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Stefan Müller-Hülsbeck

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TECHNOLOGY EVALUATION

Eluvia™ peripheral stent system for the treatment of peripheral lesions above the knee

Stefan Müller-Hülsbeck

Department of Diagnostic and Interventional Radiology /Neuroradiology, Ev. Luth. Diakonissenanstalt Flensburg, Flensburg, Germany

ABSTRACT

Introduction: Drug-eluting stents promise to reduce restenosis following endovascular treatment of diseased arteries, but technologies used in peripheral arteries of the leg have not yet achieved desired success rates.

Areas covered: The rationale behind the development of the Eluvia™ Drug-Eluting Vascular Stent (Boston Scientific, Marlborough, MA) is described and current preclinical and clinical evidence related to use of the stent is reviewed.

Expert opinion: Stents remain an important endovascular treatment option for femoropopliteal lesions, especially those that are long, occluded, and calcified. Drug-eluting stent technologies show promise to improve patency rates, potentially shifting the primary treatment preference away from balloon-based treatment. The available preclinical and clinical data on treatment with Eluvia™ suggest that prolonged paclitaxel elution in the femoropopliteal arteries prevents restenosis and may reduce the need for reintervention.

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1. Overview of the market

Peripheral arterial disease (PAD) is estimated to affect more than 200 million people worldwide, with prevalence expected to increase [1]. PAD of the lower extremities is associated with a significant clinical burden. Results from a registry initiated in 2003 showed that approximately one-third of symptomatic PAD patients had at least one vascular-related hospitalization during the 2-year follow-up period, and repeat hospitalizations are common [2].

Stent placement is one of the chief endovascular approaches for treating stenotic lesions of the peripheral arteries located above the knee (i.e. superficial femoral [SFA] and proximal popliteal arteries). In the registry noted above, nearly 10% of symptomatic PAD patients had at least one hospitalization associated with peripheral angioplasty/stenting within 2 years [2]. However, durability of the intervention is limited due to proliferative biological responses that promote neointimal formation, leading to restenosis or occlusion of the treated territory. Comorbidities such as diabetes and certain lesion characteristics increase risk of restenosis. Restenosis may necessitate reintervention (i.e. target lesion revascularization [TLR]) to maintain vessel patency. Drug-eluting stents provide a means to deliver an antiproliferative agent directly to the arterial tissue, thereby reducing incidence of restenosis and reintervention. In the coronary arteries, drug-eluting stent use has been highly successful, with associated TLR rates less than 2% at 1 year postprocedure [3]. The technology has not transferred directly to the peripheral arteries, however, because the drug delivery technology used in the coronary arteries has not been suitably tailored to the unique requirements of the SFA. Thus, observed reintervention rates following implantation of drug-eluting stents in the femoropopliteal segment are substantially higher at 10–20% [4–6].

The Eluvia™ Drug-Eluting Vascular Stent (Boston Scientific, Marlborough, MA) was designed to address demands specific to treating above-the-knee peripheral artery lesions, taking into consideration the mechanical and pathological conditions unique to this anatomy. Coronary arteries and the SFA are both considered muscular arteries, but the mechanical environment of the femoropopliteal segment differs dramatically from that of the coronary arteries. As the largest unsupported artery in the body, the SFA undergoes repetitive deformations along multiple axes during movements such as walking, sitting, standing, or climbing stairs (reviewed in [7]). This challenging mechanical environment highlights the need for a durable scaffold to predictably deliver an active pharmaceutical agent to the diseased vessel. Along with the differences in mechanical environments, preclinical studies indicate that the SFA has a lower ratio of collagen to elastin compared with coronary vessels [8], which may contribute to differential disease progression. Additionally, bone-like osteoid metaplasia present in the calcified SFA [9] mandates that the dosing of the active pharmaceutical agent is appropriate to mitigate neointimal proliferation.

Disease progression was also a consideration for the design of a purpose-built drug-eluting stent for the SFA.

CONTACT Stefan Müller-Hülsbeck muehue@diako.de Department of Diagnostic and Interventional Radiology /Neuroradiology, Ev. Luth. Diakonissenanstalt Flensburg, Knuthstr. 1, Flensburg 24939, Germany

Article highlights

- Restenosis following stent placement to treat atherosclerotic lesions in the femoropopliteal segment occurs over a longer time period than that observed following coronary stenting, necessitating a prolonged drug elution profile.
- A polymeric carrier was needed to control the duration and dose of drug released from the stent, and the fluoropolymer PVDF-HFP has a proven safety record.
- Current clinical data involving the Eluvia™ stent suggest that the polymer/drug dose combination results in an antirestenotic effect during the period when peripheral restenosis is typically observed, leading to a high clinical vessel patency rate.
- Confirmatory results from ongoing preclinical and clinical studies are anticipated.

Restenosis after endovascular therapy follows a predictable response akin to wound healing, the time course of which is dictated by the biological milieu. In the coronary environment, this time period is 60–90 days [10,11]. However, the timing of restenosis in the challenging SFA environment seems to follow a longer duration [12]. The implications of these differences for drug delivery are central to how coatings for drug-eluting stents are designed.

2. How the technology works

2.1. Device overview

The Eluvia™ stent comprises a self-expanding nitinol stent platform with a coating composed of a polymer system with an antiproliferative active pharmaceutical agent (Figure 1). The geometry of the base stent is such that it provides sufficient force and flexibility to the scaffold while ensuring that it can withstand the mechanical forces of the femoropopliteal segment, in addition to providing uniform drug coverage along the artery length and around its circumference. The stent coating consists of a primer layer, poly *n*-butyl methacrylate (PBMA), which promotes adhesion of the active layer. The active layer is composed of the fluoropolymer PVDF-HFP [poly(vinylidene fluoride-*co*-hexafluoropropylene)] and the antiproliferative agent paclitaxel [13].

2.2. Antiproliferative agent and dosing strategy

Paclitaxel, a microtubule stabilizer, was chosen for its demonstrated antirestenotic effect on peripheral arteries [4,14,15]. Although '-limus' drugs (e.g. everolimus, sirolimus) are effective in coronary arteries, previous attempts to use them in the SFA have been ineffective. The failure of previous attempts with '-limus' analogs in the SFA may have been confounded by design factors such as lack of durability of the base scaffold, use of polymers that lacked good biocompatibility, or selection of a drug-elution profile that did not match the restenotic cascade [5,6].

The dosing strategy was based on recognition that coronary and femoropopliteal arteries have similar cell biology and respond with similar antiproliferative mechanisms upon exposure to paclitaxel. However, peripheral atherosclerotic disease contains more calcium and less lipid than coronary lesions [9,16,17], and the SFA is more prone to chronic occlusions. To counteract reduced paclitaxel bioavailability in the SFA due to these differences in tissue [8] and disease composition, a dosing approach including a relatively greater total amount of released drug was adopted. Release profiles of multiple paclitaxel doses were evaluated preclinically before a dose of 0.167 µg paclitaxel/ mm^2 stent surface area was chosen for clinical testing [13,18].

2.3. Polymer selection and elution profile

A polymeric carrier was chosen in order to provide control over the dose and duration of drug release. The base polymer (PBMA) and the fluoropolymer PVDF-HFP comprise the same polymer system as is present on the Promus Element (Boston Scientific, Marlborough, MA) and the Xience V (Abbot Vascular, Abbott Park, IL) drug-eluting coronary stents [3,19] and thus its clinical safety has been studied in more than 11,000 patients. Biocompatibility of the PBMA plus PVDF-HFP system was also demonstrated in preclinical studies. The polymer demonstrated a good vascular safety profile in a porcine coronary artery stenting model [19] and did not inhibit endothelialization (i.e. healing) in a rabbit peripheral artery stenting model or promote thrombus formation in a bench blood loop model

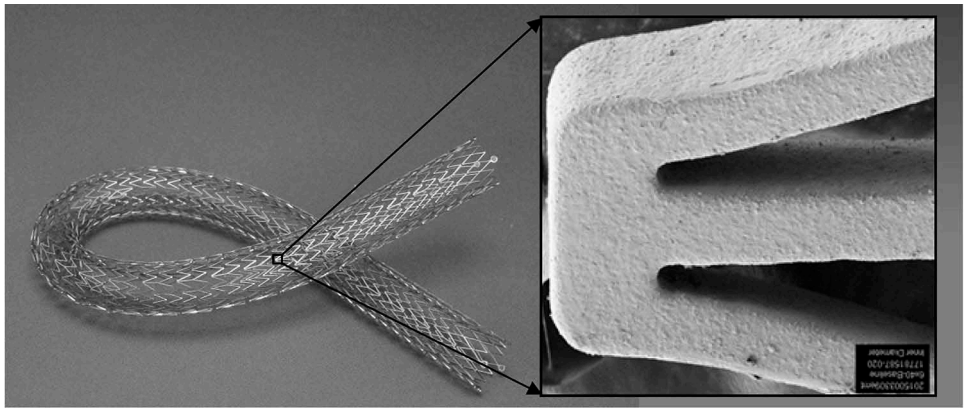

Figure 1. Photograph of an Eluvia™ drug-eluting stent and a scanning electron microscope image of a stent strut (150x magnification). Images provided courtesy of Boston Scientific.

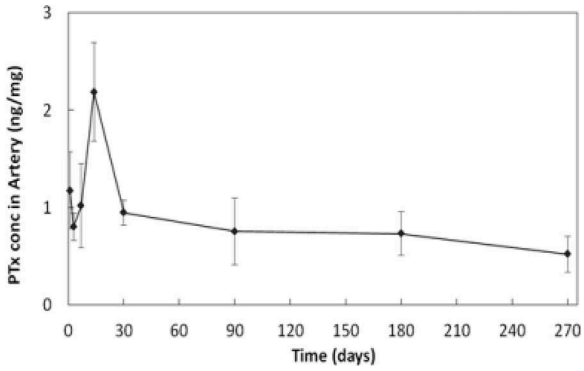

Figure 2. Paclitaxel concentration in stented swine arterial tissue. Boston Scientific data on file. Image provided courtesy of Boston Scientific. ©2016 Boston Scientific Corporation or its affiliates. All rights reserved.

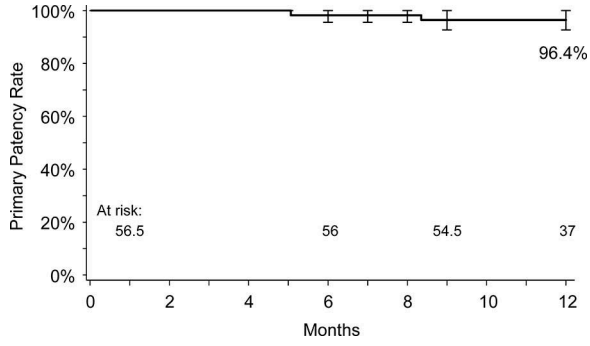

Figure 3. Kaplan-Meier estimate of primary patency at 12 months in the MAJESTIC trial. Adapted from Müller-Hülsbeck S, Keirse K, Zeller T, et al. Twelve Month Results from the MAJESTIC Trial of the Eluvia™ Paclitaxel-Eluting Stent for Treatment of Obstructive Femoropopliteal Disease. J Endovasc Ther 2016, doi: 10.1177/1526602816650206.

[20]. The ability to alter the polymer to enable different concentrations of drug in a preclinical model was also a critical aspect in the polymer system selection. In addition to drug release and biocompatibility considerations, the ideal polymer coating would withstand the extreme mechanical forces of the femoropopliteal segment and not require additional forces for deployment. Researchers at Boston Scientific evaluated multiple biostable and biodegradable polymers and determined that PVDF-HFP performed within desired parameters in tests of drug release and deployment forces, and the coating demonstrated durability during deployment and fatigue testing.

Given that restenosis incidence following stenting of the SFA peaks at about 12 months [12] – later than occurs following coronary stenting – and that the underlying restenotic cascade has a multiphase time course [21], an elution profile to overlap disease progression through at least 12 months was targeted. The pharmacokinetic profile of the selected dose through 6 months has been described by Hou et al. [13] and is shown through 270 days in Figure 2.

3. Clinical profile

Performance of the Eluvia™ stent in preclinical and clinical studies suggests that the elution profile and dose resulting from the polymer/paclitaxel combination translates into a clinically meaningful antirestenotic effect. In a porcine iliofemoral model of the vascular response to stenting, inhibition of neointimal proliferation was greater with the polymer/paclitaxel combination than with a bare metal stent through 90 days, but healing was not impeded [13]. In addition, preliminary imaging (optical coherence tomography) data from a porcine model of restenosis suggest that neointimal inhibition caused by Eluvia™ may be greater than that associated with a polymer-free paclitaxel-coated stent at 90 days [22]. Histopathologic analysis in this ongoing study is forthcoming.

The prospective single-arm MAJESTIC study included 57 symptomatic patients with stenotic or occluded lesions of the SFA and/or proximal popliteal artery who were treated with the Eluvia™ stent. By 1 year postimplant, only two patients required a revascularization procedure to address blockage of the original target lesion, leaving 96% of patients with patent stents (Figure 3) [18]. For comparison, reported revascularization-free rates at 1 year average approximately 87% for bare metal stents [23–30] and slightly higher at 90% for a drug-coated stent [4,31] in clinical trials. Procedural angiography images from a patient treated with an Eluvia™ stent in the MAJESTIC trial are shown in Figure 4. Duplex ultrasound evaluation conducted 12 months postimplantation (Figure 5) confirmed patency of the treated area.

Treatment effectiveness with Eluvia™ is undergoing further verification in the global IMPERIAL study, which is currently enrolling patients (ClinicalTrials.gov identifier NCT02574481). Results of this study will reveal whether the encouraging findings from MAJESTIC bear out in a large (>450 patients) randomized single-blind clinical study. Details regarding alternative other technologies is included in the Alternative technologies box.

4. Conclusion

The Eluvia™ stent was designed to perform in the unique environment of the SFA. Its polymeric coating allows for paclitaxel elution over a long period of time to overlap the timeline associated with peripheral arterial restenosis. The available preclinical and clinical data on treatment with Eluvia™ suggest that prolonged paclitaxel elution in the femoropopliteal arteries prevents restenosis and may reduce the need for reintervention.

Alternative technologies box

Drug-coated stents and balloons have shown superiority over standard balloon angioplasty for treating atherosclerotic lesions of the SFA and provide a benchmark for drug-eluting technologies. Primary patency is one measure of treatment effectiveness. Reported patency rates for the polymer-free paclitaxel-eluting stent ZilverPTX (Cook Medical, Bloomington IN) were 83% at 12 months, 75% at 24 months, and 66% at 5 years in a randomized trial [4,32,33]. Patency rates for the In.Pact paclitaxel-coated balloon (Medtronic, Dublin, Ireland) were 82% at 12 months and 79% at 24 months in a randomized trial [34,35] and 84% and 72%, respectively, in a multicenter registry [36,37]. The 12-month patency rate for the Lutonix paclitaxel-coated balloon (Bard, Murray Hill, NJ) was 65% in a randomized trial [38].

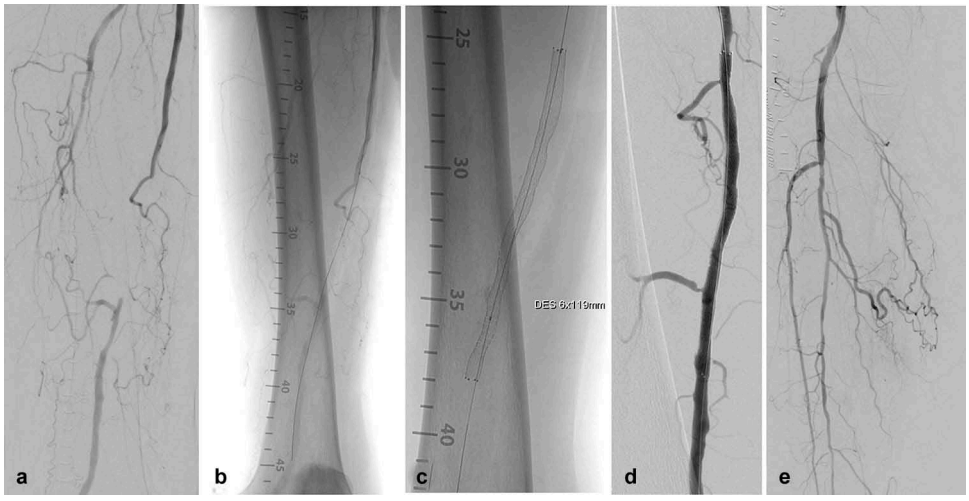

Figure 4. Eluvia™ stent implantation in the MAJESTIC study. The female patient was 73 years old and a current smoker with 100% occluded lesion in the mid-SFA with severe calcification. (A) Baseline angiography of the SFA shows the occlusion of nearly 9 cm in length. (B) Unsubtracted angiography indicates an intraluminal 0.018-inch guidewire crossing. (C) Fluoroscopic view of a 6 x 119 mm Eluvia™ stent. Note the vessel wall calcification located in the mid- and distal part of the successfully treated lesion. (D) Final angiography represents a good technical result without any significant residual stenosis. (E) The run-off is non-compromised and does not show any signs of distal embolization.

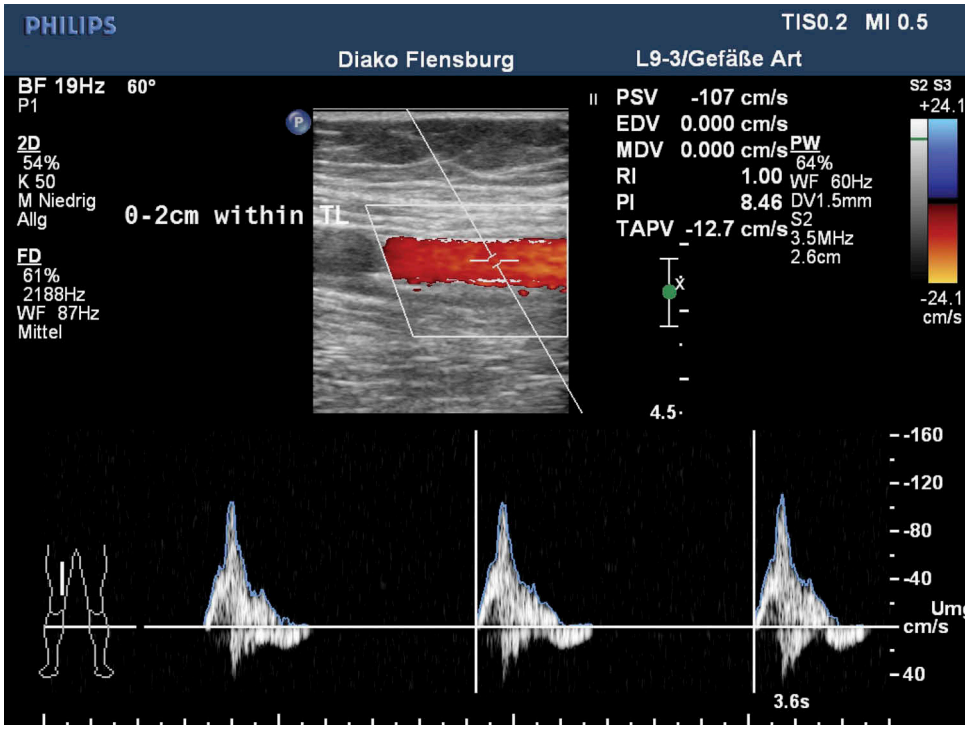

Figure 5. Duplex ultrasound at 12 months post-procedure for the case presented in Figure 4.

5. Expert opinion

A potential disadvantage of stent placement is the possibility of limiting options for future endovascular or surgical interventions. This 'leave nothing behind' philosophy garners support from studies reporting 12-month patency rates for drug-coated balloons similar to those achieved with bare metal stents (i.e. up to approximately 83% [34,36,38]). But is this strategy carrying over into clinical studies and real-world use? Indeed, the SFA lesions treated in trials of drug-coated balloons are less complex, that is more often described as TASCII A or B [39], than those typically treated with stents. Furthermore, stent use is common even in clinical studies intended to assess balloon performance. In one clinical study of a drug-coated balloon which allowed stratification to stent treatment, primary stenting was selected over balloon-only treatment for approximately 25% of patients [40], and in a registry of patients treated with a drug-coated balloon, 23% of patients also had a stent implanted [41]. Provisional stenting rates after acute percutaneous angioplasty (PTA) failure in the

aforementioned and other recent clinical trials averaged approximately 13% [34,36,38,40,42]. In a study designed to compare efficacy of balloon-based PTA with that of a drug-coated stent, 50% of those patients who had been randomly assigned to the PTA arm received provisional stents [4]. The composition of these study cohorts suggests that a substantial proportion of atherosclerotic patients undergoing PTA ultimately requires a stent scaffold. In addition, availability of a stent that provides a high patency and associated very low reintervention rate would mitigate the relevance of the 'future options' argument against a stent-based approach [43]. Together, these observations suggest that performance of drug-eluting stents such as Eluvia™ could challenge the 'leave no implant' philosophy if longer term use continues to demonstrate low reintervention rates.

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Declaration of interest

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