

Vascular calcifications/Expert

Atherosclerosis

Clinical symptomatology

Vascular calcifications (atherosclerosis) can lead to complaints and symptoms as well as a severely diminished quality of life with increasing age. The calcifications essentially lead to an increasingly reduced peripheral blood circulation and result in oxygen deficiency. Occlusion of an arterial blood vessel leads to clinical manifestations such as myocardial infarction when coronary arteries are blocked and stroke when cerebral arteries are blocked.

The leading vascular disease of the limbs is atherosclerosis as well and the abbreviation PAD (= peripheral arterial disease) is often used in the literature.

As a disease, PAD presents with a reduced blood flow and thus a limited oxygen supply to the more distal tissues, which leads to the classic symptomatology of PAD: pain, limited mobility and tissue damage. In more severe PAD, starting with stage III according to Fontaine-Ratschow, which is also defined as CLI (critical limb ischemia), quality of life is significantly reduced, and life expectancy is greatly diminished (www.dga-gefaessmedizin.de/uploads/media/S3_PAVK_15-11-30.pdf). As an example, the following is quoted from the competence network PAVK: The 5-year survival rate with critical limb ischemia (CLI) is less than 50%, which is significantly less than the most common malignant diseases such as breast or colon carcinomas.

The number of patients with PAD is significantly increasing worldwide and thus the proportion of women suffering from PAD is also increasing which should drive research in this area to the forefront.

In the Lancet, a review published by Fowkes et al. in 2013, compared the worldwide prevalence of PAOD between years 2000 and 2010. ^[1] This study showed that the prevalence of PAD has increased considerably in European and North American countries: the worldwide data for PAD in 2010 were 202 million people living with this condition. This prevalence has increased by 23% within the specified 10 years. "Recent studies analyzed occlusive PAD in male patients and found that in the age group of 45-49 years, 3% of patients were symptomatic for PAD; however, in the age group 70-75 years the figure was six times higher". Europe currently has the highest proportion of older people in the world and is expected to retain this leading position for the next 50 years, therefore PAD will remain a serious issue. ^[1]</ref>

The greatest anatomical and therefore therapeutic challenge in PAD is the superficial femoral artery (SFA). The majority of severe and treatable stenoses and occlusions manifest themselves in this region. The superficial femoral artery is susceptible to the development of symptomatic PAD, since two-tier bifurcations are present and, additionally (especially in the adductor canal), enormous bending, compression, rotation and shear forces act on the SFA. ^[2]

The relevance of PAD and several other factors such as an increased prevalence of atherosclerotic

diseases, increasing life expectancy, as well as economic and industrial aspects of the global market for the treatment of this disease have led to a rapid development of diverse technologies in PAD. The most well-known is probably the introduction of stents. Stents are small metal mesh tubing that are very flexible while remaining stable. These stents are folded and inserted into the vessel via a catheter and then usually unfold by retracting an outer sheath surrounding the mesh material. Most of the stents are made of a nickel-titanium alloy, or nitinol for short. They can be uncoated (bare) or coated with medication ("drug-eluting" or "drug-covered").

In the field of peripheral vascular surgery and medicine, interest in endovascular therapies since the 2000s has focused on the introduction of new and innovative revascularization systems, i.e. systems within the vessel "tube" that can expand or dissolve the blockages. The treatment strategy "endovascular first" has become the gold standard for PAD and in most cases open traditional surgery is only performed as a second intervention. There is a rapid development of new technologies for revascularization, especially the SFA. Therefore, in addition to uncoated stents and atherectomy systems, various drug coatings have been and are being further developed globally with great enthusiasm as a means of resorbing the inserted materials.

Here are a few aspects of the background to this technological development: It is based on the fact that the therapy of percutaneous-transluminal balloon angioplasty (or PTA for short in the literature), which was the standard intervention until now, led to significantly high restenosis rates in the affected section of the vessel. Restenosis rates of >70% after one year were reported. Thus, the first stents were compared to PTA. The following table provides an overview:

Table 1: Summary of previous studies on uncoated femoropopliteal implanted "bare metal" stents (BMS)

Study	n=	Design	Lesion length/mm	Primary endpoint	Result @12Months
RESILIENT	134 LIFE stents	RCT Control: PTA	≤160	TLR PSVR>2.5	81.3%
STROLL	250 Smart stents	Non-randomized Single arm	≤150	TLR PSVR>2.0	81.7%
DURABILITY I	151 Everflex stents	Register	≤120	TLR PSVR>2.5	79%
SUPERA SFA	SUPERA stent	Register	≤90	TLR PSVR>2.4	85%
SUPERA 500	495 SUPERA stents	Register	≤126	TLR PSVR>2.4	84%
SUMMIT	EPIC stent	Register	≤69	TLR PSVR>2.5	92%
MUENSTER	441 BMS	Register	≤105	TLR	87.3% 80.3 @ 24 months

Taken from DFG proposal (until Phase II): StenDEB Full Proposal July 2014, E. Schönefeld

One of the first publications on PAD was published in Bern by Baumgartner's research group.^{[3][4]} The first conclusion was that women were underrepresented in the study groups investigated until now, with the usual distribution within the study groups for atherosclerotic vascular diseases being 1/3 women compared to 2/3 men. Independent of this, however, women seemed to be more seriously ill at the onset of the therapy/intervention; i.e. they were in a higher or more severe stage of PAD,

were usually older and their outcome were worse in the short to medium follow-up interval. Bechter-Hugl et al. from Austria then examined the pelvic floor and its vessels, i.e. the more common iliac vessel area and the supply of iliac stents in men versus women.^[5] Again, the results did not allow any causal conclusions to be drawn, but the observation was similar to the Bern results. In the study of Bechter-Hugl et al. women were also older and more seriously ill than the men in the group at the start of therapy, and their outcomes were also worse in the short and medium term.

In the case of PAD several studies could verify sex differences. Some of these studies have raised controversial discussions. These sex differences reflect the challenge of diagnosis and therapeutic consequences of PAD in women. The consensus remains, however, that women are being older at the start of therapy or at the time of intervention. In addition, women are not only older but also suffer from a more advanced stage of PAD.^{[6][7]} Ortmann et al. were able to show that women with critical limb ischemia (CLI) usually suffered from a more severe and diffuse form of atherosclerosis than men, which indicates women would require more extensive intervention (for example, more stents) and are therefore generally speaking more difficult to treat.^[3] Lo et al. also found in a 2014 study that women with PAD who underwent vascular surgery presented with a more advanced stage of the disease.^[8] The results correlate with the studies conducted in Münster: First, a group of endovascular interventions was stratified by sex and re-subanalyzed in 2013 and a group of open femoropopliteal interventions in 2016 were evaluated.^{[9][10]} The presence of risk factors in patients with PAD differed also depending on sex. Men, for example, are more likely to be smokers as compared to women.

Controversial debate is ongoing whether the incidence of diabetes in PAD is different depending on the sex of the patients. While, for example, Ortmann et al. reported a reduced incidence of diabetes in women in one study, the same authors suggested later an increased incidence of secondary diabetic disease in women with PAD.^{[3][6][7]}

In result-oriented studies, post-interventional and post-operative results were worse in women with PAD.^{[6][7]} In 2013, the Journal of Cardiovascular Surgery published a study evaluating primary femoropopliteal stent implantation in a large population of Belgian and Münster patients.^[9] A total of 517 patients were prospectively enrolled in the study between September 2006 and August 2010. Data evaluation was performed in a statistical model (time-to-event model). The evaluation with sex stratification based on a Cox regression analysis was published in 2015 from the same group.^[10] The primary study endpoint was to evaluate the primary stenting. Secondary endpoints included secondary patency, leg preservation and overall mortality. Both patient groups (male and female) showed similar primary patency rates after 5 years (64.3% versus 58.1%, $p=0.11$). A statistically significant difference between the male (M) and female (F) population was detected with benefit for M in secondary patency (71.9% versus 66.8% after 5 years; $p=0.005$). Limb preservation showed no differences between M and F (83.3% vs. 82.6%; $p=0.63$), although women were significantly older and had significantly more cardiovascular risk factors at the start of endovascular therapy (68.5 years ± 9.7 SD vs. 74.3 years ± 9.6 SD, $p<0.001$).

Subgroup analysis showed a higher incidence of CLI (critical limb ischemia or stage III and IV according to Fontaine Ratschow) in women (32.1% vs. 16.9%; $p<0.001$). TASC classification (the TASC classification encompasses lesion morphology, i.e. the appearance of the constriction; e.g. how long? How narrow? Complete obstruction?) was comparable between men and women ($p=0.52$), although complete obstruction and involvement of deeper vascular segments were more common in women ($p=0.04$ and $p=0.001$). The analysis indicated that the female sex was an independent risk factor for restenosis in the higher-grade findings (i.e. TASC C and D lesions with a primary patency (PP for short) of 39.8% vs. 62.0%, $p=0.002$).

517 patients, of which 333 were male and 184 were female, could be included and analyzed according to sex. It was noticed that in addition to the more severe PAD of the women, their average age was also significantly higher (74.3 years vs. 68.5 years, $p < 0.001$). Among men, only nicotine consumption was significantly higher with regard to comorbidities compared to women. Both patient groups showed similar primary patency rates after 5 years: 64.3% vs. 58.1% in women, $p = 0.11$. A statistically significant difference between the male (M) and female (F) population was detected with

benefit for M in secondary patency (71.9% vs. An odds ratio (OR) of 1.5 was calculated for the female sex, meaning that women have a 1.5-fold increased risk of developing secondary re-occlusion or re-stenosis in the surgical site. Secondary in this case means despite further intervention or re-intervention.

Limb preservation showed no difference between men and women, which could be reflected in corresponding amputation rates (1.5% each; $p = 0.83$). Neither overall mortality ($p = 0.63$) nor 30-day mortality showed significant differences between men and women.

Summary of the results

Endovascular treatment of femoropopliteal disease by stent implantation shows no sex difference in the long term. However, poorer secondary patency rates were observed in women, also an independent risk factor for developing restenosis in TASC C/D lesions. In addition, it would be beneficial to prospectively randomize drug-eluting and uncoated stents in women.

From a morphological perspective, histological processing of PAD material shows a typical light microscopic image. No sex differences are found here; as is the case in coronary arteries, for example. The distribution of PAOD processes may be more diffuse in females, but the development, dynamics and image do not show any differences in comparison to male vessels.

Literature

[Click here to expand literature references.](#)

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