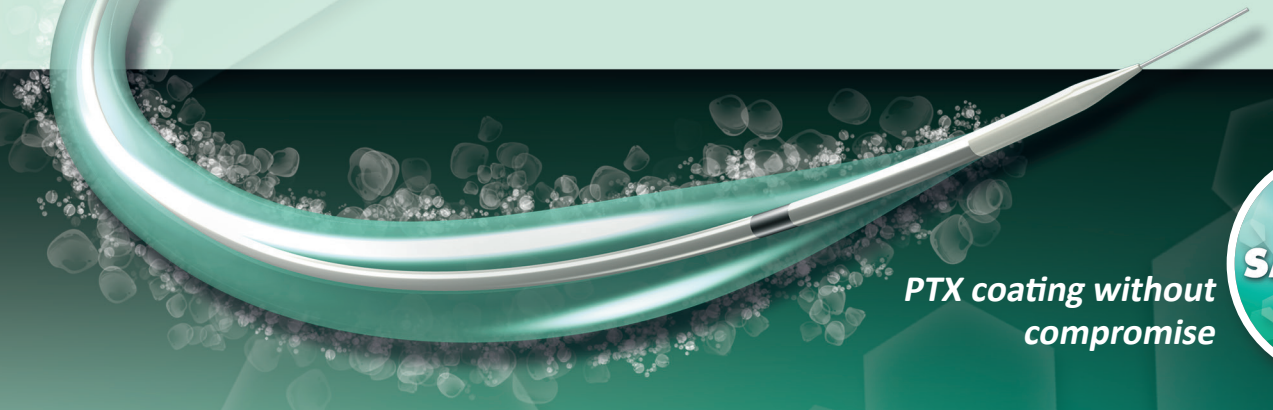
January 2017

vascularnews

EDUCATIONAL SUPPLEMENT

A New DCB Era of Safety and Efficacy

LEGFLOW: Making a difference in DCB technology



PTX coating without compromise

SAFEPAX®

In this supplement:

CARDIONOVUM®
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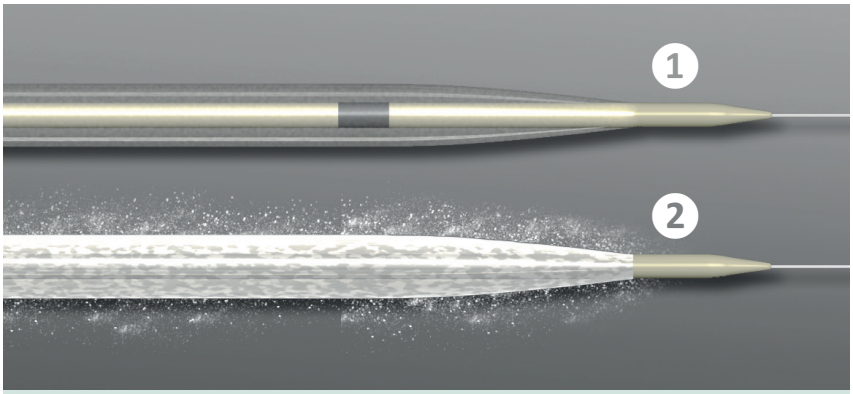
Introduction

Leading the future of drug-coated balloon catheter technologies

The SAFEPAX technology, used on CARDIONOVUM drug-coated balloons, ensures no coating pitfalls, only high performance and superior outcomes, leading to the safest superficial femoral artery and below-the-knee revascularisation therapy.

By Dr Michael Orlowski, Chief Technology Officer, CARDIONOVUM

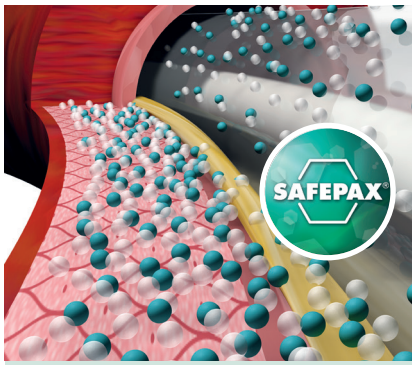
Dr Michael Orlowski



"Stable" (1) vs. "unstable" (2) paclitaxel coating
(1) LEGFLOW DCB paclitaxel coating of invisibly small 0.1µm particles appears as safe as plain angioplasty.
(2) Other DCBs with "unstable" and brittle balloon coatings, consisting of large 2–3µm (visible) paclitaxel crystals, bear a risk for the physician and patient.

The SAFEPAX technology is a unique, high-quality paclitaxel balloon coating used on the surface of the LEGFLOW paclitaxel-coated peripheral balloon dilatation catheter and the new APERTO high-pressure, paclitaxel-coated arteriovenous shunt, both from Cardionovum. But what makes the new SAFEPAX paclitaxel coating used on LEGFLOW and APERTO so different from other drug-coated balloons (DCBs) available on the market?

The brand name SAFEPAX explains it in two syllables. SAFEPAX stands for a stable paclitaxel balloon surface quality coating, and consists of an exclusive proprietary release matrix (drug excipient) with a specific ammonium salt solution compound, which seals the paclitaxel on the balloon surface to ensure maximum protection from body contact with a cytotoxic substance.



Paclitaxel release matrix
Consistent and predictable drug delivery to the artery lesion site results in a homogenous and maximised drug absorption into the arterial tissue.

Coating finesse

The coating of various DCBs on the market does not show any comparable paclitaxel coating finesse. Many DCBs apply a paclitaxel coating that is mixed with a highly water-soluble drug excipient. Amongst many other examples, urea and BTHC belong to the group of hydrophilic substances, which provide unstable DCB surface coating.

A whitish-looking balloon surface is a sign of unprotected, loose cytotoxic paclitaxel particles on the DCB surface. These particles can easily break off the balloon surface during DCB preparation for clinical application. Cytotoxic paclitaxel particles can fall on the patient's blanket, as often experienced, and might even contaminate the cath lab environment.

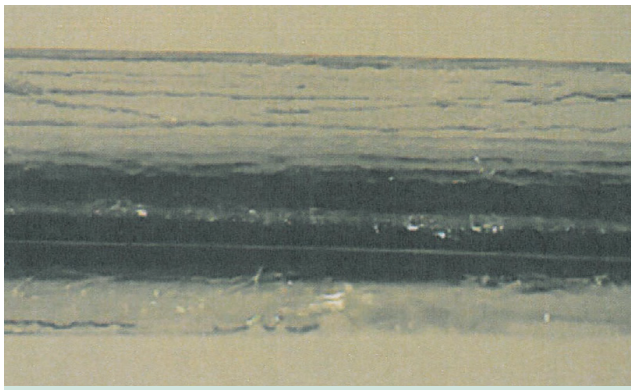
No extra loading tool required

Another unique characteristic of LEGFLOW is that it does not require an extra balloon loading tool. The LEGFLOW DCB passes the haemostasis valve and the introducer without any loss of paclitaxel. Detailed technical test data are available upon request at CARDIONOVUM.

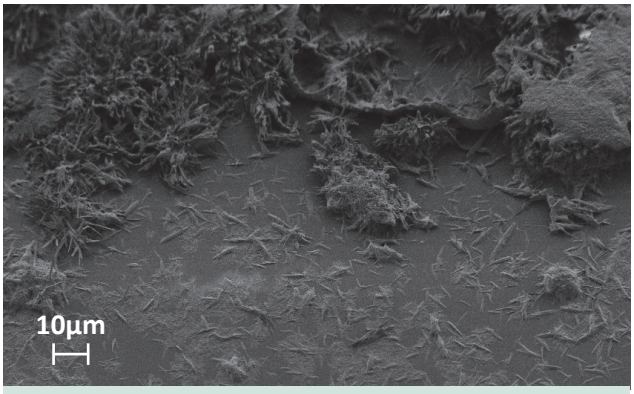
Both DCBs from CARDIONOVUM—LEGFLOW and APERTO—set a reference class for safety of the balloon surface, and protection from cytotoxic substances during patient treatment. The technology used on these devices ensures no thrombotic or embolic adverse effects that might be caused by a high wash-off of large paclitaxel crystals of about 2–3µm, which can easily adhere to the diseased vessel wall or cause paclitaxel embolisation from unstable balloon coatings. LEGFLOW's SAFEPAX coating technology, which incorporates invisibly small paclitaxel particles of only 0.1µm, makes a measurable difference. LEGFLOW DCB features a controlled and drastically minimised paclitaxel wash-off potential effect—there is nothing comparable to this out there.

Minimum drug loss

The moderate hydrophobic drug coating of LEGFLOW limits paclitaxel wash-off to a maximum of 10%. Serial SAFEPAX coating tests, simulated under blood conditions at a temperature of 37°C, and with a DCB tracking time of up to five minutes, confirmed minimum drug loss (10%). LEGFLOW ensures a sufficient and reproducible drug delivery to the lesion site. The SAFEPAX drug coating eliminates any noticeable systemic paclitaxel delivery



LEGFLOW's SAFEPAX invisible 0.1µm nano-paclitaxel coating
Microscopy of the LEGFLOW DCB surface showing no visible paclitaxel particles.



Unstable drug coating with large paclitaxel crystals that do not bind onto the balloon surface—the cause of a high paclitaxel wash-off effect
Microscopy of other DCBs' surface coated with BTHC and paclitaxel.

to the blood stream. LEGFLOW allows a focused paclitaxel delivery to the arterial lesion segment. Only during balloon inflation, at the beginning of the nominal balloon inflation/vessel dilatation, with the pressure at 6.0 bar, the paclitaxel coated SAFEPAX balloon surface opens up to ensure a targeted drug release into the arterial vascular tissue of the dilated lesion segment.

CARDIONOVUM provides a professional technology for a perfect paclitaxel drug delivery.

APERTO Shunt DCB

Vascular access rescue with a micronised paclitaxel-coated balloon

By Matteo Tozzi,[1] Marco Franchin,[1] Anna Maria Ierardi,[2] Filippo Piacentino,[2] Federico Fontana[2]

Collaborators: Alessandro Angrisano,[1] Maria Cristina Cervarolo,[1] Andrea Gattuso,[1] Monica Macchi,[2] Antonino Tarallo[1]

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The leading cause of haemodialysis vascular access failure is thrombosis. Different critical moments in haemodialysis vascular access life are identifiable: in native fistulae, for example, maturation and development of stenosis at the arteriovenous anastomosis site; similarly, in prosthetic vascular access the development of stenosis at the prosthetic venous anastomosis is the main cause of thrombosis. It is noteworthy that the modification in physiological haemodynamics was well recognised as the main trigger for stenosis development or primary native fistula failure.[1]

In the literature, the importance of an early detection of vascular access stenosis and the consequent prompt treatment has been widely stressed. In fact, early identification of stenosis has been proposed as key for decreasing the rate of failure.[2] However, angioplasty with conventional balloons did not confirm expected results.[3] This evidence could be partially explained by the difficulty of clarifying the pathophysiology of vascular access stenosis. Nevertheless, the introduction of drug-coated balloons (DCB) for arteriovenous stenosis management has exceeded this limit. In fact, the medical industry has provided a technology capable of controlling specifically those cell proliferation processes leading to intimal hyperplasia. Accordingly, preliminary evidence confirmed the superiority of DCB over conventional angioplasty.[4]

Currently, different DCBs are being commercialised. Although the use of paclitaxel is common to many devices, it is important to note that several differences exist in terms of coating and excipients. This could be reflected in disparities in drug lost during manipulation, uneven coating, washing-off during navigation, peaks in drug uptake, crystallisation of the drug and possible consequent embolisation.

The aim of this study is to present our single-centre, 25-month experience with a new micronised paclitaxel releasing high-pressure shunt balloon dilatation catheter (APERTO OTW, Cardionovum) employed on both native and prosthetic vascular access. Primary endpoints of the present paper were technical success, complication rate and restenosis percentage.

Prof Matteo Tozzi

Materials and methods

The present is an experience with analysis of prospectively collected data in a 25-month period. All the consecutive patients that received an angioplasty treatment for vascular access stenosis between October 2014 and November 2016 were identified. According to the National Kidney Foundation (NKF) Kidney Disease Outcomes

Quality Initiative (KDOQI), patients with the following characteristics were referred for angiographic examination: flow rate <400–500ml/min in the fistula and <600 ml/min in grafts; static venous dialysis pressure/mean arterial pressure >0.5; and arterial dialysis pressure/mean arterial pressure >0.75. Additionally, all the patients surgically treated for vascular access thrombosis received a completion angiography after surgery in the operating theatre. Patients did not receive a central venous catheter and continued to undergo dialysis through the vascular access.

A predilatation angioplasty was performed routinely with cutting balloons (Boston Scientific) or with focal-force angioplasty balloons (Advance Enforcer, Cook Medical). Finally, angioplasty was performed with a DCB (APERTO OTW, CARDIONOVUM). The DCB was inflated for 120 seconds at 15 atm. A successful angioplasty was defined as a procedure free from complications and with a residual stenosis inferior to 30%. Postoperatively, all patients started anticoagulant therapy using enoxaparin sodium 2,000IU once per day plus antiplatelet therapy for 12 days after the procedure.

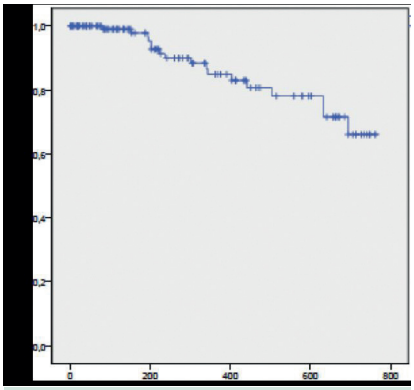
All patients were followed monthly through a clinical, haemodynamic and ultrasound monitoring computer-assisted software (SPIDER).[5] According to von Allmen *et al*, the completeness of follow-up was tested with follow-up index (FUI).

Continuous variables are reported as median (range: minimum–maximum) while age as mean (±SD; range: minimum–maximum) and follow-up as mean (median; range: minimum–maximum; interquartile range). For counts and categorical data, frequencies are reported with percentage in parentheses. Survival analysis was estimated with Kaplan-Meier. The statistical analysis was performed with PSPP 0.7.9 for Linux.

Results

We enrolled 81 patients; there were 50 (60.7%) males. Overall, mean age was 67±12 years (range, 30–87). One hundred and thirty five stenoses were treated. Twenty two (27.2%) patients were treated for different stenoses: two times (n=15, 68.2%), three times (n=5, 22.8%), four times (n=1, 4.5%), and five times (n=1, 4.5%). Arteriovenous fistulae were as follows: prosthetic forearm fistulae (n=51, 37.8%), prosthetic arm fistulae (n=46, 34.1%), native proximal fistulae (n=28, 20.7%), native distal fistulae (n=10, 7.4%). Angioplasty was performed as completion of a surgical procedure in 24 cases: fistulae thrombectomy (n=20) and fistulae creation (n=4).

Between prosthetic fistulae, stenoses were as follows: venous anastomosis (n=43, 44.3%), forearm outflow (n=35, 36.1%), axillary vein (n=14, 14.4%), arterial anastomosis (n=5, 5.2%). Between native fistulae, stenoses were as follows: cephalic vein (n=29, 76.3%), arteriovenous fistula (n=5, 13.2%), axillary vein (n=4, 10.5%)



Graph 1 Kaplan-Meier estimator of patients free from restenosis after DCB angioplasty.

Angioplasty was technically successful in the 95.5% of cases. Intraoperative complications occurred in six (4.5%) cases: thrombosis in five (83.3%) and pseudoaneurysm in one (16.7%). All complications were treated at our hospital. No in-hospital mortality or major local or systemic morbidity was observed.

No patient was lost during the follow-up, and the mean follow-up time was 300 days (range 30–771, median 226, IQR 88–466). Completeness of follow-up was satisfactory and FUI was 0.9.

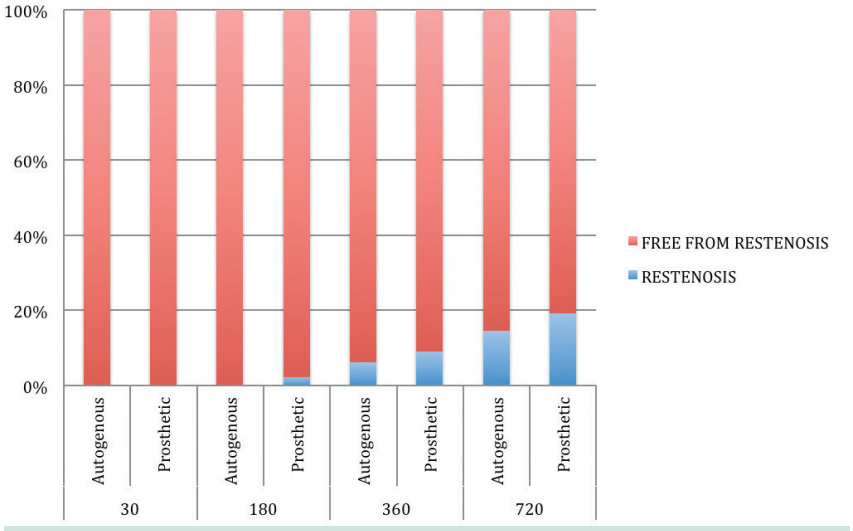
Cannulation of the vascular access was routinely performed after angioplasty and a central venous catheter placement was not necessary in any case. Two (1.5%) patients died during the follow-up; the causes of death were not related to procedure and included myocardial infarction (n=1) and cerebral haemorrhage (n=1).

Permanent graft failure was absent at 24 months. Overall, in 25 cases a significant restenosis was documented. In 20 (80%) cases restenosis was documented during follow-up or as a result of haemodynamic changes during haemodialysis. In the remaining five (20%) cases, restenosis was documented after access thrombosis. In all cases restenosis was treated with four stent grafts.

Restenosis rate was calculated with Kaplan-Meier estimator and was 0%, 2.2%, 15.1% and 33.9% at 30, 180, 360 and 720 days, respectively. The survival curve is reported in Graph 1. Restenosis rate varied depending on type of access and is reported in Graph 2.

Discussion

In the literature, the effectiveness of DCB angioplasty for peripheral vascular and coronary atherosclerosis has been largely debated. Finally, treatment of both primary lesion and restenosis has proven to be useful.[6] Recently, this techonology has been applied to vascular access stenosis and preliminary results demonstrating superiority in comparison to angioplasty with conventional or cutting balloons.[4] Unfortunately, the lack of robust data represents the main current bias to validate its applicability. The present study documented encouraging results obtained in a rather large population of patients treated with a single DCB (APERTO OTW) and with a medium-term follow-up. Previous studies revealed that intimal hyperplasia is characterised by activation of smooth muscle cells and fibroblasts with high mitotic index that migrate to the intimal layer deposing extracellular matrix and promoting neoangiogenesis in an inflammatory environment.[7] Endothelium activation under the haemodynamic stimulus (shear stress, radial forces, cyclic intimal stretching) promotes cytokines and growth factors production rather than nitric



Graph 2 Restenosis rate divided on the base of vascular access type: autogenous (0%, 0%, 6.1%, 14.7%) and prosthetic (0%, 2%, 9%, 19.2%) respectively at 30, 180, 360 and 720 days after angioplasty.

oxide underproduction. Platelet-derived growth factor (PDGF) plays an important role in cell migration. Basic fibroblast growth factor (bFGF) rules angiogenesis that fosters inflammatory cell migration. Finally, tumour necrosis factor beta (TNF-b) is involved in collagen production leading to stenosis.[8] *In vivo* experiences conducted with selective inhibition of these factors demonstrated reduction in stenosis development.[9] However, the employment of anti-inflammatory and immunosuppressive drugs leads to systemic complications. Consequently, new technologies have been developed allowing the release of immunosuppressive drugs through stents or angioplasty balloons at target sites. It is noteworthy that some authors advocated angioplasty as the possible cause of inflammation and consequent restenosis.[3] Therefore, it is even more evident that the association of vessel dilatation with anti-inflammatory or immunosuppressive drugs could improve angioplasty outcome and explain our positive results. Conversely, in the authors' opinion, the preliminary treatment with cutting or focal-force angioplasty balloons generates intimal damage that aids in achieving a better diffusion of the drug through the vessel layers.[10] Furthermore, the apparent superiority of our data over those previously published can be explained by the different design of the device. First of all, paclitaxel particles were micronised (0.1µm, while generally particle diameter is between 2µm and 3µm) with the intention of improving drug intramural absorption. Additionally, it minimises the risk of drug agglomerate embolism or uneven uptake. Secondarily, a new generation of ammonium salt excipient (SAFEPAX) was adopted. The ammonium salt coating presents high elasticity and low hydrophilicity ensuring drug adherence in dry state and low drug loss during manipulation and navigation. Moreover, it avoids drug crystallisation ensuring a more uniform uptake over the whole stenosis.

Conclusion

DCB permits a leap forward in the treatment of vascular access stenosis combining a therapy with the mechanical treatment of a stenosis. In our experience the new paclitaxel-releasing high-pressure shunt balloon dilatation catheter has proven to be safe and effective. Complications were absent and patency rate was superior if compared to data previously published on standard angioplasty or other DCBs. Improvements in results make clear that the success of DCB technology is not attributable only to a delivered drug but equally to an appropriate coating and excipient that reduce loss of drug during manipulation and navigation and optimise its uptake.

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Interview: Prof Matteo Tozzi

Drug micronisation with SAFEPAX is the key point in the success with APERTO

Prof Matteo Tozzi spoke to *Vascular News* about his experience with DCBs in the treatment of failing arteriovenous fistulae.

You have conducted a retrospective analysis of 81 patients treated with DCBs for failing fistulae. How do you interpret these results?

These promising results show that paclitaxel should be the therapy of choice for intimal hyperplasia. Conventional angioplasty alone treats only the consequence of intimal hyperplasia, which is vascular access stenosis.

You routinely use DCBs in your daily practice. How comfortable are you treating a wide range of arteriovenous fistula patients and lesions with APERTO?

In our experience the results with different types of lesions in both native and prosthetic arteriovenous access reinforce the advantages of using the APERTO DCB in a broad range of lesions all along the arm vasculature.

What is your treatment algorithm with the DCB in arteriovenous fistulae?

Our treatment is based on a strict diagnostic follow-up of the arteriovenous fistula and on DCB angioplasty for all the stenoses with haemodynamic or clinical impairment.

Have your reported results increased your confidence with DCBs or even changed your treatment algorithm?

Yes. Following our preliminary results, over the last two years we have shifted treatment towards the use of DCBs over conventional angioplasty alone.

Male	50 (61.7%)
Age, (years ± SD)	67±12
Risk factors	n (%)
CVD	49 (60.5)
Hypertension	31 (38.3)
Diabetes	28 (34.6)
Smoking	19 (23.5)
IHD	28 (34.6)
COPD	14 (17.3)

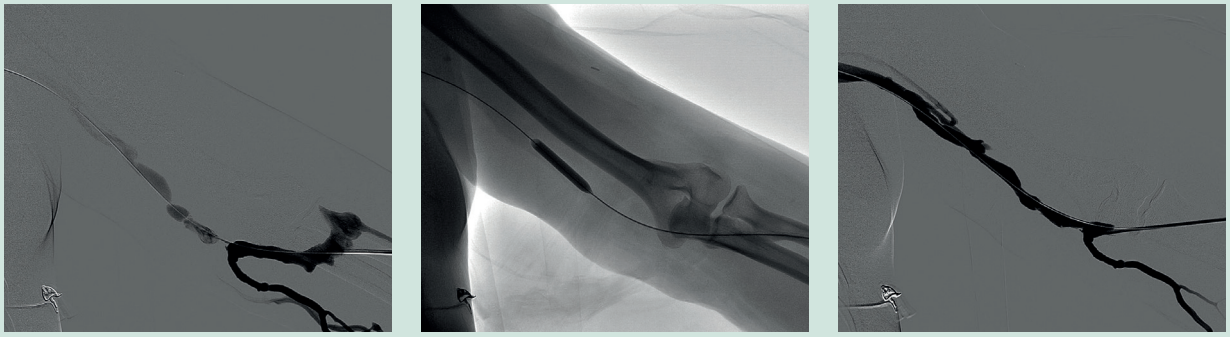
Tozzi's patient characteristics

What are your sizing rules in arteriovenous fistula treatment in terms of anastomosis, graft, arterialised vein, etc?

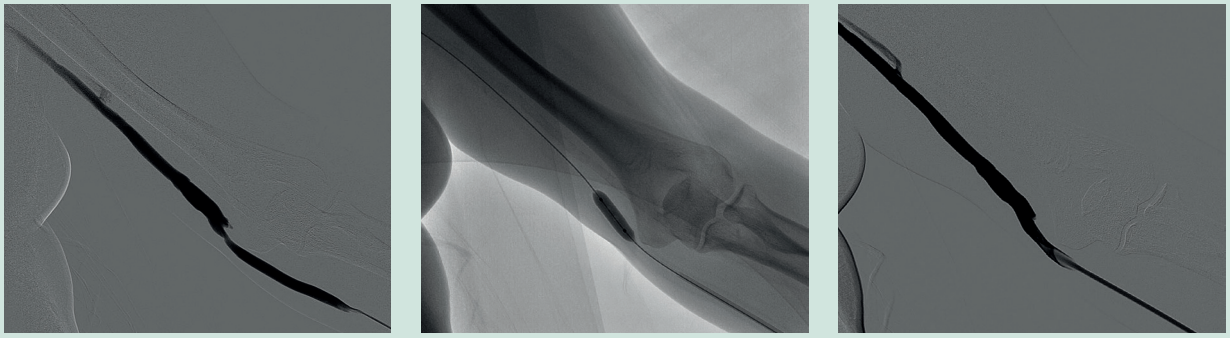
It is mandatory to differentiate each case. First of all, native arteriovenous fistula maturation failure and local or diffuse stenosis (vessel diameter inferior to 6mm) are always treated. Additionally, venous stenosis in arteriovenous fistulae or prosthetic vascular access outflow is treated when clinically symptomatic and when luminal diameter is reduced by more than 50%. Finally, haemodialysis malfunction due to inflow stenosis associated with stenosis of native fistula or arterial-to-graft anastomosis is equally treated. Balloon diameter is always estimated based on ultrasound assessment of the diameter of the nearest healthy vessel.

Data are still scarce for arteriovenous fistula patients treated with DCBs. How do you evaluate differences in coating such as particle size and coating stability between different devices?

The improvement in clini-



Steno-occlusive native AVF treated with APERTO OTW 6x40mm



Prosthetic venous side stenosis treated with focal-force PTA balloons and APERTO OTW 6x20mm

cal results obtained with DCBs in more recent papers reflect the advances in technology, mainly in coating and excipient. Most DCBs employ paclitaxel but results depend on drug loss during manipulation and navigation and on drug uptake. Our encouraging results suggest that drug micronisation associated with SAFEPAX is the key point in the success with APERTO.

What is your definition of "success" in arteriovenous fistula treatment with a DCB?

Success in arteriovenous rescue means, first of all, immediate availability of the vascular access without the need for central venous catheter placement. Secondly, it is mandatory to ensure that the patient will have a viable haemodialysis treatment for as long as possible. Finally, a fast treatment will result in an improvement in quality of life.

By experience, what interval would you recommend before being back to dialysis using the treated arteriovenous fistulae?

In our experience the DCB angioplasty has never delayed the haemodialysis treatment.

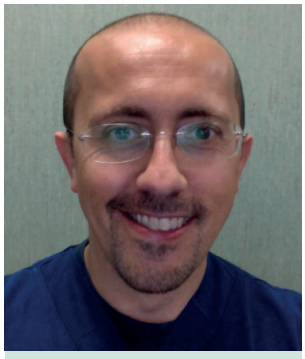
Peripheral intervention

LEGFLOW DCB for the treatment of infrainguinal disease in the real world

By Prof Eugenio Stabile, University of Naples Federico II, Naples, Italy

Traditional balloon angioplasty as a standalone treatment for infrainguinal atherosclerotic disease remains limited by acute elastic vessel recoil and the occurrence of restenosis due to cellular proliferation in response to arterial injury. Stent deployment can certainly mitigate vessel recoil; however, stent thrombosis, the need for long-term dual antiplatelet therapy and stent fracture, which contribute to restenosis and thrombosis, remain major limitations. These limitations have led to the development of drug-coated balloons (DCBs) using paclitaxel—which is highly lipophilic and has favourable tissue kinetics—as the antiproliferative drug. To improve efficacy, DCBs are prepared with a coating mixture of paclitaxel and an excipient, which is a hydrophilic spacer that facilitates local uptake into the vessel wall resulting in greater inhibition of neointimal growth.[1]

Most of the clinical trial data available so far (ie. THUNDER, FemPac, PACIFIER, LEVANT, IN.PACT trials) assessed the treatment of femoropopliteal lesions comparing DCB with standard angioplasty and predominantly included patients with claudication (Rutherford class 3 or less) as opposed to



Prof Eugenio Stabile

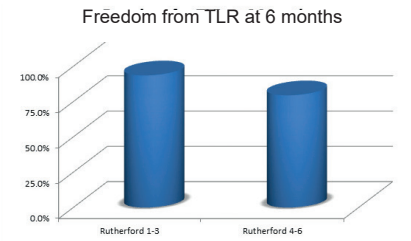


Figure 1
Freedom from TLR at six months in the LEG-DEB registry—the graph illustrates freedom from target lesion revascularisation in patients undergoing angioplasty of the femoropopliteal artery using a new generation DCB (LEGFLOW, Cardionovum). A good vessel patency at six months is seen independently from clinical presentation (Rutherford class).

patients with critical limb ischaemia.[2]

The use of older-generation DCBs, using coating mixtures composed of a drug excipient matrix and relatively large paclitaxel crystals, has shown promising results in the prevention of post-angioplasty restenosis in the femoropopliteal artery. This was demonstrated by a reduction in late lumen loss, target lesion revascularisation and angiographic restenosis with DCB use.[2]

In patients with critical limb ischaemia (Rutherford class ≥4) the long-term efficacy of angioplasty is particularly hampered by the occurrence of restenosis of the treated arterial segment due to the presence of more pronounced systemic inflammation, a less efficient risk factor control (ie. diabetes) and limited options for supervised exercise after the procedure due to the presence of ischaemic tissue lesions.[3]

LEG-DEB critical limb ischaemia group confirms successful outcomes

Currently, data for patients with critical limb ischaemia disease are limited, and available registries and trials do not provide any clear data about DCBs' therapeutic efficacy in this group of patients, where a more efficient drug delivery is deemed necessary to prevent recurrences.[2]

It is important to highlight that the devices used so far have several technical limitations such as inconsistent drug-coating concentrations, significant overall drug loss, use of large paclitaxel particles, and/or initially too high balloon-artery drug transfer rates resulting in early high drug-in-tissue concentrations followed by a fast loss of drug in tissue levels. All these limitations can reduce the therapeutic efficacy of the drug released on the arterial wall and reduce clinical efficacy in more challenging cases (ie. critical limb ischaemia patients).

In order to overcome these limitations, a new-generation DCB, covered with a homogenous and stable surface coating using extremely small, non-visible paclitaxel particles, and not requiring the use of extra DCB protection and insertion tool, has been developed.

The LEG-DEB registry[4] is a multicentre, international prospective registry designed to evaluate the safety and efficacy, at six months, of a new generation paclitaxel DCB (LEGFLOW; CARDIONOVUM)[5] for the treatment of femoropopliteal artery disease (infrainguinal obstructions) in "real-world" patients (including patients with claudication or critical limb ischaemia).

Four European institutions are enrolling patients in this registry (Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy; Vascular Surgery Clinic, UMBAL Sv Georgi EAD, Plovdiv, Bulgaria; Department Vascular Surgery and Angiology, Tokuda Hospital Sofia, Bulgaria; and Vascular Clinic ZNA Hospital Stuivenberg, Antwerp, Belgium).

In a first report from the LEG-DEB registry, six-month outcomes of 123 consecutive patients undergoing angioplasty of the superficial femoral artery and/or popliteal artery were reported. Among the patients, two-thirds (64.2%) were treated for claudication and one-third (35.8%) for critical limb ischaemia. All types of femoropoplitel lesions were included—*de novo*, restenosis, in-stent restenosis, long lesions and occlusions.

Despite a mean lesion length almost 2cm longer than reported in other studies (ie. LEVANT and ILLUMINATE), freedom from target lesion revascularisation was obtained in 88.6% of all patients. This was higher in patients with claudication (93.6%) and still favourable in patients with critical limb ischaemia (79.5%, Figure 1).

While the data reported for the claudicant population are comparable to those observed in LEVANT I, ILLUMINATE and the IN.PACT SFA Italian registry, those reported for the critical limb ischaemia population of the LEG-DEB registry were seen for the first time. It has to be considered that LEVANT I enrolled only 6% of critical limb ischaemia patients, ILLUMINATE only 2% and the IN.PACT SFA Italian registry only 7.6%.

In the LEG-DEB registry, more than 30% of the patients presented with critical limb ischaemia and the study results, at six months, provide clear evidence that new-generation DCBs can deliver reasonable long-term outcomes in this complex setting.

The reported data also suggest that the use of a new-generation paclitaxel DCB represents a safe and effective therapeutic strategy for the endovascular treatment of femoropopliteal obstructions in different clinical (ie. diabetic patients) and anatomical (lesion length >100mm, restenosis, in-stent restenosis) settings.

These data will need to be confirmed with longer-term follow-up. As of today, a glimpse of the 12-month follow-up results in this patient population seems to confirm a very good rate of freedom from target lesion revascularisation in both claudicants and critical limb ischaemia patients.

Preliminary below-the-knee results are promising

The treatment of below-the-knee lesions with DCBs has been challenged by the results of the IN.PACT DEEP study, which was halted prematurely due to a trend toward an increased rate of major amputations in the DCB study arm. Several reasons have been used to explain the increased amputation rates in the DCB arm (ie. inappropriate lesion preparation or particle embolisations).

A new-generation DCB, with a low crossing profile and covered with a homogenous and stable surface coating using extremely small (0.1µm) non-visible paclitaxel particles compared to 2–3µm large paclitaxel particles on other DCBs, could provide a valuable solution for this issue.

The LEG-DEB registry is collecting data on the LEGFLOW use also in below-the-knee vessels to evaluate the role of new-generation DCBs in the treatment of these complex atherosclerotic occlusions. To date more than 30 patients have been included in the registry and have six-month follow-up available.

In these patients, no unplanned amputations occurred at six months. These data, although preliminary, could support the idea that new-generation DCBs could be the definitive solution to provide long-term benefit to below-the-knee interventions.

Eugenio Stabile, Division of Cardiology, Department of Advanced Biomedical Sciences, "Federico II" University, Naples, Italy

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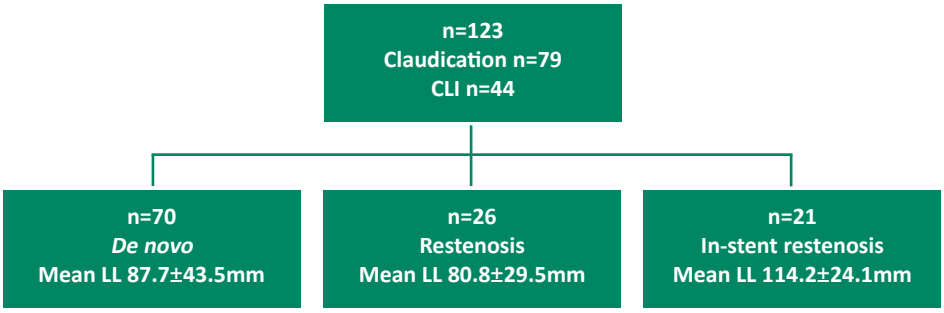
THE LEG-DEB REGISTRY IN NUMBERS

The LEG-DEB Registry is a prospective, multicentre, single-arm study of the LEGFLOW DCB in femoropopliteal arteries in a real-word population. An interim analysis of the six-month results was published by Stabile *et al* in the *International Journal of Cardiology* in August 2016.



LEG-DEB six-month freedom from target lesion revascularisation (TLR) and how it compares with other DCB studies

ALL patients	Claudication	CLI	*De novo*	Restenosis	In-stent restenosis
88.6%	93.6%	79.5%	88.1%	80.7%	100%

Superior freedom from TLR

In the LEVANT I study with the Lutonix DCB, freedom from TLR for all patients at six months was 87%, with lesion length 80.8±37mm and most patients having Rutherford class 2–3.

In LEG-DEB the freedom from TLR rate was superior **(88.6%)** even though the study included restenosis, in-stent restenosis and CLI with lesion length of up to 130mm.

The LEVANT I (Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis) Trial for Femoropopliteal Revascularization

Scheinert *et al. Jacc Cardiovasc Int* 2014

Claudicants: Similar TLR with lesions 20% longer

In claudicants, LEG-DEB showed a similar rate of freedom from TLR at six months **(93.6%)** to those from a multicentre Italian registry with the IN.PACT DCB (95.6%) and the ILLUMENATE first-in-human study with the Stellarex DCB (96%).

However, the claudicant group treated with LEG-FLOW had lesions 20% longer (91.3±53.46mm) than those in the Italian registry (76.3±38.3mm) and in ILLUMENATE (72±47mm).

Clinical Evaluation of a Paclitaxel-Eluting Balloon for Treatment of Femoropopliteal Arterial Disease – 12-Month Results From a Multicenter Italian Registry

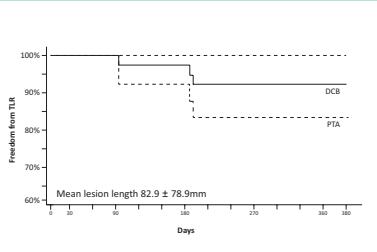
Micari *et al. Jacc Cardiovasc Int* 2014

Two-Year Results of a Low-Dose Drug-Coated Balloon for Revascularization of the Femoropopliteal Artery: Outcomes From the ILLUMENATE First-in-Human Study

Schroeder *et al. Cath Cardiovasc Int* 2015

In-stent restenosis: No reinterventions at six months

In in-stent restenosis patients, the use of LEGFLOW in the LEG-DEB study showed **100%** freedom from TLR at six months. An earlier experience with the IN.PACT DCB device showed a higher rate of TLR.



Drug-Eluting Balloon for Treatment of Superficial Femoral Artery In-Stent Restenosis

Stabile *et al. J Am Coll Cardiol* 2012

Interview: Prof Jean-Paul de Vries

RAPID: "Combination of LEGFLOW and stent seems to be the best option for challenging SFA lesions"

Prof Jean-Paul de Vries, Department of Vascular Surgery, St Antonius Hospital, Nieuwegein, The Netherlands, is the principal investigator of the RAPID trial, a first-of-its-kind study in the drug-coated balloon field that assessed the treatment of superficial femoral artery lesions with a combination of drug-coated balloon (LEGFLOW) and stenting (SUPERA, Abbott Vascular). De Vries spoke to *Vascular News* about the trial.

Prof Jean-Paul de Vries

What was the idea behind the combination of SUPERA and LEGFLOW?

In recent years the SUPERA stent has been proven to be a good option for long-segment superficial femoral artery (SFA) lesions. Moreover, drug-coated balloons (DCBs) such as LEGFLOW are also a useful adjunct in long-segment SFA obstructions. Stents must be used in cases of acute recoil of the SFA post-angioplasty or in cases of flow limiting dissections. It seems a reasonable choice to combine the best of both worlds.

How do you interpret the results of the trial?

RAPID includes a challenging patient population with >70% of patients suffering from a long-segment SFA occlusion. These are the majority of patients we treat nowadays. In my practice we hardly see patients with short SFA (<5–10cm) stenoses. These patients will have supervised exercise therapy and the majority will never undergo endovascular intervention. Long-segment occlusions are challenging to treat only with stenting or plain angioplasty. Combination, as in this trial, of a stent and LEGFLOW seems to be the best option for these patients.

At what stage is the publication of the trial results?

We have submitted the short-term results of the RAPID trial to a peer-reviewed journal and are awaiting the feedback of the reviewers to our resubmission. We were pleasantly surprised to notice that the combination of LEGFLOW DCB and stenting with SUPERA results in similar one-year outcomes compared to prosthetic supragenicular bypass grafts. And it is evident that after learning about morbidity and mortality rates patients prefer the endovascular approach instead of bypass surgery.

You use DCBs in your practice. How comfortable are you treating a wide range of patients, lesions and indications with LEGFLOW?

LEGFLOW is unique regarding the size of paclitaxel particles. They are so small (0.1µm) that they cannot reflect light and are invisible. In addition, with smaller paclitaxel particles we have better structure and a reduced risk of adverse events. Moreover, the nano-paclitaxel particles are completely embedded in the ammonium salt compound based excipient (SAFEPAX technology). Therefore, there are no paclitaxel particles on the exterior of LEGFLOW and there is no risk of wash-off during the introduction of the device, which minimises the risk of distal emboli. There are no paclitaxel peaks on the balloon like in other DCBs. We are very comfortable using the LEGFLOW DCB in our daily practice, especially in more complex SFA lesions.

Given the combined therapy used in the RAPID trial, one could question whether the trial could have shown the efficacy of LEGFLOW as a standalone approach. What is your opinion about this?

This could only be scientifically answered with in a single-arm registry including RAPID-like SFA obstructions and the use of LEGFLOW DCB as a standalone treatment. However, in case of acute recoil, flow-limiting dissections or residual stenosis >30% (spot) stenting will be necessary to improve outcomes.
The results of the RAPID trial emphasise the need for an endovascular-first strategy in patients with long-segment SFA lesions without a suitable great saphenous vein and in patients who are at higher risk for venous supragenicular bypass grafts.

How do you see combined therapies in general?

In recent years drug-coated technologies have become the most appropriate endovascular treatment for SFA disease. DCBs such as LEGFLOW and drug-eluting stents (DES) seem to be almost equally effective for short-segment SFA lesions. DCB may be preferred in concentric and fibrotic lesions, whereas DES may be a better option in eccentric and calcified ones. In any case, when using a DCB such as LEGFLOW you do not leave anything behind. A good alternative may be the use of atherectomy followed by DCB but robust data are lacking. In my opinion, long-segment lesions demand combination therapy, more than TASC A and B lesions. The current combination of LEGFLOW with SUPERA is equal to prosthetic bypass grafts. It would be interesting to study the combination of atherectomy followed by LEGFLOW and, if needed, spot-stenting.

There are little data for critical limb ischaemia (CLI) patients treated with DCB. An article in this supplement shows positive results with LEGFLOW in this group of patients. How do you analyse different outcomes related to CLI?

We can propose more than 10 different combinations of devices and treatment modalities in CLI patients with complex SFA lesions. It is all about the length of the lesions, whether the lesions are concentric or eccentric, the amount of calcification, stenosis vs. occlusion, etc. In the next two to three years several randomised controlled trials will be published regarding different treatment modalities. Every endovascular specialist should review the literature carefully to choose his/her preferred treatment option, and focus mainly on level I evidence.

Where do you see the use of drug-coated devices in the future?

Drug-eluting devices such as LEGFLOW or DES are essential to prevent restenosis and reduce the risk of reintervention. The objective should be to maximise neointimal inhibition by maintaining therapeutic tissue levels over a long time. As SFA restenosis continues to remain the main limitation of a broader adoption of endovascular means, drug-eluting technologies will be a key feature for success. Both DCBs and DES will have a place in the armamentarium of the endovascular specialists.

THE RAPID TRIAL IN NUMBERS

RAPID is a randomised controlled trial comparing LEGFLOW DCB vs. plain angioplasty followed by SUPERA stenting in "real-world" long-segment femoropopliteal lesions. The results were presented at LINC 2016.

160 patients included (100%)

- *De novo* symptomatic lesion in the SFA >5cm. Rutherford class 2–6
- At least one patent below-the-knee artery lesion crossed by guidewire

Randomisation

LEGFLOW paclitaxel-coated balloon + nitinol stent

Standard PTA balloon + nitinol stent

Follow-up at 1, 6, 12 and 24 months with DUS, ABI, toe pressure, and peripheral arterial questionnaire

Dual antiplatelet regimen for three months

Baseline patient characteristics

	CONTROL	LEGFLOW	p value
Gender (male)	48/74 (64.9%)	45/66 (68.2%)	0.722
Diabetes (yes)	20/70 (28.6%)	18/63 (28.6%)	1.000
Smoking (yes)	35/71 (49.5%)	31/64 (48.4%)	1.000
SVS Risk Score (0–24)			0.923
Rutherford class pre-procedure			
2	33/70 (47.1%)	32/64 (50%)	0.873
3	27/70 (38.6%)	21/64 (32.8%)	
4	4/70 (5.7%)	6/64 (9.4%)	
5	4/70 (5.7%)	4/64 (6.25%)	
6	2/70 (2.8%)	1/64 (1.6%)	
Right leg	38/70 (54.3%)	32/64 (50%)	0.729

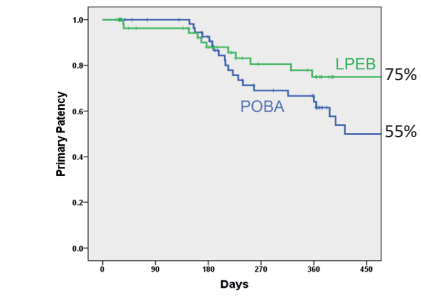
Baseline lesion characteristics

	CONTROL	LPEB	p value
Lesion length on pre-procedural imaging (mm)	116.7±66.7	120.1±69	0.890
Lesion length on angiogram (mm)	155.8±72	157±73.1	0.873
Occlusions	48/69 (69.5%)	43/64 (67.2%)	1.000
Right leg	38/70 (54.3%)	32/64 (50%)	0.729
TASC A	8/69 (11.6%)	7/71 (9.8%)	0.865
TASC B	32/69 (46.4%)	36/71 (50.1%)	
TASC C	29/69 (42.0%)	28/71 (39.4%)	

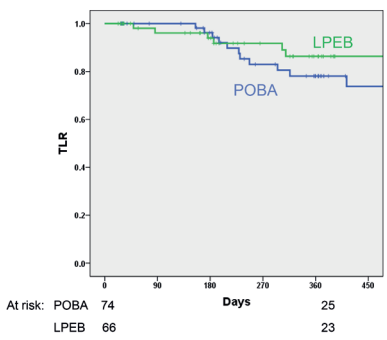
Lesion length and occlusion rates with other devices were the following, respectively: Lutonix 107.9mm and 21%; SUPERA 64.3mm and 24.6%; IN.PACT 89.1mm and 23.7%; Zilver PTX 53.9mm (occlusion N/A)

The rate of TASC C lesions with other devices were the following: Lutonix 1.7%; SUPERA 5.7%; IN.PACT 11.7%; Zilver PTX 36.7%

Primary patency



Freedom from TLR



Interview: Dr Peter Goverde

"Drug-coated devices will become the gold-standard for PAD in the future"

Dr Peter Goverde, ZNA Vascular Clinic, ZNA Stuivenberg Hospital, Antwerp, Belgium, principal investigator of the MAGNIFICENT trial, talks about this randomised, multicentre study comparing the use of LEGFLOW DCB vs. plain angioplasty in femoropopliteal arteries.

What is the importance of the MAGNIFICENT trial?

Currently there are several drug-coated balloon (DCB) randomised controlled trials being conducted and this is the only way to confirm if this "rather new" technology is safe and efficient. Because there were no randomised controlled trial data available on the use of LEGFLOW in the superficial femoral artery and popliteal artery, the MAGNIFICENT randomised controlled trial was designed. It is a multicentre trial being run in Belgium, France and Germany and will include 130 patients in a head-to-head comparison with plain angioplasty for the treatment of *de novo* lesions or restenosis in the superficial femoral artery and in the popliteal artery (P1–P2) by assessing the binary restenosis rate with duplex ultrasonography at 12 months. With this trial we aim to validate the results of our real-life follow-up study and hope that we will be able confirm the excellent data we have seen in several "real-world" registries. I anticipate that enrolment will be concluded

by May 2017, so we could have six-month data by the end of 2017.

Given the number of DCBs on the market, how do you select which product to use?

There are more than a dozen DCBs on the European market and as we are overwhelmed by data and publicity it is becoming very difficult for physicians to choose the right balloon for the job. We have data from big and small randomised controlled trials showing that different DCBs do well and when you try to compare the outcomes of the different studies it is a tough choice to decide which balloon to use—because all industry studies support the usage and benefit of their DCB. In my opinion it is important that you take into account not only the trial results but also paclitaxel particle sizes and coating characteristics such as stability, wash-off effect, tissue penetration etc, in your decision of which DCB you should use.

In your opinion, what is LEGLOW's applicability in peripheral arterial disease?

In Belgium drug-coated balloons are not reimbursed yet so we do not use these devices routinely. However, with the data from our latest real-world survey we will probably alter our treatment strategy. In a prospective, single-centre, real-world follow-up study in our ZNA Vascular Clinic we retrieved and analysed data of 75 patients treated with LEGFLOW. We had clinical in-hospital follow-up at one month, six months and one year. There were 51 male and 24 female patients (mean age 67.6 years), 69.3% were smokers and 54% were diabetics. The patients suffered from Rutherford-Becker class 2 to 5 with a mean of 3.8. We treated 27 superficial femoral artery lesions, 24 femoropopliteal lesions, and 24 below-the-knee lesions. More than one fifth (22.7%) of the lesions were *de novo* stenosis, 39 patients had a restenosis and 19 were treated for in-stent restenosis. The mean lesion length was 116.2mm. Around 34% had moderate to severe calcifications (meaning more than 50% circumferential calcium presence). In all cases we performed predilatation with an uncoated balloon and in 25.3% we found necessary to place a stent. We observed no in-hospital complications and we had one target vessel revascularisation in a 30-day period in a Rutherford-Becker 5 patient. At six-month follow-up with duplex ultrasound we observed absence of binary restenosis in 92% of the cases. The endpoints at one year showed five target vessel revascularisations, three target lesion revascularisations and one toe amputation. During the one-year duplex ultrasound follow-up we observed absence of binary restenosis in 85.3% of the patients. These results support the treatment of a wide range of patients and lesion types with LEGFLOW.

Dr Peter Goverde

Has your experience changed your treatment algorithm?

The decision to use either an uncoated balloon or a DCB is based mostly on lesion appearance, lesion response to the initial therapeutic action and, of course, the Belgian reimbursement policy. When treating a long chronic total occlusion with a moderate to severe calcium load, it is unlikely that plain angioplasty with or without DCB will be successful. In such a case atherectomy, if the crossing path of the wire allows it, can be considered. If performing mechanical debulking is not possible, then rigorous predilatation followed by DCB and stenting would be my choice. When treating lesions with less severe characteristics, a predilation would be done first and this would be followed by an assessment of the lesion appearance together with an estimation for the need of a scaffold. To finish the intervention I would favour the use of a DCB with the back-up of a bare metal stent in case of flow limiting issues such as dissection or recoil.

How do you see combined therapies in general (eg. DCB plus stent, atherectomy plus DCB)?

Regarding the use of atherectomy with DCB, there is limited information about the long-term benefit of this therapeutic combination. We have some small randomised controlled trials that are investigating the role of atherectomy followed by DCB, such as the ADCAT study (Turbohawk [Medtronic] plus a DCB vs. DCB alone) and the OPTIMIZE study (Diamondback [Cardiovascular Systems, Inc] plus a DCB vs. DCB alone), and these could give us additional information on the benefit of this combination. Regarding stent placement, at the moment the tendency is, when we have mechanical flow limitation after angioplasty, to use a scaffold as a bailout. And in the majority of cases I think DCBs will be used prior to stent placement.

What is your opinion about the use of DBCs below the knee?

It is still a problem that data concerning the efficacy and safety of drug-coated balloons for the treatment of critical limb ischaemia and below-the-knee lesions are conflicting and inconclusive. At the moment we do not have sufficient randomised or even core-lab controlled multicentre data that could support the use of DCBs in the tibial artery segment. At this time it is still uncertain whether DCBs using coating techniques similar to those used for femoropopliteal procedures will work or have the same effect below the knee. It is still unknown if the differences in vessel wall characteristics together with the different degrees of calcification, the smaller vessel diameter, or a loss of drug during the wash-off in the way down to the tibial target area, are responsible for the failure of most of the DCB below-the-knee trials. In my opinion, the stability of the coating will have a crucial role in the outcome of below-the-knee interventions, but also regarding this topic there is no sufficient evidence.

How do you evaluate differences in coating such as particle size and coating stability?

Most of the DCBs are coated with 2–3µm paclitaxel crystals risking adverse embolic or thrombotic effects or obstructing the smaller distal vasculature with potentially devastating consequences. The nanocrystalline particles on the LEGFLOW DCB are smaller in size (0.1µm), avoiding these complications. LEGFLOW, with 3µg/mm² paclitaxel coverage, is also covered with shellolic acid which ensures a stable coating and provides a balloon surface protection. This coating prevents the paclitaxel particles to fall or wash-off during catheter preparation, insertion or manipulation. This way a safe and predictable drug delivery to the target lesion site is guaranteed and physicians and patients are protected from contact with the drug, which are both important benefits.

Where do you see the use drug-coated devices such as DCBs in the future and which do you think will become the standard of care?

With the experiences we have had with the current DCBs and their promising results, drug-coated devices will become the gold standard for the treatment of lower limb arterial lesions. Maybe drugs and coatings will change in the future but DCBs will take a prominent role in the treatment of peripheral arterial disease. Also scaffoldings will probably change as devices such as drug-eluting stents and bioabsorbable scaffolds will become more important as a bailout for angioplasty—so local drug therapy and different coatings and polymers will play a crucial part in the future endovascular peripheral therapy.

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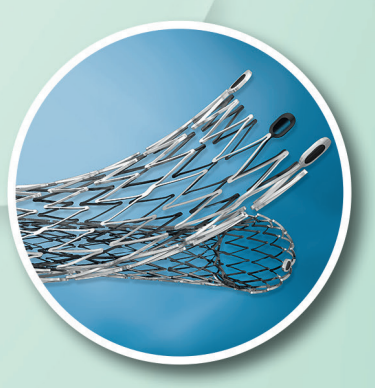

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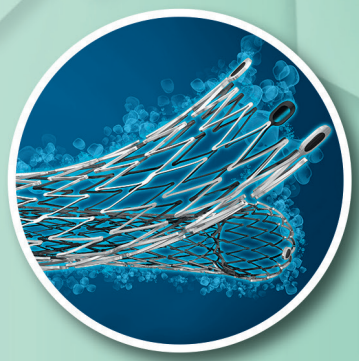

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