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Preventing Leg Amputations in Critical Limb Ischemia With Below-the-Knee Drug-Eluting Stents

The PaRADISE (PReventing Amputations using Drug eluting StEnts) Trial

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Objectives We investigated the efficacy and safety of using balloon expandable drug-eluting stents (DES) to prevent amputations in patients with below-the-knee critical limb ischemia.

Background Critical limb ischemia patients have a 1-year amputation rate of 30% and a mortality rate of 25%. Most patients with critical limb ischemia have severe below-the-knee arterial disease that limits the use of bypass surgery or balloon angioplasty.

Methods In all, 106 patients (118 limbs) were treated with DES in this prospective, nonrandomized trial. No patients were excluded because of comorbidities or unfavorable anatomy. Primary end points were major amputation and mortality, each stratified by Rutherford category.

Results The mean patient age was 74 ± 9 years. There were 228 DES implanted (83% Cypher [Cordis, Johnson & Johnson, Warren, New Jersey], 17% Taxus [Boston Scientific, Maple Grove, Minnesota]). The number of stents per limb was 1.9 ± 0.9, and 35% of limbs received overlapping DES (length of 60 ± 13 mm). There were no procedural deaths, and 96% of patients were discharged within 24 h. The 3-year cumulative incidence of amputation was 6 ± 2%, survival was 71 ± 5%, and amputation-free-survival was 68 ± 5%. Only 12% of patients who died had a preceding major amputation. Rutherford category, age, creatinine level, and dialysis ($p \leq 0.001$ to 0.04) were predictors of death but not amputation. Target limb revascularization occurred in 15% of patients, and repeat angiography in 35% of patients revealed a binary restenosis in 12%.

Conclusions Treating below-the-knee critical limb ischemia with DES is an effective and safe means of preventing major amputation and relieving symptoms. Procedural complications and limb revascularization rates were low. Limb salvage and survival rates in patients treated with DES exceed those of historic controls. (J Am Coll Cardiol 2010; 55:1580–9) © 2010 by the American College of Cardiology Foundation

Critical limb ischemia (CLI) is a common and devastating manifestation of peripheral arterial disease. The diagnosis is established when patients present with ischemic rest pain, ulcerations, or gangrene of the leg associated with evidence of reduced arterial blood flow to the foot (1). Within the first year of illness, 30% suffer a major amputation (MA), 25% will die, and 20% endure with unresolved pain or tissue loss (1,2).

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Preventing MA in CLI is arguably the most important goal and is predicated on the ability to restore and maintain straight line tibial arterial flow to the foot. Although many consider surgical bypass the therapeutic cornerstone, this approach is infrequently exercised because of poor surgical targets, lack of suitable conduits, advanced age, and multiple comorbidities that result in prohibitive surgical morbidity and mortality (1,2). Consequently, transtibial amputation remains the most frequent treatment for CLI when pain, tissue loss, and infection become intractable (3).

The less invasive nature of percutaneous transluminal angioplasty (PTA) makes it an attractive alternative to bypass surgery. However, its reliability and durability is limited, with a 1-year primary tibial patency rate of 20% to

60% (4,5). Consequently, tissue perfusion is often inadequate to heal tissue loss and resolve rest pain.

The BASIL (Bypass Versus Angioplasty in Severe Ischemia of the Leg) study compared PTA to surgical bypass for treating leg ischemia. After 2 years, both approaches achieved therapeutic equipoise with regard to amputation and survival. However, each modality had significant limitations. At 1 month, 20% of PTAs failed, whereas the combined mortality, stroke, and coronary event rate with surgery was 15%. Furthermore, although the BASIL study patients were at relatively low risk with favorable anatomy, the amputation-free survival at 1 and 3 years was approximately 70% and 55%, respectively (6).

Previously, we demonstrated that many limitations associated with below-the-knee (BTK) PTA could be circumvented by using balloon expandable coronary stents (7). Nevertheless, despite elimination of early interventional failures and hemodynamic improvement, this approach was suboptimal because of late in-stent restenosis ranging from 20% to 60% (8,9).

With the advent of coronary artery drug-eluting stents (DES), we postulated that the logical next step was to incorporate this technology into an algorithm for treating infragenual CLI (7). Subsequently, a number of single-center studies have demonstrated that BTK DES is safe and associated with low rates of in-stent restenosis or occlusion (8–13). To date, however, only small numbers of patients have been reported, and there is little long-term follow-up available.

In this communication, we present the results of the PaRADISE (PReventing Amputations using Drug eluting StEnts) trial, which represents the largest cohort and longest follow-up of CLI patients treated with primary BTK DES. In lieu of a control arm, the PaRADISE study data were compared to historic data from the TASC II (Trans-Atlantic Inter-Society Consensus II) document and level-1 evidence from the BASIL trial (1,6).

Methods

Between May 10, 2003, and March 1, 2009, CLI patients were sequentially enrolled in the institutional review board-approved, single-center and -operator PaRADISE trial. All patients gave written informed consent for primary implantation of the Food and Drug Administration-approved coronary DES stents (Cypher, Cordis, Johnson & Johnson, Warren, New Jersey, or Taxus, Boston Scientific, Maple Grove, Minnesota). Critical limb ischemia was defined according to the Second European Consensus Document (14). Patients were stratified according to the Rutherford-Becker scale where categories 4, 5, and 6 corresponded to resting pain, minor ulcerations, and gangrene, respectively (15). Patients with uninterruptible ankle-brachial indexes (i.e., incompressible vessels) were stratified according to their Rutherford presentation. No patients were excluded because of age, renal insufficiency, dialysis, prior stroke, heart failure, unstable angina, cancer, or other life-limiting illnesses.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
BTK = below the knee
CLI = critical limb ischemia
DES = drug-eluting stent(s)
MA = major amputation
PTA = percutaneous transluminal angioplasty
SFA = superficial femoral artery
TASC = Trans-Atlantic Inter-Society Consensus

Interventional technique. We have previously described the techniques for BTK stenting (7,16). The interventional objective was to establish straight-line flow to the foot in 1 tibial vessel. Patients were enrolled when the 0.014-inch wire crossed the targeted BTK lesion. Lesions were pre-dilated to test lesion compliance, and stents were deployed to achieve a slight negative residual compared to the distal reference vessel. Technical success was defined as a residual post-stent stenosis of ≤20.0%, and angiographic success was defined as restitution of straight-line tibial flow to the foot. To limit institutional costs, a goal of 2 DES per limb was set. Long-segment disease was treated by stenting the inflow and total occlusions lesions and treating the intervening arterial segments with long balloon PTA (Amphirion, Invatec, Brescia, Italy).

Patients with significant above-knee lesions were contemporaneously treated using a variety of endovascular techniques. Patients with SFA occlusions that could not be recanalized were considered candidates for tibial stenting by the antegrade popliteal approach if the popliteal segment was adequately collateralized (16).

Pharmacologic therapy. Before intervention, all patients were started on a regimen of aspirin 81 mg, clopidogrel 75 mg daily, or ticlopidine 250 mg bid. Patients received unfractionated heparin, 40 to 50 U/kg. Glycoprotein inhibitors were not routinely used. Patients with renal insufficiency (creatinine ≥1.3 mg%) were hydrated with D5W-sodium bicarbonate (150 mEq/l) infusion continued for 12 to 24 h. After the procedure, indefinite thienopyridine, aspirin, and lipid therapy was encouraged.

Clinical follow-up and end points. Routine follow-up was at 1, 3, and 6 months and every 6 months thereafter. Primary end points were MA (amputation above the ankle), all-cause mortality, tissue healing, and relief of rest pain. Planned digital or transmetatarsal amputations were not considered clinical failures if the amputation healed. Deaths were confirmed using the Social Security Death Index, and amputations were documented by review of hospital records and patient contact.

Major adverse events included stroke, myocardial infarction, major infections, compartment syndrome, flow-limiting dissection, distal embolization, vessel occlusion, retroperitoneal bleed, pseudoaneurysm, hematomas, and contrast nephropathy delaying discharge or dialysis.

Repeat angiography was performed for delayed tissue healing, recurrent symptoms, or incidental to angiographic evaluation of other vascular territories. Repeat intervention was driven by failure-to-heal ulcerations or unresolved

symptoms. Asymptomatic new lesions or in-stent restenosis were not pre-emptively treated.

Statistical analysis. Descriptive data are presented as the mean ± SD. Categorical and continuous outcomes were compared by Fisher's exact test and Welsh's *t* test, respectively. All time-to-event analyses were performed on a patient level with the outcome of the first leg treated unless otherwise specified. Kaplan-Meier survival plots were created for overall survival and amputation-free survival. Cox proportional hazard models for overall survival and amputation-free survival were used to estimate the simultaneous effect of age, kidney function coded as creatinine ≤2/>2/dialysis, Rutherford score, and statin use selected for face-value validity. The functional form of the predictors was estimated using Martingale residuals. The effect of other predictors was evaluated by adding them to the basic model one at a time.

The cumulative incidence of amputation was estimated using Aalen's estimator. Because of the small number of events, predictors were evaluated only univariately using Fine-Gray regression of the subdistribution hazard.

Survival estimates for the BASIL study were taken from the BASIL text when available and read from the Kaplan-Meier curves. The corresponding standard errors were estimated using Peto's formula based on the survival probability and the number at risk given at the bottom of each figure, resulting in conservative p values. An unpooled z-test was used to compare the survival estimates from the BASIL study and the current study. Analysis was performed in SAS version 9.2. (SAS Institute, Cary, North Carolina) and R 2.8.1 with the cmprsk 2.2.0 package.

Results

Angiographic evaluation was performed on 118 consecutive patients (130 limbs). The patient flow is illustrated in Figure 1. Twelve patients were excluded because of failure to cross total occlusions (6 SFA: 2 popliteal and 4 tibial). Thus, 106 patients (118 limbs) received 1 or more DES. Patient demographics are seen in Table 1. The mean patient age was 74 ± 9.8 years (age range 44 to 96 years), and 29% were over the age of 80 years. Females were on average 3 years older than males (p = NS).

Patients with indeterminate ankle-brachial indexes (16%) were nearly equally distributed among the 3 Rutherford

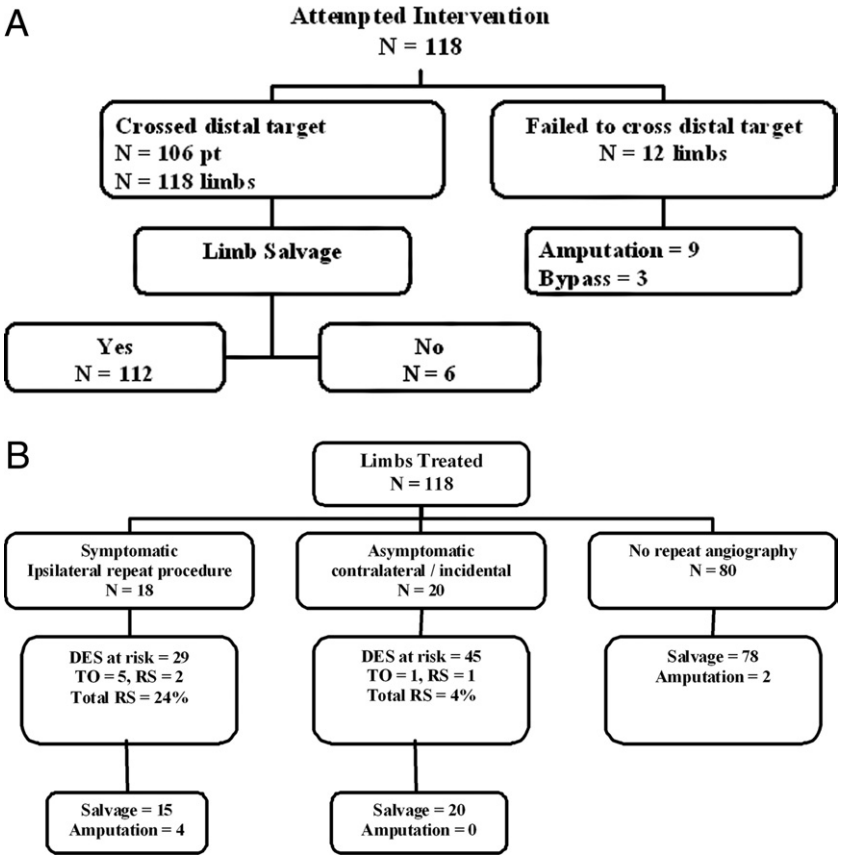

Figure 1 Patient Flow Diagram

(A) Clinical outcomes. **(B)** Angiographic outcomes. RS = binary restenosis; TO = total occlusion.

Table 1 Patient Characteristics

	Male (%)	Female (%)	p Value
n	72	34	0.003
Age at entry, yrs	73.8 ± 10	76.0 ± 8	0.24
Diabetes mellitus	35 (49)	15 (44)	0.68
Creatinine, mg%*	1.6 ± 0.7	1.4 ± 1.0	0.41
eGFR, ml/min/1.73 m^2	53 ± 23	51 ± 32	0.80
Lipid therapy	56 (79)	26 (76)	0.80
Coronary artery disease	41 (59)	16 (44)	0.21
Tobacco	27 (38)	8 (22)	0.13
Dialysis	1 (1)	3 (9)	0.10
Died	17 (24)	8 (23)	1.00
Age at death, yrs	80 ± 8.5	77 ± 7.9	0.31
Died without major amputation	16/17 (94)	6/8 (75)	0.23
Age at last follow-up of living, yrs	75 ± 10	78.9 ± 8.7	0.06
Limbs treated	80	38	
Rutherford-Becker category			
4	31 (39)	14 (37)	0.83
5	24 (30)	12 (31.5)	1.0
6	25 (31)	12 (31.5)	1.0
Tibial run-off, patent vessels	1.0 ± 0.8	0.8 ± 0.8	0.89
Above-knee intervention	35 (44)	21 (55)	0.32
Major amputations	2 (3)	4 (11)	0.07
Minor amputations	6 (8)	4 (11)	0.74

Values are n, mean ± SD, or n (%). *Excluding patients on dialysis.
eGFR = estimated glomerular filtration rate.

categories. The contralateral retrograde approach was used 92% of the time. Contemporaneous SFA or popliteal artery interventions were performed in 48% of limbs. Occlusion of all 3 tibial vessels or jeopardized single vessel run-off was present in 74% of patients. Technical success in delivering stents was 100%. Angiographic success was 96% with 5 failures to establish continuous flow to the ankle. Examples of tibial interventions are seen in Figures 2 and 3. A total of 228 stents were deployed, and 35% of patients received overlapping stents (mean length of 60 ± 13 mm) (Table 2).

Clinical follow-up was 100%, and the mean length of follow-up was 27.4 ± 18.6 months (range 2.4 to 69 months). Outcomes are seen in Table 3. There was 1 major adverse event (failure to maintain SFA patency resulting in a MA). In the first year, there were 6 MAs and none thereafter. Rest pain was relieved in 93% of patients, and all but 1 of 10 planned minor amputations healed (Table 3). Two additional patients underwent late femoral-popliteal bypass. In these cases, femoral-tibial bypass was avoided because of DES-maintained tibial outflow. The mean length of hospital stay was 1.2 days. Contrast nephropathy occurred in 4 patients, although none required dialysis.

The cumulative incidence of amputation at 3 years was 6 ± 2% (Fig. 4A). Among patients alive at 3 years, 96% were without a MA, and among those who died, 88% did not have a MA. Cumulative incidence of amputation curves stratified by Rutherford category is seen in Figure 4B. Rutherford 4 and 5 patients had a nonsignificant trend in favor of improved limb survival compared with category 6 patients. None of the clinical covariates was a significant predictor of MA (Table 4).

During follow-up, 25 patients died, with a mean survival of 12.8 ± 9.2 months (range 1.5 to 36 months) after the procedure. The Kaplan-Meier survival curves with and without stratification by Rutherford category are depicted in Figures 5A and 5B. Survival at 3 years was 71 ± 5%. Cox multivariable analysis identified entry age, creatinine/dialysis, and Rutherford category (4 or 5 vs. 6) as positive predictors of mortality (Table 5). The PaRADISE study amputation-free survival versus the BASIL trial results are compared in Figure 6. In nearly all cases, DES patients fared statistically better than either surgery or PTA patients, with the exception of bypass surgery at the third year (Table 6).

Repeat angiographic evaluation was performed in 38 patients (Fig. 1B): 18 were evaluated for recurrent ipsilateral symptoms, and 20 asymptomatic patients underwent angiography incidental to other vascular procedures. Thus, 36% of patients and 33% of the DES-implanted patients underwent angiographic evaluation at a mean interval of 256 ± 244 days after the initial procedure. Stent failure (binary restenosis or occlusion) was present in 24% of patients who presented with symptoms, whereas two-thirds of these patients had progressive disease involving the SFA or popliteal arteries. In these patients, 6 additional DES were placed at sites of previous intervention and 11 were placed at sites remote from the initial intervention. Four patients who had repeat interventions subsequently underwent BTK amputations. For asymptomatic patients (20 limbs, 45 at-risk stents), stent failure was 4%. Overall restenosis and occlusion were statistically less with the Cypher stent than with the Taxus stent ($p \leq 0.003$).

Discussion

The unique observations of the PaRADISE trial can be summarized as follows. 1) CLI patients treated with DES had a 3-year limb salvage of 94%, which significantly exceeds historical expectations for either PTA or bypass surgery. 2) A strategy of primary DES for BTK-CLI is safe and minimizes early procedural morbidity and mortality. 3) A DES for CLI is durable. Stent failures were few, and the need for repeat intervention was low. Wound healing and relief of resting pain were demonstrated in 93% of patients. 4) Compared with historic controls, mortality may be favorably influenced by a DES-centered strategy.

Major leg amputations and the PaRADISE study. The PaRADISE study 1- and 3-year freedom from MA was 96% and 94% respectively. Only 12% of patients who died had a MA. There was a nonsignificant trend favoring improved limb salvage in Rutherford 4 and 5 patients versus Rutherford 6, 97% vs. 88% (Fig. 4B). This observation is reasonable since patients with extensive tissue loss are less likely to heal even

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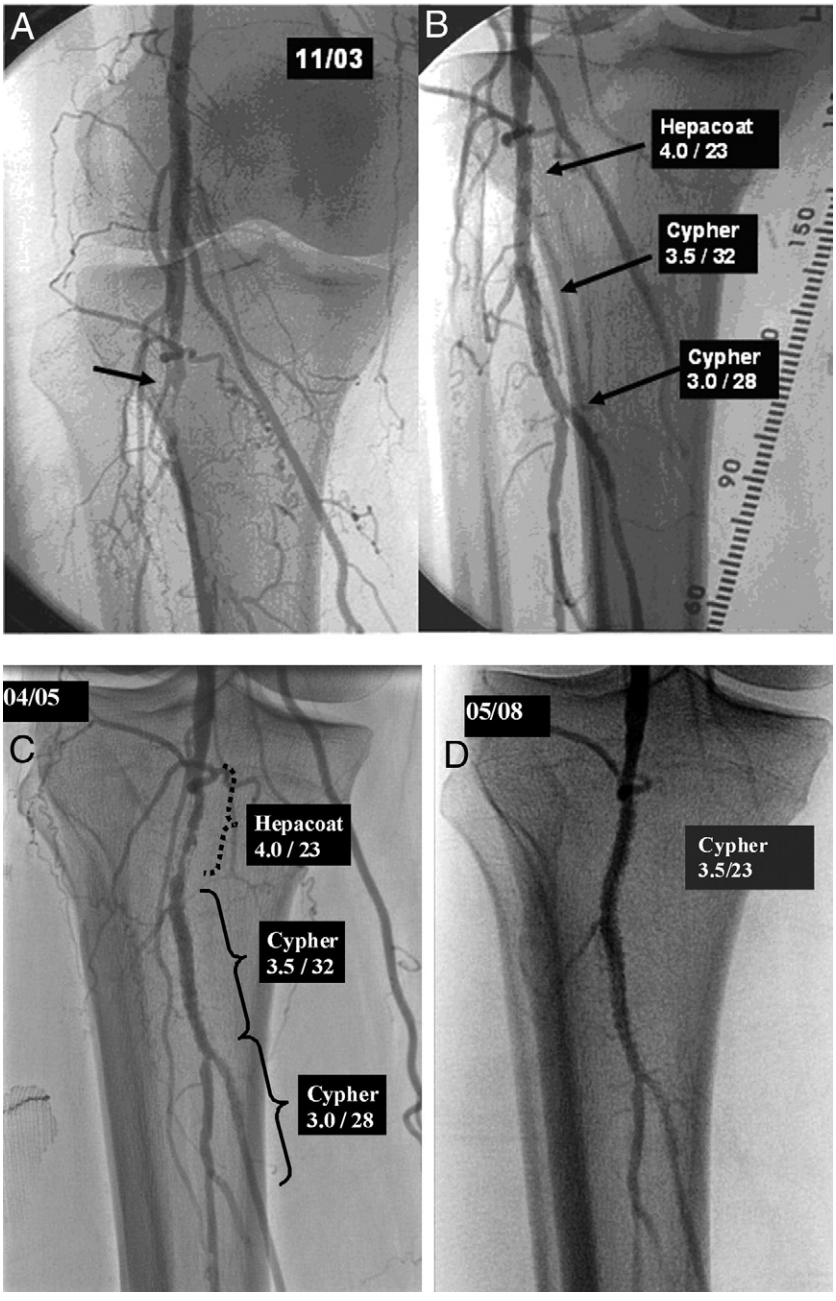

Figure 2 **Bare-Metal In-Stent Restenosis Successfully Treated With DES**

(A) An 87-year-old patient, Rutherford 5 critical limb ischemia (CLI). The **arrow** indicates popliteal artery occlusion. **(B)** After placing a proximal 4.0 mm bare-metal stent (BMS) and 2 overlapping 3.5-mm Cypher drug-eluting stents (DES). **(C)** The patient returned 17 months later with rest pain. Note in-stent restenosis of the BMS **(dotted brackets)** and the patent DES **(solid brackets)**. **(D)** Incidental angiography 18 months after treating in-stent restenosis with a 3.5-mm × 23-mm Cypher stent.

with optimal revascularization. These data suggest that more timely referral of CLI patients for endovascular-based DES therapy might further reduce amputations.

The TASC II benchmarks a 1-year MA rate of 30% with an additional 20% who fail to resolve their symptoms, whereas the PaRADISE study patients had a 6% 3-year amputation rate, and symptoms resolved in 99% of unamputated limbs. The 1- and 3-year amputation rate in the BASIL study were surprisingly low at 11% and 18%. However, comparing the BASIL study to the PaRADISE study is problematic because of differences in study design and data reportage. The BASIL study patients were a selected low-risk cohort. Nearly 90% of patients screened were excluded for unsuitable anatomy or comorbidities precluding surgery. Additionally, <25% of patients had true CLI. Furthermore, only one-third underwent tibial bypass, underscoring the low-risk nature of these pa-

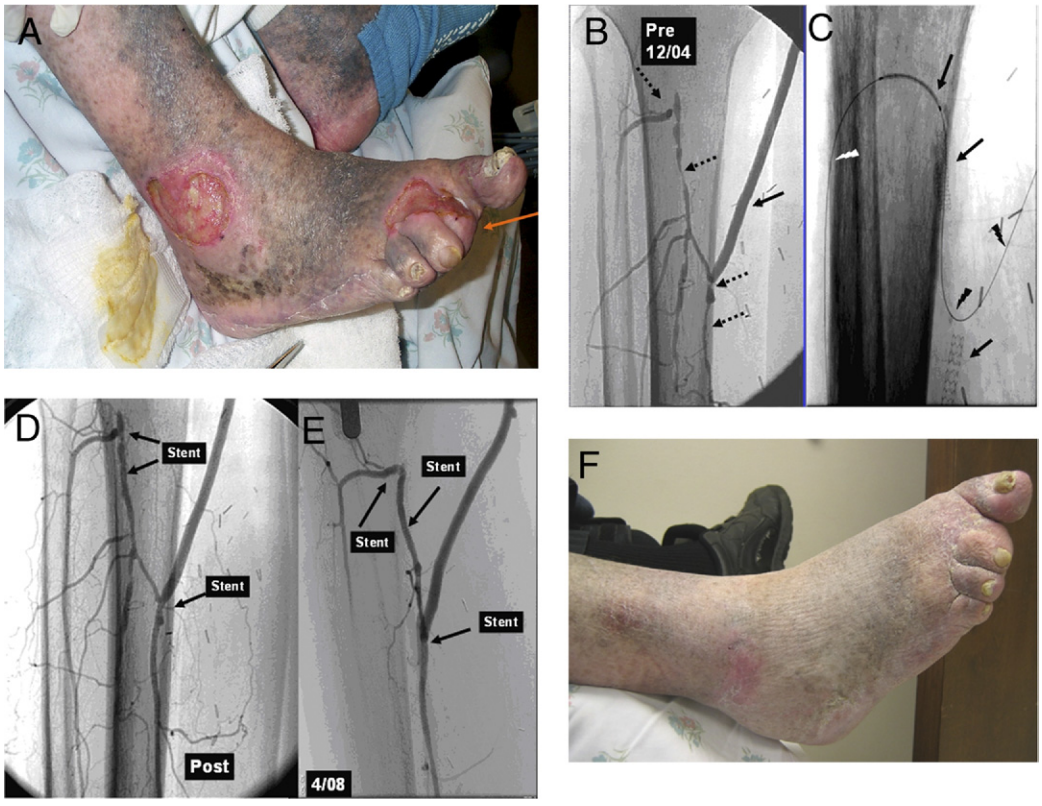

Figure 3 **Demonstration of the Technical Ease With Which DES Can Be Delivered to Challenging Tibial Anatomy**

(A) A 68-year-old patient with Rutherford 6 critical limb ischemia (CLI) 1 year after femoral-posterior tibial bypass. Toe amputation **(arrow)** and ankle ulcer failed to heal. **(B)** The **solid arrow** points to bypass graft insertion proximal to posterior tibial lesion; the **dotted arrows** note additional tibial lesions. **(C)** The ability to place drug-eluting stent (DES) in challenging anatomy from the retrograde contralateral approach is demonstrated. The **arrows** trace wire course into the anterior tibial artery. **(D)** Completion angiogram. **(E)** Angiography 4 years after initial implant. **(F)** Clinical response 3 months after intervention.

tients. Consequently, the BASIL study cohort was composed of low-risk patients with the most favorable arterial anatomy.

In contrast, the PaRADISE study patients were not excluded for comorbidities, and they had more challenging anatomy by definition as all patients had BTK intervention. Nevertheless, despite these differences, at 3 years the PaRADISE study maintained a 13 ± 6.3% limb survival advantage over the BASIL trial.

Table 2 **Drug-Eluting Stent Characteristics**

Stent	n (%)
Cypher*	188 (83)
Taxus†	40 (17)
Stents per limb (range)	1.9 ± 0.9 (1–5)
Single stent length, mm	26.9 ± 5.8 (8–33)
Mode	28
Diameter, mm	2.9 ± 0.4
Mode	3.0
Limbs with overlapping stents	41 (35%)
Length of overlap, mm	61 ± 15
Range	36–99
Mode	56
Median diameter stent, mm	3.0
Angiographic restenosis/Taxus	5/40 (12.5%)
Angiographic restenosis/Cypher	4/188 (2.5%)

*Cordis, Johnson & Johnson; †Boston Scientific.

We hypothesize that improved limb salvage was principally related to sustained tibial artery patency resulting from DES implants. Although assessing stent patency was not our primary focus, the data suggest that long-term patency was maintained in the overwhelming majority of patients. The flat slope of the limb survival curve (Fig. 4) suggests that the DES repair was durable. Additionally, because 74% of patients had either single or no tibial vessel run-off, the expected consequence of stent failure would be recurrence of symptoms and failure to heal ulcerations or minor amputations. This inference is supported by the observation that within 6 months of a failed surgical reconstruction, 40% of patients will undergo a MA and 20% will die (17). Finally, 34% of patients had repeat angiographic evaluation. In asymptomatic patients, the binary restenosis rate was 4% (2 of 45 stents), whereas in symptomatic patients, the binary restenosis rate was 24% (7 of 29 stents) (Fig. 1B). Thus,

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Table 3 Clinical Outcomes After Intervention

	Clinical Status			
	RB 4 (%)	RB 5 (%)	RB 6 (%)	p Value
Procedure to discharge, days	1.2 ± 0.8	1.1 ± 0.6	1.2 ± 0.9	NS
Number of limbs	44	37	37	
Clinical status, n				
Healed/relief of rest pain	43 (98)	36 (97)	32 (86)	0.09
Worsened	1 (2)	1	5	
Major amputation	1*	1	4	NS
Minor amputations not healed	0	0	1	NS
Minor amputation healed	0	2	7	0.004
Procedure-related death	0	0	0	NS
Contrast nephropathy	1	1	2	NS
Procedure-related amputation	1	0	0	NS
Myocardial infarction	0	0	0	NS
Stroke	0	0	0	NS
Infection	0	0	0	NS

*Above-knee amputation.
NS = not significant; RB = Rutherford-Becker category.

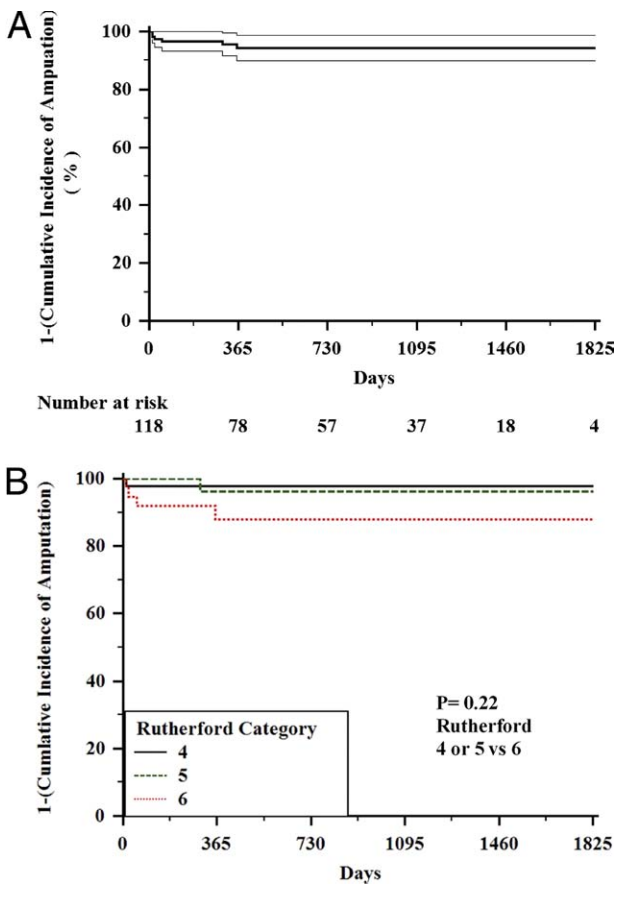

Figure 4 Rate of Major Amputations in Patients Treated With Below-the-Knee Drug-Eluting Stents

(A) 1 − cumulative incidence of amputation curve and confidence limits. **(B)** 1 − (cumulative incidence of amputation) stratified according to entry Rutherford category.

the combined angiographic restenosis rate was 11%, although this may represent an overestimation because nearly two-thirds of the asymptomatic patients did not undergo angiography. These data, in conjunction with previous studies, suggest that use of DES for tibial intervention is safe, effective, and durable.

Mortality and CLI. In the PaRADISE trial, the first- and third-year mortality rates were 87 ± 4% and 71 ± 5%, respectively (Fig. 5A). When compared with the TASC II study, the mortality in the PaRADISE study at 1 year was lower than in the TASC II study at 3 years. When contrasted with the BASIL study surgical group, the mortality benefit of the PaRADISE study was only apparent during the first year, which primarily reflects the differences in procedural mortality (Table 6). However, unlike the BASIL trial, the PaRADISE study patients were older (35% vs. 25% >80 years), had worse renal function (creatinine 1.8 mg/dl vs. 1.3 mg/dl), and included all patients regardless of clinical status. Consequently, the survival

Table 4 Cumulative Incidence of Amputation: Univariate Fine-Gray Analysis

Covariate	p Value	Hazard	95% CI
Age	0.09	0.94	0.87–1.01
Creatinine*	0.94	1.06	0.26–4.21
Dialysis	0.08	5.26	0.8–34.5
Diabetes mellitus	0.34	2.27	0.96–12.2
eGFR	0.79	0.99	0.96–1.03
Male vs. female	0.34	0.46	0.09–2.38
Rutherford 6 vs. 4 and 5	0.10	4.14	0.76–22.6
Statin	0.10	0.27	0.05–1.31
Above-knee intervention	0.96	0.96	0.19–4.72
Stents per leg	0.37	0.57	0.17–1.94

Data are depicted as 1 − (cumulative incidence of amputation) for display purposes. *Excluding patients on dialysis.
CI = confidence interval; eGFR = estimated glomerular filtration rate.

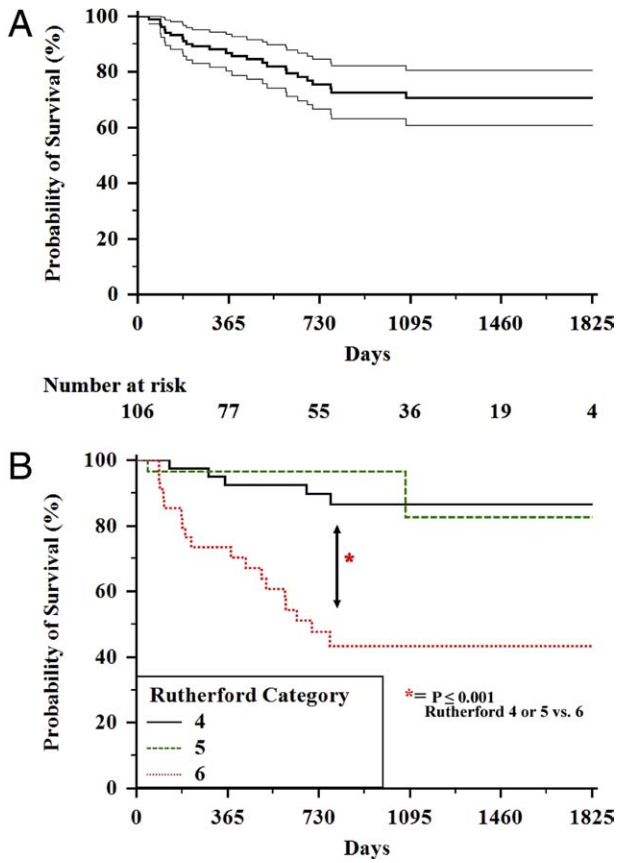

Figure 5 All-Cause Mortality in Patients Treated With Below-the-Knee Drug-Eluting Stents

(A) Kaplan-Meier survival curve with confidence limits. **(B)** Kaplan-Meier survival curves stratified according to entry Rutherford category.

benefit in the PaRADISE study might have been greater had the BASIL trial included a similar patient set.

The PaRADISE study survival was independently correlated with Rutherford category. At 3 years, patients in categories 4 and 5 had significantly better survival (87 ± 6% and 83 ± 13) than did patients in category 6, for whom survival was a dismal 43 ± 9% ($p \leq 0.001$ for category 4 and 5 vs. 6) (Fig. 5B). These observations have important implications for future CLI trials because outcomes must be normalized according to entry Rutherford categories.

Table 5 Cox Analysis Overall Survival

Covariate	p Value	Hazard	95% CI
Age	0.03*	1.06	1.006–1.116
Creatinine >2 vs. <2	0.0013*	5.09	1.89–13.75
Dialysis vs. creatinine <2	0.11	3.26	0.75–14.01
Rutherford 6 vs. 4 and 5	0.0009*	5.35	1.98–14.44
Statin	0.04*	0.36	0.14–0.96
Sex†	0.37	1.55	0.59–4.08
Above-knee intervention†	0.91	1.06	0.41–2.75
Stents per leg†	0.16	1.46	0.86–2.47
Ejection fraction ≤40%†	0.56	1.13	0.31–4.07

*Significant covariate. †Other factors added 1 at a time, controlling for first 5 variables.
CI = confidence interval.

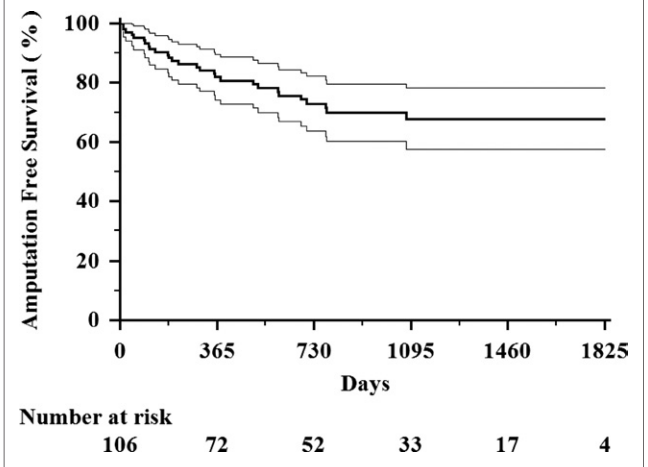

Figure 6 The PaRADISE Trial Amputation-Free Survival

Kaplan-Meier amputation-free survival curve (combined death and major amputation).

Unlike previous CLI studies, 90% of the PaRADISE study patients were maintained on a regimen of life-long dual antiplatelet agents, and nearly 75% received statins. In comparison, only 66% of BASIL study patients received aspirin and fewer than one-third received statins. The rationale for dual antiplatelet agents was predicated on extensive coronary DES data demonstrating improved stent patency with combined aspirin and thienopyridines (18). Additionally, recent studies suggest that survival and limb salvage are favorably influenced when vascular patients are treated with thienopyridines and statins (19,20).

Rationale for treating BTK CLI with DES. The limitations of balloon PTA for BTK CLI are well documented. The recent meta-analysis by Romiti et al. (4) found a 23% failure rate at 1 month and a 1-year primary patency of 58% after crural PTA. Kudo et al. (5) observed that only ≤25% of tibial vessels were patent 3 years after PTA. To overcome these limitations, we postulated that tibial PTA with BMS might improve early outcomes (7). This approach was predicated on the similarities between coronary and tibial vessels regarding histology, vessel diameter, and risk factors. However, analogous to coronary intervention, the late benefits of BMS were partially mitigated by in-stent restenosis rates between 20% and 60% (18,19,21).

A number of small, single-center BTK-DES have been reported. Siablis et al. (8) observed that after 6 months, 92% of BTK DES were patent compared to 68% of BMS. Scheinert et al. (9) found the occlusion/binary restenosis rates for provisional BTK BMS stenting were 17% and 39%, respectively, versus no events with the Cypher DES. Similar favorable results have been reported by

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Table 6 Comparison of Outcomes in the PaRADISE Study Versus BASIL Study: Amputation-Free Survival and Overall Survival

Outcome	1 Year (p Value)	2 Years (p Value)	3 Years (p Value)
Amputation-free survival			
PaRADISE vs. BASIL PTA	10.9 ± 5.0 (0.03)	11.0 ± 6.1 (0.07)	15.9 ± 7.3 (0.03)
PaRADISE vs. BASIL surgery	13.9 ± 5.0 (0.01)	12.0 ± 6.0 (0.05)	10.9 ± 7.0 (0.12)
PaRADISE vs. PTA + surgery	12.4 ± 4.5 (0.01)	11.5 ± 5.4 (0.03)	13.1 ± 6.3 (0.04)
Overall survival			
PaRADISE vs. BASIL PTA	5.0 ± 4.3 (0.25)	2.6 ± 5.8 (0.65)	8.7 ± 7.0 (0.22)
PaRADISE vs. BASIL surgery	9.0 ± 4.4 (0.04)	7.6 ± 5.8 (0.19)	5.7 ± 6.9 (0.41)
PaRADISE vs. PTA + surgery	6.9 ± 3.9 (0.07)	5.2 ± 5.2 (0.32)	7.1 ± 6.1 (0.24)

Positive values indicate higher survival in the PaRADISE study.
PTA = percutaneous transluminal angioplasty.

others (10–13). A meta-analysis by Biondi-Zoccai et al. (21) reviewed 18 BMS and DES studies and concluded that sirolimus-eluting stents appear to be superior to BMS or paclitaxel-eluting stents in terms of angiographic and clinical outcomes.

Technical and safety considerations. The PaRADISE study is the first BTK DES trial to test a strategy of primary and not provisional ("bail-out") stenting. Analogous to contemporary coronary intervention, we believed that primary stenting would translate into improved outcomes secondary to less arterial trauma, need for fewer stents, reduced contrast load, shorter procedures, and fewer reinterventions. As noted in the BASIL trial, contemporary PTA was associated with a 20% 1-month failure rate whereas early reintervention in PaRADISE was <2%.

Overlapping stents were placed in 35% of patients, with lengths ranging up to 96 mm. Despite treating more diffuse disease, stent delivery was easy, and the presence of overlapping stents did not predict subsequent stent failure or amputation. When diffuse disease (≥96 mm) was encountered, PTA was used to treat the midvessel lesion while reserving DES for inflow and intervening areas of prior total occlusion. Preliminary observations suggest that placement of a more proximal DES has a positive "wash-out" effect on the downstream PTA site.

Although Taxus stents failed more frequently than Cypher stents, the number of events were too small to draw firm conclusions. Siablis et al. (22) evaluated the efficacy of paclitaxel DES in 32 limbs with CLI and observed that, at 9 ± 4 months, the restenosis and occlusion rates were 77% and 24%, respectively. The reason for these less favorable outcomes is not clear, although these patients were treated with provisional stenting and dual platelet agents were discontinued after 6 months. Nevertheless, differences between the antiproliferative and thrombotic effects of sirolimus versus paclitaxel cannot be discounted (23).

Mechanical stent deformation is a potential concern. Consequently, we avoided stenting distal to the ankle, where the tibial arteries lose their compartmental protection. Cypher stents placed in the distal popliteal or ostial anterior tibial arteries were occasionally subject to strut misalignment and restenosis. We suspect that this may be secondary to out-of-plane biomechanical forces exerted by the interosseous membrane and more mobile stented popliteal artery. The issue of tibial stent crush was addressed by Karnabatidis et al. (24), who found a combined fracture/compression rate of 3.3% of 396 tibial stents evaluated. However, nearly all these events were associated with stents placed below the ankle.

Limitations of the PaRADISE study. The PaRADISE study was a nonrandomized study designed to test proof of principle that primary tibial stenting with DES was effective and safe. Although not ideal, the TASC II study and BASIL study data are reasonable "first pass" comparators to benchmark the outcomes of contemporary CLI therapies. Ultimately, industry must sponsor randomized "primary" DES versus PTA studies to substantiate and refine these findings.

The PaRADISE study was a single-center and single-operator trial, and thus the possibility of referral bias cannot be discounted. Had the PaRADISE trial included a greater number of Rutherford 6 patients, the outcomes might have been less dramatic. Nevertheless, the data support the safety and efficacy of BTK DES. From a technical standpoint, the greatest interventional limitation was not sustaining tibial patency but, rather, accessing the tibial vessels in the face of chronically occluded femoral-popliteal arteries. In the future, hybrid procedures, namely, femoral-popliteal bypass with adjunctive BTK DES, can be considered for these challenging patients.

Revascularization was not always as complete as desired secondary to limits placed on the number of stents per leg. More than one-half of patients returning for repeat revascularization required stenting in a different tibial vessel or at a site removed from the initial target. Whether multivessel revascularization will improve salvage compared to the surgical approach of establishing single-vessel flow needs to be evaluated. Additionally, the merits of dedicated long versus overlapping DES, crush-resistant DES for unprotected areas, and small-diameter stents need further investigation.

Future studies will need to address the health economics and quality of life issues associated with a DES-centered strategy. We anticipate that improved limb salvage should result in significant savings secondary to reductions in

bypass surgery, amputation, infections, graft surveillance, and shorter hospitalizations. Additionally, the benefits of preserving independent living and avoiding custodial care should not be underestimated.

Finally, the PaRADISE study was not designed to evaluate angiographic restenosis. Nevertheless, restenosis itself may not be a rate-limiting end point as long as tibial patency is maintained long enough to permit tissue healing and resolution of symptoms. Future studies will need to evaluate the biologic response to BTK stenting with DES.

Conclusions

Treating BTK CLI with DES appears to be a safe and effective means of preventing major amputations and relieving symptoms. Procedural complications and revascularizations were low. Patients treated with DES have significantly fewer major amputations and higher survival rates than historic controls. These data support a DES-first approach when treating infrapopliteal CLI. Based on the accumulating evidence, we propose industry-sponsored trials to reaffirm these findings and evaluate the health care economic impact of a DES-centered paradigm for treating CLI.

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