Are Drug-Eluting Stents Now the Default Strategy for Superficial Femoral Artery Intervention?

Drug-Eluting Stents Are the Default Strategy for Superficial Femoral Artery Intervention Now

Mark W. Burket, MD

Drug-eluting stents (DES) are the default strategy for superficial femoral artery (SFA) intervention in 2015 because they have been evaluated in a large number of patients over a long follow-up period with outcomes superior to other treatment options. No other therapy can make that claim. The SFA and the contiguous popliteal artery constitute the femoropopliteal (FP) segment, which is among the human body’s most hostile vascular environments. It is extremely long, exposed to external compression, and undergoes marked conformational changes every time the leg is flexed. Because it courses posterior to the knee joint, there is obligatory longitudinal compressive force with knee flexion (Figure 1). Magnetic resonance angiography studies demonstrated 13% shortening of the SFA between supine and fetal positions. There are 60° of SFA torsion produced by simultaneous knee and hip flexion. Given these anatomic and dynamic challenges, it is hardly surprising that treatment strategies for established FP atherosclerosis suffer from marked limitations.

Multiple Imperfect Solutions

When a disease process lacks 1 definitive cure, a wide variety of marginally effective solutions frequently surface. Such is the case with FP occlusive disease. The spectrum of treatment options is broad, ranging from exercise therapy as the least intrusive option, to bypass surgery as the most intrusive. In between these extremes lies a seemingly endless variety of endovascular options.

Less Is Less

Perhaps the most universally available and cheapest treatment strategy for symptomatic lower extremity vascular disease is exercise therapy. Supervised exercise programs are more effective than unsupervised and have received a class I recommendation from the American College of Cardiology and the American Heart Association. The requirement for supervision is problematic in that it mandates a commitment of time and effort that may be unachievable for many patients, especially if exercise facilities are not in their immediate vicinity. Furthermore, at least in the United States, it places a direct financial burden on the patient because third-party payers do not reimburse for exercise treatment of peripheral vascular disease (PVD). In addition to these limitations, it is important to assess the effects of supervised exercise in quantitative terms. A review of 25 randomized controlled trials (RCT) comparing supervised exercise with no intervention demonstrated that the maximum walking distance (MWD) increased by 180 meters, and pain-free walking distance increased by 128 m in the treatment groups. Although these measures achieved statistical significance, they may prove inadequate for a patient whose ambulatory goals include thousands of meters per day for occupational or recreational pursuits.

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Pharmacotherapy has limited efficacy for symptomatic SFA disease. The effect of cilostazol, as was the case for exercise therapy, is statistically significant, but quantitatively limited. An assessment of 9 RCTs demonstrated that the drug was associated with a 42.1-m improvement in MWD over placebo. In addition, some patients are unable to take this medication because of its contraindication in those with a history of congestive heart failure. Headache (occurring in 28%), diarrhea (19%), and abnormal stools (15%) are significantly more frequent with cilostazol than with placebo and may lead to its discontinuation. It requires twice daily dosing on an empty stomach.

Pentoxifylline is also approved for use in patients with symptomatic PVD, but is no different than placebo in terms of change in MWD. In the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) document, pentoxifylline is classified as having insufficient evidence to support its use in claudication.

Lipid-lowering therapy has shown little, if any, improvement in claudication associated with lower extremity atherosclerosis. A 354-patient trial comparing atorvastatin with placebo showed no significant improvement in maximal treadmill walking time at 12 months. Smaller studies comparing simvastatin with placebo showed improved walking performance, whereas a 385-patient study revealed no improvement with the combination of niacin and lovastatin.

In conclusion, measures to treat PVD conservatively, without physical alterations to anatomy, produce modest functional improvement at best. Given the variability in individual response to treatment, and some patients’ limited ambulatory objectives, as well, this approach may suffice for certain patients, but many others will experience lifestyle-limiting symptoms and a significantly decreased quality of life. Thus, it is safe to say that conservative therapy cannot be relied on as the default approach to SFA disease.

Figure 1. A, The femoropopliteal arterial segment (represented by the solid black line) is not coaxial with the femur and tibia. B, With knee flexion this relationship creates an excess of arterial length, partially compensated by vessel tortuosity (C). Reproduced from Wensing et al with permission from the publisher. Copyright © 1995, John Wiley & Sons Ltd.

More Is Less
At the opposite end of the spectrum from exercise and pharmacotherapy lies surgical revascularization. This option is rarely exercised in patients with isolated FP disease because of concern about morbidity, mortality, and late graft failure. A recent assessment of 2404 infragenual operations, the majority of which involved FP bypass, revealed a 30-day death rate of 2.7% and major complications in 18.7%. Wound infection occurred in 9.4% and graft thrombosis in 7.4%. In a series of 1404 patients undergoing lower extremity bypass, 24% experienced unplanned hospital readmission within 30 days, with wound infection serving as the single most common inciting reason. Neuropathic pain persists in surgical incision sites in 24% of patients after 1 year. In critical limb ischemia, FP bypass with the use of a venous conduit has a 5-year patency of 66%, dropping to 33% when polytetrafluoroethylene (PTFE) graft material is used and the distal anastomosis is below the knee.

Few studies have compared surgical bypass with endovascular therapy. In a RCT of 452 patients with critical limb ischemia (rest pain, ulceration, or gangrene) comparing bypass surgery with percutaneous transluminal angioplasty (PTA), amputation-free survival and quality of life were similar between the 2 treatments, but surgery was associated with higher cost.

In summary, bypass surgery is associated with substantial mortality, perioperative complications, unplanned hospital readmissions, and overall cost. From the standpoints of patient safety and healthcare economics, more is indeed less. Surgery is not the default treatment for SFA disease.

The Sweet Spot: Endovascular Therapy
Dotter was both innovative and controversial when he created an entirely new option for treating PVD. In his 1964 procedure, he treated a critical popliteal artery stenosis by expanding the vessel lumen with a tapered PTFE dilating catheter. For the next half-century, countless modifications of that procedure were pursued, all with the singular goal of enhancing blood supply without the need for surgery. Proposed treatments have varied widely in mechanism, complexity, cost, and the quantity and quality of supporting clinical data.

The first major improvement in endovascular equipment came with Gruentzig’s balloon catheter. In 1974 a man with claudication became the first person to undergo PTA. Remarkably, after >40 years, PTA remains the standard of reference for all percutaneous technologies.

The appeal of endovascular therapy was obvious. Conscious sedation and local anesthesia completely side-stepped the complexity, risk, and expense of general anesthesia. With no incision, the associated bleeding, pain, and risk of infection were eliminated. Thus, there is little surprise that in the decade starting in 1990, open surgery for lower extremity PVD declined, whereas endovascular procedures increased 10-fold.
Beyond Angioplasty

Although the advantages of PTA over surgery in terms of economics and patient safety are substantial, the technique has limitations. Flow-limiting dissection or vessel recoil may lead to procedural failure. Initially, successful procedures are at risk for late restenosis or occlusion.

The likelihood of developing restenosis or reocclusion depends on several variables. Robust literature supports worse long-term patency in patients with diabetes mellitus, poor tibial runoff, or a procedural indication of critical limb ischemia (as opposed to claudication). Longer lesions have lower patency. Posttreatment residual stenosis ≥30% portends a worse outcome.

Given the variability in lesion complexity, patient comorbidities, patency definitions, etc, PTA restenosis rate estimates vary widely. A generally accepted performance goal is that suggested by the VIVA Physicians Group, which includes a 1-year primary patency (PP) of 33%. Acute and long-term limitations of PTA preclude its acceptance as a default treatment strategy for FP occlusive disease. These weaknesses have served as stimuli for the development of a broad selection of supplemental or alternative endovascular treatments. Mechanical plaque removal (atherectomy), laser, cutting or scoring balloons, drug-eluting balloons (DEBs), bare metal stents (BMS), PTFE-covered stents, and DES are among the most common options proffered.

Atherectomy

In the formative years of percutaneous intervention, Dotter compared his dilating technique with “footprints in the snow,” resulting in curative compression of atherosclerotic plaque. The often dense, fibrotic, and calcific nature of FP “snow,” resulting in curative compression of atherosclerotic plaque. Posttreatment residual stenosis ≥30% portends a worse outcome.

Despite its appeal, atherectomy suffers from numerous limitations that preclude it from becoming the default strategy for FP atherosclerosis. Shortcomings include device complexity, a lack of randomized trial data, risk of distal embolization, risk of perforation, and excessive cost in comparison with other percutaneous options. Most clinical results are derived from registries. A 58-patient RCT of directional atherectomy to PTA in lower extremity PVD showed no difference in initial procedural success or target lesion revascularization (TLR); however, there was significantly more distal embolization with atherectomy. Concern about distal embolization of atheromatous debris has prompted the use of embolic protection devices and their Food and Drug Administration clearance for use in this setting. Adding the expense of a protection device to the already substantial price of an atherectomy catheter puts equipment cost in the range of $5000, in excess of virtually every other percutaneous strategy. Despite this excessive cost, data supporting superior outcomes are lacking. For example, Marmagkiolis compared 12-month PP in 6024 patients with FP disease treated with 7 different types of endovascular devices. Only cryoplasty and laser had worse outcomes than directional atherectomy. Given the current intense interest in the cost-effectiveness of medical treatment, it is hard to support the use of a strategy that carries some of the highest cost with no data showing superior outcomes.

To sum up, complexity, cost, complications, and deficient trial data keep atherectomy from achieving default status for FP intervention.

Bare Metal Stents: Proven Benefit

Although PTA is clearly in the sweet spot between conservative therapy’s limited efficacy and surgery’s morbidity and mortality, it suffers from serious limitations. It offers no reliable answer to vessel recoil or flow-limiting dissection. Its well-recognized Achilles heel is a high rate of restenosis and concomitant need for TLR. To address these limitations, metallic stents were advocated as early as the 1980s (Figure 2).

Prospective series demonstrated a clear signal of benefit, but more convincing evidence has come from RCT comparing nitinol stents to PTA. Schillinger randomly assigned 104 patients with FP stenosis or occlusion (mean length 13 cm) to BMS or PTA. Stenting was performed in 32% of the PTA group because of a suboptimal result. At 12 months, the stent group had less restenosis (37% versus 63%, P=0.01). MWD and ankle-brachial index were significantly better with stenting at 12 months. Restenosis rates remained lower with stents at 2-year follow-up both by intention-to-treat analysis (45.7% versus 69.2%, P=0.031) and by treatment-received analysis (49.2% versus 74.3%, P=0.028) (Figure 3). Dick reported less restenosis and higher MWD with stents at 1 year in a smaller RCT of similar design.

The multicenter Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery (RESILIENT) trial randomly assigned 206 patients with claudication to either BMS or PTA. Freedom from TLR was significantly higher at 3 years with stenting (75.5% versus 41.8%, P<0.0001). Clinical success, defined as an improvement of at least 1 category on the Rutherford scale, without the need for additional intervention, was higher in the stented group (63.2% versus 17.9%, P<0.0001).

A multicenter Japanese registry including 2400 limbs in 1889 consecutive patients followed for 5 years demonstrated a significant association between stent use and freedom from restenosis (P=0.027). This observation was independent of lesion severity.

Nearly all commonly used FP BMS are fabricated from a nitinol tube, with 1 notable exception, the Supera stent (Abbott Vascular), which is constructed from woven nitinol wires. Nonrandomized registry data reveal high PP (12-month,
84.7%–87.7%; 24-month, 76.1%) and no stent fractures.\textsuperscript{47–49} This device is the most expensive bare metal stent, requires meticulous vessel preparation, and is technically challenging to deploy.

These data lend strong support to stent placement being superior to PTA as a means to reduce restenosis and TLR, and to improve meaningful clinical outcomes. There is, however, more to the story.

Bare Metal Stents: Proven Liabilities

Although nitinol stents address the most striking weaknesses of PTA, they create a new set of liabilities.

Reports of stent fracture appeared shortly after nitinol tube stents became commercially available,\textsuperscript{50} but alarm produced by these reports mitigated over time. Different stents made of the same alloy had vastly different failure rates. When multiple stents were deployed in a single vessel, regions of overlap created inflexible zones that accentuated movement and fatigue in adjacent regions. These facts created a reasonable expectation that longer stents (requiring fewer per vessel), and those created with different manufacturing processes, could result in fewer failures. Indeed, in the Zilver PTX RCT the fracture rate was only 0.9% at 12 months.\textsuperscript{51} The Safety and Effectiveness Study of EverFlex Stent to Treat Symptomatic Femoral-popliteal Atherosclerosis (Durability II) evaluated 287 patients with lesions up to 18 cm treated with stents up to 20 cm in length,\textsuperscript{52} yet had only 0.9% radiographic fracture at 3 years. Thus, given improvements in stent manufacture over the past decade, fracture is not a major concern.

A persistent problem is that of in-stent restenosis (ISR), occurring in ≈30% of patients by 12 months.\textsuperscript{23,25,26} Longer lesions show more frequent restenosis (≈50%) than shorter lesions.\textsuperscript{26,52} There is no definitive treatment for ISR.

Numerous treatment options have been proposed to treat FP ISR. PTA alone is ineffective, with 6-month TLR of up to 48.2%\textsuperscript{53} and 1-year patency rates of ≈28%.\textsuperscript{54} Cutting balloon angioplasty is no better.\textsuperscript{55}

Excimer laser has received Food and Drug Administration approval for treatment of FP ISR. This is not so much a testament to its efficacy, but rather that PTA is so much worse. The Photoblebration Using the Turbo-Booster and Excimer Laser for In-Stent Restenosis Treatment (PATENT) study enrolled 90 ISR patients, all of whom received laser, and 87.8% received adjunctive PTA.\textsuperscript{56} Distal embolization was seen in 10%. Twelve-month PP was only 37.8%. Excimer laser plus PTA was compared with PTA alone in 250 patients in Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis (EXCITE ISR).\textsuperscript{53} Laser had higher procedural success (93.5% versus 82.7%, $P<0.01$) and lower, but still substantial, TLR (26.5% versus 48.2%, $P<0.005$) at a follow-up of only 6 months.

Debulking ISR with directional atherectomy has been found lacking in clinical trials. Zeller treated 43 lesions, with supplemental stenting in 4, to achieve 12-month patency of 54% and 47% TLR.\textsuperscript{57}

To summarize, BMS show clear benefits over PTA, but do not completely address the problem of restenosis. The search for something better has continued.
Polytetrafluoroethylene-Covered Stents

BMS share the common vulnerability of nearly all percutaneous vascular interventions, that of the development of neointimal hyperplasia, and subsequent loss of patency. PTFE-covered stents address this weakness by adding a physical barrier between the vessel wall and lumen, thus precluding obstructive intravascular tissue growth. The VIBRANT RCT tested the hypothesis that this barrier would result in higher PP. It permeates into and binds to abluminal (outer) surface of a nitinol tube stent without the use of a binding agent. This obviates any potential polymer-related complications.

Zilver PTX (Cook Medical, Bloomington, IN) has become the default treatment for most FP occlusive disease on the basis of extensive registry and, more importantly, RCT data. The landmark Zilver PTX multicenter RCT enrolled 474 patients with a unique design that allowed independent comparisons of the PTX stent with PTA and to BMS use (Figure 4). Study design and execution were outstanding and included approval by the Food and Drug Administration, the Japanese Pharmaceuticals and Medical Devices Agency, and German healthcare regulatory authorities. Oversight was provided by an independent Data Safety Monitoring Board, and a Clinical Events Committee adjudicated adverse events. Independent core laboratories evaluated angiograms, radiographic testing for stent fracture, and duplex ultrasound interrogations. When coupled with a 5-year follow-up interval, including duplex ultrasound assessment of patency in all stented patients, the Zilver PTX randomized trial became the most exhaustive evaluation of any modern therapy for FP disease. The Zilver PTX stent is now Food and Drug Administration approved, bears the Conformité Européenne mark, and is approved for use in multiple countries worldwide.

The Zilver PTX RCT included 2 points of randomization. Patients with symptomatic FP disease (Rutherford category ≥2, ≥50% diameter stenosis, ≤14 cm lesion length) were treated with either PTA or a Zilver PTX stent. A second randomization took place if PTA alone failed to produce an acceptable result. Patients with ≥30% residual diameter stenosis, flow-limiting dissection, or ≥5 mm Hg mean translesional pressure gradient after PTA received a BMS or a Zilver PTX stent. This allowed multiple comparisons, including Zilver PTX versus PTA, Zilver PTX versus BMS, and Zilver PTX versus optimal PTA plus provisional BMS. In each comparison, at all time points, Zilver PTX showed superiority. At 2 years, the initial randomization revealed a PP of 74.8% with DES, 26.5% with PTA, and 53.4% for optimal PTA. The secondary randomization showed 83.4% Zilver PTX patency versus 68.4% (P=0.05) in those treated with provisional BMS. DES 2-year freedom from TLR was 86.6%. Event-free survival (freedom from major adverse events and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6) was 86.6% DES versus 77.9% PTA (P=0.02) in the initial randomization. Clinical benefit, defined as freedom from persistent or worsening claudication, rest pain, ulcer, or tissue loss was sustained in 81.8% DES, 75.1% BMS, and 53.4% PTA (P<0.01). Provisional DES clinical benefit was also superior to provisional BMS (83.9% versus 68.4%).

The Zilver PTX trial is unique in that it provides 5-year, randomized, core laboratory– adjudicated data in a significant number of patients (M. Dake, Vascular Interventional Advances, Las Vegas NV, November 4, 2014).
was superior to optimal PTA or provisional BMS in PP (66.4% versus 43.4%), freedom from TLR (83.1% versus 67.6%; Figure 5) and clinical benefit (79.8% versus 59.3%; P<0.01 for all). Superiority was also seen with provisional DES versus provisional BMS, albeit in a smaller subset of patients. Stent fracture rate was only 1.9% at 5 years.

In parallel to the RCT, the Single-Arm Study enrolled 787 patients with 900 FP lesions with no restriction on lesion length (mean, 99.5 mm; maximum, 400 mm). This study used an independent radiographic core laboratory to assess stent fracture, a data safety monitoring board, and a clinical events committee. Occlusion was present in 38.3% at baseline, restenosis in 24.3%, and ISR in 13.2%. Up to 4 Zilver PTX stents could be used per limb. Despite lesion complexity and multiple stent use, PP was 86.2% at 1 year, and freedom from TLR was 90.5% at 1 year and 80.5% at 2 years. Matched cohorts from the registry were compared with patients enrolled in 4 contemporary BMS trials. The Zilver PTX stent was associated with 32% to 59% relative reduction in restenosis and 67% to 81% reduction in TLR. Also, despite the use of multiple stents in long lesions in the registry, 1-year stent fracture was only 1.5%. Event-free survival (using the same definition as the randomized trial) was 89% at 1 year. Ankle-brachial index, walking speed, and MWD all showed significant improvement (P<0.001).

The Single Arm Study helps to establish DES as the default strategy for perhaps the most challenging of all FP presentations, that of ISR. This registry represents the largest prospective assessment of ISR treatment, including 108 patients and 119 lesions (mean length 133 mm, 33.6% > 150 mm, 31.1% total occlusion, 8.4% with severe stent fracture). One-year PP was 78.8%. Freedom from TLR was 81% at 1 year and 60.8% at 2 years. These represent the best data for any proposed therapy for FP ISR.

Runner-Up: Drug-Eluting Balloons
The second-best strategy for FP atherosclerosis is DEB. It fails to achieve first place for several reasons.
As described in the discussion above, BMS placement is superior to PTA. This is not surprising given the FP segment’s propensity to exhibit diffuse, long-segment disease that often results in recoil, residual stenosis, and flow-limiting dissection after balloon treatment only. PTA, whether with a coated or uncoated balloon, cannot address these problems.

Even the best DEB data fall well short of those available for DES in terms of study design and duration of follow-up. This is not to say that DEB trials are not good, just that DES evaluation has been better. Randomized data are limited.

The standard format to evaluate DEB has been by comparison with PTA. As discussed in detail above, that is hardly a challenging comparison. PTA suffers from high acute failure, long-term restenosis, and TLR rates.

IN.PACT SFA compared DEB with PTA in a 2:1 randomization in 331 patients with 8.9 cm mean lesion length and demonstrated better PP at 1 year with DEB (82.2% versus 52.4%, \( P<0.001 \)) and lower TLR (2.4% versus 20.6%, \( P<0.001 \)).

Long-term data are not available. Despite the preference for balloon-only treatment, 9% of patients required stents.

MoxY Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries (LEVANT 2) randomized PTX-coated balloon treatment 2:1 versus PTA in lesions averaging 6.3 cm. Although superior 1-year PP by Kaplan-Meier analysis was demonstrated (73.5% versus 56.8% for PTA, \( P<0.001 \)), there was no difference in TLR. By 2 years, PP had slipped to 58.6% for DEB versus 53% for PTA, well below the 74.8% PP achieved by Zilver PTX at 2 years.

The longest follow-up for DEB treatment comes from the Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries (THUNDER) trial, which also randomized DEB to PTA. By 5 years, TLR was lower with DCB (21% versus 56% \( P=0.0005 \)), however, 5-year follow-up was not included in the original study protocol, and was sketchy. Only 31 patients underwent vascular imaging, with no core laboratory assessment, and another 15 had telephone follow-up at 5 years.

Although useful, these trials do not provide the much more relevant comparisons between DEB and BMS, DES and BMS, and offer remarkably sparse follow-up beyond 1 year.

As described above, DES treatment for FP ISR showed favorable results. At this point, it is impossible to assess the role of DEB in this application, because series examining their use have been small, with widely discrepant 1 year patency (38% to 92%), sometimes achieved with adjunctive stent placement. RCTs comparing DEB with PTA are currently enrolling, but, given the strikingly poor results with PTA in this application, even positive studies will prove little.

Wrap-Up

The conclusion, then, is that DES treatment rises above other options for most patients requiring SFA intervention. Conservative therapy requires excellent compliance for limited benefit. Surgery has prohibitive morbidity, mortality, and cost. PTA serves as a standard of reference, but little else. Many expensive endovascular strategies lack convincing supportive data. DEBs are attractive options for simple lesions, but long-term results are sparse. DES are not perfect, but, for now, are the best there is.

Disclosures

Dr Burket has received research support from Biotronik, Bard Vascular, and Cook Medical. He has served as a consultant for Biotronik and Covidien. He has been a speaker for Cook Medical.

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In rebuttal to my esteemed colleague’s well-written defense that femoropopliteal default therapy should be drug-eluting stent technology, given the strong scientific data set, one has to consider 3 principal issues raised by Dr Burket’s article.

First, let us agree that the superficial femoral and popliteal arteries are an inhospitable location for any endovascular therapy and the scientific data set are porous at best.

Second, some listed data, being retrospective real-world registries, have little scientific bearing on the debate at hand, given the non-core laboratory–adjudicated events or outcomes. Further, bare metal stent outcomes with the Supera stent in the SUPERB trial are on a par with drug-eluting stents at 1 and 3 years. Also, IN.PACT 2-year data showing sustained primary patency 73% with a sustained low target lesion revascularization rate remain exceptional.

Last, the most critical issue remains at 12 months, Zilver PTX versus IN.PACT DCB versus DEFINITIVE E or SUPERB, seem to suggest that all devices have an equipoise among trials and among patients with femoropopliteal disease. Again, the issue is not in our successes, but in our failures, and how restenosis impacts further treatment when needed. The treatment of restenosis is the great unknown as to timing and recurrence in the scientific landscape and when and if clinically relevant. Ultimately, for us to debate this subject and make fair and salient points requires direct comparator trials at 1 year and beyond to 3 and 5 years.

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Response to Burket

Lawrence A. Garcia, MD

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