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Short-term Results of the RAPID Randomized Trial of the Legflow Paclitaxel-Eluting Balloon With Supera Stenting vs Supera Stenting Alone for the Treatment of Intermediate and Long Superficial Femoral Artery Lesions

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Abstract

Purpose: To report a randomized trial comparing the Legflow paclitaxel-eluting balloon (PEB) + Supera stenting to Supera stenting alone in patients with intermediate to long superficial femoral artery (SFA) lesions. **Methods:** The multicenter RAPID trial (*controlled-trials.com*; identifier ISRCTN47846578) randomized (1:1) 160 patients (mean age 67 years; 102 men) with Rutherford category 2–6 ischemia to treatment with Legflow PEB + Supera stent or Supera stent alone in intermediate to long SFA lesions (mean lesion length 15.8±7.4 vs 15.8±7.6 cm, respectively). The efficacy outcome was primary patency, defined as freedom from restenosis on duplex ultrasound or angiography. **Results:** Baseline characteristics including the percentage of occlusions were similar between groups. In the intention-to-treat analysis, the estimated primary patency at 1 year was 68.3% (95% CI 56.7% to 79.9%) in the PEB + Supera group vs 62.0% (95% CI 49.1% to 74.9%) in the Supera group (p=0.900). Per-protocol analysis showed a 12-month primary patency estimate of 74.7% (95% CI 63.1% to 86.3%) in the PEB + Supera group vs 62.0% (95% CI 49.1% to 74.9%) in the control group (p=0.273). Secondary patency estimates at 12 months (per-protocol analysis) were 89.0% (95% CI 80.6% to 97.4%) vs 98.0% (95% CI 94.1% to 100%; p=0.484); the estimates for freedom from clinically driven target lesion revascularization (CD-TLR) were 83.0% (95% CI 72.8% to 93.2%) and 77.8% (95% CI 66.6% to 89.0%; p=0.277), respectively. **Conclusion:** The short-term results from the multicenter RAPID randomized controlled trial indicate that the Legflow PEB is safe and feasible for the treatment of intermediate to long SFA lesions. In this trial, at least 70% of the patients suffered an occlusion. The PEB group had higher rates of primary patency and freedom from CD-TLR, although there were no statistically significant differences vs controls.

Keywords

balloon angioplasty, drug-coated balloon, drug-eluting balloon, multicenter trial, paclitaxel, peripheral artery disease, randomized trial, self-expanding stent, superficial femoral artery

Introduction

Peripheral artery occlusive disease (PAOD) is an increasing problem in elderly patients, affecting up to 21.6% in those older than 75 years.[1] Patients presenting with critical limb ischemia usually have multisegmental disease with involvement of the infrainguinal arteries[2]; >50% of all PAOD cases involve the superficial femoral (SFA) and popliteal artery.[3]

Over the past decade, endovascular repair has become the preferred treatment for femoropopliteal occlusive disease,[4–6] but no consensus has emerged concerning the optimal endovascular strategy. Depending on lesion length and complexity, different guidelines vary in their approach regarding short (<5 cm), intermediate (5–15 cm), and long-segment (>15 cm) SFA lesions.[4–6]

For intermediate lesions, most guidelines and studies favor primary stenting over standard balloon angioplasty (BA),[7–9] but in-stent restenosis (ISR) remains one of the major drawbacks.[10] While sirolimus-eluting stents have failed to show a significant beneficial effect in the SFA,[11] paclitaxel-eluting balloons and paclitaxel-eluting stents have had a favorable outcome.[12–17] For short lesions, there is growing evidence that supports a "leave nothing behind" strategy with bailout stenting,[18] preferably with a drug-coated balloon (DCB)[16,18,19] to reduce neointimal hyperplasia and prevent restenosis.[14,20] However, robust evidence from large randomized controlled trials is still lacking for intermediate- and long-segment SFA lesions, especially regarding chronic total occlusions (CTOs). This type of challenging SFA lesion forms the bulk of the real-world lesions in daily vascular practice.

The Supera stent (Abbott Laboratories, Abbott Park, IL, USA) is a unique self-expanding nitinol stent. Six pairs of interwoven nitinol wires are constructed in a helical pattern to optimize flexibility and to withstand compression as well as the complex forces at the distal SFA. The deployment system allows the physician to stack Supera stents in certain lesion locations. It is important not to elongate the Supera stent during deployment and to prepare the target artery in such way that the stent will be deployed at its nominal diameter to optimize the compression resistance. The Supera stent and related clinical outcomes have been described in detail.[21]

The RAPID trial was designed to test safety and efficacy of the Legflow paclitaxel-eluting balloon (PEB; Cardionovum GmbH, Bonn, Germany) in combination with primary Supera stenting in patients with intermediate to long SFA lesions compared to primary Supera stenting alone.

Methods

Study Design and Patient Enrollment

The RAPID trial was a prospective, multicenter, randomized trial designed to enroll patients with symptomatic PAOD caused by intermediate (5–15 cm) or long-segment (>15 cm) lesions confined to the SFA. Each participating physician at the 8 sites (7 Dutch and 1 German) had implanted at least 10 Supera stents before the start of the RAPID trial, and all physicians performed >100 endovascular femoropopliteal interventions a year. The full study protocol, which was approved by the ethics committees of each study site, was published,[22] and the trial was registered on the Current Controlled Trials website (*controlled-trials.com*; identifier ISRCTN47846578). All study procedures were conducted in accordance with good clinical practices and applicable laws.

Inclusion and exclusion criteria are presented in Table 1. In short, eligible patients had to be adults with de novo atherosclerotic lesions ≥50 mm long confined to the SFA. Based on these criteria, the trial enrolled 160 patients (mean age 67 years; 102 men) between June 2012 and May 2016. Patients were randomly assigned 1:1 to dilation with either

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Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
≥18 years old	Life expectancy <1 year
De novo lesions ≥50 mm confined to the SFA	Previous treatment of the target lesion
PSVR ≥2.4 on duplex or ≥50% stenosis on either CTA or MRA. Occlusions	Unwilling or unable to comply with the follow-up schedule
≥1 Patent BTK runoff artery with uninterrupted flow to the pedal arch	Inability to understand and comply with the informed consent
Rutherford category 2–6 ischemia	Pregnancy or breast-feeding
Passage of lesion with guidewire prior to randomization	Severe renal failure (eGFR <30 mL/min/1.73 m^2)
	Allergy to iodinated contrast agents
	Contraindication to dual antiplatelet regimen
	Obstruction caused by SFA aneurysmal disease or dissections

Abbreviations: BTK, below the knee; CTA, computed tomography angiography; eGFR, estimated glomerular filtration rate; MRA, magnetic resonance angiography; SFA, superficial femoral artery.

a Legflow PEB (n=80) or standard BA (n=80), after which all patients were treated with a self-expanding Supera nitinol stent. The demographics, comorbidities, and lesion characteristics of the groups are presented in Tables 2 and 3. The mean treated lesion length was 15.8±7.4 cm in the PEB + Supera group and 15.8±7.6 cm in the Supera group. Both groups had a high percentage of occlusions: 76.3% vs 70.0%, respectively.

Candidates for the trial were informed of the risks and benefits of participation in the study and gave written informed consent. Central block randomization was performed using an automated web-based randomization tool; only an independent administrator had rights to access the randomization database solely for maintenance purposes. Patients were randomized after passage of a guidewire and confirmation of distal intraluminal position. Once enrolled, patients were blinded regarding the received treatment, as were all personnel performing postoperative clinical evaluations and testing.

Study Device

The Legflow PEB is coated with nanocrystalline 0.1-µm paclitaxel particles embedded in an ammonium salt compound; the excipient prolongs the availability of paclitaxel in the vessel wall, thereby exerting a strong antiproliferative effect. The nanocrystalline particles are not on the exterior of the furled balloon, so there is no risk that paclitaxel will flake off during PEB insertion in the sheath or if dislodgement occurs and the balloon migrates distally.

Table 2. Baseline Characteristics of the Study Population.[a]

	PEB + Stent (n=80)	BA + Stent (n=80)	p
Age, y	67.6±7.5	67.0±8.0	0.626
Men	52 (65.0)	50 (62.5)	0.869
Rutherford category			0.836
2	37 (46.2)	39 (48.8)	
3	29 (36.2)	28 (35.0)	
4	7 (8.8)	5 (6.3)	
5	6 (7.6)	5 (6.3)	
6	1 (1.3)	3 (3.8)	
ABI			
Rest	0.59±0.20	0.61±0.19	0.480
After exercise	0.34±0.18	0.38±0.19	0.225
Toe pressure, mm Hg			
Digit 1	59±28.9	64±40.0	0.513
Digit 2	61±48.3	96±71.8	0.245
SVS risk score (0–24)	5.8±3.2	5.5±3.0	0.547
Creatinine, µmol/L	80.9±21.8	82.7±27.5	0.649
Risk factors			
Diabetes	23 (28.8)	24 (30.0)	0.863
Smoking, current or recent	40 (50.0)	39 (48.8)	1.000
BMI, kg/m^2	26.4±4.9	27.1±4.3	0.375

Abbreviations: ABI, ankle-brachial index; BA, balloon angioplasty; BMI, body mass index; PEB, paclitaxel-eluting balloon; SVS, Society for Vascular Surgery.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage).

Table 3. SFA Lesion Characteristics of the Study Population.[a]

	PEB + Stent (n=80)	BA + Stent (n=80)	p
TASC II class			0.747
A	8 (10.0)	10 (12.5)	
B	40 (50.0)	35 (43.8)	
C	15 (18.8)	20 (25.0)	
D	17 (21.3)	15 (18.8)	
Side (right)	44 (55.0)	45 (56.3)	0.873
Occlusion	61 (76.3)	56 (70.0)	0.476
Length on angiogram, cm	15.8±7.4	15.8±7.6	0.996
Long lesions (≥15 cm)	40 (50.0)	44 (55.0)	0.526
Reference diameter, mm	5.1±0.7	5.2±0.8	0.624

Abbreviations: BA, balloon angioplasty; PEB, paclitaxel-eluting balloon; SFA, superficial femoral artery; TASC, TransAtlantic Inter-Society Consensus.
[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage).

Treatment Protocol

All patients were prescribed acetylsalicylic acid at least 1 week before the intervention. The procedure was begun in standard fashion, with heparin (5000 units) administered intravenously following sheath insertion. After guidewire passage and randomization, patients assigned to the Legflow group had the target lesion predilated with a standard balloon undersized 1 mm according to the instructions for use. PEB angioplasty was subsequently performed with a Legflow balloon sized 1 mm larger than the reference diameter of the SFA, both to facilitate drug delivery and for vessel preparation of the Supera stent. The proximal and distal treatment zone of the PEB had to extend 1 cm beyond the anticipated stent location. If >1 PEB was needed, overlap had to be at least 1 cm. Minimal inflation time was 120 seconds. In case of insufficient balloon expansion, focal dilation with a standard balloon was mandatory, respecting the drug delivery zone. In the Supera only group, vessel preparation required an angioplasty balloon sized 1 mm larger than the selected Supera stent diameter. In both groups, implantation of a single stent was preferred.

A 300-mg loading dose of clopidogrel was administered after the procedure in patients who were not on dual antiplatelet therapy prior to treatment. Dual antiplatelet therapy with clopidogrel (75 mg/d) for 3 months and acetylsalicylic acid (100 mg/d) indefinitely was recommended. All patients were scheduled at 1, 6, 12, and 24 months to undergo duplex ultrasound, a treadmill test, and ankle-brachial index (ABI) and toe pressure measurements.

Definitions and Study Outcomes

Device success for the Legflow PEB was defined as exact deployment of the device according to the instructions for use. Technical success referred to successful vascular access, completion of the endovascular procedure, and <30% residual diameter stenosis on completion angiography or a <10 mm Hg pressure gradient across the treated lesion.

The primary outcome was primary patency, defined as the absence of binary restenosis determined by a peak systolic velocity ratio ≥2.4 on duplex or >50% stenosis on digital subtraction angiography. Other outcomes were secondary patency (patency reestablished after occlusion), freedom from clinically driven target lesion revascularization (CD-TLR), reocclusion, amputation, sustained Rutherford class improvement, and sustained ABI and toe pressure improvement.[22] Safety outcomes were freedom from death and freedom from major adverse limb events at 30 days and freedom from all-cause death at 1 year.

Statistical Analysis

The study sample size was powered to demonstrate an absolute 25% reduction in binary restenosis between the 2 groups. The power calculation was based on data from key studies showing a 2-year restenosis rate of ~15% to 20% in patients treated with PEB[14,20] and up to 40% in those treated with bare metal stenting (BMS).[8,23] A sample size of 160 lesions was necessary to reach a statistical power of 80% with α=0.05.

Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage). Categorical variables were compared using the chi-square or Fisher exact test as appropriate. Student *t* tests for independent samples were used to compare groups of continuous variables. Patency, freedom from CD-TLR, and the safety outcomes were compared between groups using the Kaplan-Meier method; group differences were assessed with the log-rank test. Survival estimates are given with the 95% confidence interval (CI). All clinical data were analyzed by Syntactx, an independent core laboratory (New York, NY, USA) using SPSS software (version 24.0 for Windows; IBM Corporation, Armonk, NY, USA).

Results

Device success for the Legflow PEB was 100%. Technical success was achieved in 97.5% of subjects in the PEB + Supera group vs 100% of subjects in the Supera group. Seven patients in the PEB + Supera group were not included in the per-protocol analysis (Figure 1) owing to geographic miss in 5 and severe lengthening of the Supera stent requiring surgical exploration in 2. In the latter 2 patients, vessel preparation of the SFA before stenting was insufficient due to an undersized balloon relative to the Supera stent diameter. One patient in the PEB + Supera group and 3 patients in the Supera group were lost to follow-up due to withdrawal of consent.

Efficacy Outcomes

In the intention-to-treat analysis, the estimated primary patency at 1 year (Figure 2A) was 68.3% (95% CI 56.7% to 79.9%) in the PEB + Supera group vs 62.0% (95% CI 49.1% to 74.9%) in the Supera group (p=0.900). Per-protocol analysis showed a 12-month primary patency estimate of 74.7% (95% CI 63.1% to 86.3%) in the PEB + Supera group vs 62.0% (95% CI 49.1% to 74.9%) in the control group (p=0.273; Figure 2B). Secondary patency estimates at 12 months (Figure 2C) were 89.0% (95% CI 80.6% to 97.4%) vs 98.0% (95% CI 94.1% to 100%; p=0.484); the estimates for freedom from CD-TLR were 83.0% (95% CI 72.8% to 93.2%) and 77.8% (95% CI 66.6% to 89.0%; p=0.277), respectively. Serial angiograms of 2 patients with CD-TLR are shown in Figure 3. Comparison of patients suffering TransAtlantic Inter-Society Consensus (TASC) A/B lesions with TASC C/D patients did not result in any significant differences regarding primary and secondary outcomes.

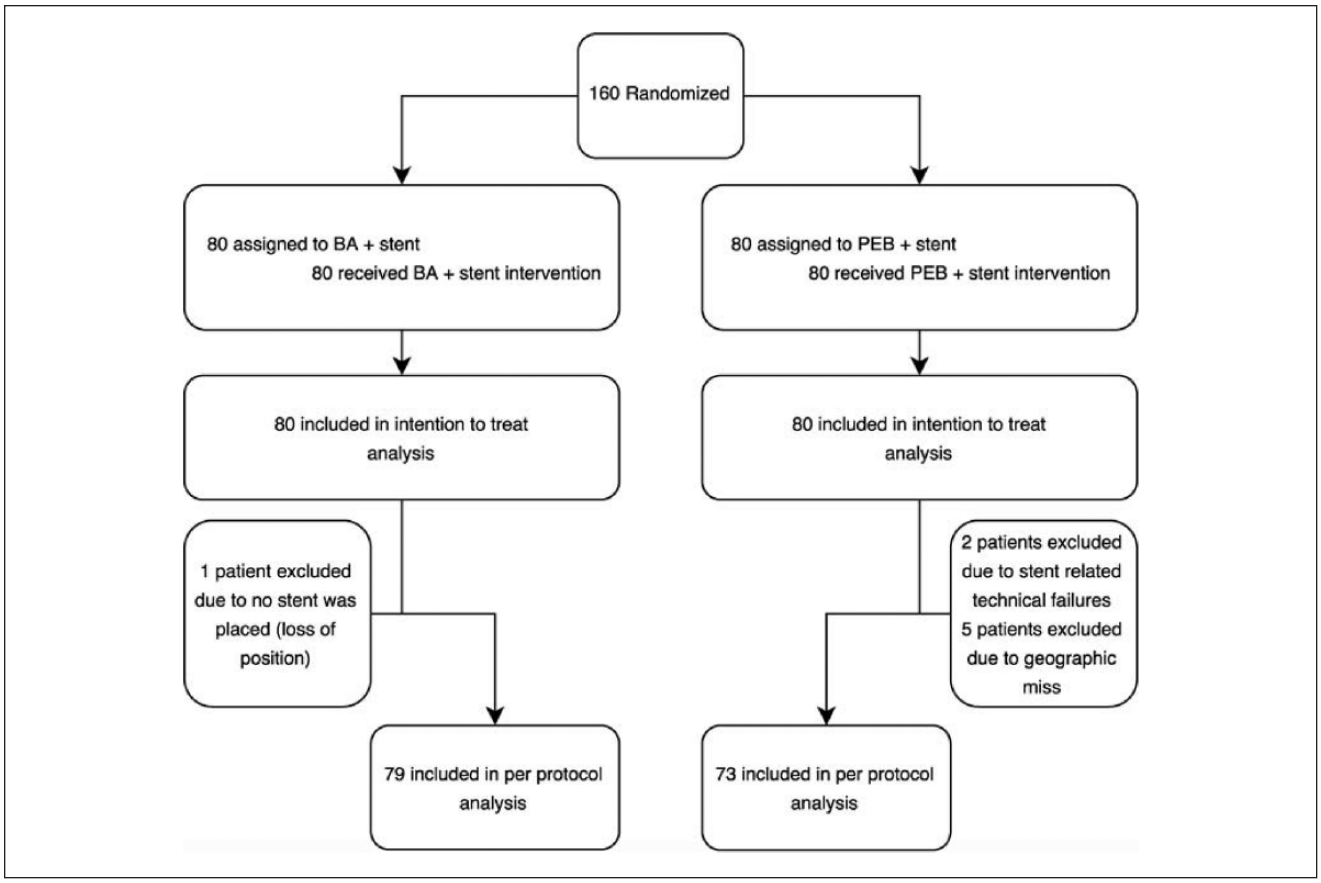

Figure 1. Patient flow in the trial. BA, balloon angioplasty; PEB, paclitaxel-eluting balloon.

Safety Outcomes

There were no deaths or major adverse limb events within 30 days in either group; at 12 months, rates for freedom from both of these endpoints were 82.6% (95% CI 74.6% to 90.6%) in the PEB + Supera group vs 90.3% (95% CI 80.9% to 99.7%) in the Supera group (p=0.456). Freedom from all-cause mortality at 12 months was 98.0% (95% CI 94.1% to 100%) in the PEB + Supera group (1 cardiac arrest at 9 months) vs 96.1% (95% CI 90.8% to 100%; p=0.483) in the Supera group (1 sudden death at 7 months and 1 lung cancer at 11 months).

Functional Outcomes

Both groups showed improvement compared to baseline regarding Rutherford category, ABI, and toe pressures (Table 4). There were no statistically significant differences between the groups at 12 months.

Discussion

Over the past few years, the optimal treatment strategy for SFA lesions has been the subject of investigation in numerous trials. The use of antirestenotic technology, either DCBs or drug-eluting stents (DES), has proven its ability to inhibit neointimal hyperplasia and its efficacy in reducing restenosis in the SFA.[13–15,17,19,24] Results have shown a clear benefit of standard nitinol stents and DES over BA in both short and long lesions of the SFA,[7–9,11,17,23,25–30] but these studies included only a low percentage of occluded lesions (25%–53%).

The advent of DCBs offered a new option for the treatment of atherosclerotic disease. Short SFA lesions (TASC A/B) were the first to be investigated in several randomized trials, which demonstrated a significant benefit of DCBs over BA.[13–16,19,20] DES also perform better in these lesions compared to BA, with patency rates of 96% and 90.3% at 12 months in the Zilver PTX and MAJESTIC trials, respectively.[17,31] The DEBATE-SFA trial was the first SFA trial to compare a PEB with primary stenting to BA with primary stenting,[24] but this trial included lesion lengths varying from only short to intermediate and had a large proportion of noncalcified lesions (60%–65%).

With respect to the treatment of long SFA lesions (TASC C/D), the guidelines still recommend surgical revascularization as the preferred treatment strategy.[4] Early attempts with endovascular treatment of TASC C/D lesions using BA

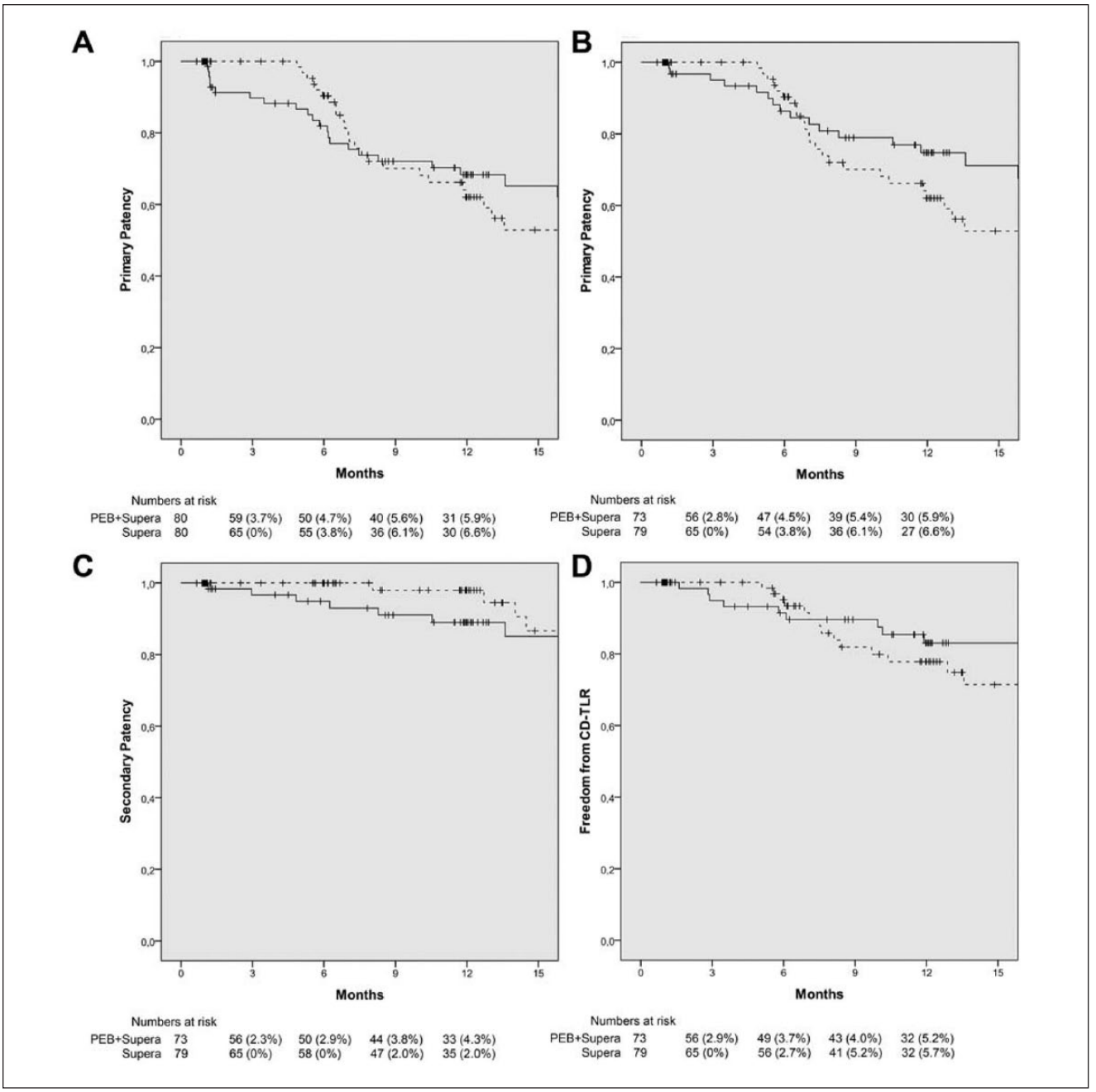

Figure 2. Primary patency for the (A) intention-to-treat cohort (p=0.900) and (B) the per protocol patients (p=0.273). (C) Secondary patency for the per-protocol cohort (p=0.484) and (D) freedom of clinically driven target lesion revascularization in the per-protocol analysis (p=0.277). Solid lines represent the paclitaxel-eluting balloon (PEB) + Supera group, dotted lines the Supera group. Below the graphs are patients at risk at each interval with standard errors of the estimated survival in parentheses.

resulted in low technical success (high percentage of bail-out stenting) and high restenosis rates.[8,32] Primary stenting using a standard nitinol stent significantly increased technical success rates and short-term patency in TASC C/D lesions compared to BA.[8,33] However, this approach is limited by in-stent restenosis (ISR). Moreover, an association between the stented lesion length and higher stent fracture rates with reduced patency has been demonstrated in several trials.[11,34] Also, longer lesion length is associated with an increase in late lumen loss,[12] and stenting of CTOs is correlated with high stent fracture rates.[35]

The Supera stent was selected for the RAPID trial because of the high patency rates and zero fractures reported in the literature.[29] However, current data on performance of

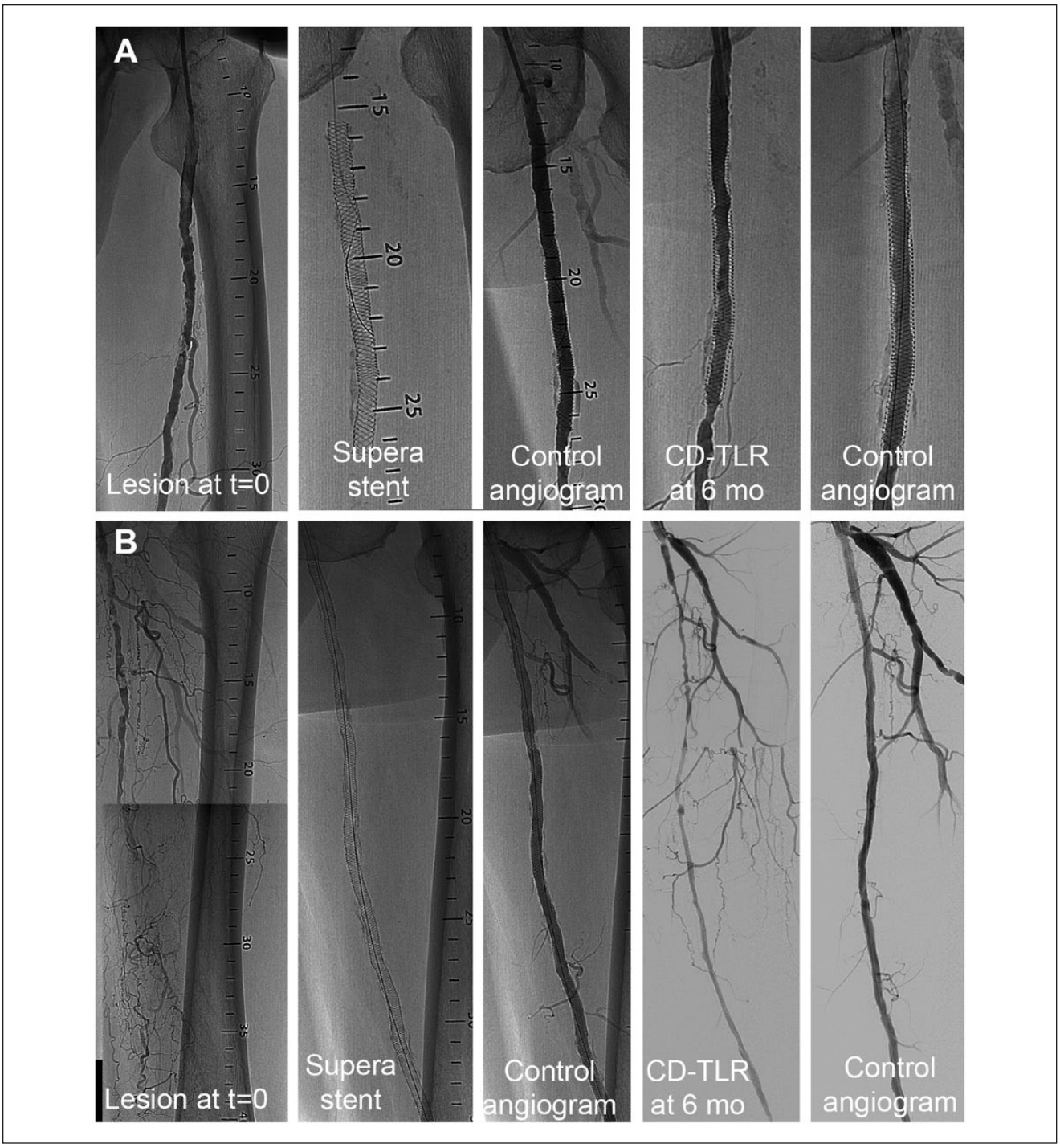

Figure 3. (A) Angiograms from a patient with an intermediate length lesion who developed restenosis at 6 months and was retreated. (B) Angiograms from a patient with restenosis at 10 months in a long lesion that was retreated (some images are constructed from overlapping angiograms).

the Supera stent in intermediate and long complex SFA lesions have proven to be excellent.[25–27,30,36] The main difference between regular nitinol stents and the Supera stent is the lack of chronic outward force, which is assumed to be the most important contributor to ISR. For this reason, it is questionable whether DCB support can further improve these patency rates.

The primary patency (per-protocol analysis) of the PEB + Supera group is comparable to the TASC C/D lesion subgroup analysis of the Zilver-PTX trial[37] and new-generation

Table 4. Changes in Rutherford Category, ABI, and Toe Pressures in the Study Population.[a]

	PEB + Stent (n=80)	BA + Stent (n=80)	p
Rutherford category improvement			
1 mo	−2.42±1.10	−2.38±1.15	0.807
6 mo	−2.18±1.09	−1.98±1.25	0.366
12 mo	−2.40±0.90	−1.94±1.48	0.083
ABI			
Rest			
Baseline	0.60±0.21	0.61±0.19	0.773
1 mo	0.89±0.20	0.96±0.15	0.032
6 mo	0.86±0.19	0.92±0.17	0.121
12 mo	0.82±0.19	0.87±0.20	0.248
Postexercise			
Baseline	0.35±0.19	0.38±0.19	0.463
1 mo	0.72±0.22	0.82±0.18	0.065
6 mo	0.66±0.26	0.73±0.27	0.311
12 mo	0.63±0.20	0.63±0.31	0.928
Toe pressure, mm Hg			
Digit 1			
Baseline	59±28.8	64±40.5	0.557
1 mo	104±45.2	112±36.1	0.303
6 mo	98±32.3	111±36.3	0.096
12 mo	94±33.4	103±47.7	0.434
Digit 2			
Baseline	61±48.3	96±71.8	0.245
1 mo	107±41.2	107±42.3	0.979
6 mo	89±44.6	100±33.0	0.425
12 mo	95±42.8	96±36.6	0.908

Abbreviations: ABI, ankle-brachial index; BA, balloon angioplasty; PEB, paclitaxel-eluting balloon.
[a]Data are presented as the means ± standard deviation.

prosthetic femoropopliteal bypasses.[38,39] It is obvious that an endovascular means is preferable in patients with long-segment SFA obstructions compared to a more invasive bypass revascularization. In the current analysis, the differences in primary patency estimates for the groups were not statistically significant, but this may be due to a type II error. It is also possible that the antiproliferative effect of the Legflow DCB is not as strong as has been demonstrated for other DCBs.[15,19]

Remarkably and unexpectedly, the efficacy data do not match with other studies using DCBs + primary stenting[24] or with Supera studies.[25–27,29,30,36] This holds for both groups and also in the intention-to-treat as well as the per-protocol analyses. Angiograms in patients with ISR were analyzed with a special focus on stent configuration (nominal, lengthening, or shortening), but it offered no explanation for the relatively low primary patency rates. Plausible reasons could be that substantially longer lesions and more CTOs were included in the RAPID trial. Moreover, most of the publications regarding the use of the Supera stent in the SFA have been single-center series without a control group. It may be argued that the current multicenter randomized trial better reflects reality. Furthermore, loss of patency was seen in the first 2 months after treatment in the PEB+Supera group. There is no obvious explanation for this effect, but similar results have been appreciated in the other trials.[13,14,17]

Limitations

When drafting the protocol for this study, the power analysis was based on BMS data showing a restenosis rate of 30% to 40%,[8,23] since not many studies regarding the Supera stent were available. This might have caused an underpowered trial, since the average reported restenosis rate of the Supera stent currently is <30% to 40%. Another possible limitation of this trial might be an unequal distribution of patients in the participating centers, resulting in some low volume centers. The influences of anatomical and lesion specific characteristics were not analyzed in the current study because of the fact that <50% of patients completed the 1-year follow-up.

One other major drawback of the current study is the fact that unsuccessful delivery and deployment of the Supera stents could not be linked to the primary outcome. Thorough evaluation of the postprocedure Supera stent configurations, such as too dense packing and under/oversized stent diameters, as well as the calcium score of the treated SFA lesions will be determined when all 2-year follow-up images are available from the core laboratory analysis (per study protocol).

Conclusion

The short-term results from the multicenter RAPID randomized controlled trial indicate that the Legflow PEB is safe and feasible for the treatment of intermediate to long SFA lesions. In this trial, at least 70% of the patients suffered an occlusion. The PEB group had higher rates of primary patency and freedom from CD-TLR, although there were no statistically significant differences vs controls.

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