

# The State of Stenting in Below-the-Knee Applications

Assessing stent options and additional technologies for below-the-knee interventions.

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Endovascular treatment of peripheral artery disease (PAD) in crural arteries is challenging due to their small caliber, calcification, long occlusions, and heavy burden of disease. Percutaneous transluminal angioplasty (PTA) is usually reserved for patients with critical limb ischemia (CLI) and has grown in popularity due to its minimally invasive nature and ease of repeatability compared to open surgical bypass. Although new technologies and techniques have facilitated high rates of immediate technical success, elastic recoil, dissection, and long-term patency remain a challenge. Stenting has been used to overcome these challenges to improve both short- and long-term success. This article summarizes the growing evidence in the field.

## BARE-METAL STENTS

The goal of stenting has been to treat an unsatisfactory result due to elastic recoil, residual stenosis, flow-limiting dissection, or perforation. A randomized controlled trial (RCT) compared several bare-metal stents (BMSs; balloon-expandable and self-expanding) to PTA in 38 limbs.<sup>1</sup> In this small and underpowered study, there was no statistical advantage to BMS in terms of survival (74.7% vs 69.3%), limb salvage (91.7% vs 90%), or primary (56% vs 66%) or secondary (64 vs 79.5%) patency rates after 12 months. In a 2009 systematic review, data were pooled from 18 nonrandomized studies comprising 640 patients who had below-the-knee (BTK) stent implantation at experienced centers; 232 had balloon-expandable BMSs, 116 self-expanding BMSs, 272 balloon-expandable drug-eluting stents (DESs), and 20 bioresorbable stents.<sup>2</sup>

Investigators found that bailout stenting after unsatisfactory PTA derived satisfactory angiographic results but no patency advantage. Balloon-expandable and self-expanding stent types were similar in both primary patency (73% vs 79%;  $P = .18$ ) and clinical outcomes (target lesion revascularization [TLR], 18% vs 6%,  $P = 1.0$ ; limb salvage, 98% vs 96%; both  $P = 1.0$ ) after a median follow-up of 12 months.

BMSs are effective in treating residual stenosis, elastic recoil, and dissection after PTA, but they do not result in improved long-term patency due to significant restenosis.

## DRUG-ELUTING STENTS

The use of coronary DESs in arteries BTK is known to reduce the neointimal proliferation response to vascular wall injury, which leads to a reduction in the luminal area (negative remodeling), recurrent stenosis, and loss of patency. In contrast to the low-level evidence that exists for the use of other endovascular technologies, the use of DESs is supported by results from four RCTs<sup>3-6</sup> and five meta-analyses.<sup>7-11</sup>

The YUKON-BTK trial randomized 161 patients with CLI (47%) and intermittent claudication (53%) to treatment with a polymer-free, 2% sirolimus-coated stent or the same stent uncoated.<sup>3</sup> The DES achieved a superior 12-month primary patency (80.6% vs 55.6% for the BMS;  $P = .004$ ). There was also a nonsignificant trend toward improvement in TLR (9.7% vs 17.5%;  $P = .29$ ). At longer follow-up (mean, 2.8 years), limb salvage was higher in CLI patients; however, this was not statistically significant (97.4% vs 87.1%;  $P = .10$ ); the primary end-

point of freedom from amputation, target vessel revascularization (TVR), acute myocardial infarction (AMI), and death favored DESs (65.8% vs 44.6%;  $P = .02$ ).

The DESTINY trial randomized 140 CLI patients to primary treatment with an everolimus-eluting stent or BMS comparator.<sup>4</sup> At 12-month follow-up, primary patency was higher in the DES group compared with the BMS group (85.2% vs 54.4%;  $P = .0001$ ) and late lumen loss and TLR were lower (0.78 vs 1.41 mm;  $P = .001$ ; and 8% vs 35%;  $P = .005$ , respectively). Once again, these results were found to be in favor of DESs.

The ACHILLES trial randomized 200 patients with CLI and occlusive tibial disease (< 120 mm; mean length, 27 mm) to treatment with a sirolimus-eluting stent or standard PTA.<sup>5</sup> The primary endpoint was 12-month, in-segment binary restenosis determined by quantitative angiography, which once again was found to be in favor of the DES (22.4% vs 41.9%;  $P = .019$ ). This result was even more pronounced when diabetic patients were analyzed separately (17.6% vs 53.2%;  $P < .001$ ); however, there was no significant difference seen in clinically driven TLR (CD-TLR; 10% vs 16.5%;  $P = .257$ ) or limb salvage (86.2% vs 80%;  $P = .3$ ), reflecting the multiple factors that impact those endpoints.

The IDEAS trial compared paclitaxel drug-coated balloons (DCBs) with DESs (zotarolimus-, sirolimus-, or everolimus-eluting stents) for longer lesions (> 70 mm), in patients with Rutherford class 3 to 6 disease.<sup>6</sup> Fifty patients (52 limbs) were randomized, and the 6-month angiographic restenosis rate was lower in the DES group (28% vs 57.9%;  $P = .046$ ). There were no differences in CD-TLR, major amputation, or survival rates.

More recently, the 5-year follow-up data from the PADI trial, which randomized 137 patients to PTA/BMS versus DES (paclitaxel-eluting stainless-steel stent), showed that amputation-free survival rates are significantly higher in the DES group compared to PTA/BMS (31.8% vs 20.4%;  $P = .041$ ).<sup>12,13</sup> Although this is only one study, these unique long-term results emphasize the potential in BTK drug-coated technology. The SAVAL trial is a large, multicenter RCT designed to evaluate a long nitinol, self-expanding paclitaxel-coated stent in the infrapopliteal circulation (NCT03551496). Recruitment has completed, and results are eagerly awaited.

Finally, a meta-analysis that included seven trials (801 patients; 329 DES, 409 control) was published.<sup>10</sup> At a median follow-up of 12 months, there was improved primary patency (odds ratio [OR], 3.49; 95% CI, 2.38-5.12;  $P \leq .00001$ ), freedom from TLR (OR, 2.19; 95% CI, 1.3-3.69;  $P = .003$ ), major amputation (OR, 0.56; 95% CI, 0.31-0.99;  $P = .049$ ), and improvement in Rutherford

class (OR, 1.62; 95% CI, 1.01-2.59;  $P = .046$ ), but no effect on mortality (OR, 1.05; 95% CI, 0.68-1.62;  $P = .91$ ) with the use of DES.

Overall, these studies demonstrate a consistent 12-month primary patency benefit with DESs for short lesions BTK, superior to standard therapy of PTA or BMS.

## DRUG-ELUTING RESORBABLE SCAFFOLDS

Coronary drug-eluting resorbable scaffolds (DRSs) were first applied to crural arteries by Kum et al in 2012. Before that, absorbable magnesium stents with no drug coating had been evaluated in trials, however, they demonstrated poor patency rates, inferior to PTA alone. Since then, three single-center observational studies and a pooled analysis have been published on polymer-based DRSs,<sup>14-17</sup> a device has been CE Mark-approved for use in arteries BTK (Motiv bioresorbable scaffold, Reva Medical), and a large, multicenter RCT has commenced enrollment (LIFE-BTK, NCT04227899).

The longest follow-up study of DRSs was recently published.<sup>16</sup> Forty-eight patients were enrolled, treating 55 limbs (72.7% CLI) with 71 scaffolds, and they were followed with duplex ultrasound for a mean of 35.2 months. Binary restenosis was detected in 11/71 (15.5%) scaffolds. At 12, 24, 36, 48, and 60 months, primary patency was 90.8%, 90.8%, 79.7%, 76.3%, 72.3%, respectively, and freedom from CD-TLR rates were 97.2%, 97.2%, 90.7%, 90.7%, and 90.7%, respectively. However, lesions were very short (mean length, 20.1 mm). The pooled analysis published from three institutions examined the use of 189 scaffolds in 121 patients (126 limbs).<sup>17</sup> Most (75%) had CLI, 63% were calcified and 22% were chronic total occlusions. Freedom from restenosis was 91.7% and 86.6% at 12 and 24 months, respectively, and freedom from CD-TLR was 97.2% and 96.6%, respectively. Major amputation occurred in 1.6% of the limbs. Overall survival was 85% at 24 months.

The LIFE-BTK study is a prospective, randomized, multicenter, controlled trial that commenced enrollment in January 2020. It will enroll 225 patients and randomize 2:1 to the Esprit DRS (Abbott) or PTA. The 6-month primary endpoints are major adverse limb event (MALE) and perioperative death (POD) for safety and primary patency and limb salvage for efficacy. A 5-year follow-up is planned after the completion of enrollment in late 2021.

## POST-PTA DISSECTION REPAIR

Postangioplasty dissection is common after PTA of the crural arteries. It may result in acute occlusion or restenosis, which can limit patency. The Tack Endovascular System (Philips) includes four preloaded

nitinol implants (each 6 mm in length) and comes in a 4-F system for BTK use. The focal repair of dissection has been an area of promise and offers a much-needed option in treating this condition after PTA.

The TOBA II BTK study was a prospective, multicenter, single-arm study designed to evaluate the device in 233 patients across 41 sites around the world. The study completed enrollment in July 2019 and published 12-month results in 2020.<sup>18</sup> All patients had post-PTA dissection and received at least one Tack implant (range, 1-16). There was successful resolution of 100% of the 341 treated dissections. At 12 months, 93.4% (170/182) of patients remained free of the composite endpoint of MALE plus POD. Tacked segment patency was 81.3% and limb salvage was 96.8% at 12 months; freedom from CD-TLR and amputation-free survival were 83.1% and 89.3%, respectively. Sustained Rutherford class improvement was reported in 82.4% of evaluated patients, with 62.4% improving  $\geq 3$  categories ( $P < .001$ ). Ninety (72.5%) of 124 index wounds healed or improved. The authors concluded the device was safe and effective to use for post-PTA BTK lesions.

## CONCLUSION

A first-line endovascular strategy is now preferred for most patients with CLI and occlusive disease of the crural arteries. This is particularly true in the elderly, diabetic patients, and those without suitable venous conduit. The accumulated body of evidence supporting the use of coronary DESs in the treatment of focal disease of infrapopliteal arteries is impressive and rivals that of any other lower limb revascularization strategy. DESs improve patency, reduce binary restenosis, and sustain improvement in Rutherford-Becker category, freedom from repeat interventions, and wound healing. However, recent results from DRS and Tack devices suggest these less bulky and permanent devices may also have a role. The challenge for the future will be to extend this evidence to apply the technology across the full spectrum of disease patterns, including long-segment occlusions, tibial bifurcations, and pedal circulation. ■

1. Randon C, Jacobs B, De Ryck F, Vermassen F. Angioplasty or primary stenting for infrapopliteal lesions: results of a prospective randomized trial. *Cardiovasc Intervent Radiol*. 2010;33:260-269. doi: 10.1007/s00270-009-9765-6
2. Biondi-Zoccai GG, Sangiorgi G, Lotrionte M, et al. Infragenicular stent implantation for below-the-knee atherosclerotic disease: clinical evidence from an international collaborative meta-analysis on 640 patients. *J Endovasc Ther*. 2009;16:251-260. doi: 10.1583/09-2691.1
3. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. *J Am Coll Cardiol*. 2012;60:587-591. doi: 10.1016/j.jacc.2012.04.035
4. Bosiers M, Scheinert D, Peeters P, et al. Randomized comparison of everolimus-eluting versus bare-metal stents in patients with critical limb ischemia and infrapopliteal arterial occlusive disease. *J Vasc Surg*. 2012;55:390-398. doi: 10.1016/j.jvs.2011.07.099
5. Scheinert D, Katsanos K, Zeller T, et al. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease:

- 1-year results from the ACHILLES trial. *J Am Coll Cardiol*. 2012;60:2290-2295. doi: 10.1016/j.jacc.2012.08.989
6. Siablis D, Kitrou PM, Spiliopoulos S, et al. Paclitaxel-coated balloon angioplasty versus drug-eluting stenting for the treatment of infrapopliteal long-segment arterial occlusive disease: the IDEAS randomized controlled trial. *JACC Cardiovasc Interv*. 2014;7:1048-1056. doi: 10.1016/j.jcin.2014.04.015
7. Fusaro M, Casse S, Ndrepepa G, et al. Drug-eluting stents for revascularization of infrapopliteal arteries: updated meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2013;6:1284-1293. doi: 10.1016/j.jcin.2013.08.007
8. Katsanos K, Spiliopoulos S, Diamantopoulos A, et al. Systematic review of infrapopliteal drug-eluting stents: a meta-analysis of randomized controlled trials. *Cardiovasc Intervent Radiol*. 2013;36:645-658. doi: 10.1007/s00270-013-0578-2
9. Antoniou GA, Chalmers N, Kanesalingham K, et al. Meta-analysis of outcomes of endovascular treatment of infrapopliteal occlusive disease with drug-eluting stents. *J Endovasc Ther*. 2013;20:131-144. doi: 10.1583/1545-1550-20.2.131
10. Varcoe RL, Paravastu SC, Thomas SD, Bennett MH. The use of drug-eluting stents in infrapopliteal arteries: an updated systematic review and meta-analysis of randomized trials. *Int Angiol*. 2019;38:121-135. doi: 10.23736/S0392-9590.19.04049-5
11. Yang X, Lu X, Ye K, et al. Systematic review and meta-analysis of balloon angioplasty versus primary stenting in the infrapopliteal disease. *Vasc Endovascular Surg*. 2014;48:18-26. doi: 10.1177/1538574413510626
12. Spreen MI, Martens JM, Hansen BE, et al. Percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia (PADI) trial. *Circ Cardiovasc Interv*. 2016;9:e002376. doi: 10.1161/CIRCINTERVENTIONS.114.002376
13. Spreen MI, Martens JM, Knippenberg B, et al. Long-term follow-up of the PADI trial: percutaneous transluminal angioplasty versus drug-eluting stents for infrapopliteal lesions in critical limb ischemia. *J Am Heart Assoc*. 2017;6:e004877. doi: 10.1161/JAHA.116.004877
14. Dia A, Venturini JM, Kalathiya R, et al. Single arm retrospective study of bioresorbable vascular scaffolds to treat patients with severe infrapopliteal arterial disease. *Catheter Cardiovasc Interv*. 2019;94:1028-1033. doi: 10.1002/ccd.28546
15. Kum S, Ipema J, Chun-Yin DH, et al. Early and midterm experience with the Absorb everolimus-eluting bioresorbable vascular scaffold in Asian patients with chronic limb-threatening ischemia: one-year clinical and imaging outcomes from the DISAPPEAR Registry. *J Endovasc Ther*. 2020;27:616-622. doi: 10.1177/1526602820922524
16. Varcoe RL, Menting TP, Thomas SD, Lennox AF. Long-term results of a prospective, single-arm evaluation of everolimus-eluting bioresorbable vascular scaffolds in infrapopliteal arteries. *Catheter Cardiovasc Interv*. 2021;97:142-149. doi: 10.1002/ccd.29327
17. Huizing E, Kum S, Ipema J, et al. Mid-term outcomes of an everolimus-eluting bioresorbable vascular scaffold in patients with below-the-knee arterial disease: a pooled analysis of individual patient data. *Vasc Med*. 2021;26:195-199. doi: 10.1177/1358863X20977907
18. Geraghty PJ, Adams GL, Schmidt A, et al. Twelve-month results of Tack-optimized balloon angioplasty using the Tack endovascular system in below-the-knee arteries (TOBA II BTK). *J Endovasc Ther*. 2020;27:626-636. doi: 10.1177/1526602820944402

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