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Review

German guideline on the diagnosis and treatment of peripheral artery disease – a comprehensive update 2016

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Summary: The prevalence of peripheral artery disease (PAD) is increasing worldwide and is strongly age-related, affecting about 20 % of Germans over 70 years of age. Recent advances in endovascular and surgical techniques as well as clinical study results on comparative treatment methods strengthened the need for a comprehensive review of the published evidence for diagnosis, management, and prevention of PAD. The interdisciplinary guideline exclusively covers distal aorta and atherosclerotic lower extremity artery disease. A systematic literature review and formal consensus finding process, including delegated members of 22 medical societies and two patient self-support organisations were conducted and supervised by the Association of Scientific Medical Societies in Germany, AWMF. Three levels of recommendation were defined, A = „is recommended/indicated", B = „should be considered", C = "may be considered", means agreement of expert opinions due to lack of evidence. Altogether 294 articles, including 34 systematic reviews and 98 RCTs have been analysed. The key diagnostic tools and treatment basics have been defined. In patients with intermittent claudication endovascular and/or surgical techniques are treatment options depending on appropriate individual morphology and patient preference. In critical limb ischaemia, revascularisation without delay by means of the most appropriate technique is key. If possible and reasonable, endovascular procedures should be applied first. The TASC classification is no longer recommended as the base of therapeutic decision process due to advances in endovascular techniques and new crural therapeutic options. Limited new data on rehabilitation and follow-up therapies have been integrated. The article summarises major new aspects of PAD treatment from the updated German Guidelines for Diagnosis and Treatment of PAD. Limited scientific evidence still calls for randomised clinical trials to close the present gap of evidence.

Keywords: Peripheral artery disease, diagnosis, treatment, update, guideline update

Introduction

An update of the German national guideline on peripheral artery disease (PAD) became necessary to close the gap between the valid 2009 guideline recommendations and recent advances. Endovascular techniques have progressed and new scientific evidence provided by clinical trials is available. PAD is a specialty dominated by extensive and increasing clinical practice but lacking powerful randomised clinical trial (RCT) evidence, particularly in the field of endovascular and open surgery as well as pharmacological and non-pharmacological therapeutic strategies after revascularisation procedures. National registry data demonstrate that PAD patients are undertreated regarding their risk factors and comorbidities [1]. The Transatlantic Intersociety Consensus (TASC)-classification [2] has been the basis of the therapeutic decision process for the last decade. Its four types A-B-C-D classify peripheral atherosclerotic vascular lesions of increasing length and complexity. According to TASC, type A and B lesions were recommended to be treated endovascular-first, type C and D lesions were typically first addressed for surgical repair. With increasing experience of intervention and advanced stent technologies, such as drug eluted and covered stent grafts of increasing lengths, bifurcational stents, and covered angioplasty catheters, the endovascular procedures recently have become increasingly successful. Patients request non-surgical procedures as an alternative approach without risk of narcosis and lower invasive character. A renunciation from the TASC guided approach has become the consequence of the scientific literature evaluation.

We present hereby a summary of the German guideline [3], highlight major changes, and explain the underlying scientific evidence. The aim is to facilitate clinical decision making in patients with PAD.

Methods

A formal update process according to the international guidelines for guideline preparation was undertaken and supervised by the German member society of the Council for International Organizations of medical Sciences (AWMF). A systematic guideline and literature research, dating back to the editorial deadline of the guideline in April 2009 until 30th April 2015, was performed addressing three predefined key questions of scientific interest: 1. Significant value of endovascular strategies 2. Early revascularisation of patients at high risk for amputation 3. Special aspects of PAD in geriatric patients. After deletion of duplications and abstract screening, 294 full text publications have eventually been considered, including 17 Cochrane reviews, 17 meta-analyses, three guideline sources (American Heart Organization, European Society of Cardiology, National Institute for Health and Care Excellence), 98 RCTs, and 148 cohort analyses (see Figure 1). The literature was evaluated by delegated experts from 22 medical societies, including angiologists, radiologists, vascular surgeons, cardiologists, and general practitioners who are involved in the treatment of PAD patients as well as two patient self-support organisations. For evidence graduation, the Oxford scheme was used. For level of recommendation (LoR) three grades were used: A ("is recommended"), B ("should be considered"), and C (= expert consensus/"may be considered") - means the text of recommendation was agreed by >75% of guideline working group members due to lacking scientific evidence.

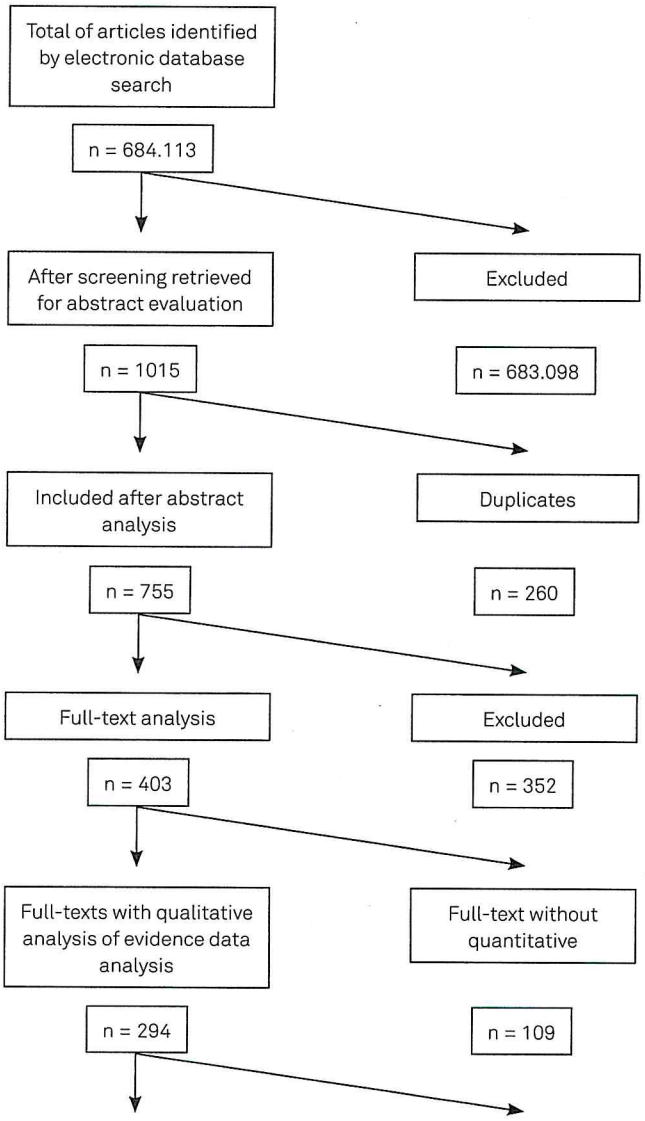

Figure 1. Flow diagram of article selection process through the systematic review

Epidemiology

Most robust data on the prevalence of PAD are provided by the German getABI registry, reporting 3–10% of the population to be affected [4], 20% of all patients are 70 years of age and older. The ratio of asymptomatic and symptomatic patients is 4:1 [5]. Men are more often affected than women but only at younger ages [6]. A rising worldwide prevalence is expected due to prolonged life expectancy [7].

Hospital admission rates in Germany increased between 2005 and 2009 by 32% [8].

All patients with PAD have an increased cardiovascular morbidity and mortality, e.g. a fourfold risk of myocardial infarction (OR 3,3;95%CI:2,1–5,0) or at least a twofold increase of ischaemic stroke (OR 4,2;95%CI 1,8–9,5) [9]. Patients with critical limb ischaemia (CLI) carry an increased risk of major amputation without revascularisation [10]. Mortality rates in asymptomatic patients within five years are 19% and increase in symptomatic patients to up to 24% [11].

The prognosis of patients with intermittent claudication (IC) is determined by cardiac or cerebrovascular complications. Only 2% have a major amputation within 10 years [2]. The risk of CLI is low, 25% deteriorate with walking distance, 50% remain stable.

A major problem of PAD patients is insufficient awareness of the cardiovascular high risk profile and undertreatment related to risk factor management.

Diagnostics

History, symptoms, and physical examination

The guideline separates therapeutic strategies according to the clinical presentation of pain related to walking (= IC)

or ischaemic rest pain (CLI) with or without ulceration (Table I)

History of risk factors, comorbidities, clinical symptoms of walking impairment and pain as well as physical examination, including palpation of the pulses, skin status, and feet are mandatory basics. Palpable pulses at the distal leg sites do not exclude PAD, a missing pulse does not proof PAD.

Every patient with PAD should receive feet inspection regularly (LoR A).

Ankle-brachial index (ABI)

The ABI is the primary non-invasive test to proof PAD at a value of <0.9 with high prognostic significance. The lowest pressure measured in the arteries of both ankles is divided by the lowest brachial systolic pressure [12]. ABI at rest can be normal or borderline if a proximal arterial occlusion has good collateral perfusion. In case of clinical suspicion but normal ABI, an exercise induced ABI drop of >20 % can unmask PAD [13].

In patients with an ABI of >1.4 due to stiff, calcified arteries (media sclerosis), e.g. in diabetes or end stage renal disease, alternative measurements of the toe brachial index (TBI) are recommended to detect PAD [14].

Duplex ultrasound

Duplex ultrasound has become standard to detect, localise, and quantify severity of PAD [15]. In the majority of cases no additional diagnostic method is needed to plan conservative therapies. Digital subtraction angiography (DSA) is used almost exclusively during endovascular procedures, or in case of complex findings, before surgical procedures. In case of an inconclusive or unavailable ultrasound, a contrast enhanced magnetic resonance angiography (MRA) (considering contraindications, e.g. pacemaker) or multidetector computed tomography (CTA) (considering radiation and nephrotoxicity) can be performed.

Duplex ultrasound is the preferable diagnostic method to localise and quantify severity of PAD (LoR A).

The decision to perform any additional angiographic diagnostic procedure beyond DUS should be made in collaboration with endovascular specialists and surgeons (expert consensus).

A comprehensive diagnostic algorithm of the step-by-step approach is presented in Figure 2.

Table I. Fontaine or Rutherford classification systems of peripheral artery disease

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
II a	Walking distance > 200 m	I	1	Mild claudication
II b	Walking distance < 200 m	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

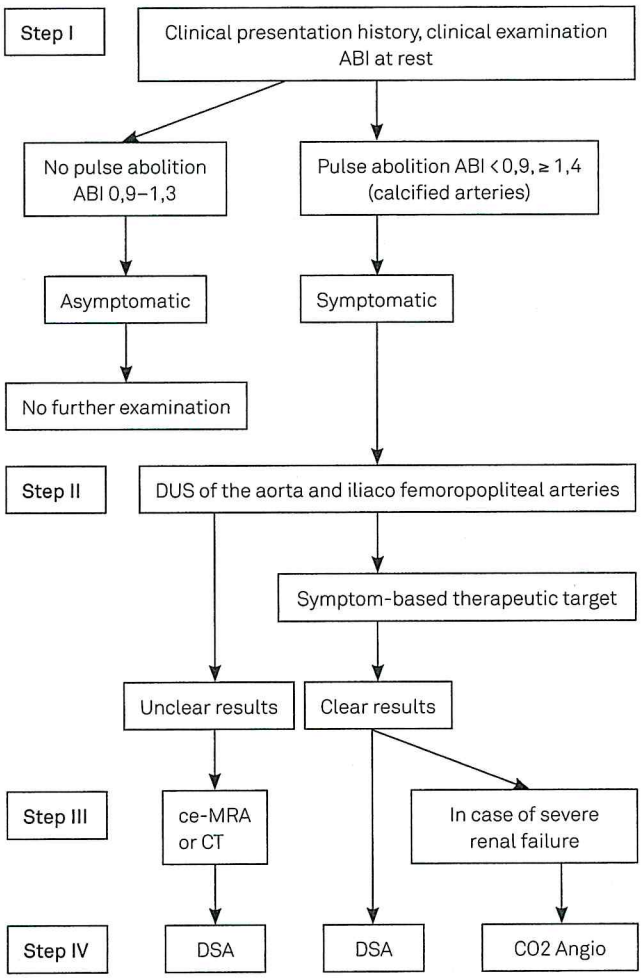

Figure 2. Diagnostic algorithm for PAD. ABI: ankle-brachial-index; ce-MRA: contrast-enhanced magnetic resonance angiography; CO2 Angio: carbon dioxide angiography; CTA: computed tomographied angiography; DSA: digital subtraction angiography; DUS: duplex ultrasound.

Conservative therapy

General aspects

Risk factor modification, treatment of co-morbidities, and supervised exercise therapy to improve peripheral blood flow are treatment basics.

In IC, improving walking distance as well as sustaining mobility and quality of life (QoL) are key therapeutic targets. In CLI, reducing pain and preventing amputation are fundamental. In both clinical situations it is necessary to reduce cardio- and cerebrovascular complications.

Aspirin (symptomatic patients) and statins (asymptomatic and symptomatic patients with PAD) are pharmacological standard therapies (LoR A). Due to limited data on statins in PAD, no LDL-Cholesterol treatment target has been defined but every patient without a contraindication should receive a statin [16]. Omega-2 fatty acids and nicotinamide have no positive effect on morbidity or mortality. Hypertensive patients should have a target blood pressure below 140/90 mmHg [17]. ACE-inhibitors improve walking distance [18]. Beta blockers are not contraindicated in PAD.

Intermittent claudication

Regular supervised exercise training is the preferable therapeutic method in patients with IC. Validated training programmes show similar long term outcomes compared to endovascular therapy alone [19, 20]. Prospective trials with at least three months follow-up showed improved walking distance (109 m; 95%CI 38–180 m) and overall quality of life [21].

A supervised exercise training should be offered to all patients as basic treatment element (LoR A).

Vasoactive substances in claudication are only recommended in case of impossible or limited exercise training ability and significantly reduced quality of life. Cilostazol and naftridrofuryl are both effective treatments [22, 23] (expert consensus).

Pentoxifyllin, L-arginine, buflomedil or ginkgo biloba as well as all other tested substances and procedures have not proven to be efficient in intermittent claudication.

Critical limb ischaemia

Pain therapy, antibiotics in case of infections, and standardised wound treatments are supportive therapies to arterial revascularisation as the standard treatment of CLI (LoR A). There is no conclusive evidence on the effectiveness of prostanoids [24].

A multidisciplinary approach is strongly recommended to treat people with CLI (LoR A). This includes endovascular angiologists and radiologists, vascular surgeons, and diabetologists in case of diabetic patients.

Arterial revascularisation

General aspects

Arterial revascularisations, either endovascular or surgical, are symptomatic treatments and do not stop the underlying progressing atherosclerotic disease. They are only indicated in symptomatic patients and after careful evaluation of the alternative therapeutic option "of optimal conservative treatment alone" [20]. The majority of available RCT data do not differ between IC and CLI. Endovascular procedures should be used first, if possible and reasonable (consensus).

Decisions on the optimal arterial revascularisation strategy should be made in collaboration with an endovascular specialist and a vascular surgeon and should consider the stage of the disease, the expected outcome, and risk and effort (expert consensus).

Intermittent claudication

The strategy of conservative-first treatment has already been outdated by current international guidelines [25, 26]. Low risk endovascular interventions in iliacal or femoropopliteal lesions or surgical repair of femoralis communis occlusions are regarded as first choice when not willing to wait for success of conservative treatments strategies. Primary patency rates five years after aortoiliac (stent) intervention are about 60–85%, secondary patency rates between 80–98% [27, 28]. Long term data after femoropopliteal stents are still missing, after three years 42% to 76% patency rates are reported [29]. Main decisional criteria in IC should be a reduced quality of life caused by limited pain-free walking distance.

A surgical strategy should be considered in case of failed or impossible endovascular revascularisation of iliacal or common femoral occlusions or combined lesions with concomitant occlusion of the superficial femoral artery. They carry a low risk of complication and may restore a relevant pain-free walking distance to allow the patient to readjust to regular exercise training.

Critical limb ischaemia

Arterial revascularisation should be attempted without delay, using the technique of highest anticipated success rate, taking the potential risk of the respective technique

into account. Endovascular and surgical revascularisations are complementary strategies, no superiority of one approach to the other has been proven [10, 30]. Endovascular-first approach should be considered, if the expected technical and clinical success rate is comparable to a surgical approach [31, 32] (expert consensus).

Hybrid techniques should be considered, if appropriate and locally available [33].

An endovascular-first approach should be preferred, if short- and long term outcome is anticipated to be comparable to surgical approach (LoR A).

Procedural decision should consider localisation, morphological complexity and length of the vascular lesion, comorbidities, local centres' expertise, and individual patients' preference.

Primary patency rates vary, depending on those factors, between 65% and 95% [10, 28, 34–36] iliac-femoropopliteal, and between 40–60% infrapopliteal [10, 36].

Primary stent-PTA (percutaneous transluminal angioplasty) is recommended in long (>10 cm) femoropopliteal lesions [35] (LoR B). Drug-eluting balloons inhibit restenosis of femoropopliteal disease [37]. The long term outcome of drug-eluting stents and balloons in infrapopliteal disease is still unclear. Short-term results demonstrated increased patency and absence of target lesion revascularisation [32, 38].

Stent implantation in segments with high level of mobility (e.g. common femoral and popliteal artery) are generally not recommended and reserved for situations without options, e.g. failed PTA. Studies with drug- eluting balloons are underway.

Some specified procedures have been agreed being primarily suitable for surgical repair:
- Aorto – biiliac occlusions
- Occlusion of common femoral artery
- Occlusion of external iliac or superficial femoral artery, involving the common femoral artery
- Long occlusions of superficial femoral and popliteal artery
- Long occlusions of popliteal or infrapopliteal arteries and open distal crural or tibial arterial segments

Lists of angiomorphological and clinical criteria have been defined to support a surgical-first treatment strategy.

Vascular morphology:
- Occlusions with predicted poor technical success rates or high risk of reocclusions
- Occlusions in segments with predicted poor revascularisation and/or patency rates in the distal downstream segments
- Occlusions with low distance to the common femoral artery, where stents could reduce the outcome of subsequently needed surgical revascularisation

Clinical criteria for surgical revascularisation:
- Complex lesion and coexisting severe renal failure, which may cause irreversible renal failure, if high amount of contrast agent is needed for endovascular intervention

Autologous vein grafts provide best patency results and should be used whenever available [39] (LoR A).

Clinical criteria for endovascular revascularisation:
- Risks, which increase morbidity and mortality of surgical approach
- No available autologous vein graft

In case of contraindications for revascularisation, ischaemic pain relief and anti-infective therapy are key to prevent amputation. In case of unavoidable amputation, the level should carefully be evaluated to improve healing rates, optimise rehabilitation with a stump suitable for ambulation with prosthesis and minimise quality of life reductions. A therapeutic decisional flowchart is presented in Figure 3.

In multisite artery disease, proximal inflow lesions should be treated prior to distal lesions (expert consensus). Any revascularisation should be accompanied by a validated exercise training program [20] (expert consensus).

Follow-up care after revascularisation

Beyond the general benefit of antiplatelet treatment with aspirin for reduction of cardiovascular morbidity and mortality, a dosage between 50–300 mg, in all patients with PAD, aspirin improves patency rates after endovascular interventions.

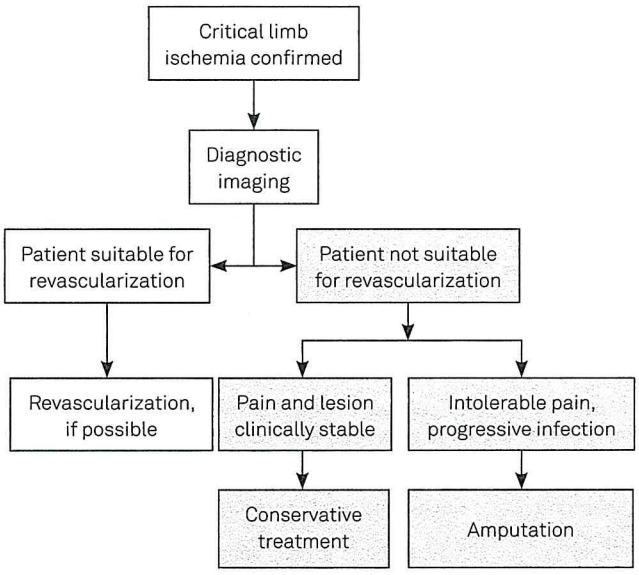

Figure 3. Therapeutic algorithm for patients with critical limb ischaemia

We recommend 100 mg ASS or clopidogrel in all symptomatic patients with PAD and in the long term treatment after invasive procedures (LoR A).

Table II. Treatment strategies according to the Fontaine' stages

	Fontaine stage			
Therapeutic strategy	I	II	III	IV
Risk factor management: *Smoking cessation, antidiabetic/antihypertensive therapy, statins*	+	+	+	+
Antiplatelet agents: *Acetylsalicylic acid or Clopidogrel*	(+)	+	+	+
(Supervised) exercise therapy	+	+		
Pharmacotherapy: *Cilostazol or Naftidrofuryl*		+		
Wound care				+
Endovascular therapy		+*	+	+
Surgical therapy		+*	+	+

Legend. + Recommendation; * depending on appropriate individual morphology and patient preference

Data of cardiac studies show an additional positive effect of a combination therapy with clopidogrel 75 mg daily after stent implantation. Specific PAD data comparing efficacy of aspirin alone and combination regimens with dipyridamole or several thienopyridines, e.g. clopidogrel, prasugrel, ticagrelor, are lacking. Anticoagulation improves outcome after arterial embolisation, thrombotic occlusions, and concomitantly to fibrinolytic therapy. We do not generally recommend anticoagulation in patients with PAD after invasive procedures (LoR A). In a few patients with venous bypasses and poor outflow, an oral anticoagulation with Vit-K -antagonists (INR 3) may be useful [40].

Validated patient support programmes, teaching systematic exercise training, risk factor optimisation, and regular medical care should be offered to all patients after revascularisation to improve quality of life and address the progressive underlying atherosclerotic disease (expert consensus).

An overview of the treatment strategies according to the Fontaine stages is presented in Table II and the key therapeutic recommendations of the German 2016 Guideline Update are summarised in Table III.

Table III. Therapeutic recommendations for patients with PAD

	Grad*	LoR
All Patients with PAD who smoke are advised to stop smoking, are offered medical doctors' support, nicotine replacement therapy, and smoking cessation programs	A	1
Statins are recommended for secondary prevention of cardiovascular events and antiplatelet therapy is recommended in patients with asymptomatic and symptomatic PAD	A	1
Supervised exercise programs are offered to all patients with CI as basic therapy	A	1
Cilostazol or Naftidrofuryl are only recommended in patients with IC, if quality of life is severely reduced, maximum walking distance is < 200 m, and there is no or limited possibility of effective exercise training	Expert consensus	
Systemic antibiotic therapy is recommended in patients with CLI and infections	A	2
A primary endovascular approach may be offered all patients with IC, if they were informed about risk factor modification and supervised exercise programs and if occlusions is suitable for endovascular interventions.	Expert consensus	
A primary endovascular approach should be considered in all aortoiliac lesions independent of the TASC class. Comorbidities, patients' preference, and experience of the endovascular and surgical teams should be considered.	Expert consensus	
In patients with CLI inflow lesions before outflow lesions are recommended being treated endovascular-first, if expected short and – long-term outcome are comparable to surgical approach.	A	2
Femoropopliteal lesions should be treated endovascular-first independent of the TASC class. In TASC D lesions with low risk, not impaired life expectancy (> 2 years), and available autologous vein surgical bypass graft should be first choice.	B	2
In CLI infrapopliteal lesions should be treated endovascular-first. Open surgery can be recommended in case of long, complex infrapopliteal occlusions, if endovascular approach has failed or symptoms persist	Expert consensus	
Antiplatelet therapy with aspirin (100mg) or clopidogrel is recommended in all patients before, during, and after endovascular or surgical revascularisation, as long as no contraindications arise.	A	1
After infrainguinal endovascular approach with stent implantation temporary dual antiplatelet therapy can be considered to improve patency rate.	Expert consensus	
Anticoagulation with vitamin K antagonists should not regularly be considered in patients with femoropopliteal or infrapopliteal autogenous vein bypass, because of increased risk of bleeding.	A	2
Patients with PAD should be screened regularly regarding walking distance, rest pain, and ischaemic lesions	B	3

LoR: level of recommendation; * according to the Oxford Scheme of scientific evidence

Conclusions

PAD is a frequent and underestimated vascular atherosclerotic disease, strongly related to age and associated with cardio- and cerebrovascular co-morbidities. The basic treatments are aspirin, statins, and exercise therapy. Vasoactive treatments are used, if exercise training failed or is not applicable. Endovascular and surgical treatments are complementary strategies, which should be chosen in collaboration with specialists, considering anatomical and individual specificities as well as local medical expertise. Patients with IC can be treated targeting on symptom relief and improved quality of life. Patients with CLI need revascularisation without delay to prevent amputation and to improve poor prognosis. Endovascular revascularisation should be preferred, if the benefit-risk evaluation predicts the same outcome as surgical revascularisation. The TASC classification is no longer an appropriate model to choose between endovascular and surgical-first approaches. Recent advances in endovascular techniques, including drug-eluting stents and balloons, have shown acceptable patency rates in longer and complex vascular lesions. Comprehensive RCT data on the majority of open questions in PAD are still missing.

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Prof Dr. G. Rümenapf: Received attendance fees for attending congresses as well as travel and accommodation expenses from Jotec GmbH.

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