Peripheral Artery Disease

Percutaneous treatment of peripheral artery disease...
stenosis might overestimate the gradient by partial obstruction of the residual lumen. In clinical practice, financial limitations will be the main driver for catheter-based pressure gradients, and in most peripheral interventions, vessel diameters, particularly in the aorta-iliac segment, will allow adequate estimations of the hemodynamic impact of a stenosis with a small catheter (eg, 4F or smaller). Pressure gradients are also useful when assessing balloon angioplasty results and deciding whether further steps like stent implantation are necessary. For example, in the Dutch Iliac Stent Trial,3 optimal angioplasty without a residual pressure gradient had long-term results comparable to primary stenting in short iliac lesions. For femoropopliteal and below-the-knee interventions, the importance of pressure gradient measurement is completely unclear. Because these arteries are smaller, catheter-induced gradients are more likely and pressure wires are probably preferable for assessing the hemodynamic significance of a stenosis in these small arteries.

**Balloon Versus Stent: When Do We Need to Stent?**

In general, stenting offers superior results to PTA in longer lesions (≥6 cm), in chronic total occlusions, and in heavily calcified arteries. Stenting is also indicated if there is a suboptimal result after PTA. PTA alone often requires longer balloon inflations compared with predilation before primary stenting. For example, in several clinical trials, at least 2 inflations of at least 1 minute each were used as minimal inflation times for PTA, whereas some authors have used much longer inflations (eg, 25 minutes) to obtain an acceptable PTA result. Nevertheless, generally accepted indications for stenting are conditions in which PTA does not improve flow to the ischemic area such as a flow-limiting dissection after (long-term inflation) PTA, a residual stenosis <50% leading to flow limitation, acute or subacute recoil >50% leading to flow limitation, and acute or subacute reocclusion after (long-term inflation) PTA.

**Stents Versus PTA in Specific Locations**

**Aortoiliac Arteries**

Long-term outcomes after iliac artery endovascular interventions are similar to outcomes after open surgical revascularization with less morbidity. As a result, most guidelines recommended endovascular treatment as the treatment of first choice for almost all patients with iliac artery obstructions, including complex and long lesions. Rates of restenosis at 1 year range from 5% to 25%, depending on the length and location of the target lesion.9–13 In the Dutch Iliac Stent Trial,9 279 patients were treated either with primary stenting (n=143) or with plain balloon angioplasty (n=136) and selective stenting. Patency at 2 years was similar between primary stenting and balloon angioplasty with selective stenting (71% versus 70%, respectively). In addition, long-term data from this trial on ankle-brachial index, iliac patency, and quality of life did not support a difference between the 2 groups.11 From these data, primary PTA and selective stenting for suboptimal results (eg, a systolic pressure gradient >10 mm Hg in the target vessel) was the recommended strategy for treating iliac arteries.9–13

However, criticisms of the Dutch Iliac Stent Trial include the inclusion of only very short and simple lesions and the fact that stenting may offer greater benefits in more complex disease. It has been further speculated that the introduction of nitinol stents may have improved the results of iliac stenting through a reduced risk of peripheral embolization during the procedure and improved long-term results with respect to the occurrence of restenosis. However, there are as yet no comparative data between balloon-expanding and self-expanding nitinol stents. The only randomized data for iliac nitinol stents come from the multicenter randomized Cordis Randomized Iliac Stent Project—US (CRISP-US) trial2 comparing 203 patients who received either a nitinol self-expanding stent (n=102) or a self-expanding Elgiloy stent (n=101) after suboptimal iliac artery angioplasty. Disappointingly, at 12 months, primary patency was 95% versus 91%, a nonsignificant difference, and functional and hemodynamic outcomes were comparable between the 2 groups. Nevertheless, primary technical success rates were significantly higher in the nitinol stent group (98% versus 88%). From these findings, particularly the excellent 5% restenosis rate at 12 months with nitinol stents,3 many interventionists advocate the use of nitinol stents as the primary endovascular treatment option for iliac artery obstructions. Nevertheless, from a clinical perspective, data on walking distance or limb salvage in patients treated with PTA or different types of stents are still lacking.

**Femoropopliteal Arteries**

The femoropopliteal segment remains the most challenging area with respect to restenosis and reocclusion after endovascular treatment. During movements like walking or stair climbing, various forces are exerted on this vessel, including flexion, longitudinal and lateral compression, and torsion, which may influence long-term outcomes after endovascular treatment. Restenosis rates after PTA vary between 40% and 60% at 1 year,4,15 with up to 70% failure at 1 year after PTA of extensive superficial femoral artery (SFA) disease and angioplasty of lesions <10 cm.15 Balloon-expanding endovascular stents in the femoropopliteal segment resolved the problems of early elastic recoil, residual stenosis, and flow-limiting dissections after plain balloon angioplasty, but 5 randomized, controlled trials failed to demonstrate a beneficial effect of SFA stenting with stainless steel stents compared with plain balloon angioplasty.16–19 Self-expanding nitinol stents offer improved durability in the femoropopliteal segment, and even long segment occlusions respond well to nitinol stenting. Figure 1 shows the restenosis rates of several randomized, controlled trials comparing self-expanding nitinol stents with PTA in the femoropopliteal segment, including the Vienna, ASTRON (astron stent trial), Femoral Artery Stenting Trial (FAST), and A Randomized Study Comparing the Edwards Self-Expanding LifeStent versus Angioplasty-alone In Lesions Involving the SFA and/or Proximal Popliteal Artery (RESILIENT) trials.4,7,20–22 In summary, short lesions with a mean length of up to 6 cm seem to respond well to PTA and should be stented only for flow-limiting dissection or recoil (Figure 1). Lesions of a mean of ≥8 cm showed better patency rates after nitinol stent implantation. In terms of clinical outcomes in claudicants, in the Vienna study,4 patients’ walking...
distance after 1 and 2 years was also improved by the use of stents. Limb salvage rates in patients with critical limb ischemia have not yet been shown to be reduced by the use of stents in the femoropopliteal area.

Below-the-Knee Arteries
Endovascular treatment for below-the-knee arteries is traditionally reserved for patients with critical limb ischemia. This condition is typically characterized by diffuse and long segmental disease of all 3 tibioperoneal arteries rather than by short focal obstructions. Conventional balloon angioplasty with long balloons and long inflation times frequently yields astonishingly good immediate results with the use of modern, low-profile, long-segment angioplasty balloons, which are available in up to 200-mm lengths (Figure 2). The restenosis rate with these long balloons is still considered extremely high, ranging between 60% and 80% at 6 months, although limb salvage rates are in the range of 90% according to the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial and cohort studies. Stenting with BMS, both self-expanding nitinol stents and modern balloon-expanding products, did not improve restenosis rates. Therefore, the use of BMS in below-the-knee arteries was restricted to spot stenting in bailout situations when balloon angioplasty failed. In terms of clinical outcomes like walking distance and limb salvage, data are still lacking.

New Stent Types: Evidence for Durability, Stent Fracture, and Restenosis

New BMS
Many of the initial bare nitinol stents have clinically relevant rates of in-stent restenosis and therefore suboptimal patency rates. Stent fractures, which may increase restenosis, are less frequent with the newer generation of nitinol self-expanding stents. Recent stent improvements designed to decrease stent fracture include rearranging strut alignment toward helical connecting bridges or a full helical stent designs. The second generation of nitinol stents have enhanced flexibility, particularly in the axial direction, owing to fewer cell interconnections and a more spiral orientation of the interconnections. Despite these improvements, there is no definite proof of any impact of stent design on the restenosis rate.

The enhanced flexibility and superior fracture resistance of the latest stent generation, in combination with the production of long nitinol stents of up to 20 cm in length, enable the endovascular treatment of more difficult and complex lesions. Recent registry studies suggest that the newer stent designs may have more acceptable long-term results in the femoral artery. The Leipzig SUPERA (supera stent) registry with 107 SFA lesions demonstrated a 24-month patency rate of 76%23 and no stent fractures were observed. In the Durability-200 Study, the Protégé EverFlex 200-mm-long self-expanding nitinol stent (ev3 Endovascular Inc, Plymouth, MN) was assessed in 100 patients with femoropopliteal TransAtlantic Inter-Society Consensus C and D lesions at least 150 mm in length (average lesion length, 24 mm).24 The primary patency at 12 months was 64.8% (judged by duplex ultrasound imaging).
Another new development is the availability of low-profile self-expanding nitinol stents, which can be deployed via a 4F sheath. Low-profile delivery systems with long shafts also increase the feasibility of treating selected SFA lesions by the transbrachial or transradial approach.

**Drug-Eluting Stents**

The concept of combining the advantages of the mechanical scaffolding properties of nitinol stents with the antiproliferative action of drugs is based on the proven effectiveness of this concept in decreasing restenosis and reintervention in interventional cardiology. Because restenosis is particularly high with femoral-popliteal interventions, DES studies in the peripheral circulation have focused on this territory.

**DES in the Femoropopliteal Arteries**

Only a few trials have been conducted on the use of DES in the femoropopliteal arteries, and the positive results seen in coronary studies could not be reproduced until recently. Two trials using DES releasing limus derivatives failed to demonstrate any advantage in patency compared with BMS. Sirolimus Coated Cordis Self-Expandable Stent (SIROCCO) was the first randomized trial with a DES in the infragenual arteries. It was a multicenter, double-blind study of a sirolimus-eluting self-expanding nitinol stent compared with the same BMS in the SFA. The study was performed in 2 phases because, after an interim analysis demonstrating a rather high stent fracture rate, the maximally allowed lesion length was reduced to 14.5 cm with a maximum of 2 implanted stents. The mean lesion length in the 93 patients included in SIROCCO II was 8.3 cm. At 24 months, the in-stent restenosis rate, measured by duplex ultrasound, in the sirolimus group was 22.9% versus 21.1% in the BMS group (*P*>0.05). The lack of a significant difference between the sirolimus-eluting stent and the BMS may be related to the unexpectedly low restenosis rate in the BMS group. The efficacy of DES may also be limited by incomplete suppression of neointimal hyperplasia between the stent struts, especially with larger stent strut distances.

The Safety and Efficacy Study of the Dynalink-E Everolimus Eluting Peripheral Stent System (STRIDES) was a prospective, nonrandomized, single-arm trial using an everolimus-eluting self-expanding nitinol stent in 104 patients with femoropopliteal disease and a mean lesion length of 9.0 cm. Primary patency defined as freedom from restenosis (>50%) in-stent restenosis was 94% and 68% at 6 and 12 months, respectively, and plain radiographic examination of 122 stents revealed no evidence for stent fracture after 12 months. However, a retrospective comparison with the Vienna Absolute trial demonstrated nearly identical restenosis rates with the corresponding BMS; unfortunately, no formal study has compared these results yet.

The Zilver PTX stent with a polymer-free paclitaxel coating (dose, 3 μg/mm²) on the abluminal side of the stent struts uses a nonlimus drug delivery system. The Zilver PTX Single-Arm Study included 787 patients with implantation of 2.2 stents per patient for a mean lesion length of 100±82 mm, and 22% of the lesions were >15 cm. After 12 months, the fracture rate was 1.5%. The 12-month primary patency rate, evaluated by duplex sonography with a peak systolic velocity ratio of <2.5, was 86.2%. Especially interesting were the data of a subgroup analysis of patients with femoropopliteal in-stent restenosis demonstrating a 1-year primary patency of 80%, which was much higher than in historical controls using other treatment modalities. After 2 years, there was also a sustained clinical benefit concerning improved Rutherford class and improved ankle-brachial index and patient-reported walking distance. The authors concluded that there was an ~50% reduction in restenosis compared with published BMS results.

Recently, the 12-month results of the Zilver PTX Randomized Study were reported. This prospective, randomized, multicenter trial with 479 patients (Zilver PTX, n=241; angioplasty, n=238) had 2 randomization protocols. First, the patients were randomized to treatment with either traditional PTA or the Zilver PTX. In the angioplasty group, about half of the patients had suboptimal angioplasty and underwent secondary randomization to provisional stenting with a Zilver PTX (n=61) or bare metal Zilver (n=59). Inclusion criteria included a maximum lesion length of 14 cm, and the mean lesion length was 63 and 66 mm, respectively. The primary patency rate (with duplex sonography and patency defined by diameter stenosis <50%) was 83.1% in the Zilver PTX group and 65.3% in the optimal PTA group. To examine the drug effect, the investigators conducted a head-to-head comparison of secondary randomization to provisional stenting with Zilver PTX or BMS and found 12-month patency rates of 89.9% and 73%, respectively (*P*=0.01; Figure 3). Stent fractures were rare in both Zilver PTX and BMS patients, with an overall rate of 0.9% through 12 months, and no fractures resulted in clinical sequelae. Very recently, the 24-month update of this randomized trial was reported. The primary patency remained significantly improved in the Zilver PTX arm compared with patients with successful PTA (74.8% versus 57.8%; *P*=0.029).

In terms of clinical end points like walking distance or limb salvage, no data are available yet from randomized, controlled trials.

![Figure 3. Reported patency rates (defined as freedom from restenosis >50%) in the Zilver PTX trial at 12 months using different treatment strategies for femoropopliteal lesions with a mean lesion length of ~6 cm. DES indicates drug-eluting stent; BMS, bare metal stent.](image-url)
**DES in Below-the-Knee Arteries**

Preliminary reports of several single-center nonrandomized studies indicated that sirolimus-eluting stents may reduce the risk of restenosis after infrapopliteal endovascular treatment. The Yukon study was a prospective, randomized, multicenter, double-blind trial in 161 patients comparing a polymer-free sirolimus-eluting stent with a placebo-coated BMS in patients with either intermittent claudication or critical limb ischemia with a de novo lesion (mean lesion length, 31 mm) in an infrapopliteal artery. The 1-year primary patency rate, detected with duplex sonography, was significantly higher in the sirolimus-eluting stent group (80.6%) than in the BMS group (55.6%; \( P = 0.004 \)), and the 1-year secondary patency rates were 91.9% and 71.4% (\( P = 0.005 \)), respectively. The authors concluded that midterm patency rates of focal infrapopliteal lesions are substantially improved with a sirolimus-eluting stent compared with a BMS; unfortunately, clinical outcome data like walking distance for claudicants and limb salvage rates for critical limb ischemia patients are still missing.

The preliminary 12-month results from the Cordis-sponsored Comparing Angioplasty and DES in the Treatment of Subjects With Ischemic Infrapopliteal Arterial Disease Study (ACHILLES), a prospective, randomized, multicenter trial in 200 patients comparing balloon angioplasty and the Cypher Select Plus stent, were recently reported. The mean lesion length was ≈27 mm. After 12 months, the in-segment binary restenosis rate, as measured by quantitative angiography on an intention-to-treat basis, was 19% for the DES arm and 42% for the PTA arm (\( P = 0.006 \)).

The Abbott Vascular-sponsored Drug Eluting Stents in the Critically Ischemic Lower Leg (DESTINY) study is also a randomized, multicenter trial comparing a DES (Xience V with everolimus) and the Multilink Vision BMS in 140 patients with critical limb ischemia and infrapopliteal lesions. The data were recently presented, and there was a significant improvement in the 12-month primary patency rate with Xience V (85%) compared with the Vision (54%). The results of quantitative angiographic analysis after 12 months also demonstrated a statistically significant reduction of in-stent late lumen loss (0.78 versus 1.41 mm; \( P = 0.001 \)).

Looking at these data (Figure 4), we can conclude that the use of DES compared with PTA and BMS in the infrapopliteal vessels enables improved 1-year primary patency rates of at least 80%. However, this morphological improvement has not yet translated into improved clinical parameters such as increased limb salvage rates, decreased patient mortality, or lower rates of clinically driven reintervention. This may also be due to rather low patient numbers within the studies. Furthermore, the issue of stent crushing should be considered because DES are balloon-expandable stents. Currently, they are available only in short lengths, whereas patients with critical limb ischemia, especially diabetics mellitus, mostly have long-distance lesions of the lower-leg arteries.

**Future Development of DES**

A potential future improvement in local drug application for the necessary time span without the disadvantages of permanent stent implantation can be expected by the development of completely bioabsorbable DES. Two main types of bioabsorbable stents currently exist: polymer stents and metallic stents. Polymer stents seem not to be good candidates for endovascular use because of their strut thickness and lack of radial force. Absorbable metal stents have the potential to perform well, although current infrapopliteal studies have yielded unsatisfactory results. To date, no studies with bioabsorbable stents have been conducted in the SFA. Drastic technological improvements are mandatory before absorbable metal stents can be considered for everyday practice.

**Drug-Eluting Balloons**

The concept of using a balloon catheter to deliver an antiproliferative drug directly at the site of injury has gained interest during the last years. The use of DEBs may be an effective alternative to the use of DES because any stentless technology for the improvement of long-term patency is preferable to overcome the drawbacks of stenting. DEBs have a number of advantages over standard angioplasty and stent technologies: homogeneous drug delivery to the vessel wall; drug release without the need to use a polymer, which may induce chronic inflammation; application in locations where stent implantation is not desirable like motion segments in the common femoral or popliteal arteries; and the potential to reduce antiplatelet therapy.

Otherwise, there are potential problems with use of DEBs without further stents, especially in complex lesions, such as the failure to provide a mechanical scaffold for the prevention of acute recoil and the inability to treat dissection flaps. Furthermore, in severely calcified arteries, DEBs might be less effective because lower drug concentrations reach the vessel wall. Another problem could be inhomogeneous drug distribution in eccentric lesions. This limitation may be overcome by combining the use of DEBs with initial atherectomy. Possible drug loss on the way to the target lesion, another potential problem, can probably be prevented with the use of long guiding catheters or sheaths.
Economic aspects also have to be considered. Because DEBs are designed for single inflation only and the treatment of long lesions might necessitate the use of multiple balloons, DEB technology may not be cost-effective in such patients. In the meantime, different methods have been developed by different companies to coat the balloon with an antiproliferative agent. This is important for biological efficacy; therefore, it will be necessary to evaluate the safety and efficacy of each method separately without generalizing study data to the whole group of DEBs. Currently, there is a rapidly increasing clinical study program using DEBs in different locations and indications. Because the available data are very promising, one can expect an increased use of DEB technology over the next years, at least in the treatment of in-stent restenosis.

**DEB in Aortoiliac Arteries**

This new technology has been used only anecdotally in this segment, so systematic data are missing.

**DEB in the Femoropopliteal Arteries**

Three randomized trials have demonstrated a significant improvement in midterm patency with drug-coated balloons compared with plain balloon angioplasty. In the multicenter Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries (THUNDER) trial, 154 patients with femoropopliteal disease were randomized to treatment with standard balloon catheters coated with paclitaxel (3 \( \mu \)g/mm²), uncoated balloons with paclitaxel dissolved in the contrast medium, or uncoated balloons without paclitaxel. At 6 months, the mean angiographic late lumen loss was 1.7±1.8 mm in the control group compared with 0.4±1.2 mm (\( P<0.001 \)) in the group treated with paclitaxel-coated balloons. The rate of revascularization of target lesions at 6 months was 37% in the control group, 4% in the group treated with paclitaxel-coated balloons (\( P<0.001 \) versus control), and 29% in the group treated with paclitaxel in the contrast medium, or uncoated balloons without paclitaxel. At 6 months, the mean angiographic late lumen loss was 1.7±1.8 mm in the control group compared with 0.4±1.2 mm (\( P=0.41 \) versus control); at 24 months, the rates increased to 52%, 15% and 40%, respectively. An efficacy similar to that of the paclitaxel-coated balloon compared with the uncoated balloon was reported in the Femoral Paclitaxel (FemPac) trial including 87 patients. The recently presented Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT I) trial is a randomized, 2-arm study comparing the Moxy DEB (paclitaxel dose, 2 \( \mu \)g/mm²) and standard balloon angioplasty for the treatment of femoropopliteal stenosis in 101 patients (75 after dilatation with a standard balloon and another 26 with a stent after insufficient PTA results). The primary end point of late lumen loss at 6 months was significantly reduced from 1.09 to 0.46 mm by the DEB. Clinical outcome data showing beneficial effects on walking distance and limb salvage are still missing.

**DEBs in Below-the-Knee Lesions**

Below-the-knee arteries seem to be a good indication for DEBs because of the presence of mostly long lesions in small vessels and the well-known high recurrence rate after PTA with uncoated balloons. However, compared with the femoropopliteal region, the advantage of DEBs in below-the-knee interventions has still to be demonstrated by randomized trials. Initial registry data from Leipzig in 107 patients with long lesions (mean lesion length, 17 cm) demonstrated an impressive reduction of restenosis after 3 months from 69% with a standard PTA balloon to 31% with the IN.PACT Amphilron paclitaxel-coated balloon. Several other studies using different devices are currently ongoing or planned.

**Atherectomy**

The principle of atherectomy is based on plaque removal to increase the gain in lumen size with intervention. Although several atherectomy systems have been developed, there are significant risks of complications (perforation and embolization), and none has convincingly improved clinical results beyond balloon and stent technologies. Currently, 3 main atherectomy systems are available, mainly with the goal of reducing the need for stenting in critical locations close to joints. The limited data available come almost exclusively from femoropopliteal applications and focus only on restenosis rates; again, clinical outcome data are missing.

**SilverHawk Atherectomy**

In a recent small, randomized, controlled trial comparing 29 patients treated by filter-protected atherectomy and 29 patients treated with balloon angioplasty, target lesion revascularization at 12 months was 16.7% versus 11.1%, respectively (\( P=NS \)). Secondary stenting was performed in 62% of the patients in the balloon angioplasty group versus 28% in the atherectomy group (\( P=0.017 \)). Thus, atherectomy offered no improvement in clinical results compared with balloon angioplasty other than the reduced need for stents. Although the SilverHawk device is approved for femoropopliteal use in the United States, no larger studies have compared this device with balloon angioplasty or stents. In ongoing studies, atherectomy in conjunction with DEB is under investigation as a potentially promising concept for avoiding stents in difficult locations such as lesions across joints that experience repeated flexion and other forces.

**Rotational Atherectomy**

Several rotational atherectomy systems have been used in femoropopliteal arteries in retrospective patient series. These series suggest a reduced need for stents, but no studies have assessed the efficacy of rotational atherectomy compared with PTA.

**Excimer Laser Atherectomy**

Laser atherectomy was introduced 2 decades ago for peripheral interventions but has not been tested in a published randomized trials. Current data do not allow the recommendation of laser for endovascular peripheral artery disease treatment, and further studies are necessary.

**Covered Versus Noncovered Stents**

The concept of covered stent graft implantation within the native artery to exclude the disease seems appealing, and stent grafts have been evaluated for several years in iliac and femoropopliteal locations. In patients with acute vascular...
rupture and bleeding, covered stents are live-saving tools and are considered mandatory equipment for all catheterization laboratories (Figure 5). However, it is uncertain whether covered stent grafts are superior to PTA or conventional stenting in de novo or restenotic lesions.

Two recently published studies favor the use of Viabahn stent grafts for femoral applications. In extremely long lesions (>20 cm), these devices were equivalent to prosthetic bypass surgery, and complication rates seemed to have dramatically decreased as a result of lower profile introducer sizes. Similarly, the devices showed superior results compared with balloon angioplasty in another randomized trial. Nevertheless, it remains to be determined whether the mechanical properties of these devices can withstand the forces exerted in the femoropopliteal segment and whether acute and subacute stent graft thrombosis can be reduced by an active (heparin) coating of the devices.

In our practice, stent grafts are used exclusively for bailout bleeding situations.

Conclusions
Several novel technologies have become available recently for peripheral artery interventions. Unfortunately, comparative prospective data are still lacking for many devices. From the current perspective, the concepts for restenosis prevention by DES and DEBs are under systematic investigation, and preliminary data from randomized trials show promising short-term outcomes in certain indications. Nevertheless, PTA and BMS remain standard treatments for aortoiliac, femoropopliteal, and below-the-knee interventions with acceptable results in many situations.

Disclosures
None.

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