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Drug-Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery

The DEBATE-SFA Randomized Trial (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery)

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Objectives This study sought to compare paclitaxel-eluting balloon (PEB) with conventional percutaneous transluminal angioplasty (PTA), followed by systematic implantation of a self-expanding nitinol bare-metal stent (BMS) in patients at risk for restenosis.

Background PTA is an effective strategy for treating atherosclerosis of the femoropopliteal axis (FPA). Whereas PEB have shown advantage over uncoated balloons in the treatment of simple lesions, it is unknown whether these results are applicable to complex degrees of FPA atheroma.

Methods A total of 104 patients (110 FPA lesions in 110 limbs) were randomly assigned to either PEB + BMS or PTA + BMS. The primary endpoint was 12-month binary restenosis. Secondary endpoints were freedom from target lesion revascularization and major amputation. Post hoc subanalyses were performed for the comparison of long (≥100 mm) versus short lesions and true lumen versus subintimal approach.

Results Mean lesion length was 94 ± 60 versus 96 ± 69 mm in the PEB + BMS and PTA + BMS groups ($p = 0.8$), respectively. The primary endpoint occurred in 9 (17%) versus 26 (47.3%) of lesions in the PEB + BMS and PTA + BMS groups ($p = 0.008$), respectively. A near-significant ($p = 0.07$) 1-year freedom from target lesion revascularization advantage was observed in the PEB + BMS group. No major amputation occurred. No significant difference was observed according to lesion characteristics or technical approach.

Conclusions Pre-dilation with PEB angioplasty prior to BMS implantation, as compared to PTA + BMS in complex FPA lesions, reduces restenosis and target lesion revascularization at 12-month follow-up. Restenosis reduction is maintained irrespective of lesion length and recanalization technique. (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery [DEBATE-SFA]; NCT01556542) (J Am Coll Cardiol Intv 2013;6:1295–302) © 2013 by the American College of Cardiology Foundation

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Endovascular intervention is considered the treatment of choice for peripheral artery disease of variable severity (1). In particular, percutaneous transluminal angioplasty (PTA), frequently followed by stent implantation (2), is used for treating, with high initial success rate, the challenging atherosclerosis of the femoropopliteal axis (FPA), often characterized by long, calcific total occlusions (2–5). The main drawback of this strategy, however, is its unacceptable restenosis rate, ranging from 40% to 60% at 12 months (6). Different from the coronary vasculature, limus-based drug-eluting stents (DES) have failed to demonstrate sustained effectiveness in the FPA setting (7–9), whereas encouraging results have been reported for a paclitaxel-eluting polymer-free nitinol self-expanding DES (10). These findings have raised the question of whether the drug itself, the polymer coating, or the stent platform is the key to long-term success in the FPA.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CLI = critical limb ischemia
DAPT = dual antiplatelet therapy
DEB = drug-eluting balloon(s)
DES = drug-eluting stent(s)
DUS = duplex ultrasonography
FPA = femoropopliteal axis
ISR = in-stent restenosis
LLL = late lumen loss
PEB = paclitaxel-eluting balloon(s)
PTA = percutaneous transluminal angioplasty
TLR = target lesion revascularization(s)

Drug-eluting balloons (DEB), a treatment modality that allows homogeneous delivery of an antiproliferative drug (paclitaxel-eluting balloon [PEB]) to the vessel wall without leaving prosthetic material behind, are an effective strategy for treating FPA lesions (11–14). However, it is unknown whether these results might be applicable to relatively complex degrees of FPA atherosclerosis, which may require mechanical scaffolding to avoid elastic recoil and prevent occlusive dissections (15). Therefore, in this setting, the combination of DEB with stenting might be an important concept to explore as a treatment modality.

The aim of the DEBATE-SFA (Drug Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery) trial was to investigate the safety and efficacy of PEB angioplasty compared with pre-dilation with conventional uncoated balloon catheters before systematic implantation of a self-expanding nitinol stent in terms of reduction of restenosis in a population with FPA artery stenosis or occlusion.

Methods

Study design. The DEBATE-SFA trial was a prospective, single-center, randomized, parallel-group, open-label involving the blinded evaluation of endpoints trial (16). It was approved by the local ethics committee and was carried out in accordance with the Helsinki declaration. All patients provided written informed consent.

Patients. We prospectively enrolled 104 patients with 110 lesions in 110 limbs presenting with either intermittent claudication or critical limb ischemia (CLI), selected from 177 patients consecutively referred to the catheterization laboratory of our institution for peripheral angiography and percutaneous revascularization between November 2010 and November 2011. Eligible patients were older than 18 years. Angiographic inclusion criteria were: de novo stenosis $\geq$50% or occlusion of at least 40 mm in length located in the superficial femoral artery or popliteal artery; presence of a clear healthy segment between the lesion in the superficial femoral artery and common femoral artery and between the popliteal and tibioperoneal trunk; and presence of at least 1 patent tibial vessel with distal runoff (below-the-knee artery was considered patent if free from obstructive lesions determining angiographic stenosis >70%). Exclusion criteria were: life expectancy <1 year; contraindication for combined antiplatelet therapy; known allergy to nickel or paclitaxel; and need for major amputation at the time of enrollment. Failure to recanalize intended below-the-knee arteries in CLI patients at risk of major amputation was also considered an exclusion criterion. After enrollment and before angioplasty, lesions were randomly assigned 1:1 to undergo either PEB followed by nitinol bare-metal stent (BMS) implantation (PEB + BMS group) or standard PTA followed by nitinol stent implantation (PTA + BMS group) according to a computer-generated random series of numbers. Randomization was performed by block randomization (blocks of 10 patients).

In patients requiring bilateral FPA revascularization, the second limb was treated within 1 month from the first intervention.

Procedures. Angiography, angioplasty, and stent implantation were performed according to institutional standards. Vascular access was obtained through the common femoral artery, in either antegrade or retrograde fashion, according to anatomical characteristics and lesion location, using a 6-F sheath to achieve adequate support. All patients were administered an intra-arterial bolus of unfractionated heparin (70 to 100 U/kg). After diagnostic angiography, a conventional guidewire was advanced to cross the target lesion. Multilevel, multivessel, and bilateral interventions were allowed as clinically needed. Long diffuse lesions or multiple adjacent lesions were cumulatively considered and treated as a single target.

All lesions underwent pre-dilation with an uncoated balloon, undersized with respect to the vessel diameter. Thereafter, in patients randomized to PTA + BMS, a nitinol stent was implanted, whereas in the PEB + BMS group, further dilation of at least 120 s with a paclitaxel-coated balloon (In.Pact Admiral, Invatec/Medtronic, Santa Rosa, California), maintaining a vessel/balloon diameter ratio of 1:1 preceded nitinol stent implantation. Size and length of PEB were chosen, referring to a ruler placed

behind the patient's leg; sizing was 1:1 to the reference vessel diameter. All stents in both groups were post-dilated with conventional balloon, maintaining a vessel/balloon diameter ratio of 1:1.

The In.Pact system features the balloon with FreePac, a proprietary, natural coating. The hydrophilic spacer, necessary to separate paclitaxel molecules and facilitate drug elution into the arterial wall, is urea. This technology is able to release the majority of the drug within the first 30 s. The paclitaxel concentration is 3 $\mu g/mm^2$ and the total drug load depends on both size and length of the balloon (17).

PEB was inflated from 10 mm proximal to 10 mm distal to the target lesion; in lesions requiring >1 balloon, a 5-mm balloon overlap was allowed to obtain a uniform drug elution in the treated vessel. Self-expanding nitinol stents (Maris, Invatec/Medtronic) were then implanted in all lesions. The stent dimensions were chosen such that the nominal diameter exceeded the reference vessel diameter by 1 mm and the length exceeded the lesion length by about 5 mm proximal and distal in order to stay within the pre-dilation area. Deployment of a second stent was allowed in cases where 1 stent did not cover the entire lesion, was positioned incorrectly, or a dissection extended beyond the stent margins. In this case, further pre-dilation with DEB was always performed to ensure complete drug coverage of the stented segment. Technical success was defined as residual stenosis <30% by visual estimation. Procedural success was defined as achievement of technical success without complications. Femoral sheaths were removed when activated clotting time was <150 s, achieving access site hemostasis by manual compression in all patients. All patients received dual antiplatelet therapy ([DAPT] aspirin 100 mg/day plus clopidogrel 75 mg/day). Patients not already taking clopidogrel or aspirin were administered a loading dose of 300 mg of each drug at least 12 h before the procedure. Aspirin was then continued indefinitely, whereas clopidogrel was continued for 1 month and 3 months, respectively, in PTA + BMS and PEB + BMS groups.

Follow-up. Post-operative evaluation was deferred to physicians who were unaware of the assigned intervention. At 12 months, target lesions were evaluated by repeat angiography; in the case of consent withdrawal for angiography or presence of severe renal impairment, a duplex ultrasonography (DUS) scan was performed. All target lesion revascularizations (TLR) were clinically driven and confirmed angiographically before treatment.

Endpoints and definitions. The outcome was documented with angiography. Before, immediately after the intervention, and 12 months later, angiography of the target vessel was performed in identical projections (2 orthogonal planes for each treated lesion). The target lesion was identified by an image of the vascular anatomy and specific landmarks

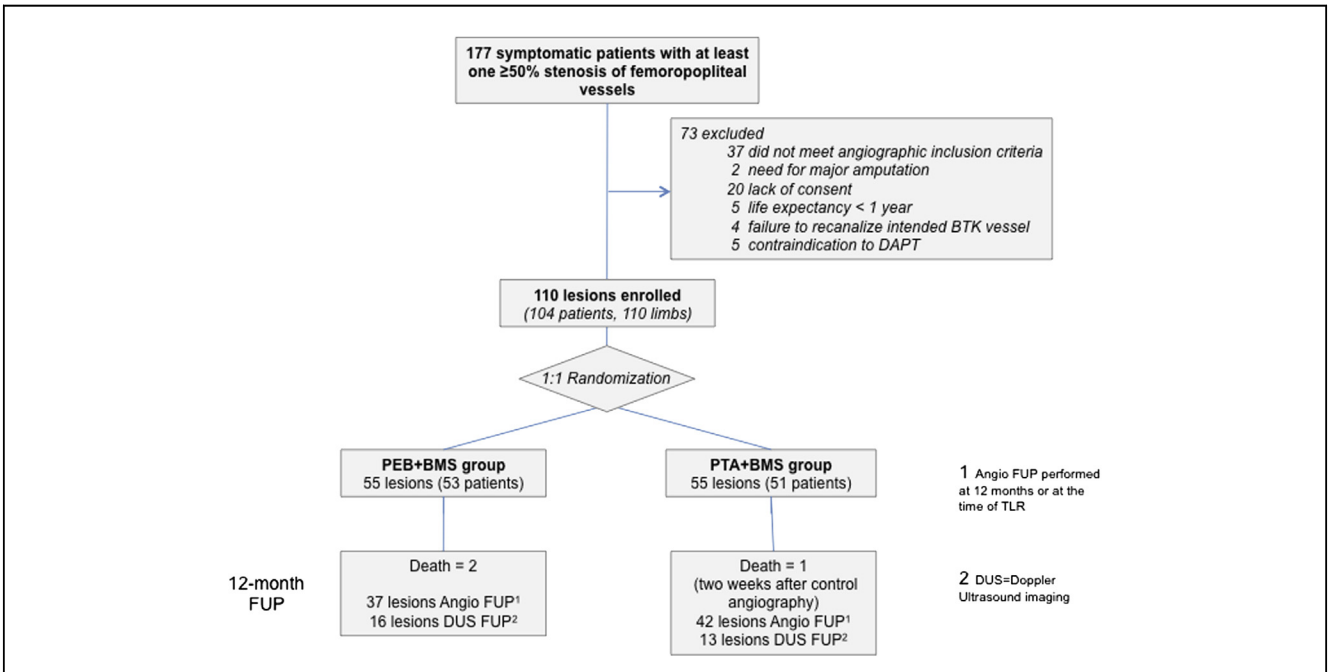

Figure 1. Study Flow

BMS = bare-metal stent(s); BTK = below-the-knee lesion; DAPT = dual antiplatelet therapy; DUS = duplex ultrasonography; FUP = follow-up; PEB = paclitaxel-eluting balloon; PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.

Table 1. Baseline Patient Demographics and Clinical Characteristics

	PEB + BMS (n = 53)	PTA + BMS (n = 51)	p Value
Age, yrs	74 ± 9	76 ± 8	0.2
Female	13 (24.5)	19 (37.3)	0.3
Diabetes	41(77.4)	36 (70.6)	0.5
Hypertension*	47 (88.7)	45 (88.2)	1
Dyslipidemia†	33 (62.3)	27 (52.9)	0.4
Smokers	25 (47.2)	28 (54.9)	0.4
Coronary artery disease	21 (39.6)	18 (35.3)	0.7
Cerebrovascular disease	11 (20.8)	9 (17.6)	0.8
Dialysis	5 (9.4)	3 (5.9)	0.7
Intermittent claudication	11 (20.8)	16 (31.4)	0.2
Critical limb ischemia	42 (79.2)	35 (68.6)	0.2
ABI	0.33 ± 0.22	0.31 ± 0.18	0.6
Rutherford class, %			
3	11 (20.8)	16 (31.4)	0.5
4	11 (20.8)	11 (21.6)	
5	29 (54.7)	21 (41.1)	
6	2 (3.7)	3 (5.9)	

Values are mean ± SD or % (n). *Hypertension was defined as serial blood pressure measurements >140/90 mm Hg. †Dyslipidemia was defined as history of increased low-density lipoprotein, triglycerides, and/or low high-density lipoprotein or use of lipid-lowering agents.

ABI = ankle-brachial index; BMS = bare-metal stent; PEB = paclitaxel-eluting balloon; PTA = percutaneous transluminal angioplasty.

Table 2. Baseline Lesion Characteristics

	PEB + BMS (n = 55)	PTA + BMS (n = 55)	p Value
SFA location	41 (74.5)	45 (81.8)	0.5
Popliteal location	14 (25.5)	10 (18.2)	0.5
Lesion length, mm	94 ± 60	96 ± 69	0.8
Total occlusions	30 (54.5)	38 (69.1)	0.1
RVD baseline, mm	5.01 ± 0.5	5.12 ± 0.5	0.5
MLD baseline, mm*	0 (0/1)	0 (0/0.78)	0.06
DS baseline, %	91 ± 10	94 ± 9	0.1
MLD post stent, mm	4.87 ± 0.56	4.89 ± 0.49	0.9
Calcification			
None	33 (60.0)	36 (65.5)	0.8
Moderate	10 (18.2)	8 (14.5)	0.8
Severe	12 (21.8)	11 (20.0)	0.8
Pre-dilation	55 (100.0)	55 (100.0)	1
Length of stented segment, mm	114 ± 61	116 ± 72	0.5
Concomitant BTK PTA	33 (60.0)	30 (54.5)	0.8
Technical success†	55 (100.0)	55 (100.0)	1
Procedural success‡	53 (100.0)	51 (100.0)	1

Values are mean ± SD or % (n). *Values are expressed as median (quartile range) and compared with Mann-Whitney *U* test. †Achievement of >30% residual stenosis by visual estimate. ‡Achievement of technical success without procedural complications.

BTK = below-the-knee lesion; DS = diameter stenosis; MLD = minimal lumen diameter; RVD = reference vessel diameter; SFA = superficial femoral artery; other abbreviations as in Table 1.

(collaterals, bone landmarks) and a second image showing the inflated balloon(s). These images were compared with follow-up angiograms.

Binary restenosis was defined as a >50% diameter stenosis (by angiography) or a peak systolic velocity ratio ≥2.5 (by DUS) at follow-up. The in-stent restenosis (ISR) lesions were classified by visual estimate on angiography: class I, focal (≤50 mm in length) ISR group, included lesions positioned at the stent body, the stent edge, or a combination of these sites; class II, diffuse (>50 mm in length) ISR group, includes not only stent body lesions, but also stent edge lesions; and class III is the totally occluded ISR group (18). Angiograms and DUS scans were assessed in a blinded fashion by independent operators and reviewed by 2 readers without knowledge of clinical status and randomization group.

The primary endpoint of the study was the comparison of 12-month binary restenosis rate, by either angiography or DUS. The key secondary endpoint was the incidence of TLR. TLR was only performed if clinically indicated (reoccurrence of symptoms, either claudication or CLI), and when a target lesion diameter stenosis of ≥50% was present. Major amputation at 12 months, defined as unplanned amputation of the target limb where prosthesis was required for standing or walking, was another secondary endpoint.

Post hoc exploratory comparisons were performed between long (≥100 mm) versus shorter lesions and true lumen versus subintimal recanalization. Finally, as a confirmatory analysis, late lumen loss (LLL), defined as the difference in minimum lumen diameter of the target lesion between the time points immediately following intervention and the 12-month follow-up angiography or at the time of a clinically driven TLR was calculated by quantitative angiography

Table 3. 12-Month Target Lesion Evaluation

	PEB + BMS	PTA + BMS	P Value
Lesions, n	55	55	
Lesions evaluated, n*	53	55	0.9
Angiographic assessment	37 (69.8)	42 (76.4)	0.5
Duplex assessment	16 (30.2)	13 (23.6)	0.5
Restenosis	9 (17.0)	26 (47.3)	0.008
Lesions diagnosed by angiography, n	8 (88.9)	22 (84.6)	0.5†
Lesions diagnosed by DUS, n, PSVR ≥2.5	1 (11.1)	4(16.4)	
RVD, mm	5.11 ± 0.6	5.05 ± 0.5	0.5
MLD, mm	3.59 ± 1.42	2.12 ± 1.47	<0.001
DS, %‡	20.7 (17.7/27.0)	41.2 (34.8/82.3)	<0.001
Late lumen loss, mm‡	0.86 (0.80/0.94)	1.68 (1.60/4.2)	<0.001

Values are n, % (n), or mean ± SD. *Two patients died in the PEB + BMS group before lesion evaluation. †The p value refers to a chi-squared test comparing the percentages of restenosis diagnosed by angiography versus duplex in the 2 study groups. ‡Values are expressed as median (quartile range) and compared with Mann-Whitney *U* test.

DUS = duplex ultrasonography; PSVR = peak systolic velocity ratio; other abbreviations as in Tables 1 and 2.

and compared between the PTA + BMS and PEB + BMS groups.

Statistical analysis. The study sample size was powered to demonstrate an absolute 25% reduction in binary restenosis provided by PEB + BMS as compared to PTA + BMS. At the time of study inception, data from the most pertinent related studies were considered, showing a 1-year restenosis rate of about 20% in patients treated with PEB (12) and of 30% to 40% in those treated with stenting (19,20). However, as our institutional activity is focused on diabetic patients presenting with CLI (21), we expected to enroll a higher-risk population, and a 12-month restenosis rate of 45% in the PTA + BMS group was projected. Considering a dropout rate of 5%, a sample size of 110 lesions was deemed necessary to reach a statistical power of 80% ($1 - ß \geq 0.80$; $\alpha = 0.05$).

Continuous data are expressed as mean values ± SD. Categorical variables were compared with the use of the chi-square test or Fisher exact test. Student t tests for independent samples were used to compare groups on continuous variables.

Kaplan-Meier curves (log-rank [Mantel-Cox] test) were used to compare freedom from TLR between the 2 study groups. Statistical analyses were performed with SPSS (version 17.0 for Windows, SPSS Inc., Chicago, Illinois).

Results

Patients and lesions. Between November 2010 and November 2011, 104 patients (110 lesions in 110 limbs) were enrolled (Fig. 1). Clinical characteristics are summarized in Table 1. The majority of patients was diabetic and was referred for CLI. Baseline lesion and procedural characteristics are presented in Table 2. Mean lesion length was slightly less than 100 mm in both groups. Over 50% of the lesions were total occlusions. Concomitant below-the-knee revascularization was performed in 57% of cases, as clinically needed. No significant difference was observed between the 2 study groups in the incidence and outcome of these revascularizations. Technical and procedural success was achieved in all lesions.

Follow-up and clinical outcome. No major adverse events occurred in-hospital. Two patients in the PEB + BMS group died before the 12-month assessment (1 due to heart failure, the other due to sepsis). One patient in the PTA + BMS group died 2 weeks after target lesion follow-up evaluation due to sudden cardiac death (Fig. 1). No major amputation occurred. Twelve-month evaluation is summarized in Table 3. A total of 79 lesions (73%) were reviewed by repeat angiography, whereas 29 lesions (27%) were evaluated by ultrasonography (7 and 5 due to consent withdrawal for control angiography, 9 and 8 due to severe renal impairment in the PEB + BMS and PTA + BMS groups, respectively).

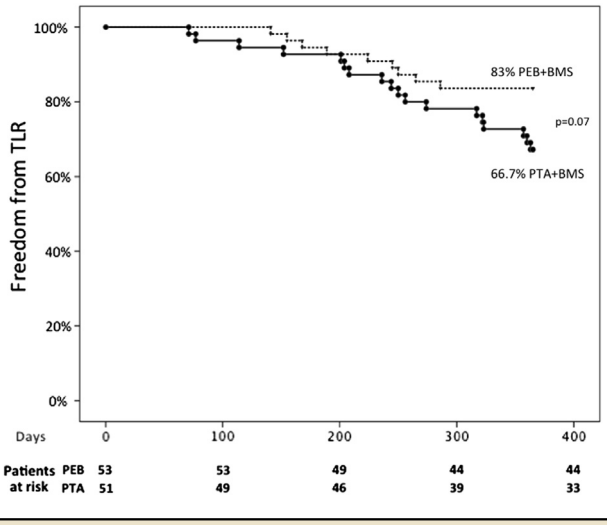

Figure 2. 12-Month Freedom From TLR

Kaplan-Meier curve comparing freedom from TLR between the 2 study groups showing a near-significant 1-year freedom from TLR advantage in the PEB group. Abbreviations as in Figure 1.

The primary endpoint, binary restenosis, occurred in 9 (17%) versus 26 (47.3%) of lesions in PEB + BMS and PTA + BMS groups, respectively ($p = 0.008$). Kaplan-Meier analysis showed a near-significant 1-year freedom from TLR advantage in the PEB group (Fig. 2).

Long lesions (≥100 mm) showed a reduced restenosis rate in the PEB + BMS versus PTA + BMS groups (21% vs. 62%, $p = 0.01$) (Fig. 3). Restenosis rate was significantly lower in the PEB + BMS than in the PTA + BMS group, irrespective of the recanalization approach (true lumen vs. subintimal) (Fig. 4). LLL was significantly lower in the PEB + BMS group compared with the PTA + BMS group (Table 3).

Three stent fractures (2 in the PEB group) were detected at angiographic follow-up. At 12 months, 45 patients in the PTA + DEB group versus 30 in the PTA + BMS group improved at least 2 Rutherford classes (81.8% vs. 54.5%, $p = 0.02$).

Discussion

The results of this randomized study indicate that a strategy of PEB + BMS is superior to conventional PTA + BMS in patients with complex, de novo femoropopliteal lesions, significantly reducing the primary endpoint of binary restenosis of more than 2×. This impressive result was even more evident in very long lesions and was obtained irrespective of the adopted technique (true lumen vs. subintimal). This reduction in restenosis translated into a reduction in clinically driven TLR of borderline significance (Fig. 5).

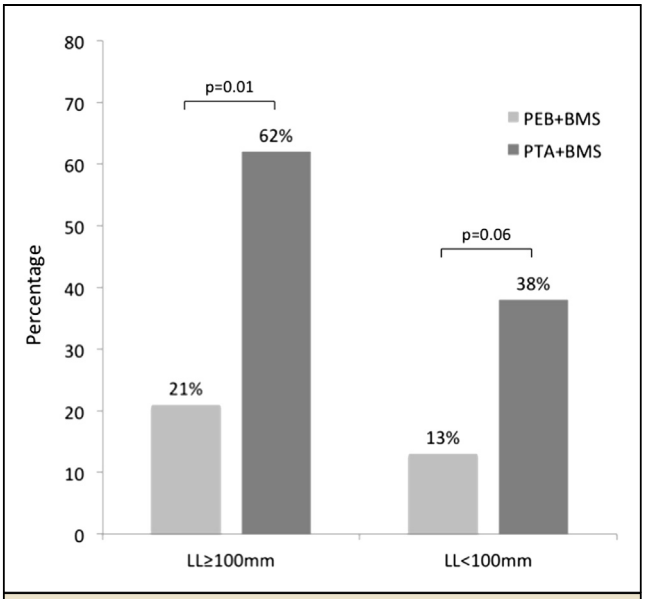

Figure 3. Restenosis and Lesion Length

Restenosis rate in lesions ≥100 mm versus <100 mm: Long lesions (≥100 mm) showed a reduced restenosis rate in the PEB + BMS versus PTA + BMS groups. LL = lesion length; other abbreviations as in Figure 1.

In femoropopliteal lesions, conventional PTA plus nitinol stent strategy obtained encouraging results when compared with standard PTA, but it still carries a relevant risk of restenosis (2,20), especially in long and complex lesions (19). Our trial showed an unfavorable outcome in the PTA + BMS group when compared with PEB. Previous preliminary observational data reported for the Maris stent (Medtronic, Minneapolis, Minnesota) showed an increased risk of restenosis/reocclusion (22), and this could partly explain our results. In the RESILIENT (Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery) trial, Laird et al. (2) randomized 206 patients with obstructive lesions of the superficial femoral and proximal popliteal arteries and intermittent claudication to stenting versus standard PTA. The stent group (n = 134) showed a freedom from TLR rate of 87.3% at 12 months. If compared with these data, we observed a clearly higher TLR rate in the PTA + BMS group. However, the RESILIENT stent population was younger as compared with our sample (68 vs. 76 years), with a lower percentage of diabetes (40% vs. 70%), had better ankle-brachial index (0.71 vs. 0.31) and clinical status (0% vs. 68% of patients in Rutherford class ≥4), lesion length was 70 mm versus 96 mm, and total occlusions were 17% versus 69.1%.

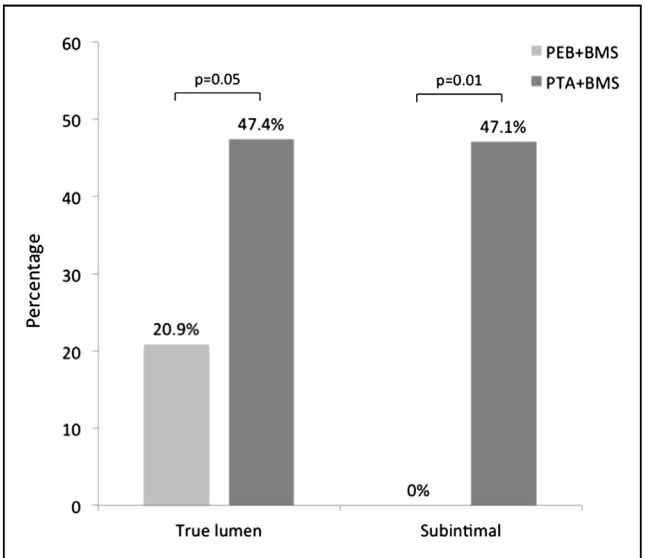

Figure 4. Restenosis and Revascularization Technique

Restenosis rate in true lumen versus subintimal revascularization: Restenosis rate was significantly lower in the PEB + BMS than in the PTA + BMS group, irrespective of the recanalization approach (true lumen vs. subintimal). Abbreviations as in Figure 1.

In the setting of femoropopliteal lesions, even sirolimus- and everolimus-eluting stents have failed to demonstrate additional benefit (7–9,23,24), whereas paclitaxel (an irreversible inhibitor of microtubules polymerization) (17) DES perform significantly better than BMS do (10). DES, however, though providing a mechanical scaffold, are potentially limited by the nonhomogeneous wall contact of the drug and by the long-term irritative effect of metal and polymer (25).

The use of DEB may be an effective alternative to DES, as any stentless technology for the improvement of long-term patency might be preferable to the long-term persistence of a foreign body. Potential drawbacks of a DEB-alone strategy, however, are the elastic recoil phenomenon, and the occurrence of flow-limiting dissection, as very calcific stenosis or total occlusions are commonly found in the femoropopliteal vessels. It is indeed likely that the rate of bailout stenting for such complex lesions in real-world interventions is higher than the 10% to 20% reported in DEB randomized trials (26) or registries (27).

Whereas DAPT is recommended for at least 1 month after infrainguinal BMS implantation (28), there is still no consensus about the duration of DAPT following DEB + PTA (ranging from 1 to 3 months or more in different studies [12,13,27]), and particularly in the case of PEB + stent implantation. As per protocol design, we administered a 3-month DAPT in patients treated with PEB and stent implantation to limit the occurrence of stent thrombosis, which could arise from incomplete stent strut re-endothelization due to the antiproliferative effect of the paclitaxel. Such duration appeared safe; of note, no stent thrombosis was observed in our study population during the follow-up period.

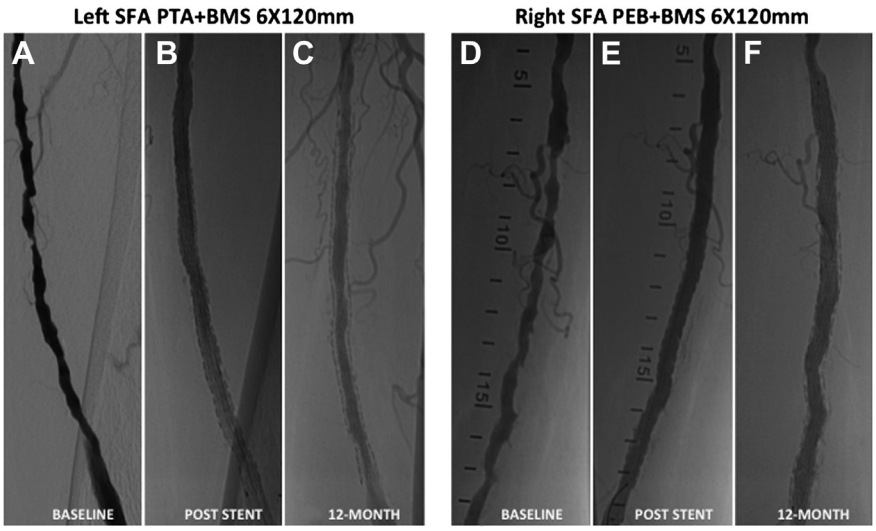

Figure 5. Comparison in a Single Patient With Bilateral, Specular SFA Lesions of the Effects of PEB Versus Conventional Angioplasty

This 73-year-old man was treated on the left limb **(A to C)** prior to study enrollment with conventional angioplasty plus stent, whereas the right superficial femoral artery (SFA) received PEB prior to stenting as part of the study **(D to F)**. Twelve-month angiographic follow-up (at different time points) is reported, showing diffuse neointimal regrowth with focal areas of significant (>50%) restenosis on the left side versus maintained patency on the right side. Abbreviations as in Figure 1.

To our knowledge, the DEBATE SFA study is the first randomized trial to investigate the efficacy and safety of PEB angioplasty prior to systematic nitinol self-expanding stent implantation versus conventional PTA followed by stenting in patients at high risk of restenosis. In the recently published PACIFIER (Paclitaxel-Coated Balloons in Femoral Indication to Defeat Restenosis) trial (which tested the same DEB platform) (14), procedural protocol limited stent use only for provisional or bailout situations. Stents were actually employed in only about 20% of patients enrolled in both arms. Target lesions binary restenosis rate was 8.6% in DEB plus provisional/bailout stenting, which appears lower than the 17% rate observed in the DEB plus systematic stenting arm of the present study. However, we enrolled more diabetics (73% vs. 35.5%), more patients in Rutherford class ≥4 (74% vs. 4%), dialysis patients were not excluded, mean lesion length was longer (approximately 95 mm vs. 70 mm), and total occlusions were more frequently present (62% vs. 31%). It is thus likely that the baseline characteristics of the enrolled population might explain this discrepancy.

Our study also provides some insights regarding the issue of DEB safety. The achieved reduction in binary restenosis and TLR was due to a sizable reduction in neointimal regrowth, which was nonetheless uniformly present, with a positive LLL of around 1.3 mm. No cases of negative LLL (associated in the coronary experience with stent malapposition and ultimately thrombotic event [29]) or arterial aneurysm were seen. It should be noted that a negative LLL has recently been observed in some patients treated with PEB in the PACIFIER trial, especially in those with the most severe baseline stenoses (14). This discordant finding, besides the obvious effect of stenting, may be potentially explained by the different procedural DEB deployment technique, which involved, in our study, aggressive lesion preparation with an uncoated balloon prior to DEB in all patients, whereas pre-dilation was adopted in <10% of patients of the PACIFIER trial. Nonuniform drug distribution by the very compliant DEB (17) when inflated in complex stenosis could potentially explain this effect.

Study limitations. First, the study reflects a single-center experience and involves a relatively small sample, which, although sufficient to detect differences in the primary endpoint, was not powered to test differences in hard clinical endpoints. Second, evaluation of binary restenosis was performed in most cases by angiography; however, the use of ultrasonography in a small percentage of patients could represent a potential bias. Third, we chose to perform systematic stenting in both groups. Our sample, however, was procedurally complex and this strategy reflects our current practice in high-risk patients. We concede, however, that this is a controversial point and that our study does not provide an answer. Finally, due to the financial constraints of running an independent trial, an external data adjudication committee or core lab was lacking.

Conclusions

The DEBATE-SFA trial demonstrates that pre-dilation with PEB angioplasty prior to nitinol self-expanding stent

implantation, compared with conventional PTA followed by stenting, reduces restenosis and TLR at 12-month follow-up. Restenosis reduction is maintained irrespective of lesion length and recanalization technique. Further studies may confirm whether a systematic or provisional stenting strategy is preferred when using DEB, or they may investigate and compare PEB + BMS strategy with newer DES technology.

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