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ORIGINAL ARTICLE

RECENT DEVELOPMENTS IN THE MANAGEMENT OF CRITICAL LIMB ISCHEMIA

Drug coated balloon supported Supera stent *versus* Supera stent in intermediate and long-segment lesions of the superficial femoral artery: 2-year results of the RAPID Trial

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ABSTRACT

BACKGROUND: Endovascular treatment of occlusive disease of the superficial femoral artery (SFA) has evolved from plain old balloon angioplasty (POBA) through primary stenting strategy to drug eluting technology-based approach. The RAPID Trial investigates the added value of drug coated balloons (DCB, Legflow) in a primary stenting strategy (Supera stent) for intermediate (5-15 cm) and long segment (>15 cm) SFA lesions.

METHODS: In this multicenter, patient-blinded trial, 160 patients with intermittent claudication, ischemic rest pain, or tissue loss due to intermediate or long SFA lesions were randomized (1:1) between Supera + DCB and Supera. Primary endpoint was primary patency at 2 years, defined as freedom from restenosis on duplex ultrasound (peak systolic velocity ratio <2.4).

RESULTS: At 2 years, primary patency was 55.1% (95% CI: 43.1-67.1%) in the Supera + DCB group *versus* 48.3% (95% CI: 35.6-61.0%) in the Supera group (P=0.957). Per protocol analysis showed a primary patency rate of 60.9% (95% CI: 48.6-73.2%) in the Supera + DCB group *versus* 49.8% (95% CI: 36.9-62.7%) in the Supera group (P=0.469). The overall mortality rate was 5% in both groups (P=0.975). Sustained functional improvement was similar in both groups.

CONCLUSIONS: The 2-year results in the current trial of a primary Supera stenting strategy are consistent with other trials reporting on treatment of intermediate and long SFA lesions. A DCB supported Supera stent strategy did not improve patency rate compared to a Supera stent only strategy.

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KEY WORDS: Femoral artery; Peripheral arterial disease; Angioplasty, balloon; Stents.

Endovascular repair for peripheral arterial occlusive disease (PAOD) in the superficial femoral artery (SFA) has gained widespread acceptance and has become the primary treatment method for all lesions regardless of lesion length and complexity.[1-3] This has largely been driven by technical advancements enabling successful crossing and opening of the lesion and with increasing patency rates by the use of drug eluting technology and third generation stents. For short and intermediate SFA lesions, there is evidence that supports a "leave nothing behind" strategy.[4]

However, robust evidence for optimal treatment of long-segment SFA lesions, especially regarding chronic total occlusions (CTO), is still lacking. The RAPID Trial aimed to investigate the added value of a drug coated balloon (DCB) (Legflow, Cardionovum GmbH, Bonn, Germany) in a primary stenting strategy with the Supera stent (Abbott Laboratories, Abbott Park, IL, USA) in intermediate (5-15 cm) and long (>15 cm) SFA lesions. The short-term results of the RAPID Trial showed that there were no significant differences between the Supera + DCB and Supera group with respect to efficacy, mortality and other safety endpoints.[5] In the current report, the 2-year results of the RAPID Trial are presented.

Materials and methods

The study protocol has been published in full prior to commencement of this trial.[5, 6] The study design was approved by the principal ethics committee (Verenigde Commissies Mensgebonden Onderzoek, chair dr. V.H.M. Deneer, 27-04-2012) and by each site's institutional review board or ethics committee under number NL39391.100.12 and trial identifier ISRCTN47846578. All patients provided written informed consent.

Study design

The RAPID Trial is a prospective, multicenter, patient-blind randomized trial, including intermediate (5-15 cm) and long (>15 cm) lesions of the SFA. 160 patients were randomized in a 1:1 fashion to an intervention group which is primary Supera stenting supported with a Legflow DCB or a control group consisting of Supera stenting only.

Patient population

Patients had to be ≥18 years, suffering from symptomatic peripheral arterial occlusive disease (PAOD Rutherford 2-6) and presenting with de novo SFA lesions with a length of ≥50 mm, ostial lesions being admissible. Important exclusion criteria were life expectancy <1 year, obstruction caused by thrombosis, aneurysmal disease, acute obstruction and dissection.

Study endpoints

The primary end-point was primary patency, which was defined as the absence of binary restenosis (peak systolic velocity ratio (PSVR) ≥2.4 on duplex ultrasound (DUS) or >50% stenosis on digital subtraction angiography [DSA]) at 2 years. Follow-up visits were at 1 month, 6 months, 1 year and 2 years with DUS, Ankle Brachial Index (ABI) and toe pressure measurements.

Secondary end-points were: freedom from clinically driven target-lesion revascularization (CD-TLR), secondary patency and sustained functional outcomes such as Rutherford class, ABI and toe pressure measurements[6] and primary sustained clinical improvement (defined as an upward shift of at least one category per Rutherford classification at 2 years compared to baseline and without the need for reintervention).

Safety end-points were freedom of periprocedural deaths (PPD), major adverse limb events (MALE) and freedom from all-cause mortality at 2 years.

Statistical analysis

The RAPID Trial was powered to demonstrate a 25% reduction in restenosis rate in favor of the Supera + DCB group. 160 lesions were necessary to reach a statistical power of 80% with α=0.05.

Continuous data are presented as means±standard deviation; categorical data are provided as counts (percentage). χ^2 or Fisher Exact Test (when appropriate) were used to compare categorical variables. Continuous variables were compared using Student's *t*-tests for independent samples. Kaplan-Meier (KM) estimates were used comparing patency, freedom from CD-TLR, and safety outcomes; log-rank test was used to evaluate group differences. Survival estimates are given with a 95% confidence interval (CI). Unadjusted and adjusted crude effect analyses were performed by using the Cox proportional hazards model. All data were analyzed using SPSS software (version 24.0 for Windows; IBM Corporation, Armonk, NY, USA).

Results

Baseline and procedural characteristics

The RAPID Trial included 160 patients randomized to treatment with Supera + DCB (N.=80) and Supera (N.=80). Seven patients in the Supera + DCB group were not included in the per protocol analysis. Five patients due to geographic miss and two patients due to stent related technical failures. Three patients in the Supera group were not included in the per protocol analysis due to stent related technical failures (Figure 1).

Demographics, comorbidities, and lesion characteristics were similar between the Supera + DCB and Supera groups and have been published before.[5] Mean lesion length was 15.8±7.4 cm (range 5.0-33.0 cm) in the Su-

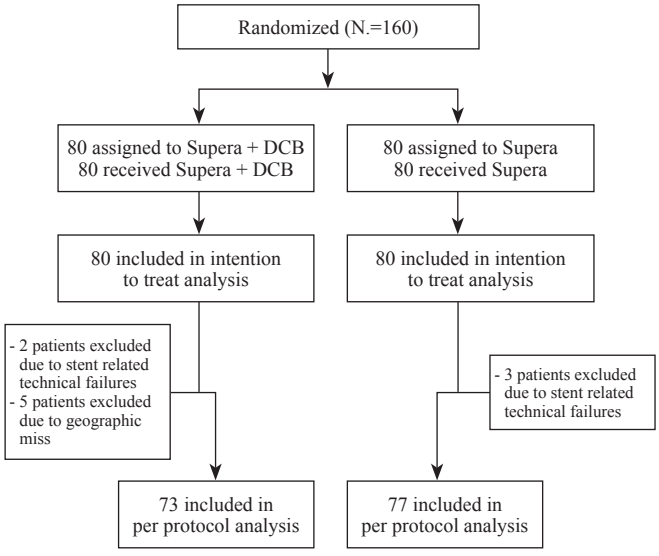

Figure 1.—Patient inclusion in the trial.
DCB, drug-coated balloon.

pera + DCB group and 15.9±7.6 cm (range 5.0-35.0 cm) in the Supera group (P=0.926). In the Supera + DCB group 76.3% of lesions were total occlusions *vs.* 70.0% in the Supera group (P=0.713). Ostial involvement was present in 25% of the lesions in both groups (P=1.000). In addition, over a third of the lesions (38.8% in the Supera + DCB group *vs.* 36.3% in the Supera group (P=0.984) had bilateral calcifications according to the Peripheral Arterial Scoring System (PACCS).[7]

Efficacy outcomes through 2 years

In the intention to treat analysis, the KM estimate of primary patency rate at 2 years was 55.1% (95% CI: 43.1-67.1%) in the Supera + DCB group *versus* 48.3% (95% CI: 35.6-61.0%) in the Supera group (P=0.957) (Figure 2A). Unadjusted crude effect hazard ratio for using a DCB was 0.987 (95% CI: 0.607-1.605; P=0.957). When adjusted for baseline and lesions characteristics crude effect hazard ratio for using a DCB was 0.335 (95% CI: 0.052-2.162; P=0.250).

Per protocol analysis showed a KM estimate of primary patency rate of 60.9% (95% CI: 48.6-73.2%) in the Supera + DCB group *versus* 49.8% (95% CI: 36.9-62.7%) in the Supera group (P=0.469; Figure 2B). Per protocol KM estimate of secondary patency were 83.1% (95% CI: 73.9-92.3%) *vs.* 82.3% (95% CI: 72.7-91.9%) (P=0.941) and freedom of CD-TLR 75.4% (95% CI: 64.8-86.0%) *vs.* 73.0% (95% CI: 62.0-84.0%) (P=0.957) in the Supera + DCB group and Supera group, respectively (Figure 3A, B).

Safety outcomes at 2 years

KM estimates of freedom from MALE and PPD at 2 years were 68.5% (95% CI: 57.7-79.3%) in the Supera + DCB group *vs.* 75.2% (95% CI: 64.8-85.6%) (P=0.224) in the Supera group. KM estimate of freedom from all-cause mortality was 92.8% (95% CI: 85.9-99.7%) (N.=4) in the Supera + DCB *vs.* 93.7% (95% CI: 87.6-99.8%) (N.=4) (P=0.975) in Supera group. There were seven deaths in

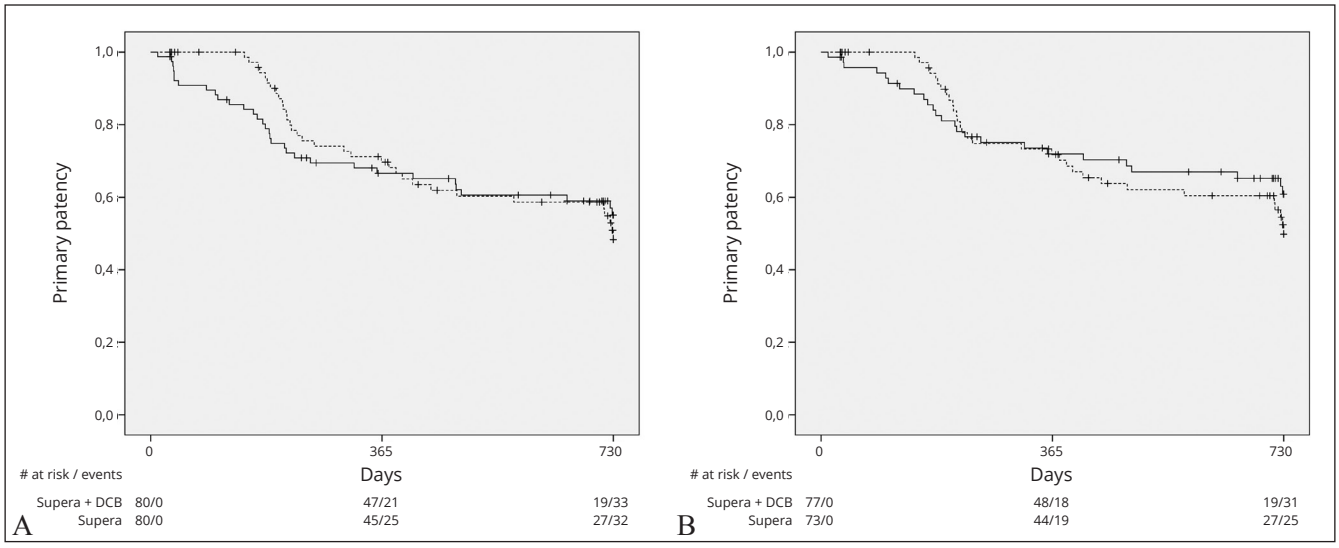

Figure 2.—A) Kaplan Meier (KM) estimates of primary patency (intention to treat analysis; P=0.957); B) KM estimates of primary patency (per protocol analysis; P=0.469). Solid line represents the Supera + drug-coated balloon group, dotted line represents the Supera group.

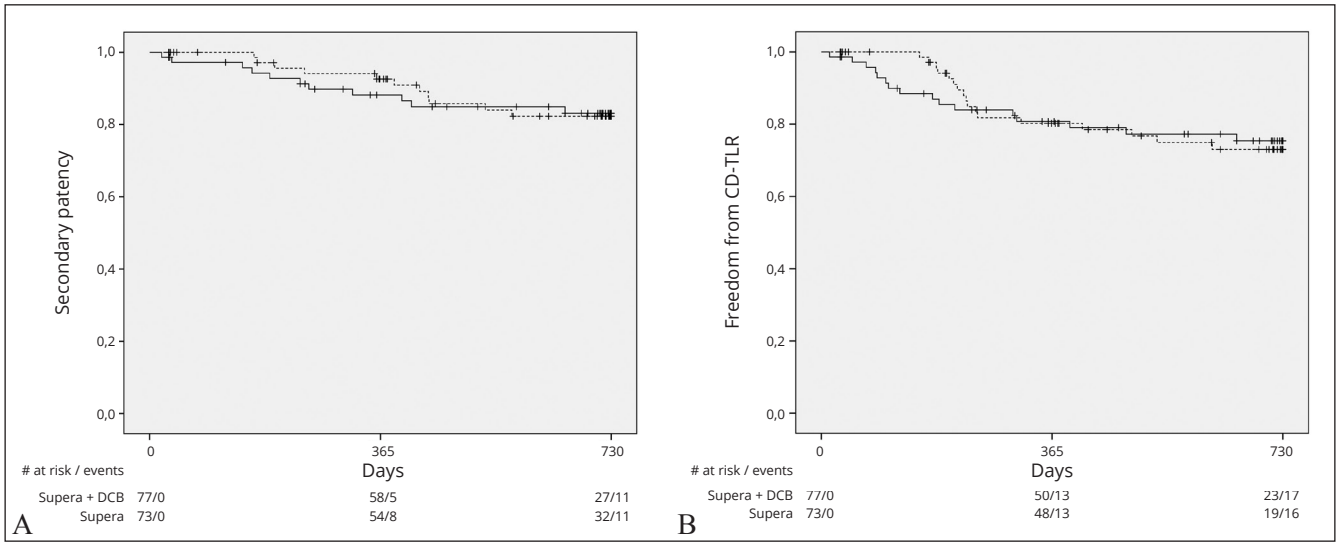

Figure 3.—A) Kaplan Meier (KM) estimates of secondary patency (per protocol analysis; P=0.941); B) KM estimates of freedom of clinically driven target lesion revascularization (CD-TLR) (per protocol analysis; P=0.957). Solid line represents the Supera + drug-coated balloon group, dotted line represents the Supera group.

total, which accounted for eight events, as one of these patients was included in the trial with both legs (both in the Supera + DCB group). Causes of death in the Supera + DCB group were; cardiac arrest (9 months), abdominal sepsis (24 months) and 1 death due to unknown causes (accounted for 2 events at 14 and 17 months), in the Supera group there were 3 deaths due to unknown causes (7, 12 and 22 months) and 1 due to lung cancer (11 months).

Functional outcomes

Both groups showed sustained improvement compared to baseline regarding Rutherford classification, ABI and toe pressures (Table I). There were no statistically significant differences between the groups, except for ABI improvement in rest after 1 month.

The KM estimate of the primary sustained clinical improvement was 62.6% (95% CI: 49.5-75.7%) in the Supera + DCB group and 58.5% (95% CI: 45.6-71.4%) in the Supera group (P=0.581).

Discussion

The RAPID Trial is the first multicenter randomized controlled trial to compare a primary Supera stenting strategy with or without the support of a DCB in intermediate and long SFA lesions. The 2-year results of this trial show that the use of the Legflow DCB in the SFA is safe, without an increased risk in all-cause mortality. However, there is no

TABLE I.—*Changes in Rutherford class, ankle brachial index (ABI) and toe pressures of the study population.*

	Supera + DCB	Supera	P
Rutherford class improvement			
Baseline	2.75 (0.97)	2.87 (1.06)	0.492 *
1 month	-2.39 (1.09)	-2.36 (1.18)	0.859 *
6 month	-2.23 (1.11)	-2.10 (1.36)	0.551 *
12 month	-2.36 (1.04)	-2.10 (1.50)	0.227 *
24 month	-2.08 (1.41)	-2.09 (1.43)	0.986 *
ABI			
Rest			
Baseline	0.60 (0.20)	0.61 (0.19)	0.791 *
1 month	0.89 (0.18)	0.97 (0.15)	0.016 *
6 month	0.88 (0.19)	0.90 (0.20)	0.463 *
12 month	0.84 (0.19)	0.91 (0.20)	0.223 *
24 month	0.83 (0.17)	0.85 (0.16)	0.432 *
Postexercise			
Baseline	0.34 (0.18)	0.38 (0.20)	0.442 *
1 month	0.79 (0.26)	0.85 (0.20)	0.276 *
6 month	0.73 (0.27)	0.74 (0.26)	0.864 *
12 month	0.72 (0.22)	0.69 (0.31)	0.558 *
24 month	0.65 (0.27)	0.68 (0.25)	0.647 *
Toe pressure			
Hallux			
Baseline	59 (30.0)	64 (41.2)	0.599 *
1 month	106 (44.6)	111 (37.3)	0.522 *
6 month	95 (34.4)	108 (35.6)	0.070 *
12 month	93 (32.6)	97 (45.9)	0.633 *
24 month	94 (40.0)	90 (36.5)	0.674 *

Continuous data are shown as mean (SD).
PEB: paclitaxel eluting balloon; ABI: Ankle Brachial Index.
*One-way ANOVA.

statistically significant difference in KM estimates of primary patency or in any other of the secondary endpoints such as freedom from CD-TLR between the two groups.

For short (<5 cm) and intermediate (5-15 cm) lesions, adequate vessel preparation and finalizing treatment with a DCB or bail-out stenting in case of flow limiting dissections has been proven to be an effective treatment approach.[8-12] However, treatment of complex and long-segment (>15 cm) SFA lesions remains challenging and although many adopt an endovascular first strategy, it is limited by the occurrence of restenosis and a high need for bailout stenting.

During the design of the study, data on the Supera stent became available with high patency rates at short-term follow-up in short and intermediate SFA lesions.[13] Patency rates seemed higher compared to standard laser-cut nitinol stents and therefore the Supera stent was selected for the trial. Surprisingly, the 2-year RAPID primary patency rates are lower, compared to other reported patency rates of the Supera.[13-16] In comparison, the 12 months results of the SUPERB Trial showed a primary patency of 79%, but included less challenging lesions (mean lesion length 7.8 cm±4.3 cm, 25% CTO's).[15] Freedom from CD-TLR was 84% at 2 years, comparable to the results of the RAPID Trial.

Data on long SFA lesions and Supera stenting is mainly based on several single center retrospective experiences. The results of the Leipzig registry sub cohort of lesions >15 cm with 53% CTOs and 52% of the SFA lesions with moderate or severe calcifications are comparable to RAPID outcomes with a primary patency rate at 2 years of 62%.[14] Brescia *et al.* published their experience with the Supera stent in long SFA lesions. They used only clinical primary stent patency (defined as clinical resolution of symptoms and freedom from secondary interventions and comparable to freedom from CD-TLR) to determine efficacy. Mean lesion length was 24.0 cm (range 3-51 cm), clinical primary stent patency was 83.1% at 2 years, similar to freedom from CD-TLR rates in the RAPID Trial.[17]

The idea to support the Supera with a DCB comes from data available from studies demonstrating an added benefit of drug coated technology in preventing restenosis.[8, 10-12, 18-23] The 2-year results of the RAPID Trial are consistent with other trials reporting on intermediate and long SFA lesions (Table II, Figure 4, 5).[8, 10, 22, 24-30] Both primary patency rate and freedom from CD-TLR decline with increasing lesion length, higher CTO rate and longer follow-up.

TABLE II.—*Overview of reported 2-year primary patency rates, freedom from clinically driven target lesion revascularization (CD-TLR), lesion length and occlusion rate of various trials.*

	Lesion length	CTO rate	Primary patency	Freedom from CD-TLR
RAPID	15.8	76.3	60.9	75.4
Zilver-PTX[24]	6.6	32.8	74.8	86.6
ILLUMINATE[25]	7.2	19.2	75.2	88.9
MAJESTIC[22]	7.8	46.0	83.5	92.8
LEVANT I[10]	8.1	42.0	57.0	64.0
IN.PACT SFA[8]	8.9	25.8	78.9	90.9
IN.PACT SFA JAPAN[26]	9.2	16.2	79.8	90.9
IN.PACT Global[27]	12.1	35.5	x	83.3
CONSEQUENT[28]	13.7	23.1	72.3	80.9
ACO-ART I[29]	14.7	57.0	64.6	86.5
REAL-PTX DCB group[30]	15.0	53.3	56.0	80.0
REAL-PTX DES group[30]	15.6	52.0	64.6	80.1

Lesion length in cm; CTO rate, primary patency and freedom from CD-TLR in %. CTO: chronic total occlusions; CD-TLR: clinically driven target lesion revascularization.

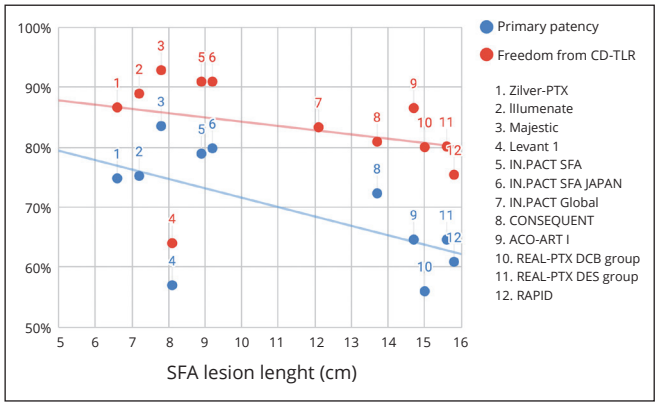

Figure 4.—Overview of 2-year primary patency and freedom from clinically driven target lesion revascularization (CD-TLR) *versus* lesion length reported by various trials.

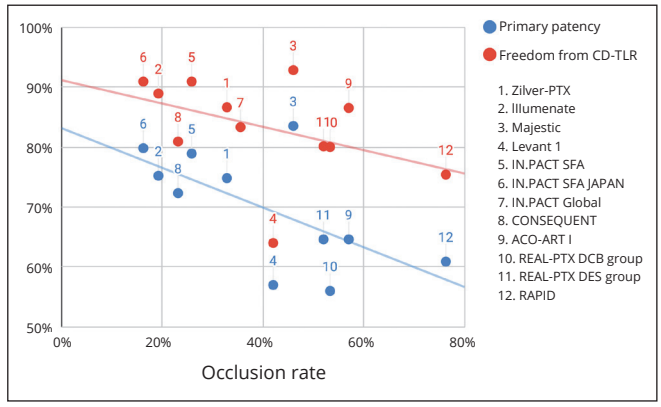

Figure 5.—Overview of 2-year primary patency and freedom from clinically driven target lesion revascularization (CD-TLR) *versus* percentage of occluded lesions reported by various trials.

Recently, there has been much debate regarding the safety of paclitaxel eluting balloons.[31] The RAPID Trial did not show a significant difference in any of the safety outcomes at 2 years, including all-cause mortality. This data is in line with recently presented 5-years data from the Acoart I Trial[32] and a patient-level meta-analysis of the IN.PACT Admiral DCB (Medtronic, Dublin, Ireland).[33]

Limitations of the study

The power analysis for this trial was calculated on data from early generation laser-cut nitinol stent studies showing a restenosis rate of almost 50% at 2 years.[34] Since the reported restenosis rate of the Supera stent is <50%, in combination with the reported technical failures, this assumption might have resulted in an underpowered study population.

A second limitation is that during the design of the study, the distribution of the subjects across the participating centers was not stratified. This resulted in high and low enrolling centers, which could have had an effect on the results. Four out of eight centers included <15 patients.

The trial was not sufficiently powered to perform reliable sub analyses on center effects or extended subgroup analyses.

Conclusions

The 2-year results of a primary Supera stenting strategy are consistent with other trials reporting on treatment of intermediate and long SFA lesions. The Legflow DCB is safe to use in long SFA lesions, but did not improve patency rates compared to a Supera-only strategy.

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