Update: Drug-Eluting Stents in Tibial Arteries

Two-year results from the Leipzig Cypher BTK registry.

BY DIERK SCHEINERT, MD

Patients with peripheral arterial disease (PAD) and chronic critical limb ischemia (CLI) experience excessive pain and delayed wound healing due to limited arterial blood flow to the affected limbs. Although arterial revascularization with restoration of straight-line, pulsatile arterial blood flow is the major therapeutic goal in these patients, in many cases, surgical techniques are not applicable because of the general medical condition and myriad comorbidities present in this patient cohort.[1,2] Furthermore, surgical bypass grafting is often not a viable option due to the lack of suitable distal outflow vessels or the absence of venous graft material. As a result, interventional endovascular techniques are increasingly used for below-the-knee (BTK) lesions in patients with CLI.

Although bare-metal stents (BMSs) are helpful in bailout situations to achieve a reasonable acute result, restenosis and reocclusion rates are very high.[3,4] At our institution, systematic angiographic follow-up of patients receiving a coronary BMS in the tibial artery reveal restenosis rates exceeding 50% at only 12 months.

SUMMARY OF SESs VERSUS BMSs DATA

Drug-eluting stents (DESs) have been shown to be very effective in the treatment of coronary artery disease, and preliminary evidence suggest the same may hold true for patients experiencing symptomatic infrapopliteal obstructions. Bosiers et al documented positive outcomes with sirolimus-eluting stents (SESs) in patients with severe CLI in a small, nonrandomized, single-center trial in late 2004 to early 2005.[5] Twenty-four stents were deployed to treat 23 short BTK lesions in 18 patents. The investigators documented 100% procedural success, 94.4% 6-month survival, and 94% 6-month limb salvage success. Additionally, this study was the first to utilize Quantitative Vascular Analysis to assess late-lumen loss as a primary endpoint, as opposed to binary restenosis rate, on the grounds of improved sensitivity. The investigators concluded that infrapopliteal DESs were an effective and safe treatment in patients with severe BTK CLI.

In our previous, nonrandomized, single-center, registry study, we demonstrated SESs to be safe and effective in the treatment of focal infrapopliteal lesions.[6] This study comprised two arms with 60 patients in total, in whom sirolimus (n=30) and bare-metal (n=30) coronary stents were compared. Six-month data showed cumulative major adverse events of 10% for the SESs compared to 46.6% for BMSs. Although the prevalence of bypass surgery was similar for both types of intervention (0% for each), major amputation

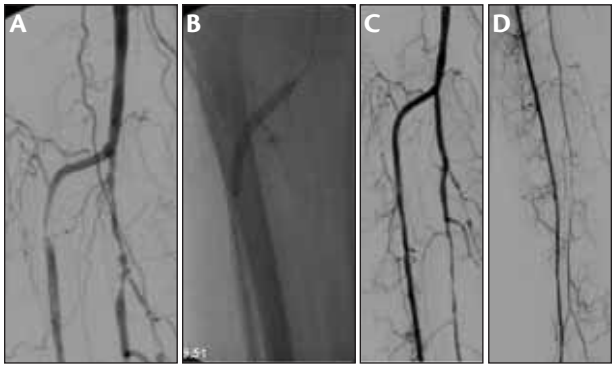

Figure 1. High-grade stenosis of the anterior tibial artery (A), treated by direct stenting with a 3.5-mm X 33-mm Cypher (Cordis Corporation, a Johnson & Johnson company, Miami, FL) stent (B), and the final result with restored single-vessel runoff to the foot (C, D).

(0% vs 10%) and target lesion revascularization (0% vs 23.3%) were significantly lower in the SES-treated population compared to the BMS-treated population. Moreover, occlusion (0% vs 17.4%), restenosis >50% (0% vs 39.1%, *P*=.0007), and mean degree of in-stent restenosis (1.8±4.8% vs 53±40.9%, *P*<.0001) were also significantly lower in the SES-treated population than the BMS-treated population.

Siablis and colleagues conducted a nonrandomized, prospective, single-center study comparing SESs (n=29) and BMSs (n=29) in bailout/suboptimal BTK revascularization.[7] The results at 6 months revealed SES outcomes with higher primary patency (92% vs 68.1%, *P*<.002) and decreased in-stent (4% vs 55.3%, *P*<.001) and in-segment (32% vs 66%, *P*<.001) restenosis.

Although recent 1-year results from Siablis et al showed no significant differences between SES- and BMS-treated groups with respect to mortality, minor amputation, or limb salvage, significant differences in patency and restenosis were observed. Specifically, higher primary patency (odds ratio [OR] 10.401, *P*<.001) and significantly less in-stent (OR .156, *P*<.001) and in-segment (OR .089, *P*=.001) binary restenosis was observed in the SES-treated patients compared to the BMS-treated patients.[8] The investigators concluded that SESs reduce the rate of restenosis in the infrapopliteal arteries and the rate of repeat procedures at the 1-year mark.

Long-Term Safety and Efficacy: The Leipzig Cypher BTK Registry

At our institution, a prospective, nonrandomized, single-center registry was assembled to investigate the long-term clinical outcomes of patients receiving BTK SES intervention for symptomatic focal infrapopliteal obstructions. Patients with symptomatic PAD (Rutherford class 3 to 6) and an angiographically proven infrapopliteal lesion with a maximum length of 30 mm and a reference vessel diameter of 3 mm to 3.5 mm were eligible.

TABLE 1. BASELINE CLINICAL DATA

Characteristics	Baseline Data
Number of participants (n)	74
Mean age, y	71.9
Male gender	52 (70.3%)
Cardiovascular risk factors	
- Diabetes mellitus	58 (78.4%)
- Arterial hypertension	67 (90.5%)
- Hyperlipoproteinemia	33 (44.6%)
- Smoker	23 (31.3%)
Cerebrovascular disease	18 (24.3%)
Coronary heart disease	48 (64.9%)
Rutherford class 3	23 (31.1%)
Rutherford class 4	18 (24.3%)
Rutherford class 5	33 (44.6%)

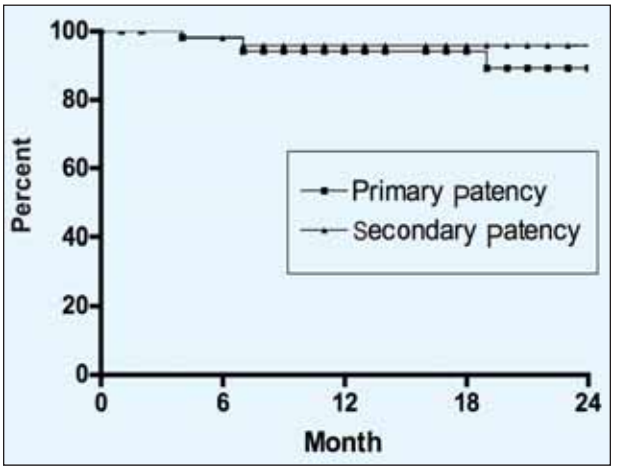

Figure 2. Primary and secondary patency rates at 24 months.

Only patients with single lesions treatable with a single stent were enrolled in the registry (n=74). All patients were treated with a single sirolimus-eluting balloon-expandable coronary Cypher stent that was 33 mm in length and had a nominal diameter of 3.5 mm (Figure 1).

Baseline clinical data for all patients enrolled in the registry are shown in Table 1. Stent implantation was successfully performed in all patients without periprocedural complications. In all cases, procedural success (<25% residual stenosis) was confirmed by angiography. There was no need for additional treatments after stent implantation (eg, additional stents). Patients were scheduled in 6-month intervals for follow-up visits to assess clinical status. In addition, angiographic follow-up was performed within 6 and 12 months and yearly thereafter to monitor the patency of the vessel defined by absence of binary angiographic restenosis of >50% diameter reduction. Safety of the intervention was also monitored through recording deaths, major amputations above the metatarsal level, target lesion revascularization, and need for bypass surgery.

Clinical Follow-Up

A clinical follow-up with assessment of the clinical status and recording of adverse clinical events was conducted for all patients with clinical visits every 6 months. During the clinical follow-up period, there were 15 deaths in total, but none could be attributed to the intervention. Additional adverse events associated with the treated leg included two (2.7%) major amputations above the metatarsal level, one

TABLE 2. MAJOR CLINICAL ADVERSE EVENTS

Event	Frequency
Death	15 (20.2%)
Major amputation	2 (2.7%)
Bypass surgery	1 (1.3%)
Target lesion revascularization	1 (1.3%)
Total number of adverse events	19 (25.7%)

TABLE 3. ANGIOGRAPHIC FOLLOW-UP DATA

Characteristic	Frequency
Surviving patients	59 (79.7%)
Follow-up available	47 (63.5%)
Follow-up time	11.7±7.4 months
Stent occlusion	2 (4.2%)
Restenosis >50%	1 (2.1%)

(1.3%) patient required bypass surgery, and one (1.3%) patient required target lesion revascularization with balloon angioplasty (Table 2). There was no need for additional stent placement. In total, major adverse events were observed in 19 (25.7%) patients.

Angiographic Follow-Up

In addition to the clinical follow-up, an angiographic follow-up was conducted for 47 of the 59 surviving patients with a mean follow-up time of 11.7±7.4 months. During this time, one patient (2.1%) reached the primary endpoint (binary angiographic restenosis rate >50%), and there were two cases (4.2%) of stent occlusion (Table 3). Accordingly, both primary and secondary patency rates, as calculated by Kaplan-Meier methods, remained high at 6 months (98.2%, 98.2%), 12 months (94.1%, 95.9%), and 24 months (89.2%, 95.9%) (Figure 2). Moreover, there were no cases with stent fractures, and no significant issues with stent thrombosis could be observed.

DISCUSSION

Despite the recent, tremendous improvements in interventional devices and techniques, patients with infrapopliteal obstructions remain a high-risk and difficult-to-treat cohort. In several studies, it could be demonstrated that SESs have a consistent and profound effect on the reduction of reobstructions after endovascular procedures. The 2-year data derived from our BTK SES registry add additional strength to the available evidence, demonstrating the long-term safety of the technique and showing that efficacy (in terms of patency and freedom from restenosis) can be maintained in the SES cohort. High vessel patency seems to be associated with superior clinical outcomes in endovascular interventions, and a low rate of 2-year amputation and revascularization was seen in the study cohort. Given the poor global prognosis of CLI patients, patency at 2 years can be considered a long-term endpoint within a cohort with reduced remaining life expectancy. Notably, incidence of mortality in our study was far higher than that of amputation, revascularization, >50% restenosis, or reocclusion.

From a technical standpoint, it was very important to note that despite dedicated screening for stent fractures, none were recorded, supporting the applicability of balloon-expandable stents for focal infrapopliteal disease. Moreover, subacute stent thrombosis, which has been a major concern in the coronaries, was seen in only one patient, who remained completely asymptomatic.

Most of the limitations regarding the evidence for SES use in BTK are related to the fact that, due to the limited length of the devices and economic factors in most of the studies, stent usage had to be limited to relatively focal infrapopliteal disease. Moreover, while there is growing familiarity and acceptance of DESs in endovascular procedures to treat BTK lesions, we believe that existing data—albeit positive and hopeful—must be considered against the fact that there exists no randomized clinical trial data comparing drug-eluting stents with the current BTK interventional standard of PTA. To this end, we intend to subject our current findings to further scientific scrutiny in a randomized, multicenter European trial examining PTA versus Cypher with 200 patients, which will soon start with financial support from Cordis. ■

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