

Below-the-Knee Drug-Eluting Stents

Is there a role for this readily available device in treating critical limb ischemia?

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"Those who do not remember the past are condemned to repeat it."

—George Santayana

The anatomic common denominator that unites patients with critical limb ischemia (CLI) is the presence of severe below-the-knee (BTK) arteriopathy. To relieve symptoms and heal wounds, it is axiomatic that successful limb salvage must restore straight-line pulsatile flow to the foot. Thus, any technique that furthers this goal merits serious consideration. When evaluating the worth of therapeutic options, we have come to rely on the concept of evidence-based medicine. Therefore, it is puzzling that many in the endovascular community ignore the one CLI technology that has an abundance of evidence supporting its effica-

cy and safety: drug-eluting stents (DES). With this in mind, the purpose of this article is to review the rationale and data supporting the use of DES as a primary treatment for patients with CLI.

What evidence supports the use of DES for treating CLI?

Navigating through the forest of competitive BTK technologies is difficult because of the absence of comparative clinical data. However, the use of DES for treating CLI stands out as the one exception to this information void. There is now substantial level A and B evidence that supports the use of DES as a primary treatment of patients with BTK CLI. DES have undeniably revolutionized coronary artery intervention. More than a decade of intense clinical and benchtop scrutiny has elucidated the

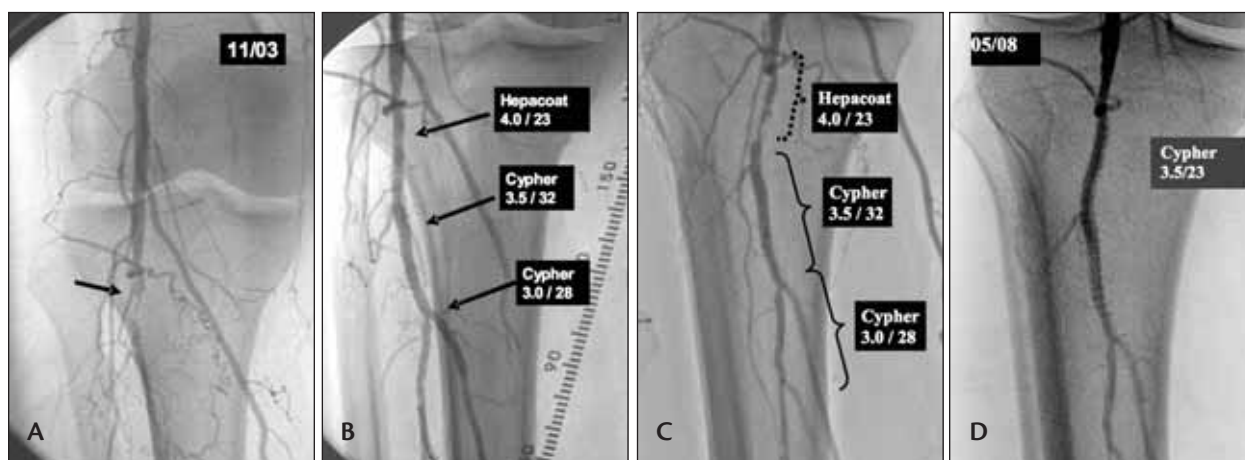


Figure 1. An 87-year-old man with Rutherford class 5 CLI. Arrow indicates popliteal artery occlusion (A). Angiogram after placement of two overlapping Cypher DES distally and one 4-mm BMS proximally (B). Patient returned 17 months later with rest pain. Dotted bracket outlines larger-diameter BMS in-stent stenosis, and solid bracket outlines patent DES (C). Incidental angiogram 18 months after treating in-stent restenosis with a 3.5-X 23-mm Cypher DES (D). The patient remained asymptomatic until his death this year at the age of 93. A year before he died, angiography revealed patent DES 6 years after implantation.

TABLE 1. REGISTRY STUDIES EVALUATING THE USE OF DES FOR BTK CLI

| Author | Year | DES | Limbs | Design | No. of Stents | Primary Stent Versus Bailout Stent | Primary Patency or Comments |
|---------------------------|------|-----------------------|------------|-------------------|---------------|------------------------------------|-----------------------------|
| Balzer ¹ | 2010 | Sirolimus | 128 | Registry | 341 | Primary | 83% at 18 mo |
| Bosiers ² | 2006 | Sirolimus | 18 | Registry | 24 | Primary | 100% at 6 mo |
| Commeau ³ | 2006 | Sirolimus | 30 | Registry | 106 | Bailout | 97% at 7 mo |
| Feiring ⁴ | 2010 | Sirolimus/ primary | 118 | Registry | 228 | Primary | 12% TLR at 36 mo |
| Feiring ⁵ | 2007 | Sirolimus | 5 | Registry | 11 | Primary | 100% at 18 mo |
| Grant ⁶ | 2008 | Sirolimus/ primary | 10 | Registry | 17 | Primary | 10% TVR at 12 mo |
| Karnabatidis ⁷ | 2011 | Everolimus | 81 | Everolimus vs BMS | 332 | Bailout | 81% vs 68% TLR at 36 mo |
| Fischman ⁸ | 2010 | Sirolimus | 56 | Registry | 101 | Bailout | 82% at 16 mo |
| Rastan ⁹ | 2010 | Sirolimus | 104 | Registry | 256 | Primary | 84% at 12 mo |
| Rosales ¹⁰ | 2008 | Sirolimus | 24 | Registry | 41 | Primary | 95% at 12 mo |
| Scheinert ¹¹ | 2006 | Sirolimus | 30 | Sirolimus vs BMS | 30 | Primary | 100% vs 82% at 6 mo |
| Siablis ¹² | 2007 | Sirolimus | 29 | Sirolimus vs BMS | 66 | Bailout | 92% vs 68% at 6 mo |
| Siablis ¹³ | 2007 | Primary | 29 | Registry | 62 | Bailout | 30% at 1 y |
| Siablis ¹⁴ | 2009 | Sirolimus | 103 | Sirolimus vs BMS | 239 | Bailout | 63% vs 35% at 2.5 y |
| Total | | | 765 | | 1,854 | | |

Abbreviations: TVR, target vessel revascularization.

biology, safety, and efficacy of this device. Based on the body of this evidence, the obvious question is whether treating BTK CLI with DES would be equally as effective as it has been for coronary intervention.

Because a comprehensive review of data on DES for treating BTK CLI is beyond the scope of this article, I will only attempt to highlight some of the more salient findings gleaned from 14 single-center studies (Table 1) and three randomized trials (Table 2). Despite significant differences in study design, the conclusions drawn from these studies are remarkably uniform. These findings can be summarized as: (1) DES are safe and easy to use BTK; (2) DES stabilize early BTK interventions with minimal procedural failures; (3) DES significantly reduce target

lesion revascularization (TLR) and binary restenosis compared with either balloon angioplasty or bare-metal stents (BMS); and (4) DES interventions are durable, appear to reduce major amputations compared with historical controls, and may reduce overall mortality.

This year, three European industry-supported CLI DES trials were presented. The ACHILLES trial¹⁵ randomized CLI patients to either the Cypher DES (Cordis Corporation, Bridgewater, NJ) or percutaneous transluminal angioplasty (PTA). The binary restenosis rates after 1 year were 19% with the Cypher DES and 49% with angioplasty. The DESTINY trial¹⁶ randomized patients to the Xience DES (Abbott Vascular, Santa Clara, CA) versus the MultiLink Vision BMS (Abbott Vascular). Primary

TABLE 2. RANDOMIZED CONTROLLED TRIALS OF BTK DES

| Trials | Stent/Drug | Finish | No. of Patients | Lesion Length | Endpoints |
|-------------------------|---|--------|-----------------|---------------|---|
| ACHILLES ¹⁵ | Cypher vs PTA (sirolimus) | 2010 | 200 | ≤ 120 mm | Binary restenosis 19% vs 49% at 1 y |
| DESTINY ¹⁶ | Xience (everolimus) vs MultiLink Vision | 2010 | 140 | ≤ 40 mm | Primary patency 85% vs 54% at 1 y; TLR 34% vs 9% at 1 y |
| YUKON-BTK ¹⁷ | Yukon DES (sirolimus) vs Yukon BMS | 2010 | 177 | ≤ 45 mm | Primary patency 81% vs 56% at 1 y |
| Total | | | 517 | | |

patency rates at 1 year were 85% versus 54%, and TLR was 9% versus 34% with DES versus BMS, respectively. The YUKON-BTK trial compared a proprietary non-polymer sirolimus stent to the same uncoated BMS.¹⁷ The 1-year primary patency rate for DES was 81% versus 56% for the BMS. Thus, after 1 year, all three randomized trials strongly endorsed the superiority of DES over balloon PTA or BMS.

The first single-center, randomized trial of DES was reported by Scheinert et al,¹¹ who treated patients who had focal tibial lesions with either the Cypher DES or a BMS. At 6 months, angiographic follow-up showed a binary restenosis rate of 39% in the BMS group; there was no restenosis in the DES group. Employing a similar study design, Siablis et al¹² observed nearly identical findings with a primary patency rate of 92% with Cypher and 68% with BMS and a binary restenosis rate of 55% with BMS versus 4% for Cypher. Table 1 lists additional single-center studies.

Long-term data regarding the outcomes in CLI patients who were treated with BTK DES have been reported (Table 2). After 3 years of observation, the PARADISE trial⁴ reported that major amputations in Rutherford class 4 to 6 patients were only 8%. Subset analysis of Rutherford class 6 patients revealed an amputation rate of 14%. These findings are in contradistinction to the expected 40% to 50% 3-year major amputation rate with conventional therapy. Moreover, 6 months after intervention, there were no further amputations. The TLR rate was 15%, and the binary restenosis rate was 12%. These data suggest that BTK DES provide a lasting and durable arterial repair. Karnabatidis et al⁷ and Siablis et al¹⁴ also reported 3-year data. In these studies, the authors noted statistically superior and sustained primary patency with everolimus- or sirolimus-based DES compared to BMS.

In conclusion, BTK DES registry data report 1,854 DES implanted in 765 limbs with CLI. There are an additional 517 patients who have been randomized to balloon

angioplasty or BMS versus DES. With the exception of a single paclitaxel DES study,¹³ all of the reported studies are concurrent in their findings, reporting that DES for CLI is a safe and effective treatment that is superior to either balloon angioplasty or BMS.

Why isn't balloon angioplasty sufficient for BTK CLI?

When treating CLI, the primary goal of angioplasty is to restore maximal and stable conduit flow. There is agreement that stand-alone balloon angioplasty is frequently suboptimal in virtually every arterial bed studied. This is especially true in the case of BTK angioplasty, in which the lesions tend to be complex. Risk factors predicting poor PTA outcomes include small vessel diameter, lesion length, patient gender, chronic kidney disease, diabetes, or poor runoff. The limitations of balloon angioplasty in CLI are well documented.

Giles et al¹⁸ observed that 1 year after PTA, the freedom from amputation, restenosis, or reintervention was only 18% for Rutherford class 6 patients and somewhat better at 50% for Rutherford class 4 and 5 patients. A meta-analysis by Romiti et al¹⁹ observed that at 1 year, < 60% of PTA sites were patent, with a 10% immediate rate of failure. The PTA arm in the BASIL trial²⁰ was associated with a procedural PTA failure rate of 20% and a 1-year reintervention rate of 59%. With the results of PTA being so poor, one wonders why it is considered the gold standard for BTK intervention. In fact, the entire atherectomy industry has evolved primarily because of the unpredictable early results and poor long-term results of PTA.

What is the rationale for using coronary stents to treat CLI?

The advent of stents resulted in a quantum improvement in the procedural safety and technical success of vascular intervention. Before coronary stents (and similar to today's endovascular environment), there were a

plethora of competing interventional techniques (eg, atherectomy [mechanical, rotational, and laser], long balloons, curved balloons, perfusion balloons, drug-eluting balloons, and cutting balloons). However, with the development of flexible and, later, drug-eluting coronary stents, these competitive modalities rapidly fell out of favor because of inferior results and higher complication rates. Today, nearly all arteries benefit from stenting compared with balloon angioplasty, and one has to think long and hard for a reason not to place DES when engaging in coronary intervention.

The same conceptual paradigm suggests that stents placed in the tibial arteries should behave in a fashion similar to coronary stents because both vessels are medium-sized muscular arteries, share a similar histology and luminal dimension (approximately 2–4 mm in diameter), and both respond to endothelial-dependent vasodilators such as nitroglycerin. Furthermore, they react to the mechanical stress of balloon angioplasty in a similar fashion.

Feiring et al²¹ evaluated this hypothesis and investigated the safety and efficacy of using coronary BMS as a primary mode of treating patients with severe tibial claudication and CLI. This study showed that BMS were highly effective in stabilizing the initial intervention. Analogous to the effect that coronary stents have on maximizing conduit flow, BMS normalizes ankle-brachial indexes on par with what is seen after successful tibial bypass without surgery's attendant morbidity and mortality.²¹ Recently, others have confirmed the ability of BTK coronary stents to normalize ankle-brachial indices.^{9,12} To date, only BTK stents have shown the ability to stabilize the artery and maximize postinterventional blood flow.

Are BMS as effective as DES for treating CLI?

Level A data show that BTK interventions with DES are superior to BMS. Whereas technical success rates are equally as high for both devices, the binary restenosis and TLR were substantially higher for BMS. A recent meta-analysis²² of BTK stenting showed a 37% binary restenosis rate with BMS compared to 17% for DES. Recent randomized data indicate at least a 30% higher binary restenosis for BMS than for DES.^{16,17}

Why not use DES only for failed angioplasty?

There are no dedicated studies evaluating the strategy of primary versus provisional BTK DES. Nevertheless, this controversy has been resolved twice in favor of primary stenting as it applies to coronary intervention. It is now understood that even cosmetically appealing postintervention angiograms frequently disguise suboptimal flow. For this reason, primary stenting is favored over provi-

sional stenting because of the greater acute gain, more predictable early outcomes, lower TLR rates, faster procedure time, and less contrast expenditure. Consequently, the same analogy should be operative for BTK DES therapy. If it were not for the matter of cost, it is unlikely that the issue of provisional stenting would be of much importance.

Because many BTK lesions are long, what is the utility of current DES?

In our experience, about half of BTK lesions are focal (< 33 mm, a single stent length), and the rest are more diffuse. However, what frequently appears to be a long tibial occlusion is actually a focal lesion that masks a hibernating vessel that is structurally intact but under-visualized secondary to inadequate collateral filling. In the PARADISE trial, 35% of the stents deployed were overlapping, with a mean length of 61 ± 15 mm. In this group of patients, multivariate analysis failed to show any adverse effect of overlapping stents.⁶ An example of this is demonstrated in Figure 1.

The ACHILLES trial¹⁵ design allowed up to 120 mm of stenting, whereas DESTINY¹⁶ allowed for only 40 mm using two stents. These studies have not yet reported the subset analyses, although the overall results have continued to show the superiority of DES. Whether there is a point of diminishing returns related to stent length is not clear at this time and will require further analysis. In our practice, we shy away from the “full metal jacket” approach and rather selectively stent the culprit lesion(s) and sites of total occlusion. Nevertheless, the prospect of longer DES is conceptually appealing, and appropriate strategies for treating longer lesions need investigation.

Aren't DES and BMS subject to fracture and subsequent restenosis?

First-generation stainless steel stents may be more subject to misalignment and mechanical deformation compared to second-generation cobalt chromium stents. There is no evidence that minor disruptions in stent architecture are a risk factor for restenosis. Similar to coronary intervention, we have found that the greatest risk factors for restenosis are geographic misses and incomplete stent expansion. Fortunately, the areas most amenable to BTK stenting (with the exception of the anterior tibial genu and distal popliteal artery) occur in areas that are subject to little dynamic stress. Furthermore, these stents are not subjected to external crush because they remain protected by the three tibial muscular compartments.

In our practice, we do not stent below the ankle because this territory is unprotected and is subject to

torque and extravascular compressive forces that will crush the stent. Karnabatidis et al²³ found a 3% incidence of BMS deformation out of 369 BTK stents. However, the majority (11 out of 12) of these events occurred with stents that were placed below the ankle. To date, it appears that stent malformation is a relatively minor issue with BTK stenting, although this is not to say that self-expanding stents (SES) for the ankle and pedal vessels would not have utility.

Won't long balloons or drug-coated balloons work just as well as DES?

Although long balloons appear to be an important part of the BTK armamentarium, this hypothesis has not been tested. To date, there is no evidence that long balloons prevent elastic recoil, improve conduit flow, or prevent restenosis compared with shorter balloons or other interventional modalities. Moreover, even if drug-coated balloons are effective in reducing restenosis, these balloons have no special effect on maximizing acute gain or maintaining early conduit patency. Some have advocated first using a drug-coated balloon and then stabilizing the intervention with a BMS. But is this approach any better than a primary DES?

Does BTK stenting preclude future tibial bypass surgery?

BTK stents will not interfere with bypass surgery because these stents are only deployed in areas of stenosis or occlusion that are not anastomotic sites chosen for bypass. In contradistinction, injudicious stenting of the superficial femoral artery (SFA) and popliteal arteries with SES may indeed alter the preferred surgical site.

Studies have shown that DES for SFA disease is minimally effective.

BTK DES should not be confused with SFA drug-eluting SES. Whereas the dosimetry for 2- to 4-mm vessels have been optimized and proven to reduce restenosis, the femoropopliteal arteries are much larger, have a greater plaque-to-lumen burden, and are subject to more mechanical stress than tibial vessels.

Isn't the cost of DES prohibitive compared to other devices?

To our knowledge, there are no cost-benefit analyses of any of the BTK technologies. However, preliminary evaluation suggests a favorable economic balance for the use of DES in CLI. First, the cost of a DES is half of what it was 7 years ago. At current rates, the cost of two DES is equivalent to a single atherectomy catheter. The average number of DES used in most studies is nominally two per

limb. Second, studies suggest that a DES-centered strategy results in the lowest (sustained) amputation rate to date,⁴ as well as a nearly 30% to 50% reduction in binary restenosis compared to BMS or PTA. Additional cost savings may accrue secondary to a reduction in failed angioplasty (eg, the need for repeat intervention, preventing amputation or bypass surgery, and faster wound healing). Note that the cost of a single amputation is upward of \$70,000 for the first year, not including adjunctive wound care, rehabilitation, prosthesis fitting, custodial care, modification of living quarters, and quality-of-life issues.²⁴

In experienced hands, limb salvage rates are high regardless of the device used. Why do we need DES?

Unfortunately, not all physicians can attain the level of skill of those who have been published. However, the unstated goal of medical innovation is to make marginal operators good and good operators great. The burden of CLI is immense, and there are not enough physicians to treat this devastating disease. BTK DES simplify the procedure and provide stable and lasting results.

What are the limitations of DES for BTK intervention?

Although DES for BTK CLI has been granted CE Mark approval in Europe, in the United States, there is neither US Food and Drug Administration approval nor specific Centers for Medicare & Medicaid Services reimbursement. Consequently, treating patients with this approved coronary device in an unapproved anatomic location is off-label. Physicians are wary of using off-label equipment for fear of excessive scrutiny, and catheterization laboratory managers are hesitant to allow widespread use of off-label stents when there is no reimbursement. Until there is hospital reimbursement for the product, the use of BTK DES will be limited. Consequently, it is imperative that industry obtain an investigational device exemption, step up to the plate, and launch a multicenter, randomized trial evaluating BTK DES versus balloon angioplasty immediately.

CONCLUSION

There is currently a large body of literature that consistently supports the efficacy and safety of using DES to treat BTK CLI. This product is readily available, requires no specific capital outlay, and simplifies the treatment of CLI, requiring little additional training. The next step is to encourage industry to establish a definitive, large multicenter trial with the specific goal of obtaining US Food and Drug Administration clearance and Centers for Medicare & Medicaid Services reimbursement for this game-changing device. ■

(Continued on page 72)

(Continued from page 69)

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