



Clinical Review of Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease

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Abstract

Background—Sustained benefits of drug-eluting stents in femoropopliteal arteries have not been demonstrated. This prospective, multinational, randomized study was designed to compare the 12-month safety and effectiveness of a polymer-free, paclitaxel-coated nitinol drug-eluting stent (DES) with percutaneous transluminal angioplasty (PTA) and provisional bare metal stent (BMS) placement in patients with femoropopliteal peripheral artery disease. The ZENFLEX Pro™ Peripheral Drug-eluting Stent System is indicated for improving luminal diameter in the treatment of de novo or restenotic symptomatic lesion(s) in native vascular disease of the above-the-knee femoropopliteal arteries with reference vessel diameter from 4.0 mm to 6.5

Methods and Results—Patients were randomly assigned to primary DES implantation (n=236) or PTA (n=238). Demographics and lesion characteristics were similar between groups (eg, average lesion length, approximately 65±40 mm). One hundred twenty patients had acute PTA failure and underwent secondary random assignment to provisional DES (n=61) or BMS (n=59). Primary end points were the 12-month rates of event-free survival and patency in the primary DES and PTA groups. Compared with the PTA group, the primary DES group exhibited superior 12-month event-free survival (90.4% versus 82.6%; $P=0.004$) and primary patency (83.1% versus 32.8%; $P<0.001$), satisfying the primary hypotheses. In the secondary evaluations, (1) the primary DES group exhibited superior clinical benefit compared with the PTA group (88.3% versus 75.8%; $P<0.001$), (2) the provisional DES group exhibited superior primary patency (89.9% versus 73.0%; $P=0.01$) and superior clinical benefit (90.5% and 72.3%, $P=0.009$) compared with the provisional BMS group, and (3) the stent fracture rate (both DES and BMS) was 0.9% (4/457).

In addition, a comparison clinical study was applied in order to evaluate and review the compliance of data collected with European medical device directive MDD 93/42/EEC, Medical device Regulation MDR 2017/745 and BS EN ISO 14155:2020; the evaluation shall take into consideration the state of the artery.

Conclusions—Femoropopliteal peripheral artery disease treatment with the paclitaxel-eluting stent was associated with superior 12-month outcomes compared with PTA and provisional BMS placement.

In patients who required TLR, DES had a significantly longer length of time to reintervention vs DCB (average 373 days), although no difference in mortality was observed.

Based on the assessment applied; it has been noted that the statistical significant has been considered during this randomized clinical trial; selection of patient was optimum, the assessment was applied for the randomized clinical study where adequate clinical performance, outcomes, clinical safety and clinical benefits were addressed correctly. MDD 93/42/EEC, Medical device Regulation MDR 2017/745 and BS EN ISO 14155:2020. Ta

Keywords: femoropopliteal arteries, BMS, DES, PTA, DES implantation.

Introduction

Endovascular therapy is one option commonly used to treat patients with lifestyle-limiting intermittent claudication or critical limb ischemia caused by femoropopliteal peripheral artery disease (PAD). However, data supporting specific therapies are limited. Percutaneous transluminal balloon angioplasty (PTA) is associated with unacceptable 1-year restenosis rates (often 60%)¹⁻³ that worsen with lesion complexity. Some first-generation stents were associated with outcomes similar to PTA.^{4,5} More recently, self-expanding nitinol stents have demonstrated improved patency results, yet restenosis remains a limitation, with 12-month rates between 20% and 37% reported.^{3,6-8}

Success in coronary artery intervention⁹⁻¹² led to investigation of drug-eluting stents (DES) in the superficial femoral artery (SFA). Six-month results with polymer-based sirolimus-eluting¹³ and everolimus-eluting¹⁴ stents were favorable, but benefits were not sustained.

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Paclitaxel has been shown to inhibit neointimal hyperplasia, is highly lipophilic, is avidly protein-bound, and partitions into and is retained by arterial tissue.¹⁵⁻¹⁷ In recent clinical trials, paclitaxel-coated balloons in the SFA have been associated with improved outcomes compared with PTA,^{18,19} further suggesting that prolonged paclitaxel delivery may be unnecessary for inhibiting restenosis.

The purpose of the ZENFLEX Pro Randomized Clinical Study was to evaluate the safety and effectiveness of a self-expanding nitinol DES with 3 $\mu\text{g}/\text{mm}^2$ polymer-free paclitaxel coating on its outer surfaces.

WHAT IS KNOWN

- Restenosis and loss of patency remain limitations of percutaneous transluminal balloon angioplasty (PTA) and bare metal stents (BMS) in the endovascular management of patients with symptomatic femoropopliteal peripheral artery disease.
- Data are limited regarding successful use of drug-eluting stents (DES) in the treatment of femoropopliteal artery disease.

WHAT THE STUDY ADDS

- The ZENFLEX Pro is a randomized study of a paclitaxel-coated, self-expanding nitinol stent (DES) versus PTA and provisional stenting (BMS versus DES) for lesions up to 14 cm long in the above-the-knee femoropopliteal artery.
- DES in moderate-length femoropopliteal lesions resulted in superior outcomes at 12 months compared with PTA and BMS, supporting use in this lesion subset.
- The results with DES in a broader population of patients with femoropopliteal disease, including lesions longer than 14 cm, could complement the present study.

Methods

Study Design

The ZENFLEX Pro Randomized Clinical Study was a prospective, multinational, controlled trial designed to randomly assign 480 patients with symptomatic PAD involving the above-the-knee femoropopliteal arteries to receive PTA or primary DES (paclitaxel-coated ZENFLEX Pro Drug-Eluting Stent, Zhejiang Zylux Medical Device Co., Ltd. Bloomington, IN) treatment. Because PTA often fails acutely, the study included a secondary random assignment to treatment with either the DES or bare metal stent immediately after acute PTA failure, providing a direct comparison of the outcome with BMS versus DES in the setting of provisional stenting. To minimize bias, block randomization by site (randomly assigned block sizes of 4 or 6 patients) was performed using an interactive voice response system.

Patients with up to 2 de novo or restenotic lesions of the above-the-knee femoropopliteal artery (1 per limb) meeting the general inclusion/exclusion

criteria provided written informed consent before the procedure. Major inclusion criteria included Ruther-

ford category 2 and resting ankle brachial index (ABI) <0.9. Major exclusion criteria included untreated >50% diameter stenosis (DS) of the inflow tract, lesion pretreatment with adjunctive devices, and previous target vessel stenting. Study enrollment occurred only after satisfying the arteriographic inclusion/exclusion criteria, which included lesion length 14 cm, 50% DS, reference vessel diameter 4 to 9 mm, and at least 1 patent runoff vessel (<50% DS throughout its course).

The protocol was approved by the US Food and Drug Administration (FDA) under an Investigational Device Exemption, by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), by German authorities, and by the institutional review board or ethics committee at each site. The study was overseen by an independent Data Safety Monitoring Board and was conducted in accordance with Good Clinical Practices.

A Clinical Events Committee (CEC) adjudicated major adverse events, and core laboratories provided independent analyses for arteriographic and radiographic imaging (Brigham and Women's Hospital Angiographic Core Laboratory, Boston, MA) and duplex ultrasound imaging (VasCore, Massachusetts General Hospital, Boston, MA).

Interventions

Pre procedure data collection included Rutherford classification, ABI, and Walking Impairment Questionnaire²⁰ (WIQ; a validated measure of patient-perceived walking performance). After baseline arteriography, eligible patients were randomly assigned to either PTA or DES treatment.

Stents were implanted to fully cover the target lesion(s) and were placed at least 1 cm below the SFA origin and above the medial femoral epicondyle. Predilation and postdilation were at the physician's discretion, with residual DS <30% required for procedural success.

PTA was performed according to institutional standard practice. Acute PTA failure was defined as 30% DS noted on arteriography (including persistent, flow-limiting dissections) or a 5mm Hg mean transstenotic pressure gradient. The protocol required 1 PTA was performed according to institutional standard practice. Acute PTA failure was defined as 30% DS noted on arteriography (including persistent, flow-limiting dissections) or a 5 mm Hg mean trans-stenotic pressure gradient. The protocol required 1 repeat, 2- to 3-minute balloon inflation before PTA was considered a failure. Patients who had acute PTA failure underwent secondary random assignment to receive either provisional BMS or DES. PTA treatments that did not acutely fail were considered optimal PTA, and these patients did not receive stents.

Within 3 days after the procedure, all patients underwent ABI assessment and duplex ultrasonography, and high-resolution stent radiographs in 2 planes (1 with the leg straight

and 1 with the leg bent 90° at the knee) were obtained for stented patients.

Medical Therapy

The same antiplatelet regimen was recommended for all patients: clopidogrel starting at least 24 hours before the intervention or a procedural loading dose of 300 mg orally; continued clopidogrel therapy for at least 60 days after the procedure; and lifelong aspirin therapy. In Japan, clopidogrel was not available; therefore, ticlopidine was an acceptable substitute.

Follow-Up

Follow-up included telephone contact at 1, 3, and 9 months to assess overall patient condition. The 6- and 12-month in-clinic data collection included ABI, Rutherford score, WIQ, and duplex ultrasound evaluation of patency. High-resolution stent radiographs in 2 planes (1 with the leg straight and 1 with the leg bent 90° at the knee) were also obtained at 12 months to assess stent integrity.

Primary End Points

As required by regulatory authorities, the primary safety and effectiveness hypotheses compared the primary DES and PTA groups. Both analyses were performed per the initial random assignment (ie, intention-to-treat analyses). The primary safety end point was event-free survival (EFS) at 12 months defined as freedom from both (1) CEC-adjudicated major adverse events (death, amputation, clinically driven target lesion revascularization [TLR], target limb ischemia requiring surgical intervention, or surgical repair of the target vessel) and (2) worsening of the Rutherford score by 2 classes, or to class 5 or 6. Clinically driven TLR was defined as reintervention performed for 50% diameter stenosis identified by duplex ultrasound and arteriography within ±5mm of the target lesion after documentation of recurrent clinical symptoms of PAD.

The primary effectiveness end point was primary patency (including the region 5 mm proximal and distal to the target lesion) at 12 months. Patency was conservatively defined as duplex ultrasound-derived peak systolic velocity ratio <2.0 from core laboratory analysis or $<50\%$ DS from arteriographic core laboratory analysis, when available. As pre-specified, acute PTA failure was counted as a loss of patency for the primary effectiveness end point.

Secondary Evaluations

Protocol-specified secondary evaluations included comparison of the patency rates for provisional DES versus provisional BMS placement after acute PTA failure, comparison of clinical outcomes (ABI, Rutherford score, WIQ) at 12 months for the primary DES versus PTA groups, and stent integrity based on core laboratory analysis of radiographs. Additional evaluations included comparison of patency rates for primary DES versus optimal PTA and primary DES versus PTA with provisional stent placement and assessment of a post treatment clinical benefit index (defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after the initial study treatment).

Statistical Analysis

Sample size was estimated on the basis of available literature describing femoropopliteal PTA outcomes.^{21–26} The calculation assumed the 12-month primary patency rates were 65% and 80% in the PTA and DES groups, respectively. Power analysis was performed using a logistic regression model assumed to contain the treatment effect and 3 binary covariates.²⁷ The treatment effect was assumed to be the same at each level of the binary covariates. An overall model χ^2 statistic with 4 degrees of freedom resulted in a sample size of 413 patients, to provide 80% power. Primary patency was assessed using a generalized estimating equations (GEE) model on a per-lesion basis to account for multiple treated lesions per patient. Independence of multiple lesions was assumed for all lesion analyses, except the primary patency outcome.

The non inferiority primary safety hypothesis was assessed on a per-patient basis using a Z-statistic constructed from the Kaplan-Meier estimates: $Z=(EFS_{DES}-EFS_{PTA}+6)/SE$, where $EFS_{(PTA \text{ and } DES)}$ are Kaplan-Meier estimates for 12-month EFS rates; 6 is the minimum difference of practical interest; and SE is the standard error of $EFS_{DES}-EFS_{PTA}$. The power is 0.92, assuming worst-case event-free survival rates (0.50 and 0.55 in the PTA and DES groups, respectively; $\alpha=0.05$, $\beta=0.10$, and 207 patients per treatment arm). Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC). The primary methods were Fisher exact test (categorical patient characteristics), unpaired t test (continuous patient characteristics), paired t test (ABI and WIQ), Kaplan-Meier with the log-rank test (time to primary patency) or Z-test (safety), and GEE model (logit for patency and multinomial for Rutherford). The family of probability values for tests of EFS and patency were adjusted for multiplicity. Other probability values are unadjusted.

Results

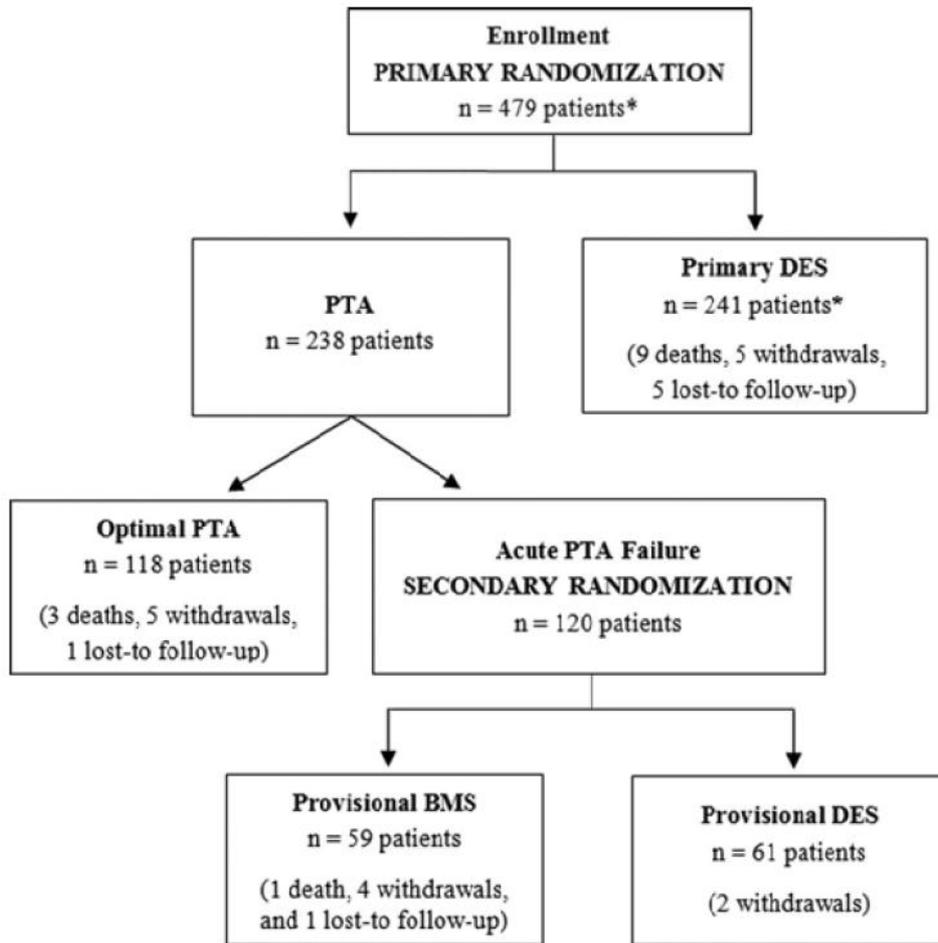
Between March 2005 and August 2008, 479 patients (238 in the PTA group, and 241 in the DES group) were enrolled at 55 institutions in the United States, Japan, and Germany (Figure 1). Demographics, comorbidities, and lesion characteristics were similar for the groups (Table 1). These included approximately 91% of patients with claudication (Rutherford classification 2–3) and 9% with critical limb ischemia (Rutherford classification 4 – 6), an average lesion length of approximately 65 ± 40 mm, and approximately 27% total occlusions.

Procedures

Three hundred fifty-nine primary DES were placed (mean, 1.5; median, 1; range, 1– 4 stents per patient), with a procedural success rate of 95%. One hundred twenty patients (120/238, 50.4%) in the PTA group had acute PTA failure. After secondary random assignment, 59 and 61 patients with acute PTA failure underwent provisional stent placement, provisional stent

placement (a group that does not count acute with 93 BMS and 94 DES placed to treat 62 and 63 lesions, respectively. Overall, the most commonly

used stent diameters were 6 and 7 mm (91.7%) and the most common length was 80mm (55.9%).



*** Note:** Includes 5 live case patients enrolled in the DES group as part of national continuing medical education conferences, and as pre-specified, these were not included in the PP or ITT analyses.

Figure 1. Study flow diagram, including patient enrollment by original random assignments, deaths (all-cause), withdrawals, and subjects lost-to follow-up through 12 months. PTA indicates percutaneous transluminal angioplasty; DES, drug-eluting stent; and BMS, bare metal stent.

Table 1. Baseline Characteristics

	PTA Group		DES Group		P Value
Patient characteristics					
Mean age, y	67.7±10.6		67.9±9.6		0.88
Male sex, n	152	(63.9%)	155	(65.7%)	0.70
Body mass index	28.2±5.6		28.4±5.3		0.71
Claudication (Rutherford class 2–3)	90.7%		90.2%		> 0.99
Critical limb ischemia (Rutherford class 4–6)	8.5%		8.9%		
Diabetes, n	100	(42.0%)	116	(49.2%)	0.13
Type I, n	13	(13.0%)	19	(16.4%)	0.56
Type II, n	87	(87.0%)	97	(83.6%)	
Hypertension, n	194	(81.5%)	210	(89.0%)	0.02*
Hypercholesterolemia, n	166	(69.7%)	180	(76.3%)	0.12
History of smoking, n	200	(84.0%)	204	(86.4%)	0.70
Renal disease, n	25	(10.5%)	24	(10.2%)	>0.99
Pulmonary disease, n	38	(16.0%)	45	(19.1%)	0.39
History of myocardial infarction, n	41	(17.2%)	50	(21.2%)	0.29
Lesion characteristics					
Lesions, n	251		247		0.63
Lesion location, n					
SFA	232 (92.4%)		229 (92.7%)		
SFA/popliteal	6 (2.4%)		9 (3.6%)		
Popliteal	13 (5.2%)		9 (3.6%)		
Previous intervention to study lesion, n	14 (5.9%)		13 (5.5%)		0.69
Vascular access, n					0.78
Contralateral	189 (86.7%)		211 (85.4%)		
Ipsilateral	29 (13.3%)		36 (14.6%)		
Occlusion, n	62 (24.7%)		73 (29.6%)		0.20
Lesion length, normal-to-normal, mm	63.1±40.7		66.4±38.9		0.35
Lesion length, † >20% DS, mm	53.2±40.3		54.3±40.8		0.76
MLD in lesion, mm †	1.1±0.9		1.0±0.9		0.44
Percent diameter stenosis, † %	78.4±17.1		79.6±17.0		0.44
Lesion calcification, † n					<0.001*‡
None	12 (4.8%)		4 (1.7%)		
Little	95 (38.2%)		62 (25.9%)		
Moderate	55 (22.1%)		85 (35.6%)		
Severe	87 (34.9%)		88 (36.8%)		
Ulcerations, † n	47 (19.0%)		40 (16.8%)		0.55

PTA indicates percutaneous transluminal angioplasty; DES, drug-eluting stent; SFA, superficial femoral artery; DS, diameter stenosis; and MLD, minimum lumen diameter.

P values are based on *t* test for continuous variables and Fisher exact test for categorical variables.

*Statistically significant.

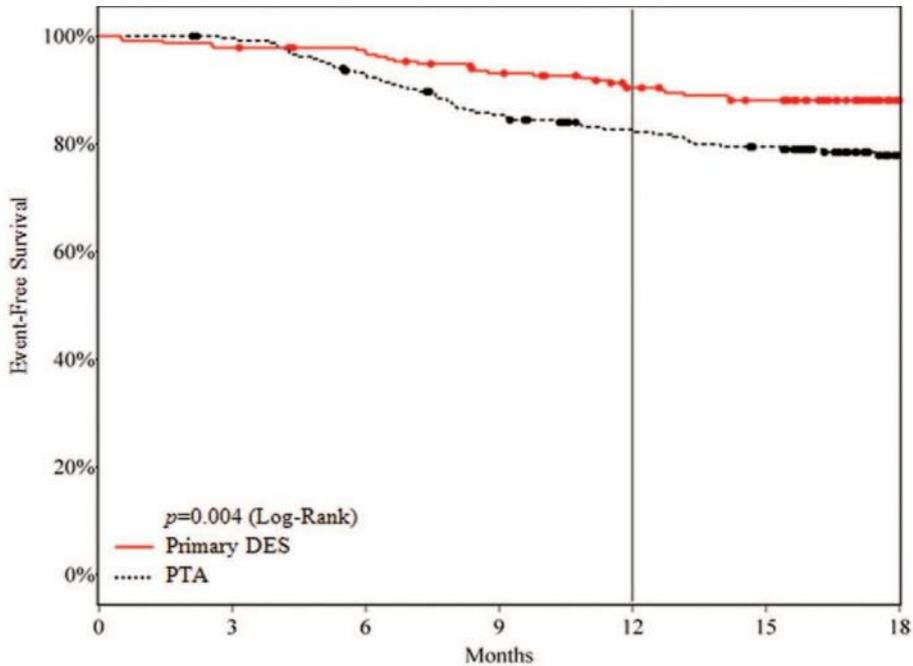
†Core lab data.

‡Indicates that overall, the DES group had significantly more calcification than did the PTA group.

Safety

The primary DES group exhibited EFS superior to the PTA group (including approximately 50% optimal PTA, 25% provisional BMS, and 25%

provisional DES). The 12-month EFS rates were 90.4% for DES and 82.6% for PTA ($P=0.004$; Figure 2), satisfying the primary safety hypothesis.



Kaplan Meier Estimates of Event-Free Survival, Values Represent Patients								
Months Post-procedure	EFS ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	0	236	235
1	100.0 ± 0.0%	99.1 ± 0.6%	0	2	0	0	236	233
6	93.2 ± 1.7%	97.0 ± 1.1%	16	7	5	3	215	225
12	82.6 ± 2.5%	90.4 ± 1.9%	40	22	15	16	181	197

Figure 2. Twelve-month primary safety outcomes. The black curve shows 82.6% event-free survival (EFS) for the percutaneous transluminal angioplasty (PTA) group and the red curve shows the significantly higher ($P=0.004$) 90.4% EFS for the primary drug-eluting stent (DES) group. The corresponding life table is included.

There were no procedure- or device-related deaths, and amputation and worsening of Rutherford classification were rare, with similar frequencies in the study groups (Table 2). The most common major adverse event was clinically driven TLR. The core laboratory determined arteriographic diameter stenosis immediately before TLR was $80 \pm 16\%$ (mean \pm SD), and TLR occurred significantly less often ($P=0.01$) in the DES group.

There were no procedure- or device-related deaths, and amputation and worsening of Rutherford classification were rare, with similar

frequencies in the study groups (Table 2). The most common major adverse event was clinically driven TLR. The core laboratory determined arteriographic diameters tenosis immediately before TLR was $80 \pm 16\%$ (mean \pm SD), and TLR occurred significantly less often ($P=0.01$) in the DES group 9.5%; 21/220) than in the PTA group (17.5%; 39/223).

All-cause death (eg, malignancy, pulmonary disease, congestive heart failure) included 4 patients in the PTA group and 9 patients in the DES group ($P=0.17$). Other reported effects related to the paclitaxel coating ornitinol stent.

Table 2. Major Adverse Events

12-Month Major Adverse Events†	PTA Group	DES Group
Death	0	0
Amputation (toe)	0 (0.0%)	1 (0.5%)
Clinically driven TLR‡	3 9 (17.5%)	21 (9.5%)*
Worsening of Rutherford classification by 2 classes or to a class 5 or 6	2 (0.9%)	0 (0.0%)

PTA indicates percutaneous transluminal angioplasty; DES, drug-eluting stent; and TLR, target lesion revascularization.

* $P=0.01$ compared with DES group.

†Independently adjudicated by the Clinical Events Committee to be device-related and/or procedure-related.

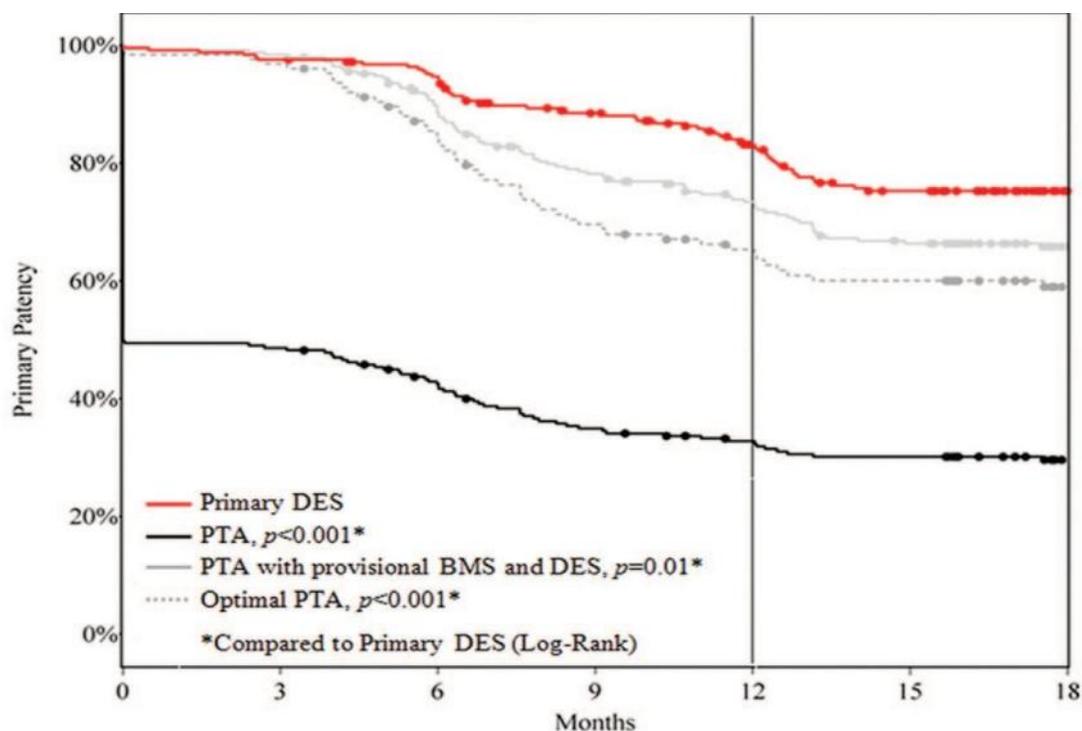
‡Clinically driven TLR was defined as reintervention performed for 50% diameter stenosis arteriographically identified within ± 5 mm of the target lesion, after documentation of recurrent clinical symptoms of peripheral artery disease.

Effectiveness

The 12-month primary patency rate of 83.1% for the primary DES group was significantly superior ($P<0.001$; GEE and log-rank test, [Figure 3](#)) to the 32.8% for the PTA group (as adverse events were consistent with this patient population and reported at similar rates in both study groups. There were no reports of hypersensitivity reactions or adverse drug pre specified, acute PTA failure was counted as a loss of patency), satisfying the primary effectiveness hypothesis.

The secondary comparisons included in [Figure 3](#) also showed superior 12-month primary patency

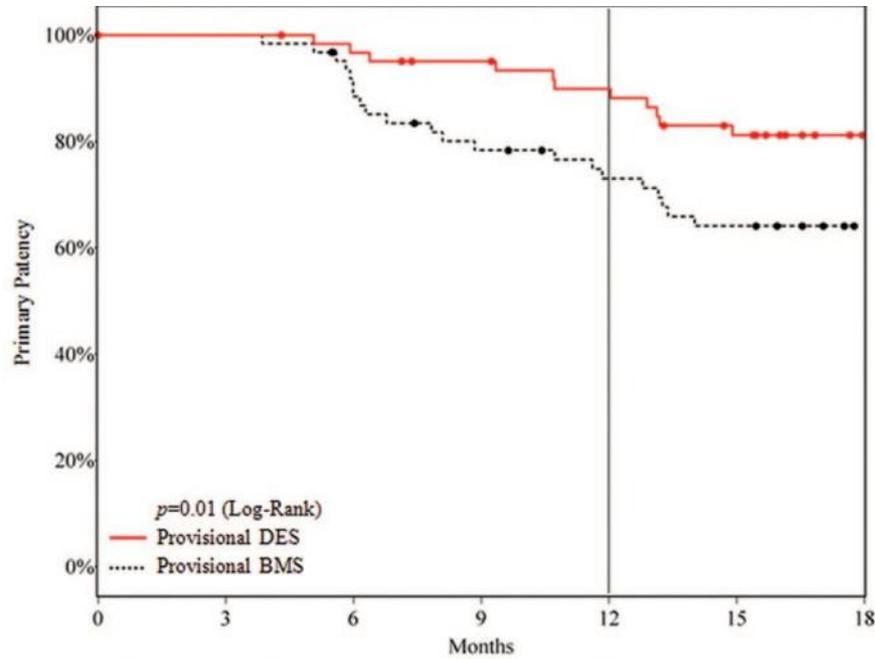
with primary DES placement. Specifically, the 83.1% patency rate for primary DES placement was significantly superior ($P<0.001$) to the 65.3% rate for optimal PTA, a group that excludes patients who had acute PTA failure. In addition, the 83.1% patency rate for primary DES placement was significantly superior ($P=0.01$) to the 73.4% rate for PTA with provisional stent placement (a group that does not count acute PTA failure as a loss of patency and therefore comprised patients with optimal PTA (50%), and patients with provisional BMS (25%) and provisional DES placement (25%) after acute PTA failure).



Kaplan Meier Estimates of Primary Patency, Values Represent Lesions								
Months Post-procedure	Primary Patency ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES
0	49.8 ± 3.2%	99.6 ± 0.4%	126	1	0	0	125	246
1	49.4 ± 3.2%	99.2 ± 0.6%	127	2	0	0	124	245
6	42.5 ± 3.1%	94.7 ± 1.4%	144	13	5	3	102	231
12	32.8 ± 3.0%	83.1 ± 2.4%	167	40	10	26	74	181

Figure 3. Twelve-month primary effectiveness outcomes (**red and black curves**). The **black curve** shows the 32.8% primary patency rate for the percutaneous transluminal angioplasty (PTA) group (as pre specified, acute PTA failure was a loss of patency and accounts for the drop in the PTA patency curve on day 0), and the **red curve** shows the significantly higher ($P<0.001$) 83.1% primary patency rate for the drug-eluting stent (DES) group. The corresponding life table is included. Secondary evaluations also show that the primary patency rate for the DES (**red curve**) is (1) significantly higher ($P<0.001$) than the 65.3% primary patency rate for optimal PTA, a group that excludes patients who had acute PTA failure (dotted gray curve), and (2) significantly higher ($P=0.01$) than the 73.4% primary patency rate for PTA with provisional stent placement, a group that does not count acute PTA failure as a loss of patency and therefore consists of patients with optimal PTA (50%) and those who underwent provisional bare metal stent (BMS) (25%) and provisional DES (25%) placement after acute PTA failure (**solid gray curve**).

The protocol-specified secondary evaluation of the pro-visional stent groups provided a direct assessment of the paclitaxel effect and showed a superior 12-month primary patency rate of 89.9% for DES compared with 73.0% for BMS ($P=0.01$; (Figure 4) in the setting of provisional stenting.



Kaplan Meier Estimates of Primary Patency, Values Represent Lesions								
Months Post-procedure	Primary Patency ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	1	62	62
1	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	1	62	62
6	88.4 ± 4.1%	96.7 ± 2.3%	7	2	2	2	53	59
12	73.0 ± 5.8%	89.9 ± 3.9%	16	6	5	5	41	52

Figure 4. Secondary 12-month evaluation comparing the effectiveness of provisional bare metal stents (BMS) and drug-eluting stents (DES). The **black curve** shows the 73.0% primary patency rate for patients undergoing provisional BMS placement after acute percutaneous transluminal angioplasty (PTA) failure; the **red curve** shows the significantly higher ($P=0.01$) 89.9% primary patency rate for patients undergoing provisional DES placement after acute PTA failure. The corresponding life table is included

Clinical Outcomes

The ABI values, Rutherford scores, and walking impairment scores each significantly improved ($P<0.001$) from before treatment to 12 months in both the PTA and primary DES groups, with no significant differences between the groups (Table 3). Additionally, the posttreatment clinical benefit index was sustained through 12 months in 88.3%

of patients in the primary DES group, compared with 75.8% of patients in the PTA group (including those who underwent provisional DES and BMS placement after acute PTA failure; $P<0.001$, Figure 5). The clinical benefit index was also sustained through 12 months in 90.5% of patients in the provisional DES group, compared with 72.3% in the provisional BMS group ($P=0.009$, Figure 6).

Table 3. Clinical Outcomes and Post treatment Clinical Benefit Index Results

PTA Group Measurement	DES Group			
	Baseline	12 Months	Baseline	12 Months
ABI	0.68±0.2	0.89±0.20*	0.67±0.2	0.91±0.23*
Rutherford classification, † % of patients				
0	0%	45.4%	0%	44.7%
1	0.8%	21.7%	0.9%	20.9%
2	46.2%	20.3%	52.5%	23.3%
3	44.5%	10.1%	37.7%	9.2%
4	4.7%	1%	5.9%	1.9%
5	3.4%	1.5%	3%	0%
6	0.4%	0%	0%	0%
Walking scores, maximum possible=100% ‡				
Walking distance	26.3±28.6%	57.7±36.9%*	25.0±27.6%	57.8±37.9%*
Walking speed	29.7±30.3%	58.2±35.7%*	27.5±27.1%	55.7±37.1%*
Climbing	38.7±32.5%	61.5±34.0%*	35.9±32.2%	55.6±37.3%*
Sustained posttreatment clinical benefit index, § % of patients	N/A	75.8%	N/A	88.3%
Worsened posttreatment clinical benefit index, § % of patients				
Persistent or worsening claudication, or rest pain		20.1%		7.9%
Ulcers or tissue loss		4.1%		3.8%

PTA indicates percutaneous transluminal angioplasty; DES, drug-eluting stent; and ABI, ankle-brachial index.

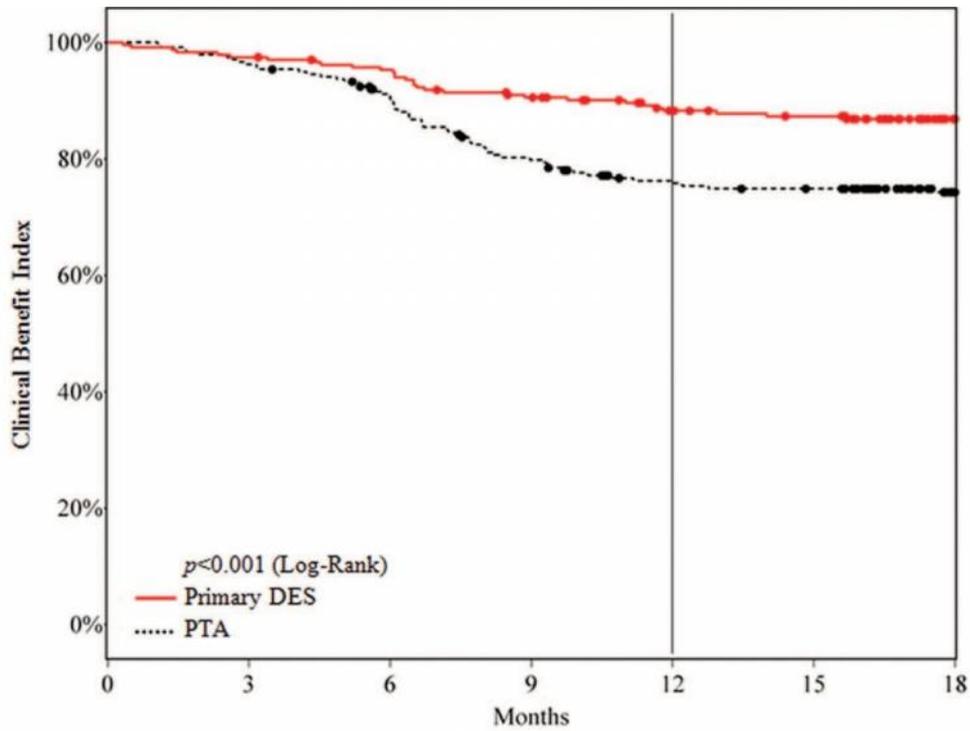
* $P < 0.001$ compared with baseline; paired t test.

†Rutherford classification significantly improved ($P < 0.001$; generalized estimating equations multinomial model) from baseline to 12 months in the PTA group and in the DES group.

‡Walking scores were obtained from the Walking Impairment Questionnaire, 20 which is a validated measure of patient-perceived walking performance. Patient responses are weighted and the weighted average is reported, with a maximum possible score of 100% in each category.

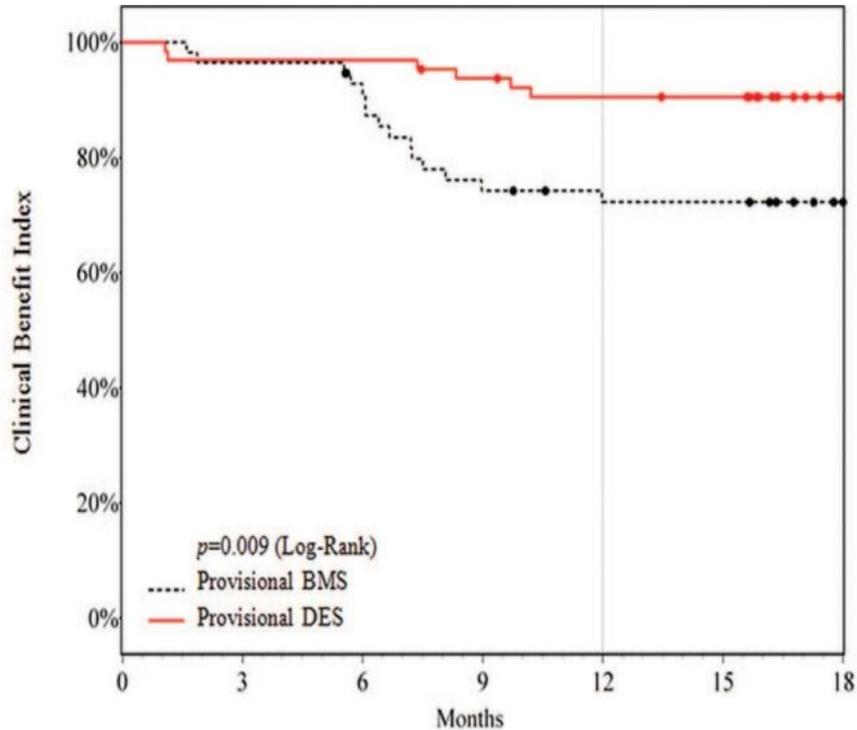
§Post treatment clinical benefit was defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after the initial study treatment.

$P < 0.001$ compared with PTA group; paired t test.



Kaplan Meier Estimates of Clinical Benefit Index, Values Represent Patients								
Months Post-procedure	Clinical Benefit ± Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES	PTA	Primary DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	0	237	234
1	100.0 ± 0.0%	99.1 ± 0.0%	0	2	0	0	237	232
6	90.2 ± 0.0%	95.3 ± 0.0%	23	11	6	2	208	221
12	75.8 ± 0.0%	88.3 ± 0.0%	56	27	15	16	166	191

Figure 5. Twelve-month post treatment clinical benefit index results for primary drug-eluting stents (DES) compared with percutaneous transluminal angioplasty (PTA) treatment. The clinical benefit index was defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after the initial study treatment. The **black curve** shows that 75.8% of patients in the PTA group maintained clinical benefit; the **red curve** shows that 88.3% of patients in the primary DES group maintained clinical benefit ($P<0.001$). The corresponding life table is also included.



Kaplan Meier Estimates of Clinical Benefit Index, Values Represent Patients								
Months Post-procedure	Clinical Benefit ± Standard Error		Cumulative Failed		Cumulative Censored		Number Remaining	
	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES	Provisional BMS	Provisional DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	0	56	64
1	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	0	56	64
6	90.9 ± 3.9%	96.9 ± 2.2%	5	2	2	0	49	62
12	72.3 ± 6.1%	90.5 ± 3.7%	15	6	4	2	37	56

Figure 6. Twelve-month post treatment clinical benefit index results for provisional drug-eluting stents (DES) compared with provisional bare metal stent (BMS) treatment. The clinical benefit index was defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after the initial study treatment. The **black curve** shows that 72.3% of patients undergoing provisional BMS placement after acute percutaneous transluminal angioplasty (PTA) failure maintained clinical benefit; the **red curve** shows that 90.5% of patients undergoing provisional DES placement after acute PTA failure maintained clinical benefit ($P=0.009$). The corresponding life table is included.

Stent Integrity

There were no periprocedural stent fractures (i.e, 529/529 stents were free from fracture after implantation). At 12 months, 453 of 457 (99.1%)

DES and BMS were free from fracture, yielding a 12-month fracture rate of 0.9% (4/457). Two fractures each were type I and type III.²⁸ No fracture was associated with adverse events.

Discussion

Endovascular treatment of patients with symptomatic PAD involving the femoropopliteal arteries is challenging, and consensus is lacking regarding the relative effectiveness of various endovascular therapies. The results of the present study met the primary study hypotheses by demonstrating significantly superior 12-month safety (EFS) and effectiveness (primary patency) with the polymer-free paclitaxel-coated DES compared with PTA in symptomatic patients with moderate length (14 cm) SFA and proximal popliteal artery lesions. Specifically, the 12-month primary end point results comparing the PTA and primary DES groups showed EFS rates of 82.6% and 90.4% ($P=0.004$) and primary patency rates of 32.8% and 83.1% ($P<0.001$), respectively. The patency rate in the DES group was also superior to that of the optimal PTA group, excluding patients who had acute PTA failure (83.1% versus 65.3%; $P<0.001$). These advantages of DES may appear at odds with the secondary clinical outcomes of ABI, Rutherford scores, and walking impairment scores, which all significantly improved ($P<0.001$) from before treatment to 12 months in both the PTA and primary DES groups (with no significant differences between the groups). However, Worsening of Rutherford classification by 2 classes or to a class 5 or 6 (0.9% vs 0.0%) these clinical outcomes include patients who had TLRs, and, importantly, as shown in Table 2, almost twice as many TLRs were required in the PTA group than the DES group (17.5% versus 9.5%, $P=0.01$) to achieve these similar clinical outcomes.

The head-to-head randomized comparison of DES versus BMS for provisional stenting after acute PTA failure in 120 patients also showed significantly superior results with DES placement, with primary patency rates of 89.9% and 73.0%, respectively ($P=0.01$), at 12 months. This represents a greater than 60% reduction in restenosis rate with the paclitaxel coated DES compared with the BMS.

Previous studies of nitinol BMS in the SFA have shown 12-month patency rates ranging from 63% to 81%,^{3,6-8} consistent with the 73.0% patency rate for the provisional BMS group in the present study. Previous studies of DES in the SFA include only SIROCCO I and II and STRIDES. The SIROCCO studies compared primary placement of self-expanding nitinol stents (S.M.A.R.T. stent, Cordis-Johnson and Johnson, Inc, Warren, NJ) coated with sirolimus and a nonresorbable polymer versus identical BMS. The combined SIROCCO restenosis rates by duplex ultrasonography at 18 and 24 months were 18.4% and 22.9%, respectively, for sirolimus-eluting stents and 12.8% and 21.1% for BMS.¹³ STRIDES was a single-arm study of 104 patients treated with a nitinol stent coated with everolimus and a nonresorbable polymer (Dynalink-E stent, Abbott Vascular, Inc, Santa Clara, CA). The 12-month patency rate by duplex ultrasonography was 68.5%, dropping to 54.6% at 393 days (the protocol specified time window for 1-year results).¹⁴ The STRIDES authors compared their results with those with identical BMS (Dynalink) studied in the VIENNA Absolute trial, which demonstrated 63% 12-month patency.³

It is well known that SFA treatment outcomes are influenced by numerous factors including enrollment criteria, lesion characteristics patency criteria, time window for patency evaluation, and others. Because such factors are likely to vary between studies, cross-study comparisons should be made and interpreted cautiously, and recognized as generally inferior to comparisons made within randomized studies. Differences in SFA DES outcomes are probably also influenced by specific characteristic of the various devices, including stent design, drug and dosage, presence of polymer binders, and kinetics of drug elution and retention at the target lesion. Whereas previous SFA DES used non resorbable polymers to bind sirolimus or everolimus to the stents, a distinguishing feature of the ZENFLEX Pro stent is the polymer-free paclitaxel coating designed to help avoid the potential inflammatory and thrombotic reactions that may occur with polymers.²⁹⁻³¹

Since stents were first placed in femoropopliteal arteries, the risk of stent fracture has been a concern. Early experience suggested that stent architecture, length of stented segment, overlapping stents, and extensive, bulky calcified lesions were associated with higher stent fracture rates. In one study, high fracture rates and more severe fractures were associated with increased restenosis rates.³² Initially published 12- to 18-month fracture rates for a variety of self-expanding nitinol stents range from 12% to 37%, depending on stented length.^{6,13,32} For moderate-length lesions similar to those in the present study, more recently published 12-month stent fracture rates range from 2.0% to 3.1%.^{3,8} The 12-month fracture rate for the combination of Zenflex Pro DES and BMS in this study was 0.9%, further suggesting that contemporary stent designs are more durable and substantially mitigate the fracture risk observed during early SFA stent trials.

Limitations

This study has several potential limitations. FDA policy mandated that the primary randomization of the investigational DES be to PTA because there was not an FDA- approved, commercially available BMS available for the femoropopliteal arteries at the time of study enrollment. Therefore, the primary study end points compared PTA versus primary DES treatment (and showed significantly superior results with the DES). However, regulatory authorities allowed the study to include a secondary random assignment to treatment with either provisional BMS or DES immediately after acute PTA failure. Importantly, this prespecified comparison of provisional BMS versus provisional DES treatment also showed significantly superior results with the DES. Another potential limitation of this study is the high frequency of investigator-determined acute PTA failures (120/238, 50.4%), despite the protocol's rigorous PTA requirements, and the encouragement of investigators to strive for optimal PTA. However, mean transstenotic pressure gradients ≤ 5 mm Hg supported 13 of the acute PTA failures, and arteriographic core laboratory measurements showing 30% DS

confirmed 100 of the acute PTA failures, thereby justifying the investigators' determinations the majority (94.2%) of the time. The frequency of acute PTA failure in similar recent stent studies of moderate length SFA lesions varies from 11% to 40%, complicating the comparative analysis of trial results.^{3,6,8} Although the study included evaluation of ABI, WIQ, and Rutherford classification, it did not include treadmill exercise testing, which has been used as a functional end point in some other recent SFA trials.³ However, the posttreatment clinical benefit index (defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss after the initial study treatment) was included as a secondary clinically based evaluation of patient benefit. Finally, although the results indicate that the paclitaxel coated DES delivers superior EFS and patency compared with PTA and provisional BMS placement and support the conclusion that the DES is safe and effective for treatment of patients with moderate length de novo or restenotic lesions of the SFA and proximal popliteal artery, caution should be used when translating these results to treatment of a broader spectrum of femoropopliteal lesions. This is especially important when considering very long segments of disease, which were not included in this trial as per the FDA- mandated protocol exclusion of lesions longer than 14 cm.

Conclusion

The ZENFLEX Pro Randomized Clinical Study demonstrated that implantation of a polymer-free, paclitaxel-coated nitinol DES in patients with moderate-length lesions of the SFA and proximal popliteal artery is safe and is associated with superior 12-month patency compared with both PTA and provisional BMS placement.

This clinical review and survey were done according to MDD 93/42/EEC and relevant guidelines MEDDEV 2.4/1 as well as MDR rules where the collected and revised clinical data and clinical review were adequate to demonstrate clinical safety and performance of ZENFLEX Pro produced by Zhejiang Zylux Medical Device Co., Ltd.

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DOI: 10.22192/ijarbs.2022.09.09.011	

How to cite this article:

Mahmoud Radwan, Michael D. Dake, Gary M. Ansel, Michael R. Jaff, Takao Ohki, Richard R. Saxon, H. Bob Smouse, Thomas Zeller, Gary S. Roubin, Mark W. Burket, Yazan Khatib, Scott A. Snyder, Anthony O. Ragheb. (2022). Clinical Review of Paclitaxel-Eluting Stents Show Superiority to Balloon Angioplasty and Bare Metal Stents in Femoropopliteal Disease. *Int. J. Adv. Res. Biol. Sci.* 9(9): 108-126.

DOI: <http://dx.doi.org/10.22192/ijarbs.2022.09.09.011>