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

Endovascular Therapy for Femoropopliteal Disease: Drug-Eluting Stents Are Not the Default Therapy

Lawrence A. Garcia, MD

Lower extremity arterial obstruction leading to ischemic claudication or critical limb ischemia is generally caused by atherosclerotic obstructive disease and affects an estimated 40 million Americans where up to 10 million are symptomatic. Treatment options in the past have ranged from simple medical therapy and exercise programs to revascularization strategies. These revascularization approaches have included surgical bypass or endovascular therapies. Treatment for arterial obstructive disease in the infrainguinal femoropopliteal location has generally become accepted with few exceptions as an endovascular first location. To date, there remains no clear-cut de facto gold therapy for endovascular applications in the lower limb with the best outcomes that we can apply to most if not all our patients who present with symptomatic lower limb disease (Table). Current data from numerous trials at various lengths of outcome duration (ranging from 12 to 60 months) have shown that there remains a consistent but steady decline in primary patency with all devices over time. There has been a robust interest in what should be the default therapy for lower extremity disease. However, to date, there is little information that suggests that an upfront use of stenting, in particular, drug-eluting stents (DES), should become the primary therapy. In the following debate it is hoped that it will convey the critical point that a non-DES and likely a leave-nothing-behind strategy approach should be the default. One critical qualifier in this debate is that, for any conclusions to be drawn and any arguments to be made, they are simply speculative, because none of the trials described below can be directly compared. Here, the inference of comparison is within the confines of this debate and should be accepted as an inference on the generality of comparisons for this debate.

Response by Burket on p 336

Background

One issue that remains critical is where and when failure occurs, whether simple restenosis or occlusion to the lesion, and how best to treat these failures, particularly when an endoprosthesis is already in place because of its use at the index procedure. One of the earliest questions of revascularization has been answered through the Mild to Moderate Intermittent Claudication (MIMICS) trial where revascularization of the iliac/femoropopliteal segments had a better outcome with either absolute walking distance, ischemic claudication distance, or simple ankle-brachial index at 1- and 2-year durations. Interestingly, this trial did not delineate angioplasty or stenting in the form of revascularization, but only that it occurred and was better than medical therapy and exercise.

Stenting Data

The Vienna Absolute trial was the first randomized data set comparing stenting with angioplasty. In this trial, at a metric of 10 cm, the investigators reported their outcomes at 1 and 2 years. What is critical with this trial is that it was the first large-scale randomized trial comparing stenting with...
Table. Patients Enrolled and Lesion Lengths Tested With Device Studied and Outcomes at 1 Year With PSVR listed

<table>
<thead>
<tr>
<th>Trials*</th>
<th>Patients, n</th>
<th>Device</th>
<th>Lesion Length, cm</th>
<th>1-y Primary Patency, % (PSVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIMIC</td>
<td>81</td>
<td>PTA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ABSOLUTE</td>
<td>104</td>
<td>Stent</td>
<td>10.2</td>
<td>63 (2.5)</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>137</td>
<td>Stent</td>
<td>6.3</td>
<td>81 (2.4)</td>
</tr>
<tr>
<td>DURABILITY</td>
<td>287</td>
<td>Stent</td>
<td>8.9</td>
<td>77 (2.5)</td>
</tr>
<tr>
<td>STROLL</td>
<td>250</td>
<td>Stent</td>
<td>7.7</td>
<td>81 (2.5)</td>
</tr>
<tr>
<td>ZilverPTX</td>
<td>240</td>
<td>DES-SES</td>
<td>5.4</td>
<td>83 (2.0)</td>
</tr>
<tr>
<td>THUNDER</td>
<td>54</td>
<td>DCB</td>
<td>7.4</td>
<td>74 (2.4)</td>
</tr>
<tr>
<td>LEVANT</td>
<td>476</td>
<td>DCB</td>
<td>6.3</td>
<td>65 (2.5)</td>
</tr>
<tr>
<td>IN.PACT</td>
<td>301/220</td>
<td>DCB</td>
<td>8.9</td>
<td>90 (2.4)</td>
</tr>
<tr>
<td>DEFINITIVE LE</td>
<td>598/201</td>
<td>DA</td>
<td>7.8</td>
<td>78 (2.4)</td>
</tr>
</tbody>
</table>

DA indicates directional atherectomy; DCB, drug-coated balloon; DES, drug-eluting stent; NA, not available; PSVR, peak systolic velocity ratio; PTA, percutaneous transluminal angioplasty; and SES-self-expanding stent.

*MIMIC indicates the Mild to Moderate Intermittent Claudication trial; ABSOLUTE, Balloon Angioplasty Versus Implantation of Nitinol Stents in the Superficial Femoral Artery trial; RESILIENT, Randomized Study Comparing the Edwards Self-Expanding Lifestent Versus Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery trial; DURABILITY, US Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal by Using the Protégé Everflex Nitinol Stent System; STROLL, S.M.A.R.T. self-expanding nitinol stent for the treatment of atherosclerotic lesions in the superficial femoral artery; THUNDER, Local Taxan with Short Time Contact for Reduction of Restenosis in Distal Arteries; LEVANT, Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis; IN.PACT, Drug Coated Balloon Versus Standard Angioplasty for the Treatment of Superficial Femoral and/or Popliteal Peripheral Artery Disease; DEFINITIVE LE, Determination of Effectiveness of a Directional Plaque Excision System for the Treatment Of Intrainguinal Vessels/Lower Extremities.

angioplasty alone. Beyond the critical finding of primary patency at the end of the 12- and 24-month period at 63% and 54%, respectively, was the fact that the clinical (symptomatic) benefit of stenting was lost at 2 years in comparison with the angioplasty (percutaneous transluminal angioplasty [PTA]) alone arm, despite having a maintained patency benefit of the endoprosthesis (Figure 1A).

One of the first trials regarding stenting outcomes for the United States was the Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone in Lesions Involving the SFA and/or Proximal Popliteal Artery (RESILIENT) trial that reported outcomes to 12 months and, recently, their outcomes to 3 years using the Lifestent. In their initial trial at 12 months, the primary patency was 80% in comparison with 40% for the PTA group (Figure 1B) on a lesion length of 6.4 cm with target lesion revascularization (TLR) rates of 87.3% and 45.1%, respectively.5,6 Their 3-year data supported the use of the stent in this modest lesion length group to 75.5% TLR rate at 36 months (primary patency was not reported at 36 months).

In the Safety and Effectiveness Study of EverFlex Stent to Treat Symptomatic Femoral-popliteal Atherosclerosis (Durability II),7 in a lesion length of 11 cm, the primary patency using a peak systolic velocity ratio (PSVR) of 2.0 was 67.7% and a Kaplan–Meier patency of 77.2%. It is interesting that the 3-year outcomes with this trial revealed primary patency of 60% that was 71% for lesions <8 cm and only 50% for lesions >8 cm. The clinically driven TLR rate was 70% at 3 years.

In the S.M.A.R.T. Self-Expanding Nitinol Stent for the Treatment of Atherosclerotic Lesions in the Superficial Femoral Artery (STROLL)8,9 trial, a lesion length of 7.7 cm had a primary patency of 81.7% by Kaplan–Meier estimates at 12 months. Their 3-year data, presented and nonpublished, revealed a TLR rate of 75.8% (Figure 1D).

Why Consider Leaving Nothing Behind

One potential benefit from a leave-nothing-behind strategy is it may allow for similar patency rates with the failure mode being the same restenosis or restenotic pattern as in stenting data. However there remains no impediment to retherapy and no limit to the options for retherapy, because there is an absence of an endoprosthesis.10–17 The recent data from DEFINITIVE AR12 suggest that a combined therapy of atherectomy with drug-coated balloons (DCBs) may provide a signal that allows similar 1-year outcomes to the most robust randomized trial using DES. In addition, 24-month outcome data will evaluate whether there is late catch-up or failure. This trial has only been presented, and the main scientific data set has yet to be released in a peer-reviewed fashion.

The DES Conundrum

Data on the efficacy of DES derives from Zilver PTX.18 This trial had a single randomization evaluating the DES to optimal PTA. In those with suboptimal PTA, a second randomization between DES and BMS Zilver stents was performed. The primary outcome was a duplex end point of patency using a PSVR of 2.0. At 12 months, the primary patency was 84%. However, if one looks at the completion of the cohort through 14 months, this patency in reality was 76%.

Beyond the first year, the benefit of patency was preserved for the subsequent several years culminating in the 5-year 64% primary patency rate.19 The benefit persisted throughout the
reporting period and increased in comparison with the PTA arm, suggesting that the decline in patency is slowed with time using the DES in comparison with either the PTA or BMS cohorts (Figure 2). This remains the best and most robust data set in the scientific landscape.

What is the problem then? We have a great data set at 5 years that no other device has produced. First, the lesion length in this trial was only 5.3 cm. This is exceedingly short and unlikely to represent a real-world experience. Another key shortfall of the DES data thus far is critical. The original reporting data are at a hard end point of 12 months, and, if one gets the entire cohort through the 14-month window in the primary patency, the patency falls to 76% on the Kaplan–Meier estimates. Why bring this up? Well, let’s first look at the data set from a non-DES stent trial. The Superb data had a PSV of 2.0 mandated by the Food and Drug Administration from an objective performance goal criteria to avoid further randomization to PTA. In this trial, the lesion length was 8.1 cm. Furthermore, the primary patency at 12 months was 86% (Figure 1C). How is this possible?—a longer lesion length, similar PSVR, and greater patency? Well, again, if one goes to the 14-month window, then the primary patency falls to 79%. But again this appears better than the data point of Zilver PTX at a longer lesion metric.

What’s the point? Critically, the patency is one thing we all focus on and discuss and compare in all the machinations we choose. However, the opposite is what is the critical point here. In all groups, the average failure for devices is 20% to 25% at 1 year and more at 2 to 3 years such that, for Zilver, we are at 35% failure at 60 months.

**The Gorilla in the Room—Stent Failure**

How we do treat these failures is equally daunting to the initial therapy in some cases. There has been 1 study that now has gained Food and Drug Administration approval for therapy for in-stent restenosis. In the Excimer Laser Randomized Controlled Study for Treatment of Femoropopliteal In-Stent Restenosis (ExCITE) trial, where 240 patients with stent restenosis were randomly assigned to laser atherectomy with angioplasty versus simple angioplasty alone, lesion lengths ranged over 30 cm in 20% patients with an average of 19 cm in each group. Total occlusions were between 30% and 36% in each group, respectively. The primary success (defined as clinically driven TLR), and not primary patency for the combination of laser plus angioplasty at 1 year, was just <50% in comparison with <30% for simple angioplasty. In other words, using the least objective metric, clinically driven TLR laser plus angioplasty works in only 50% of the cases treated. This clearly impacts the outcomes of stent failures, whether bare metal or DES.

**Leaving Nothing Behind**

What if we take an alternative view with 2 additional trials. Let’s start with the Drug Coated Balloon Versus Standard...
Angioplasty for the Treatment of Superficial Femoral and/or Popliteal Peripheral Artery Disease (IN.PACT) and LUTONIX data sets. These DCB trials produced some of the most anticipated data in recent memory. The IN.PACT data had a lesion length of 10 cm and compared DCB with PTA alone. The stenting rate in this trial was only 6%, suggesting that this is a DCB trial alone in the SFA for the lesion length tested. The primary patency at a PSVR of 2.0 was 89% at 12 months. But again, as noted previously, if we look at the 14-month window, the primary patency decreases to 79% (Figure 3A). This is important; again, not only does this primary patency fall under 80%, but this trial also had the greatest difference from 12 to 14 months of 10%. The 24-month outcome data will be presented this year. Again, this remains critical in the context of the scientific landscape. First, leaving nothing behind and only treating with PTA improves on the outcome noted with leaving an endoprosthesis behind and further beats both the DES and non-DES platforms. Further data will be mandatory to understand the long-term benefit or lack thereof regarding these platforms. However, the original DCB trial data which started the world’s interest in a leave-nothing-behind strategy at 5 years has seen no late catch-up from the treated cohort.

Lutonix also has published and presented their 1- and 2-year data, respectively. These data revealed that the primary patency at 12 months was 74% on a lesion length of 8.1 cm, and at 14 months 67% (Figure 3B). Again, we see the decline when the entire cohort reports to an outcome rather than a hard end point of 12 months. Lastly, at 2 years, the primary patency was 58%, recently presented, but nonpublished.

Have there been any other data to support alternative therapy to principally treating with stenting for the lower limb?
Excision System for the Treatment Of Infrapinguinal Vessels/ Lower Extremities (DEFINITIVE LE) trial\textsuperscript{11} reported core laboratory–adjudicated outcomes using directional atherectomy (SilverHawk, Medtronic) in both claudicants and critical limb ischemic patients, enrolling 800 subjects (599 claudicants and 201 patients with critical limb ischemia). This is clearly one of the largest trials reporting the use of atherectomy specifically. If we look at the claudicant group (598 subjects with 1 subject being censored for an informed consent infringement), the primary patency using a PSV of 2.4 was 78\% overall (Figure 4). However, this patency number is exceedingly misleading, because this trial enrolled all anatomic levels (femoral, popliteal, and tibial locations) because this protocol was not driven to understand the outcomes and where this device can best be used in the therapy of both claudicants and patients with chronic limb ischemia, its patency is a summation of the outcomes for SFA, popliteal, and tibial circulations. When we specifically look at the SFA for the target location in both short, medium, and long lesions defined as <4 cm, 4 to 10 cm, and >10 cm, the primary patency in this trial was 79\%, 83\%, and 67\%, respectively, in 671, 162, and 189 lesions, respectively, in the 743 claudicant patients. Importantly, the overall stenting rate in this trial was only 3\%, so these outcomes are truly a reporting of directional atherectomy alone in these anatomic locations. These numbers also represent final cohort numbers, not hard 12-month numbers as other trials have reported. Unfortunately, this trial will not report beyond 12 months.

This trial, however, did spawn a second trial, DEFINITIVE AR.\textsuperscript{12} In this pilot trial looking at claudicants, atherectomy using the SilverHawk device in conjunction with DCB was evaluated in comparison with DCB alone in a randomized trial of 110 patients. The overall outcome failed to show any significant incremental benefit between directional atherectomy plus DCB and DCB alone. However, the group with lesion lengths >10 cm and those with heavy calcification showed remarkable benefit of the combination therapy with the DCB therapy alone at 91\% primary patency at 12 months in comparison with 68\% and 63\% in comparison with 48\% at 12 months, respectively. Understanding that these numbers are not duplex but angiographic end points makes this data point very strong, but argues the need for a larger trial for comparison of these end points. Until we have this trial in its full statistically powered and peer-reviewed publication, we cannot place it into the scientific landscape, although its signal bears notice.

Conclusions

So what can we conclude? What remains critical and very clear is that, despite the heterogeneity of the trials listed above, each individual study has a critical outcome that has moved us forward in the scientific pursuit of what is best for our patients who present with lower limb arterial obstructive disease. Unfortunately, with only a few exceptions, these trials are set to and only for the indication of a device and, as such, drive the lesion lengths to be very short and not likely to represent real-world patients we treat every day. Furthermore, the outcomes we quote are evaluations at 12 months and not an entire subject cohort at 14 months. Taken in context, all trials fail to suggest any one device as the gold or default standard of care. If one understands these limitations of the trials, then I think we can deduce that, in no circumstance, has the upfront need for an endoprosthesis, particularly a DES platform, outperform any 1 device at the 12-month or 24-month end point. Furthermore, the data set from non-DES platforms seems to perform just as well as the DES platforms to the same duration without a drug coating. Indeed, a leave-nothing-behind strategy performs well and, in fact, to the same degree at 12 and 24 months in comparison with the stent trials, both non-DES and DES varieties. The idea that we should use a DES as default therapy is inaccurate and not justified given the scientific data. Importantly, the better thought might be to treat first either with DCB alone or, if longer lesions, then a combination of directional atherectomy with adjunctive DCB would produce the best overall results without the initial need for an endoprosthesis.

Critically, and probably the most important issue in this debate remains, everything we have suggested above could be made very simple and not merely conjecture or apples/oranges comparisons if we just started to have, first, an understanding
of the failure mode of these devices. Understanding the patterns of restenosis would be critical to know which device is best for our patients regarding particular lesion subsets (calcifications, occlusions, etc) or to know how or which fails in either focal or diffuse patterns. Second, this whole debate screams for comparative trials between devices. This critical ideal is glaringly missing in the data set for the lower limb, and further discussions as to which device or particular paradigm is best seem short sighted without this critical and key information.

Disclosures
Dr Garcia has received research grants and has served as national/global principle investigator for studies conducted through Medtronic and Abbott. He serves as a noncompensated consultant to Medtronic, Abbott, and Boston Scientific. He holds major equity in Arsenal, Primacea, Tissue Gen, CV Ingenuity, Scion Cardiovascular, Spirox, and Essential Medical. He is the founder of Elite Vascular Consultants.

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Response to Garcia

Mark W. Burket, MD

Dr Garcia is a well-established and highly regarded expert in peripheral vascular disease clinical care and research. In his article, he makes a compelling case for a “leave nothing behind” strategy, an approach with which he has considerable experience. The argument is based largely on the rationale that reintervention, if required, is substantially easier if there is no stent with which to contend. In this regard, I completely agree with Dr Garcia. The problem with “leave nothing behind” lies not in its logic, but in the lack of data to support it. In contrast, drug-eluting stent treatment boasts, in Dr Garcia’s words, “the best and most robust data set in the scientific landscape.” A large randomized cohort of subjects, followed meticulously for 5 years, confirmed a statistically significant advantage for drug-eluting stents over conventional therapy. No studies of drug-eluting balloons, atherectomy, or their combination come anywhere near this standard. Dr Garcia concedes that the Zilver PTX trial generated, “a great data set at 5 years that no other device has produced” and concludes that the debate “screams for comparative trials between devices.” I agree. And yet no atherectomy versus drug-eluting stent trial has ever been formulated. Until such a study can be conducted, it is hard to advocate the exorbitant cost associated with “leave nothing behind.” For example, atherectomy (with distal embolic protection) followed by a drug-eluting balloon produces an equipment cost more than triple that of a drug-eluting stent. Show me the data, and then we’ll talk!
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