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New Innovations in Drug-Eluting Stents for Peripheral Arterial Disease

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Abstract
Purpose of Review The purpose of this paper was to provide a review of the burden of peripheral arterial disease; to examine older therapies and their limitations; and especially to highlight new treatment innovations as well as the data supporting their use.
Recent Findings Building on the success of paclitaxel in the prevention of restenosis in the peripheral circulation, the newest generation drug-eluting stent is presented, which combines paclitaxel with a polymer—allowing the drug to be eluted slowly over 12 months. The positive results of the pilot MAJESTIC study led to the ongoing IMPERIAL trial. Limited data of bioresorbable scaffolds in above and below-the-knee applications are also reviewed.
Summary Endovascular therapy of peripheral arterial disease has had many advances in the preceding two decades. However, drug-eluting stent technology has had the greatest impact to date and holds great promise for the future.

Keywords Drug-eluting stent · Bioresorbable scaffold · Peripheral arterial disease · Claudication · Innovations · Review

Background and Introduction

Peripheral arterial disease (PAD) is increasingly common in developed countries, affecting between 8 and 12 million people in the USA [1]. This number is likely to increase in the future due to the aging population and increased physician and patient awareness. Although 20 to 50 % of patients with PAD are asymptomatic, they are still at significant risk of adverse outcomes due to the co-prevalence of coronary, renovascular, and cerebrovascular disease. Five-year mortality approaches 30% in this population and 5-year lower extremity amputation risk is 2–5% or higher in particular patient subsets, such as those with diabetes mellitus or active smoking status. Furthermore, if patients experience rest pain, their amputation-free survival drops to 50% in 12 months without treatment [2].

Despite advances in the recognition, diagnosis and treatment of PAD, a significant proportion of patients remains symptomatic despite optimal medical therapy, risk-factor modification, and a supervised exercise program. These patients continue to have a 10% 1-year and a 20% 3-year risk of major adverse clinical events [3]. Revascularization has not only proven to be helpful for patients with limb-threatening ischemia or disabling claudication, but also improved health-related quality of life in claudicants with lifestyle-limiting symptoms [4]. What follows below is a description of the progression of revascularization device approaches and recent advances in the endovascular treatment of PAD, with a special emphasis on drug-eluting stent technology.

Percutaneous Transluminal Angioplasty and Bare-Metal Stents

The majority of peripheral arterial atherosclerotic lesions are located in the femoropopliteal arteries [5]. The 2011 American College of Cardiology/American Heart Association (ACC/AHA) focused update of the 2005 guidelines recommend percutaneous transluminal angioplasty (PTA) as first-line therapy for superficial femoral and popliteal artery obstructive disease,

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with only provisional stenting as a class I recommendation. In fact, the same guidelines gave a class III recommendation for primary stenting of femoropopliteal disease [6]. In spite of multiple advances in technology and a very satisfying increase in the amount of controlled data in the field, the more recent 2016 ACC/AHA guideline on the management of patients with lower extremity peripheral arterial disease did not clarify this issue any further [7].

Although effective in simple lesions, the primary limitation of PTA in the femoropopliteal vessels is restenosis, with rates ranging from 30 to 80% in the superficial femoral artery (SFA) [3]. Rocha-Singh et al. performed a 2007 analysis that included data from both the PTA control arms of three randomized FDA device trials conducted by industry, as well as a review of the medical literature. They found the 12-month vessel patency rate to equal 33% with a mean lesion length of 8.7 cm [8].

Bare-metal stents (BMS) have improved the 12-month vessel patency rate to the 50–80% range; however, the ultimate patency is still highly dependent on lesion length [3]. Representative examples include the FAST trial, where mean lesion length was 45.2 mm and associated with a 12-month restenosis rate of 32% [9], as compared to the restenosis rate of 46% in the VIASTAR trial with a longer mean lesion length of 173 mm [10]. Figure 1 is a representation of SFA stent trials with independent outcome adjudication that demonstrates a nearly straight-line relationship between patency and lesion length in the SFA.

The Drug-Eluting Stent Era Is Born

Given the triumph of drug-eluting stent (DES) at inhibiting restenosis in the coronary bed, and the attendant need identified in other vascular beds, there was a rapid move to study this technology in the peripheral arterial circulation. Initial efforts mimicking this successful coronary technology using cytostatic sirolimus or its analogs (e.g., everolimus) using a durable polymer met with no definitive outcome improvements in both randomized (STROLL) [12] and single-arm (STRIDES) studies [13]. These agents are generally not resident in the arterial tissue for the necessary time course (months) following implant, hence the need for polymers that elute continuously for the required time. Alternatively, paclitaxel, a lipophilic protein-bound agent, which inhibits neointimal hyperplasia by a cytotoxic mechanism and is retained by the arterial tissue in prolonged fashion without need for modification, has proven effective in the peripheral femoropopliteal circulation. It is incorporated into the ZILVER PTX stent (Cook Medical, Bloomington, IN), which is constructed using a slotted tube open-cell nitinol stent spray-coated on its abluminal surface with paclitaxel (3 μg/mm^2) and is polymer-free. The landmark 2011 ZILVER PTX trial that evaluated the safety and effectiveness of the device was a defining one for DES treatment of PAD [14••]. In that trial, patients were randomly assigned to primary DES implantation with the paclitaxel-eluting stent (n = 236) or PTA (n = 238). The average lesion length was 65 ± 40 mm, with other demographics and lesion characteristics being similar between the two groups. Of the 238 patients assigned to PTA, 120 had acute PTA failure and underwent a secondary randomization to provisional DES (n = 61) or provisional BMS (n = 59). The primary safety end points of the trial were 12-month event-free survival, and the primary effectiveness endpoint was primary patency in the DES and PTA groups. Event-free survival was defined as both adjudicated major adverse events (death, amputation, clinically driven target lesion revascularization (TLR), target limb ischemia requiring surgical intervention, or surgical repair of the target vessel) and worsening of the Rutherford score by two classes, or to class 5 or 6. Primary patency was defined as freedom from duplex-determined binary restenosis plus clinically driven target lesion revascularization. The results of this trial showed that 12-month event-free survival was superior in the primary DES group, as compared with the PTA group (90.4 versus 82.6%; P = 0.004). Furthermore, primary patency was superior in the primary DES group compared to the PTA group (83.1 versus 32.8%; P < 0.001). Patency rates were also superior in the provisional DES group as compared to the provisional BMS group (89.9 versus 73.0%; P = 0.01). Furthermore, these results were sustained through 5 years in an extended follow-up study [15•].

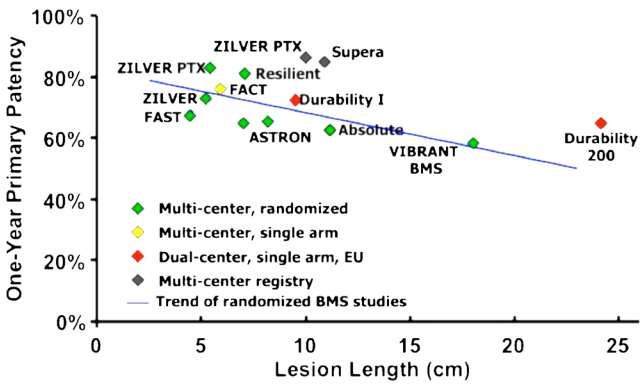

Fig. 1 The relationship between lesion length and 1-year vessel patency in the SFA and popliteal territories. (Reprinted from: Weinstock BS. Vascular Disease Management 2014;11(4):E76-E86, with permission from HMP Communications) [11]

Continued DES Evolution

The Eluvia stent (Boston Scientific, Marlborough, MA) is built on the Innova stent system. It is a self-expanding high-purity nitinol stent constructed using a closed-cell design at

each end of the stent and an open-cell design along the stent body. Eluvia is similar to the Zilver PTX stent in that it uses paclitaxel as its anti-restenosis agent. However, it differs from Zilver PTX in that it is polymer-based (Fig. 2), whereas Zilver PTX is polymer-free. The drug and polymer combination is intended to elute drug, in a controlled fashion, over the first 12 months after implant, which is the period of time when restenosis is most likely to occur [16, 17] (Fig. 3).

In October 2016, the MAJESTIC first-in-human clinical experience evaluating the Eluvia self-expanding paclitaxel-eluting stent was published [18•]. In this prospective, single-arm, multicenter trial, 57 patients with chronic lower limb ischemia and a moderate lesion length (mean 70.8 ± 28.1 mm) in the superficial femoral and/or proximal popliteal arteries were treated with the Eluvia DES. Endpoints were similar to those in Zilver. There were no safety signals or stent fractures noted, and the primary patency at 12 months with the Eluvia DES was a remarkable 96% which, although MAJESTIC was a small trial, is the highest patency rate reported among prior DES trials. Two-year data presented at the 2016 CIRSE meeting in Barcelona demonstrated sustained results, with a 91.3% freedom from TLR by Kaplan-Meier estimate (Fig. 4).

Given the positive results of the MAJESTIC trial, the pivotal IMPERIAL clinical trial was initiated at the start of 2016 and quickly completed its enrollment in approximately 14 months. IMPERIAL is a global, prospective, multicenter trial that randomized patients in a 2:1 fashion to receive the Eluvia or Zilver PTX DES, respectively, and is meant to evaluate the comparative safety and effectiveness of the Eluvia DES versus Zilver PTX for the superficial femoral and/or proximal popliteal artery lesions up to 140 mm in length. It will also have a sub-study that will evaluate longer lesions between 140 and 190 mm in length. This trial plans to enroll up to 535 patients at up to 75 sites worldwide and provide up to 5 years of follow-up [20]. Given the lack of head-to-head data available among the multitude of devices available for SFA/popliteal disease, this comparative trial is a welcome advent in the endovascular therapies category.

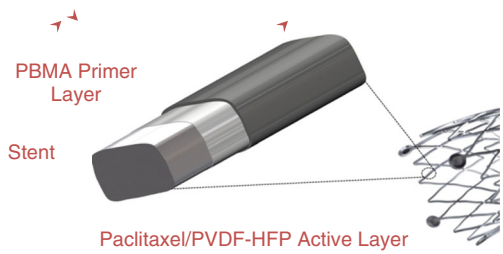

Fig. 2 Eluvia coating stent design demonstrating the dual polymer construction. The primer layer promotes adhesion of the active layer to the stent surface, and the active layer provides the controlled release of paclitaxel. (With permission from Boston Scientific Corporation)

DES Below the Knee: Special Considerations

Infrapopliteal arterial disease, while increasingly prevalent, remains difficult to treat endovascularly due to the small caliber of these vessels, the length of disease, and the marked degree of calcification present in many cases, especially in diabetics and renal failure patients. Three major trials published in 2012 paved the way for our understanding of drug-eluting stents in this challenging arterial bed.

The ACHILLES trial [21] was a prospective, randomized, multicenter comparison of PTA versus the balloon-expandable Cypher SELECT polymeric sirolimus-eluting stent (SES) in the treatment of symptomatic infrapopliteal arterial disease, most of which was in the proximal third of the circulation. A total of 200 patients were enrolled in a 1:1 randomization, and the total infrapopliteal lesion length was relatively short for this vascular bed at 27 ± 21 mm. The trial's primary endpoint was in-segment binary restenosis as measured by follow-up quantitative angiography through 12 months, which were significantly lower among the SES-arm patients compared to the PTA-arm patients (22.4 versus 41.9%; $P = 0.019$).

Next, the YUKON-BTX trial [22], a prospective, double-blind, randomized multicenter study, compared a polymer-free SES to the same placebo-coated BMS for the treatment of intermittent claudication and critical limb ischemia. The trial randomized 161 patients with Rutherford-Becker categories 3 to 5 PAD. Importantly, lesions were focal and short, with a mean lesion length of 31 ± 9 mm. The primary endpoint was 1-year primary patency, which was defined as freedom from in-stent restenosis (luminal narrowing of ≥ 50%) detected by duplex ultrasound or angiography. Primary patency rates at 1 year were significantly higher in the SES group than in the BMS group (80.6 versus 55.6%; $P = 0.004$). This finding was further substantiated by an extended follow-up study looking at event-free survival for the next 1100 days after stenting the aforementioned 161 patients. Event-free survival rates, defined as freedom from target limb amputation, target vessel revascularization, myocardial infarction, and death, were 65.8% in the SES group and 44.6% in the BMS group ($P = 0.02$) [23].

Finally, the DESTINY trial [24], also a prospective, multicenter trial compared DES to BMS for below-the-knee PAD with primary outcome measures of 1-year primary patency rates and target lesion revascularization. DESTINY randomized patients to the Xience V, an everolimus-eluting stent (EES) with a durable polymer versus the Multi-Link Vision BMS. Patency at 12 months was defined as the absence of ≥ 50% restenosis based on quantitative angiography. The results showed 1-year primary patency rates were 85 versus 54% ($P = 0.0001$) and TLR was 9 versus 34% ($P = 0.001$) with DES versus BMS, respectively. In summary, drug-eluting stents can be utilized in the tibial arteries and appear to improve vessel patency compared with angioplasty alone.

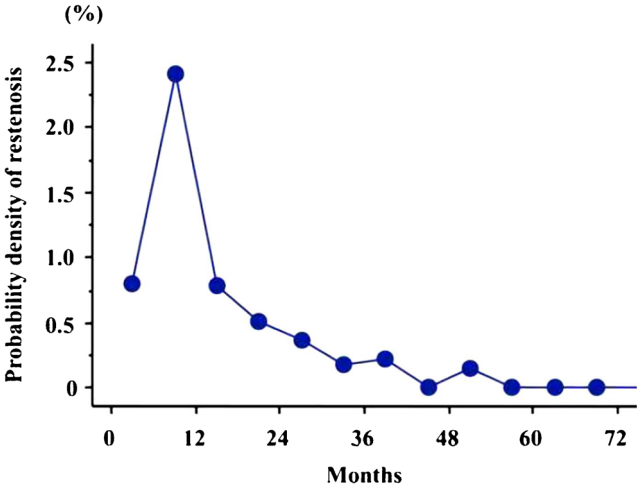

Fig. 3 Restenosis following SFA intervention appears to peak between 6 and 12 months. (With permission from: Iida O et al. Catheter Cardiovasc Interv. 2011 Oct 1;78(4):611–7) [16]

Bioresorbable Scaffolds

Although bioresorbable scaffolds (BRS) have not had nearly as big an impact in the coronary circulation after approval as metallic DES did, they nevertheless have attractive features for the lower limb such as drug delivery capability and flexibility/biodegradability which minimizes/eliminates the potential issue of stent fracture.

Above the knee, data for BRS is mixed. Several devices have failed to show effectiveness and have been abandoned without a publication trail. The Abbott Vascular bioresorbable everolimus-eluting vascular scaffold (BVS) was tested in 35 patients with external iliac [4] and SFA (31) disease in the ESPRIT I study [25]. Although lesion length was quite limited (36 mm), the 1- and 2-year binary restenosis rates were nevertheless promising at 12.1 and 16.1%, respectively. Subsequent analysis found that the BVS that were undersized relative to the reference vessel performed suboptimally, raising the possibility of even better results if such procedural elements are better controlled. The status of this program remains unclear.

Most recently, data for bioresorbable vascular scaffolds in the treatment of below-the-knee PAD has revealed encouraging results. Varcoe et al. reported on their investigation of the everolimus-eluting bioresorbable vascular scaffold for the indication of focal tibial and distal popliteal lesions [26]. Thirty-eight limbs in 33 patients were treated for either critical limb ischemia or severe claudication. Mean lesion length was 19.2 ± 11.6 mm. Patients had Doppler ultrasound performed at 1, 3, 6, 12, and 24 months for the detection of binary restenosis. During a mean follow-up of 12 ± 3.9 months, five patients died and the remainder was available for the follow-up analysis. They reported a primary patency rate of 96 and 84.6% at 12 and 24 months, respectively [21], which compares favorably to historical controls.

Conclusions

Endovascular interventions for the treatment of PAD have come a long way since their inception. In the past 5 years, drug-eluting stent technologies have materially improved the stubborn restenosis rates of the PTA and earlier stent eras. As outlined in the results above, drug-eluting stents serve an important role both in above and below-the-knee PAD treatment. Drug-eluting stent trials have reported 12-month primary patency rates either nearing or exceeding 90%, with second generation stents such as Eluvia poised to potentially improve on these results. The ultimate contribution of bioresorbable scaffolds remains unclear at this time. Compared to the results seen with BMS and/or PTA alone, endovascular interventions

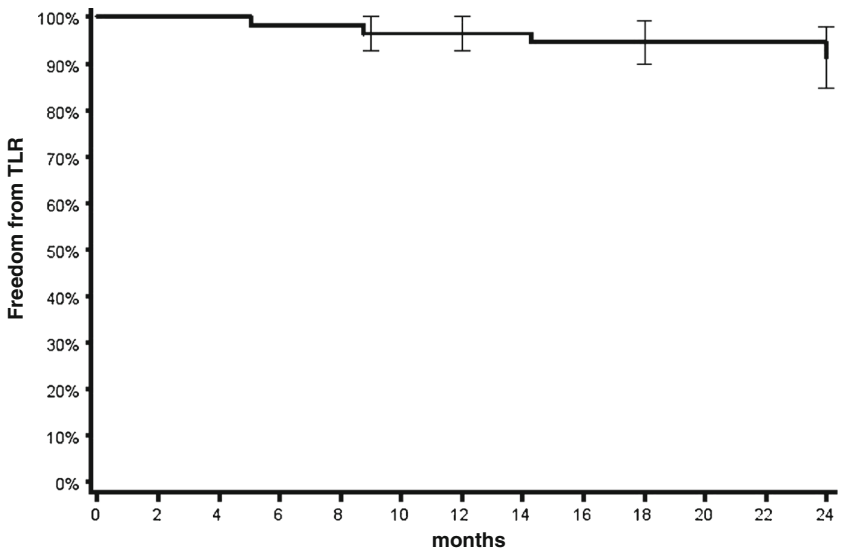

Fig. 4 Results for the MAJESTIC trial, demonstrating a ~ 92% freedom from TLR at 24 months with the Eluvia drug-eluting stent for SFA and popliteal artery disease. (From: Muller-Hulsbeck, presented at CIRSE 2016) [19]

with drug-eluting stents hold a promising future for improved hard outcomes as well as the all-important quality-of-life metrics for our patients with PAD and possibly for cost-effectiveness.

Compliance with Ethical Standards

Conflict of Interest Roi Altit declares no conflict of interest.

William A. Gray reports personal fees and institutional research support from Boston Scientific Corporation, Medtronic, and Spectranetics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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