

## **PVD I: MANAGEMENT OF INFRAINGUINAL DISEASE**

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### **Summary**

- The overall volume of percutaneous peripheral arterial procedures is growing but the percentage share for interventional radiologists is declining.
- Only 5% of patients with intermittent claudication will develop critical limb ischemia but approximately 50% of patients with critical limb ischemia will undergo major amputation.
- Long-term patency after femoropopliteal PTA is influenced by lesion length and morphology, outflow status, and presence of diabetes.
- Drug-eluting PTA shows promising initial results
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- PIER, or sub-intimal angioplasty, is a therapeutic option for patients with critical limb ischemia and long-segment infrainguinal arterial occlusions.
- Femoropopliteal stenting generally reserved for salvaging PTA failures and long lesions might have improved mid-term patency compared to PTA.
- Nitinol self-expandable stents are preferable for the femoropopliteal segment.
- Femoropopliteal stent fractures can occur over time, especially with multiple stents and are likely related to increased stent failure.
- Only one ePTFE covered stent (Viabahn) and a single Nitinol stent (Intracoil) have FDA approval for the use in the femoropopliteal artery.
- Multiple ablating atherectomy technologies are available for the treatment of femoro-popliteal and tibial occlusive disease .
- Limited randomized data are available to compare different treatment options.
- Infrapopliteal interventions become increasingly important for limb salvage in critical limb ischemia.

## **INTRODUCTION**

The treatment of peripheral arterial disease (PAD) is steadily evolving into new interventional and surgical technologies in particular for the treatment of infrainguinal arterial occlusive disease. Despite the choice of multiple treatment options and devices, many questions about indication, outcome and cost effectiveness remain. The following text is meant to provide an overview over current treatment options, technologies and devices based on available evidence and the experience and opinions of the authors. Interventional radiologists (IRs) must be familiar with all the available treatments for PAD to continue to manage these patients.

## **PREVALENCE AND CLINICAL MANIFESTATION OF PAD**

Although PAD is a common disease, symptoms vary and many patients do not need treatment (1). Thorough clinical and non-invasive evaluation of patients prior to angiography is important. Treatment should not only be based on anatomic criteria (i.e. the presence of occlusive disease), but more importantly on clinical ground as well as the proposed treatment outcome. Patients who present with PAD, will likely return with the same or a different vascular event (2). It should be obvious that once a patient presents with PAD, an effort should be made to reduce associated cardiovascular risk factors. The two most common risk factors for PAD are smoking and presence of diabetes. Unfortunately it is often uncommon for patients to get appropriate treatment and follow-up (3).

The prevalence of PAD based on non-invasive testing is age dependent (2.5% in patients < 60 years of age, 13% at ages 65-69, 16% at ages 70-74, and 22% at age > 75 (4)). In the US, 5 million people suffer from intermittent claudication (IC), the most common clinical disease presentation of PAD. The underlying mortality due to the cardiovascular risk profile in this patient population is close to 50% in 10 years (5,6). Multi-segment arterial involvement is present in 20% of patients with intermittent claudication and intermittent claudication is five times more common in diabetics than in non-diabetics. Since many patients are asymptomatic, the prevalence of PAD is higher than the prevalence of claudication or other signs of PAD (6).

Chronic critical limb ischemia (CLI) is the progression of IC with persistently recurring rest pain for more than 2 weeks, ulceration, or gangrene at the foot, with an ankle systolic pressure less than 50mmHg (Fontaine III and IV; Rutherford 4-6) (7). In this stage multilevel arterial disease involvement is common. Approximately 5% of patients with IC will progress to CLI over the next 5 years, and the incidence of CLI is estimated at 1 new patient per 1000 population per year (8). The majority of patients with CLI will undergo some form of revascularization procedure, and 50% will eventually require major amputation. The mortality rate of patients with CLI is up to 70% at 5 years (9).

## **CLINICAL INVOLVEMENT OF INTERVENTIONAL RADIOLOGISTS**

In the changing health care environment, IRs are no longer sole providers of endovascular therapies leading to competition with other specialties in the treatment of PAD. In fact a recent review of the relative role of IR in the management of patients with PAD demonstrated a decline of IR performing percutaneous peripheral interventions. Although the absolute number of procedures increased over a 5 year period even for IR, the relative percentage of procedures performed by IR declined from 63% (1997) to 42% (2002). The largest increase in procedure volumes was seen by vascular surgeons (398%) and cardiologists (181%) (10).

In order to maintain a role in treatment of PAD patients, cooperative solutions such as vascular centers or relations to primary care physicians should be sought. IRs must be able to follow patients, be available for pre procedural evaluation, post procedure care, and provide further evaluation and therapy if needed. One way to establish IR as a provider for patients with PAD is to become active in screening and evaluating patients in the SIR sponsored "legs for life" screening program.

## SELECTION OF PATIENTS FOR INFRAINGUINAL INTERVENTION

### Clinical indications

The ideal treatment of patients with IC remains controversial. Randomized clinical trials comparing revascularization with bypass surgery or PTA to exercise found benefit of supervised exercise programs with or without revascularization (11,12).

Seventy-five percent of patients with IC, treated with smoking cessation and a monitored exercise program, can expect improvement or stabilization of their walking distance within 6-12 months (13,14). The remaining 25% of these patients will usually deteriorate to severe chronic ischemia, with the likelihood for amputation in 5 or more years being approximately 10%. The best predictor of deterioration of PAD is an ABI <0.5. Percutaneous treatment of infra-inguinal disease for claudication depends on severity of symptoms, age, co-morbidities, cardiovascular risk factors, and other issues (15-17). Any proposed intervention should be associated with minimal risk and provide acceptable durability.

The incidence of patients with CLI is increasing. These patients need aggressive treatment and approximately 50% will indeed receive some type of revascularization. These patients often have severe multilevel atherosclerotic and infrapopliteal disease. The Trans Atlantic interSocietal Consensus of management of peripheral arterial disease (TASC) working group recommendation on the management of PAD (17) which was recently updated to TASC II is a comprehensive document and should be referred to as an important reference on patient selection and a guide for the various treatment modalities. Compared to the initial TASC I recommendations, TASC II suggests an increased role for endovascular therapy in the infrainguinal segment including longer lesions and more calcified lesions

### Anatomic considerations

In femoropopliteal arteries, the TASC II document introduces useful guidelines for selecting between percutaneous and surgical treatment as follows (recommendation 37):

- Type A lesion: endovascular therapy is treatment of choice;
- Type B lesion: endovascular therapy is preferred;
- Type C lesion: surgical therapy should be considered for low risk patients;
- Type D lesion: surgery is the treatment of choice.

#### Morphological classification of femoropopliteal lesions

##### **TASC-A**

- Single stenosis < 10 cm in length
- Single Occlusion < 5cm in length

##### **TASC-B**

- Multiple lesions (stenosis or occlusion) < 5 cm in length
- Single lesion < 15 cm in length confined to SFA
- Heavily calcified or multiple stenoses < 5 cm in length
- Focal popliteal stenosis

##### **TASC-C**

- Multiple lesions > 15 cm in length
- Recurrent lesion after 2 endovascular therapies

##### **TASC-D**

- Chronic total occlusion of entire CFA or SFA
- Chronic total occlusion of popliteal artery and proximal trifurcation

It is generally agreed that treatment of infrapopliteal arteries should be reserved for patients with CLI. Predictors of improved outcome include shorter lesion and lesser number of vessels treated.

Recently another clinical practice guideline for the diagnosis and treatment of patients with PAD has been completed by the American College of Cardiology (ACC) and American Heart Association (AHA) Task Force and includes recommendations with different level of scientific evidence. The goal of this comprehensive document is to significantly improve the care for patients with PAD. The final version which included input from the Society of Interventional Radiology, and a pocket guide can be downloaded at [www.ACC.org/clinical/guidelines/PAD/index.pdf](http://www.ACC.org/clinical/guidelines/PAD/index.pdf). and should be used as a reference (16).

## **PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA)**

### **Mechanism of PTA**

Balloon PTA causes irreversible overstretching of the vessel wall, fracturing of the diseased intima, plaque and plaque compression. This leads to limited medial tearing with intimal-medial dehiscence, disruption of smooth muscle intracellular junctions, and stretching of the outer adventitial layer (18,19). Cautious selection of appropriate balloon size with 10-20% oversizing is key. Vascular inflammatory reaction plays a crucial role in the progression of atherosclerosis and development of restenosis. Levels of C reactive protein (CRP), serum amyloid A (SAA) and fibrinogen as markers of vascular inflammation are elevated after PTA and less so stenting and its increase predicts restenosis (20,21).

### **Outcome of femoro-popliteal PTA**

Long-term success and morbidity rates of femoro-popliteal PTA vary and are not clearly defined. A metaanalysis of 12 femoropopliteal angioplasty papers performed by Adar et al. demonstrated a five year patency rate of 60% (22). Johnston found a 53% success rate at five years for femoropopliteal stenoses associated with good run-off, but only 31% for stenoses associated with poor run-off (23). For occlusions with good run-off, a success rate of 36% at five years versus 16% with poor run-off was also noted. This compares with a five-year patency rate of about 80% using surgical bypass autologous vein grafts or 38% for synthetic PTFE bypass graft (24, 25). These older reports however do not take into account the refinements of current balloon systems and overall improved technique. Furthermore the lack of uniform reporting standards, small patient numbers, difference in lesion complexity and clinical appearance and the inconsistency in follow-up make comparison to alternate endovascular techniques difficult. In addition the large number of technical factors such as dilatation pressure and duration, balloon to vessel ratio in diameter and length could be of importance but are rarely accounted for. This is highlighted in Dorrucchi's recent literature analysis including 112 studies to provide general information on PTA performance: weighted primary patency averages ranged from 69% (1 year) to 48% (5 year) and were dependent on a) lesion morphology, b) lesion length, c) patency of run-off vessels and d) presence of diabetes. (26)

In general, careful lesion selection is important to avoid technical failures and complications. Recent progressive symptoms or recent change in the morphology of a lesion can alert to the presence of thrombus in the diseased segment which can lead to distal embolization during treatment. Immediate technical failures of PTA are usually related to: 1) an inability to cross the lesion; 2) inability to dilate a lesion; 3) elastic recoil of the lesion; and 4) acute thrombosis related to either spasm or an obstructing intimal flap. The lesions that fail to respond are typically long occlusions (greater than 10cm), eccentric calcified lesions, or vessels with disease at multiple levels (27). Several tools such as stents, aspiration embolectomy, mechanical thrombectomy and local intra-arterial thrombolytic infusions can be used to manage immediate technical failures or complications.

## **Predictors of long-term patency after PTA**

The multicenter STAR registry looked at predictors of long-term patency of femoropopliteal PTA (28) in 219 limbs in 205 patients. Clinical risk factors (the presence of diabetes or renal failure) were associated with a significantly lower patency. A diabetic patient is five-times more likely than a nondiabetic patient to have an occlusion after PTA. Angiographic appearance of lesions can also be a predictor of late failures. If more than one site is treated, there is an increased rate of late failure after PTA. Longer lesions were associated with a lower long-term patency as well. The status of tibial run-off vessels had a more complex relationship to late failures. Patients with patent three run-off vessels did better (eight-fold) than the ones with a single, diseased (50-90% stenosis) run-off vessel. There were no significant differences in patency among patients who had at least one patent tibial vessel. No other morphologic feature, such as occlusion vs. stenosis, had a significant affect on long-term patency. The presence of an intimal flap did not significantly affect late failures. Variables that were not associated with an increase in late failures include: age, sex, aspirin or warfarin (Coumadin), hypertension, CAD, or tobacco use.

The causes of late failures are usually related to: a) progression of the underlying atherosclerotic lesion; b) delayed elastic recoil; or c) restenosis secondary to intimal hyperplasia. The development of intimal hyperplasia is a complex process. There are no predictors for excessive intimal hyperplasia but any trauma to the media leads to smooth muscle cell proliferation, deposition of extracellular matrix and development of intimal hyperplasia (29,30). Smooth muscle cells that have been stimulated migrate from the media through the internal elastic membrane into the intima and begin their mitotic activity within 2-3 days (31,32). Approximately one week after injury, the number of smooth muscle cells reaches its maximum and eventually plateaus. The thickness of the myointimal layer peaks at approximately 8-12 weeks. This process however can be significantly prolonged in diabetic patients. The prevention of intimal hyperplasia after endovascular intervention is one of the major goals of any new treatment modality.

## **Below the Knee Bypass Surgery or PTA**

The primary indication for tibial PTA is limb salvage. Treatment options for patients with tissue loss are often limited. Surgical bypass has long been considered standard of care but remains unsuitable for difficult arterial anatomy, lack of endogenous bypass graft material, extent of tissue loss and comorbidity. One also has to keep in mind that CLI is associated with significant morbidity and mortality possibly preventing surgery (33).

Surgical bypass to tibioperoneal vessels with suitable saphenous vein graft material can have 5 year patency of 60% with limb salvage rates of 80% but can require surgical revision in up to 20% of patients (34).

With the advent of low profile PTA technology even longsegment tibioperoneal disease can be treated. A large single center study followed almost 1000 patients over 5 year period after tibioperoneal PTA and reported a limb salvage rate of 88% with a reintervention rate of 13% (35). This compares favorably with the surgical results. A recent randomized study (BASIL trial) comparing surgery to PTA in patients with CLI and tibioperoneal arterial occlusive disease showed no difference in amputation free survival but found lower costs and decreased hospital stay for the endovascular arm at 1 year. A subgroup analysis however demonstrated a lower amputation rate in patients who lived longer than 6 months (36).

The ultimate goal of any therapy is limb salvage and prevention or reduction of amputation. Unlike endovascular therapy for claudication, longterm patency for tibioperoneal PTA might not be necessary after tissue healing. Technical success rates approach 95%, with limb salvage rates at 2-3 years of 44% - 85% and patency rates as high as 75% (37-43). The absence of "straight-line" run-off vessel portends a poor outcome with infrapopliteal PTA for limb salvage (43).

Some operators will now treat patients with moderate to severe IC and sole presence of tibioperoneal disease.

## **Postprocedural Medical Therapy**

There is strong evidence that routine antiplatelet therapy is indicated after angioplasty. Aspirin has been the mainstay, but not everyone has adequate response to aspirin (44). The CAPRIE study indicated a benefit of treatment of clopidogrel (Plavix) for patients with PAD. The relative risk reduction of any vascular event over the use of aspirin was 24% (45). In patients treated with angioplasty the effect of clopidogrel on the long-term patency of the vessel is unclear. Still, the risk appears low and the drug is probably more effective than aspirin. Since aspirin and clopidogrel work by different mechanisms of platelet inhibition, there likely is some synergy. Therefore aggressive post-PTA treatment would include both aspirin and clopidogrel. The duration of clopidogrel therapy after PTA remains matter of debate.

Routine use of Warfarin (coumadin) is even less clear. There is no large study of coumadin in angioplasty patients. A randomized study of aspirin versus coumadin in 2690 bypass grafts showed no improvement in vessel patency with coumadin compared to aspirin alone (46). The risks associated with coumadin are certainly higher than with aspirin. Coumadin is reserved in our practice for post-PTA patients who are at high risk for thrombosis. Examples of this include patients with recurrent bypass thrombosis, and patients with a known or strongly suspected hypercoagulable state. Occasionally we have used coumadin for patients with recurrent thrombosis of covered SFA stents.

## **PERCUTANEOUS INTENTIONAL EXTRALUMINAL RECANALIZATION (PIER)**

PIER, or subintimal angioplasty, has been refined by Bolia (47) who has performed 1500 procedures in the UK. The principal objective is to create a subintimal dissection space. Utilizing an angled guidewire and a hydrophilic directional catheter, the subintimal space is entered proximal to an occlusion. A wire loop is formed, wire and catheter are advanced until reentry into the true lumen distal to the occlusion is achieved. A balloon is then used to create a lumen in the subintimal space that connects to the true lumen proximal and distal to the lesion being treated. This technique is starting to gain recognition, and an increasing number of operators have adopted this technique.

Subintimal angioplasty should be used primarily in patients with CLI who have long-segment occlusions of infrainguinal vessels. Examples include: long stenoses or occlusions (>30cm) of the SFA or tibial vessels, flush SFA or tibial vessel origin occlusions, occlusions where there is a large proximal collateral that makes entering the occluded segment difficult, cases where attempts at crossing a lesion were complicated by vessel perforation, and in occlusions with reconstitution at a bifurcation or trifurcation. It is particularly useful in long stenoses or occlusions of the SFA (TASC-D) and tibial vessels where conventional angioplasty has poor long term patency. Clinically, the biggest impact of subintimal angioplasty is in chronic critical limb ischemia (CLI). Subintimal angioplasty is at some centers the first line treatment in CLI for up to 65% of patients can be managed with this method without the need for surgery.

Subintimal Angioplasty has also been used for femoropopliteal occlusions in patients with longstanding IC. There has been some skepticism regarding the value and durability of this procedure in patients with intermittent claudication. The most recent article demonstrated that the technique can be of value in patients with intermittent claudication with a reported patency rate of 64% at 60 months (48).

Initial technical success rates of 80-85% have been reported with 50-58% primary patency at 3 years for lesions of a mean length of 11-15cm (49). The length of occlusion does not have a major influence on the technical success or re-occlusion rates. However the lack of randomized trials to compare PIER to surgical bypass or conventional PTA and the fact that higher level technical skills and experience are necessary might reserve this technique for nonsurgical candidates. Furthermore the patency rates after PIER have been reported as low as 30% at 2 years (50).

## CUTTING BALLOONS

Cutting balloons (CB) are PTA balloons that contain a series of thin microtomes attached to a noncompliant balloon. When inflated, these microtomes expand longitudinally into the plaque and vessel wall and deliver a controlled incision resulting in plaque disintegration. In theory CB has advantages in fibrotic or thick walled vessels that are resistant to conventional PTA. Also less force is necessary compared to conventional PTA resulting in theoretical decrease in a neoproliferative response. CB are now available up to 8 mm in diameter (Boston Scientific).

The use of CB remains investigational. They may be of some use in resistant lesions. Examples include recalcitrant calcified stenoses, stenoses occasionally seen inside bypass grafts, thick scar seen at graft anastomoses, or the intimal hyperplasia seen within stents. There is case report evidence suggesting the benefit of CB in in stent restenoses (51-53).

Limited clinical data on infrainguinal intervention are available using the cutting balloon. In a small series, CB devices were found useful in the short term for treatment of peripheral arterial stenoses resistant to conventional PTA (54). CB also proved superior to PTA for treatment of resistant peripheral arterial bypass graft stenosis. In a comparative cohort study, technical success (74% vs. 83%) and 1 year primary patency rate (36% vs 50%) was superior in vein grafts for the CB group (55). Ansel et al. reported salvage of 89.5% of threatened limbs after mean follow-up of 1 year using CB angioplasty in popliteal and infrapopliteal vessels (56). A recent prospectively randomized single center trial comparing CB to PTA in short segment *de novo* SFA lesions did not prove a benefit of CB, In contrary the 6 months US determined restenosis rate was significantly higher in the CB group compared to PTA (62% vs 32%) (57)

Other cutting balloons have come on the market to address the shortcomings of conventional PTA. The AngioSculpt Scoring Balloon Catheter (AngioScore, Inc., Fremont, CA) initially developed for the treatment of complex coronary artery lesions combines a semicompliant balloon with laser cut nitinol scoring wire encircling the balloon in a helical pattern. Current devices are available in 2- to 6-mm diameter and 10- to 40-mm lengths and mainly used in the infrageniculate vessels. Data remain scant. In a small nonrandomized multicenter study 42 patients with CLI treated with the AngioSculpt Scoring Balloon had a procedural success rate of 100%, a secondary dissection rate and stent placement of 10%, and an 86.3% limb salvage rate at 1-year follow-up (58 and *Peeters P et al. PTA advancements: use of AngioSculpt Scoring Balloon for infra-popliteal lesions in patients with critical limb ischemia—12 month results. In Press*)

## DRUG COATED PTA

Neointimal hyperplasia resulting in lumen loss after successful PTA remains the dominant biological process leading to PTA failure. Thus pharmacologic inhibition of neointimal proliferation also the basis for drug-eluting stents seems reasonable to achieve longterm success. Initial trials with paclitaxel coated balloons in coronary in-stent restenosis were followed by two trials investigating treatment of *de novo* and restenotic lesions in the SFA and popliteal arteries. The initial multicenter randomized trial comparing paclitaxel-coated and uncoated balloons (THUNDER) (59) demonstrated that patients in the paclitaxel-coated balloon group had far less late lumen loss and less target lesion revascularization compared to the control group. This difference was maintained over the 2 year follow-up period (15% vs 52%). In the second study (60) late lumen loss in the control group was less, and the difference to the group treated with the coated balloon smaller. The PTA procedure did not differ from performing conventional PTA with similar inflation pressures and 1-minute standard inflation times. An interesting approach would be the balloon drug delivery in combination with atherectomy devices particular in lesions that are deemed of "stent" limits. It has to be pointed out that drug eluting balloons are not commercially available in the US.

## ATHERECTOMY

Atherectomy removes plaque from *de novo* or restenotic lesions of any length. It may be particularly useful in difficult anatomic locations such as ostial disease of the SFA and in the popliteal artery and

trifurcation vessels. Proponents have also used the technique as stand alone treatment for longer diseased segments. Although not approved for this indication it has been successfully used for the treatment of in-stent restenosis. The fact that small atherectomy devices (2mm) are available, it can be used in the tibioperoneal arteries for treatment of chronic critical limb ischemia (61).

During percutaneous atherectomy atherosclerotic plaque and or intimal hyperplasia is mechanically removed. In theory, by physically removing the pathologic process, atherectomy reduces the degree of trauma to the media, reduces the incidence of intimal-medial dehiscence, eliminates the problem of elastic recoil, and acquires material for histologic evaluation. A number of first generation devices (Simpson AtheroCath; Transluminal Endarterectomy Catheter–TEC; Auth Rotablator) have been evaluated in the past, but despite their theoretical advantages, prohibitively high restenosis rates and no definite benefit over PTA could be demonstrated and their use has remained limited.

The **Silverhawk** atherectomy catheter (Fox Hollow, Redwood City, CA) has brought renewed interest in this technology. Approved by the FDA in June 2003 for use in lower extremity arteries, the Silverhawk device consists of a flexible monorail catheter designed to track over a 0.014-inch guide wire. Directional plaque excision is accomplished with a cutting assembly located at the distal end of the catheter, comprised of a battery-operated cutting disc rotating at 8000 rpm contained within a tubular housing with a lateral window. Atheromatous plaque is stored in a distal nose cone compartment, and focal lesions can be treated in a small amount of time. Once the storage compartment is full, the Silverhawk device has to be removed over the 0.014-inch wire, and the atheromatous tissue is removed from the nose cone. Theoretically, the Silverhawk catheter minimizes stretching of the vessel and reduces barotrauma to its wall, because the device does not involve inflation of a balloon, as opposed to older generation atherectomy devices. The Silverhawk device is available in multiple sizes, thus allowing treatment of a wide range of vessel sizes from the common femoral artery to the tibial vessels ( $\geq 2\text{mm}$ ).

#### **Indication and Clinical Studies with the Silverhawk atherectomy**

No randomized studies are available to compare the results of Silverhawk-atherectomy with other well established endovascular treatments.

In the femoropopliteal segment, Zeller et al. have used the Silverhawk device in 52 patients with stable chronic lower limb occlusive disease (62). They used additional PTA or stenting in 58% and 6% of cases respectively. More than 80% of their patient population was free of symptoms after 6 months of follow-up.

In the infrapopliteal arteries, Zeller et al. have also reported their experience in 52 lesions present in 33 patients who had intermittent claudication (49%) or CLI (51%) (63). Twenty-nine percent of lesions required predilation, and additional PTA or stenting was performed in 29% and 4% of cases respectively. Technical success (residual stenosis less than 30%) was achieved in 96% of cases. The restenosis rates (defined as  $>70\%$ ) were 14% and 22% at 3 and 6 months respectively. The cumulative event-free survival rates were 91% at 3 months and 77% at 6 months.

Just recently Kandzari reported the results of a prospective, multi-center registry involving 160 lesions in 74 limbs treated with atherectomy. Treatment included the femoral popliteal as well as the trifurcation vessels. The average plaque excision time was 39 +/- 28 minutes. Eleven percent of patients had to undergo adjunctive angioplasty and 6% adjunctive stent placement. The investigators found no evidence of perforation, embolization or major bleeding. The target revascularization rate was 4% at 6 months. Furthermore, amputation was less extensive than initially planned in 82% of patients at 6 months (64).

The Treating Peripherals with SilverHawk Outcomes Collection (TALON) registry is a multicenter, prospective, nonrandomized, observational database. Recent data from this registry included analysis of 728 patients and 1,517 lesions treated with the SilverHawk catheter. Lesion lengths were approximately 6.3 cm for femoropopliteal and 3.5 cm for tibioperoneal vessels. Approximately 17% of patients required additional therapy including stenting. At 6 and 12 months, the target lesion revascularization was 10% and 21%, respectively, with a durable improvement of the ankle-brachial index (65).

The main limitation to the use of the Silverhawk catheter is the presence of extensive or dense calcification of the arterial wall. It is difficult to cut these in part bulky plaques with the risk of distal embolisation. This risk was recently highlighted by a case series of 10 consecutive patients treated with atherectomy of the femoropopliteal artery in the presence of a distal embolic protection device. The investigator reported debris retrieval in each case (66). The clinical consequence of these atheroemboli and comparison to other endovascular techniques remain unclear. Treatment of longer lesion can add time to the treatment since intermittent removal and cleaning of the device from atherosclerotic material is necessary. Expense is also an issue in particular for the cases where additional PTA or stenting is necessary.

### **New Atherectomy Devices**

New atherectomy devices are being investigated for the use in infrainguinal intervention. The orbital atherectomy System by Cardiovascular Systems is debulking atheroma by using a sanding action of an orbiting diamond-coated crown mounted on the end of a flexible drive shaft, and placed over a .014" guidewire. Orbital atherectomy with the **Diamondback 360°** is conceptually similar to rotational atherectomy (Rotablator, Boston Scientific, Natick, MA) with exception of using an orbital path around the periphery of the lumen, thereby minimizing the risk of deep vascular injury. Market as an effective way to debulk challenging calcified lesions in the femoropopliteal and below-the-knee vessels with any plaque morphology, comparative data are lacking: Recently the prospective, non randomized multi-center study (OASIS trial), to evaluate the efficacy and safety of this device (Diamondback 360°) in peripheral intervention was completed. In 201 lesions (50% calcified), a 4% device related complication rate and a 2.4% TLR at 6 months was reported. Adjunctive therapy (PTA, stent) was necessary in 42%. The device can be used in small infrageniculate vessels due to a low crossing profile. Longterm and comparative results are missing.

The Pathway PV Atherectomy is a new rotational atherectomy device including flushing and aspiration to retrieve atheromatous material and avoid distal embolization. The results of a prospective multicenter study was recently presented enrolling 172 patients with <10cm femoropopliteal lesions. The technical success rate was 99% and TLR at 6 months was 14%. Almost 70% received adjunctive PTA or stent placement (Zeller T, TCT 2008). The value of debulking atherectomy still has to be defined.

### **LASER THERAPY**

Light amplification stimulated by emitted radiation (LASER), has generated more controversy than clinical benefit in the management of PAD in the past. The advent of excimer laser assisted PTA which consists of intense, short pulses of ultraviolet light to achieve penetration, atheroablation and recanalization, has led to renewed interest in LASER technology for the treatment of PAD. The advantage of pulsed laser is the negligible risk of thermal injury compared to the historical hot tip lasers. The 308 nm excimer laser uses flexible fiber optic catheters. Tissue is ablated only if in contact with the laser with no significant surrounding thermal injury.

In the past laser-assisted angioplasty has not proved to be any better than PTA (67-69) and therefore, most interventional radiologists have abandoned this procedure. Renewed interest in laser assisted PTA in CLI of femoropopliteal and tibioperoneal disease comes mainly from the cardiology community. Advances in laser catheter design and technology have lead to increased utilization of laser treatment in complex peripheral arterial disease (70).

Recently, the results of the LACI multi-center trial were published. In this prospective registry, 155 limbs in 145 patients were treated, all of which had critical limb ischemia. Sixty percent of limbs had complete, long segment occlusions with a median total length of 11 cm. Adjunctive balloon angioplasty was performed in 96% and adjunctive stenting was performed in 61% of all lesions. The initial procedural success was 85%. The amputation rate at 6 months was 7%; re-intervention was performed in 15% of patients (71).

Despite these data there are no longterm or comparative data for Excimer laser assisted PTA. Due to the small laser size (2.5 mm maximal diameter) adjuvant PTA and stenting is necessary to achieve adequate lumen. Furthermore the added expense of the device does prevent widespread availability outside the cardiology community.

## **VASCULAR STENTS**

The utilization of stents in femoral-popliteal intervention remains controversial. In order to understand the role of stents in the femoral and popliteal arteries, one has to consider the effect of stents on the arterial physiology. After the stent is deployed into the arterial wall, the metallic surface is coated with a layer of fibrin and the subsequent growth of endothelial cells creates a "neointima". This process of re-endothelialization requires two to six weeks. The implanted stent also induces thrombogenic events, particularly if the stent incompletely apposes the arterial wall. This thrombus formation can prevent the proliferation of endothelial and smooth muscles cells and ultimately lead to stent occlusion. Thrombus formation, however, often is self-limiting if the flow is maintained throughout the stented segment. Another factor to consider is the diameter of the femoral and popliteal arteries. Any endoprosthesis will likely reduce the radius of the vessel and therefore influence the flow velocity (law of Poiseuille). That is the main reason that femoral-popliteal prosthetic bypass grafts less than 6 mm in diameter have a high propensity for occlusion. The importance of a sufficient diameter is also demonstrated in a prospective study using self-expandable stents in the femoral-popliteal segment: arteries with a diameter less than 5 mm had a significantly lower long-term patency rate (72).

The most challenging lesions for femoral-popliteal intervention are the higher-grade lesions (type B to type D), which include long segment stenosis and occlusions. Balloon angioplasty often fails due to recoil or intimal dissection. Stents in these cases appear to be promising to convert early PTA failure into success.

### **Nitinol self-expandable stents**

With the first generation of vascular stents (i.e., Wallstent, Palmaz, Strecker), the results of infra-inguinal stenting have been disappointing in most series due to intimal hyperplasia in the stent or at stent edges that converts early gains into late failures due to thrombosis and subsequent occlusion. Various stent designs used in the past including balloon expandable stents are now largely replaced by new generations of nitinol stents (e.g. Smart, Luminexx, Conformexx, Protégé, Absolute, Life Stent, Dynalink) just to name a few. These new designs allow for better wall apposition with improved radial strength and more precise placement due to minimal dynamic shortening. Clinical experience with these new stents in the femoropopliteal arteries shows initial success over PTA. Non randomized studies have also reported encouraging mid-term results, with 3-year primary patency rates up to 76% for SFA lesions (73). A recent single center randomized study compared primary implantation of nitinol stents to PTA in the SFA. Approximately 50 patients were randomized into each group. Thirty-two percent of patients in the angioplasty arm underwent secondary stenting due to suboptimal PTA results. At 6 months, the angiographic restenosis rate was 24% in the stent group and 43% in the angioplasty group. At 1 year, restenosis as detected by duplex ultrasound was 37% in the stent and 63% in the PTA group demonstrating a clear benefit for SFA stenting (74).

However the initial promising results were confounded by reports of nitinol stent fractures, which were reported for the first time in the SFA in the SIROCCO phase I study (18.1% of stents) (75). The fractures were associated with placement of multiple overlapping stents in long lesions. Scheinert further showed in

the FESTO data that the stent fracture rate with various designs can be as high as 37%. The restenosis rate was four- to sixfold higher in the fracture group compared with the nonfractured group. These fractures rarely occurs with coil stent designs, suggesting that they are more compatible with the biomechanical forces present in the SFA (76). Recently a metanalysis of the current literature confirmed the cumulative incidence of stent fractures ranging from 2% to 65%, i.e. 0.6 to 60 per 1000 person-months. Stent fractures occur more frequently in the distal superficial femoral artery and are common when multiple stents are deployed and overlap. Stent fractures are progressive over time, associated with a higher risk of in-stent restenosis and re-occlusion (77). Thus these fractures are not inconsequential.

These data have have led to reluctance by many operators to commit a patient readily to stents in the femoropopliteal artery. Also, a meta-analysis published by Muradin et al., demonstrated similar long-term patency rates of PTA and stenting in femoropopliteal vessels (78). Stents, however, performed better than PTA alone in more severe femoropopliteal disease, such as occlusions and in patients with CLI. This is echoed in a recent study pooling 10 randomized trials comparing PTA with primary stenting in 1,343 patients with short (mean length 43.3 mm to 45.8 mm) SFA lesions (TASC A). Follow-up duration was 9 to 24 months across trials. While the technical failure rate was higher in the PTA group (17.1% vs 5.9%) and restenosis tended to be lower in the primary stenting group (37.6% vs 45.3%), the primary outcome (TLR) was equivalent between groups as were secondary outcomes such as mortality and amputation. The use of nitinol stents was associated with a higher technical success rate and a trend for lower TVR (Gurm et al: Routine stent implantation vs. percutaneous transluminal angioplasty in femoropopliteal artery disease: A meta-analysis of randomized controlled trials. *Eur Heart J* 2009; in print)

Well designed trials including randomization, multicenter design with independent core lab evaluation are now underway to better define the use of self-expandable nitinol stents in the treatment of infrainguinal occlusive disease and providing level 1 evidence for treatment algorithms. The RESILIENT trial randomizing patients with femoropopliteal disease and lesion length < 150 mm to PTA or Life Science stent implantation, is the first to report preliminary 12 month data. A surprising difference in TLR [54% (PTA); 13% (Stent)] and primary patency [38% (PTA); 80% (Stent)] was found (Katzen B, ISET 2008). Another multicenter trial (FAST trial) randomizing patients to PTA versus Luminexx stent placement however did not find a significant difference in patency or TLR at 12 months (79). Difference in stent design and flexibility might have played an important role in the diverging outcome of those 2 trials. A different study design is followed by the DURABILITY II trial, a single-arm trial design with a point estimate for PTA restenosis in the SFA. The nitinol stent would have to show superior 12-month patency rate compared to a historical PTA point estimate. Furthermore the trials' hypothesis is placement of a single potentially long nitinol stent, (up to 200 mm), may translate into a reduced incidence in stent fractures and, therefore, a reduced 12-month TLR rate. Final results of these trials are eagerly awaited.

Despite continued uncertainty of the role of stents in the infrainguinal segment the initial recommendation (TASC) to reserve stent placement for PTA failure might have to be revisited in light of improved stent technology. Better understanding of biomechanical forces exerted on the SFA, salvage of stent failure and cost benefit evaluations however need to be considered when using a permanently implantable device in the femoropopliteal segment.

### **Stenting of tibioperoneal disease**

There is limited experience using stents in the infrapopliteal vessels. In one study of 24 patients, follow-up included clinical assessment, Doppler sonography and angiography at 12 months. The primary and secondary patency rates at 12 months were 43.5% and 65.2%, respectively (80). Feiring reported in a single center retrospective analysis the outcome of stent placement in 82 patients with claudication or CLI and tibioperoneal disease. Clinical improvement was 96%, (limited) amputation and reintervention in 20% and 5% respectively. The fact that all CLI patients survived the 1 year study period might suggest an overall lower risk group influencing these results (81). The only randomized but single center experience is the study by Rand comparing carbofilm coated short balloonexpandable stents to PTA in infrapopliteal arteries. For the stent group the cumulative primary patency rate at 6 months was 83.7% versus 61.1% for PTA (82). Various stent designs are investigated in the infrapopliteal segment. Nitinol selfexpandable

stents delivered through a 4 Fr sheath showed a high primary patency rate of 80% at 6 months (83). One has to keep in mind that tibioperoneal stenting in limb salvage cases not necessarily requires longterm patency. In 3 months most of the arterial ulcers are healed and provided shortterm patency of the index procedure. Even in cases of restenosis, recurrence of ulcers often does not occur.

A recent study investigated the use of sirolimus coated stents in the treatment of tibioperoneal arterial disease with enrollment of 30 patients in a single center study. The short term limb salvage was 100% with an amputation rate of 6% and a primary patency rate of 96% at 7 months (84).

The verdict about the role of stents as a tool for failed PTA or as a primary treatment is still out. The lack of comparative trials, in particular, a comparison of the outcome of atherectomy, PTA or (drug-eluting) stent placement for failed angioplasty is mandatory in light of an increasing need for durable outcome for the enlarging numbers of patients with CLI.

### **Post stenting medical therapy**

Early stent thrombosis is a rare complication, but in small vessels it is a larger concern. Furthermore, because of intimal hyperplasia and the risk of late stent thrombosis, we believe that more aggressive anticoagulation treatment is beneficial. As a matter of fact most recent studies cited here include daily administration of aspirin (80-100 mg daily) indefinitely and clopidogrel (75 mg daily) ranging from 1-6 months after the intervention. In addition a loading dose of clopidogrel is often given during or before the intervention. Despite its lack of approval for peripheral interventions, clopidogrel is now widely used after femoropopliteal and tibioperoneal stent placement. In general antiplatelet therapy is indicated to reduce the risk of MI, stroke or vascular death in patients with PVD (Level I evidence) (16).

### **Covered Stents**

The main reason to use covered stents in the femoropopliteal segment is to slow intimal hyperplasia, decrease cellular in-growth and ultimately preventing luminal narrowing and occlusion. Stent grafts provide a similar material to the surgically placed prosthetic grafts. The initial experience utilizing an expandable nitinol stent covered with woven polyester, Cragg EndoPro System, demonstrated substantial complication rates and limited patency (85). A prospective multi-center trial of the Hemobahn (Gore Technologies, Phoenix, AZ) utilizing a flexible nitinol stent covered with thin walled radially enforced ePTFE, compared to PTA was never fully published. The initial report included stenting of iliac and femoropopliteal arteries in 141 limbs (86). Ninety percent of all patients were claudicators. Eighty femoral lesions were treated, 72% of these were TASC A or B. Although the technical success rate was 100%, the initial acute thrombosis rate was 4% and the reocclusion rate at one year was reported to be 20%. The primary patency rate was 90% at 6 months and 79% at 12 months, respectively. Deutschmann in a single center study reported disappointing results using the same stent-graft (87). The technical success rate was 94%; the primary patency rate at 3 and 6 months was only 61 and 49%. Twenty-two percent of all patients had early reocclusions at less than 1 month and an additional 49% of all grafts were occluded at an average of 7.6 months. Significant intimal hyperplasia was seen at the leading and trailing edges of the stent and the highest reocclusion rate was seen in stents over 10 cm in length. Saxon as part of the initial trial reported his results and found 2 year patency in the Viabahn group to be significantly better compared to the PTA group (87% versus 25%) (88). At 4 years primary patency of 55% and secondary patency of 79% was maintained without evidence of stent fractures. Clearly devices of 5 mm had an inferior patency of below 40% at 1 year indicating the need for a suitable sized artery (89). The similarity of stent graft materials and synthetic surgically bypass grafts lends itself to the comparison of the two techniques. Indeed Kedora recently published a single center randomized trial enrolling 86 claudicators with femoro-popliteal occlusive disease into Viabahn stentgraft placement or surgical femoro-popliteal bypass graft placement with Dacron or ePTFE grafts (90). The primary patency at 1 year was identical at 73.5% for the endograft and 74.2% for the surgical group demonstrating equality of surgical and endovascular techniques at 1 year in a head to head comparison.

The Viabahn graft is the only endograft and only the second implantable FDA approved device for the SFA. The VIBRANT multicenter randomized trial comparing the Viabahn stent graft to nitinol stents is enrolling patient with long segment lesions (TASC C,D) and looking for a longterm patency comparison at 3 years. Data from this trial will be helpful to determine the role of stent grafts in this patient population.

Recently, SFA endarterectomy was used in combination with the aSpire covered stent (Vascular Architects Inc.) in long (26.2 cm) lesions with 68.6% patency at 16 months (91). This stent is made of a spiral-shaped nitinol frame with open ePTFE covering that allows flexibility for bending and partial covering of the vessel wall to maintain side branch patency. However, 12% of patients in this study needed percutaneous intervention in the follow-up period. Long-term clinical evaluation of the aSpire covered stent as an adjunctive to PTA for long femoropopliteal occlusive lesions is awaited. A recent presentation indicated the disappointing number of reinterventions to preserve primary assisted patency (Lenti M, Society for Vascular Surgery 2006).

In summary, covered stents do appear satisfactory in providing patency rates that are similar or even improved compared to non-covered stents and superior to PTA. Although some advocate the use of covered stents in long-segment femoropopliteal occlusions, further studies are necessary to include newer covered stent designs and cost benefit analysis to assess its role in the treatment of occlusive femoropopliteal arterial disease.

## **DRUG-ELUTING STENTS**

Drug eluting stents are metal stents that contain a drug suppressing intimal hyperplasia embedded in a slow-release polymer. The two main drugs being studied are sirolimus (rapamycin, Wyeth) and paclitaxel. Recent literature on drug-coated stents in the coronary arteries has shown excellent outcomes with low rates of target lesion revascularization at long-term follow-up. There has been one published trial in the SFA (75). In the initial phase of this randomized trial (SIROCCO I) that compared sirolimus-eluting vs. bare SMART stents, 6 month angiographic follow-up demonstrated a statistically improved mean vessel diameter in the sirolimus group, although it failed to show a statistical improvement in restenosis (36 patients). In the extension phase of the same trial (SIROCCO II), 57 additional patients with SFA lesions were randomized to treatment with sirolimus-slow-eluting vs. bare SMART stents. Although there was a trend for inhibition of intimal hyperplasia in the sirolimus group, there were no statistically significant differences among the endpoints between the bare and drug-eluting stent groups (92). A recent multicenter randomized trial sponsored by Cook compares PTA to a drug eluting stent (Zilver, paclitaxel coating) and in case of PTA failure a second randomization to a bare or coated Zilver stent. Preliminary data at 6 months randomizing 30 patient in each arm showed similar event free survival but almost 50% in the PTA group were secondarily randomized to bare or coated stents. The stent fracture rate compared to the SIROCCO trials was very low at 1% (Dake M, TCT 2008). Although initially promising, concluding results are pending.

## **BRACHYTHERAPY**

Restenosis after PTA in the femoro-popliteal segment remains a challenge. The predominant mechanism of neointimal proliferation and hyperplasia seem to be reduced by endovascular brachytherapy utilizing beta and gamma sources as proven to be beneficial in the coronary and peripheral vasculature (93, 94).

In femoropopliteal arteries, radiation can be delivered with either a radiation-filled balloon or a radioactive wire advanced into the affected vessel (95, 96). In the PARIS trial, 40 patients received high-dose gamma radiation (14 Gy) after conventional PTA in SFA lesions averaging almost 10 cm, which resulted in a 6-month angiographic restenosis rate of 17%, and a 12-month clinical restenosis rate of 13% (97). Wolfram et al. used brachytherapy after stenting SFA lesions averaging 12 cm in 33 patients (98). Although they observed a high rate of late thrombotic occlusions that required thrombolysis, only 12% of 33 arteries had in-stent restenosis at 6 months. In a recent 5 year followup study from a prospective randomized endovascular brachytherapy trial in the femoro - popliteal segment assigned patients to endovascular brachytherapy with iridium-192 or no treatment after initial PTA. The initial 6 month beneficial result

showed a significant reduction of restenosis in 102 patients: 29.4% for PTA and brachytherapy vs 56.9% for the PTA alone. At 5 years however the recurrence rate was comparable in both groups (70.5%). The only difference was the time to recurrence which was significantly delayed in the PTA plus endovascular brachytherapy group by approximately 11 months (99).

Thus despite initial encouraging results, brachytherapy might not have the desired longlasting effect. Furthermore the significant logistical ramifications for instituting a brachytherapy program will likely not propel this therapeutic option into mainstream therapy.

## **ENDOVASCULAR CRYOTHERAPY (CRYOPLASTY)**

Cryoplasty, the application of cold thermal energy during balloon angioplasty is a new therapy which addresses two major challenges of conventional balloon angioplasty: early technical failure by intimal dissection or elastic recoil, and late restenosis caused by neointimal proliferation causing negative remodeling. Although arterial stents have addressed the issues of dissection and elastic recoil, a durable solution for neointimal proliferation with restenosis remains elusive. Early experience suggests that targeted delivery of cryotherapy within vessels may have the effect of altering the biologic vascular response, resulting in a more benign healing following balloon injury in a non proliferative fashion (100). Cryoplasty is theoretically more homogeneous and less injurious than standard balloon angioplasty as it causes interstitial saline in the arterial wall to freeze. In vitro and in vivo studies have identified three main effects which are thought to contribute to the beneficial outcome:

- a) A more uniform dilation of the vessel - microfractures weaken the plaque and large tears are avoided;
- b) A reduction in elastic recoil – freezing induced changes in collagen and elastin fibers result in short term loss of vessel elasticity;
- c) Apoptosis – osmotic forces in the presence of ice cause smooth muscle cells to eject water; there is non inflammatory cell death with reduction in neointimal formation and constrictive remodeling (100-102).

Balloon inflation is achieved with nitrous oxide cooling the balloon to -10 degree C. The balloon has an automated inflation time of 20 seconds at 8 ATM. As nitrous oxide is vaporized in the balloon it not only delivers the inflation pressure but also cold thermal energy to the arterial wall. This is delivered via a dedicated system using pressurized cartridges. Standard balloon diameters (2.5 to 8 mm) and balloon lengths of 20, 40, and 60 mm are available.

### ***Indication for Cryoplasty***

Long stenoses, occlusions or in-stent restenosis have been treated in the SFA and other arteries. Cryoplasty may be useful in longer lesions, and areas in which stenting is to be avoided. Also Cryoplasty has the potential for increased durability compared to simple PTA.

In a series of femoropopliteal lesions less than or equal to 15 cm (stenoses or occlusions), Fava et al. had a 93% technical success rate in 15 patients. Follow-up angiography at 6 months showed an insignificant change in residual stenosis, claudication and ABI's improved, and at follow-up angiography at 14 months there was patency in 83.3% (103).

In a study of 102 patients with claudication from 16 participating centers, femoropopliteal lesions (TASC type A, B or C) were treated with a technical success rate of 85.3% reported by Laird et al (104). There was a low dissection rate of 6.9%. In a subset of patients with total occlusions, the technical success rate of cryoplasty alone was 67%; this rate was increased to 100% when adjunctive stent implantation was used. The overall rate of "bailout" stent implantation needed to treat failure of cryoplasty was 8.8%. For all lesion types in this series (stenoses and occlusions), there was a 9 month clinical patency rate of 82.2%.

Recently another study looked at the efficacy of cryoplasty in tibio- peroneal disease intervention. This multi-center registry enrolled over 100 patients. The procedural success was 97% and the freedom from major amputation 93% at 6 months. The estimated amputation rate in this patient population would have been significantly higher at 25% (BTK CHILL Registry, Das T; TCT 2006).

The initial promising results seem to be increasingly questioned. In an enlarged single center patient cohort, the freedom from restenosis rate in successfully treated lesions was strikingly lower from the previous experience reported by the same investigators: 57% at 12 months and 49% at 24 months compared to 82.2% (12 months). In particular, cryoplasty performed poorly in heavily calcified lesions, vein graft lesions, and in-stent restenotic lesions. Excluding these challenging lesion subtypes from the analysis resulted in a freedom-from-restenosis rate of 61% at 12 months and 52% at 24 months. Intention-to-treat analysis further weakened the results to 47% and 38% at 12 and 24 months, respectively (105). This particularly disappointing since the mean lesion length in the study was 3.9 cm (TASC A) which should have resulted in much better patency rates.

Although long term followup as well as randomized comparative trial to alternative options are lacking these recent results are not encouraging to find a role for cryoplasty in the treatment of femoral popliteal disease.

## **CONCLUSION**

In patients with PAD, all therapeutic options should be considered. Many patients in particular with minimal symptoms can be treated with medical management such as progressive walking program and suppression of risk factors. Despite this conservative management, further therapy will be needed in at least 25% of these patients.

Following a baseline non-invasive evaluation, cross – sectional imaging and or diagnostic angiography should be performed since at least a third of patients will demonstrate a lesion amenable to endovascular therapy. The appropriate intervention should be chosen based on the underlying vascular anatomy, the associated risk factors, the availability of a vein for a bypass graft, the patient's desires, and the technical expertise of the physicians involved.

PTA remains the primary treatment tool in the femoro-popliteal and tibial arteries. Use of vascular stents in the femoropopliteal system appears to be beneficial in patients with a sub optimal PTA result and long lesions (TASC C,D). Unfortunately, stents are limited by restenosis and potential fractures. Medical therapy, new generation atherectomy devices, stent-grafts, drug-eluting stents, Laser, brachytherapy, and cryotherapy are all being investigated as means of prolonging the patency. These and other potential tools for endovascular therapy will continue to expand the role of the interventional radiologist in the management of vascular disease.

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