Supplement to

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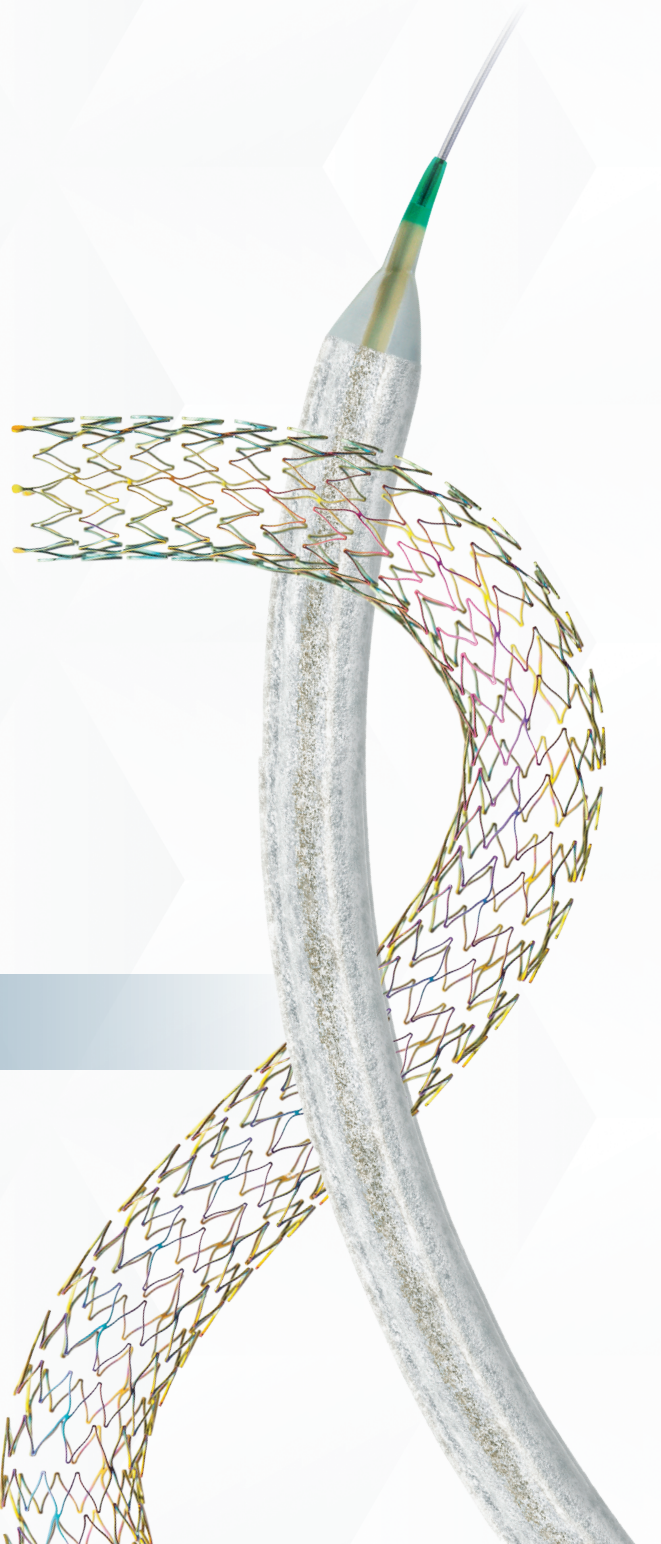
Endovascular TODAY

EUROPE

2018 | Volume 6, No. 6

MAXIMIZING OUTCOMES. MINIMIZING BURDEN.

HOW TO REACT IN THE SFA



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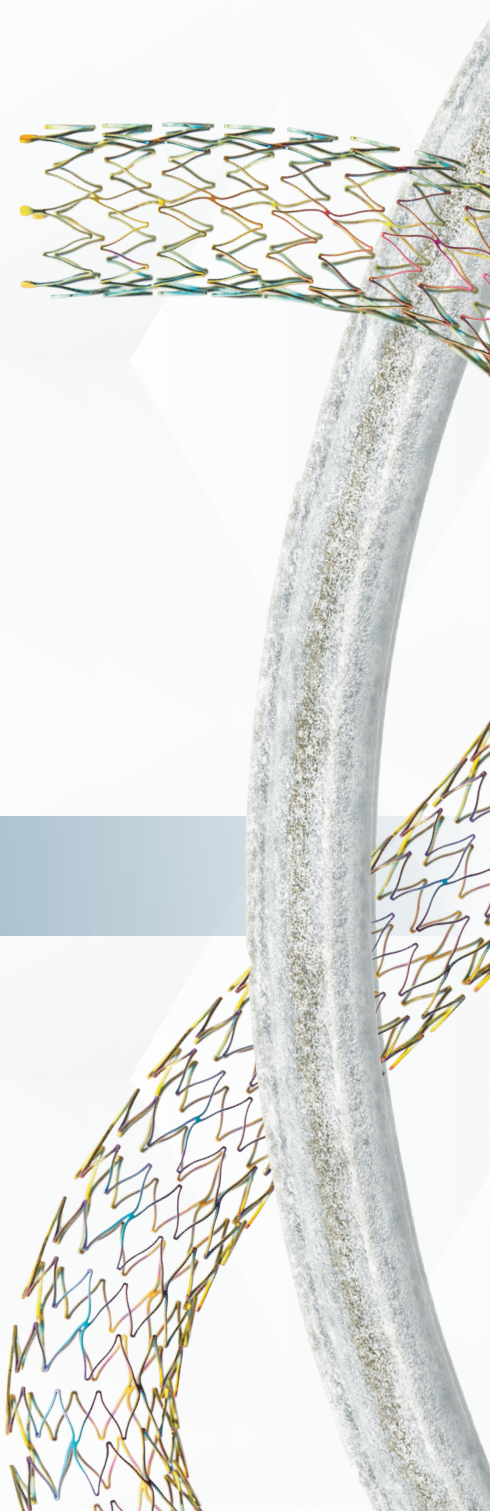

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The Importance of Vessel Preparation

Properly preparing lesions before use of drug-eluting technologies has become a crucial step of the treatment algorithm.

BY RALF LANGHOFF, MD

Vessel preparation has gained importance as a crucial component of endovascular procedures. With the development of the leave-nothing-behind strategy, vessel preparation has been a key focus. For some interventions, dedicated pretreatment of the lesion is mandatory. Plaque modification is important when it comes to local drug delivery to the lesion via either balloon or stent. Adequate lesion pretreatment enhances the drug penetration into the vessel wall, which promotes and increases the antirestenotic properties.

In severely calcified arteries, the benefit of drug-coated balloons (DCBs) is less distinct due to the mechanical barrier in the arterial wall. This challenge can be overcome by dedicated vessel preparation such as atherectomy or scoring/cutting balloon angioplasty.[1,2] Additionally, the mechanism of vessel preparation affects the procedural success rate and long-term outcomes.[3,4] Consequently, vessel preparation has shifted from a trend to a consistent element of treatment algorithms.

FACILITATING VESSEL PREPARATION

Vessel preparation minimizes the risk of dissections, maximizes the luminal gain, and prepares the vessel bed for stents, vascular mimetic implants, and/or local drug delivery. Vessel preparation should be considered regardless of whether the lesion is stenotic or occlusive and is especially crucial if calcium is present.[5]

Today, vessel preparation consists of undersized balloon predilatation, angioplasty with scoring or cutting balloons, or atherectomy. Scoring or cutting balloons may be considered in calcified or very fibrotic lesions. The rationale behind this technology is that the entire force is focused on a wire or blade edge mounted on the balloon. This setup leads to a controlled plaque incision or a controlled dissection with less barotrauma to the entire lesion. Scoring or cutting balloons may be the first consideration in bifurcation and ostial lesions with the intention to minimize an expected plaque shift.

Every balloon angioplasty will create a certain extent of vessel injury. Larger dissections should be prevented, but microdissections will occur after any balloon-based intervention. There is a lack of scientific data on how to perform a standardized balloon angioplasty. Performance varies between medical specialties, vessel localizations, personal experience, and even the day of the week—balloon inflation times are presumably longer on Mondays compared to a Friday afternoon.

Zorger et al[6] investigated the influence of 30-second inflations compared to 180-second inflations and demonstrated that all procedural success endpoints (eg, bailout stenting, incidence of major dissections, and need for further intervention) were in favor of the long inflation time (Table 1).

The significance of a dissection after infrainguinal balloon angioplasty remains an active area of debate. There is no dedicated measuring tool to accurately define where and when a stent-based approach is preferred in infrainguinal arteries. Color-coded duplex ultrasound, intravascular

TABLE 1. OUTCOMES OF LONG VERSUS SHORT BALLOON INFLATION TIME

	Inflation time (s) 30 (n = 37)	Inflation time (s) 180 (n = 37)	*P* value
Major dissections (grade 3–4)	16	5	.010
Minor or no dissections (grade 1–2)	21	32	.010
Further interventions	20	9	.017
Stents	4	1	
Prolonged dilation	16	8	
Residual stenosis (> 30%)	12	5	N/A

Reprinted with permission from Zorger N, Manke C, Lenhart M, et al. Peripheral arterial balloon angioplasty: effect of short versus long balloon inflation times on the morphologic results. J Vasc Interv Radiol. 2002;13:355-359.

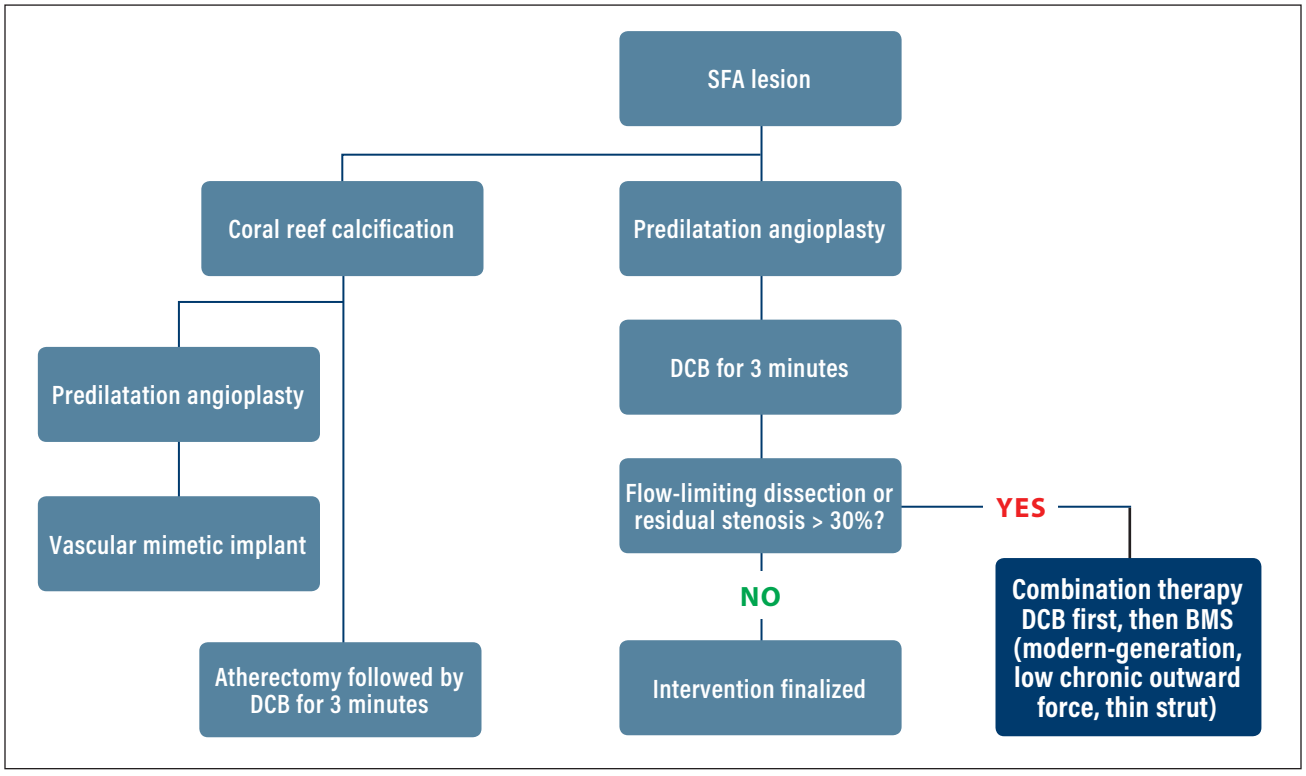

Figure 1. Treatment algorithm for SFA lesions. BMS, bare-metal stent.

ultrasound, optical coherence tomography, and fractional flow reserve measurements via pressure wire could add valuable guidance to the stenting approach.

Recently, Fujihara et al demonstrated in a registry[7] that an increase in the severity of superficial femoral artery (SFA) dissections is negatively correlated to primary patency and the rate of freedom from target lesion revascularization. In various current treatment algorithms, vessel preparation outcome predicts the ongoing pathway (Figure 1).

The absence of flow-limiting dissections after a crucial vessel preparation and the absence of significant vessel calcification justifies a DCB-only approach. If flow-limiting dissections occur, a stent-based intervention is needed, either with or without additional DCB treatment.[8,9]

The role of drug-eluting stents (DESs) in this algorithm remains a matter of debate, and regional reimbursement influences their scope of application. In Germany, for example, DESs are not well reimbursed. Consequently, the market share for DESs in Germany is low despite good supporting data. DESs are effective and have shown sustainable results in SFA trials compared to bare-metal stents.[10,11]

In coral reef calcified arteries, directional atherectomy (DA) can prepare the vessel bed for DCB treatment. Reducing the barrier within the vessel wall to boost drug uptake can lead to safe and durable therapy. Robust data to prove this concept are still pending. The ongoing REALITY trial (NCT02850107) may provide more detailed results but is still randomizing patients.

The DEFINITIVE AR trial[1] was a pivotal feasibility trial to investigate combination therapy (DA and DCB) compared to a DCB-only approach and find if the results of either therapy could be improved by combining them. The trial also identified patient subgroups where the combination of DA and DCBs could be more beneficial than in others. Results suggest that in longer and more calcified lesions, there is a trend of superiority of combining DA and DCBs. Patency was improved compared to using DCBs alone, especially in patients who underwent effective DA vessel preparation. Effectiveness was defined by < 30% residual stenosis after DA but before DCB use, presumably because the vessel preparation led to enhanced drug effectiveness and improved flow patterns as the endoluminal gain was optimized.

Calcium is the biggest challenge to a successful outcome. Although several different attempts to score the amount and distribution of calcium have been established, none is entirely accepted. The Peripheral Arterial Calcium Scoring System (PACSS score) (Table 2) is probably the most widely used.[12] Sophisticated techniques to prepare the vessel (eg, the so-called *pierce technique*) have been used. A

TABLE 2. PROPOSED PERIPHERAL ARTERIAL CALCIUM SCORING SYSTEM (PACSS)[12] (KRISHNA J. ROCHA-SINGH ET AL)
Proposed fluoroscopy/DSA-based Peripheral Arterial Calcification Scoring Systems (PACSS): Intimal and medial vessel wall calcification at the target lesion site as assessed by high-intensity fluoroscopy and digital subtraction angiography (DSA) assessed in the anteroposterior projection.
Grade 0: No visible calcium at the target lesion site
Grade 1: Unilateral calcification < 5 cm: (a) intimal calcification, (b) medial calcification, (c) mixed type
Grade 2: Unilateral calcification ≥ 5 cm: (a) intimal calcification, (b) medial calcification, (c) mixed type
Grade 3: Bilateral calcification < 5 cm: (a) intimal calcification, (b) medial calcification, (c) mixed type
Grade 4: Bilateral calcification ≥ 5 cm: (a) intimal calcification, (b) medial calcification, (c) mixed type
Reprinted from Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: prevalence, mechanism, detection, and clinical implications. Catheterization Cardiovasc Interv. 2014;83:E212–E220.

Japanese group used direct needle puncture of intra-arterial calcified plaques after successful wire passage to enable balloon delivery.[13]

Most recently, a report on the pave-and-crack technique as an aggressive but efficient way of vessel preparation showed sustained 12-month data on severely calcified SFA lesions (mostly PACSS grade 4 patients). To prepare the vessel before implanting a biomimetic implant (Supera stent, Abbott Vascular) safely, the implantation of a stent graft was necessary. Intensive angioplasty with high-pressure balloons under injection of local anesthesia into the arterial wall was then possible without fearing a vascular rupture.[14] The interventionalist ensures a nominal deployment of the Supera stent to its intended diameter via extensive vessel preparation.

CLINICAL CASE

A 69-year-old woman possessing all atherosclerotic risk factors (hypertension, hypercholesterolemia, diabetes, current smoker) presented with severe claudication in her left leg due to a long (29 cm) TASC D SFA occlusion (Figure 2) with moderate calcification in the distal Hunter's canal. To achieve a good wire passage into the chronically occluded SFA, a small stump of the SFA was visualized in an oblique view and helped to find the arterial ostium.

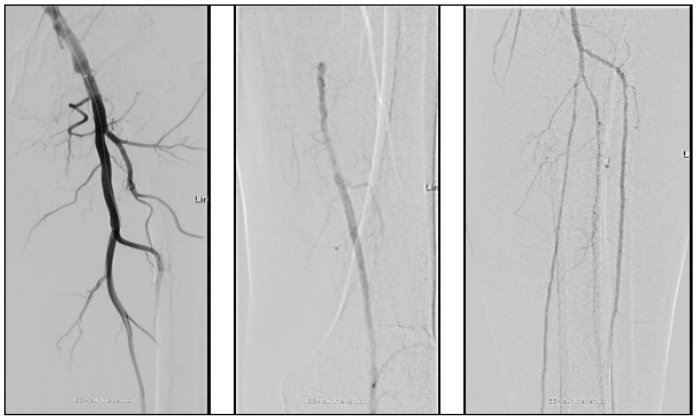

Figure 2. A 69-year-old woman presented with a long SFA occlusion.

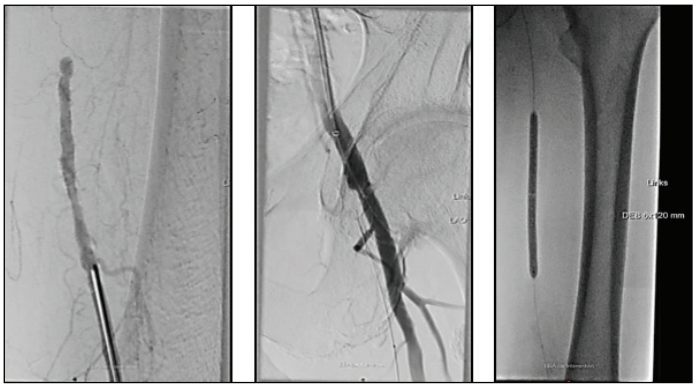

Figure 3. Retrograde access and DCB angioplasty.

We began with a crossover approach, but due to a failed reentry into the true lumen, we switched to a retrograde access. Under fluoroscopic guidance, we punctured the distal SFA (Figure 3). After successful retrograde lesion crossing and externalization of the retrograde wire, we performed a predilatation of the entire lesion with an undersized 4-mm Passeo-18 balloon (Biotronik; 3-minute inflation time with nominal pressure). We then followed with three 6- X 120-mm Passeo-18 Lux DCBs (Biotronik) to apply paclitaxel to the lesion site (Figure 4).We could not identify any severe dissection on angiography and consequently left the lesion unstented.

Careful vessel preparation was performed after successful wire passage. This procedure led to an encouraging technical success, which motivated us to leave the lesion without any mechanical implant.

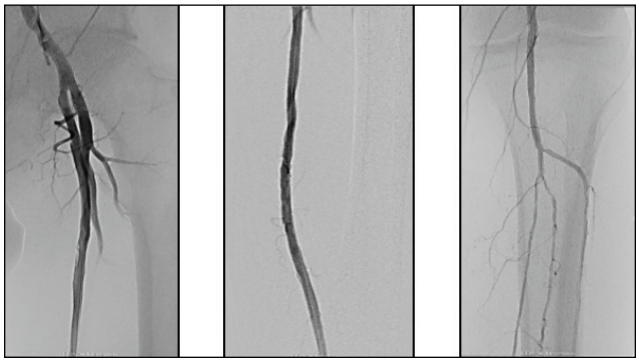

Figure 4. Final result after vessel preparation and DCB.

Treatment Workflow:

- Crossover approach with a 6-F, 45-cm Fortress sheath (Biotronik)
- 0.035-inch NaviCross support catheter (Terumo Interventional Systems)
- 0.035-inch, 260-cm, stiff, angled GlideWire (Terumo Interventional Systems)
- Retrograde access by direct puncture of the distal SFA/P1 segment with 18-gauge needle (Cook Medical)
- 0.018-inch, 260-cm angled GlideWire Advantage (Terumo Interventional Systems)
- Sheathless approach with a 90-cm, 0.018-inch CXI support catheter (Cook Medical)
- Externalization of the retrograde wire
- Stepwise predilatation with a 4- X 200-mm Passeo-18 balloon
- Stepwise angioplasty with three 6- X 120-mm Passeo-18 Lux DCBs without geographical miss

CONCLUSION

Vessel preparation has progressed from fiction to fact. It has become an integral part of current endovascular procedures and treatment algorithms with the goals of maximizing the lumen, preparing the vessel bed for definitive treatment, and minimizing the risk of dissections and peripheral emboli. ■

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Disclosures: None.

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How Can DCB Design Impact Clinical Outcomes?

The technology and clinical outcomes of the Passeo-18 Lux DCB.

BY MARIANNE BRODMANN, MD, AND GUNNAR TEPE, MD

Clinical performance of a medical device derives directly from its technical design and characteristics. Drug-coated balloons (DCBs) have to address several complex and contradictory demands. In an ideal case, a DCB must ensure a perfect balance between drug retention during the transfer to the lesion and an effective drug transit to the vessel wall to optimize the drug uptake. This transfer needs to be realized in a rather short time window, and the therapeutic drug dose should remain in the tissue for several weeks. This perfect balance can only be achieved through a combination of the balloon platform, the drug, the excipient, and the coating process.

DRUG

The most crucial component of every DCB is the drug. Paclitaxel has been the drug of choice for peripheral DCBs because of its highly lipophilic profile, fast tissue absorption, and the long tissue retention, which is a determinant for a positive long-term result, especially in the superficial femoral artery (SFA).

Paclitaxel's mode of action has been known since the 1960s and its use in oncology. It acts at the β-tubulin level, impairs the microtubular assembly, and halts the cell cycle assembly between the G2 and M phase. The paclitaxel dose and coating formulation directly impacts biological performance. Excessive drug amount on the balloon can cause a systemic effect, and an amount that is too low impairs the effectiveness of the treatment.

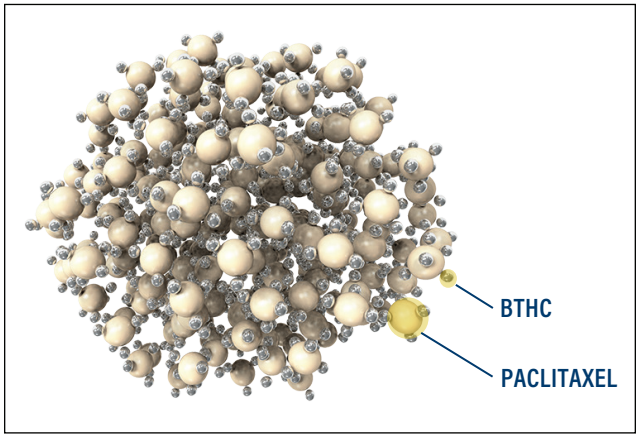


Figure 1. Paclitaxel and BTHC microcrystalline structure.

There are different morphologic forms of paclitaxel used as coatings: amorphous, hybrid, macrocrystalline, crystalline, microcrystalline, and nano encapsulation; amorphous and microcrystalline are the forms most often used by medical device manufacturers. As shown by Granada et al, the type of crystallinity influences the pharmacokinetic behavior of the coating.[1] Despite releasing more particles than an amorphous coating, the crystalline coating allows a better transfer and much higher retention into the vessel wall.

COATING PROCESS

Coating homogeneity is key; uniform drug coating will lead to uniform vessel wall coverage during drug transfer. The coating process allows a good homogeneity as well as a dose control and reproducibility among the produced units.

The principal determinant of a DCB's biologic effect is the quantity and homogeneity of the drug transferred to the tissue wall. Unfortunately, due to the current technical capabilities, it is commonly accepted that only a reduced quantity of drug is actually transferred to the vessel wall. Some of the active component is washed off during navigation of the balloon to the target lesion, and some of the drug stays on the balloon after the inflation.

EXCIPIENT GOVERNS EFFICACY: BTHC, A HIGH-DRUG-RETENTION EXCIPIENT

The excipient is the other key element of a DCB coating. An excipient will protect the active drug component from washing off prematurely and optimize the drug uptake into the vessel wall. Excipient performance will determine the overall technical performance of the device, ensuring adequate balance between these two contradictory needs.

A

Device	Excipient	Type	Solubility
Passeo-18 Lux	Butyryl-tri-hexyl citrate (BTHC)	Hydrophobic	Very low
Lutonix (BD Interventional)	Polysorbate/ sorbitol	Hydrophilic/ hydrophobic	Fast dissolving
In.Pact (Medtronic)	Urea	Hydrophilic	Fast dissolving

B

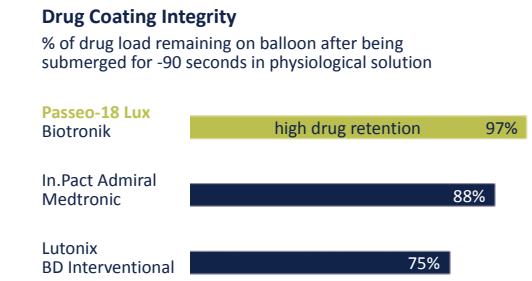


Figure 2. The Passeo-18 Lux's hydrophobic BTHC excipient is less soluble than hydrophilic alternatives (A), ensuring more drug is available at the lesion site (B).

Butyryl-tri-hexyl citrate (BTHC) is the excipient of the Passeo-18 Lux, which was screened among dozens of other excipients and selected for its capability to adhere to the balloon, low amount of particles generated, stability, and hydrophobic characteristics (Figure 1). BTHC is a hydrophobic excipient, meaning it tends to repel water. This characteristic helps prevent the drug from washing off prematurely during the transit to the target lesion, thus maximizing the drug availability at the target (Figure 2) (Data on file at Biotronik).

Does the presence of excipient correlate with clinical results? The only randomized controlled trial (RCT) conducted with a DCB without an excipient has been the only one that did not show significant improvement over the comparator percutaneous transluminal angioplasty (PTA) device.[2]

PROLONGED DRUG PRESENCE

The combination of BTHC and paclitaxel ensures an efficient performance of the drug at the target lesion over time. A preclinical porcine study demonstrated a prolonged presence of paclitaxel in the target vessel tissue up to 28 days following treatment (Figure 3) (Data on file at Biotronik). Systemic blood levels decreased to low levels after 7 days (Figure 4) and reached levels below quantification at day 28. There were no signs of adverse events related to the Passeo-18 Lux.

LIMITING DRUG LOSS DURING INSERTION

Keeping the drug safe and unaltered on the balloon during insertion in the introducer sheath is one of the main challenges for DCB manufacturers. Passeo-18 Lux uses a SafeGuard (Figure 5), a small plastic tube that protects the coating during handling, as well as protecting the user from getting in contact with the paclitaxel.

The principal benefit of the SafeGuard is to avoid contact between the coating and the valve of the introducer sheath and therefore protect the coating from scratches that could result in drug loss or particulate generation. Independent testing demonstrated the benefit of SafeGuard in terms of drug loss (Data on file at Biotronik). It has been proven that the drug loss inside the introducer sheath valve was reduced by 94% (Figure 6). Using SafeGuard will result in a low 1.5% drug loss into the valve, thus offering very efficient protection against preliminary drug loss.

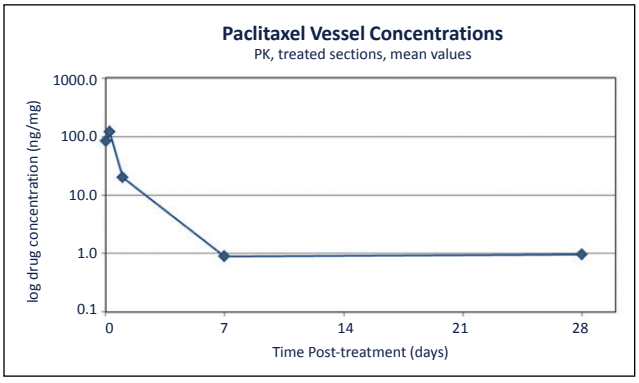


Figure 3. Local pharmacokinetic profile of paclitaxel in a porcine animal model.

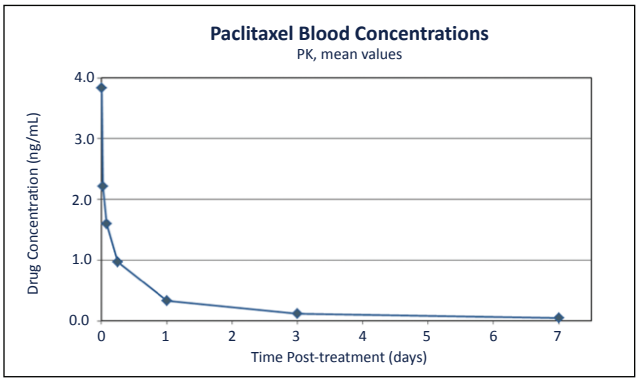


Figure 4. Normalized systemic paclitaxel blood concentrations over time.

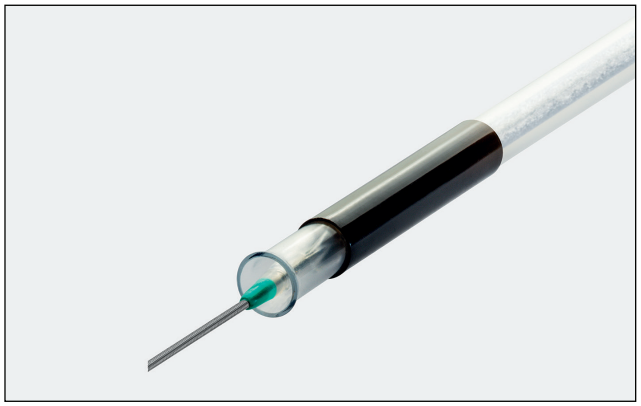


Figure 5. The SafeGuard is a small plastic tube that protects the Passeo-18 Lux's drug coating.

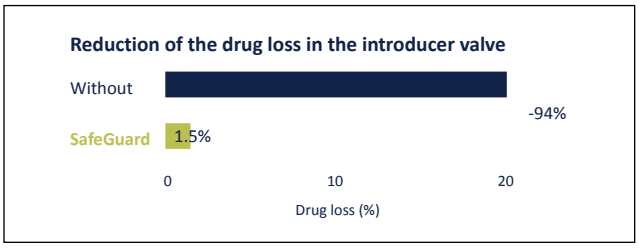


Figure 6. Independent testing demonstrated a 94% reduction in drug loss when SafeGuard was used. Data on file at Biotronik.

PARTICLE EMBOLIZATION

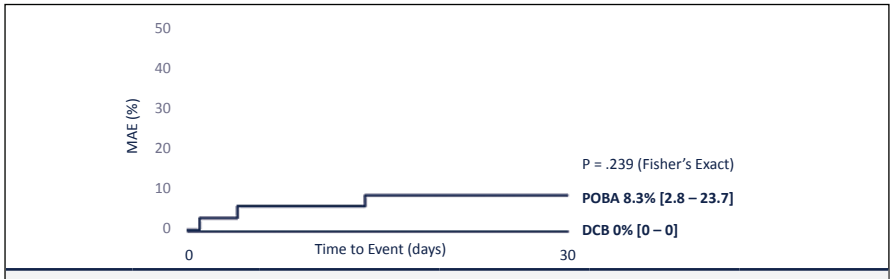
After release of the IN.PACT DEEP results,[3] particle embolization became a highly discussed topic, but what is the real impact of downstream particle embolization? Histologically, there is an impact, as proven multiple times by Dr. Renu Virmani's research.[4] In the clinical setup, the principal consequence of distal embolization would be amputation (minor or major), but it is difficult to correlate these findings to clear clinical consequences. Thus far, the main RCTs conducted in the SFA comparing DCB to standard PTA showed a very limited, if any, number of amputations. For the below-the-knee (BTK) indication, where particle embolization is considered the most harmful, the BIOLUX P-II RCT showed a 0% amputation rate at 30 days for the Passeo-18 Lux arm versus 2.8% for standard PTA (Figure 7).[5] Though not statistically significant, these results show a trend toward safe use of Passeo-18 Lux in the BTK indication.

CLINICAL OUTCOMES FROM THE BIOLUX P-III REGISTRY

RCTs have proven the efficacy of DCB technology in the SFA region both in the short (≤ 12 months) and long term. There are now published and reviewed data for a sustained benefit of up to 3 years for the In.Pact Admiral DCB (Medtronic).[6]

The transmission of this DCB data to real-world patients' symptoms and lesions is still a subject of debate. One of the main criticisms is that RCTs thus far have excluded a considerable number of patients, especially highly calcified and long, complex lesions as well as certain patient subsets, such as those with critical limb ischemia (CLI). All-comers registries try to overcome these issues. The BIOLUX P-III registry[7,8] is one of the largest real-world DCB registries to date and has no exclusion criteria. It is a prospective, global, multicenter, all-comers registry, with the goal of further investigating the Passeo-18 Lux DCB's safety and efficacy in infrainguinal arteries in a real-world environment.

The primary endpoints are freedom from major adverse events (MAEs) at 6 months and freedom from clinically driven target lesion revascularization (CD-TLR) at 12 months. There were no limitations concerning patient characteristics or lesion characteristics, and use of additional devices was allowed. The registry was performed at 47 sites in 16 countries (Europe, Australia, Singapore, and Malaysia). The full cohort of the registry included 882 subjects with 1,085 lesions. There was an extension of enrollment to complete some predefined subgroups after the initially planned full cohort of 700 patients was completed. In the end, a total of 332 patients with CLI, 418 patients with diabetes, 150 patients with BTK lesions, 141 patients with heavily calcified lesions, 305 patients with complex lesions (TASC C/D), and 103 subjects with in-stent restenosis were included.



	Death	Major Amputation	TLR	TVR	TL Thrombosis
DCB (%)	0%	0%	0%	0%	0%
POBA (%) [CI]	0%	2.8% [0.4 – 18.1]	5.6% [1.4 – 20.7]	5.6% [1.4 – 20.7]	0%

Figure 7. BIOLUX P-II showed a 0% amputation rate at 30 days for the Passeo-18 Lux arm.[5]

Patient and Lesion Characteristics

Compared to RCTs in this space, baseline patient characteristics included patients who were older (mean age, 70.1 ± 10.3 years), a higher percentage of women (36%), a high percentage of patients

with diabetes (47.6%), and 51.6% of patients had previous interventions. It is the only DCB registry thus far that has enrolled Rutherford 6 patients (9%).

Lesion baseline characteristics included a mean lesion length of 89 ± 77.1 mm, 54.1% were de novo lesions, 24.9% were total occlusions, 10.6% were in-stent restenosis, and 10.4% were restenotic lesions. Within this variety, 76.1% of lesions were calcified, with 44.6% showing either moderate or heavy calcification; 32.6% of lesions were TASC C/D, and 17.1% were located in the BTK area.

Procedural Approach

In 73% of the lesions, vessel preparation (mainly predilatation with standard PTA [88.3%], but other methods including cutting/scoring balloons and atherectomy were applied) was performed to increase drug uptake. The bailout stent rate was considerably low at 15.7%.

Results

At 365 days, freedom from CD-TLR was 93.5% (91.8%, 94.9%), and primary patency was 84.3% (81.8%, 86.4%). Not only was efficacy well proven, but there were no safety issues. Efficacy on one site was accompanied by a freedom from MAEs (defined by composite of device- and procedure-related mortality through 30 days, major target limb amputation, and CD-TLR) rate of 89.7% (87.4%, 91.6%). MAEs were adjudicated by an independent clinical events committee.

Although 332 patients with CLI were included in this real-world registry, the rate of freedom from major amputation at 12 months was 97.4% (96.1%, 98.3%).

These morphologic findings were consistent with clinical improvement—the most important finding for the patient; 81.9% of patients improved by at least one Rutherford classification after 1 year.

When we look at the BIOLUX P-III full cohort in context with other DCB registry data, it should be noted that:

- This registry addresses the largest CLI cohort so far (42.6% vs IN.PACT Global, 11%[9])
- 47.6% of enrolled patients had diabetes versus an average of 40% in comparative registries
- 17.1% of BTK lesions were treated within the full BIOLUX P-III cohort compared to no BTK lesions included in any other real-world DCB registries so far
- Freedom from TLR was no different from other DCB registries (93.5% vs IN.PACT Global's 92.6%)

CONCLUSION

Despite the fact that most DCBs are efficient, they are not equal. Excipient and coating characteristics will govern the overall performance of a DCB and impact the clinical outcomes. A hydrophobic excipient such as BTHC will prevent paclitaxel from being prematurely washed off, enabling better transfer of the drug to the lesion. Microcrystalline paclitaxel will ensure that drug remains in the tissue up to 28 days after treatment to inhibit the restenosis process.

These factors allow Passeo-18 Lux to claim significant advantage over standard PTA in terms of safety and efficacy in the SFA indication[10] and safety over standard PTA in BTK treatment.[5] The more recent real-world registry, BIOLUX P-III, showed excellent results in a very complicated patient population that included a high rate of patients with CLI and diabetes, especially in the BTK subgroup, which sends a strong signal that a DCB could be a valuable option for this indication.[7,8] The Passeo-18 Lux technology is providing a robust clinical program to prove the safety and efficacy of this DCB in varied patient populations. ■

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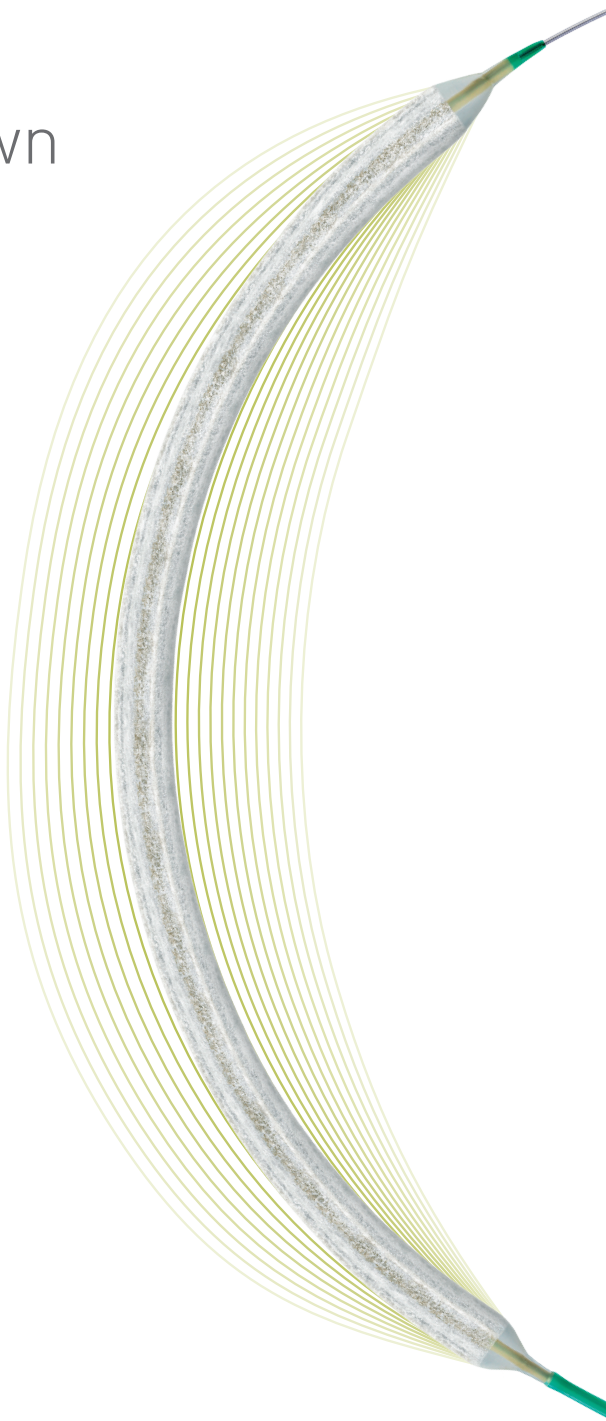
Disclosures: Study support from B. Braun Melsungen AG, Bard, Bayer, Biotronik, Boston Scientific Corporation, Gore & Associates, Medtronic, and Shockwave Medical, Inc.; advisory board for B. Braun Melsungen AG and Medtronic.

Passeo-18 Lux

Peripheral Drug-Coated Balloon Catheter

Benefit is consistently shown in challenging population.



Full-cohort[1]

results at 12-month, n=882

Patients per subgroup:

CLI	Diabetics	BTK
42.6%	**47.6%**	**17.1%**

PP*, ** **84.3%**

Fcd-TLR** **93.5%**

Passeo-18 Lux

- Clinically proven
- Effective drug delivery***
- Prolonged drug presence***

1. BIOLUX P-III All-Comers Real-World Experience with Passeo-18 Lux Paclitaxel-coated balloon in infra-inguinal artery: 12-month results in Full-Cohort patients. Presented at Charing Cross 2018.

* DUS not mandated in every visit; ** Kaplan Meier estimates; *** Drug retention while in transit to the lesion and prolonged Paclitaxel presence in the vessel wall. BIOTRONIK data on file.

CLI = Critical Limb Ischemia; PP = Primary Patency; Fcd-TLR = Freedom from clinically driven Target Lesion Revascularization; BTK = Below the Knee; RCC = Rutherford Clinical Classification

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How Self-Expanding Bare-Metal Stent Design Can Affect Procedural Results

Clinical outcomes in treatment of femoropopliteal artery disease with the Pulsar-18 stent.

BY JOS C. VAN DEN BERG, MD, PHD, AND MICHAEL LICHTENBERG, MD, FESC

The use of self-expanding nitinol slotted-tube stents for the treatment of femoropopliteal stenotic and occlusive disease has been an essential part of endovascular therapy for the last 2 decades. With the advent of drug-coated balloons, the use of self-expanding stents has decreased, and currently, there is a tendency to follow a leave-nothing-behind approach. This method has led to a shift from primary stenting in the superficial femoral artery (SFA) and proximal popliteal artery toward a bailout-only stenting strategy. In daily practice, however, and especially when dealing with long, calcified lesions, there is still a need for stenting. Therefore, it is important to be aware of the stent design factors that influence clinical outcomes, a role that is typically underestimated.[1] This article provides an overview of these design features and how they relate to clinical results.

CHRONIC OUTWARD FORCE

Chronic outward force (COF) is the radial force that a self-expanding stent exerts at expansion and is related to the stent design, strut thickness, the stent material (the so-called spring constant), and also the amount of oversizing with respect to the vessel diameter. This is the force to which the artery will be continuously exposed after implantation. There are two more radial forces in addition to COF: the radial resistive force that occurs under concentric compression and the crush resistance that occurs under focal compression.

COF applies for all self-expanding stents. The more a stent is oversized, the higher the COF will be. When looking at different stents, however, we can see that significant differences occur between the various stent designs depending on the degree of oversizing (Figure 1).

Figure 1 shows that there is a difference not only of the curve's height that represents the COF under different amounts of oversizing but also in the curve's steepness, with an almost horizontal course of the self-expanding stent with the lowest COF. The latter finding is especially of importance because it shows that even with an oversizing of 2 mm (which generally is considered to be too much oversizing), no significant increase of COF is perceived by the vessel wall. The relatively small increase in COF related to the degree of oversizing is important in clinical practice because in irregular lesions, stent expansion even after postdilation may not be homogeneous.

Implanting stents in arteries leads to a typical response that follows a response-to-injury sequence of events that is comparable to that of wound healing.[2] In a numerical modeling experiment, it was found that, especially in arteries with heavily calcified plaques, oversizing should be avoided because the low stiffness of the plaque will lead to increased stress to the arterial wall.[3] A similar

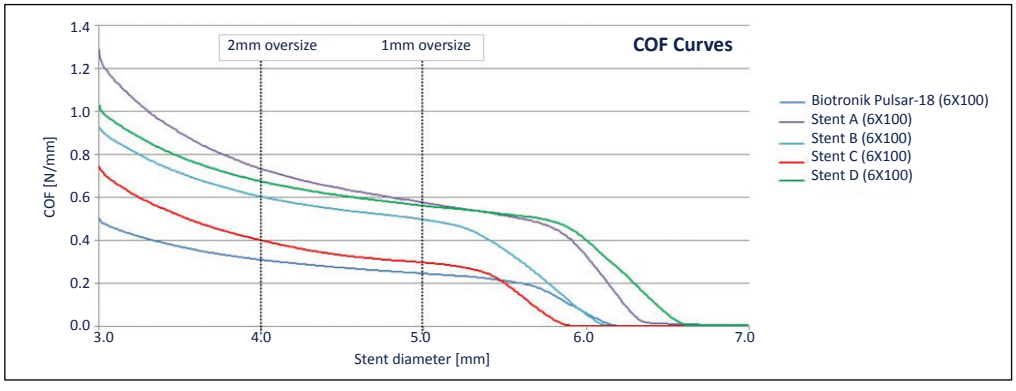

Figure 1. Comparing the COF under different amounts of oversizing in various stents.

study revealed that a higher oversizing ratio will lead to a significant increase in wall shear stress and structural stress that can be associated with damage to the arterial wall and disruption of the laminar blood flow, while not contributing to a significant luminal gain.[4] Given the continuous character of these radial forces (due to the self-expanding design), the damage will continue to accumulate, therewith creating a mechanical environment that is prone to induce restenosis. Therefore, the interventionalist should take care not to oversize nitinol stents in order to improve clinical outcomes.

Related Preclinical Animal Studies

Two animal experiments have shown the negative effect of oversizing on the occurrence of restenosis. The first study looked at the effects of overlapped nitinol self-expanding stents into the iliofemoral arteries of 14 swine.[5] Because of variations in target artery size, the stent-to-artery ratio ranged from 1.2:1 to 1.9:1 (in clinical practice, oversizing of 1 mm is typically recommended, eg, a 6-mm stent in a 5-mm artery, which corresponds to a ratio of 1.2). During the implantation, quantitative angiography was used to assess the arterial lumen and stent diameters. At 6 months, an angiographic study and histologic analysis were performed.

Initially, stent expansion was not complete (ranging from 4.7 mm to 7.1 mm), and stents were seen to conform to the diameter of the target artery. At 6-month follow-up, it was noted that continuous expansion over time had led to an enlargement to nearly the nominal stent diameter (of 8 mm). Histologic examination showed significant effects of oversizing, with marked increases in injury and luminal area stenosis. A statistically significant linear correlation between the stent-to-artery ratio and area stenosis was found. The authors concluded that severe oversizing (eg, a stent-to-artery ratio of 1.4:1) resulted in a histologic response that includes exuberant neointimal proliferation and luminal stenosis.

In the second study, nitinol stents were implanted with a stent-to-artery ratio between 1 and 2.3 and showed similar results.[6] Also, this study used quantitative angiography to calculate the arterial and minimal luminal diameter. Follow-up consisted of quantitative angiography and histomorphometry after 5 months. Stent segments were divided into "normal-sized" (stent-to-artery ratio < 1.4) and "oversized" (stent-to-artery ratio ≥ 1.4). All stent segments were seen to expand almost to their near nominal diameter during follow-up. Normal-sized stent segments increased their diameter by 6% and oversized segments by 29%. A significant correlation between oversizing and restenosis by both angiography and histomorphometry

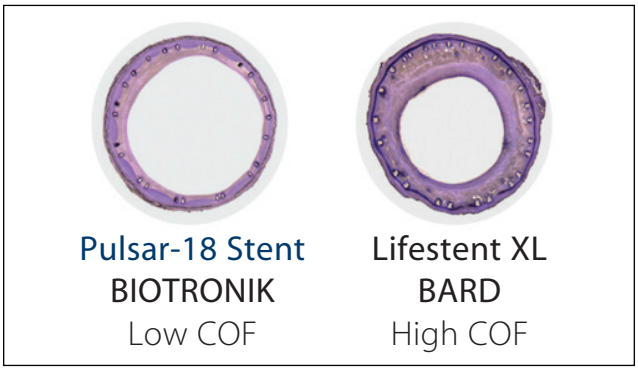

Figure 2. Preclinical results in a porcine model. The low-COF Pulsar-18 stent (Biotronik) caused less neointimal hyperplasia at 90 days compared to a high-COF stent.

was observed. Again, oversizing was shown to correlate in a linear and positive fashion with neointimal proliferation and restenosis, and this is most likely due to the chronic physical stimulus exerted by the continuing expansion of the stents.[5] Continuous expansion of a self-expanding stent may even lead to stent strut migration to the adventitia.[1,7] In a study presented by M. Funovics during CIRSE 2017, a comparison was made in a swine model between a low-COF and a high-COF stent, using the same amount of oversizing. At 28 and 90 days, it was observed that the low-COF stent-treated segments demonstrated a smaller neointimal area and area stenosis, lower injury (evaluating the internal elastic lamina [IEL], media, and external elastic lamina), and inflammation scores (Figure 2).

The outcomes of the VIPER clinical study, which evaluated a heparin-bonded expanded polytetrafluoroethylene-covered stent graft in femoropopliteal artery disease, reflected the findings from these animal studies.[8] A statistically significant difference in primary patency was seen between devices with a less than 20% oversizing at the proximal landing zone and those with more than 20% oversizing (88% vs 70%, $P = .047$).

Figure 3 shows a fluoroscopic image after stent implantation (6- X 80-mm Pulsar-18 in 2011, Biotronik) in a severely calcified lesion, with lack of full stent expansion

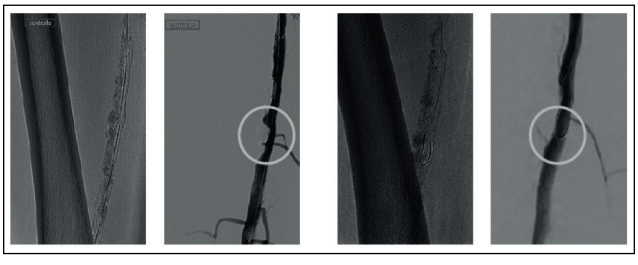

Figure 3. Case example showing long-term vessel support of a 6- X 80-mm Pulsar-18 stent even in calcified lesions.

in an area of focal calcification, and an angiographic residual stenosis of less than 30% (circle; with a high-COF stent, the stress exerted on the vessel wall would be significant, potentially leading to neointimal hyperplasia); a fluoroscopic image that was obtained 5 years later when the patient returned for treatment of an ipsilateral iliac lesion shows full stent expansion and angiographically, a full patency of the stented segment. This figure illustrates the chronic impact of the stent and its COF on a long-term clinical outcome. With a constant low COF applied to the vessel, patency can be achieved over a long-term follow-up even if the vessel is not fully open immediately after the procedure.

STRUT THICKNESS

As mentioned previously, the strut thickness is an important factor that determines the COF of a stent. With a stent strut thickness of 140 µm, the Pulsar-18 stent has the thinnest struts of modern self-expanding stents (others range from 178–228 µm), leading to the lowest metal-to-artery ratio (Figure 4). Despite the fact that there is less material, bench testing has shown that fracture rates are similar to or lower than those with other nitinol slotted-tube stents (Data on file at Biotronik). This low fracture rate is of utmost importance, because it is known that with certain stent designs, there is a high risk of stent fractures, especially when treating long lesions in the femoropopliteal segment.[9]

The strut thickness also plays a role in the development of the inflammatory response, as a lower injury score for thin-strutted stents was demonstrated in a published study investigating the effect of endovascular stent strut geometry.[10] The occurrence of early restenosis and the development of myointimal hyperplasia in stented blood vessels have been attributed to deep vascular injury with IEL fracture.[10]

This relation was demonstrated in a study that aimed to evaluate the vascular wall response to superficial injury (without IEL rupture) after balloon angioplasty and intravascular (balloon-expandable) stent placement in porcine arteries and the determination of the effect of stent strut geometry on the degree of vessel injury and early restenosis. Two different stents were used, one with rectangular struts and smooth corners, and the other with thicker struts and sharper corners. The latter stent was designed specifically to induce large wall stress concentrations. Intravascular ultrasound was used in all deployments to ensure accurate balloon sizing and to avoid stent overexpansion and deep vascular injury during the procedure. Histomorphometric analysis was performed 90 days after the implantation. Histologic examination showed that the arteries where thick-strut stents were implanted had a statistically higher incidence rate of deep vascular injury with IEL fracture. The arteries that incurred a deep injury showed a 10-fold increase in myointimal thickening as compared to the arteries where the IEL remained intact. This myointimal thickening resulted in a statistically higher restenosis rate than in the arteries without deep injury.

This phenomenon is even more present in vessels with a high plaque burden (where the occurrence of IEL injury is more likely). In cases where only a superficial injury was seen, there was no correlation between the amount of vessel wall/medial layer compression and the development of restenosis from myointimal hyperplasia.

The authors therefore concluded that the maintenance of an intact IEL is an important factor in the prevention of myointimal hyperplasia and restenosis in stented porcine iliac arteries.[10] Stent strut profile can increase local vessel wall stress concentrations, which will lead to rupture of the IEL and eventually an exaggerated response to injury. Stent designs should therefore focus on low-profile struts with geometries that allow reduction of local stress concentrations. Several studies in the coronary arteries have demonstrated that the use of thinner struts will lead to a significantly lower restenosis rate.[1,10]

THE PULSAR-18 STENT

Pulsar-18 is a laser-cut self-expanding nitinol stent

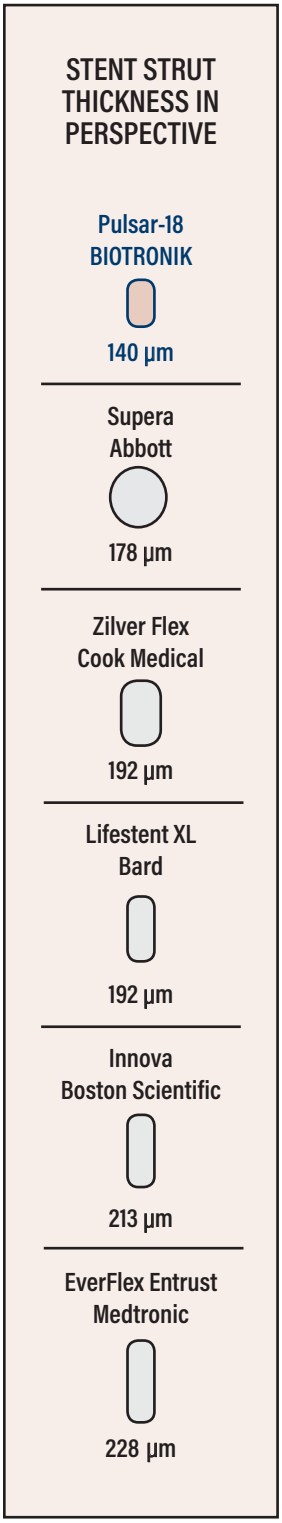

Figure 4. The Pulsar-18 stent has the thinnest struts of modern self-expanding stents.

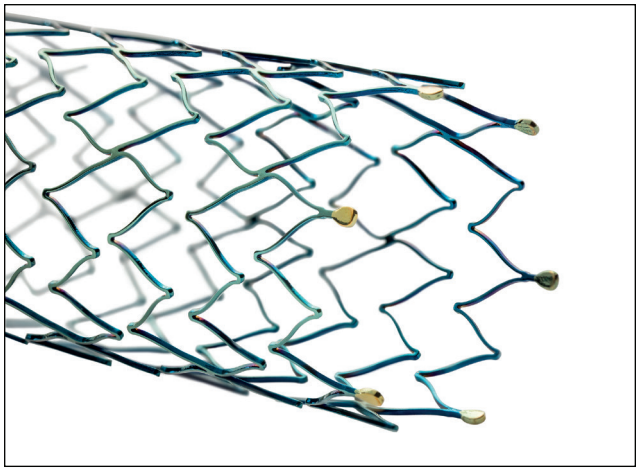

Figure 5. The Pulsar-18 is a laser-cut self-expanding nitinol stent with a flexible, thin-strut, open-cell design with peak-to-valley segments and six radiopaque markers at each end.

loaded on a low-profile 4-F–compatible over-the-wire coaxial delivery system. The stent has a flexible, thin-strut, open-cell design with peak-to-valley segments and six radiopaque markers at each end (Figure 5). It is completely covered with a passive amorphous silicon carbide coating. It has been specially designed with high flexibility, thin struts, and low COF to fulfill the demands of the SFA anatomy.

Pulsar's safety and efficacy has been investigated through an extensive clinical program in more than 1,000 patients treated with a 4-F endovascular approach across a range of lesion lengths and difficulties (Figure 6).[11-20]

4-F–COMPATIBLE ENDOVASCULAR MATERIAL IS SAFE AND EFFECTIVE IN THE TREATMENT OF FEMOROPOPLITEAL OCCLUSIVE DISEASE

The 4-EVER (4-F Endovascular Treatment Approach to Infrainguinal Disease) multicenter, nonrandomized, prospective trial was designed to observe the safety and efficacy of treating symptomatic femoropopliteal occlusive disease using 4-F–compatible devices without any closure device.[11] There were 120 patients (82 men; mean age, 71 ± 9.7 years; range, 47–90 years), primarily claudicants, treated for 120 femoropopliteal lesions (90% TASC A/B; mean lesion length, 71 mm ± 45.9 mm) in five European centers using 4-F Fortress sheaths, Pulsar stents, and Passeo-18 balloons (all from Biotronik).

Technical success was achieved in all 120 patients. No closure devices were used; the mean manual compression time was 8.1 minutes. There were access site complications (significant hematomas) in 3.3%, mostly in patients who were on warfarin therapy. The duplex-controlled 12-month primary patency rate was 81.4%, with a freedom from target lesion revascularization (TLR) rate of 89.3% and a survival rate of 93%. After 24 months, the primary patency rate of 72.3% and freedom from TLR rate of 82.7% confirmed the 12-month results and showed consistent outcomes over a longer follow-up period.

This trial demonstrated 100% technical success with a 4-F endovascular approach, with fewer access site complications (rate, 0.9% for patients who were not on warfarin) and reduced manual compression time compared to historical values for 6-F treatments, thus supporting the supposition that 4-F endovascular treatment is safe and effective for TASC A and B lesions in the SFA.

TASC C and D Lesions

To observe the Pulsar's performance in difficult lesions, the TASC D study was initiated.[12] The study included 22 patients with chronic total occlusions of the femoropopliteal arteries with an average lesion length of 245 mm, all presenting with critical limb ischemia (CLI) and successfully recanalized using the Pulsar-18 self-expanding stent.

Technical success, defined as establishment of an antegrade straight line flow to the foot through a reopened SFA, was achieved in all patients; 100% of patients had a complete wound healing of their lesions

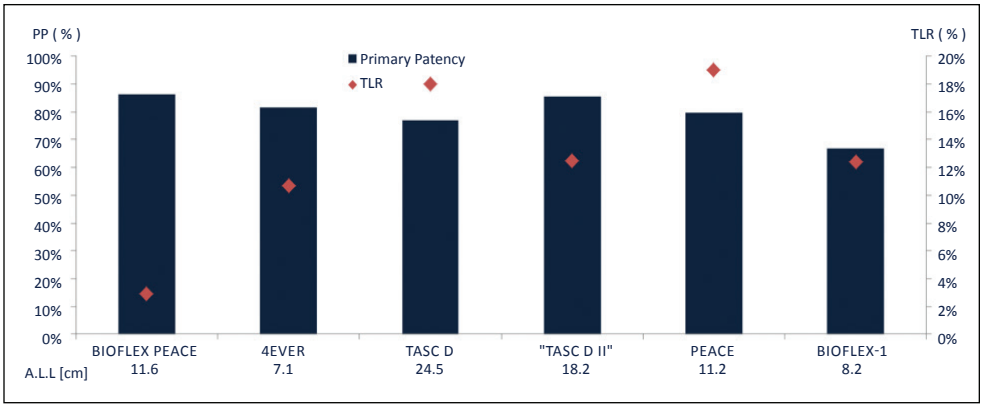

Figure 6. Primary patency and TLR after 12 months of Pulsar stent in several prospective studies show consistency across different lesion lengths.[11-20]

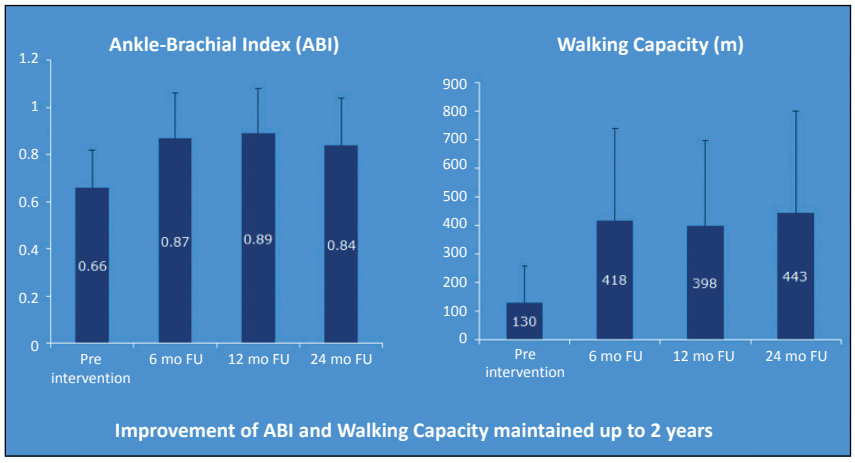

Figure 7. BIOFLEX PEACE clinical success after 2 years.[12] FU, follow-up.

during 6-month follow-up. After 12 months, the primary patency rate was 77%, and no major amputation had to be performed, resulting in a 100% limb salvage rate.

A limitation of the trial was the small study population with only 22 patients; however, outcomes showed that a low COF stent like the Pulsar-18 stent can achieve beneficiary primary patency and freedom from TLR rates in long lesions.

The TASC D II study additionally confirmed these results.[15] Thirty-six patients were enrolled in this all-comers registry. The average lesion length of 18.2 cm was longer than that in many of the competitive studies. After 12 months, a promising primary patency rate of 85.4% and a freedom from TLR rate of 87.5% were achieved, thus showing that the Pulsar-18 outcomes are consistent across different lesion lengths and lesion types (TASC A–D).

Furthermore, in the PEACE trial, a prospective, multicenter, all-comers registry including 148 patients with symptomatic femoropopliteal lesions, a subgroup analysis comparing TASC A/B to TASC C/D showed no difference in clinical outcomes ($P = .55$).[14] Overall primary patency was 87.4% after 6 months and 79.5% after 12 months. The overall freedom from TLR rates were 93.2% and 81% at 6 and 12 months, respectively. The dedicated subgroup analysis found no significant differences between patients with diabetes versus those without ($P = .92$), with CLI versus non-CLI ($P = .92$), patients with renal insufficiency versus the overall population ($P = .8$), patients with lesion length > 100 mm versus the overall population ($P = .09$), or patients with chronic total occlusions versus the overall population ($P = .67$).

BIOFLEX PEACE has been designed to provide more answers to the PEACE study.[13] It is a multicenter, all-comers registry investigating the effectiveness of the Pulsar-18 nitinol stent in the treatment of medium-length femoropopliteal lesions in 160 patients. Patients eligible for study inclusion included those with symptomatic peripheral artery disease of Rutherford category 2 to 5 due to > 70% stenosis or occlusion of the SFA or the popliteal artery. Clinical evaluation, duplex ultrasonography, painless walking distance, and ankle-brachial index were evaluated at baseline and after 6, 12, and 24 months (Figure 7).

At baseline, 41.9% of the treated lesions were moderately to heavily calcified, and 39.8% were considered complex TASC C or D lesions. The patient demographics were mixed: 71.9% were smokers, 33.1% had diabetes, and 15.3% had CLI.

The 12-month results showed a primary patency rate of 86.4% and freedom from clinically driven TLR of 97.1%; 81% of patients showed an improvement of at least one Rutherford class and change in ankle-brachial index from 0.66 at baseline to 0.89 at 12-month follow-up. After 24 months, clinical success could be maintained, demonstrating a primary patency rate of 78% and a freedom from TLR rate of 92.4%.

Pulsar stents used in BIOFLEX PEACE were implanted with an oversizing of 0.8 mm, which shows that in the real-world setting, interventionalists are aware of the importance of low COF and thus apply as minimal oversizing as possible.

CONCLUSION

The importance of the relation between stent design and clinical outcomes in the treatment of femoropopliteal artery disease has been shown in multiple studies. Low COF in combination with a thin strut design of a self-expanding nitinol stent results in less vessel wall injury, leading to a low injury response of the vessel. This feature translates clinically in lower restenosis rates. When stents are used, design characteristics should be considered as an important factor when choosing a stent.

The positive results of the Pulsar-18 stent registries support the endovascular approach in patients with different disease complexities and lesion lengths. Modern next-generation nitinol stents like the Pulsar-18 demonstrate high primary patency rates and event-free follow-up, supporting the safety and effectiveness of this treatment concept. ■

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Disclosures: Receives speaker honoraria and unconditional financial grants to complete the PEACE and BIOFLEX PEACE studies from Biotronik.

Sponsored by Biotronik

Combining a Drug-Coated Balloon and a Bare-Metal Stent: The REsponse Adapted Combination Therapy (REACT) Strategy

Allowing vessel response to guide appropriate treatment for SFA disease.

BY KOEN DELOOSE, MD, AND B. PATRICE MWIPATAYI, MD, MMED, MCLINED, FCS, FRACS

Infrainguinal peripheral artery disease (PAD) affects more than 200 million people worldwide. This number will increase in the future with greater prevalence of atherosclerotic risk factors and aging populations.[1]

The femoropopliteal segment is probably the most challenging area in the endovascular treatment field. Frequently, bone-like calcified plaque burden that is exposed to numerous internal and external mechanical stressors such as flexion, extension, elongation, compression, and external compression make this particular artery difficult to treat.[2]

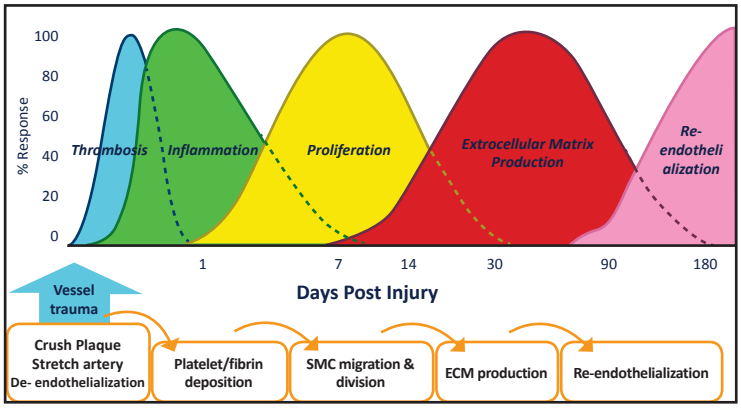


Figure 1. The restenotic cascade following vessel injury.

BACKGROUND

It is widely accepted that a durable solution for superficial femoral artery (SFA) disease requires blocking of the restenotic cascade (Figure 1), which extends up to 18 months in PAD (in contrast to the 6 months in the coronary arteries) using antiproliferative agents such as paclitaxel.[3-5] Drug-coated balloons (DCBs) and drug-eluting stents (DESs) seem to be the ideal carriers.

Current results examining the effects of DESs are more than acceptable. The Zilver PTX (Cook Medical) showed a primary patency rate of 84.4% (vs 68% in the group for optimal percutaneous transluminal angioplasty [PTA] with or without bailout stenting as needed) and freedom from target lesion revascularization (TLR) rate of 91.6% (vs 80% in the optimal PTA with or without stent group). Even at 5 years, the Zilver PTX demonstrates a 41% reduction in restenosis and a 48% reduction in reintervention compared to standard care.[6]

Likewise, the Eluvia DES (Boston Scientific Corporation), although in a smaller number of patients, has an impressive patency rate of 96.4% at 1 year and a freedom from TLR rate of 85.3% at 3 years.[7]

After a period of time, the drug dissipates, and only the metal stent remains. Although this is not problematic in short lesions, the efficacy of nitinol stents in longer lesions decreases with increased lesion length because of the length of the metallic implant and associated potential complications (eg, physical irritation, fractures, restenosis). Additionally, stenting of longer lesions results in greater interference with the femoropopliteal geometry and imposes a mechanical burden that leads to chronic mechanical stress.

For these reasons, interventionalists favor the use of DCBs in a strategy of leaving nothing behind. Without a permanent scaffold, the natural vessel motion is not "caged," preserving the viability of future endovascular and surgical intervention options and reducing the length of time for which dual antiplatelet therapy is required.

Evidence for improved patency rates and freedom from TLR has been provided both in pivotal DCB trials in ideal

situations[8-14] and in registries of more daily practice patient cohorts, which is a more important outcome for patients and health care providers.[15]

Although evidence suggests that the performance of DCBs is independent of lesion complexity, there continues to be a bailout stent ratio > 40% in long lesions (> 20 cm), severely calcified lesions, and a high number of chronic total occlusions.[15-17] In arteries that are obstructed by overwhelming atherosclerotic plaque deposition, balloon angioplasty increases the vessel lumen through uncontrolled dissection, resulting in longitudinal tears and creating tissue flaps with varying degrees of severity. Additional data also suggest that untreated dissections following plain old balloon angioplasty (POBA), including non–flow-limiting dissections, are associated with reduced patency.[18]

THE "AS LESS AS REASONABLY ACHIEVABLE" STRATEGY

Although the leave-nothing-behind strategy appears attractive, it is only feasible in a controlled, straightforward "pivotal trial" scenario. In real-world scenarios for an endovascular interventionalist, an "As Less as Reasonably Achievable" strategy (ALARAS) seems a more appropriate daily principle to adhere to.[19] This strategy maintains the natural motion of the femoropopliteal artery by placing scaffolding only where needed. A cyclical bending-torsion-elongation movement in this arterial segment applies tremendous biomechanical stress to implants in general. It is logically acceptable that long stents will fracture under this stress, while with ALARAS, the long nonstented segments of the vessel wall are probably compensating for some of these forces with focal scaffolds.[20]

The combination of DCBs and the modern generation of nitinol stents works well. Early trials including DEBATE SFA[21] and RAPID[22] clearly demonstrated the safety and efficacy of this therapy. In the single-center DEBATE SFA study, the added value of the combination of the In.Pact Admiral balloon (Medtronic) and the Maris SX stent (Medtronic) in comparison with the Maris SX alone was statistically significant. The primary endpoint, 12-month binary restenosis, occurred in nine (17%) versus 26 (47.3%) of lesions in the DCB plus bare-metal stent group and standard balloon plus bare-metal stent group, respectively (P = .008). The multicenter randomized RAPID trial improved the performance of the Supera stent (Abbott Vascular) by adding the Legflow DCB (Cardionovum).

The DEBAS study was a prospective study performed at three hospitals in Perth, Australia.[23] The Pulsar-18/35 self-expanding stent (Biotronik) and Passeo-18 Lux DCB (Biotronik) were used to treat severe and complex femoropopliteal arterial occlusive disease. The treatment rationale was that in complex Trans-Atlantic InterSociety Consensus (TASC) C and D lesions, angioplasty alone would damage the intima, causing flow-limiting dissections that often required stent implantation. Stent placement in long lesions has been associated with high restenosis rates. However, inflating a DCB* within the stent may help to ensure that the barotrauma is evenly spread across the stented length without substantially impeding drug transfer. The rationale for the use of thin-strut stents was that they decrease the distance between the DCB and the vessel wall owing to the low metal-to-artery ratio (Figure 2), and it may also be true that when the space left between struts is larger, more drug can go through. This geometric principle of thin struts reducing distance between drug coating and wall is independent of stent type or stent material. In the DEBAS study, we investigated when the DCB is inflated within the stent,* the scoring effect can cause plaque surface modification and may allow enhanced paclitaxel transfer, especially in calcified lesions.

The DEBAS study included 51 limbs from 44 patients between October 2007 and April 2010. The mean age of the patients was 67.6 years, and 72.7% were men. Chronic PAD severity was classified as Rutherford class 3 in 41.2%, class 4 in 31.4%, and class 5 in 27.4% of limbs. The most common preexisting risk factors were hypertension (70.4%), hyperlipidemia (52.3%), diabetes mellitus (54.6%), and smoking (38.6%). Of note, 16% of the treated lesions were in popliteal arteries, and the lesions were predominantly TASC D (51%) and C (45.1%),

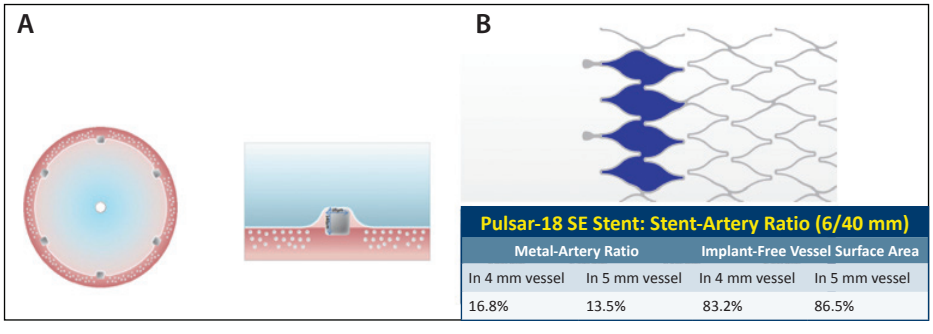
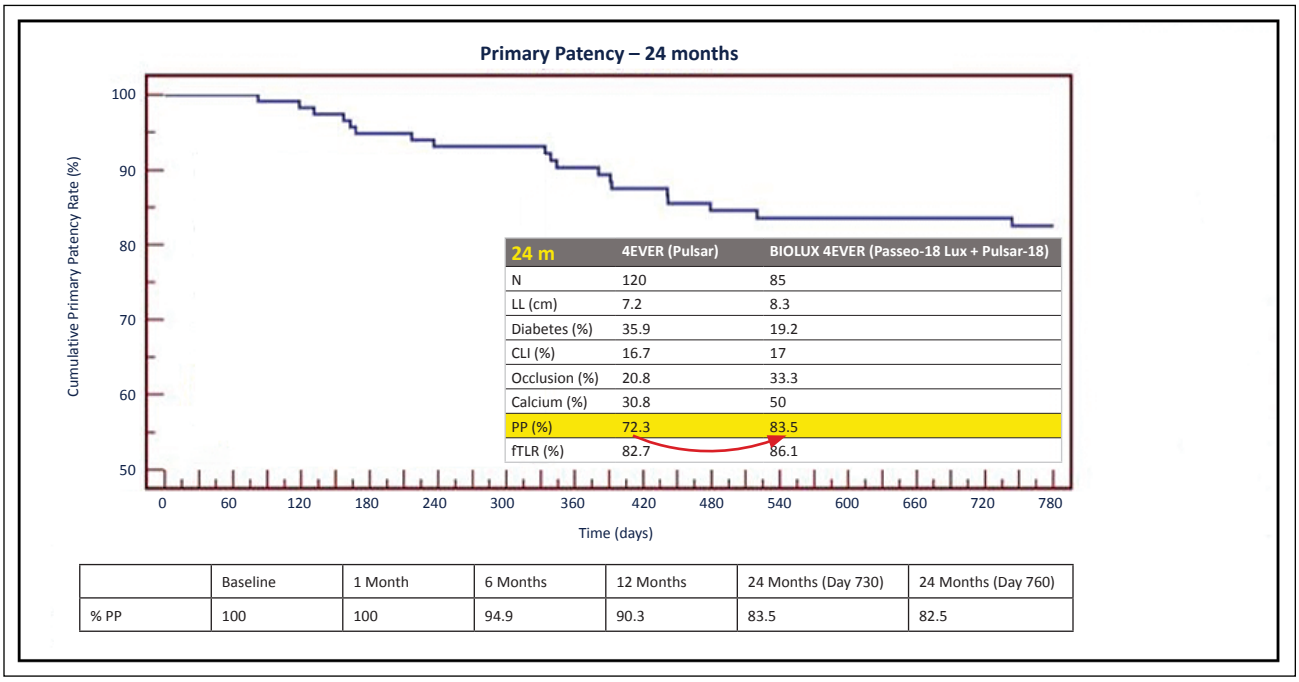


Figure 2. Combined thin strut and narrow width showing that the smallest section of vessel wall around the stent struts receives no direct paclitaxel (PTX) (A). Thinner and narrower struts provide a larger area for PTX contact with the vessel wall (B).

*Not in the Passeo-18 Lux Instructions for Use.



	Baseline	1 Month	6 Months	12 Months	24 Months (Day 730)	24 Months (Day 760)
% PP	100	100	94.9	90.3	83.5	82.5

Figure 3. The 2-year patency results of the BIOLUX 4EVER study compared with those in the 4EVER data.

with 32 (62.7%) chronic total occlusions. All lesions were treated successfully. The mean lesion length was 200 ± 74.55 mm (95% confidence interval [CI], 167.09–208.01 mm) with a mean number of stents per limb of 1.57 ± 0.7 (95% CI, 1.37–1.76). Distal embolization occurred in two patients. The primary patency rates at the 12- and 24-month follow-up were 94.1% (95% CI, 82.9%–98.1%) and 88.2% (95% CI, 75.7%–94.5%), respectively. The assisted primary patency was 94.1% (95% CI, 82.9%–98.1%), and secondary patency was 96.1% (95% CI, 85.2%–99%) at 24-month follow-up. The freedom from clinically driven TLR rate was 94.1% (95% CI, 82.9% – 98.1%) at 12-month follow-up and 88.2% (95% CI, 75.7%–94.5%) at 24-month follow-up, with two patients requiring a bypass graft. The freedom from TLR rate was similar in longer and shorter lesions: 93.7% (95% CI, 63.2%–99.1%) for lesions shorter than 120 mm versus 85.7% (95% CI, 69%–93.8%) for lesions longer than 120 mm at 24-month follow-up. The stent fracture rate at 12-month follow-up was only 2%, and the cumulative stent fracture rate at the 24-month follow-up was 9.8% (but it was only in one case that stent frature was associated with an impact on the clinical outcome).[23]

The BIOLUX 4EVER trial offers another good example of this "combination" concept. This prospective, multicenter, nonrandomized study enrolled 120 patients in five Belgian centers. Predilatation with the Passeo-18 Lux drug-releasing balloon (Biotronik) followed by implantation of the Pulsar-18 stent (Biotronik) was performed. Approximately 20% of the enrolled patients were diabetic. The mean lesion length was 83.3 mm, and 33% were occlusions. The primary patency rate at 12-month follow-up was 89.9%, and the freedom from TLR at 1 year was 93.6%. Preliminary results at 2-year follow-up were presented at Charing Cross this year and showed a primary patency rate of 83.5% and freedom from TLR rate of 86.1%.[24]

When numerically comparing the results from DEBAS with those of the BIOLUX 4EVER and 4EVER trials[25]—where only the same self-expanding Pulsar 18 stent was used—improved primary patency (by 13% and 8%, respectively) was observed, with sustained benefits at 24 months (by 11%), suggesting a trend for positive effect of paclitaxel from the use of Passeo-18 Lux (Figure 3).

RESPONSE-ADAPTED COMBINATION THERAPY

The strategy of the BIOLUX 4EVER trial (in contrast with the DEBAS approach), where dilatation of the lesion is initially performed by a DCB, followed by scaffolding with a bare-metal stent, allows implementation of the ALARAS principle. This is the basis for REsponse Adapted Combination Therapy (REACT): after extensive vessel preparation (POBA, debulking, etc), the lesion is dilated with a DCB, and a scaffolding stent is implanted when necessary.

Unfortunately, the previous "when necessary" description remains a major unsolved challenge. To optimally apply

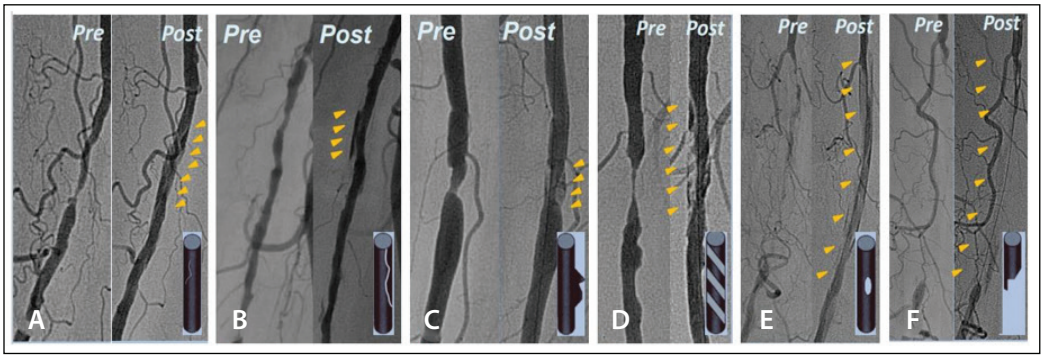


Figure 4. Grading A to F dissections in the SFA, where A to C seem to be minor flow-limiting dissections, and D to F are serious flow-limiting dissections. Reprinted with permission from Fujihara M, Takahara M, Sasaki S, et al. Angiographic dissection patterns and patency outcomes after balloon angioplasty for superficial femoral artery disease. J Endovasc Ther. 2017;24:367-375.[27]

the ALARAS principle and the REACT strategy, it is necessary to clearly identify when and where, as well as which scaffold is indicated. Angiographic images, even with additional projections, are sometimes insufficient to clearly determine if a dissection needs a scaffold. Currently, there is no angiographic definition or validated method for grading of dissection in the peripheral arteries. Although it has been widely used, the classification developed by the National Heart, Lung, and Blood Institute to grade coronary artery dissection as A to F based on angiographic appearance is often difficult to extrapolate to peripheral arteries.[26] Fujihara et al tried to create a modified version, but it was artificial, subjective, and based on a single angiographic anteroposterior view.[27] Evaluation of additional values using several adjunctive procedural assessments with standard angiography is required (Figure 4).

At present, adequate flow dynamic and functional measurement guidelines are lacking.

The classic, easy, and inexpensive duplex ultrasound technique can be used intraoperatively as an adjunctive method to angiographically identify dissections, flow patterns, systolic velocities, and complications.

Intravascular ultrasound (IVUS) and optical coherence tomography use either a transducer or a fiber attached to a catheter to generate ultrasound waves or infrared light, respectively, and produce a 360° cross-sectional view of the vessel. They can be performed during the procedure for morphologic assessment adjunctive to angiography and intra-arterial pressure measurement to identify dissections. Of course, these techniques require experience and dedicated protocols, and criteria need to be developed for peripheral applications.

Another potential assessment method is intra-arterial pressure (gradient) measurement using a pressure guidewire. After calibration, the pressure wire is positioned distally with respect to the most distal angioplasty area and then slowly pulled back to the more proximal position. In addition, measurements in the proximal pre-angioplasty area are performed. Thus, it is feasible to determine the mean pressure gradient, defined as the difference between the mean pressure in the healthy area distal to the lesion and the mean proximal pre-lesion pressure.

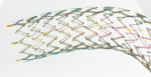
Although there is a lack of experience in peripheral arteries, this technique is of great help in guiding the operator through definitive treatments in the coronary arteries.

Economic drawbacks will probably limit widespread use of these technologies, but more insights and potential correlations with other, less costly methods could be offered in study settings.

To address the above issues, a global, multicenter, prospective pilot study, the BIOTRONIK REACT trial, was developed. The purpose of the study is to examine the incremental value of several procedural assessments adjunctive to standard angiography for use in identifying flow-limiting dissection and residual stenosis, and to better inform the operator about the stent requirement. In addition, the study will evaluate the safety and efficacy of the REACT algorithm with the Passeo-18 Lux DCB and Pulsar-18 self-expanding stent for the treatment of de novo or restenotic lesions in the superficial femoral and/or proximal popliteal arteries.

The following techniques will be evaluated: procedural duplex ultrasound and intra-arterial pressure measurement alone or in combination with IVUS.

The primary objective of the study is to evaluate the diagnostic performance of intraprocedural duplex ultrasound added to angiography. As a secondary diagnostic endpoint, the performance of intra-arterial pressure measurement, with or without IVUS, will be assessed for sensitivity and specificity for translesion pressure gradients, peripheral fractional flow reserve, dissection characteristics, and new categorization of peripheral dissections.



Additionally, procedural endpoints will be measured using the REACT approach: technical success rates, stent length, and the ability to reduce the length and number of stents (ALARAS), using additional diagnostic tools.

CONCLUSION

The REACT trial aims at refining ALARAS in the treatment of challenging SFA disease by blocking the prolonged restenotic cascade, avoiding the use of nonfunctional metal implants, and appropriately applying scaffolds based on objective, flow dynamic criteria, while being guided by vessel response. ■

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Assessing the Economic Impact of Peripheral Interventions

The difficulties in weighing cost-effectiveness in treatment algorithms remain.

BY YANN GOUËFFIC, MD, PHD, AND VALÉRY-PIERRE RICHE

Algorithms for the endovascular treatment of femoropopliteal lesions still suffer from a lack of head-to-head comparison between devices. In 2014, Katsanos et al reported a meta-analysis that compared balloon angioplasty against drug-coated balloons (DCBs), drug-eluting stents (DESs), covered stents, and bare-metal stents; all investigated treatments showed reduced restenosis rates and target lesion revascularization against standard balloon angioplasty, with DCBs and DESs as the most efficient.[1]

Bailout stenting rates vary considerably across DCB studies. In randomized controlled trials such as BIOLUX P-I, IN.PACT SFA, LEVANT 2, or ILLUMENATE, bailout stenting ranged from 2.5% to 7.3%.[2-5] In all-comer registries such as BIOLUX P-III, ILLUMENATE Global, LUTONIX Global SFA registry, and IN.PACT Global, the bailout stenting rates range from 15% to 25.2%.[6-9]

Although drug-eluting therapies such as DESs or DCBs appear as a promising strategy to treat femoropopliteal lesions, few data are available to assess the impact of these devices on health care expenditure.

HEALTH CARE EXPENDITURE ASSESSMENT

Health care costs continue to escalate, with innovation often increasing the overall cost of treating patients, while hospital budgets are under pressure to reduce hospital stays and treatment cost. Cost utility or effectiveness analyses are needed to compare the costs and outcomes of different medical strategies during a defined time. For instance, cost utility analysis evaluates outcomes of an intervention in terms of the quality and the quantity of life lived, or quality-adjusted life-years (QALYs). A QALY of 0 is death, and a QALY of 1 equates to 1 year in perfect health.

The most common option for assessing quality of life in patients with peripheral artery disease is the EuroQol 5-dimensions questionnaire (EQ-5D), a standardized instrument for measuring generic health status focusing on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D is available in 171 languages; however, the questionnaire lacks specificity. For this reason, other questionnaires have been developed for patients with peripheral artery disease, such as the Walking Impairment Questionnaire (WIQ). The WIQ assesses self-reported walking capacity for claudicants and includes subscales for walking distance, speed, and stair climbing. It is widely used and validated as a self-administrated tool; however, it is not validated in all countries and could be relatively complex to use for some patients. Some authors believe that the overall WIQ score only moderately correlates with mean walking distance, even after correction.[10]

The incremental cost-effectiveness ratio (ICER) is an economic evaluation comparing two medical strategies by calculating the cost differential divided by the differential of outcomes (Figure 1). A four-part cost-effectiveness plan diagram helps visualize an ICER by highlighting whether a treatment is worth pursuing when the cost and outcomes are balanced (Figure 2). The best scenario includes a less expensive and more effective medical strategy compared to the current alternative treatment.[11]

$$\text{ICER} = \frac{\text{COST 1} - \text{COST 2}}{\text{QALYs 1} - \text{QALYs 2}}$$

$$\text{ICER} = \frac{\text{COST 1} - \text{COST 2}}{\text{Patency 1} - \text{Patency 2}}$$

Figure 1. The ICER compares cost-effectiveness of two treatments by dividing the cost differential by the outcome differential (eg, QALY, patency, etc).

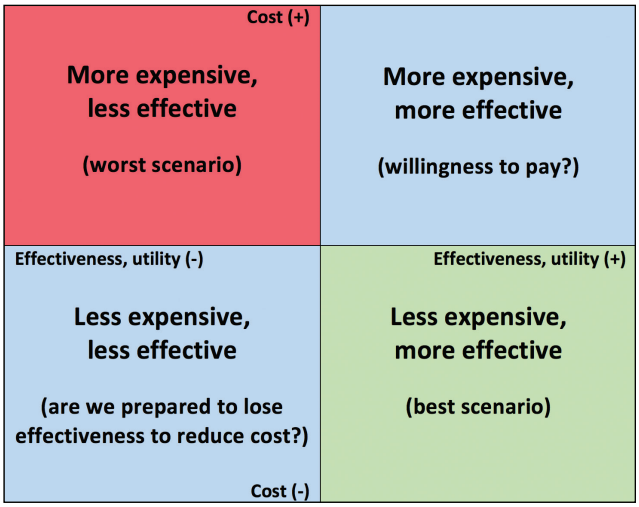

Figure 2. Visualization of an ICER with a cost-effectiveness plan diagram.

REACT APPROACH

The BIOTRONIK REsponse Adapted Combination Therapy (REACT) treatment algorithm begins with a predilatation of the target lesion with standard balloon angioplasty, followed by the Passeo-18 Lux DCB (Biotronik). Angiography is then performed in at least two planes to assess the DCB's technical success (Figure 3). If residual stenosis (> 30%) or a flow-limiting dissection are present and persist after prolonged inflation of the DCB (≥ 5 minutes), stenting of the lesion will be performed, where needed, with the Pulsar-18 bare-metal stent (Biotronik).

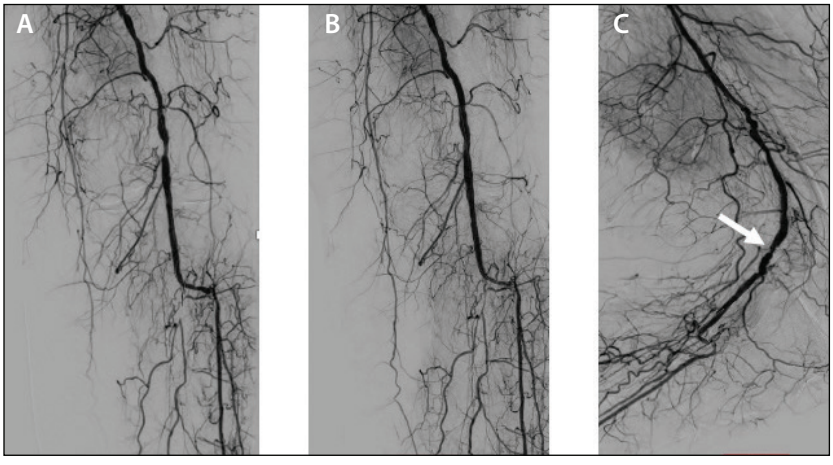

Figure 3. An 83-year-old woman underwent successful vessel preparation (A) before being treated with a DCB for a popliteal lesion. In a first angiogram assessment (B), the morphologic result seemed correct, but a second angiogram assessment at a 45° angulated view showed a residual stenosis > 30% (C), demonstrating the importance of assessing outcomes on at least two planes.

The REACT treatment concept aims to minimize metal burden and the associated foreign body reaction, risk of stent fracture, and possibility of an inhomogeneous drug transfer to the arterial wall due to DES malapposition, as well as maintaining opportunities for subsequent reintervention later. On the other hand, stenting—whether it is focal or not—increases procedural cost due to the combined use of DCBs and stents.

Angiography, even with additional projections, is sometimes insufficient to clearly determine if a dissection is flow-limiting and whether subsequent stenting is needed. There is currently no definition nor validated method to define flow-limiting dissection for peripheral arteries. For this reason, adjunctive procedural assessments (eg, intravascular ultrasound) could be used to assess DCB morphologic intraoperative results. Of course, the incremental use of several adjunctive procedural assessments could increase time and cost procedure and therefore alter health care expenditure. However, the potential increase of the procedure cost and time must be balanced with a presumed reduced usage of stents, as well as the cost and poor outcome of reintervention for in-stent restenosis.

BIOREACT PILOT STUDY

The main objective of the BIOREACT pilot study (NCT03547986) is to assess the incremental value of several intraoperative diagnostic methods (procedural duplex ultrasound, intra-arterial pressure measurement alone or associated with intravascular ultrasound, optical coherence tomography, and quantitative vascular angiography) added to biplanar angiography to identify flow-limiting dissections. As a secondary objective, BIOREACT will identify valuable health care costs of adjunctive procedural assessments. The protocol is based on the REACT approach, and EQ-5D and WIQ will be used to define the QALYs and help characterize the health economic aspect of the REACT approach.

CONCLUSION

It is not yet known which treatment strategy for peripheral intervention has the best cost-effectiveness profile. Additional intraoperative assessments may be a key benefit in identifying the proper treatment protocol on a case-by-case basis, saving valuable costs long term by reducing subsequent

reinterventions or making reinterventions less burdensome. ■

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Disclosures: Receives grants/research support from Abbott Vascular, Bard Peripheral Vascular, Medtronic, Terumo Interventional Systems, and Spectranetics, a Philips company; receives honoraria and travel support from Abbott Vascular, Bard Peripheral Vascular, Boston Scientific Corporation, Cook Medical, Medtronic, Vycon, Terumo Interventional Systems, and Spectranetics, a Philips company.

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Disclosures: None.

REACT

REsponse **A**dapted **C**ombination **T**herapy

Passeo-18 Lux and Pulsar-18: excellent 24-month clinical outcomes, proven individually[1,2] and in combination.[3,4*]

Individually:

Passeo-18 Lux
91.7%[1]
Freedom from CD-TLR

BIOLUX P-III

Pulsar-18
92.4%[2]
Freedom from CD-TLR

BIOFLEX PEACE

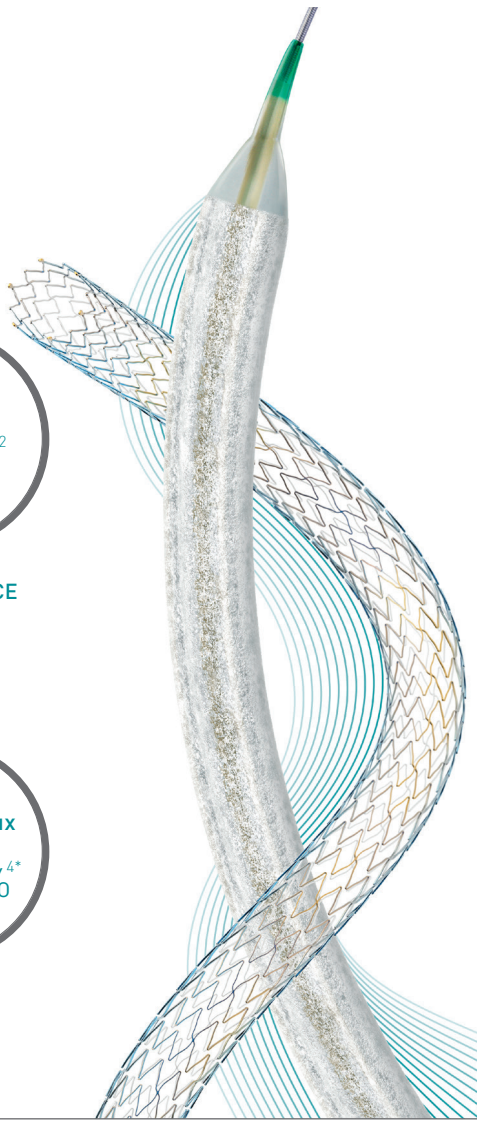
In combination:

Passeo-18 Lux + Pulsar-18
86.1%[3]
Freedom from TLR

BIOLUX 4EVER

Pulsar-18 + Passeo-18 Lux
88.0%[4*]
Freedom from CD-TLR

DEBAS



Passeo-18 Lux
Drug-Coated Balloon

- Clinically proven[5]
- For challenging patient groups
- Effective drug delivery[6**]

Pulsar-18
Self-Expanding Stent

- Clinically proven[7]
- Thin struts
- Low COF

Above presented numbers represent 24-month results.

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* The use of Passeo-18 Lux for post-dilatation is not within the indication for the product.
**Drug retention while in transit to the lesion and prolonged paclitaxel presence in the vessel wall.

Freedom from TLR = Freedom from Target Lesion Revascularization; Freedom from CD-TLR = Freedom from Clinically Driven Target Lesion Revascularization.

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