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Sustained Safety and Effectiveness of Paclitaxel-Eluting Stents for Femoropopliteal Lesions

2-Year Follow-Up From the Zilver PTX Randomized and Single-Arm Clinical Studies

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Objectives A prospective, multinational randomized controlled trial (RCT) and a complementary single-arm study evaluated the 2-year safety and effectiveness of a paclitaxel-coated drug-eluting stent (DES) in patients with superficial femoral artery lesions. The RCT compared the DES with percutaneous transluminal angioplasty (PTA) and provisional bare-metal stent (BMS) placement.

Background Local drug delivery for superficial femoral artery lesions has been investigated with the intent of limiting restenosis similarly to DES for the coronary arteries. One-year outcomes of DES in the superficial femoral artery are promising, but longer-term benefits have not been established.

Methods In the RCT, patients were randomly assigned to primary DES implantation (n = 236) or PTA (n = 238). Acute PTA failure occurred in 120 patients, who underwent secondary randomization to DES (n = 61) or BMS (n = 59) placement. The single-arm study enrolled 787 patients with DES treatment.

Results Compared with the control group, the primary DES group demonstrated significantly superior 2-year event-free survival (86.6% vs. 77.9%, $p = 0.02$) and primary patency (74.8% vs. 26.5%, $p < 0.01$). In addition, the provisional DES group exhibited superior 2-year primary patency compared with the provisional BMS group (83.4% vs. 64.1%, $p < 0.01$) and achieved higher sustained clinical benefit (83.9% vs. 68.4%, $p = 0.05$). Two-year freedom from target lesion revascularization with primary DES placement was 80.5% in the single-arm study and 86.6% in the RCT.

Conclusions Two-year outcomes with the paclitaxel-eluting stent support its sustained safety and effectiveness in patients with femoropopliteal artery disease, including the long-term superiority of the DES to PTA and to provisional BMS placement. (Evaluation of the Zilver PTX Drug-Eluting Stent in the Above-the-Knee Femoropopliteal Artery; NCT00120406; Zilver® PTX™ Global Registry; NCT01094678) (J Am Coll Cardiol 2013;61:2417–27) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ABI = ankle-brachial index
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EFS = event-free survival
PTA = percutaneous transluminal angioplasty
SFA = superficial femoral artery
TLR = target lesion revascularization
WIQ = Walking Impairment Questionnaire

Peripheral artery disease commonly affects the superficial femoral artery (SFA). To treat the broad range of symptoms, current interventional options include bypass surgery and endovascular therapies, such as percutaneous transluminal angioplasty (PTA) and self-expanding metallic stent implantation. Traditional bypass surgery provides durable outcomes but is associated with increased morbidity and prolonged recovery relative to the less invasive endovascular approaches (1). Longer-term studies of endovascular interventions also highlight limited outcomes, particularly for more challenging lesions such as chronic occlusions and long-segment SFA disease. As previously reported, the 1-year patency rate following PTA of the SFA is between 22% and 60% (2–4). Although stents improve initial patency compared with PTA alone, the sustained benefit remains suboptimal, in particular for longer SFA lesions, with 1-year patency rates of 63% to 81% (4–6).

In an effort to combat the formidable challenge of neointimal hyperplasia that confronts all endovascular interventions in the femoropopliteal segments, interventional treatments that include local drug delivery to the SFA have been investigated with the intent to limit restenosis in much the same way as drug-eluting stents (DES) have shown improved outcomes in the coronary arteries (7–9). These SFA treatments have included paclitaxel-coated balloons, which have shown promise compared with PTA alone (10,11). Nitinol stents modified to deliver antiproliferative agents to the vessel wall have also been evaluated, but sustained benefit has not previously been demonstrated (7–9).

The purpose of the Zilver PTX Randomized Clinical Trial and Single-Arm Study was to investigate the safety and effectiveness of a paclitaxel-coated DES for treating femoropopliteal disease. The DES evaluated in these studies is the Zilver PTX nitinol stent (Cook Medical, Bloomington, Indiana), which incorporates a self-expanding, flexible nitinol stent platform with a 3 $\mu g/mm^2$ polymer-free coating of paclitaxel on its outer surface. As reported previously, these studies support the 1-year safety and effectiveness of the DES in patients with de novo or restenotic lesions of the above-the-knee femoropopliteal artery (12,13). Moreover, in the randomized trial, implantation of the DES provided superior 1-year patency compared with both PTA and provisional bare-metal stent (BMS) placement (12). Herein, 2-year outcomes from both studies are reported.

Methods

Detailed descriptions of study design, inclusion and exclusion criteria, methods, and follow-up through 1 year for the Zilver PTX Randomized Clinical Trial and Single-Arm Study were previously reported (12,13). The inclusion criteria for the randomized trial included Rutherford category ≥2, ≥50% diameter stenosis, reference vessel diameter 4 to 9 mm, lesion length up to 14 cm, and at least 1 patent runoff vessel with <50% stenosis throughout its course. Exclusion criteria included untreated >50% stenosis of the inflow tract and previous target vessel stent placement. The inclusion and exclusion criteria for the complementary single-arm study were broader, and the study included previous target vessel stent placement and lesions up to 28 cm. Approval was obtained from each site's institutional review board or ethics committee, and patients provided written informed consent. Both studies were overseen by an independent data safety monitoring board and monitored in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practices. To determine their relationship to the study procedure or device, major adverse events were adjudicated by an independent clinical events committee. Briefly, the studies enrolled a total of 1,261 patients with symptomatic disease of the above-the-knee femoropopliteal arteries. The randomized trial included 238 patients randomized to PTA and 236 patients randomized to primary DES treatment (Fig. 1). One hundred twenty patients with acute PTA failure were subsequently randomized to provisional DES (n = 61) or provisional BMS (n = 59; Zilver, Cook Medical) placement. The single-arm study enrolled 787 patients treated with the DES. In total, 1,084 patients received the DES (Zilver PTX).

Interventions. Rutherford classification, ankle-brachial index (ABI), and Walking Impairment Questionnaire (WIQ; a validated measure of patient-perceived walking performance) (14) were assessed before the procedure. Stents were placed at least 1 cm below the SFA origin and above the medial femoral epicondyle to fully cover the target lesion(s). Pre-dilation and post-dilation were at the physician's discretion, with residual stenosis <30% required for procedural success. For patients randomized to the PTA group, PTA was performed according to institutional standard practice, and patients with acute PTA failure (i.e., ≥30% stenosis or a ≥5 mm Hg mean trans-stenotic pressure gradient) underwent secondary randomization to provisional BMS or provisional DES placement.

Medical therapy. The same antiplatelet regimen was recommended for all patients: clopidogrel (ticlopidine in Japan) starting at least 24 h before the intervention or a procedural loading dose of 300 mg, continued clopidogrel or ticlopidine therapy for at least 60 days post-procedurally, and lifelong aspirin therapy.

Follow-up. At 18 months, patients were contacted by telephone for an assessment of overall medical condition. At 2 years, patients underwent a clinical assessment, which included Rutherford classification, ABI, and WIQ. As prespecified, patency was not evaluated beyond 1 year in the

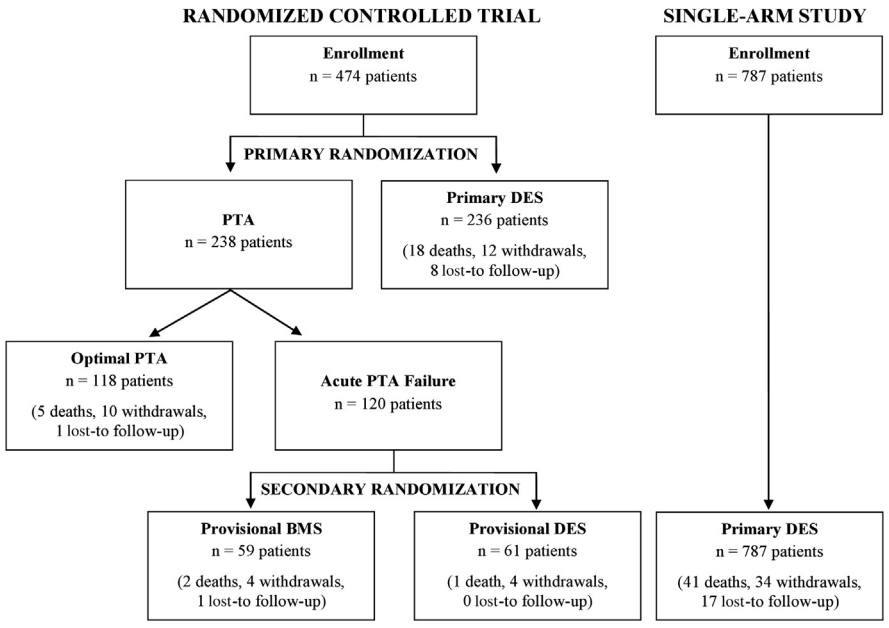


Figure 1 **Patient Flow Diagram**

Enrollment by original random assignments, deaths (all-cause), withdrawals, and lost to follow-up through 2 years are shown. BMS = bare-metal stent(s); DES = drug-eluting stent(s); PTA = percutaneous transluminal angioplasty.

single-arm study. However, the randomized trial specified that all patients in the primary DES group, the provisional stent groups (both DES and BMS), and a subgroup of PTA patients (long-term PTA subgroup) undergo duplex ultrasound annually through 5 years to evaluate patency. Patients were assigned to this long-term PTA subgroup using adaptive random selection, with a goal of obtaining ultrasound follow-up beyond 1 year for approximately 50 patients with successful PTA. According to the protocol, patients who experienced PTA failure acutely (intraprocedurally) or within 1 year were removed from the long-term PTA subgroup, and their spots were filled by the subsequently enrolled PTA patients. Additionally, as PTA failures accumulated before reaching the approximately 50 patient goal, the adaptive random selection increased the likelihood of assignment of PTA patients to the long-term PTA subgroup. PTA patients not assigned to the long-term PTA subgroup were censored at 13.5 months. This resulted in a subgroup of 42 patients (45 lesions) with successful PTA who were eligible for duplex ultrasound follow-up beyond 1 year. This subgroup represents 58% of the PTA patients who maintained patency through 1 year. Additionally, as previously reported (12,13), stent integrity was assessed using radiographs taken at 1-year follow-up, with the next evaluations at 3 and 5 years in the randomized trial.

Definitions. Major adverse events included death, amputation, clinically driven target lesion revascularization (TLR), target limb ischemia requiring surgical intervention, and surgical vessel repair. Clinically driven TLR was defined as reintervention performed for ≥50% diameter stenosis within ±5 mm of the target lesion after documentation of recurrent clinical symptoms. Event-free survival (EFS) was defined as freedom from adjudicated major adverse events and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6. At 2 years, primary patency was evaluated in the randomized trial and defined as <50% stenosis from duplex ultrasonography (peak systolic velocity ratio <2.0) or from arteriography when available (3). All ultrasound examinations in the randomized trial were independently reviewed by a core laboratory (VasCore, the Vascular Ultrasound Core Laboratory, Massachusetts General Hospital, Boston, Massachusetts). Clinical benefit was defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss.

Statistical analysis. Outcomes through 2-year follow-up have been assessed for available patients from both the randomized trial and the single-arm study. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). The number of observations represents patients, treated lesions, treated limbs, or implanted stents as specified. Continuous variables are summarized with mean ± SD, with p values calculated using standard *t* tests. Dichotomous and polytomous variables are reported as counts and percentages, with p values calculated using Fisher exact tests. Kaplan-Meier analyses were performed to assess EFS, freedom from TLR, clinical benefit, and patency over time, with p values calculated using the log-rank test and adjusted for multiplicity. The generalized estimating

equation model was used to assess the influence of covariates on patency and freedom from TLR.

Results

Of the 1,261 patients enrolled in the complementary studies, 908 were eligible for 2-year follow-up, with data available for 781 patients. Demographics, comorbidities, and lesion characteristics are shown in Table 1. The mean lesion length was approximately 65 ± 40 mm in the randomized trial and 99.5 ± 82.1 mm in the single-arm study.

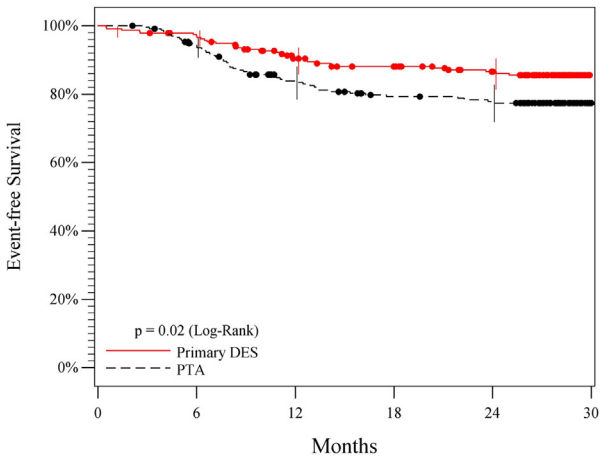
Safety. In the randomized trial, the EFS rate through 2 years for the primary DES group was significantly superior to that for the PTA control group (86.6% vs. 77.9%, log-rank p = 0.02) (Fig. 2). As pre-specified, the overall PTA control group included patients with optimal PTA, with provisional BMS placement after acute PTA failure, and with provisional DES placement after acute PTA failure. These 3 cohorts comprised approximately 50%, 25%, and 25% of the overall PTA control group, respectively. The 2-year EFS rate for primary DES placement in the single-arm study was 79.3%. The most common adverse event in

Table 1 Patient and Lesion Characteristics (12,13)

	Randomized Trial			Single-Arm Study
Characteristic	PTA Group	DES Group	p Value	DES
Patient characteristics				
Patients	238	236	—	787
Mean age (yrs)	67.7 ± 10.6	67.9 ± 9.6	0.88	67.1 ± 9.5
Men	152 (63.9%)	155 (65.7%)	0.70	578 (73.4%)
Body mass index (kg/m^2)	28.2 ± 5.6	28.4 ± 5.3	0.71	27.4 ± 4.3
Claudication (Rutherford class 2 or 3)	90.7%	90.5%	>0.99	88.6%
Critical limb ischemia (Rutherford classes 4–6)	8.5%	8.7%		11.0%
Diabetes	100 (42.0%)	117 (49.6%)	0.11	285 (36.2%)
Type 1	13 (13.0%)	19 (16.2%)	0.56	29 (10.2%)
Type 2	87 (87.0%)	98 (83.8%)		256 (89.8%)
Hypertension	194 (81.5%)	210 (89.0%)	0.02*	627 (79.7%)
Hypercholesterolemia	166 (69.7%)	180 (76.3%)	0.12	458 (58.2%)
History of smoking	200 (84.0%)	204 (86.4%)	0.70	632 (80.3%)
Renal disease	25 (10.5%)	24 (10.2%)	>0.99	89 (11.3%)
Pulmonary disease	38 (16.0%)	45 (19.1%)	0.39	71 (9.0%)
History of myocardial infarction	41 (17.2%)	50 (21.2%)	0.29	123 (15.6%)
Lesion characteristics				
Lesions	251	247	—	900
Lesion location				
SFA	232 (92.4%)	229 (92.7%)	0.63	857 (95.2%)
SFA/popliteal	6 (2.4%)	9 (3.6%)		NA
Popliteal	13 (5.2%)	9 (3.6%)		43 (4.8%)
Previous intervention to study lesion	14 (5.6%)	13 (5.3%)	0.68	219 (24.3%)
Vascular access				
Contralateral	189 (86.7%)	211 (85.4%)	0.78	NA
Ipsilateral	29 (13.3%)	36 (14.6%)		NA
Occlusion†	68 (27.4%)	79 (32.8%)	0.20	345 (38.3%)
Lesion length,‡ normal-to-normal (mm)	63.2 ± 40.5	66.4 ± 38.9	0.31	99.5 ± 82.1
Lesion length,†‡ >20% stenosis (mm)	53.2 ± 40.3	54.6 ± 40.7	0.50	NA
MLD in lesion† (mm)	1.1 ± 0.9	1.0 ± 0.9	0.38	0.8 ± 0.9
Percent diameter stenosis† (%)	78.4 ± 17.1	79.8 ± 17.0	0.38	84.6 ± 16.4
In-stent restenosis	NA	NA	—	119 (13.2%)
Ulcerations†	47 (19.0%)	40 (16.7%)	0.55	NA
Lesion calcification†				
None	12 (4.8%)	4 (1.7%)	<0.01*§	176 (19.6%)
Little	95 (38.2%)	62 (25.7%)		294 (32.7%)
Moderate	55 (22.1%)	85 (35.3%)		261 (29.0%)
Severe	87 (34.9%)	90 (37.3%)		168 (18.7%)

Values are n (%) or mean ± SD. *Statistically significant difference between the PTA and DES groups in the randomized trial. †Arteriographic core laboratory data for randomized trial and site data for single-arm study. ‡p values were determined using Wilcoxon tests. §Overall, the DES group had significantly more calcification than the PTA group.

DES = drug-eluting stent(s); MLD = minimal luminal diameter; NA = not applicable; PTA = percutaneous transluminal angioplasty; SFA = superficial femoral artery.



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	94.4 ± 1.5%	97.0 ± 1.1%	13	7	6	3	217	225
12	83.9 ± 2.4%	90.4 ± 1.9%	37	22	15	16	184	197
24	77.9 ± 2.8%	86.6 ± 2.3%	50	30	22	33	164	172

Figure 2 **2-Year Primary Safety Outcomes**

The **black curve** shows 77.9% event-free survival (EFS) rate for the percutaneous transluminal angioplasty (PTA) group, and the **red curve** shows the significantly higher (p = 0.02) 86.6% EFS rate for the primary drug-eluting stent (DES) group. The life table is included.

both studies was clinically driven TLR. On the basis of Kaplan-Meier estimates, the 2-year freedom from TLR rate with primary DES placement was 86.6% in the randomized trial and 80.5% in the single-arm study (Fig. 3).

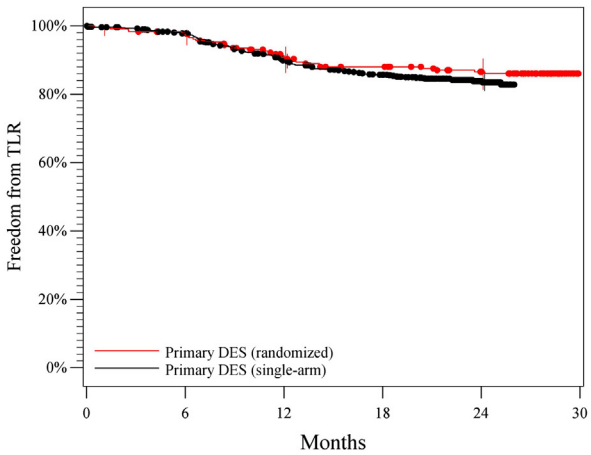
There were no device-related deaths in either study. In the randomized trial, all-cause death (e.g., malignancy, pulmonary disease, congestive heart failure) included 8 patients (3.4%) in the PTA group and 18 patients (7.6%) in the primary DES group through 2 years. In the single-arm study, all-cause death through 2 years included 41 patients (5.2%). There was no significant difference in the all-cause death rates among these 3 groups (p = 0.12). Amputation (<1%) and worsening of Rutherford classification (<2%) were rare in both studies through 2 years. There were no reports of adverse drug effects related to the paclitaxel coating.

Patency. In the primary analysis for the randomized trial, the 2-year primary patency rate of 74.8% for the primary DES group was significantly superior (log-rank p < 0.01; Fig. 4) to the 26.5% for the long-term PTA subgroup. As pre-specified for the primary analysis, acute PTA failure was counted as a loss of patency. Primary DES treatment was also significantly superior (p < 0.01) to PTA for several patient and lesion subgroups analyzed (Fig. 5).

In secondary analyses (Fig. 4), the 2-year primary patency rate for the primary DES group was: 1) significantly superior (log-rank p < 0.01) to the 53.4% rate for the optimal PTA group (a group that excluded patients who experienced acute PTA failure); 2) significantly superior (log-rank p < 0.01) to the 57.3% rate for the patients with optimal PTA and provisional BMS placement after acute PTA failure; and 3) significantly superior (log-rank p = 0.01) to the 64.3% rate for the overall PTA control group that consisted of patients with optimal PTA (50%) and with provisional BMS (25%) or provisional DES (25%) placement after acute PTA failure. Additionally, of PTA lesions that were still patent at 1 year, 13.7% (10 of 73) lost patency between 12 and 24 months, compared with 9.3% (17 of 182) of primary DES lesions (p = 0.37) (Fig. 6).

Finally, in the randomized trial, evaluation of the provisional stent groups, which provides a direct assessment of the paclitaxel effect, showed a superior 2-year primary patency rate of 83.4% for provisional DES compared with 64.1% for provisional BMS (log-rank p < 0.01) (Fig. 7). Through 2 years, there was no significant difference in patency for primary DES compared with provisional DES placement (log-rank p = 0.11). Of BMS lesions that were still patent at 1 year, 12.2% (5 of 41) lost patency between 12 and 24 months, compared with 7.4% (4 of 54) of provisional DES lesions (p = 0.49) (Fig. 6).

Covariates. An analysis of covariates for TLR and patency was performed, which included all DES patients from the



Kaplan Meier Estimates of Freedom from TLR, Values Represent Patients								
Months Post-procedure	Freedom from TLR ± Standard Error		Cumulative Failed		Cumulative Censored		Remaining at Risk	
	Primary DES (randomized)	Primary DES (single-arm)	Primary DES (randomized)	Primary DES (single-arm)	Primary DES (randomized)	Primary DES (single-arm)	Primary DES (randomized)	Primary DES (single-arm)
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	6	235	778
1	99.6 ± 0.4%	99.6 ± 0.2%	1	3	0	13	234	768
6	97.4 ± 1.0%	97.7 ± 0.5%	6	17	3	42	226	725
12	90.8 ± 1.9%	89.3 ± 1.2%	21	77	16	144	198	563
24	86.6 ± 2.3%	80.5 ± 1.7%	30	120	32	423	173	241

Figure 3 2-Year Freedom From TLR Outcomes for Primary DES Patients

The **red curve** shows 86.6% freedom from target lesion revascularization (TLR) in the randomized trial, and the **black curve** shows 80.5% freedom from TLR in the single-arm study. The life table is included. DES = drug-eluting stent(s).

randomized trial (Table 2). Smoking was the only significant factor in the TLR analysis, with the TLR rate significantly reduced for DES patients who had never smoked compared with those still smoking. Duration of dual-antiplatelet therapy was the only significant factor in the patency analysis. There was a higher patency rate for DES patients on dual-antiplatelet therapy at 1 month compared with those not on dual-antiplatelet therapy. However, there was no evidence of a higher patency rate for DES patients on dual-antiplatelet therapy at both 1 and 3 months compared with 1 month only.

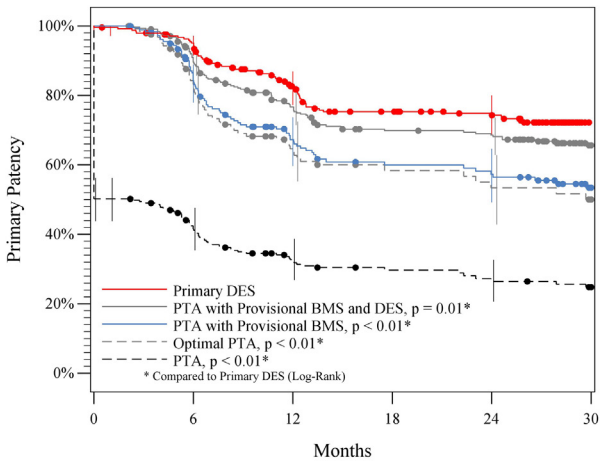
Clinical benefit. The Rutherford classification, ABI, and WIQ score each significantly improved ($p \leq 0.01$) from pre-procedure to 2 years in both the primary DES and PTA groups in the randomized trial, with no significant differences between the groups. In the single-arm study, these scores also significantly improved ($p < 0.01$) from pre-treatment to 2 years.

On the basis of Kaplan-Meier estimates in the randomized trial, the post-treatment clinical benefit index was sustained through 2 years in 81.8% of the primary DES group compared with 71.3% of the overall PTA control group (log-rank $p < 0.01$) (Fig. 8). Patients in the provisional DES group also sustained greater clinical benefit through 2 years compared with the provisional BMS group (83.9% vs. 68.4%) (Fig. 9).

Discussion

The previously published 1-year results of the Zilver PTX Randomized Clinical Trial document the benefits of a paclitaxel-coated DES over BMS-assisted PTA for the treatment of patients with femoropopliteal disease, including improved freedom from TLR and vessel patency (12). This included a direct comparison of provisional DES with BMS placement after failed primary PTA, which showed significantly greater 1-year patency with the DES. This benefit at 1 year amounted to a 50% reduction in restenosis with the DES relative to the BMS. These statistically significant differences are bolstered by the 1-year outcomes published for the complementary Zilver PTX Single-Arm Study, which evaluated patients with more complex lesions and detailed similar TLR and patency rates for the DES to those reported from the randomized trial (13).

Ever since initial clinical trials for the treatment of patients with coronary artery disease showed superior effectiveness of DES compared with BMS at 6 to 12 months, there have been questions concerning the sustainability of these benefits in certain groups. Now, long-term follow-up after coronary interventions confirms the durability of the initial results for DES compared with BMS, especially for patients with diabetes and for smaller coronary arteries (15–17).



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	50.2 ± 3.2%	99.6 ± 0.4%	125	1	0	0	126	245
1	50.2 ± 3.2%	99.6 ± 0.4%	125	1	0	1	126	244
6	41.6 ± 3.1%	95.1 ± 1.4%	146	12	5	4	100	230
12	32.7 ± 3.0%	82.7 ± 2.5%	167	41	11	23	73	182
24	26.5 ± 3.1%	74.8 ± 2.9%	177	58	41	39	33	149

Figure 4 2-Year Primary Effectiveness Outcomes

The **black curve** shows the 26.5% primary patency rate for the percutaneous transluminal angioplasty (PTA) group (as pre-specified, acute PTA failure was a loss of patency), and the **red curve** shows the significantly higher ($p < 0.01$) 74.8% primary patency rate for the drug-eluting stent (DES) group. The life table is included. Secondary evaluations also show that the primary patency rate for the DES **(red curve)** is 1) significantly higher ($p < 0.01$) than the 53.4% rate for optimal PTA **(dashed gray curve)**, a group that excluded patients who experienced acute PTA failure; 2) significantly higher ($p < 0.01$) than the 57.3% rate for optimal PTA with provisional bare-metal stent (BMS) placement **(solid blue curve)**; and 3) significantly higher ($p = 0.01$) than the 64.3% rate for the overall PTA control group **(solid gray curve)**, which consisted of patients with optimal PTA (50%) and with provisional BMS (25%) or provisional DES (25%) placement after acute PTA failure.

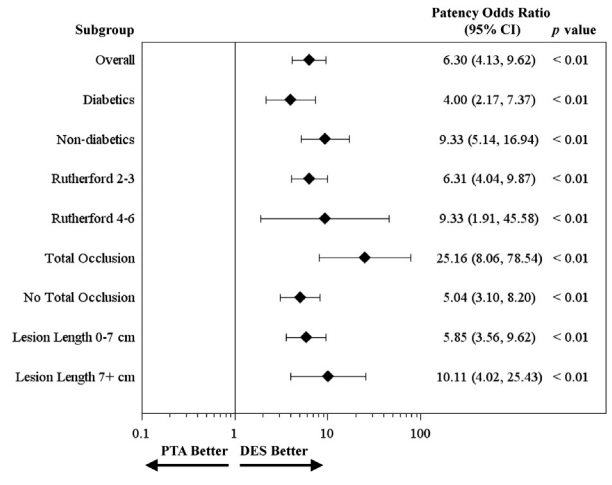


Figure 5 Patency Odds Ratio for DES Compared With BMS Among Subgroups of Interest

The **diamonds** indicate the point estimates, and the **lines** indicate the 95% confidence intervals (CIs). BMS = bare-metal stent(s); DES = drug-eluting stent(s).

Long-term benefits after DES placement in the femoropopliteal arteries have not been demonstrated previously. Two-year patency results from the randomized trial and TLR rates from both the randomized and single-arm studies reinforce the 1-year DES outcomes previously published for both Zilver PTX studies (12,13). The 2-year freedom from TLR rate for single-arm study patients is similar to that in the randomized trial, considering the more challenging lesions (e.g., longer, in-stent restenosis) enrolled.

The 2-year freedom from TLR for primary DES implantation in the randomized trial of 86.6% compares favorably with recently published BMS trials. The 2-year freedom from TLR in the RESILIENT (Randomized Study Comparing the Self-Expanding LifeStent vs. Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery) trial, which enrolled femoropopliteal lesions of lengths comparable to those in the Zilver PTX randomized trial, was 77.8% (18). Similarly, the 2-year patency of 74.8% for the primary DES group in the randomized trial compares favorably with published BMS outcomes, including the 2-year patency rate of 54.3% for the BMS studied in longer femoropopliteal lesions in the

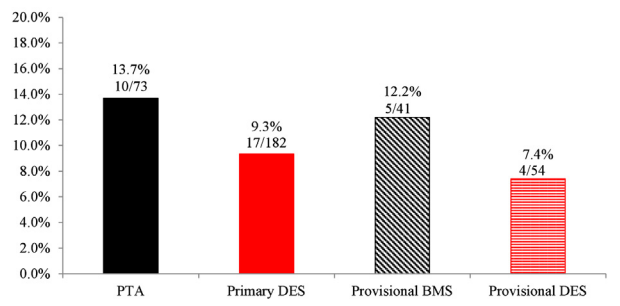


Figure 6 **Percentage of Lesions With Loss of Patency Between 12 and 24 Months**

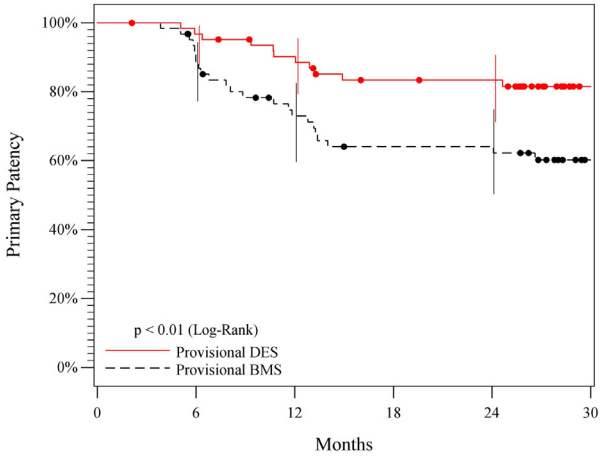
Of lesions that were still patent at 1 year, 13.7% in the percutaneous transluminal angioplasty (PTA) group **(black bar)** and 9.3% of the primary drug-eluting stent (DES) lesions **(red bar)** lost patency between 12 and 24 months. Of provisionally stented lesions that were still patent at 1 year, 12.2% treated with provisional bare-metal stents (BMS) **(black hashed bar)** and 7.4% treated with provisional DES **(red hashed bar)** lost patency between 12 and 24 months.

ABSOLUTE (Balloon Angioplasty Versus Stenting With Nitinol Stents in the Superficial Femoral Artery) trial (19).

The Zilver PTX randomized trial showed significantly greater 2-year patency in the primary DES group compared with the long-term PTA subgroup (74.8% vs. 26.5%, $p < 0.01$). The results showed no evidence of late convergence between these groups, as the loss of patency between 1 and 2 years was 9.3% with primary DES and 13.7% with PTA.

The randomized trial also demonstrated significantly greater 2-year patency in the provisional DES group compared with the provisional BMS group (83.4% vs. 64.1%, $p < 0.01$). Again, there was no evidence of late convergence between these groups, as the loss of patency between 1 and 2 years was 7.4% for provisional DES and 12.2% for provisional BMS. The loss of patency between 1 and 2 years in the provisional BMS group is also similar to the reduction in patency over an identical period in published BMS trials for SFA disease, including a 13.8% loss of patency during year 2 in the ABSOLUTE trial (19). In the same trial, the loss of patency during year 2 for the PTA arm was 15.8% (19).

A covariate analysis for patients receiving the DES in the randomized trial included many of the factors generally considered to have potential impact on TLR and patency, such as reference vessel diameter, lesion length, calcification, total occlusion, and diabetes. Only smoking significantly affected TLR, and only dual-antiplatelet therapy significantly affected patency. Specifically, DES patients adhering to dual-antiplatelet therapy at 1 month had a higher patency rate than those on single-antiplatelet therapy. A significant added benefit, however, could not be demonstrated for DES



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	0	62	63
1	100.0 ± 0.0%	100.0 ± 0.0%	0	0	0	0	62	63
6	88.4 ± 4.1%	96.8 ± 2.2%	7	2	2	1	53	60
12	72.9 ± 5.8%	90.2 ± 3.8%	16	6	5	3	41	54
24	64.1 ± 6.3%	83.4 ± 4.8%	21	10	6	7	35	46

Figure 7 **Secondary 2-Year Evaluation Comparing the Effectiveness of Provisional BMS and Provisional DES**

The **black curve** shows the 64.1% primary patency rate for lesions undergoing provisional bare-metal stent (BMS) placement following acute percutaneous transluminal angioplasty (PTA) failure, and the **red curve** shows the significantly higher ($p < 0.01$) 83.4% primary patency rate for lesions undergoing provisional drug-eluting stent (DES) placement after acute PTA failure. The life table is included.

Table 2 Covariate Analysis

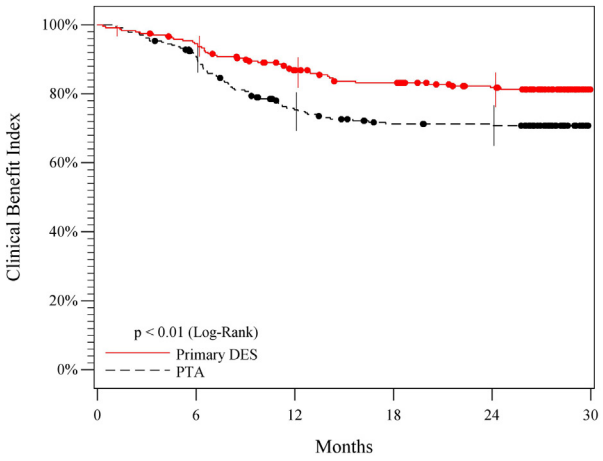
2-Year Covariate	TLR p Value	Patency p Value
Diabetes	0.63	0.16
Smoking status	0.02*	0.19
Rutherford classification	0.81	0.87
Number of patent runoff vessels	0.59	0.44
De novo/restenotic lesions	0.07	0.81
Pre-dilation	0.53	0.26
Percent diameter stenosis	0.92	0.57
Total occlusion	0.09	0.66
Reference vessel diameter	0.55	0.07
Calcification	0.22	0.35
Lesion length	0.75	0.60
Lesion location	0.56	0.45
Acute PTA failure	0.45	0.36
Dual-antiplatelet therapy	0.55	0.03†

*Statistically significant. Odds ratio of 0.29 (95% confidence interval: 0.07 to 1.13) for never smoked versus still smoking. †Statistically significant. Odds ratio of 0.36 (95% confidence interval: 0.11 to 1.17) for no antiplatelet therapy versus antiplatelet therapy only at 1 month.
PTA = percutaneous transluminal angioplasty; TLR = target lesion revascularization.

patients on dual-antiplatelet therapy over a longer interval of 3 months. This finding is not conclusive, but weighing the positive and negative consequences when determining the duration of dual-antiplatelet therapy in patients receiving DES, as well as BMS, in the SFA is important to further consider. Also, the optimal administration of antiplatelet therapy with peripheral DES should not be assumed identical to the coronary artery DES experience.

In terms of potential adverse drug effects related to the paclitaxel coating on the DES, published 1-year results from the randomized and single-arm studies did not report any untoward events (12,13). Similarly, no adverse effects or reactions associated with the paclitaxel coating were observed through 2 years in either study.

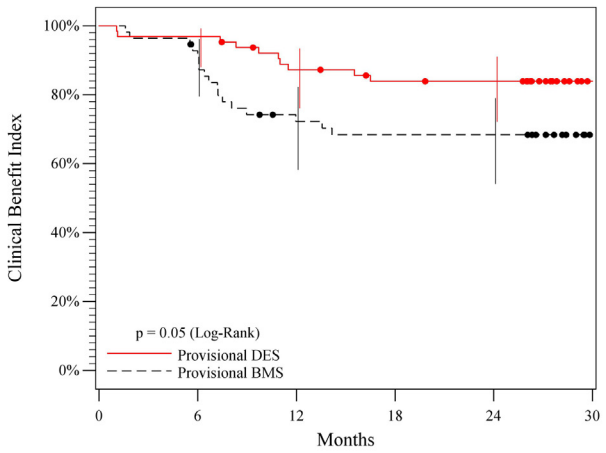
Study limitations. A limitation of the randomized trial is the inability to make a comprehensive comparison of the primary therapies at 2 years using all of the patients initially randomized to the PTA control group. Before initiating enrollment, there was agreement among investigators that follow-up of all patients in the PTA group beyond the 1-year primary endpoint was unnecessary and impractical. Consequently, it was determined to provide follow-up beyond 1 year for all patients receiving stents (primary DES, provisional DES, and provisional BMS) and a subgroup of control patients who experienced successful initial PTA and maintained patency through 1 year (long-term PTA subgroup). These patients were selected by a pre-specified process of adaptive random selection, which allowed a long-term (2-year) comparison between DES and



Kaplan Meier Estimates of Clinical Benefit Index, Values Represent Patients								
Months Post-procedure	Clinical Benefit ± 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	237	240
1	100.0 ± 0.0%	99.2 ± 0.6%	0	2	0	0	237	238
6	90.7 ± 1.9%	94.6 ± 1.5%	22	13	5	2	210	225
12	75.4 ± 2.8%	86.9 ± 2.2%	57	31	13	14	167	195
24	71.3 ± 3.0%	81.8 ± 2.6%	66	42	21	31	150	167

Figure 8 2-Year Post-Treatment Clinical Benefit Index Results for Primary DES Compared With 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 71.3% of patients in the percutaneous transluminal angioplasty (PTA) group maintained clinical benefit, and the **red curve** shows that 81.8% of patients in the primary drug-eluting stent (DES) group maintained clinical benefit ($p < 0.01$). The life table is included.



Kaplan Meier Estimates of Clinical Benefit Index, Values Represent Patients								
Months Post-procedure	Clinical Benefit ± 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	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%	87.3 ± 4.2%	15	8	4	2	37	54
24	68.4 ± 6.4%	83.9 ± 4.7%	17	10	4	5	35	49

Figure 9 2-Year Post-Treatment Clinical Benefit Index Results for Provisional DES Compared With Provisional BMS Treatment

The **black curve** shows that 68.4% of patients undergoing provisional bare-metal stent (BMS) placement after acute percutaneous transluminal angioplasty (PTA) failure maintained clinical benefit, and the **red curve** shows that 83.9% of patients undergoing provisional drug-eluting stent (DES) placement after acute PTA failure maintained clinical benefit. The life table is included.

PTA by following 42 optimal PTA patients who maintained patency through the 1-year primary endpoint. The PTA patients who maintained patency through 1 year and were not randomized to the long-term PTA subgroup were censored at 13.5 months, the pre-specified end of the 1-year follow-up window. Accordingly, a limitation of the study is the potential for bias introduced by the selection of the long-term PTA subgroup. However, through 1 year, the patency rate for the long-term PTA subgroup was not significantly different from the rest of the optimal PTA group (log-rank $p = 0.08$).

There was similar improvement ($p \leq 0.01$) in Rutherford classification, ABI, and WIQ score from pre-procedure to 2 years in both the primary DES and PTA groups in the randomized trial. However, these clinical outcomes include patients who had TLR, and more frequent TLR was required in the PTA group than the DES group to achieve these similar clinical outcomes. The protocol also did not include treadmill exercise testing. However, the evaluation of the post-treatment clinical benefit index (defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss) allowed a secondary clinically based evaluation of patient benefit through 2 years. These results favored the DES over the PTA control group and also favored provisional DES over provisional BMS.

Finally, although the randomized trial results demonstrate sustained superior EFS and patency through 2 years for primary DES compared with PTA and for provisional DES compared with provisional BMS, the study lacked a primary BMS group and therefore did not directly compare primary DES with primary BMS. It is also important to recognize the limitation of broadening the implications to femoropopliteal lesions longer than 14 cm, which were excluded from the randomized trial. However, the 2-year outcomes from the complementary single-arm study, which included lesions up to 40 cm long (with a mean length of approximately 10 cm and approximately one-quarter >15 cm), reinforce the patency results from the randomized trial, with similar TLR rates at 1 and 2 years in both studies.

Conclusions

The combination of 2-year outcomes from the complementary Zilver PTX studies, including safety, patency, clinical benefit, and the absence of adverse events related to the paclitaxel drug coating, support the sustained safety and effectiveness of the DES in patients with de novo or restenotic femoropopliteal arterial lesions, the superiority of the DES to PTA, and the long-term benefit of the drug coating over the corresponding BMS.

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REFERENCES

1. Goshima KR, Mills JL Sr., Hughes JD. A new look at outcomes after infrainguinal bypass surgery: traditional reporting standards systematically underestimate the expenditure of effort required to attain limb salvage. J Vasc Surg 2004;39:330–5.
2. Gray BH, Sullivan TM, Childs MB, Young JR, Olin JW. High incidence of restenosis/reocclusion of stents in the percutaneous treatment of long-segment superficial femoral artery disease after suboptimal angioplasty. J Vasc Surg 1997;25:74–83.
3. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69:910–9.
4. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006;354:1879–88.
5. Bosiers M, Torsello G, Gissler HM, et al. Nitinol stent implantation in long superficial femoral artery lesions: 12-month results of the DURABILITY I study. J Endovasc Ther 2009;16:261–9.
6. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv 2010;3:267–76.
7. Duda SH, Bosiers M, Lammer J, et al. Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: the SIROCCO II trial. J Vasc Interv Radiol 2005;16:331–8.
8. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther 2006;13:701–10.
9. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. J Vasc Surg 2011;54:394–401.
10. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689–99.
11. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation 2008;118:1358–65.
12. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv 2011;4:495–504.
13. Dake MD, Scheinert D, Tepe G, et al. Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral and popliteal arteries above the knee: twelve-month safety and effectiveness results from the Zilver PTX single-arm clinical study. J Endovasc Ther 2011;18:613–23.
14. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP, for the Vascular Clinical Trialists. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. Circulation 1995;92:614–21.
15. Schampaert E, Moses JW, Schofer J, et al. Sirolimus-eluting stents at two years: a pooled analysis of SIRIUS, E-SIRIUS, and C-SIRIUS with emphasis on late revascularizations and stent thromboses. Am J Cardiol 2006;98:36–41.
16. Ormiston JA, Turco MA, Hall JJ, et al. Long-term benefit of the TAXUS Liberte stent in small vessels and long lesions. TASIUS ATLAS program. Circ J 2011;75:1120–9.
17. Stone GW, Ellis SG, Colombo A, et al. Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS Clinical Trial Program. J Am Coll Cardiol Intv 2011;4:530–42.
18. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. J Endovasc Ther 2012;19:1–9.
19. Schillinger M, Sabeti S, Dick P, et al. Sustained benefit at 2 years of primary femoropopliteal stenting compared with balloon angioplasty with optional stenting. Circulation 2007;115:2745–9.

Key Words: angioplasty ■ drug-eluting stent(s) ■ paclitaxel-eluting stent(s) ■ peripheral arterial disease.