Drug-Coated Balloons: Hope or Hype?

A stentless technology is an attractive option if it achieves acute and long-term results that are at least comparable to current devices in the femoropoliteal anatomy.

BY THOMAS ZELLER, MD

Peripheral arterial disease is a common and devastating manifestation of systemic atherosclerosis. Despite an initial technical success rate of higher than 95% for percutaneous transluminal angioplasty to recanalize the superficial femoral artery (SFA) using dedicated crossing and reentry devices,[1,2] recanalization procedures are limited by restenosis rates of 40% to 80% in the treated segments after 6 to 12 months.[3,4] At the level of the pelvic arteries, balloon-expandable stents or self-expanding nitinol stents are used with excellent acute and longer-term revascularization rates.[5] However, despite being more effective than balloon angioplasty for preventing restenosis, the benefit of nitinol stenting in infrainguinal vessels is only fair, with 1-year restenosis rates still being in the range of 20% to 50% depending on and increasing with lesion length.[4,6,7] These rates are even higher in diabetic patients.[8] Recently published and presented studies investigating drug-eluting devices—balloons and stents—have shown a substantial improvement in the durability of endovascular treatment for femoropopliteal vessels.[9-11]

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MODE OF ACTION

Late thrombotic complications due to delayed and incomplete endothelialization of the stent struts have called the long-term safety of drug-eluting stents (DES) into question. Incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES, especially those used for femoropopliteal lesions due to larger stent strut distances.

New concepts to overcome the limitations of DES should avoid the need for sustained drug release from stent struts to allow for earlier endothelialization and vessel wall healing after the angioplasty trauma. Paclitaxel blocks proper microtubal formation and inhibits smooth muscle cell division and migration. Moreover, it inhibits inflammatory responses by suppressing excretion of growth factors, such as platelet-derived growth factor, which mediates vascular smooth muscle cell migration to the intima. Paclitaxel inhibits extracellular matrix secretion and breakdown. However, paclitaxel does not inhibit endothelial cells.

PRECLINICAL TRIALS

Preclinical studies, including cell culture experiments[12] and the porcine coronary overstretch model,[13] showed that short exposure to paclitaxel can result in prolonged inhibition of cell proliferation and neointimal hyperplasia, provided that the drug reaches the vessel wall in a sufficient concentration. Because paclitaxel is a lipophilic drug that would not penetrate the vessel wall in a sufficient concentration, the drug has to be combined with a hydrophilic spacer, such as iopromide (Paccocath or Cotavance, Bayer Radiology & Interventional, Indianola, PA), urea (FreePac, Medtronic, Inc., Minneapolis, MN), butyryl-trihexyl citrate (Paseo-18 Lux, Biotronik, Lake Oswego, OR), or shellac (Freeway, Eurocor, Bonn, Germany). The hydro-

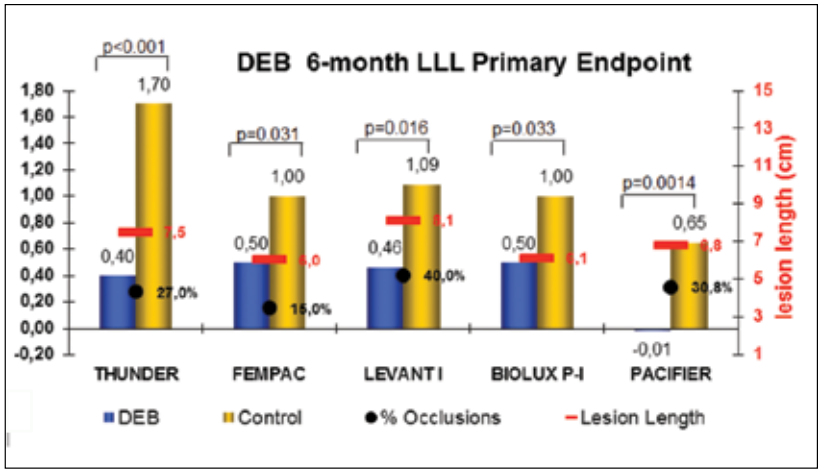

Figure 1. Late lumen loss at 6 months comparing the THUNDER, FemPac, LEVANT I, and PACIFIER trials. LLL, late lumen loss.

philic spacer creates a porous coating with a high-contact surface between the lipophilic drug molecules and the vessel wall. This leads to a uniform and almost complete release of the target drug dose after one balloon expansion, which guarantees a high bioavailability of paclitaxel on the target side for rapid drug absorption by the vessel wall.

The finding of effective inhibition of neointimal formation using paclitaxel-coated balloons in the porcine model of coronary overstretch was confirmed in both first-in-man clinical trials (PACCOCATH-ISR I and PACCOCATH-ISR II) assessing the safety and efficacy of this device in coronary in-stent restenosis.[14]

Except the Moxy balloon (Lutonix, acquired by Bard Peripheral Vascular, Inc., Tempe, AZ) (2 µg/mm^2), all current CE Mark-certified drug-coated balloons (DCBs) in Europe are standard angioplasty balloons coated with paclitaxel at a dose of 3 µg/mm^2 of balloon surface in a specific matrix coating.

Albrecht et al[15] investigated whether the preclinical coronary data on the efficacy of DCBs could be translated to peripheral arteries. In the porcine model, stenosis in stented segments of the SFA was significantly reduced by local short-term administration of paclitaxel delivered via balloon or in a contrast medium during balloon angioplasty and stent implantation.

EUROPEAN CLINICAL TRIAL RESULTS

The THUNDER trial[10] was a randomized, controlled, multicenter study comparing Paccocath paclitaxel-coated and conventional uncoated balloon catheters with respect to efficacy and tolerance in inhibiting restenosis. In this trial, a total of 154 patients with stenosis or occlusion of the superficial femoral or popliteal arteries was enrolled. Patients were treated with an uncoated balloon (control group), a Paccocath balloon (approximately 3 µg/mm^2 of paclitaxel), or an uncoated balloon and paclitaxel dissolved in the contrast medium (eg, Ultravist, Bayer Radiology & Interventional; 17.1 mg paclitaxel in 100 mL).

The primary endpoint was late lumen loss of vessel segment at 6 months. At 6-month follow-up, treatment of patients with Paccocath balloons was found to be associated with significant reductions in late lumen loss compared to patients of the control group or patients treated with paclitaxel dissolved in the contrast medium (Figure 1). Importantly, the rate of target lesion revascularization at 6, 12, and 24 months after intervention remained significantly lower in the Paccocath group compared with both other groups. Only 4% of the patients in the Paccocath group received additional stents (vs 22% in the control group). No increase in thrombotic or embolic events was observed in the Paccocath group.

In the FemPac trial,[11] 87 patients were randomly assigned to treatment with either standard balloon angioplasty or the Paccocath balloon. Forty-two patients were allocated to the control group, and 45 patients were allocated to the Paccocath group. At 6-month follow-up, patients who had been treated with the Paccocath balloon had significantly reduced late lumen loss compared with the control subjects. The difference between both treatment groups was maintained at 18 to 24 months after intervention. Patients in the DCB group showed improvement in Rutherford class, but there was no difference in the improvement of ankle-brachial index. Nine percent of the patients in the Paccocath group versus 14% in the control group required additional stent implantation in the target lesion. The FemPac trial confirmed the results of the THUNDER trial, demonstrating that short-term exposure of injured peripheral arteries to paclitaxel may be sufficient to inhibit restenosis.

The LEVANT I trial[16] enrolled 101 patients with de novo lesions that had to be predilated with an undersized balloon. If predilatation was successful, the patients were randomized to treatment with either a paclitaxel-coated Moxy balloon (drug dose approximately 2 µg/mm^2 paclitaxel; n = 37) or a standard balloon (control group; n = 38) sized according to the ref-

TABLE 1. LEVANT I TRIAL 6-MONTH OUTCOMES			
6-month angiographic follow-up (entire cohort)	POBA (n = 35)	Moxy (n = 39)	*P* Value
Late lumen loss, mm	1.09	0.46	.016
Freedom from TLR and > 50% restenosis, %	49	72	NS
6-month angiographic follow-up (balloon group)	POBA (n = 24)	Moxy (n = 31)	NS
Late lumen loss, mm	1.19	0.45	NS
Freedom from TLR and > 50% restenosis, %	42	71	NS
6-month angiographic follow-up (stent group)	POBA (n = 11)	Moxy (n = 8)	NS
Late lumen loss, mm	0.9	0.49	NS
Freedom from TLR and > 50% restenosis, %	64	75	NS
Abbreviations: NS, not significant; TLR, target lesion revascularization.			

erence vessel diameter. Patients with insufficient results after predilatation received a stent and were then randomized for postdilatation using either a Moxy balloon (n = 12) or a standard balloon (n = 14). The primary endpoint was angiographic late lumen loss at 6-month follow-up. In patients observed at 6-month follow-up, late lumen loss and target lesion revascularization rates were significantly reduced in the Moxy group (Table 1).

The PACIFIER study enrolled 91 patients with lesion lengths ranging from 3 to 30 cm (mean, 7 cm) who were randomized to be treated either with a paclitaxel-coated In.Pact Pacific balloon (Medtronic, Inc.) (n = 44) or standard balloon angioplasty with provisional stenting (n = 47). Stent rates were 21% and 34%, respectively. The primary endpoint was angiographic late lumen loss at 6 months, with a significantly better outcome for the DCB cohort (-0.01 mm vs 0.65 mm; *P* = .0014).[17] Binary restenosis rates were 8.6% and 32.4% (*P* = .01), respectively. Figure 1 shows the 6-month late lumen loss outcomes of the THUNDER, FemPac, LEVANT I, and PACIFIER trials.

The BIOLUX PI trial included 68 patients with lesion lengths of 3 to 200 mm (mean, 61 mm) who were randomized to either a DCB cohort (n = 33) or a plain old balloon angioplasty (POBA) cohort (n = 35). The DCB consisted of a mixture of paclitaxel (3 µg/mm^2) and an excipient (butyryl-trihexyl citrate), which keeps the paclitaxel in a microcristalline structure and degrades to citric acid and alcohol. At 6 months, angiographic binary restenosis rates were 11.5% versus 34.6% (*P* = .048), and late lumen loss was 0.6 mm versus 1.1 mm (*P* =.038) for the DCB and POBA cohorts, respectively.[18]

A meta-analysis of the 6-month results of the THUNDER, FemPac, LEVANT I, and PACIFIER trials resulted in an absolute risk reduction for restenosis for DCBs of 26.7% and for target lesion revascularization of 25.5%, respectively.[19]

An Italian multicenter registry included 105 patients with femoropopliteal lesions, with up to 15-cm lesion lengths and a mean lesion length of 76.3 ± 38.3 mm. Provisional stenting was indicated in 12% of the cases. The duplex-derived 1-year primary patency rate was 83.7%, and the 1-year target lesion revascularization rate was 8.7%. A significant improvement of quality of life and the absolute walking distance (from 111 to 361 m) was reported.[20]

Cioppa et al presented their preliminary 1-year outcomes for the treatment of calcified lesions with directional atherectomy followed by DCB angioplasty. The duplex-derived 1-year restenosis rate (peak systolic velocity > 2.5) was 10%.[21]

ONGOING EUROPEAN TRIALS

A wide range of multicenter controlled trials is still ongoing, with a focus on native femoropopliteal lesions (FREERIDE, ADVANCE 18 PTX, ISAR-STATH, etc.). Several trials are investigating the performance of DCBs for specific indications such as in-stent restenosis (FAIR, COPA CABANA, ISAR-PEBIS) or as an adjunct to plaque removal (DEFINITIVE AR) in native arteries using directional atherectomy or for in-stent restenosis using photoablation with the excimer laser (PHOTOPAC). The FREEWAY trial is investigating the additive effect of postdilating bare-nitinol stents with DCBs.

ONGOING AND PLANNED US TRIALS

The LEVANT 2 international trial plans to enroll 476 patients with native femoropopliteal lesions in a ran-

domized controlled study design (2:1 randomization of a Moxy cohort vs a POBA cohort) and assess outcomes out to 5 years; enrollment was completed in July 2012. This randomized control trial will be followed by a large-scale, single-arm trial that will be enrolling more than 1,000 patients.

The INPACT SFA II trial will enroll patients in a 2:1 fashion into a prospective randomized controlled trial in the US comparing the In.Pact Admiral DCB (Medtronic, Inc.) with POBA; together with the European INPACT SFA I trial, approximately 450 patients will be enrolled. This trial will also be supplemented by a large-scale international single-arm study.

SUMMARY

Paclitaxel-coated balloons—independent from their excipients as currently shown in five European trials—substantially improve technical and clinical midterm results of angioplasty compared to POBA and are in the range of the Zilver PTX trials[9,22] and the best bare-metal nitinol stent trial results.[7] The key advantage of DCB treatment is avoiding implants. As a result, dual-antiplatelet therapy is only indicated for 1 month, if ever. DCB angioplasty is a relatively fast procedure and potentially repeatable many times. Plaque modulation or plaque removal before DCB angioplasty might further improve longer-term outcomes. Thus, DCBs are a real hope and not hype! ■

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