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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.

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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]

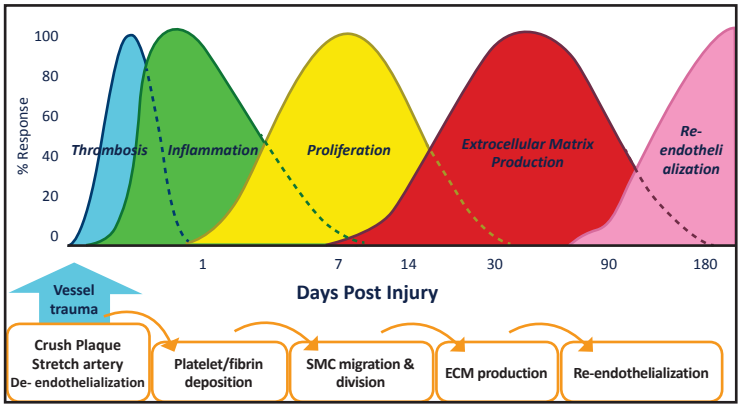


Figure 1. The restenotic cascade following vessel injury.

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%),

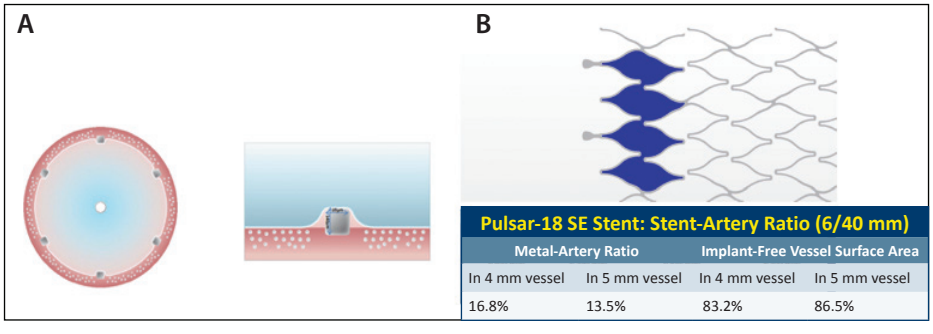
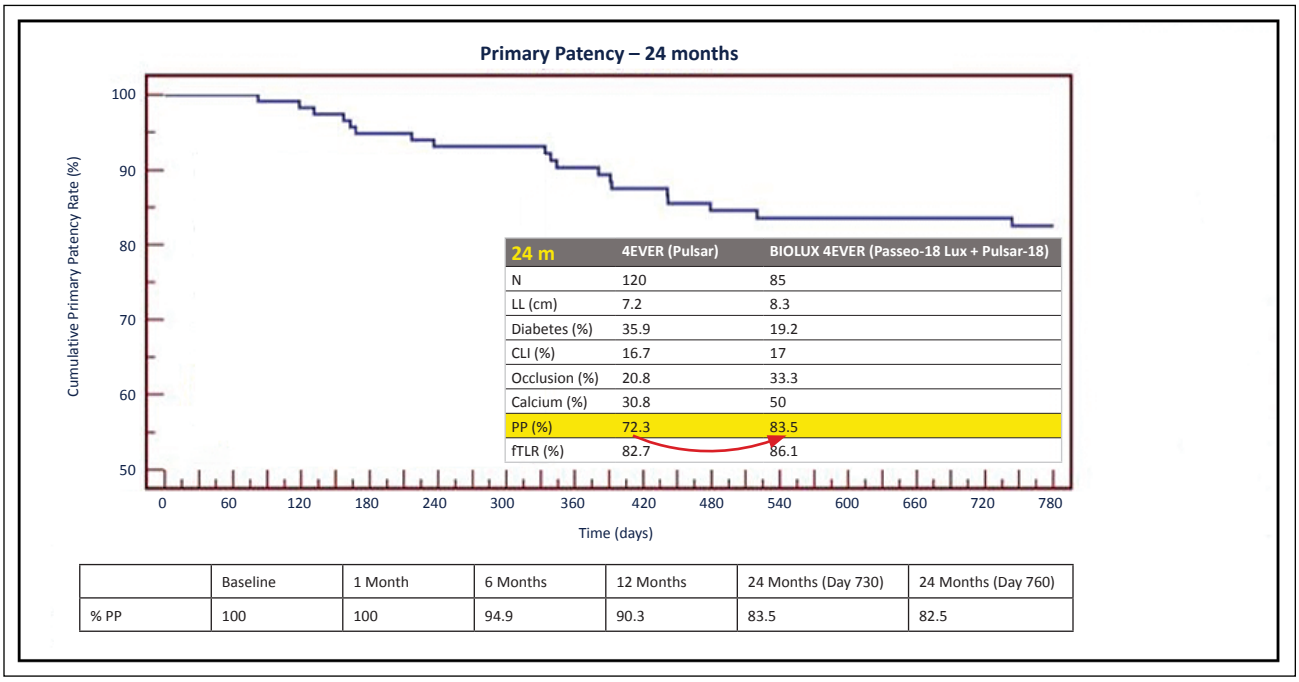


Figure 2. Combined thin strut and narrow width showing that the smallest section of vessel wall around the stent struts receives no direct paclitaxel (PTX) (A). Thinner and narrower struts provide a larger area for PTX contact with the vessel wall (B).

*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

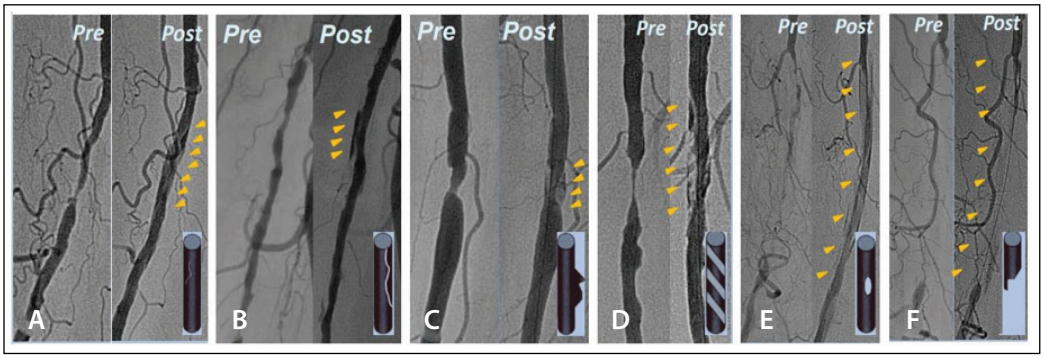


Figure 4. Grading A to F dissections in the SFA, where A to C seem to be minor flow-limiting dissections, and D to F are serious flow-limiting dissections. Reprinted with permission from Fujihara M, Takahara M, Sasaki S, et al. Angiographic dissection patterns and patency outcomes after balloon angioplasty 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.

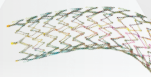
Although there is a lack of experience in peripheral arteries, this technique is of great help in guiding the operator through definitive treatments in the coronary arteries.

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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