

# SFA Disease: Deciding What to Leave Behind

Evaluating the value of drug delivery and the role of permanent implants in treating superficial femoral artery disease.

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When Laura Shaw refused leg amputation after presenting with gangrenous toes in 1964, there were no endovascular options to treat her femoropopliteal (FP) disease, until Charles Dotter offered to treat her with a Teflon dilating catheter.<sup>1</sup> Her foot was saved, and endovascular therapy was born. In the ensuing 55 years, the proliferation of treatment options has been mind-boggling, providing new options but also making it hard for physicians and patients to decide on the best treatments for superficial femoral artery (SFA) disease. One important component in the decision-making process is consideration of what may happen months or years after an initially successful procedure. Will what is left behind restrict future therapy?

## LEAVING A DRUG BEHIND

In the current era, the question of what to leave behind is not limited to simply metal or polymer implants. There are now robust data supporting placement of antiproliferative drug therapy into the vessel wall at the end of the procedure. *[Editors' note: A recent meta-analysis by Katsanos et al explored a trend toward higher mortality rates in patients randomized to paclitaxel-coated/eluting therapies in randomized trials (please see page 10 for more information). Further evaluation of this meta-analysis and its findings is ongoing. As such, in-depth discussion has not been included in this article and will be covered elsewhere in Endovascular Today.]*

## DRUG-COATED BALLOONS

Drug-coated balloons (DCBs) have become a first-choice therapy for many interventionalists. Well-conducted randomized controlled trials (RCTs) provide solid evidence for the superiority of DCBs over percutaneous transluminal angioplasty (PTA) with uncoated balloons.

LEVANT 2 evaluated 476 patients with FP lesions up to 15 cm in length and found higher 12-month primary

patency with the paclitaxel-coated Lutonix DCB (BD Interventional) treatment than with PTA (65.2% vs 52.6%, respectively;  $P = .02$ ).<sup>2</sup> The study design called for randomization only if patients appeared unlikely to require a stent after predilation. Provisional stenting occurred in 2.5% of DCB patients and 6.9% of those treated with PTA. The Lutonix DCB became the first balloon to receive FDA approval for use in the SFA.

Next to receive FDA approval was the In.Pact Admiral DCB (Medtronic). This paclitaxel-coated balloon was evaluated in 331 patients in the IN.PACT SFA RCT with a 2:1 randomization scheme between In.Pact Admiral and PTA.<sup>3</sup> Freedom from clinically driven target lesion revascularization (CD-TLR) at 4 years was 76.8% with the DCB and 70.4% with PTA ( $P = .04$ ). The first CD-TLR occurred later with the DCB than with PTA (739.2 days vs 302.9 days;  $P < .001$ ). Bailout stenting occurred in 7.3% of DCB interventions and 12.6% in the PTA arm.<sup>3</sup> Outcomes were also good in the IN.PACT Global study, a 1,535-patient real-world registry that allowed inclusion of longer lesions, in-stent restenosis, and lesions as far distal as the P3 popliteal segment. Freedom from CD-TLR was 83.3% at 24 months, with target limb amputation in only 0.7%. The rate of provisional stent placement was 21.2%.<sup>4</sup> Another real-world registry had a similar stenting rate of 23%.<sup>5</sup>

The Stellarex DCB (Philips) became the third paclitaxel-coated balloon to receive FDA approval. The ILLUMENATE RCT employed a 2:1 randomization scheme in 300 patients. The 12-month CD-TLR rate in the DCB arm was 7.9% versus 16.8% with PTA ( $P = .02$ ). The bailout stenting rate was 6% in both arms.<sup>6</sup>

## DCBs: COSTS VERSUS EFFECTIVENESS

As previously noted, extensive RCT data have convincingly confirmed the superiority of DCB over PTA. In response to this, the Centers for Medicare & Medicaid

Services provided a transitional pass through (TPT) payment, which offset the additional up-front cost incurred by hospitals when outpatient FP interventions included DCB use. Thus, there was no financial disincentive for DCBs in hospital outpatient settings. However, the TPT expired in 2018. Because DCB devices cost approximately \$1,200 more than uncoated balloons, hospital profit margins decrease by \$1,200 for each DCB used. Given the narrow operating margins of hospitals in the current era, there is a significant financial disincentive for hospitals to use DCBs. On the other hand, lower TLR rates associated with DCBs result in lower expenditures during follow-up. The resultant savings benefit patients and third-party payers, whereas there is no benefit to hospitals.

In a hospital outpatient setting, the physician performing the intervention experiences no financial impact from DCB use; however, this is not true in an office-based laboratory (OBL). Physicians who perform procedures are typically the owners of OBLs. In this context, the physician/owner experiences a \$1,200 loss in income for each DCB used. Hence, for both hospitals and OBLs, financial incentives are not at all aligned with clinical outcomes data.

### REDUCING THE PRESSURE TO STENT

DCB trials were specifically designed to evaluate DCB treatment as a stand-alone strategy, and thus stent use was typically strongly discouraged. As a result, non-flow-limiting dissections and moderate degrees of recoil with residual stenosis that might have been treated with stents in other contexts were left alone. Although this required a considerable degree of restraint on the part of the operators, they were typically rewarded with favorable long-term patency. But what about flow-limiting dissections or severe residual stenoses that fail to yield to aggressive PTA? Invariably, these lesions (which were not included in RCTs) continue to be stented. However, could a different treatment algorithm avoid these problems in the first place and thus prevent the need to decide whether or not to stent?

“Vessel preparation” is a term that lacks a universally accepted definition, but it entails some form of treatment designed to improve upon simple PTA. It covers a spectrum of techniques including prolonged (several minutes) balloon inflation, focused-force balloon treatment, lesion scoring, a variety of atherectomy options, and most recently, intravascular lithotripsy (IVL). Some of the touted benefits of these therapies include improved lesion compliance, avoidance of “barotrauma” (another term lacking a clear definition), better luminal gain, enhanced penetration of antiproliferative therapy into the vessel wall, and fewer or less severe dissections.

It seems apparent that these strategies may facilitate PTA in such a way that there is little incentive to place a stent. If there is no significant residual stenosis and no dissection, why bother?

Discussions about vessel preparation almost always include some reference to directional atherectomy (DA). Bailout stenting has been infrequent in several moderately sized registries. DEFINITIVE LE showed a 3.2% rate in 800 patients, and DEFINITIVE Ca++ demonstrated a frequency of 4.1% in short, calcified FP disease.<sup>7,8</sup> The SilverHawk and TurboHawk atherectomy devices (Medtronic) were used for vessel preparation in the randomized DEFINITIVE AR trial in 102 patients treated with DA plus DCB versus DCB alone. Grade C/D dissections were seen less frequently in the DA group (2.1% vs 18.5%;  $P = .01$ ). Bailout stenting was required in 3.7% of those receiving a DCB alone and in none treated with DA.<sup>9</sup> In this trial, 19 patients with severe calcification were not randomized but were enrolled in a registry arm. Only one of these patients required stent placement. These observations will be further assessed in the ongoing REALITY trial, which combines the use of the HawkOne (Medtronic) or TurboHawk atherectomy devices with the In.Pact Admiral DCB in long, moderately or severely calcified FP lesions. Provisional stenting, typically frequent in this subset of patients, will be assessed in this single-arm registry.

Patients with heavily calcified FP vessels present the greatest challenge to the “nothing left behind” approach to percutaneous intervention. These patients, typically excluded from endovascular trials, demonstrate very high rates of vessel dissection, significant residual stenosis, and need for bailout stenting. Often, after stent placement, angiographic results remain suboptimal. IVL, also referred to as *lithoplasty*, a newcomer to the field of vessel preparation, is specifically intended for this subset of patients. IVL employs sonic pressure waves to disrupt calcium contained within the vessel wall. As is the case when this mechanism is used to fragment kidney stones, hard, calcific plaque fractures, but no harm is done to adjacent soft tissue. The result is a dramatic improvement in vessel compliance, facilitating PTA.

IVL was used to treat 95 patients in DISRUPT PAD I and DISRUPT PAD II. Notably, all patients had either moderate or severe calcification. Technical success was 100% and residual stenosis was remarkably good at 23.8%.<sup>10</sup> IVL demonstrated an outstanding safety profile: 1% bailout stent use and 1% grade D dissection. In contrast to DA, no embolic events and no perforations were seen in this series. DISRUPT PAD III is currently enrolling patients with moderately or severely calcified FP lesions, with Rutherford class 2 to 4 symptoms. In this 400-patient RCT, one arm includes IVL prior to DCB

treatment and another arm treats with a DCB without antecedent IVL.

### THE INEVITABLE NEED TO STENT

Despite the most careful patient selection and vessel preparation, some patients will be left with flow-limiting dissections or recoil, resulting in unacceptably severe residual stenosis. At this point, stent placement is the only reasonable option. To do otherwise predictably results in abrupt vessel closure, residual symptoms, or progressive lumen loss. Although there is no appropriate choice other than to leave something behind, the interventionalist still has a wide range of options. The “full metal jacket” approach, popular a decade or more ago before the availability of DCBs, has fallen by the wayside. This practice of stenting the entire FP segment substantially increased the cost of the initial procedure. However, the delayed effects are more important. With increased length of overlapping stents comes an increased risk of stent fracture.<sup>11</sup> If restenosis or occlusion occurs within a long stented segment, repeat intervention becomes much more complex. Simple balloon techniques are inadequate. Subsequent interventions require more expensive equipment and more time, typically extend the treatment area both proximally and distally, and are prone to failure yet again.

Poor outcomes with full metal jacket stenting, coupled with surprisingly good DCB outcomes, even when post-DCB images were less than perfect, have fostered the desire to leave as little stent material within the FP segment as possible. Dissections that do not restrict flow and moderate residual stenoses appear to be best left alone. Stents are reserved for only those areas with severe recoil or flow-limiting dissections. A “spot stenting” approach, with short stents only where absolutely needed, seems unnerving at the time of the index procedure, but it allows for more treatment options should restenosis occur. It completely precludes the dilemma of how to treat occlusion in a full metal jacket.

An option at the opposite end of the spectrum from the full metal jacket is the minimalist approach of the Tack endovascular system (Intact Vascular, Inc.). This system has received CE Mark approval but remains an investigational device in the United States. The 6-F nitinol Tacks, appropriately sized for 2.5- to 6-mm vessel diameters, have gold radiopaque markers. The over-the-wire delivery system includes six Tacks, with a goal of allowing repair of multiple dissected regions and minimizing the luminal surface area covered with metal. Theoretically, should repeat intervention be necessary, options may be possible that would be simpler than those required to address typical in-stent restenosis.

### DOES THE TYPE OF STENT MATTER?

At least for the foreseeable future, there will continue to be a need to place stents for some FP artery disease. Choosing which stent to use, however, is often not a clear decision. Direct comparisons of different stent platforms in the same patient population are nearly nonexistent. Data have been primarily obtained by evaluation of a single stent type in retrospective studies, single-arm registries, or RCTs in which the control arm was PTA.<sup>12-14</sup> Operators are left to decide which stent to place based on characteristics such as deployment accuracy, radial strength, availability within their institution, and cost, among others.

The notable exception regarding stent-to-stent comparison is found in studies evaluating drug-eluting stents (DESs). The landmark 5-year Zilver PTX RCT compared the Zilver PTX DES (Cook Medical) to PTA.<sup>15</sup> A secondary randomization for subjects in whom PTA failed compared Zilver PTX to bare-metal Zilver stents (Cook Medical). In both arms, DESs showed superior outcomes in terms of patency and freedom from TLR, which makes a strong case for the use of DESs in FP disease. Subsequently, the IMPERIAL trial offered a head-to-head comparison of the Eluvia DES (Boston Scientific Corporation) to Zilver PTX. Both stents deliver paclitaxel but at different concentrations, and Eluvia also utilizes a polymer matrix. At 12 months, primary patency was higher with Eluvia (88.5% vs 79.5%;  $P = .01$ ), with a trend toward lower TLR (4.5% vs 9%;  $P = .07$ ).<sup>16</sup> Thus, although Eluvia appears superior at 12 months, Zilver PTX still maintains the advantage of having 5-year RCT results.

As previously mentioned, health care institutions are financially disincentivized for DCB use, despite strong RCT data verifying their superiority to PTA. The same is true with regard to DES use. Despite RCT data demonstrating DESs' superiority to PTA or bare-metal stents, hospitals and OBLs are compensated at the same rate as when much cheaper bare-metal stents are used. Thus, profit margins are less for better medical care. Hospitals and OBLs do not benefit from subsequent savings. There is a disconnect in which the hospitals and OBLs have reduced profit, but payers experience cost savings because they do not have to pay for TLR.

### CONCLUSION

The questions of what to leave behind and when remain. Based on most interpretations of the available data, the answer may be simple: some form of paclitaxel application in most cases, stenting only when needed, and as little metal as possible.

The trickiest part of the SFA treatment algorithm is how to avoid the need to place a stent. Most would concede that prolonged balloon inflation in simple lesions is

a good strategy. As lesion complexity increases, however, consensus crumbles. Many vessel preparation strategies are lacking in clinical trial data. Others, such as DA, appear to reduce stent placement but substantially increase procedure cost and complexity. Lithotripsy appears promising based on limited data, but its increased cost is not currently offset by third-party payers.

In the end, it comes down to an individual physician evaluating an individual patient and asking, “Based on my knowledge and experience, the tools at my disposal, and the anatomy before me, how can I achieve the best result now, and the one that keeps the most options open in the future?” ■

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