in the treatment of the SFA. The session concludes with Peter Goverde, who will talk more about the new generation SX stents (SMART Flex).

(Educational support from Cordis, a Cardinal Health Company)

13:30–15:00: Revascularisation of complex chronic deep vein obstruction (Main Arena 2)
Live from Bern University Hospital Heart and Vascular Center, Nils Kucher and colleagues take on an iliofemoral venous intervention of a stenosis of the external iliac vein. From Galway University Hospitals, Gerard O’Sullivan also presents a live case – a reintervention after failed varicose vein treatment around the pelvic vein. Back at the conference hall, Hendrik von Tengg-Kobligk speaks about MR and CT venography for imaging venous obstruction, followed by Stephen Black on the topic of endovascular techniques for deep vein obstructions. The session concludes with Cees Wittens on the role of surgery in the management of deep vein obstructions.

13:30–15:00: Challenging femoro-popliteal lesions (Technical Forum)
This session sees the transmission of two live cases: the first, the treatment of an in-stent occlusion with stent fractures RSFA, by Prakash Krishnan and colleagues at Mount Sinai Hospital, New York; the second comes live from AZ Sint-Blasius, Dendermonde, with Koen Deloose and colleagues. These are accompanied by presentations by William Gray on the when and where of different atherectomy systems in femoropopliteal arteries, Sven Bräunlich on approaches for thrombus-containing lesions, and Dierk Scheinert on available techniques and indications for distal protection during peripheral interventions.

16:30–18:00: Venous embolisation therapy (Main Arena 2)
Nils Kucher leads a case of pelvic congestion syndrome live from Berne, with techniques including foam sclerotherapy of varicose uterine veins and coil embolization of ovarian veins. Gerard O’Sullivan also presents a live case from Galway, a deep vein thrombosis from the common iliac vein to mid-thigh. Dr O’Sullivan will also discuss his diagnostic approach for pelvic congestion syndrome. This is followed by Mark Whiteley at the conference centre presenting on the efficacy of endovascular therapy for treating pelvic

Continued on page 10
**Continued from page 9**

congestion syndrome, and Olivier Hartung on the technical approach for treating pelvic congestion syndrome.

**16:30–18:00: Carotid interventions (Technical Forum)**

Antonio Micari and Fausto Castriota transmit live from Villa Maria Cecilia, Cotignola, with a live carotid case, and Andrej Schmidt is joined by his team in Leipzig’s University Hospital Division of Interventional Angiology. Flash presentations will be given by Marco Roffi, who discusses the latest guidelines on CAS for carotid revascularisation; Piero Montorsi speaks on proximal protection during CAS; and Alberto Cremonesi concludes with a look at new concepts for filter protection during CAS.

**Wednesday**

**12:30–13:30: Practical implantation of INCRAFT, an ultra low profile device (Main Arena 2)**

Dai-Do Do and colleagues in Berne take us through a case of percutaneous EVAR of infrarenal AAA under local anaesthesia, implanting the INCRAFT AAA Stent Graft System (Cordis, Cardinal Health). Ralf Kolvenbach then speaks about his first practical experience with the INCRAFT. He is followed by Philipp Schäfer, who discusses the improved percutaneous efficiency of the ultra low profile device.

(educational support from Cordis, a Cardinal Health Company)

**16:30–18:00: Pioneering revascularization strategies for TASC D+ lesions (Technical Forum)**

Andrej Schmidt, Daniela Branzan and colleagues transmit live from Leipzig with a case of infrarenal aortic stenosis and bilateral iliac occlusions in a patient with Leriche-Syndrome. Dr Branzan will also give a presentation on hybrid approaches for revascularization of complex peripheral obstructions. Back at LINC, Andrew Holden also speaks on Leriche syndrome, outlining techniques and results of percutaneous procedures. The session concludes with Madeleine Luther, who presents the Leipzig experience of percutaneous procedures for Leriche syndrome.
This morning sees delegates diving deep into the issues of carotid revascularisation. Amid the continuing debate over the when and where of CEA versus CAS use, Sumaira Macdonald (Silk Road Medical, Sunnyvale, California, USA) makes the case for incorporating cranial nerve injury (CNI), neuropsychometric testing and diffusion-weighted MRI (DWMRI) lesions into endpoints of carotid intervention trials.

In an interview with LINC Today, Dr Macdonald said that their inclusion would help to clarify and stratify patient risk. “Whether the patient presents with an index event consistent with a symptomatic stenotic lesion or a significant asymptomatic lesion, the intent is the same – namely to prevent subsequent stroke,” she said. “It is imperative, however, that we minimise the harm in so doing.”

Of course, this harm reduction is achieved in part through minimising procedural hazards by way of 30-day event rates. Traditionally, explained Dr Macdonald, this has meant tight control of the procedural stroke/death/myocardial infarction (MI) rate – the safety profile of the intervention.

While controversy persists about the relevance of MI as either a standalone or component part of a composite endpoint, Dr Macdonald pointed out that the impact of procedural MI on subsequent quality of life (QoL).

“It would be a mistake to ignore the impact of any procedural CNI on subsequent quality of life [QoL].”

Sumaira Macdonald
subsequent four-year mortality is beyond reproach.1

Regardless, she said, these endpoints do not go far enough to comprehensively characterise the risks of a particular intervention in any particular patient, stressing: “It would be a mistake to ignore the impact of any procedural CNI on subsequent quality of life [QoL].”

Citing past CEA versus CAS trials, Dr Macdonald demonstrated how the importance of CNI may be under- emphasised: “CREST, a randomised trial of CEA versus TF-CAS in standard risk patients demonstrated a 5.3% incidence of procedural CNI with a residual rate of 2% at six months (80% of these were motor deficits).2

“Both SAPPHIRE, a randomised trial of CEA versus TF-CAS in high risk patients, and CREST highlighted superior QoL scores for TF-CAS at 30 days.3,4 Although this difference was no longer significant at one year post-intervention, it could be argued that the SF36 ‘standard’ QoL tool used was simply too blunt and insensitive to detect CNI. CNI can take myriad forms and be variably reported (from facial paraesthesia, rendering shaving a challenge, to hypoglossal paresis, requiring a feeding gastrostomy).”

Taking into account the diminishing effects of CNI on QoL, including the possibility of their permanence, suggests that its inclusion is reasonable if we are to guide patient treatment more with greater certainty.

Turning towards procedural efficacy, Dr Macdonald noted that this historically has been equated to the longer-term prevention of subsequent ipsilateral stroke (equivalent in CEA and TF-CAS), but that this overlooks...
the potential impact of DWMRI lesions of brain and cognitive deficit on longer term functional outcomes.

Asked whether closer study of CNI, neuropsychometric testing and DWMRI lesions could tell us more about better estimating stroke risk in different patients with seemingly similar degrees of stenosis, Dr Macdonald replied: “This question is especially applicable to asymptomatic patients in an era in which best medical therapy alone is offered as the most appropriate intervention for a good proportion of patients.

“Although CNI evaluation and neuropsychometry might not have utility here, baseline DWMRI new white lesions ipsilateral to the asymptomatic carotid stenosis might direct the operator or interventionist to consider revascularisation, as these patients’ risk of stroke without revascularisation might be seen to be elevated in comparison to patients with normal MRI brain scans.”

Developing a better understanding of the form and impact of these factors, and hence devising a specific QoL tool for the types of injuries encountered, could form the way forward. Outlining current evidence and open questions, Dr Macdonald noted: “Attitudes to the utility of DWMRI new white lesions as a measure of injury vary. When they are incurred through carotid intervention, their fate and clinical relevance remain unclear. 

“However, there is good evidence that the baseline incidence of cerebral DWMRI lesions impact significantly on subsequent stroke, mortality and cognitive decline. Baseline incidence also impacts negatively on the outcomes of subsequent carotid intervention (implying that the presence of these lesions hampers cerebrovascular resilience or reserve).

“Cognitive function assessments are an entirely different story. Unfortunately, the literature is full of confounders and inconsistent messaging in the setting of carotid interventions, although there are consistent results in the setting of coronary artery bypass grafting (CABG). The test batteries may not be sensitive enough for carotid interventions in which the embolic burden is an order of magnitude less than that of CABG.”

Reaching new paradigms in trial design and data handling depends upon evidence and consensus. Increasing data volume can also impact trial funding – but how can the balance between economy and robust, applicable data be struck? While extended test batteries certainly can increase complexity and costs, Dr Macdonald pointed out that the nuances of risk may be otherwise lost: “DWMRI lesion counts and stringent neuropsychometric test batteries certainly increase trial costs and may hamper trial execution and completion on account of complexity,” she said.

“A trial that fails to recruit or does not recruit to projected targets risks withdrawal of funding, especially if government-sponsored (SPACE2 being a case in point). Even if industry-sponsored, there are fixed costs to be covered (personnel etc.) every day that the trial runs without recruitment. Of course a straightforward, elegant, cost-effective trial that answers the academic question at hand is the perfect solution but may be overly simplistic in reality.”

Moreover, trial design can bear an impact – and ensuring that studies are as far-reaching as possible can grease the wheels of technological development the world over: “Endpoints of importance to one governmental or federal agency (or society or specialty) may be less relevant to another,” said Dr Macdonald. “For example, some reports suggest that the total running and completion costs of CREST were or the order of 80 million dollars (National Institutes of Health sponsored with Abbott Vascular support). The endpoints were pre-agreed with the FDA and although the trial was completed and met its endpoints, resulting in FDA approval of the Abbott Vascular ACCULINK stent and ACCUNET...
Continued from page 13
embolic protection device (filter) for TF-CAS in standard risk patients, this did not result in the removal of CMS [Centre for Medicare and Medicaid Services] imposed coverage restrictions for TF-CAS in the USA.

“This is not a purely US-centric consideration. US reimbursement or the lack thereof impacts on industry R&D pipelines, which in turn is felt by carotid interventionists world-wide. The solution might be to design a trial that satisfies both masters, CMS and FDA, through federal agency collaboration.

“Lastly, various trial constructs vary hugely in cost. Randomised trials are expensive, as are US IDE [investigational trial exemption] trials that classically support FDA approval of devices. Post-market surveillance studies are cheaper in general and there is some evidence to suggest that this is the direction in which CMS is moving, in order to generate real world outcomes data in good volume.”

Dr Macdonald will speak during this morning’s Deep Dive session on carotid revascularisation, taking place in the Technical Forum between 8:30 and 11:45.

References
Debate surrounding the results of the series of CAS versus CEA trials has barely dampened six years on from the publication of the most recent study, CREST.1 Among the nuances of ongoing discussion (summarised recently by Cremo-nesi et al.2) sits the evidence that CAS conveys a higher risk of stroke peri-procedurally.

“CAS has had a very cyclical history,” explained Dr Veith to LINC Today, looking back to its nascent period: “There was great scepticism when it was first introduced by intervention-ists; surgeons said that it can’t ever work.

“Surprisingly, it did work. There were numerous posi-tive reports (and a lot of hype) mostly by interventional cardiol-ogist. And CAS enjoyed a rather meteoric rise.”

The decline of CAS was brought about only in part by trials such as CREST. While 2006 guidance recommended revas-cularisation in asymptomatic as well as symptomatic patients, more recent practice reflects the notion that asymptomatic pa-tients may be best treated solely by medical means.3

“In asymptomatic patients, there was a feeling, along with some evidence, that invasive treatment increased substan-tially the stroke rate in asympto-matic patients, such that they didn’t need any intervention. Some felt that most – and oth-ers felt that all – didn’t need any intervention.”

In its more recent history, a number of technological im-provements and changes in treatment predilection have perhaps rendered old trial data obsolete, bringing the apparent inferiority of CAS under new scrutiny. Dr Veith outlined the three improve-ments which, if confirmed by solid documentation, ought to bring CAS back in favour:

“There is the introduction of reversal flow cerebral pro-tection, access to the carotid through the neck rather than through the groin, and avoiding the aortic arch,” he said. “There is a proprietary system that does this, which not only avoids the aortic arch but allows good flow reversal. Those two things com-bined in the Silk Road system [Silk Road Medical, Sunnyvale CA, USA] suggest that stroke rates in high risk carotid patients will be decreased.”

The third improvement, Dr Veith continued, is the develop-ment of mesh covered stents with their potential to decrease the risk of post-procedural

“Many of us, including me, believe that most of those [asymptomatic] patients are best treated by best medical treatment.”

Frank Veith

Continued on page 16
Continued from page 15
stroke. Strokes following CAS, he explained, have tended to occur after the removal of the cerebral protection device, and hence could be due to the projection of plaque material through the interstices of the stent when flow is restored. Three mesh covered stents are currently in trial: the CGuard carotid embolic protective stent system (InspireMD, Inc., USA); the Roadsaver Carotid artery stent system (Terumo, Japan); and the Gore Carotid Stent (SCAFFOLD study; WL Gore and Associates, USA).

Ongoing and future trial data will provide the leaven for such technological improvements in CAS. But Dr Veith stressed that, while he is hopeful for the future of CAS, its usage ought to remain low. “In the past, every patient that had a little wrinkle in their carotid was getting a stent – that is never going to happen again. My opinion, which is not documented yet by hard evidence, is that CAS will enjoy another upswing – maybe not to the level that occurred five to ten years ago, but it will find more frequent use than the discouraging results of the randomised trials would suggest.

“Now, there are those who believe that all asymptomatic high-grade stenoses should be treated by CEA or CAS. But many of us, including me, believe that most of these patients are best treated by best medical treatment – by indicators that make invasive strategies favourable in asymptomatic patients. Contemporary imaging techniques, including CT and MR angiography, ought to facilitate patient stratification according to risk of ischemic stroke.4,5

Dr Veith has written and talked extensively on the overuse of both CEA and CAS,6 a topic that continues to garner great interest – and controversy. “I have changed my opinion based on what is happening,” he noted.

“I have written, and a number of others have written, that many of those patients don’t need invasive treatment. Probably only about 5 or 10% need invasive treatment. They should be treated with statins or other medical treatments for the plaques to remain benign. The great wave of enthusiasm for carotid stenting was based on the fact that the companies said that all of these asymptomatic cases have to be treated. The big question now is whether best medical treatment alone is as good as best medical treatment plus CEA or CAS. That is a whole other question.”

**Dr Veith will present, ‘Despite current level 1 evidence, the outlook for an upsurge in CAS is bright and getting brighter,’ during this morning’s Dive Deep session, taking place in the Technical Forum between 8:30 and 11:45.**

**References**

R

estenosis remains a major limitation of superficial femoral and popliteal artery revascularisation. The innate immune system is ideally suited to contain an injury and rapidly dispatch invading microbes. Macrophages and other inflammatory cells home to sites of injury and release cytokines, inflammatory proteins, and growth factors. In most circumstances this process is self-limiting as mediators of resolution, resolvins, lipoxins, etc., bring the process to a halt. However, in some cases the resolution phase is deficient and chronic inflammation ensues.

The injury to a blood vessel induced by angioplasty or atherectomy is no different as far as the body is concerned to any other injury. The liberation of inflammatory mediators may induce the migration and proliferation of smooth muscle cells and fibroblasts, as well as reversion to a more primitive cell-expressing α-smooth muscle actin. While much more work is needed in this area, it is believed that, firstly, the degree of this vascular inflammation is associated with restenosis in the femoropopliteal artery\textsuperscript{1,2}. These findings imply that immunomodulatory strategies might improve the way a vessel heals and hence the outcomes following revascularization.

Ahead of his talk this morning, LINC Today caught up with Christopher Owens (University of California, San Francisco, USA) to discuss an exciting alternative approach to this inflammatory conundrum.

He set the scene by asking “What’s different about the Dexamethasone Infusion to the

“Continued on page 18
Continued from page 17
Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization (DANCE) trial?”

Outlining the DANCE trial’s key features, he continued: “The hypothesis of this trial is that immunomodulation therapy applied locally to the adventitia of the blood vessel wall at the time of vascular intervention reduces the magnitude of the inflammatory response produced from barotrauma or laceration from the atherectomy.”

He added: “The DANCE Trial has several firsts in it. For one, it uses a novel delivery mechanism – instead of using a balloon or stent platform, it uses a microcatheter to infuse the drug directly into the adventitia.”

Drug delivery is facilitated using Mercator Medsystems’ (USA) Bullfrog Micro-Infusion catheter, an attractive method for local drug delivery because the drug can be infused into tissues around the blood vessel wall at the site of injury without the need for a permanently implanted stent or partitioning from a balloon surface. Though similar to other balloon-tipped catheters, it contains a microneedle covered by a fold of semi-rigid, yet inflatable balloon. Once inflated, the balloon microneedle is uncovered so that a drug can be delivered into the tissue.

Professor Owens went on: “This catheter has a very small hollow needle that safely pierces through the vessel to deliver drugs and other biologics directly into where they are needed most. It is an infusion therapy by which one can titrate to the desired effect. Another nice feature is that the drug can be mixed with a little contrast so that you actually have visual confirmation of on target delivery.”

He added: “This provides immediate feedback so that when you leave the lab you know for sure that you accomplished your drug-delivery goal.”

Describing another important aspect of the DANCE trial, Professor Owens said, “Secondly, we are using an anti-inflammatory drug dexamethasone: As atherosclerosis has been deemed an inflammatory disease – and the acute injury of angioplasty produces acute inflammation on top of an already inflamed artery – it makes sense to use an anti-inflammatory medication to prevent restenosis.”

“Dexamethasone, a glucocorticoid that is 20 times more potent than cortisol... has been around a long time for a good reason: It is powerful at immunomodulation as it inhibits its innate immune system nuclear transcription factors such NFκB and AP-1 among others. It also destabilises MCP-1 messenger RNA so many of the inflammatory cytokines and chemotaxins do not get made at all.

“This is important because by-products produced from overly exuberant inflammation generates the growth factors and other signals that result in vascular cell proliferation.”

Professor Owens then highlighted the third unique feature of the DANCE trial: “The adventitia is attractive as it spares the endothelium of potentially toxic drugs.”

Adventitial delivery is an efficient means of local drug delivery and is of interest for several reasons: it acts on the outer vessel layer to participate in arterial remodelling, inflammatory cell recruitment and contribution of cells to neo-intima formation; it establishes a reverse concentration gradient with the majority of the drug distributed in the adventitia and media, while sparingly exposing endothelial cells; it maximises tissue concentration and minimizing both non-target organ distribution and plasma levels and of drug.

Explaining this, he said: “It turns out that the adventitia is far from just the inert outer layer of the blood vessel containing mostly connective tissue that we thought it was. It...
Continued from page 18

has a rich haven for stem cells, myofibroblasts and inflammatory cells. It also has its own microcirculation, which is active in cell trafficking into and out of the vessel wall. So it is really the ideal location to target with an immunomodulatory approach to restenosis.

In the DANCE pilot study, Professor Owens and co-workers demonstrated that perivascular administration of dexamethasone could be feasibly and safely injected into the tissue around the blood vessel wall at the time of an angioplasty or atherectomy. The six-month outcomes showed that this treatment improved outcomes (patency) following angioplasty. A separate multi-centre DANCE trial is now ongoing in order to establish efficacy.

“We have biomarker data to support our hypothesis – we built into the trial the measurement of serum markers of inflammation thinking that if the drug really does reduce inflammation then we ought to see a signal (reduced circulating markers CRP and MCP-1) way before we the subject finishes the 12-month follow-up visit.”

He concluded saying: “Therefore this study is the first of its kind in many different ways.”

“We have biomarker data to support our hypothesis – we built into the trial the measurement of serum markers of inflammation thinking that if the drug really does reduce inflammation then we ought to see a signal (reduced circulating markers CRP and MCP-1) way before we the subject finishes the 12-month follow-up visit.”

Christopher Owens

References:
3. 2016)mmTCaBM-IDAhwmcAJ.
Changing paradigms and future concepts in peripheral interventions – how far have we come?
Main Arena 1 Tuesday 09:30–11:00

Drug coated balloon angioplasty
How much preparation is really needed?

Gunnar Tepe (Klinikum Rosenheim, Germany) was a key figure in developing the first drug-coated balloons (DCBs) for the treatment of peripheral arterial disease. Also, as the principal investigator in the THUNDER trial, he presented the first-in-man results using a paclitaxel-eluting device almost 10 years ago. LINC Today was honoured to catch up with Professor Tepe before this morning’s session on “Changing paradigms and future concepts in peripheral interventions” in which he discusses preparatory techniques prior to DCB angioplasty.

Pre-dilatation and debulking are considered essential by many, however, the question of whether they offer long-term improvements is something that Professor Tepe is keen to discuss. He began: “My talk is really about the preparation of the vessel prior to coated balloon therapy, and whether it is needed. The basic premise is that if you undersize, you might not get as much drug in the vessel as if you oversize so I would like to ask – is there any strong evidence to show that pre-dilation with a bare balloon is necessary, because it is actually is recommended in many instructions for use in all lesion types.

“I personally do not see any evidence for pre-dilation, at least in the superficial femoral artery [SFA], because when it was not performed, the DCBs were still as effective.”

He added: “So I think that there is no big need for pre-dilation in the SFA or popliteal artery, however, there is a difference for below-the-knee [BTK] lesions, where it might be a really good way to push the DCB into the lesion, as balloon angioplasty is technically more difficult in BTK, and this pre-dilatation improves drug uptake. But again there is no hard evidence.

“The second preparatory technique is debulking using Shockwave or cutting balloons, and I believe that – yes, there is a need for this, in order to enhance drug uptake in calcified arteries and restenotic lesions. But in special indications – not routinely. There are several devices that can be used; currently we don’t know which is the best device, and there are ongoing studies into which might be the best the new device.”

“Debulking studies in animals have shown increased drug uptake, but some of these have been carried out in healthy vessels in animals, not diseased human vessels, so can lack clinical pathology. Adjunctive devices for preparing or debulking

Continued on page 21
Continued from page 20
plaques with atherectomy are less rigorously studied and have niche roles."

Preparatory techniques carried out for severely calcified BTK lesions, which are very long and thin, and pose a technical challenge, Professor Tepe discussed how to prioritise preparation for complex procedures: “Some long-lesion debulking techniques can be very difficult and can add a lot of time onto an already lengthy process such as atherectomy.

‘If debulking is carried out with a current technique like Shockwave, it takes forever for very long lesions because the catheters have a limited length, whereas cutting balloons are much quicker. For debulking of very long lesions, the practicality has to be taken into account; if I have to spend hours to prepare the vessel, I won’t tend to do it.’

As one of first to use DCBs, Professor Tepe’s pioneering work and enthusiasm for DCBs is rewarded in seeing how well they perform compared to other techniques.

“When I think back over 10 years ago, when we just had this new device in our hands, and we didn’t know whether this was something that might change the outcome for patients. Also, we were told by every company that in order to release drugs over weeks or months, we would need to have drug-coated stents with special release kinetics, which is really difficult to do, and they all thought that it couldn’t be done with a DCB.”

He continued: “At this point about 11–12 years ago I wanted to start the THUNDER study1,5 so I went from company to company to raise interest and money, but – not believing in this technology – they declined. It was a challenge at the time, so now it is really nice to see that this technology has now become standard in the SFA. Nevertheless, we still need to learn more about the device.

“It is a game changer, but it is not a winner in every game; we have to learn when to use it and when not to use it, and also its limitations.”

Variable levels of crystallinity of drug coating in the DCB can impact on the performance of the DCB, commenting on his experience, Professor Tepe said, “I think that all DCB coatings are different, some are more crystalline, some are more homogenous. Of course, if there is a really homogenous coating then it might be ‘safer’ as it avoids any potential embolism, but the uptake in the vessel might be less.

“My experience is that more crystalline coatings are more effective, and I haven’t had safety issues. Yet, the type of coating does play a role and I think that the risk with the wrong coating is in the long-term where restenosis occurs at 1–2 years.”

“IT is really nice to see that this technology has now become standard in the SFA.”

Gunnar Tepe

References:
Revascularisation costing
What can we learn from Germany and the USA?

Thomas Zeller (Universitäts-Herzzentrum, Bad Krozingen, Germany) will take centre stage this morning at LINC 2016, to talk about the recalculation of the overall costs of the treatment of TASC II A and B femoropopliteal lesions. An original study, published in 2014, calculated the treatment costs from the both the payer’s (insurance company) and the provider’s (hospital) perspectives. The objective of the original cost analysis was to study the economic impact on four main endovascular strategies for the treatment of infrainguinal peripheral artery disease: plain balloon angioplasty (POBA), bare metal stents (BMS), drug-eluting stents (DES) and drug-eluting balloons (DEB).

He began: “For the original calculations, we pooled the 24-month target lesion revascularisation (TLR) data of prospective studies that had been published up to the end of 2013. At this point, no dedicated reimbursement codes had been developed for the US.”

Although the probability of TLR varied widely, (particularly following treatment with PTA or BMS) the drug-eluting strategies had a lower projected budget impact over 24 months compared to BMS and PTA in both the US and German public health care systems.

“The overall outcome of the study was that drug-eluting strategies are significantly more cost-effective than traditional treatment strategies, such as POBA and BMS,” added Professor Zeller.

Describing the recalculation, he said: “For the current recalculation, the 2016 reimbursement rates for the four different devices in Germany and the US are used. However, the current recalculation only concerns the payer’s cost perspective.”

Over a 12-month time period, savings were observed when...
Continued from page 22

using the DCB instead of a DES, in agreement with the earlier calculations. Professor Zeller commented on these findings: “The potential differences in cost savings between DES and DEB depend on country-specific reimbursement systems. Overall, both methods seem to be equally effective in reducing TLR rates, and with this, re-hospitalisation rates, which mainly drive the costs, besides that of the device.”

Professor Zeller then described some recent findings comparing DEB and POBA: “Results that are in favour of DEB still hold true, as recently published pivotal studies, in particular, the IN.PACT SFA study confirmed or even outperformed the outcome of the initial pilot studies in terms of a TLR benefit for DEB compared to POBA.”

Describing the impact on cost calculations, he continued: “The outcome of the updated cost calculation is still the same, favoring drug-eluting technologies. For the German payer parties, DES are (by trend) more cost effective as compared to DEB, whereas the outcome is the opposite in the US. The main reason for this difference is that in Germany there is a dedicated reimbursement code for DEB making them more expensive for the payers; this reimbursement code is missing for DES, meaning that DES and BMS reimbursement are equivalent.”

Professor Zeller added: “This reduced the costs for the payer party, but reduces the revenue for the provider party if a DES is used.”

Restenosis after coronary stent implantation remains a significant clinical problem, and angioplasty provides a treatment option that may overcome some of the inherent limitations of surgery. With regards to surgical procedures, Professor Zeller commented on how difficult it is to directly compare costs of these approaches in terms of training, expertise, and recovery time.

“DEB angioplasty requires experience in vessel recanalisation, but is a relatively simple procedure without a dedicated learning curve; whereas performing a good bypass anastomosis might need a longer learning curve.”

He concluded by adding: “Of course time to mobilisation lasts longer in average bypass surgery compared to an interventional procedure. But due to inherent differences in invasiveness and potential options for redo procedures, surgical revascularisation and interventional revascularisation cannot be directly compared.”

References


Suggestive of an adventure of discovery, intentional or not, this afternoon’s session entitled ‘The last frontiers: Calcified lesions’ sets the scene for a stimulating discussion lead by pioneers in the management of this challenging vascular issue.

Moderating the session alongside Gary Ansel (Columbus, USA) will be Marianne Brodmann, Professor of Internal Medicine and Substitute Head of the Clinical Division of Angiology at the University of Graz, Austria. Looking ahead to today’s session, she clarified what she considered to be the main issue relating to calcified lesions that would be central to the discussion. “The problem with calcified lesions is that we cannot deliver drug through the calcium to the vessel wall, and if we are unable to remove the calcium, there will always remain a calcium rock, which also cannot be treated by a mechanical force such as a stent,” she told LINC Today, adding that, “if this calcium is not removed or altered it becomes a barrier to accessing the vessel wall layers.”

Talks during the session include a discussion of the patterns of vessel calcification, crossing techniques for calcified chronic total occlusions (CTOs), atherectomy for calcified lesions, biomimetic interwoven stents, percutaneous bypass techniques, as well as a talk by Thomas Zeller from the Department of Angiology at University Herzzentrum Freiburg, Bad Krozingen, Germany, called ‘Disrupt it!–The Shockwave lithotripsie concept’.

Asked for her opinion of the Shockwave concept, Professor Brodmann highlighted what she found exciting, saying: “With the Shockwave concept, energy is produced within the balloon – the same system as used for kidney stone lithotripsy – effectively enabling a cracking of the calcium at the vessel wall. “This creates a channel to the inner layers of the vessel, regaining reactivity of the vessel wall again. Shockwave is hard-to-hard tissue, and soft-to-soft tissue.”
Weighing-up reintervention strategies for SFA/popliteal disease

This morning’s opening session in Main Arena 1 dives straight into the cutting-edge LINC 2016 programme with a frank and open look at the treatment strategies for complex disease in the SFA and popliteal arteries. “Generally speaking, peripheral vascular intervention [PVI] has gone through many changes over the years,” commented session speaker Jihad Mustapha (Metro Health Hospital, Wyoming, USA), who will focus on treatment strategies for reintervention (and catastrophic failure in particular) in his presentation.

With commonly-suggested reinterventional strategies for the SFA/popliteal region being PTA, drug-coated balloons or drug-eluting stents (DCB, DES), cutting balloons, cryoplasty, atherectomy or relining (with bare or covered stents), LINC Today asked for Dr Mustapha’s perspectives as to how and when approaches come in and out of favour? “Often we seem to think we have reached the pinnacle of a ‘best therapeutic option’, only to then learn that there are negatives, such as in the example of bare metal stenting [BMS],” he said.

“When BMS became available, we thought it was the answer – when we initially saw significant improvement over balloon angioplasty alone. But we later learned of the severe hypoplastic response, stent fractures, restenosis and, finally, acute thrombosis of covered stents.”

Similarly, Dr Mustapha recounted the story for atherectomy, which at first served up excellent outcomes, only to be later found to be insufficient as a standalone therapy.

“After that we then stumbled on to drug-eluting technologies, including DCBs, which have shown some very promising outcomes in the treatment of above the knee [ATK] disease. What’s becoming interesting is the evolution of physician-initiated combined therapy between different, available therapeutic devices. For example, the use of DCB with self-expanding BMS, or DCB with atherectomy.

“Although there is no strong supportive data to backup this type of use, it seems to be the thing to do from the known pathophysiological effect of both. Of course, stent fractures continue to be a severe obstacle in the genicular area, even in the presence of DCB. Initially, bailout stenting was the way to go, but today physicians would hardly ever use a stent that is prone to fracture, and tend instead to go straight to a stent that is known to tolerate the hostility of this infrainguinal section.”

By way of example, Dr Mustapha shared the case of a catastrophic event that happened following a combined therapy which, initially, seemed to pres-
ent an “excellent” result. As shown in Figure 1a, two initially overlapping stents were placed in P2 and P3 of the popliteal artery, and then subsequently pulled apart, causing aneurysmal formation at the junction (arrow), where an IN.PACT Admiral DCB balloon (Medtronic, USA) was used to prep the vessel.

The aneurysmal development and associated embolisation resulted in the loss of most of the tibial vessels. “In Figure 1b, you can see the need for the bailout method using the Supera stent [Abbott Vascular, USA] and further infrapopliteal therapies,” said Dr Mustapha.

He added: “You can see that the operator here did a great job prep the vessel for therapy in an area where normally the extent of the disease is severe. But the catastrophic cascade of events started by the choice of stents that were placed in this area. Based on that choice alone, this catastrophic failure could have been avoided.”

In essence, this is one of Dr Mustapha’s key messages – that we must learn from the decisions that turn these cases onto a path of catastrophic failure. “You can see in an angiogram taken with bent knee (Figure 2) that the tortuosity in this vessel tells the whole story,” he said. “If you don’t place a stent that will be able to combat the forces generated by this hostile vessel then this is a good time to learn that the choice of the stent after DCB in this area, such as Supera stent, would have prevented the catastrophic cascade of events that has happened so far.”

Above Left: Figure 1a. Example of a catastrophic failure. Two initially overlapping stents were placed in P2 and P3 of the popliteal artery, and subsequently have pulled apart. There is aneurysmal formation at the junction (arrow), where an IN.PACT Admiral DCB balloon (Medtronic, USA) was used to prep the vessel.

Above Centre: Figure 1b. A Supera stent (Abbott Vascular, USA) is deployed within the separated stents, thereby improving the mechanical compression of the original stent on the vessel walls.

Above Right: Figure 2: Bent-knee angiogram, clearly indicating there are multiple hinge areas in the vessel that are prone to torsion, extension, and flexion on any implanted stent.

Commenting on this use of a bent-knee angiogram, Dr Mustapha stressed that is an underutilised angiographic method, especially in complex infrainguinal disease. “I highly recommended a bent-knee
angiogram at baseline diagnostics, and at the end of the intervention,” he said.

Touching upon the effect that reimbursement has on reinter-
vention decision, Dr Mustapha cautioned that while of course it has an impact, cost savings are not even always possible due to the “must-fix” nature of the arteries in many cases. What’s more, he added that intently pursuing cost savings could inadvertently raise costs in the long-run: “If we try to save on cost in such a case, the patient can end up with a below the knee [BTK] amputation, which could increase the cost ten-fold versus the cost of implanting a stent and two balloon angioplasties,” he said.

“This is where conservative-cost endovascular reintervention was most effective. That is because even though we focus on the sick patient, at the end of the day we are conscious about the cost to the patient and the system. We will always have to walk this fine line. In my opinion it is patient first, cost second. I’m sure many agree with me, but many may disagree.”

The challenge of choosing an appropriate reintervention strategy is also compounded by the heterogeneity in study data. “We are going through this right now with many of the recent trials,” said Dr Mustapha. “It is very tricky, and sometimes becomes blinding to the operator as to which path to choose, and whom to believe; the data can be dissected in so many different ways.

“I don’t like to see this happening, and hope to see a ho-
mogenous approach of studies in the future, with more cohesive outcomes, and suggestions for the day-to-day physician who is just looking for a simple answer.”

With LINC offering a crucial forum in which to discuss the finer points of a wide range of topics, including reinterven-
tional strategies, Dr Mustapha took the opportunity to share his general views on the annual impact of the meeting. Tailoring his address to attendees directly, he said: “First of all, you have made an excellent choice in coming to LINC – where the world’s thought-leaders come together to deliver the latest in data analysis, techniques, and live cases.

“Additionally, you will learn about exciting therapies on the horizon. I can reassure you that you will walk away with solid knowledge on how to best treat your patients in a comprehen-
sive manner. Because here, not only do you listen to the lecture on the subject, but you are then able to see a live case, hear thought-leaders discuss it, and only a short walk away you can then see and handle the tools that were involved.”

Dr Mustapha presents ‘Treatment strategies for reintervention (cata-
strophic failure)’ during the sym-
posium ‘Treatment strategies for complex disease in the SFA/Pop’, held at 08:00–09:30 this morning in Main Arena 1.
Delving deeper into endovascular therapy for pelvic congestion syndrome

Venous embolisation therapy is the topic of choice this afternoon in a ‘Scrub in the with experts’ session packed with live cases, technical approaches and informative updates on various facets of the venous interventional field.

Discussing cutting-edge endovascular therapy for pelvic congestion syndrome (PCS) during the session will be Mark Whiteley, a consultant vascular surgeon from the UK, whose impressive career thus far has included the foundation of his own centre, The Whiteley Clinic, in several sites across the UK, as well as the receipt of several international, national and regional prizes for research into venous treatments. With techniques such as The Whiteley Protocol being part-and-parcel of his esteemed work, Professor Whiteley’s experience means he is a perfect candidate to share the latest insights into endovascular treatment of PCS during today’s session. With that in mind, LINC Today spoke to him to catch a glimpse of his work, and just what he will be touching upon during his presentation.

The Whiteley Clinic has a wealth of experience in PCS, and I think I can fairly say it is one of the leading centres in the UK. Perhaps we could start with a ‘potted’ history of when the clinic was founded, and whether it is also fair to say it has set a trend in ‘office-based’ centres for venous disease?

I performed the first endovenous procedure for varicose veins (radiofrequency ablation using the VNUS Closure system) in the UK on 12 March, 1999. I started running courses in this new procedure immediately, and it became clear that there was a good opportunity to open a new sort of venous practice. Therefore I set up the brand ‘The Whiteley Clinic’ in 2001.

In 2003 we moved our practice out of a private hospital and into our first dedicated unit which we built ourselves. At that stage it was an outpatient facility for consultation, duplex and sclerotherapy only, but in 2005 we built our first local anaesthetic theatre within the clinic and started performing exclusively ambulatory local anaesthetic endovenous surgery.

As far as pelvic venous embolisation is concerned, Judy Holdstock developed the transvaginal duplex ultrasound scan protocol that we used to diagnose pelvic venous reflux, but the initial treatment was performed under sedation by an interventional radiologist at a local hospital. In 2014, it became clear that we did not need the expense of a hospital, thus we opened our new local anaesthetic pelvic vein unit in our London Clinic. We have been performing local anaesthetic pelvic vein embolisation in our own clinic now since the summer of 2014.

Jumping into PCS itself, one crucial aspect is surely proper identification of the syndrome, rather than the perhaps historical perspective of ‘can’t find it, so it isn’t there’ that some have claimed can plague the detection of venous issues. With that in mind, how important
Transvaginal duplex ultrasound scanning, using the protocol developed by Judy Holdstock, is essential to identify pelvic venous reflux. This then has to be correlated with patient symptoms and clinical signs to make the diagnosis of PCS. We have recently published a research project we performed looking at the correlation of patients improving (or not) following embolisation, and whether the radiologist used the transvaginal duplex ultrasound scan to direct treatment, or used their own venogram. Results strongly suggested that transvaginal duplex ultrasound scanning was more accurate than venography even when performed at the time of embolisation.

As far as any other imaging is concerned, if the patient is lying flat then reflux is not going to be seen, as we know from a decade and a half of research into leg venous duplex ultrasoundography. Therefore MRI/MRV [MR venography] or CT scanning will not show reflux unless the patient is scanned on quite a steep incline. Venography is inaccurate, as proven in the above research, but also we know that contrast is non-physiologic and does not flow as the blood does.

As far as the techniques that measure the size of the vein, we have also recently published in the European Journal of vascular and endovascular surgery show-
ing that there is no correlation between the size of an ovarian vein and reflux. As such, any technique that reports the size of a vein is erroneous.

Finally, transabdominal duplex ultrasound scanning can only show the truncal veins and cannot see the communications deep within the pelvis. As such, transvaginal duplex ultrasound scanning using the protocol developed by Judy Holdstock is currently the gold standard, and I would not like to make a definite diagnosis of pelvic vein congestion syndrome without it.

Similarly, can you introduce the cutting-edge protocols, developed by you and colleagues, for PCS diagnosis?
I would not be able to say that currently we have a protocol for the whole diagnosis of PCS, although we are working hard towards it. What I can say is that we have a protocol for diagnosing pelvic venous reflux using transvaginal duplex ultrasoundography. We are publishing this technique in a book in the near future called ‘Advances in Phlebology and Venous Surgery Volume 1’. In addition, we run courses on how to perform this technique at our main clinic in the University of Surrey Research Park in Guildford, UK.

You will be communicating the efficacy of endovascular therapies for PCS in your presentation – can you describe the current gold-standards (foam sclerotherapy / coil embolisation, for example), and how results stack up in follow-up?
At the moment, it is far too early to give any definitive results from these comparative treatments. However, if we correlate research from other veins, such as leg veins, where foam sclerotherapy and other endovenous techniques are being used, one can project the likely results that we are going to find.

Coil embolisation, provided it has been performed correctly, causes complete atrophy and permanent closure of truncal veins. However, it does not necessarily get rid of varicosities distally, such as vulval varicose veins, vaginal varicose veins, haemorrhoids and therefore we can also assume the same will hold for any varicosities causing irritation within the pelvis in PCS.

Foam sclerotherapy alone does not work in the long term in large veins. We have recently had our research accepted for publication in the European Journal of Vascular and Endovascular Surgery in which we have shown the effect of sclerosant on the vein wall. It turns out it is not the size of vein that matters, it is the thickness of the vein wall. Hence in the truncal veins, where vein walls are usually 400 to 600 μm, foam sclerotherapy will not atrophy the whole vein, and as such will cause thrombus. This will allow recanalisation in the future, and so foam sclerotherapy by itself is unlikely to get as good results in the truncal veins.

However, foam sclerotherapy is essential for treatment of the distal varicosities. As such, there is good circumstantial evidence to show that the combination of coil embolisation of truncal veins with foam sclerotherapy of the distal varicosities is likely to be the gold standard treatment of PCS.

With your clinic’s active research focus, and are there new or refined approaches/therapies that might spark interest?
We have found that the ambulatory walk-in walk-out service of transjugular coil embolisation of pelvic veins, under local anaesthetic only, has been very successful. We have also recently presented our research showing that transvaginal duplex ultrasonography performed at the same time as coil embolisation allows ultrasound-guided foam sclerotherapy to be infused through the embolisation catheter before deployment of the coils. Although this can be done under image intensification, that relies on foam displacing contrast, or contrast being within the foam, changing the physical properties of the foam. Using transvaginal duplex ul-
trasonography during the procedure, we are able to ensure that each target vein is filled with foam to give the best possible chance of treatment. We can also use breathing patterns to push the foam into veins that we wish it to treat.

Finally, more generally, meetings such as LINC have seen somewhat of a boom in endovascular venous focus in recent years. Do you think veins are now taking a fairer share of the otherwise arterial interventional pie?

With somewhere between 30 to 40% of patients having superficial venous reflux disease of the legs, large numbers of women having pelvic congestion syndrome, 50% of adults having haemorrhoids at some time in their lives and then other conditions that are now being shown to be venous in origin, I think we can safely say that we are only just scratching at the surface of venous disease and venous intervention.

Although arterial intervention is glamorous, in sheer numbers of cases it will be massively overshadowed when patients and doctors realise what is possible in venous intervention. I suspect that we will only see a true growth in this sector when we have phlebologists who deal only with veins, and can understand venous reflux and obstruction whether it be in the legs, pelvis or elsewhere.

References

1. The Whiteley Clinic (http://www.thewhiteleyclinic.co.uk/; Accessed January 2016)
The most advanced stages of peripheral artery disease leave patients ineligible for conventional forms of revascularisation, yet a new hope has emerged from an old concept: that of deep vein arterialisation (DVA), which seems to be gaining momentum as a viable approach for limb salvage. Thursday afternoon sees Andrej Schmidt presenting technical aspects of the DVA procedure during the Expert Course, ‘Pioneering techniques for CLI and CTOs’. Dr Schmidt will also be discussing the latest options for so-called ‘no-option’ CLI patients during this afternoon’s session, ‘Multidisciplinary patient-centres approach for diabetic patient treatment’.

Joining him this afternoon is Steven Kum (Changi General Hospital, Singapore), who will be sharing his experience with the LimFlow DVA procedure (LimFlow Gmbh, Germany), in a case review of the patients his team have treated so far. He spoke to LINC Today to discuss his recent proof-of-concept study, which is now set for further trialling to secure the CE mark.

“We have intentionally chosen end-stage cases – so-called ‘no-option’ CLI,” began Dr Kum. “We have shown in our (unpublished) data that we have achieved reasonably good limb salvage of 86%, as well as wound healing rates of 80% at

Continued on page 33

“We are still learning. But this is a viable and safe alternative to amputation.”

Steven Kum

Angiograms taken before (left) and after (right) LimFlow procedure.
Potential solutions for the “no-hope CLI patient”
Global Expert Exchange Forum Tuesday 16:11–17:00

Continued from page 32

six months in this small series. These results were similar at 12 months.”

These have been the important outcomes in a group where amputation is invariable, he explained, adding that they have also shown LimFlow to be relatively safe. “We have been able to document the objective and subject performance data, including TcP02 data, resolution of rest pain, and the wound healing times,” he said. “The technology and the concept has been everything that we have wanted from a procedure to treat no-option CLI patients.

“Angiography, and understanding the anatomy has been a learning process for us. Understanding the response of the body to arterialisation of the venous bed has been interesting from a physiology point of view. This has implications for patient selection, post-operative wound care and surveillance. In addition to that, we have also learned how to re-intervene for these patients. Our experience with DCB for restenosis will be presented as a poster by one of our fellows. Our longest DCB assisted patency is 630 days.”

While the DVA re-intervention rate has been significant, Dr Kum explained, figures need to be viewed in the correct context; these are end-stage patients, where any form of conventional intervention would have been a failure. These patients also had large wounds which would, in a conventional angioplasty, likely have had to undergo re-intervention to maintain patency. “We are still learning,” stressed Dr Kum. “But this is a viable and safe alternative to amputation. With the development of Generation II devices, we expect that the procedure could be widely performed by many physicians across a variety of proficiencies.”

Some phenomena emerging from percutaneous DVA have been pleasantly surprising, and Dr Kum highlighted cases in which perfusion has been maintained despite stent graft occlusion – measured objectively on TCPO2 and infrared thermography (FLIR) – something that has also been observed in surgical DVA. “We are still trying to understand the concept, but we have some hypotheses,” he commented.

LimFlow is a dedicated system that facilitates the creation of an artificial fistula between the artery and vein as well as the removal of venous valve structures. The procedure involves two ultrasound catheters, one inserted into the target vein (the ‘receive’ catheter) and the other into the opposing artery (the ‘send’ catheter). With ultrasound-guided positioning, a wire is crossed over from the artery to the target vein, which is then predilated and stented, resulting in a bridge between the two vessels. A valvulotome is then employed to destroy the numerous venous valves which would otherwise impede flow.

Having completed the proof-of-concept study (although patient follow-up continues), Dr Kum and colleagues have begun recruitment for a wider study, enrolling patients in Leipzig and Munster as well as Singapore.

“We are hoping to get the CE mark at some time this year. We envision that in the coming year, with more physicians being exposed to the potential benefits of LimFlow, more centres will come forward and request to join us in the CE mark study.”

Steven Kum

Continued on page 34
Continued from page 34

Schmidt and Dierk Scheinert in Leipzig to name a few.”

Discussing how the technique could be applied to other anatomical areas, Dr Kum cited the angiosome concept as key to understanding where this could appropriately be achieved: “The angiosome concept has been popularised in the last several years, and it has been applied to interventional procedures. One of the problems that an interventionalist comes across is an angiosome that cannot be reconstructed conventionally.

“In our initial experience, we treated several cases — non-end-stage patients — by treating the ‘venosome’ directly. These patients were not end-stage, but they did not have the blood vessels going to a specific area according to the angiosome concept. So we applied DVA and found that this gave good results.”

Dr Kum will present case reviews during the session ‘Potential solutions for the no-hope CLI patient,’ which takes place this afternoon in the Global Expert Exchange Forum between 16:11 and 17:00 (as a continuation of the session, ‘Multidisciplinary patient-centred approach for diabetic patient treatment’).
During this afternoon’s session dedicated to developing a multidisciplinary patient-centred approach for diabetes treatment, vascular surgeon Enrico Maria Marone (Associated Professor of Vascular Surgery at University of Pavia and Scientific Institute Policlinico San Matteo of Pavia, Italy) will present the preliminary results of a large-scale epidemiological and economic study of diabetic foot.

This ongoing study is centred in the CESP Research Center on Public Health, University of Milano Bicocca (Prof. Cesana, Prof. Mantovani, Dr Ciampichini and Dr Chiodini), with collaboration from interventional cardiologist Roberto Ferraresi (Humanitas Gavazzeni, Bergamo) and diabetic physician Roberto De Giglio (Azienda Ospedaliera Ospedale Civile di Legnano).

“We have studied more than 18,000 diabetic patients with PAD,” said Professor Marone in an interview with LINC Today. “This is one of the most important study that I know on this topic.”

The data came through a data warehouse (DENALI), from the healthcare administrative databases of Lombardy. Such a database is at present exclusive to Lombardy, the largest region of Italy with almost 10 million inhabitants.

Datasets included demographic and lifestyle characteristics as well information relating to their health, comorbidities and incurred healthcare costs.

“The preliminary evaluation of this study concerned the incidence, prevalence and comorbidities,” said Professor Marone. “We have found many interesting data. First of all, the percentage of diabetic patients in the total population is 5.5% (almost 566,000 people). This 5.5% is similar to the diabetic population in the whole of Italy and in European countries. Within this over-500,000 people, we found 18,000 diabetic patients with associated peripheral artery disease (PAD). The greatest part of them, 61%, were men – so 39% female – with a mean age of 72 years.”

“Hospitalisation is the most important part of the cost. But it is also the most important factor for the survival of the patient.”

Enrico Maria Marone

Continued on page 36
Continued from page 36

Considering, amongst other things, the economic differences that exist between the north and south of Italy, Professor Marone defended the generalisation of such epidemiological findings across the country as a whole, and further afield still. “There are differences between the north and south of Italy,” he said, adding: “But these differences are not significant in terms of the national healthcare system. The national healthcare system is similar in all parts of Italy in terms of quality of treatment.”

“Yes, the Lombardy region is a lucky region – it is most similar to Germany and other European countries with high quality of life; it is richer than the south of Italy and other countries from south of Europe such as Greece, Turkey, Spain and Portugal. But I think that in the last 20 years, the level of national healthcare is similar. These results are coming from a highly populated region, and so can really be generalised to all European countries.”

Professor Marone and colleagues have evaluated all of the diabetic patients in the Lombardy region from 2002 to the end of 2009 and are now within the second study phase, collecting data pertaining to the period between 2010 and 2015. “It will be very interesting to compare the first part of this study, from 2002 to 2009, with the second part, from 2010 to 2015 – because in the last five years the number of endovascular procedures has increased and the number of amputations has reduced, so we want to evaluate in terms of survival and morbidity of these patients in these two different periods.”

Improvements in care have been offset by the increase in prevalence of diabetes, however. Defining more closely the burden that this brings upon healthcare services is highly valuable in devising improvements in management and prevention strategies.

Describing the kinds of data that feed into an understanding of the diabetes burden, Professor Marone continued to describe the results of the preliminary epidemiological evaluation: “It is very important to know that these patients present several comorbidities. The most frequent were cardiac disease, cerebral disease, chronic obstructive pulmonary disease and renal failure.”

The group calculated the mean cost (and corresponding confidence interval) to be 14,085 (12,344-16,400) euros per patient-year in the index year, and around 7,000 euros per patient-year in the following period of observation. 44% of the diabetic PAD population had at least one procedure – vascularisation, minor amputation or major amputation.

“The hospitalisation is the most important part of the cost,” continued Professor Marone, “But it is also the most important factor for the survival of the patient. Even in the preliminary results, we have seen that patients with several hospitalisations and several revascularisations have better survival than patients without hospitalisation or revascularisation – with only major amputation or without any procedure.

“So hospitalisation and follow up represent a parameter

Continued on page 36
Continued from page 37

to improve the survival of these patients, because it is important to treat these patients and to follow them, in order to treat arterial complications as soon as possible.”

The median cost of patient care during the period of observation (from 2002 to 2009) was 35,000 euros, explained Professor Marone. The burden of cost is a central part of the study, he said, but must be taken within the context of the aim of reducing morbidity and mortality.

Speaking of the ongoing evaluations the group are making, which won’t be presented this afternoon, Professor Marone explained: “We are performing several evaluations of these data of PAD in diabetic patients, not only concerning the epidemiological evaluation, but even concerning the treatment and the results of these treatments in terms of morbidity, mortality, major amputation. These results need a final evaluation from all the participants of the study and will be the topic of future publications.

“Obviously, these results are preliminary. We also want to evaluate the different groups within the data: patients without procedures; patients with revascularisation; patients with minor and major amputation. We want to follow all of these patients in order to evaluate the survival of these different subgroups. It will also be very important to evaluate the second step – from 2010 to 2015 – in order to say how the different endovascular approaches to this kind of disease will change the survival and the cost of these patients.”

Professor Marone will speak during ‘Multidisciplinary patient-centered approach for diabetic patient treatment,’ in the Global Expert Exchange Forum from 13:30 to 16:30. Professor Marone acknowledges the Lombardy region administration and Medtronic in supporting this study.
Bioresorbable scaffolds offer a revascularisation solution that promotes vessel scaffolding and anti-proliferative drug release, as well as being specifically designed to be gradually absorbed over time, allowing restoration of a vessel's contractile function, and avoidance of prolonged metallic elements in the vessel.

This afternoon, Ramon Varcoe (Prince of Wales Hospital, Sydney, Australia) will present 12-month clinical and imaging data from the first in-man study examining the use of the Absorb Bioresorbable Vascular Scaffold (BVS) System (Abbott Vascular, USA).

“For almost 10 years now we have been using drug-eluting stents, and the reason we do this is because they work,” he told LINC Today. “We have three randomised controlled trials which tell us, quite categorically, that drug-eluting stents are more effective in terms of maintaining patency, when compared to either bare metal stenting or PTA.

“A little while back we started to think about why we use these devices. Most people would be aware of their use in terms of elastic recoil and treating flow-limiting dissection, but probably fewer people have thought of their ability to deliver a drug to the area of vascular...
injury, directly to the site of where the intima is damaged, to prevent restenosis and thus prevent late lumen loss and patency failure.

“But once that elution of drug has taken place, we are left with a permanent metallic implant that serves no further purpose. In fact it acts as a chronic irritant, and it can itself insight further neointimal hyperplasia, as well as act as an artefact with cross-sectional imaging, and an impairment to further intervention or even vascular surgery.”

The Absorb BVS features a poly (L-lactide) scaffold, with a biodegradable poly (D,L-lactide) coating, alongside an everolimus drug delivery system (similar dose density and release to Abbott’s XIENCE V platform). “It reduces neointimal hyperplasia, and then as soon as it hits the aqueous environment of the human circulatory system, the ester bonds between these polymer molecules begin to break down,” continued Dr Varcoe.

“The polymer is broken down into smaller parcels, and ultimately they can be engulfed by macrophages, and processed through the Krebs cycle – in what’s quite an inert process… This is very gentle on the vessel wall.”

During his presentation, Dr Varcoe will exhibit photomicrographs comparing the Absorb BVS versus the XIENCE V at 1–42 months, stressing that, between 12 and 18 months in particular, the polymer structure of Absorb can be clearly seen to be almost completely removed and replaced by extracellular matrix. “Over time that matrix is also replaced by vascular smooth muscle cells, so that the structure itself completely disappears in around three to four years.

“What is perhaps more interesting about the device is the type of neointima that forms over its surface. When you put a permanent metallic stent in, you get a really haphazard laying down of vascular smooth muscle cells, which have no further function: they are basically just scar tissue. But with this bioresorbable structure, you get a very well-aligned laying-down of vascular smooth muscle cells, which appears very much like media.

“These vascular smooth muscle cells have a contractile phenotype which means that they can contract over time. And we’ve seen this in the Cohort B study – which was a coronary study, and also in a porcine model – that over time as the structure is lost, the vascular function is seen to return as you give it an acetylcholine challenge. So this is a new paradigm in stenting, one in which you see vascular repair: rather than a rigid tube, we see return of a healthy blood vessel.”

Dr Varcoe will also speak of his Absorb BVS study, which was set up approximately three years ago, featuring a single centre design, with three implanters, and a patient cohort suffering from CLI (the majority) or claudication.

“We used [Absorb] as a direct replacement for drug-eluting stents in our practice, which meant de novo lesions of short lengths (less than 4cm), and diameter ranges that suited the coronary size matrix of this particular device [2.5 – 4.0mm],” he said. “We were mainly targeting proximal tibial arteries, but we did include distal popliteals in the study, if that was continuous with the tibial disease.

“From the outset, in the pilot stage, we were most interested in safety and feasibility endpoints, so we focussed very much on adverse limb events in the first 30 days, and the technical success of delivering and deploying this device in the peripheral vasculature – which it was not designed for.”

As Dr Varcoe described, it became apparent quite quickly that the Absorb BVS was a safe device that could be used in...
the peripheral vasculature, thus he and his fellow investigators focussed their attention on clinical improvement and duplex ultrasound follow-up. “We saw these patients at predetermined time points of 1, 3, 6 and 12 months,” he said. “We assessed them clinically through Rutherford-Becker class, and then we used a peak systolic velocity ratio, with a very sensitive definition of 2.0, to determine patency or lack thereof. And through that we were able to define primary, assisted primary and secondary patencies, as well as target vessel and target lesion revascularisation rates [TVR / TLR].”

Results were collected from 37 limbs (32 patients), 73% of which had CLI – the age range being between 65-97 years old, and with a male to female ratio of 51/49%. The mean length of lesions was short at 18.7mm. Thus far, 48 scaffolds have been implanted, throughout the tibial vasculature, but with a particular predilection for the tibio-peroneal trunk (19 out of 48 scaffolds) because, given its size and diameter, the Absorb BVS really suits the vessel.

“So far we have had 100% procedural success,” commented Dr Varcoe, adding: “We have a pretty astonishing 12-month primary patency rate of 95.5%.”

Commenting on one patient’s outcome, he continued: “There was one acute occlusion which was unfortunately an oversight on our part. That patient was on warfarin prior to their treatment, but they had their treatment taken away, and no antiplatelet therapy was started, so the implantation went on without any protection whatsoever, and they occluded the first post-operative day.”

As such Dr Varcoe noted that he would recommend dual antiplatelet agents in all of these patients to avoid thrombosis of the scaffolds, continuing six months as mandatory.

Harking back to the patient that occluded in the study, he added: “But because we were able to salvage that one acute occlusion through endovascular means, overall we achieved an assisted primary and secondary patency of 100%, limb salvage of 100%, and then there was one TLR and TVR.”

Dr Varcoe also noted that there were four deaths – all of which were outside of the 30-day window, and all of which were unrelated to the device. Overall, the sustained clinical improvement was 73%.

To demonstrate the sorts of results that could be achieved using the Absorb BVS system, Dr Varcoe will show angiographic images of diffuse disease (tibial peroneal trunk into peroneal) which was treated using two Absorb scaffolds. Speaking of this particular case, he noted that when the patient came back at 14 months for an intervention in the same leg at a distal site, and with the opportunity to interrogate the region, he relayed how it still looked ‘pristine’, with smooth remodelling on the surface, and even a hint of positive remodelling in the proximal segment, with no evidence of significant restenosis.

He offered his concluding remarks: “This bioresorbable vascular scaffold can be implanted safely within the tibial vasculature, and so far we have seen excellent immediate angiographic results, and extremely promising 12-month primary patency results.”

Dr Varcoe will present an ‘Update on the ABSORB BTK project’ during this afternoon’s session ‘Controversial issues, new insights and pioneering solutions for Critical Limb Ischemia’, held at 15:00–16:30 in Main Arena 1.

References
The PREVENT study is a single-arm, prospective, multi-centre monitored trial to evaluate the PROMUS ELEMENT PLUS Everolimus-Eluting Stent System (Boston Scientific, USA) in below-the-knee (BTK) critical limb ischaemia (CLI) lesions of length no longer than 40mm.1,2

The everolimus-eluting PROMUS ELEMENT PLUS stent system features a platinum chromium (PtCr) design, resulting in a conformable stent with reduced recoil and higher radial strength than leading cobalt alloy stents.3

Presenting the 12-month data from the trial at LINC today will be principle investigator Marc Bosiers (AZ Sint Blasius, Dendermonde, Belgium), who took the time to describe the study design for LINC Today. “Seventy patients suffering from CLI were enrolled in this study, with a mean age of 78.29 years,” he said. “78.5% suffered from hypertension and 58.6% suffered from hypercholesterolemia.

“The mean lesion length was 22.83 mm, with 20% of the lesions being occluded, and 80% stenosed. Lesions were located in the truncus tibiofibularis (50%), tibial anterior artery (27.1%), tibial posterior artery (5.7%) and the fibular artery (17.1%). The primary endpoint of the study was primary patency at 12 months, defined as an absence of restenosis (≥ 50% stenosis) or occlusion within the originally-treated lesion (based on angiography).”

Moving on to briefly summarise the 12-month results that he will be presenting later today, Dr Bosiers said: “With a 12-month primary patency of 86.2%, and a 12-month freedom from target lesion revascularisation of 93.0%, we can conclude that the PROMUS ELEMENT PLUS stent system seems a valid, safe and effective alternative to treat short focal lesions in BTK arteries in CLI patients.”
Japanese endovascular treatment techniques and evidences will arrive centre stage this morning in a collaborative session with the Complex Cardiovascular Therapeutics (CCT) course. CCT@LINC sees the discussion of the latest in below-the-ankle (BTA), below-the-knee (BTK), and superficial femoral-popliteal (SFA-POP) interventions, as well as exploring distal bypass and aorto-iliac and femoral interventions.

The CCT meeting was founded in 2001 with the intention of exploring new techniques in the field of cardiovascular intervention. In its beginnings, CCT covered only coronary interventions, but in the past 10 years its remit of activity has expanded to include arrhythmia, surgical, and peripheral interventions and structural heart disease.

Japanese operators have been part of the leading charge in chronic total occlusion (CTO) treatments over the past two decades; Japan is host to a seminar dedicated to the topic of CTO PCI techniques – CTO Club, supported by CCT and hosted in Nagoya, Japan – which, like CCT, draws a lot of attraction from overseas. CCT 2015 was attended by 5,133 delegates, with 26% of these being foreign visitors, demonstrating the value of international exchange of technical innovations in order to keep abreast of new challenges.

“The spirit of CCT is ‘Challenge and innovation’,” cited Kazushi Urasawa (Tokeidai Memorial Hospital, Hokkeido, Japan), one of CCT’s supervisory directors, in an interview with LINC Today. “CCT’s activities have been well accepted, and the CCT live demonstration course has grown to be the biggest live course in Asia at present.”

Dr Urasawa will be co-chairing this morning’s CCT@LINC session, during which he will also be presenting on the current directions in SFA-POP interventions as an introduction to a live case transmission on the topic.

The growth in endovascular interventions in Japan over the past decades mirrors that of
much of the rest of the world, accompanying the prevalence of peripheral artery disease (PAD) and especially critical limb ischaemia (CLI). “The prevalence of diabetes mellitus has increased gradually,” explained Dr Urasawa. “The number of haemodialysis-dependent patients is also increasing.”

Alongside epidemiological and physiological variation the world over, differences in device approval and uptake between continents have indeed compelled different pathways for the development of techniques in endovascular interventions. Describing how these facets have shaped patient treatment in endovascular medicine and its allied disciplines in Japan, Dr Urasawa continued: “The biggest differences with regard to endovascular treatment between EU countries and Japan might be the accessibility to newly developed medical devices, such as CTO crossing devices, re-entry devices, drug coating balloon, drug eluting stent, debulking devices and so on.

“It usually takes a very long time to obtain approval for these devices because of the strict regulation by the Japan PMDA (Pharmaceutical and Medical Device Agency), though this environment has been slightly improved in the last several years. Yet another difference might be the lesion morphology of PAD patients. There are more than 300,000 end-stage renal failure patients who depend on haemodialysis, and these patients are the major source of CLI. Because of that, the target lesions we have to deal with are usually heavily-calcified lesions.

“Because of the limited access to new devices cited here, we had to develop various wiring techniques in order to improve the initial success rate of our endovascular therapy procedures. I have introduced trans-collateral wiring and many different types of distal punctures so far. And many Japanese physicians are regularly using these techniques in their daily practices.”

Dr Urasawa recently published on his experience on the trans-collateral wiring technique, intended to improve interventional success rate in long SFA CTO; he has also ongoing involvement in a number of prominent studies, including the recently-published data from the OLIVE registry on the endovascular treatment of infra-inguinal vessels in patients With CLI.

Elaborating on the content of the CCT@LINC 2016 session, Dr Urasawa noted: “We are going to show the latest Japanese techniques for the treatment of SFA-POP, BTK and BTA lesions though pre-recorded video lives and slide presentations. At the same time, we present the updated evidences of the Japanese endovascular techniques, which were obtained through many multi-centre clinical registries and trials.

“I do hope that CCT@LINC 2016 will be a fruitful session for the attendees of LINC 2016. Collaboration between LINC and CCT provides a good opportunity for both parties to know and learn different techniques. CCT@LINC 2016 would be a good start for this purpose.”

References
Trials focused on anticoagulant and antiplatelet therapies for the primary and secondary prevention of atherothrombotic events have been well-trodden in recent decades. While there are historical concerns of bleeding risks from combination therapies, for example warfarin and antiplatelets, more recently the advent of the novel oral anticoagulants (NOACs) has meant a pivotal breakthrough in the pharmacological arsenal for atherothrombotic events, as well as offering great potential in peripheral arterial disease (PAD). “It is very exciting to finally see new data emerging about the medical therapies for PAD,” Michael Jaff (Harvard Medical School / Massachusetts General Hospital, Boston, USA) told LINC Today. Dr Jaff will be offering his perspectives on the best medical therapy for PAD during a session, held this afternoon, aimed at probing the latest pharmacological innovations in peripheral revascularisation. As with his fellow presenters, Dr Jaff’s time at the podium will be mostly spent on the novel oral anticoagulants: “It turns out that aspirin may not be so effective in reducing major adverse cardiovascular events in patients with PAD,” he told LINC Today. “A meta-analysis of major trials in the field suggests no real impact on outcomes, therefore there is a real opportunity to assess alternate antithrombotic..."
agents (clopidogrel, etc.) or the novel oral anticoagulants. "They have demonstrated significant benefits in patients with non-valvular atrial fibrillation and venous thromboembolic diseases, but little is known about the use of these agents in arterial disorders. This is critically important, as, for example, we know little about the safety and efficacy of these agents in patients undergoing endovascular interventions for PAD, or for patients with stable PAD. This will require large scale randomised trials comparing standard therapies to these novel agents, building on what we learn from the ePAD and VOYAGER trials."

"We know little about the safety and efficacy of these [NOAC] agents in patients undergoing endovascular interventions for PAD, or for patients with stable PAD." Michael Jaff

The ePAD and VOYAGER PAD trials, which will also be presented in some detail during the session, are two central pillars hoping to hold up new insights into NOAC use in PAD. The former is a blinded, open-label multicentre RCT evaluating the safety and potential efficacy of adding edoxaban to aspirin following femoropopliteal endovascular intervention. VOYAGER PAD, on the other hand, focuses on rivaroxaban (as an additive to standard of care treatment) compared to placebo in reducing the risk of major thrombotic vascular events in patients with PAD undergoing peripheral revascularisation.

ePAD
"Compared to percutaneous coronary intervention [PCI], where there is a large body of evidence supported by data from clinical trials conducted in thousands of patients over many years, there are paltry few trials that have studied antithrombotic treatments in patients who have undergone endovascular therapy," said Frans Moll (University Medical Center Utrecht, the Netherlands), who will be exhibiting the ePAD study during this afternoon’s session.
Continued from page 46

Describing the study, he continued: “We randomised the 203rd and final patient in June of 2014, and all patients completed the trial in December 2014. I believe this trial was right up there, if not at the very top in terms of speed for enrolling PAD patients in an interventional trial … it was truly an effective collaborative effort among the research centres (in seven countries), the Steering Committee and the sponsor, Daiichi Sankyo [Japan].”

Subjects in the trial received a dose of 60mg edoxaban daily, for three months (30mg for those with renal impairment or low body weight), with a clopidogrel comparator, given as a 300mg loading dose, followed by 75mg daily for three months. All patients received 100mg of aspirin for the duration of the trial (six months).

“The primary safety endpoint was bleeding, categorised using both the TIMI and ISTH bleeding definitions,” said Professor Moll. “The primary efficacy measure was restenosis or reocclusion, defined by peak systolic velocity ratio ≥ 2.4, as measured using duplex ultrasound. Total duration of follow up was 6 months, and the endpoints were ascertained by a Clinical Events Committee, comprised of a group of experts from University Medical Center Utrecht, and the ultrasounds were read in a blinded fashion at VasCore (Massachusetts General Hospital, Boston, USA).”

While the audience will have to wait until his presentation for the full rundown of the results, Professor Moll did allude to the general positivity of the trial outcomes: “On the efficacy side, the biology of thrombosis suggests that if we optimally manage both platelet aggregation and the coagulation, vessel patency is maintained after endovascular therapy. On the safety side, I have to say that we were surprised by the results, especially given the concerns we had going into the trial about…"

Continued on page 46
Continued from page 47

the risk of bleeding in treating
patients with an anticoagulant
soon after intervention.”

He added: “If we are to
believe the strong trend
we see in this first proof
of concept study, I think I
can venture to say that a
shift in medical treatment
paradigm may well be on
the imminent horizon.

However, there has to be an ad-
equately sized study to confirm
what ePAD is suggesting.”

VOYAGER PAD
The VOYAGER study is a com-
prehensive investigation, with
an estimated enrolment of
6,500 patients,3 the demo-
graphics of which are particu-
larly high risk, as Rupert Bau-
ersachs (Klinikum Darmstadt,
Germany) described: “It is an
event-driven trial, and we expect
more than 1,000 cardiovascular
thrombotic endpoints … it is the
largest trial ever performed in
PAD patients undergoing revas-
cularisation.

“PAD patients generally
have a high risk of cardiovas-
cular mortality and morbidity
(five-year mortality = 10–15%,
plus 20% MI and stroke), but
VOYAGER aims to include even
higher risk patients – so-called
incident patients, who are just
undergoing peripheral interven-
tion or surgical revascularisation.

In addition, VOYAGER focuses
only on patients above 50 years
of age and excludes those with
only mild PAD.”

He added: “As a large piv-
otal trial – it aims for important
clinical endpoints, rather than

surrogate parameters … it is
not a trial comparing outcomes
between surgical and interven-
tional revascularisation. Also, it
is not a short-term trial looking
at parameters like target lesion
revascularisation, rather, it is a
long-term trial (over more than
30 months) aimed at avoid-
ing severe and potentially life-
threatening thrombotic compli-
cations in PAD patients.”

Although VOYAGER is still in
the recruitment phase, Professor
Bauersachs will take the time
during today’s LINC session to
introduce the study particulars,
and some of the salient talking
points. “The primary efficacy
outcome is a composite of ma-
jor thrombotic vascular events,
including myocardial infarction,
ischemic stroke, cardiovascular
death, acute limb ischaemia and
major amputation due to vascula-
ar aetiology,” he said.

“The secondary efficacy
variables will include additional
parameters, e.g. hospitalisa-
tion for a coronary or peripheral
cause, venous thromboembolic
events and all-cause mortality.

The primary safety outcome will
be major bleeding events.”

What’s more, Professor Bau-
ersachs stressed that early indica-
tions point to promising
outcomes. “We know that
patients treated with the
same low dose of riva-
roxaban after an acute
coronary syndrome event
had a 34% significant risk
reduction in cardiovascular
mortality, and a 32% risk reduc-
tion in overall mortality,” he
said.

The future for medical
therapy in PAD
In terms of an outlook for
medical therapy in PAD, Dr Jaff
weighed in to underline his
perspectives, both now and in
the future, saying: “The cur-
rent ‘best medical therapy’ in
patients with PAD includes ag-
gressive risk factor interven-
tion, antiplatelet therapy, and exercise
treatment… but we must find
out how to optimise the medical
therapy for patients with stable
PAD, when following endovas-
cular intervention, and avoid
development of myocardial
infarction, stroke, and cardiovas-
cular-related mortality.”

Professor Bauersachs added
his thoughts: “Even today, real-
life evidence shows that PAD
patients are undertreated com-
pared to coronary artery dis-
ease patients. We have to opti-
mise our treatment modalities
to improve both symptoms and

Continued on page 47
Continued from page 48

limb perfusion with advanced revascularisation techniques, and – at the same time – improve the overall outcome of our patients. Like acute myocardial infarction and acute ischemic stroke, acute limb ischemia indicates an occurrence of irreversible tissue loss, and we should try to prevent that as rigorously and persistently as possible.

Offering his concluding remarks, Professor Moll commented: “Operators continue to hone their technique as they give their patients the best chance to save their limbs, yet these patients come back soon after treatment because of loss of patency. So we have to do better with research and development of new drug therapies. We need to give endovascular therapy the same attention our coronary colleagues gave to PCI. Only when we have done this will we reduce the frequency of reintervention. These newer, more reliable oral anticoagulants may prove to be the optimal addition to age-old aspirin.”

References
2. Edoxaban in Peripheral Arterial Disease (ePAD). ClinicalTrials.gov (Available at: https://clinicaltrials.gov/ct2/show/NCT01802775; Accessed January 2016)