CLINICAL PRACTICE GUIDELINE

The Diagnosis and Treatment of Peripheral Arterial Vascular Disease

Holger Lawall, Peter Huppert, Christine Espinola-Klein, Gerhard Rümenapf

SUMMARY

Background: In peripheral arterial occlusive disease (PAOD), arterial stenosis or occlusion impairs perfusion in the territory of the distal portion of the aorta and the iliac and leg arteries. In Germany, the prevalence of PAOD rises with age, reaching 20% among persons over age 70.

Methods: This guideline was prepared by a collaboration of 22 medical specialty societies and two patient self-help organizations on the basis of pertinent publications that were retrieved by a systematic search in PubMed for articles that appeared from 2008 to April 2014, with a subsequent update to May 2015.

Results: 294 articles were assessed, including 34 systematic reviews and 98 randomized controlled trials (RCTs). The diagnostic assessment of PAOD is based on physical examination, blood pressure at the ankles, and color-coded duplex ultrasonography (grade A recommendation). Other tomographic imaging methods can be used for suitable indications. The main elements of the treatment of PAOD are the control of cardiovascular risk factors and structured vascular exercise (grade A recommendation). Acetylsalicylic acid and statins are the main drugs for symptomatic PAOD (grade A recommendation). Patients with claudication and correlated structural findings can undergo an endovascular or open surgical procedure. Critical ischemia is an indication for arterial revascularization as soon as possible (grade A recommendation); this may be performed either by open surgery or by an endovascular procedure of one of the types that are now undergoing rapid development, or one of the crural treatment options. There is inadequate evidence concerning the optimal drug regimen after revascularization procedures.

Conclusion: The diagnostic assessment of PAOD is based on physical examination, measurement of the ankle-brachial index (ABI), and duplex ultrasonography. Acetylsalicylic acid and statins are indicated for patients with symptomatic PAOD. Endovascular procedures should be used if indicated. Randomized studies are needed to provide better evidence on many open questions in the treatment of PAOD.

► Cite this as:

Lawall H, Huppert P, Espinola-Klein C, Rümenapf G: Clinical practice guideline: The diagnosis and treatment of peripheral arterial vascular disease. *Dtsch Arztebl Int* 2016; 113: 729–36. DOI: 10.3238/arztebl.2016.0729

In peripheral arterial occlusive disease (PAOD), perfusion is impaired in the territory of the distal portion of the aorta and/or the pelvic, femoral and crural arteries because of a narrowing (stenosis) or complete blockage (occlusion) of the arterial lumen. By far the most important cause of PAOD is atherosclerosis. More than 200 million persons around the world have PAOD (defined as an ankle-brachial index less than 0.9), and the number is growing (1). In Germany, the prevalence of PAOD rises with age, reaching 20% among persons over age 70 (2). Only 25% of persons with PAOD have symptoms (3).

The first German S3 guideline on the diagnosis and treatment of PAOD appeared in 2009 (4). Its recommendations have now been reassessed by an interdisciplinary group of experts under the leadership of the German Society of Angiology (*Deutsche Gesellschaft für Angiologie*, DGA). The many changes in the treatment of PAOD since 2009 are mainly due to the widespread introduction of new endovascular techniques.

The goal of this update was not just to provide current, evidence-based recommendations on the diagnosis, treatment, and post-interventional care of PAOD, but also to propose a new approach to the use of arterial revascularization procedures, differing from the exclusively morphological TASC criteria that have been used to date for this purpose (3) in Germany as elsewhere. The TransAtlantic Inter-Society Consensus (TASC) classifies PAOD on the basis of its radiological appearance. Because of the rapid development of endovascular techniques, the TASC criteria for the choice of treatment are now partly out of date.

The current state of the evidence on the treatment of PAOD is poor. Large-scale randomized controlled trials (RCTs) are still lacking that might conclusively answer the important open questions on endovascular and open surgical treatment and on post-interventional care, including the question of the optimal post-interventional drug regimen. Such trials are needed if there is to be better evidential support for the recommendations contained in this guideline.

Methods

The process of creating the guideline

The existing S3 guideline on PAOD was updated in a multistep nominal procedure by 24 collaborating

Cardiovascular Department Ettlingen, Max Grundig Klinik Bühlerhöhe: Dr. med. Lawall

Department of Diagnostic and Interventional Radiology, Klinikum Darmstadt GmbH: Prof. Dr. med. Huppert

Department of Cardiology I – Medical Clinic for Cardiology, Angiology and Intensive Care, University Medical Center, Johannes Gutenberg University Mainz: Prof. Dr. med. Espinola-Klein

Clinic for Vascular Surgery, Diakonissen-Stiftungs-Krankenhaus Speyer: Prof. Dr. med. Rümenapf

The course and results of the systematic literature search. AHA, American Heart Association; ESC, European Society of Cardiology; NICE, National Institute for Health and Care Excellence

FIGURE 1

medical specialty societies and patient organizations (*eBox 1*). The long version of the guideline can be seen online (5).

The guideline-creating procedure was based on the regulatory framework of the Association of Scientific Medical Societies in Germany (AWMF, *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*). Recommendations were formulated under the moderation of an AWMF representative (Prof. I. Kopp, Marburg) and confirmed by a consensus procedure (>75% approval required). Each recommendation was given one of three different grades, whose differing strengths were expressed by the three German verbs “soll,” “sollte,” and “kann” (roughly: “must,” “should,” and “may”). The recommendations presented here were assessed on the basis of a systematic literature review and unanimously approved. For questions of central importance on which no evidence at all was available, a recommendation was given on the basis of expert consensus.

Literature review and evidence assessment

The database of the Guidelines International Network was systematically searched for national and international guidelines published after the closure date of the old S3 guideline (2009) and up to the date of the search, i.e., 30 April 2014.

Potential reference guidelines were selected on the basis of the methodological quality criteria summarized in the German Instrument for the Evaluation of

Guidelines (DELBI, *Deutsches Leitlinien-Bewertungsinstrument*). Moreover, all available new systematic Cochrane Reviews since April 2009 were examined, chapter by chapter, for pertinent information. A systematic literature search was carried out in the Medline, PubMed, and DIMDI databases for the period 2008 to April 2014 (*Figure 1*). Relevant guidelines, reviews, and RCTs that were published up to 30 May 2015 were analyzed. From this date onward until the date of publication of the guideline, no further major changes were made in the recommendations. Evidence levels were characterized according to the Oxford scheme, described in 2009 (6).

Epidemiology

The prevalence of PAOD is 3–10% (2). Among persons aged 70 and above in Germany, its prevalence is 20%. Nearly 75% of persons with PAOD, of whatever age, have no symptoms (7). Most younger patients with PAOD are men, but the sexes are about equally represented among older patients (8).

Symptomatic PAOD is divided into the stage of intermittent claudication (IC), i.e., pain that arises on movement of the affected limb(s), and the stage of critical limb ischemia (CLI), with pain at rest and ulcer formation (*Table 1*). Patients in the CLI stage are at a significantly higher risk of undergoing a major amputation within 1 year (25% without arterial revascularization vs. 8% with successful arterial revascularization) (3, 9).

TABLE 1

Classification of PAOD: Fontaine stages and Rutherford categories

Fontaine		Rutherford		
Stage	Clinical manifestations	Grade	Category	Clinical manifestations
I	asymptomatic	0	0	asymptomatic
II a	can walk > 200 m	I	1	mild claudication
II b	can walk < 200 m	I	2	moderate claudication
		I	3	severe claudication
III	ischemic pain at rest	II	4	ischemic pain at rest
IV	ulcer, gangrene	III	5	small area of necrosis
		III	6	large area of necrosis

PAOD, peripheral arterial occlusive disease

The number of hospital admissions for CLI in Germany rose by 32% from 2005 to 2009 (10). A further rise is predicted because of the aging of the population.

Prognosis

Among patients with IC, walking ability worsens in about 25%, while the symptoms remain stable in about 50%. The risk that IC will progress to CLI is very low. Only 2% of patients with IC undergo a major amputation within 10 years (3).

Predictors for PAOD and for major amputation include advanced age, diabetes mellitus, male sex, and smoking (11). Patients with PAOD have significantly elevated cardiovascular morbidity and mortality. Overt PAOD is associated with a threefold risk elevation for myocardial infarction (odds ratio [OR] 3.3 [2.1; 5.0]) and a fourfold risk elevation for stroke (OR 4.2 [1.8; 9.5]) (12). The 5-year mortality of patients with asymptomatic PAOD is 19%; that of patients with symptomatic PAOD is 24% (11).

Nationwide health care data reveal that patients with PAOD are still undertreated with respect to their risk factors and accompanying illnesses. In one study (13), 37% of 4298 patients who underwent an amputation because of PAOD had not previously undergone either an angiogram or a revascularization procedure.

Diagnostic evaluation

History and physical examination

The relevant history includes cardiovascular risk factors and atherosclerotic comorbidities. Typical symptoms of PAOD are exercise-induced muscle pain in the lower limb(s) (IC) and pain at rest and/or trophic lesions in the foot (CLI). The pulses in the lower limbs should always be examined, but palpable pulses do not rule out PAOD. The trophic state of the skin, the temperature of the limbs, muscle bulk and strength, and the shape of the feet should all be examined and described.

All patients with PAOD should undergo regular clinical examination of the feet (grade A recommendation, level 1 evidence).

The ankle-brachial index (ABI)

Determination of the ABI by non-invasive measurement of the double occlusion pressure is a suitable test for detecting PAOD (3). The ABI value with the lower arterial pressure at the ankle is the one to be taken for diagnostic purposes (14). A value below 0.9 at rest establishes the diagnosis of PAOD (4, 15).

In patients with a proximal occlusion and adequate collateral circulation, the ABI at rest may be normal; a decline by more than 20% on exercise in a patient with intermittent claudication establishes the diagnosis of PAOD (15). If the ABI values are implausible, e.g., in patients with medial calcific sclerosis, the toe brachial index (TBI) should be used instead (16).

Imaging studies

Color-coded duplex ultrasonography is the imaging method of choice for the aorta and the iliac and femoral arteries (17). If the vessels are well seen and the findings are unambiguous, color-coded duplex ultrasonography is the only imaging study needed before either the initiation of conservative treatment or angiography with the option of proceeding to an interventional procedure (e1).

Further imaging studies (contrast-enhanced MR angiography [MRA], CT angiography, and digital subtraction angiography) are indicated if the findings might have additional implications for treatment, or if color-coded duplex ultrasonography is unavailable or has yielded unclear findings. Contrast-enhanced MRA is the study of choice in this situation (Figure 2).

The interdisciplinary care of PAOD patients involves angiologists, vascular surgeons, interventional radiologists, and (depending on the accompanying illnesses) diabetologists, cardiologists, and nephrologists.

The indication for any diagnostic angiographic procedure should be agreed upon in an interdisciplinary conference (consensus recommendation).

Treatment goals

The main objectives of treatment are the control of cardiovascular risk factors and accompanying illnesses

FIGURE 2

Diagnostic algorithm for peripheral arterial occlusive disease.

ABI, ankle-brachial index; CCDU, color-coded duplex ultrasonography; ce-MRA, contrast-enhanced magnetic resonance angiography; CO₂-angio, carbon dioxide angiography; CTA, computed tomography angiography ;i.a. DSA, intra-arterial digital subtraction angiography; PTA, percutaneous transluminal angioplasty; RI, renal insufficiency

and the improvement of peripheral blood flow in patients with symptomatic PAOD. Depending on the clinical stage, the focus of treatment may lie on cardiovascular risk reduction, improved walking ability to keep the patient mobile, improved quality of life (IC), or limb retention (CLI).

Vascular surgical and endovascular-interventional arterial reconstruction procedures for patients with PAOD should be decided upon by an interdisciplinary team in consideration of the stage of disease and the degree of difficulty and invasiveness, risks, and expected outcome of the procedure (consensus recommendation).

Fundamentals of treatment

The basic treatment of PAOD consists of structured vascular exercise, smoking cessation, and the control of cardiovascular risk factors.

For patients with symptomatic PAOD, secondary prevention with a platelet aggregation inhibitor is indicated (18).

For diabetic patients, assessment and treatment of diabetes is indicated. Diabetics with PAOD have a high risk of developing diabetic foot syndrome (19) and a high risk of amputation (OR 1.5 [1.4; 1.54]) (13). The target values for glycemic control should be adjusted to the patient's age, comorbidities, and life expectancy (20). No target value for LDL-cholesterol is given, because intervention trials in patients with PAOD and elevated cholesterol levels are lacking. All PAOD patients should be given a statin unless this is contraindicated (21). Omega-3 fatty acids and nicotinic acid preparations have no effect on morbidity and mortality.

PAOD patients with high blood pressure should be given antihypertensive drugs, with a target blood pressure below 140/90 mmHg (22). ACE inhibitors improve walking performance (23). Beta-blockers are not contraindicated in patients with PAOD. The main therapeutic recommendations are listed in *Table 2*.

TABLE 2

Recommendations on conservative treatment, revascularization, and post-interventional care in PAOD*

	Grade	LoE
Smokers should be offered a program consisting of medical care, group therapy, smoking cessation, and a cigarette substitute.	A	1
For the secondary prevention of cardiovascular events, a statin is indicated for patients with PAOD and a platelet function inhibitor (ASA, clopidogrel) for patients with symptomatic PAOD.	A	1
Structured walking exercises under supervision and regular instruction should be offered to all PAOD patients with intermittent claudication as part of their basic treatment.	A	1
Cilostazol or naftidrofuryl should be given in the claudication stage only if the patient's quality of life is markedly impaired, he or she can walk no farther than 200 m at most, and walking exercises can be performed only to a limited extent or not at all.	Consensus	1
Patients with critical limb ischemia and infection should be given systemic antibiotics.	A	2
An endovascular procedure should be offered to a patient with intermittent claudication only after the patient has been thoroughly informed about the benefits of risk factor modification and structured walking exercises, and if the stenotic or occlusive lesion seems amenable to endovascular treatment.	Consensus	2
Stenoses and occlusions of the aorto-iliac arteries should be treated endovascularly at first, whatever the TASC stage. The patient's accompanying illnesses and personal preferences should be considered, along with the local availability of high-quality vascular surgical and/or endovascular interventional care.	B	GCP
In patients with critical limb ischemia (CLI), the endovascular treatment of proximal and distal lesions has the highest priority, provided that the predicted short- and long-term symptomatic improvement after endovascular treatment is the same as that after a vascular surgical procedure. Proximal lesions should be treated first.	A	2
Stenoses and occlusions of the femoropopliteal arteries, regardless of their TASC classification, should primarily be treated endovascularly. A bypass is preferable if the following criteria are met: long-segment occlusion (TASC D), no elevation of surgical risk, life expectancy at least two years, and availability of a donor vein.	B	2
Vascular surgery should be used to treat complex, long-segment stenoses and occlusions of the infra-popliteal arteries, when endovascular treatment has failed, when the patient's symptoms persist, or when a suitable bypass vein is available.	Consensus	GCP
All patients should be given ASA (100 mg) or clopidogrel pre-, peri-, and postinterventionally(/-operatively). This treatment should be continued over the long term unless contraindicated.	A	1
After infra-inguinal endovascular treatment with stent implantation, it is recommended that ASA be given temporarily in combination with clopidogrel to improve the patency rate.	Consensus	GCP
Patients with an infra-inguinal, femoropopliteal, or distal venous bypass should not routinely be given oral anticoagulant drugs (OACs).	A	2
Patients with PAOD should undergo regular clinical follow-up with regard to the symptoms and signs of PAOD (walking performance, pain at rest, trophic disturbances).	B	3

*Note: further recommendations can be found in eTables 1–3.

ASA, acetylsalicylic acid; GCP, good clinical practice; LoE, level of evidence; PAOD, peripheral arterial occlusive disease; TASC, TransAtlantic Inter-Society Consensus

Vascular exercise and drug treatment

The treatment of choice for patients with PAOD and IC is vascular exercise, which consists of regular exercise training, walking exercises, and gymnastic exercises under professional guidance.

Structured walking exercises are the main non-pharmacological treatment and should be used in combination with the rigorous treatment of cardiovascular risk factors. In prospective studies, the performance of structured walking exercises under professional guidance for at least three months significantly increased the distance that patients were able to walk (by 109 m; 95% confidence interval [CI], 38–180 m) and significantly improved their quality of life (MD 2.15; 95% CI 1.26–3.04) (24). The functional long-term outcome of a vascular intervention as the sole treatment for

patients with claudication is no better than that of structured walking exercises (25, 26). Thus, professionally guided structured walking exercises should be offered to all patients with PAOD as part of their basic treatment (grade A recommendation, level 1 evidence).

Pharmacotherapy

Vasoactive drugs should be given in the claudication stage if the patient's quality of life is markedly impaired and walking exercises can be performed only to a limited extent or not at all.

Randomized drug trials have documented that only two drugs, cilostazol and naftidrofuryl, can significantly increase the distance patients are able to walk (27, 28). There is inadequate evidence for the benefit of pentoxifylline, L-arginine, buflomedil or ginkgo biloba in

Algorithm for the treatment of patients with critical limb ischemia.

*drugs, wound care, elimination of local pressure, analgesia, antibiotics if indicated

FIGURE 3

patients with claudication. The same holds for other alternative treatment methods.

Prostanoids have been considered a treatment option for patients with critical ischemia who cannot undergo a revascularization procedure, but their benefit is unclear (29). There is no current evidence-based alternative to arterial revascularization for these patients. Their treatment should be based on pain therapy, antibiotics in case of infection, and structured wound care.

Arterial revascularization

Endovascular and surgical treatment

Arterial reconstruction, whether by endovascular intervention or by open vascular surgery, is a type of symptomatic treatment and does not solve the underlying problem of progressive arteriosclerosis. Arterial reconstruction is not indicated for asymptomatic patients. It should be performed in patients with intermittent claudication only for strict indications, as the primary treatment outcome is no better over the long term than that of conservative treatment with vascular exercise (25, 26). The main criterion is the impairment of the patient's quality of life by the lessened mobility due to pain.

Invasive treatments should be decided upon by an interdisciplinary team in consideration of their degree of difficulty and invasiveness, risks, and expected outcomes. The clinical stage, the morphology and complexity of the vascular lesions, the accompanying illnesses, and the patient's individual wishes about treatment should all be taken into account.

The reality of patient care today presents a somewhat different picture. Liberalization of the strict indications for invasive procedures is supported in current international guidelines (30, 31): specifically, it is stated that low-risk balloon angioplasty of the aorto-iliac and femoro-popliteal arteries or thromboendarterectomy (TEA) of the femoral artery bifurcation to treat occlusion

of the common femoral artery can be offered without any prior trial of conservative treatment.

Patients with CLI should undergo revascularization as soon as possible, depending on the extent of tissue loss and inflammatory activity. There is an algorithm for treatment decisions (Figure 3). Revascularization should be attempted by all available means before proceeding to amputation. In planned amputations, the level of amputation should be chosen in consideration of the prospects for wound healing, rehabilitation, and restoration of the patient's quality of life.

Endovascular and open surgical revascularization are complementary techniques. The use of one or the other depends on the site, length, and complexity of the vascular lesion, as well as on the available therapeutic expertise and equipment and the wishes of the patient. Neither technique is clearly preferable to the other; the current state of the evidence on this question is poor (32). Hybrid procedures are feasible and reasonable, in suitable cases, as a means of reducing risks while simultaneously sparing resources (33).

For any occlusive process at any site, an endovascular procedure should always be preferred if its expected technical and clinical outcome is comparable to that of open surgery (9, 34).

Thus, endovascular revascularization is to be preferred whenever the expected short-term and long-term symptomatic improvement is comparable to that of an open vascular surgical procedure (grade A recommendation, level 2 evidence).

For lesions at multiple levels, the elimination of obstacles to inflow has priority over the treatment of more distal lesions. Structured walking exercises should be offered along with invasive treatment (26).

For patients with IC, definite indications for surgery include occlusions or stenoses of the iliac axis or femoral artery bifurcation that cannot be treated by endovascular means and lesions of the profunda femoris artery with simultaneous occlusion of the superficial femoral artery.

Patients with these problems whose individual operative risk is judged to be low or intermediate can be offered a surgical procedure as a prerequisite to regular walking exercises that must be performed thereafter. Long femoro-popliteal lesions should be treated by percutaneous transluminal angioplasty (PTA) with stent implantation (35).

In the treatment of lesions of the superficial femoral artery, drug-coated balloons lower the restenosis rate (e2). The clinical utility of drug-coated stent implants and of drug-coated balloons when used for angioplasty of the infrapopliteal arteries cannot yet be conclusively judged. Although their use has been found to lower the restenosis rate in comparison to simple PTA (36, 37), not enough information is available yet about patient-relevant endpoints (the distance the patient is able to walk, morbidity, mortality, quality of life, limb retention). The implantation of stents in vascular segments that cross a joint is generally not indicated, but it can be considered in CLI when no other treatment options are available.

The TASC classification is based on the morphological complexity of vascular lesions as revealed by angiography. It no longer provides sufficient information for decision-making about invasive treatment. Both morphological and clinical criteria must now be considered (*eBox 2*).

There are some constellations of findings in which an open vascular surgical procedure is to be recommended as the primary treatment, and an endovascular procedure is generally not indicated:

- Subrenal aortic occlusion with bilateral occlusion of the iliac arteries
- Occlusion of the common femoral artery
- Occlusion of the external iliac artery or the superficial femoral artery extending to the common femoral artery
- Long occlusion of the superficial femoral artery, the popliteal artery, and the trifurcation
- Long occlusion of the popliteal artery, the trifurcation, and all tibial arteries with well-preserved distal crural or pedal arterial segments.

Autologous venous material should be used for bypasses if possible (grade A recommendation) (38).

Post-interventional treatment

Anticoagulant drugs or platelet function inhibitors are given to prevent restenosis after bypass procedures involving venous material or prostheses (respectively) (e3). The benefit of platelet function inhibitors is supported by evidence (39). Thus, in line with the recommendations of international guidelines, routine oral anticoagulation after infra-inguinal venous bypass procedures is not recommended (18, 30, 31).

Anticoagulation is indicated to prevent recurrence of cardiac and arterio-arterial embolism, as an accompaniment to clot lysis procedures, and after the recanalization of arterial occlusions with a predominantly thrombotic component (40).

A course of rehabilitation is recommended for PAOD patients so that they can learn the requisite structured walking exercises and so that secondary

preventive measures can be optimized with resulting improvement of quality of life.

A structured post-interventional care program for patients with PAOD consists of the following: counseling about and rigorous control of vascular risk factors, regular semiannual check-ups after invasive procedures, and consideration of all potential further options for treatment. Structured vascular exercises should be offered to all patients after invasive treatment.

Overview for routine clinical practice

PAOD is common and becomes more common with age. Its treatment depends on the clinical stage. The basic treatment consists of the administration of platelet function inhibitors and statins along with structured vascular exercise. Vasoactive drugs are given only when the patient's quality of life is markedly impaired and vascular exercises can be performed only to a limited extent or not at all. In the treatment of critical limb ischemia, rapid arterial revascularization has the highest priority. Endovascular and vascular surgical techniques are complementary; the use of one or the other, or of a hybrid procedure, depends on the indication. Decisions about invasive therapy should be made on an interdisciplinary basis in vascular centers with due consideration of the risk-benefit profile.

Endovascular treatment is preferable to an open surgical bypass procedure whenever the indication is suitable. A platelet function inhibitor must be given after any invasive treatment for PAOD.

Conflict of interest statement

Dr. Lawall is a member of the UCB advisory board. He has received third-party funding for carrying out clinical trials on behalf of Astra Zeneca, Novartis, and UCB. He has been paid for preparing scientific lectures by UCB, BARO, Bayer Vital GmbH, medac GmbH, and Amgen.

Prof. Espinola-Klein is a member of the advisory boards of Merck, Sharp & Dohme GmbH, Amgen, Boehringer Ingelheim, and Daiichi Sankyo. She has received funding from Berlin Chemie for a research project that she initiated, and for carrying out clinical trials. She has received third-party funding for carrying out clinical trials on behalf of Merck, Sharp & Dohme GmbH, Astra Zeneca, Bayer Vital GmbH, and Sanofi Aventis. She has been paid for preparing scientific lectures by Bayer Vital GmbH, Pfizer Pharma GmbH, Amgen, Boehringer Ingelheim, Daiichi Sankyo, and Bristol-Myers Squibb.

Prof. Rümenapf has received reimbursement of meeting participation fees and travel and accommodation expenses from Jotec.

Prof. Huppert states that he has no conflict of interest.

Manuscript submitted on 2 June 2016, revised version accepted on 21 July 2016.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, et al.: Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; 382: 1329–40.
2. Diehm C, Schuster A, Allenberg H, et al.: High prevalence of peripheral arterial disease and comorbidity in 6,880 primary care patients: cross sectional study. *Atherosclerosis* 2004; 172: 95–105.
3. Norgren L, Hiatt WR, Dormandy JA, et al.: Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; 45: 5–67.

4. Lawall H, Diehm C, Pittrow P: S3-Leitlinie zur Diagnostik und Therapie der peripheren arteriellen Verschlusskrankheit (PAVK). VASA 2009; 38: 1–75.
5. S3-Leitlinie zur Diagnostik und Therapie der PAVK 2015. www.uni-duesseldorf.de/AWMF/II/065-003.pdf (last accessed on 25 April 2016).
6. Oxford Center for Evidence Based Medicine, L.o.E., Oxford 2009. www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009 (last accessed on 25 April 2016).
7. Alahdab F, Wang AT, Elraiyah TA, et al.: A systematic review for the screening for peripheral arterial disease in asymptomatic patients. J Vasc Surg 2015; 61: 42–53.
8. Vouyouka AG, Egorova NN, Salloum A, et al.: Lessons learned from the analysis of gender effect on risk factors and procedural outcomes of lower extremity arterial disease. J Vasc Surg 2010; 52: 1196–202.
9. Bradbury AW, Adam DJ, Bell J, et al.: Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. Health Technology Ass 2010; 14: 1–210.
10. Malyar N, Furstenberg T, Wellmann J, et al.: Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: a nationwide population-based analysis. Eur Heart J 2013; 34: 2706–14.
11. Diehm C, Allenberg JR, Pittrow D, et al.: Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation 2009; 120: 2053–61.
12. Zheng ZJ, Rosamond WD, Chambless LE, et al.: Lower extremity arterial disease assessed by ankle-brachial index in a middle-aged population of African Americans and whites: the Atherosclerotic Risk in Communities (ARIC) Study. Am J Prev Med 2005; 29: 42–9.
13. Reinecke H, Unrath M, Freisinger E, et al.: Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence. Eur Heart J 2015; 36: 932–8.
14. Espinola-Klein C, Rupprecht HJ, Bickel C, et al.: Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. Circulation 2008; 118: 961–7.
15. Aboyans V, Criqui MH, Abraham P, et al.: Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012; 126: 2890–909.
16. Hyun S, Forbang NI, Allison MA, Denenberg JO, Criqui MH, Ix JH: Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. J Vasc Surg 2014; 60: 390–5.
17. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development Group: Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. Brit Med J 2012; 345: 494–47.
18. Alonso-Coello P, Bellmunt S, McGorrian C, et al.: Antithrombotic therapy in peripheral artery disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e669–90.
19. Pfeiffer AFH, Klein HH: The treatment of type 2 diabetes. Dtsch Arztebl Int 2014; 111: 69–82.
20. Ryden L, Grant PJ, Anker SD, et al.: ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34: 3035–87.
21. Perk J, De Backer G, Gohlke H, et al.: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. Eur Heart J 2012; 33: 1635–701.
22. Lane DA, Lip GY: Treatment of hypertension in peripheral arterial disease. Cochrane Database Syst Rev 2013; 12: CD003075.
23. Shahin Y, Barnes R, Barakat H, Chetter IC: Meta-analysis of angiotensin converting enzyme inhibitors effect on walking ability and ankle brachial pressure index in patients with intermittent claudication. Atherosclerosis 2013; 231: 283–90.
24. Lane R, Ellis B, Watson L, Leng GC: Exercise for intermittent claudication. Cochrane Database Sys Rev 2014; 7: CD000990.
25. Ashimastos AA, Pappas EP, Buttnar PG, Walker PJ, Kingwell BA, Golledge J A: Meta-analysis of the outcome of endovascular and noninvasive treatment of intermittent claudication. J Vasc Surg 2011; 54: 1511–21.
26. Nordanstig J, Gelin J, Hensater M, Taft C, Osterberg K, Jivegard L: Walking performance and health-related quality of life after surgical or endovascular invasive versus non-invasive treatment for intermittent claudication—a prospective randomised trial. Eur J Vasc Endovasc Surg 2011; 42: 220–7.
27. Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G: Cilostazol for intermittent claudication. Cochrane Database Syst Rev 2014; 10: CD003748.
28. Stevens JW, Simpson E, Harnan S, et al.: Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. Brit J Surg 2012; 99: 1630–8.
29. Ruffolo AJ, Romano M, Ciapponi A: Prostanoids for critical limb ischaemia. Cochrane Database Syst Rev 2010; 1: CD006544.
30. Tendera M, Aboyans V, Bartelink ML, et al.: ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011; 32: 2851–906.
31. Rooke TW, Hirsch AT, Misra S, et al.: 2011 ACCF/AHA Focused update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Card 2011; 58: 2020–45.
32. Hinchcliffe RJ, Andros G, Apelqvist J, et al.: A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diab Metab Res Rev 2012; 28: 179–217.
33. Schrijver AM, Moll FL, De Vries JP: Hybrid procedures for peripheral obstructive disease. J Cardiovasc Surg 2010; 51: 833–43.
34. Antoniou GA, Chalmers N, Georgiadis GS, et al.: A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease. J Vasc Surg 2013; 57: 242–53.
35. Acin F, de Haro J, Bleda S, Varela C, Esparza L: Primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis of randomized controlled trials. J Endovasc Ther 2012; 19: 585–95.
36. Cassese S, Byrne RA, Ott I, et al.: Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. Circulation. Cardiovasc Interv 2012; 5: 582–9.
37. Antoniou GA, Chalmers N, Kanesalingham K, et al.: Meta-analysis of outcomes of endovascular treatment of infrapopliteal occlusive disease with drug-eluting stents. J Endovasc Ther 2013; 20: 131–44.
38. Twine CP, McLain AD: Graft type for femoro-popliteal bypass surgery. Cochrane Database Syst Rev 2010; 5: CD001487.
39. Bedenis R, Lethaby A, Maxwell H, Acosta S, Prins MH: Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. Cochrane Database Syst Rev 2015; 2: CD000535.
40. Whayne TF: A review of the role of anticoagulation in the treatment of peripheral arterial disease. Int J Angio 2012; 21: 187–94.

Corresponding author

Dr. med. Holger Lawall
Praxis für Herz-Kreislaufkrankungen Ettlingen
Max-Grundig-Klinik Bühlerhöhe
Schwarzwaldhochstr. 1
77815 Bühl, Germany
holger.lawall@gmail.com

Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref4316

eTables, eBoxes:
www.aerzteblatt-international.de/16m0729

Additional material to:

The Diagnosis and Treatment of Peripheral Arterial Vascular Disease

Holger Lawall, Peter Huppert, Christine Espinola-Klein, and Gerhard Rümenapf

Dtsch Arztebl Int 2016; 113: 729–36. DOI: 10.3238/arztebl.2016.0729

eREFERENCES

- e1. Stiegler H, Brandl R: Importance of ultrasound for diagnosing peripheral arterial disease. *Ultraschall Med* 2009; 30: 334–74.
- e2. Tepe G, Zeller T, Albrecht T, et al.: Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. *N Engl J Med* 2008; 358: 689–99.
- e3. Anand S, Yusuf S, Xie C, et al.: Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007; 357: 217–27.

eTABLE 1

Recommendations on the conservative treatment of PAOD

	Recommendation grade	LoE
Smoking cessation is urgently necessary.	A	1
Smokers should be offered a program consisting of medical care, group therapy, and a cigarette substitute.	A	1
Statins are indicated for the secondary prevention of cardiovascular events in patients with PAOD.	A	1
Nicotinic acid preparations should not be used for the secondary prevention of cardiovascular events in patients with PAOD.	A	2a
Omega-3 fatty acids should not be used for the secondary prevention of cardiovascular events in patients with PAOD.	A	2a
In patients with PAOD and arterial hypertension, the blood pressure should be treated to lessen cardiovascular mortality.	A	3
A platelet function inhibitor (ASA, clopidogrel) is indicated for the secondary prevention of cardiovascular events in patients with symptomatic PAOD.	A	1
Structured walking exercises under supervision and with regular instruction should be offered to all PAOD patients who have intermittent claudication as part of their basic treatment.	A	1
Patients with intermittent claudication should perform vascular exercises at least 3 times per week for 30–60 minutes over a period of at least 3 months.	A	1
Structured exercise programs with regular instruction are more effective than unstructured vascular exercise.	A	1
Cilostazol or naftidrofuryl should be given in the claudication stage only if the patient's quality of life is markedly impaired, he or she can walk no farther than 200 m at most, and walking exercises can be performed only to a limited extent or not at all.	Consensus	1
Other drugs or non-pharmacological treatments for patients with claudication cannot be recommended, as they have not been demonstrated to lengthen the distance the patient can walk, to reduce morbidity or mortality, or to improve quality of life.	A	1
Patients with critical limb ischemia and infection should be given systemic antibiotics.	A	2
Prostanoids can be used for the pharmacotherapy of patients with critical limb ischemia who are not suitable for a revascularization procedure.	0	2a

ASA, acetylsalicylic acid; LoE, level of evidence; PAOD, peripheral arterial occlusive disease

eTABLE 2

Main recommendations on revascularization in PAOD

	Recommendation grade	LoE
For patients with intermittent claudication, the efficacy of supervised exercise programs to increase the distance the patient can walk is comparable to that of an endovascular or vascular surgical procedure.	A	1
An endovascular procedure should be offered to a patient with intermittent claudication only after the patient has been thoroughly informed about the benefits of risk factor modification and structured walking exercises, and if the stenotic or occlusive lesion seems amenable to endovascular treatment.	Consensus	2
An open vascular surgical procedure should be offered to a patient with intermittent claudication only if the condition causes considerable suffering and an endovascular procedure is not appropriate or has been attempted unsuccessfully, or else surgery seems to be a more suitable treatment for the patient.	Konsensus	GCP
Stenoses and occlusions of the aorto-iliac arteries should be treated endovascularly at first, regardless of the TASC stage. The patient's accompanying illnesses and personal preferences should be taken into account, as well as the local availability of high-quality vascular surgical and/or endovascular interventional care.	B	GCP
Vascular surgery is appropriate when endovascular treatment fails or when vascular surgery appears to be a more reasonable option for the patient.	B	2
The endovascular treatment of aorto-iliac TASC II C and D lesions should preferably be performed with primary stent angioplasty.	B	2
In patients with critical limb ischemia (CLI), the endovascular treatment of proximal and distal lesions has the highest priority, provided that the predicted short- and long-term symptomatic improvement after endovascular treatment is the same as that after a vascular surgical procedure. Proximal lesions should be treated first.	A	2
The great saphenous vein (optimally, a single segment of it) should be used for femoropopliteal bypasses, both for patients with intermittent claudication and for those with critical limb ischemia, as it is superior to alternative types of bypass material.	Above the knee A Below the knee A	Above the knee 1 Below the knee 4
In case the great saphenous vein is unavailable or unsuitable, other autologous veins should be used.	B	4
If veins cannot be used, an alloplastic synthetic bypass graft (PTFE, dacron) can be performed instead. The utility of bioprosthetic allografts and xenografts is unclear.	0	GCP
Stenoses and occlusions at the bifurcation of the common femoral a. should primarily be treated surgically.	A	GCP
Stenoses and occlusions of the femoropopliteal arteries, regardless of their TASC classification, should primarily be treated endovascularly. A bypass is preferable if the following criteria are met: long-segment occlusion (TASC D), no elevation of surgical risk, life expectancy at least two years, and availability of a donor vein.	B	2
Primary stent angioplasty with nitinol stents is preferred for the endovascular treatment of long and intermediate-length femoropopliteal lesions.	B	2
When stenting is performed in the endovascular treatment of a long-segment femoropopliteal lesion, the implantation of a single nitinol stent is preferred to that of multiple overlapping stents, because a single stent is associated with a lower rate of stent fracture and resulting reocclusion.	B	2

If, in the endovascular treatment of a femoropopliteal lesion, the treating physicians consider it highly important for clinical angiological reasons to lessen the risk of restenosis and reintervention after angioplasty, then paclitaxel-coated balloons should be used for the angioplasty.	B	2
Lesions of the popliteal artery should be treated primarily by balloon angioplasty.	B	2
The endovascular treatment of infrapopliteal stenoses and occlusions in patients with CLI is preferable to the vascular surgical option, as the former yields equally good outcomes with respect to amputation rates and amputation-free survival while carrying a lower periprocedural morbidity and mortality. The endovascular treatment should not make the potential later creation of a bypass more difficult.	B	4
Vascular surgery should be used to treat complex, long-segment stenoses and occlusions of the infrapopliteal arteries, when endovascular treatment has failed, when the patient's symptoms persist, or when a suitable bypass vein is available.	A	GCP
In the endovascular treatment of infrapopliteal vascular lesions, a stent should not be primarily implanted; rather, a stent should be implanted only if the angiographic result after balloon PTA is still unsatisfactory.	A	2a
Infrapopliteal bypasses should consist of a single, continuous segment of the great saphenous v. This autologous vein is superior to all other types of bypass material.	B	4
If the great saphenous vein is unavailable or unsuitable for use, other autologous veins (deep vein of the leg, vein of the arm, spliced bypass) should be used for infrapopliteal bypass grafting.	B	4
The proximal anastomosis for a bypass in the lower limb should be as distal as possible while still allowing unimpeded arterial inflow. The recipient artery should be the best-preserved artery that is considered most likely to assure adequate blood supply to the foot (the angiosome concept).	B	4

ASA, acetylsalicylic acid; GCP, good clinical practice ; LoE, level of evidence; PAOD, peripheral arterial occlusive disease; TASC, TransAtlantic Inter-Society Consensus

eTABLE 3

Recommendations for post-interventional follow-up

	Recommendation grade	Evidence level
All patients should be given acetylsalicylic acid (100 mg) or clopidogrel pre-, peri-, and postinterventionally(/-operatively). This treatment should be continued over the long term unless contraindicated.	A	1
After infra-inguinal endovascular treatment with stent implantation, it is recommended that ASA be given temporarily in combination with clopidogrel to improve the patency rate.	B	GCP
Oral anticoagulant drugs should not be given after PTA of the femoropopliteal or tibial vessels.	A	1
For peripheral bypass procedures, the administration of platelet function inhibitors should be started preoperatively. They should continue to be given after surgical or hybrid procedures and should then be maintained over the long term unless contraindicated.	A	1
Patients with an infra-inguinal, femoropopliteal, or distal venous bypass should not routinely be given oral anti-coagulant drugs (OACs).	A	2
The administration of OAC, or OAC together with ASA, can be considered in individual cases if the risk of bypass occlusion is very high.	0	2
Patients with PAOD should undergo regular clinical follow-up with regard to the symptoms and signs of PAOD (walking performance, pain at rest, trophic disturbances).	B	3
Secondary prophylaxis against cardiovascular risk factors and treatment of cardiovascular comorbidities are indicated for all patients with PAOD, regardless of whether their primary treatment was conservative, medical, endovascular-interventional, or surgical.	A	1
Patients with PAOD who undergo invasive vascular procedures should have regular follow-up thereafter.	B	2
All PAOD patients should be offered structured vascular exercises under supervision as part of their basic treatment. This also applies over the long term after treatment with drugs, an endovascular intervention, or surgery.	A	2
Patients who have undergone major amputations should receive suitable prostheses and rehabilitation.	A	GCP

ASA, acetylsalicylic acid; GCP, good clinical practice; OAC, oral anticoagulation; PAOD, peripheral arterial obstructive disease; PTA, percutaneous transluminal angioplasty

eBOX 1

Participating specialty societies and their representatives

- German Society of Angiology – Society of Vascular Medicine (Deutsche Gesellschaft für Angiologie – Gesellschaft für Gefäßmedizin, DGA)
 - Dr. H. Lawall, Ettlingen*
 - Prof. Dr. K. L. Schulte, Berlin*
- German Society of Vascular Surgery and Vascular Medicine (Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin, DGG)
 - Prof. Dr. G. Rümenapf, Speyer*
 - Prof. Dr. S. Debus, Hamburg*
- German Radiological Society (Deutsche Röntgen-Gesellschaft, DRG)
 - Prof. Dr. P. Huppert, Darmstadt*
 - Prof. Dr. J. Tacke, Passau*
- German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin, DGIM)
 - Prof. Dr. A. Creutzig, Hanover
- German Society for Ultrasound in Medicine (Deutsche Gesellschaft für Ultraschall in der Medizin, DEGUM)
 - Dr. H. Stiegler, Munich
- German Society of Interventional Radiology (Deutsche Gesellschaft für Interventionelle Radiologie, DeGIR)
 - Prof. Dr. J. Tacke, Passau
- German Diabetes Society (Deutsche Diabetes Gesellschaft, DDG)
 - Prof. Dr. S. Jacob, Villingen-Schwenningen
 - Prof. Dr. S. Balletshofer, Tübingen
- German Surgical Society (Deutsche Gesellschaft für Chirurgie, DGCh)
 - Prof. Dr. W. Lang, Erlangen
 - Prof. Dr. T. Koepfel, Hamburg
- German Society for Wound Healing and Wound Care (Deutsche Gesellschaft für Wundheilung und Wundbehandlung, DGfW)
 - Dr. A. Maier-Hasseltmann, Munich
- German Cardiological Society (Deutsche Gesellschaft für Kardiologie, DGK)
 - Prof. Dr. C. Tiefenbacher, Wesel
- German Dermatological Society (Deutsche Gesellschaft für Dermatologie, DDG)
 - Prof. Dr. M. Jünger, Greifswald
- German Geriatric Society (Deutsche Gesellschaft für Geriatrie, DGG)
 - Dr. C. Ploenes, Düsseldorf
- German Neurosurgical Society (Deutsche Gesellschaft für Neurochirurgie, DGNC)
 - Dr. M. Schmutzler, Ingolstadt
- German Society of Anaesthesiology and Intensive Care Medicine (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin, DGAI)
 - Dr. M. Gleim, Kiel
- German Society of General Practice and Family Medicine (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM)
 - Prof. Dr. F. Peters-Klimm, Heidelberg
- German Nephrological Society (Deutsche Gesellschaft für Nephrologie, DGfN)
 - Dr. H. P. Lorenzen, Hanover
- German Epidemiological Society (Deutsche Gesellschaft für Epidemiologie, DGEpi)
 - Prof. Dr. P. Wild, Mainz
- German Society for Rehabilitation Science (Deutsche Gesellschaft für Rehabilitationswissenschaften)
 - Dr. A. Dohmen, Freiburg
- German Society for Sports Medicine and Prevention (Deutsche Gesellschaft für Sportmedizin und Prävention)
 - Prof. Dr. A. Schmidt-Trucksäss, Basel
- German Phlebological Society (Deutsche Gesellschaft für Phlebologie)
 - Dr. T. Hertel, Zwickau
- German Vascular League (Deutsche Gefäßliga)
 - PD Dr. C. Kalka, Brühl
 - Manfred Pfeiffer, Leimen
- Amputees' Initiative (Amputierten-Initiative e. V.)
 - Dagmar Gail, Berlin
- German Federal Pension Insurance (Deutsche Rentenversicherung Bund)
 - Dr. A. Falk, Berlin
- German Society for Research on Thrombosis and Hemostasis (Deutsche Gesellschaft für Thrombose und Hämostaseforschung, GTH)
 - Prof. C. Espinola-Klein
- Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften, AWMF)
 - Prof. Dr. I. Kopp, Marburg*

* member of steering committee

eBOX 2**Angiomorphological and clinical criteria for the choice of an open surgical vs. endovascular procedure****● Morphology of vascular lesion**

- Occlusions whose endovascular treatment is generally associated with a very low technical success rate and/or markedly elevated risks (A)
- Occlusion of distributing segments, whose endovascular treatment is not expected to bring about an adequate revascularization of more distal vascular segments which would have a similar technical success rate and permanency of effect to that achievable with bypass techniques (B und E)
- Occlusions coming so close to the distributing segment of the common femoral a. that endovascular treatment with stent implantation could create poor conditions for subsequent surgical treatment and compromise its outcome (C and D)

● Clinical criteria

- A vascular lesion of complex morphology in a patient with severe renal insufficiency, so that endovascular treatment with a large contrast load would carry a high risk of permanent renal damage
- Risk factors that significantly elevate the morbidity and mortality of open surgery
- Lack of available donor veins