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Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) Trial

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Background—Endovascular infrapopliteal treatment of patients with critical limb ischemia using percutaneous transluminal angioplasty (PTA) and bail-out bare metal stenting (BMS) is hampered by restenosis. In interventional cardiology, drug-eluting stents (DES) have shown better patency rates and are standard practice nowadays. An investigator-initiated, multicenter, randomized trial was conducted to assess whether DES also improve patency and clinical outcome of infrapopliteal lesions.

Methods and Results—Adults with critical limb ischemia (Rutherford category ≥4) and infrapopliteal lesions were randomized to receive PTA±BMS or DES with paclitaxel. Primary end point was 6-month primary binary patency of treated lesions, defined as ≤50% stenosis on computed tomographic angiography. Stenosis >50%, retreatment, major amputation, and critical limb ischemia–related death were regarded as treatment failure. Severity of failure was assessed with an ordinal score, ranging from vessel stenosis through occlusion to the clinical failures. Seventy-four limbs (73 patients) were treated with DES and 66 limbs (64 patients) received PTA±BMS. Six-month patency rates were 48.0% for DES and 35.1% for PTA±BMS (P=0.096) in the modified-intention-to-treat and 51.9% and 35.1% (P=0.037) in the per-protocol analysis. The ordinal score showed significantly worse treatment failure for PTA±BMS versus DES (P=0.041). The observed major amputation rate remained lower in the DES group until 2 years post-treatment, with a trend toward significance (P=0.066). Less minor amputations occurred after DES until 6 months post-treatment (P=0.03).

Conclusions—In patients with critical limb ischemia caused by infrapopliteal lesions, DES provide better 6-month patency rates and less amputations after 6 and 12 months compared with PTA±BMS.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00471289.

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Key Words: angioplasty ■ drug-eluting stents ■ ischemia ■ peripheral arterial disease

Critical limb ischemia (CLI) manifests with chronic ischemic rest pain, tissue loss, or both. At present, the incidence of CLI, the final stage of peripheral arterial disease, in the Western world is ≈500 to 1000 cases per 1 million inhabitants every year.[1]

Major risk factors in the development of CLI are diabetes mellitus, increased age, and smoking.[1,2] With an aging Western population and an increasing prevalence of diabetes mellitus, the burden of CLI and its costs are likely to increase in the near future.[3]

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WHAT IS KNOWN

- Drug-eluting stents (DES) reduce neointimal hyperplasia and are nowadays the reference treatment in coronary lesions.
- In the similarly sized infrapopliteal arteries, DES yield higher primary patency rates at 1 year compared with percutaneous transluminal angioplasty or bare metal stents.
- Studies thus far have failed to show a difference in clinical outcomes.

WHAT THE STUDY ADDS

- DES provide better clinical outcomes with less amputations and less serious treatment failures in patients with critical limb ischemia and infrapopliteal lesions when compared with percutaneous transluminal angioplasty±bare metal stents.
- Infrapopliteal paclitaxel-eluting DES show higher 6-month patency rates compared with the current reference treatment, percutaneous transluminal angioplasty with bail-out bare metal stents, in patients with critical limb ischemia caused by infrapopliteal lesions.
- A treatment strategy with DES should therefore be considered in patients with critical limb ischemia caused by infrapopliteal lesions.

Preventing major amputation is of particular concern in the treatment of CLI as amputation is associated with a high periprocedural morbidity and mortality and functional outcome is often poor.[4]

To avoid amputation and relieve pain, revascularization techniques attempt to restore unobstructed arterial blood flow into the affected foot.[1,5,6] The selected method of revascularization, either endovascular or surgical, depends on the local anatomic situation, condition of the patient, estimated risk, and expected patency of the reconstruction.[1,5]

Although the patency of infrapopliteal percutaneous transluminal angioplasty (PTA) and bail-out bare metal stenting (BMS), the current standard endovascular treatment, may be less than of bypass surgery, limb salvage rates are equivalent for at least middle-term outcome.[3,5,7–11] The major advantage of endovascular treatment is the lower periprocedural morbidity and mortality, which is of particular concern in typical patients with CLI, that is, older and fragile patients with systemic atherosclerosis and diabetes mellitus who are at high risk for cardiovascular events.[1]

Vascular restenosis, caused by intimal hyperplasia due to vessel injury during PTA, remains the main limitation of infrapopliteal PTA and BMS with clinical relapse and reinterventions.[7,8,10–13] Drug-eluting stents (DES) are considered a possible solution to the problem of restenosis by reducing neointimal hyperplasia, after promising results in coronary arteries.[12] There is a limited number of randomized studies concerning the use of DES in infrapopliteal arteries to date and these studies either included patients with intermittent claudication (≤68%)[13–15] or had limited follow-up (12-month angiography available in 46% of patients).[16]

The PTA and Drug Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) trial, an investigator-initiated multicenter randomized study, was conducted to determine whether DES reduce restenosis and occlusion in infrapopliteal arteries in patients with CLI and may thus decrease amputation. In this trial, 6-month patency rates and clinical outcomes at 6 and 12 months after endovascular treatment of infrapopliteal lesions in CLI are compared using either paclitaxel-eluting DES or PTA with bail-out BMS.

Methods

Study Design and Study Population

The PADI trial is an investigator-initiated, multicenter, randomized, controlled, nonblinded, double-arm study conducted in 3 major vascular centers in the Netherlands. The protocol was approved by the medical ethical boards of the participating centers and all enrolled patients gave written informed consent. The trial was registered at http://www.clinicaltrials.gov (identifier NCT00471289).

Adult patients were eligible for enrollment if they have CLI (defined as Rutherford category ≥4)[17] caused by infrapopliteal lesions.

Lesions were considered for inclusion if there was >50% luminal loss, lesion length of ≤90 mm, and reference vessel diameter 2 to 6 mm, estimated by pretreatment imaging.[18] Inflow had to be unobstructed, possibly after revascularization in the femoropopliteal segment during the same session. Outflow distal to target lesions should consist of ≥1 crural vessel with expected unobstructed runoff until the level of the ankle joint.

Detailed inclusion and exclusion criteria are available in Table I in the Data Supplement.

Randomization and Masking

After target lesions were successfully crossed with a guidewire, patient's limbs were randomly allocated to 1 of the 2 treatment strategies, PTA±BMS or DES. The attending radiological technician opened the sealed, opaque envelope containing a computer-generated random sequence on a 1:1 basis. Randomization was per limb and stratified in blocks per center. The block size (n=4) was known only to the statistician. Patients, operators, and investigators were not blinded to treatment assignment.

Study Procedures

Endovascular procedures were mainly performed by an antegrade approach using 6F sheaths. In case of failure, a contralateral retrograde transfemoral approach was used. Lesions were crossed under fluoroscopic guidance with the combination of a catheter and guidewire according to the choice of the operator, usually transluminally. Subintimal routes were used when transluminal recanalization failed.

After randomization, patients were treated according to 1 of the 2 treatment strategies.

In the DES arm, target lesions were treated with balloon expandable paclitaxel-eluting stainless steel coronary stents (TAXUS Liberté; Boston Scientific, Natick, MA). Paclitaxel, an extract derived from the Taxus brevifolia (Pacific Yew) tree, inhibits smooth muscle cell proliferation by affecting mitosis.[12] If necessary, according to the operator, mainly in cases of occlusion, lesions were predilated. The premounted DES was advanced over the guidewire and deployed at the site of the target lesion, according to the manufacturer's manual. The full length of lesions was covered, if necessary with overlapping stents. A maximum of 3 stents were allowed with a 3 to 5 mm overlap.

Patients in the PTA±BMS arm received PTA according to the normal practice of the operator. A balloon with a diameter matching the target vessel was advanced over the guidewire and inflated at the target lesion site. Average inflation time was 1 minute. If bail-out

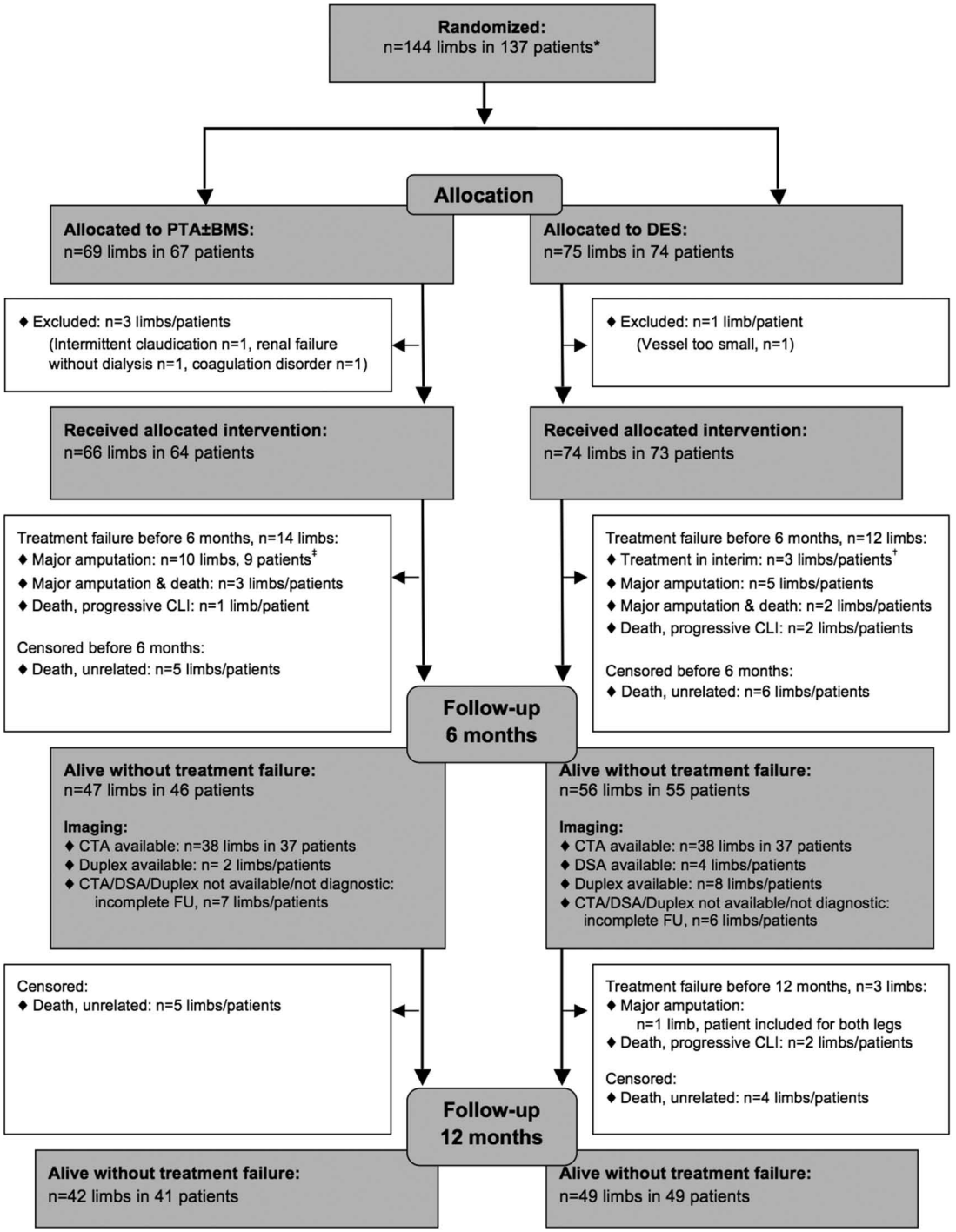

Figure 1. Flow chart, modified-intention-to-treat population. BMS indicates bare metal stent; CLI, critical limb ischemia; CTA, computed tomographic angiography; DES, drug-eluting stent; DSA, digital subtraction angiography; FU, follow-up; and PTA, percutaneous transluminal angioplasty. *Four patients included for 2 limbs with 1 limb in each arm. †One of these patients died before 1 year FU. ‡Two of these patients died before 1 year FU.

stenting was required caused by post-PTA occlusion or flow-limiting dissection, only nondrug-eluting BMS were allowed.

A maximum of 3 lesions per limb were included. When a patient was included for both limbs, each limb was randomized separately.

After the procedure, the access site was closed with a sealing device or with manual compression.

During the procedure, 5000 international units of heparin were administered intra-arterially. Post-procedure all patients were prescribed 100 mg of carbasalate calcium daily indefinitely and 75 mg of clopidogrel daily (with 300 mg loading dose) orally for ≥6 months.

Follow-Up

Patient assessments were planned before intervention, at discharge, after 3, 6, and 12 months and annually until 5 years. Assessments included medical history, physical examination including severity scoring of limb ischemia according to the Rutherford classification,[17]

Table 1. Baseline Characteristics

	PTA±BMS (n=64 Patients, n=66 Limbs)	DES (n=73 Patients, n=74 Limbs)
Mean age, y (SD)	72.9 (11.9)	74.2 (12.1)
Men	47 (73.4)	49 (67.1)
Smoking status		
Ex-smoker	12 (18.8)	18 (24.7)
Current smoker	17 (26.6)	16 (21.9)
Diabetes mellitus	43 (67.2)	44 (60.3)
Previous stroke or transient ischemic attack	13 (20.3)	12 (16.4)
Coronary disease	25 (39.1)	27 (37.0)
Venous and pulmonary thromboembolic disease	6 (9.4)	8 (11.0)
Impaired renal function (eGFR <45 mL/min per 1.73 m2)	22 (34.4)	15 (20.5)
Chronic obstructive pulmonary disease	9 (14.1)	8 (11.0)
Previous malignancy	6 (9.4)	8 (11.0)
On anticoagulation medication	58 (90.6)	67 (91.8)
Rutherford category*		
4	8 (12.1)	10 (13.5)
5	46 (69.7)	48 (64.9)
6	12 (18.2)	16 (21.6)
Increased/decreased ankle-brachial index*		
<0.4	4 (6.1)	5 (6.8)
0.4–0.7	18 (27.3)	25 (33.8)
0.7–0.9	9 (13.6)	13 (17.6)
>1.4/immeasurable	9 (13.6)	13 (17.6)
Decreased toe pressure,* mm Hg		
<40	15 (22.7)	21 (28.4)
40–50	7 (10.6)	4 (5.4)
Immeasurable	9 (13.6)	11 (14.9)

Data are number (%) unless stated otherwise. BMS indicates bare metal stent; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; and PTA, percutaneous transluminal angioplasty.

*Per index limb.

Table 2. Lesion Characteristics

	PTA±BMS (n=66 Limbs; n=91 Lesions)	DES (n=74 Limbs; n=121 Lesions)
TASC*		
B	1 (1.5)	0 (0)
C	3 (4.5)	1 (1.4)
D	62 (93.9)	73 (98.6)
No. of treated infrapopliteal arteries	1.3 (0.6)	1.4 (0.6)
Lesion length, mm	23.1±21.8	21.1±19.3
Vessel diameter, mm	2.9±0.6	2.9±0.7
Preprocedure % stenosis	83.1±16.7	83.2±15.3
Postprocedure % stenosis	10.7±20.7	3.2±9.6
Postprocedure vessel runoff distal of lesion*		
≤50% stenosis	84 (92.3)	115 (95.0)
>50% stenosis	1 (1.1)	3 (2.5)
Occluded	6 (6.6)	3 (2.5)
Lesion location*		
Infragenual popliteal artery	5 (5.5)	6 (5.0)
Tibioperoneal trunk	20 (22.0)	21 (17.4)
Tibioperoneal trunk & peroneal artery	1 (1.1)	1 (0.8)
Anterior tibial artery	27 (29.7)	35 (28.9)
Posterior tibial artery	12 (13.2)	31 (25.6)
Peroneal artery	26 (28.6)	27 (22.3)
No. of limbs treated with (bail-out) stents	14 (21.2)	74 (100)
Stents implanted per limb	0.3±0.7	1.8±0.8

Values are mean or %±SD unless stated otherwise. BMS indicates bare metal stent; DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; and TASC, TransAtlantic Inter-Society Consensus.

*n (%).

ankle-brachial index, toe pressure, and duplex sonography of the treated limb. Computed tomographic angiography (CTA) of the pelvis and lower extremities was performed at 6 months follow-up. Patency of treated sites on CTA was scored independently by 2 board-certified interventional radiologists (J.M.M. and H.O.), who were unaware of the treatment. The degree of restenosis was scored from 0% to 50.0%, 50.0% to 99.9%, or occluded. In case of discordance, lesions were reassessed simultaneously to reach consensus.

Study End Points

Primary end point of the PADI trial was primary binary patency per treated lesion at 6 months, defined as ≤50% loss of luminal diameter on CTA without reintervention in interim. If CTA was not available but digital subtraction angiography or duplex sonography was available, patency of treated sites was scored by those techniques. Loss of >50% of luminal diameter on CT, treatment in interim by means of infrapopliteal bypass or endovascular reintervention, major amputation, and death related to CLI were considered as treatment failure. An ordinal score was used to grade the severity of treatment failure from vessel restenosis, through vessel occlusion to treatment in interim, major amputation, or CLI-related death.

Additional secondary end points were ischemic categorization of the treated leg by means of Rutherford classification, minor and major amputation (at or below versus above ankle level, respectively) of the trial leg, and periprocedural (within 30 days) complications, serious adverse events, and death.

Statistical Analysis

On the basis of published data, a patency rate of 50% was assumed in the PTA±BMS arm at 6 months.[19] The study was designed to have a power of 80% to detect an elevation of the patency rate by DES to 75% with a 2-sided $P<0.05$. Taking into account a 15% loss to follow-up rate, the required sample rate had to be ≥136 patients.[18]

To evaluate difference in primary end point between PTA±BMS and DES, logistic regression with adjustment for multiple lesions within 1 limb was applied, assuming compound symmetry of the covariance matrix. For the ordinal composite end point a weighted χ^2 test was used, with weights equal to the inverse number of lesions per limb. Limbs in patients included for both limbs were considered independent for the analysis.

The observed rate of amputation, death, and the combined end point amputation or death was estimated with the Kaplan–Meier method. Patients were censored at the end of follow-up.

Table 3. Primary End Point Per Lesion After 6 Months, MITT, and PP Analysis

	PTA±BMS (n=54 Limbs*)	DES (n=62 Limbs*)	*P* Value
MITT analysis	n=77 lesions*	n=98 lesions*	
Lesions with preserved patency	27 (35.1)	47 (48.0)	0.096†
Ordinal score			0.041‡
≤50% stenotic	27 (35.1)	47 (48.0)	
>50% stenotic	23 (29.9)	15 (15.3)	
Occluded	7 (9.1)	19 (19.4)	
Amputation/leg ischemia–related death/treatment in interim	20 (26.0)	17 (17.3)	
PP analysis	n=77 lesions*	n=81 lesions*	
Lesions with preserved patency	27 (35.1)	42 (51.9)	0.037†
Ordinal score			0.009‡
≤50% stenotic	27 (35.1)	42 (51.9)	
>50% stenotic	23 (29.9)	8 (9.9)	
Occluded	7 (9.1)	17 (21.0)	
Amputation/leg ischemia–related death/treatment in interim	20 (26.0)	14 (17.3)	

Values are N (%). BMS indicates bare metal stent; DES, drug-eluting stent; MITT, modified-intention-to-treat; PP, per protocol; and PTA, percutaneous transluminal angioplasty.

*Numbers are no. of limbs/lesions with available, diagnostic imaging and those with treatment failure. Limbs/lesions in patients deceased because of unrelated causes were censored.

†*P* value adjusted for multiple lesions per patient.

‡*P* value weighted by number of lesions per patient.

Differences between the treatment strategies were assessed with the log-rank test. Differences in mean Rutherford category were analyzed with *t* test.

All end points were evaluated in the modified-intention-to-treat (MITT) analysis, excluding patients who did not fulfill all inclusion criteria or complete follow-up and who had incorrectly been included. Furthermore, patients who had died because of causes unrelated to CLI were censored. In addition, all end points were repeated in the per-protocol (PP) analysis considering analyses per lesion, in which only lesions were included which were technically treated according to randomization.

In the PTA±BMS arm all lesions were treated according to protocol and included in PP analysis. Twenty-two lesions in the DES arm were treated with PTA only and excluded from PP analysis. Eight lesions were located near a joint, 5 lesions at a bifurcation, technical failure precluded stenting in 1 lesion, and in 8 lesions only PTA was performed because of operator preference.

Analyses were performed in SPSS version 21 and SAS System 9.3 for Windows by B.E.H. and M.I.S.

Results

Patient and Lesion Characteristics

From October 2007 through February 2013, 75 limbs in 74 patients were randomly assigned to DES and 69 limbs in 67 patients to PTA±BMS (Figure 1). In the DES arm, 1 patient (1 limb) and in the PTA arm 3 patients (3 limbs) were excluded from the MITT analysis.

Table 4. Clinical Outcomes After 6 and 12 Months

	0–6 Mo		0–12 Mo		
	n	% (95% CI)	n	% (95% CI)	*P* Value*
Major amputation					0.066
PTA±BMS (n=66 limbs)	13	20.5 (10.5–30.5)	13	20.5 (10.5–30.5)	
DES (n=74 limbs)	7	9.8 (2.9–16.7)	8	11.4 (4.0–18.8)	
Death					0.52
PTA±BMS (n=64 patients)	9	14.1 (5.7–22.5)	16	25.1 (14.5–35.7)	
DES (n=73 patients)	10	13.7 (5.9–21.5)	17	23.3 (14.1–33.1)	
Major amputation or death					0.15
PTA±BMS (n=66 limbs)	19	28.8 (20.4–37.2)	24	36.4 (25.8–47.0)	
DES (n=74 limbs)	15	20.1 (12.3–27.9)	23	31.1 (20.5–41.7)	

BMS indicates bare metal stent; CI, confidential interval; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

*Overall log-rank test.

Both arms had similar baseline characteristics (Table 1). Diabetes mellitus was a common comorbidity. The overall mean baseline Rutherford category was 5.1 with a range of 4 to 6.

Almost all limbs showed extensive peripheral arterial disease; 93.9% of limbs in the PTA±BMS arm and 98.6% in the DES arm were classified as category D, according to the TransAtlantic Inter-Society Consensus (Table 2).[20] Ninety-one lesions were treated in the PTA±BMS arm and 121 lesions in the DES arm, an average of 1.4 and 1.6 lesions per limb, respectively. Lesion characteristics were similar in both arms (Table 2). Residual stenosis after treatment was significantly less in the DES than in the PTA±BMS arm (3.2% versus 10.7%; *P*=0.002). An average of 1.8 stents was implanted per limb randomized for DES. In the PTA±BMS arm, a mean of 0.3 bail-out BMS were placed per limb.

End Points

The MITT analysis showed a 6-month patency rate of 48.0% in the DES arm versus 35.1% in the PTA±BMS arm (*P*=0.096). In the PP analysis, this difference was statistically significant; 51.9% in the DES arm and 35.1% in the PTA±BMS arm (*P*=0.037; Table 3).

Lesions in the DES arm showed a more favorable composite clinical and morphological outcome than those in the PTA arm after 6 months in both the MITT (*P*=0.041) and PP analysis (*P*=0.009; Table 3).

During the first 6 months after treatment, there were 7 major amputations of the index limb (9.8%; 95% CI, 2.9%–16.7%) in the DES arm, versus 13 (20.5%; 95% CI, 10.5%–30.5%) in the PTA±BMS arm (*P*=0.10; Table 4). The major amputation rate after 1 year was 11.4% (95% CI, 4.0%–18.8%) in the DES arm and 20.5% (95% CI, 10.5%–30.5%) in the PTA±BMS arm. The Kaplan–Meier curves during the 2-year follow-up period diverged after 2 months in advantage of DES (*P*=0.066; Figure 2).

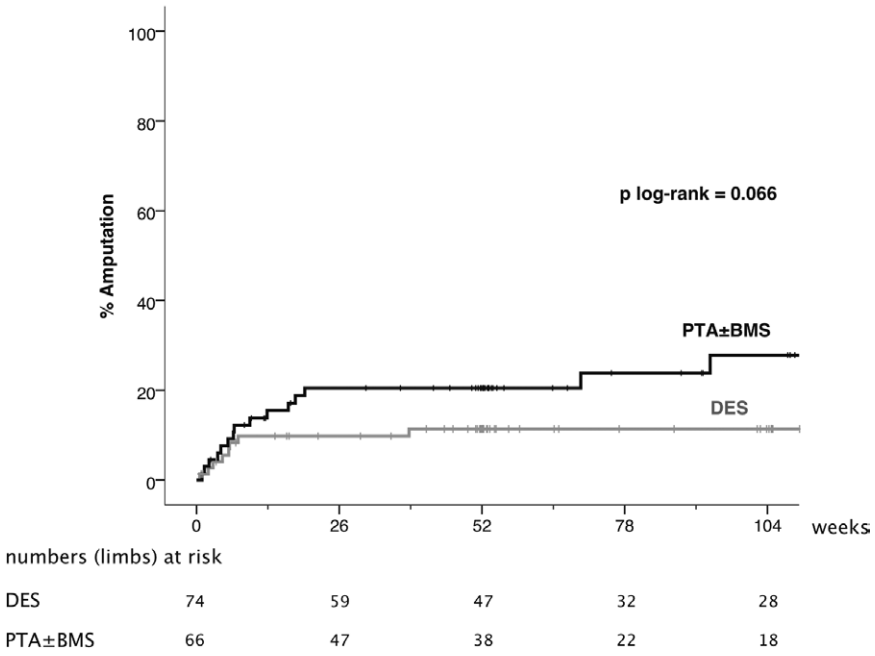

Figure 2. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of major amputation per limb after percutaneous transluminal angioplasty (PTA)±bare metal stent (BMS) and drug-eluting stent (DES).

Significantly less minor amputations occurred in the DES arm during the first 6 months after treatment (P=0.03), but not during the second 6-month interval (Table 5).

During the first post-treatment year, 17 patients in the DES arm and 16 patients in the PTA±BMS arm died, corresponding to a survival rate of 76.7% (95% CI, 66.9%–85.9%) versus 74.9% (95% CI, 64.3%–85.5%), respectively (Table 4). The Kaplan–Meier curves of survival and death or amputation until 2-year follow-up showed no significant difference between the treatment arms (P=0.52 and 0.15, respectively; Figures 3 and 4).

Three patients (4.1%) in the DES arm underwent retreatment of the affected leg within 6-month follow-up, against none in the PTA±BMS arm (P=0.098).

The mean Rutherford category,[17] ankle-brachial index, and toe pressure after 6 and 12 months improved significantly in the survivors of both groups compared with baseline (P≤0.005; Figures 5–7; Table II in the Data Supplement). These improvements were comparable in both groups.

Complications and Adverse Events

Interim analysis for safety reasons at 6-week follow-up of the first 40 patients showed an acute thrombosis rate of 5% in both arms. The incidence of periprocedural complications, complications during treatment admission, and late complications did not differ significantly between the 2 arms; neither did the number of serious adverse events. A table with complications and serious adverse events is available in Table III in the Data Supplement.

Table 5. Worst Minor Amputations

	PTA±BMS	DES	*P* Value*
0–6 mo	n=66 limbs	n=74 limbs	0.03
Toes	14 (21.2)	5 (6.8)	
Forefoot	2 (3.0)	5 (6.8)	
6–12 mo	n=42 limbs†	n=51 limbs†	0.69
Toes	2 (4.8)	4 (7.8)	

Values are n (%). BMS indicates bare metal stent; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

*Likelihood ratio test.

†In 5 limbs, data on minor amputations are missing.

Discussion

Our study shows that paclitaxel-eluting DES provide higher patency rates at 6 months in infrapopliteal stenotic or occluded lesions in patients with CLI when compared with the current reference treatment, PTA±BMS.[5]

Treatment failure was observed significantly more often in the latter group and was more severe, as is shown by the composite results. Such a composite end point better reflects the overall performance of DES compared with PTA±BMS because it combines the results of the morphological, local, and general clinical situation in patients.

This is the first study that demonstrates a difference in limb amputation rate using DES in CLI. The Kaplan–Meier curves of major amputations diverge at 2 months post-treatment with a trend toward significance at 2 years. In addition, there were less minor amputations.

Survival was comparable in both groups. The majority of deaths was not related to progression of limb ischemia, which can be explained by the fact that 25% of patients presenting with CLI are known to die within a year of onset of the symptoms, often caused by coronary heart disease.[1,2,21,22]

Surviving nonamputated patients showed improved Rutherford categories during follow-up. The decrease of Rutherford categories from 4 to 6 to stages 3 and 2 after 6- and 12-month follow up show that all these patients actually benefit from their medical care.

In interventional cardiology, DES were developed to decrease in-stent neointimal hyperplasia, which mainly occurs until 6 months post procedure.[12,23,24] Nowadays, DES are standard

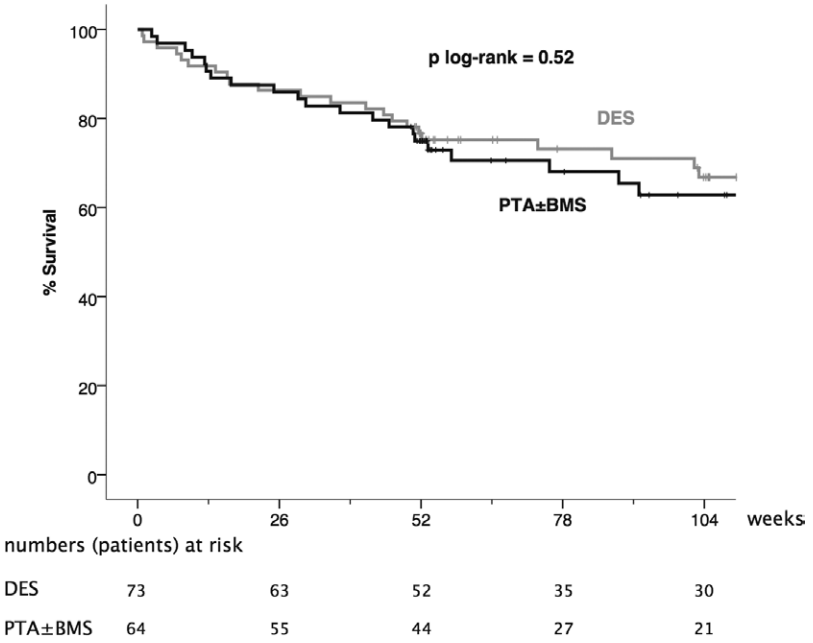

Figure 3. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of survival per patient after percutaneous transluminal angioplasty (PTA)±bare metal stent (BMS) and drug-eluting stent (DES).

treatment in coronary lesions because several meta-analyses proved their superior performance on restenosis and ischemia-driven repeat revascularization rates in comparison with BMS.[25]

Given these positive results of DES in coronary arteries, expectations arose that these stents might be efficacious in the similarly sized infrapopliteal arteries, what is supported by the results of our study. A recent meta-analysis of 3 randomized controlled trials to assess the efficacy of DES for the management of infrapopliteal arterial disease reported a significantly higher primary patency rate for DES compared with PTA or BMS at 1 year.[26] There was no difference in major amputation rates; however, this is probably because of the fact that the individual studies included patients with intermittent claudication,[13,14] in whom amputations are rare, or had follow-up in less than half of the cases.[16] We observed a lower major amputation rate in the DES group, with a trend toward significance. Furthermore, our study demonstrates that DES reduce minor amputations. In a CLI population, major amputation is a serious threat.[1,3] The severity and extensiveness of vascular disease in our patients are further reflected by the lower patency rates than anticipated in the sample size calculations. The patency and reintervention rates in our study are lower compared with studies that include patients with intermittent claudication.[13,14]

Till now, the experience with infrapopliteal paclitaxel-eluting stents is confined to small nonrandomized series that often included the use of various DES.[27–31] Although some

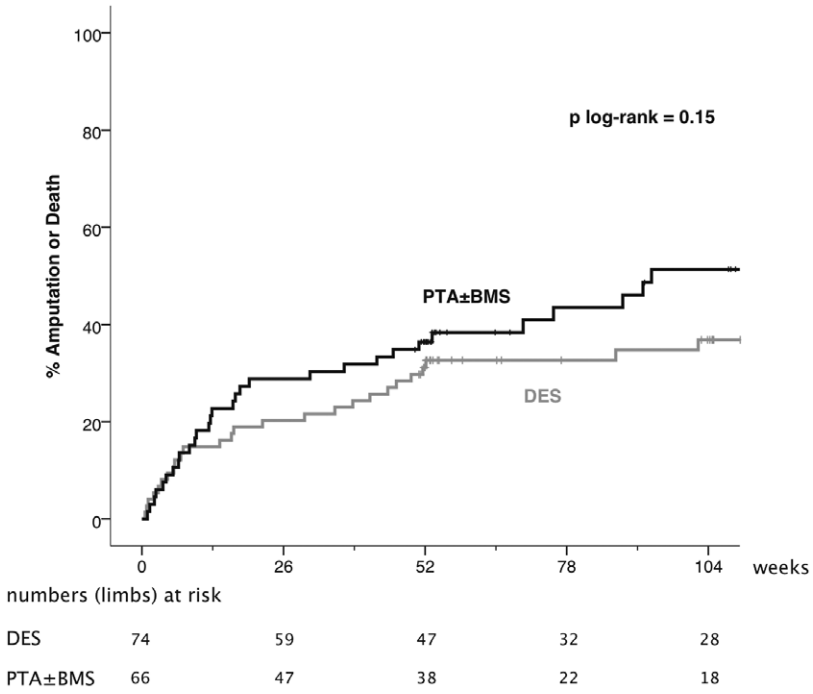

Figure 4. Kaplan–Meier curves representing the estimated 2-year cumulative incidence rates of major amputation or death per limb after percutaneous transluminal angioplasty (PTA)±bare metal stent (BMS) and drug-eluting stent (DES).

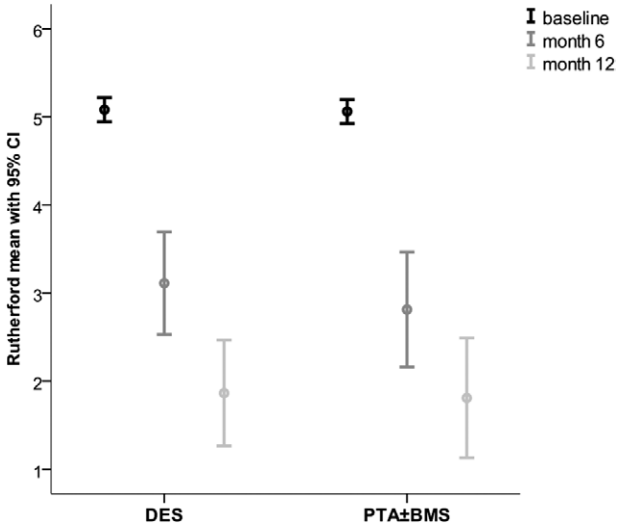

Figure 5. Mean Rutherford categories at baseline, 6 and 12 months. BMS indicates bare metal stent; CI, confidential interval; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

authors report higher infrapopliteal patency rates of sirolimus-eluting than paclitaxel-eluting stents, there are no randomized studies on this issue.[13–16,26–29,32]

Considering our relatively low complication rate, revascularization by means of endovascular techniques seems a justifiable treatment strategy in patients with CLI, who are in general elderly with substantial comorbidities and therefore less suitable for surgery.

Our study has some limitations.

Not all of our patients showed decreased ankle-brachial index and toe pressures, thereby not strictly meeting the hemodynamic criteria for CLI.[1] This is probably because of

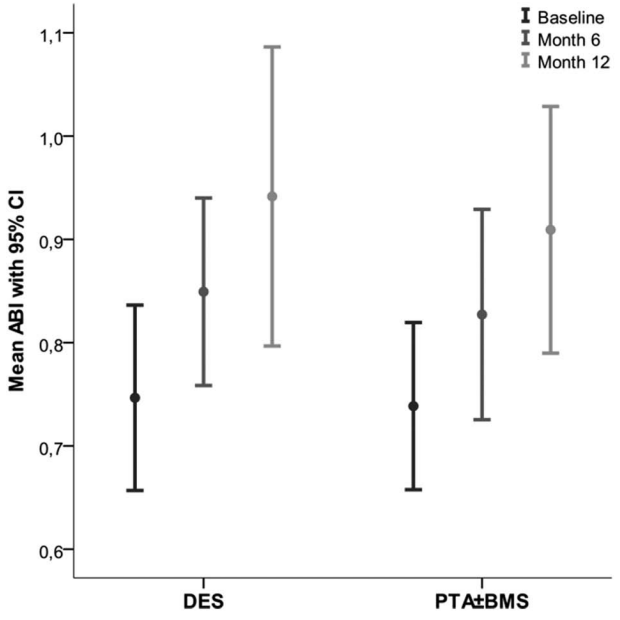

Figure 6. Mean ankle-brachial index at baseline, 6 and 12 months. BMS indicates bare metal stent; CI, confidential interval; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

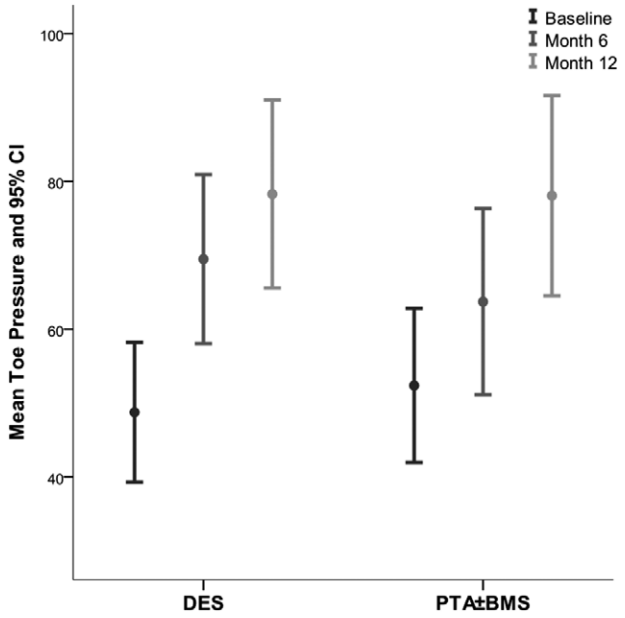

Figure 7. Mean toe pressure at baseline, 6 and 12 months. BMS indicates bare metal stent; CI, confidential interval; DES, drug-eluting stent; and PTA, percutaneous transluminal angioplasty.

the fact that >63% of our patients have diabetes mellitus, in whom ankle-brachial index values are known to be relatively elevated.[1] Toe pressures have been thought to represent a more reliable parameter in CLI but a recent study has failed to confirm this. Optimal cut-off values remain to be established in diagnosing CLI.[33] We think that the overall clinical picture of patients presenting with rest pain or tissue loss, and excluding patients with intermittent claudication, is the most important factor in properly selecting patients who need revascularization.

In 8 limbs, randomized for DES, 8 additional lesions were treated with PTA only, after treating the main lesion with DES. As a result, there is a difference between the primary end point in the MITT analysis and additional PP analysis.

Our primary end point was scored by means of CTA instead of digital subtraction angiography. CTA has been reported as an adequate tool for the assessment of arterial obstructions despite the fact that calcifications may hinder the assessment of stenosis rate.[34] Because there were no lesions excluded from treatment in either group in our study because of severe calcifications, it is unlikely that treatment results have been influenced by unequal distribution of calcified lesions. In addition, digital subtraction angiography was considered too invasive and burdening for our elder and vulnerable study population.

In those cases when the index limb had been amputated or the patient had died because of progressive ischemia before 6-month follow-up, lesions were scored as treatment failures. In these cases, amputation or related death may also have been related to progression of disease elsewhere in the arteries supporting the affected limb. Patients who died because of unrelated causes were censored. Because these numbers of deceased patients are almost equal in both groups and consistent with previously reported high mortality rates among patients with CLI, it is unlikely that this has caused any bias.

In 13 patients, imaging at 6-month follow-up is not available. Patients with lower limb ischemia show high rates of loss to follow-up and low survival rates in longitudinal studies.[1,16] Despite this challenging population, clinical follow-up was obtained in all our patients.

Finally, because this study is an investigator-initiated study, financial means were insufficient to provide patency analysis by means of a core laboratory. This was solved by assessing patency analysis independently by 2 board certified interventional radiologists.

Conclusions

In patients with CLI caused by infrapopliteal lesions, a treatment strategy with DES should be considered because they are associated with better patency and less amputations when compared with PTA±BMS, which is the current standard endovascular treatment.

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Disclosures

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Percutaneous Transluminal Angioplasty and Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia (PADI) Trial

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Percutaneous Transluminal Angioplasty versus Drug Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia, PADI trial

SUPPLEMENTAL MATERIAL

Supplemental Tables

Supplemental table 1A. Inclusion criteria

Inclusion criteria
▪ Age > 18 years.
▪ If female patient with child-bearing potential, patient may not be pregnant at the study entry and must utilize reliable birth control for the duration of her participation in the study.
▪ Patient is willing and able to comply with the specified follow-up evaluation.
▪ Critical limb ischemia, defined as Rutherford category 4 (ischemic rest pain), 5 (minor tissue loss), or 6 (major tissue loss).
▪ Stenosis (>50% luminal loss) or occlusion of an infrapopliteal artery, including the tibiofibular trunk, the anterior tibial artery, the posterior tibial artery, and the peroneal artery.
▪ Target lesion length ≤90 mm.
▪ Artery to be treated with a diameter ≥2 mm and ≤6 mm.
▪ Patent common iliac, external iliac, superficial femoral and popliteal artery on the ipsilateral side prior to randomization, possibly after treatment during the same session.
▪ At least 1 patent crural (anterior tibial, posterior tibial, or peroneal) artery with expected unobstructed runoff to ankle level after treatment.

Supplemental table 1B. Exclusion criteria

Exclusion criteria
▪ Acute limb ischemia.
▪ Previous amputation of affected limb at or above ankle level.
▪ Subacute limb ischemia which requires thrombolysis as first treatment modality.
▪ Active bleeding or bleeding diathesis.
▪ Recent (≤3 months) hemorrhagic stroke or any other CNS abnormality with increased risk of hemorrhage, such as intracranial neoplasm, arteriovenous malformation, intracranial aneurysm, or aneurysm repair.
▪ Gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks before treatment.
▪ Aneurysm in common femoral, superficial femoral, or popliteal artery on the ipsilateral side.
▪ Surgical revascularization involving the same limb within 30 days prior to the index procedure or planned surgical revascularization of the same limb within 30 days of the index procedure.
▪ Previous implanted stent at the index site.
▪ Life expectancy of less than 6 months or other factors making clinical follow-up difficult.
▪ Known allergy to acetylsalicylic acid (aspirin), clopidogrel, heparin, or paclitaxel.
▪ Known allergy to contrast media.
▪ Known heparin-induced thrombocytopenia (HIT type 2).
▪ Patient unable or unwilling to tolerate anticoagulant, anti-platelet therapy or contrast media.
▪ Creatinine clearance 20 mL/minute (as derived from Cockroft-Gault formula).
▪ Severely calcified lesions with expected resistance to stenting.

- Poor inflow due to ipsilateral stenoses or occlusions of the iliac or femoropopliteal arteries that cannot be treated during the same session.
- Significant vessel tortuosity or other parameters prohibiting access to the lesions and/or delivery of the stent.
- Patients without (expected) distal runoff to the index site.

Supplemental table 2. Mean Rutherford score, ankle brachial index and toe pressure at 6 and 12 months post treatment

	PTA±BMS	DES	p value *
Rutherford score			
	n=43 limbs	n=53 limbs	
mean (s.e.) at month 6	2.81 (0.32)	3.11 (0.29)	0.49
	n=37 limbs	n=45 limbs	
mean (s.e.) at month 12	1.81 (0.34)	1.87 (0.30)	0.90
Ankle brachial index			
	n=32 limbs	n=39 limbs	
mean (s.e.) at month 6	0.83 (0.05)	0.85 (0.04)	0.74
	n=26 limbs	n=33 limbs	
mean (s.e.) at month 12	0.91 (0.06)	0.94 (0.07)	0.74
Toe pressure (mmHg)			
	n=34 limbs	n=40 limbs	
mean (s.e.) at month 6	63.7 (6.2)	69.5 (5.7)	0.49
	n=24 limbs	n=31 limbs	
mean (s.e.) at month 12	78.1 (6.6)	78.3 (6.2)	0.98

* T-test.

PTA: percutaneous transluminal angioplasty; BMS: bare metal stent; DES: drug-eluting stent, s.e.: standard error.

Supplemental table 3. Complications and serious adverse events

	PTA±BMS	DES	p value*
	n=66 limbs	n=74 limbs	
Periprocedural complications †			
Hematoma	8 (12.1)	7 (9.5)	0.61
Material dysfunction	0	3 (4.1)	0.10
Acute thrombosis	4 (6.1)	5 (6.8)	0.87
Distal emboli	3 (4.5)	4 (5.4)	0.82
Pseudo aneurysm	0	1 (1.4)	0.34
Complications until 12 months			
Acute thrombosis	1 (1.5)	0	0.29
Wound infection	3 (4.5)	8 (10.8)	0.17
Serious adverse events			
Gastrointestinal bleeding	3 (4.5)	2 (2.7)	0.56
Ischemic cerebral event	1 (1.5)	2 (2.7)	0.63
Cerebral hemorrhage	2 (3.0)	0	0.13
Pneumonia	1 (1.5)	3 (4.1)	0.37
Decubitus	1 (1.5)	0	0.29
Cardiac disease	1 (1.5)	5 (6.8)	0.13
Renal failure	2 (3.0)	1 (1.4)	0.49
Non CLI related infection	4 (6.1)	2 (2.7)	0.33

Values are number (%). *Chi-square test. †<30 days post procedural.

PTA: percutaneous transluminal angioplasty; BMS: bare metal stent; DES: drug-eluting stent; CLI: critical limb ischemia.