Thieme

Position Paper on the Diagnosis and Treatment of Peripheral Arterial Disease (PAD) in People with Diabetes Mellitus

Joint Statement of the German Diabetes Society (DDG), The German Angiology Society (DGA) and The German Society for Interventional Radiology and Minimally-Invasive Therapy (DeGIR) German Society for Vascular Surgery and Vascular Medicine (DGG)

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This position paper is based on the current German and international guideline recommendations [1–3] and serves as a short, clinically-oriented guideline for the diagnosis and treatment of patients with diabetes mellitus and peripheral arterial disease (PAD).

Peripheral circulatory disorders of the pelvic and leg arteries are one of the complications patients with diabetic mellitus suffer from. The term covers stenoses, occlusions and – to a lesser extent – aneurysmal vascular changes of the pelvic leg arteries.

Arterial vascular lesions mostly occur in later life, however, people with diabetes mellitus are often affected prematurely. In these patients, the time of the initial manifestation also depends on the duration of the disease and the quality of metabolic control. Only 25 % of affected patients have symptoms.

Especially in patients with diabetes mellitus, atheroma of the peripheral vessels is aggravated by chronic inflammatory vessel wall processes and hypercoagulability.

Second to nicotine abuse, diabetes is the most important risk factor for the occurrence of PAD [4].

Patients with diabetes have a 2 to 4-time higher risk of developing PAD than patients without diabetes.

Up to 30 % of all patients with claudication and 50 % of all patients with critical limb ischaemia (CLI) are people with diabetes mellitus [5].

PAD patients with diabetes have specific anatomical-morphological and clinical characteristics which must be considered in the diagnostic and therapeutic approach. Compared to people without diabetes mellitus, PAD in people with diabetes mellitus develops earlier, progresses more rapidly and changes over more frequently to critical limb ischaemia (CLI). Anatomically-morphologically, a multi-segmental manifestation is typical with long, calcified stenoses/occlusions of the lower leg arteries with insufficient collateral formation. Clinically, people with diabetes mellitus often first consult their doctors because of a critical ischaemia, in part because the intermittent claudication preceding a critical ischaemia and the pain at rest can remain masked for a long time by the diabetic sensory polyneuropathy. The prognosis regarding a life without amputations is poor for people with diabetes mellitus. This is due, on the one hand, to the high ischaemia and ulcer recurrence rates and the associated minor and major amputations, on the other hand it results from the high rate of comorbidities and co-prevalence of terminal organ damage such as cardiac and renal insufficiency, each of which on its own increases mortality.

The most significant consequences of diabetic peripheral circulatory disorders are foot lesions (ulcers and gangrene) and minor and major amputations as a result of ischaemic or neuro-ischaemic diabetic foot syndrome (DFS) (▶ **Tab. 1**).

▶ **Tab. 1** Classification of PAD according to Fontaine and Rutherford.

Fontaine		Rutherford		
Stage	**Clinical picture**	**Degree**	**Category**	**Clinical picture**
I	Asymptomatic	0	0	Asymptomatic
IIa	Walking distance > 200 m	I	1	Mild IC
IIb	Walking distance < 200 m	I	2	Moderate IC
		I	3	Severe IC
III	Ischaemic pain at rest	II	4	Ischaemic pain at rest
IV	Ulcer, gangrene	III	5	Small patches necrosis
		III	6	Large patches necrosis

IC = Intermittent claudication.

WHAT DOES IT MEAN?

- The number of patients with PAD and diabetes is constantly increasing.
- The risk of amputation in people with diabetes mellitus is significantly increased in the presence of PAD.
- Timely detection of PAD reduces the amputation and cardiovascular event rates if treatment is in accordance with guidelines.
- Interdisciplinary cooperation and rapid revascularisation are crucial in critical limb ischaemia.

Diagnostics of PAD in people with diabetes mellitus

Non-invasive hemodynamic vascular function diagnostics in people with diabetes mellitus allows conclusions to be drawn about the severity of the circulatory disorder and provides prognostic information on the spontaneous course, cardiovascular risk and/or wound healing.

Targeted diagnostics facilitate choosing the appropriate therapy and enable monitoring of the course of the disease during and after vascular treatment.

VASCULAR DIAGNOSTICS FOR PEOPLE WITH DIABETES MELLITUS

- Clinical examination including recording of pulse status and capillary pulse as well as a qualitative comparison of skin colour and temperature
- Ultrasound ankle or toe pressure measurement (Ankle-brachial index; toe-brachial index)
- Colour-coded duplex sonography with pulse curve analysis
- Pulse oscillography of the digital arteries (Digital Phosphor Oscilloscopes or Light Reflection Rheography)
- Transcutaneous oxygen measurement (tcPO2)

In people with diabetes mellitus, these non-invasive diagnostic procedures should be used liberally if there is a suspicion of PAD, or if a foot lesion is present or is not healing.

In the clinical examination, it is important to examine the reactive skin circulation of the feet (capillary pulse) as well as perform palpation of the foot pulses. Although pulse examination of the

lower extremities is helpful, the frequency of PAD is overestimated in the absence of pulses. Conversely, palpable foot pulses do not rule out the presence of PAD.

The capillary pulse as a reactive filling of the skin after pressure indicates the presence of a critical circulatory problem.

People with diabetes mellitus with PAD should have a regular clinical foot examination

Ankle-brachial index (ABI) is determined using non-invasive doppler ultrasound to measure blood pressure at rest and/or after exertion and is a suitable test for detecting PAD.

Decreased peripheral pressure values are evidence of the presence of PAD and indicate the cardiovascular risk in the patient. The ABI value with the lowest ankle artery pressure is decisive for the diagnosis of PAD. An ABI value at rest below 0.9 is deemed confirmation of the presence of PAD.

In the presence of media sclerosis (ABI > 1.3), the pulse curve analysis, pulse oscillography of the digital arteries and toe pressure measurement with determination of the TBI (toe-brachial index) are of particular importance and are used for confirming PAD [1, 2].

ABI measurement important for confirming PAD and risk stratification

A vascular physician must be consulted if an ABI < 0.7, systolic toe pressures < 40 mmHg, systolic ankle pressures < 70 mmHg or a tcPO2 value < 30 mmHg is determined in patients with diabetes [3]. In such cases, the risk of developing a foot ulcer is increased (▶ **Tab. 2**).

Regional foot ischaemia may also be present with palpable foot pulses or almost normal toe pressure values (example: heel lesion in people with diabetes mellitus who require dialysis).

Non-invasive hemodynamic functional examinations of the leg vessels are required to assess severity, course and therapy stratification in patients with PAD.

Imaging procedures (ultrasound sonography, MR angiography, CT angiography, i.a. DSA) should be performed on symptomatic or at-risk patients only with therapeutic consequences.

Due to the co-morbidity of people with diabetes mellitus (kidneys, eyes, heart), interdisciplinary diagnostics and therapy planning are indicated.

IMAGING DIAGNOSTICS

- Colour-coded duplex sonography
- MR angiography of the pelvic leg arteries
- CT angiography of the pelvic leg arteries
- Intra-arterial angiography with conventional angiography or CO_2

Colour-coded duplex sonography is of particular importance as a non-invasive method. It combines haemodynamic results with morphological findings and thus allows statements to be made on the localisation and morphology of vascular lesions.

If there are unclarities, cross-sectional imaging using Contrast-enhanced-MR angiography or CT angiography is recommended, however, it is important to take consideration of contraindications and side effects. Intra-arterial angiography is designed to identify and visualise a vascular segment that is connectable for potential surgical bypass.

▶ **Tab. 2** Severity and prognosis of PAD based on Doppler values [1–3].

	ABI	Ankle pressure (mmHg)	Toe pressure (mmHg)
Peripheral Arterial Disease	< 0.9		
Media sclerosis	> 1.3		
Critical limb ischaemia		< 50	< 30
Lack of wound healing	< 0.7	< 70	< 40

The often-limited kidney function in people with diabetes mellitus plays a special role in the administration of contrast agents, whereby contrast agent-induced nephropathy with the low or isoosmolar contrast agents commonly used today has become significantly rarer. Hydration, co-morbidity and medication of the patients must be taken into account.

CO_2 angiography can be specifically used in intervention procedures and offers a possibility for reducing contrast-induced renal dysfunction. In lower leg imaging, it is supplemented by the targeted administration of a few millilitres of a contrast agent containing iodine.

The indication for further radiological diagnostics should be made on an interdisciplinary level.

Therapy of PAD in people with diabetes mellitus

Basic principles of therapy

The therapy of PAD in people with diabetes mellitus has 2 basic goals: the improvement of peripheral blood flow in symptomatic patients as well as the therapy of vascular risk factors and concomitant diseases with special consideration of coronary and cerebrovascular vascular diseases (▶ **Tab. 3, 4**).

The basic treatment up to Fontaine stage IIb includes structured walking training (e. g., also in sports groups for people with diabetes mellitus). Arm ergometric exercise treatments for walking contraindications or limitations (e. g., orthopaedic problems, PNP, DFS, etc.) are just as effective as walking training. In addition to vascular sports, weight reduction in cases of obesity, giving up nicotine in smokers and the treatment of arterial hypertension, hypercholesterolaemia and diabetes mellitus are recognised therapeutic measures.

Conservative treatment in people with diabetes mellitus with symptomatic PAD includes the administration of platelet aggregation inhibitors (ASA 100 mg or clopidogrel 75 mg daily), the administration of statins and a structured vascular sports programme [3, 4].

Anticoagulant therapy for PAD

Patients with symptomatic arteriosclerosis require platelet aggregation inhibition with ASA or clopidogrel as a secondary prophylaxis. Clopidogrel has demonstrated its superiority to ASA in symptomatic PAD patients [6]. ASA should not be routinely prescribed

to patients with healthy cardiovascular systems [7–9], this is also valid for asymptomatic PAD patients [2]. Dual therapy with ASA and clopidogrel does not present any advantages over monotherapy with ASA [10], nor does therapy with ticagrelor compared to clopidogrel [11]. For patients with stable symptomatic PAD after invasive revascularisation and a high risk of ischaemic events, a combined therapy with rivaroxaban and ASA could show a reduction of the MACE (myocardial infarction, stroke, cardiovascular death) and MALE (major adverse limb event, severe circulatory disturbance/amputation) endpoints [12]. This is equally valid for patients with diabetes mellitus. This applies equally to patients with diabetes mellitus. For this reason, the current joint guideline recommendation of the PAD Working Group of the European Society of Cardiology and the European Diabetes Society recommends the combined administration of ASA 100 mg and rivaroxaban 2 × 2.5 mg daily in patients with diabetes and PAD [13].

Therapy of hypertension in patients with PAD

In general, all patients with arterial hypertension benefit from a reduction in blood pressure [14], and patients with PAD (i. e., high-risk patients) in particular have an improved cardiovascular prognosis. In patients with PAD, blood pressure < 120 mmHg and > 160 mmHg result in more leg events [15]. For this reason, blood pressure should not be set too low in PAD patients. Renin-angiotensin system inhibitors are the drugs of choice for PAD patients. PAD patients with cardiac comorbidity can also be treated with beta-blockers for intermittent claudication and critical limb ischaemia.

RECOMMENDATION FOR ANTICOAGULANT THERAPY IN PAD

Primary prevention
No indication for platelet aggregation inhibitors (PAI)
Secondary prevention

- Asymptomatic PAD: no clear indication for PAI
- Symptomatic PAD: clopidogrel 75 mg better than ASA 100 mg
- High risk for ischemic events: rivaroxaban 2 × 2.5 mg + ASA 100 mg

RECOMMENDATION BLOOD PRESSURE TARGETS FOR PATIENTS WITH PAD

Blood pressure target in PAD patients:

- 18–65 years < 130 mmHg
- 65 years < 140 mmHg
- Overall > 120 mmHg

Renin-angiotensin system inhibitors are the drugs of choice for PAD patients.

▶ **Tab. 3** Treatment goals.

Goal	Stage	Therapy
Inhibition of PAD progression	Fontaine stage I-II Rutherford 1–3	▪ Therapy of risk factors ▪ Walking training
Risk reduction of cardiovascular events	Fontaine stage I-IV Rutherford 0–6	▪ Therapy of risk factors ▪ Walking training
Improvement of walking performance and quality of life as well as pain reduction	Fontaine II Rutherford 2–4	
Risk reduction of peripheral vascular events	Fontaine II-IV Rutherford 3–6	▪ Reduction of further vascular interventions ▪ Avoidance of acute leg ischaemia (ALI)
Salvaging the leg	Fontaine III-IV Rutherford 4–6	▪ Avoidance of minor or major amputation

▶ **Tab. 4** Stage-adapted therapy methods. Source: [1].

	Fontaine stage			
Measure	**I**	**II**	**III**	**IV**
Risk factor management: giving up nicotine, diabetes therapy, statins, blood pressure treatment	+	+	+	+
Platelet aggregation inhibitors: acetylsalicylic acid or clopidogrel	(+)	+	+	+
Physical therapy: structured vascular sports/sport for people with diabetes mellitus	+	+		
Drug therapy: cilostazol or naftidrofuryl		+		
Structured wound treatment				+
Interventional therapy		+ *	+	+
Operative therapy		+ *	+	+

+ Recommendation; * in case of excessive patient suffering and suitable vascular morphology.

Lipid therapy for diabetes and PAD

Statins and Ezetrol

There is general consensus that cholesterol-lowering therapy has a positive effect on all-cause mortality and cardiovascular events in diabetic patients with PAD, but studies on the outcome of PAD-related endpoints is significantly weaker in diabetic patients. Existing recommendations result more from subgroup analyses of large endpoint studies and observational studies on coronary heart disease and cerebral angiopathy than from prospective randomised studies on PAD. Few studies indicate a reduction in the amputation rate [16] and an improvement in the pain-free walking distance. According to a current evaluation of the Veterans Affairs study, this applies both to the superior intensified therapy (e. g., atorvastatin 40–80 mg) and low-dose therapy (e. g., atorvastatin 10–20 mg or simvastatin 10–40 mg) [17]. Although there are good indications for a reduction of the amputation and all-cause mortality rates, there are also smaller studies with no significant effect on the improvement of walking distance. On average, an improvement in the walking distance of approx. 160 m can generally be achieved in PAD patients [18].

The recommended target values for LDL cholesterol in PAD patients are an absolute LDL cholesterol target < 70 mg/dl or 1.8 mmol/l or a reduction of more than 50 % for an initial LDL cholesterol of 70–135 mg/dl or 1.8–3.5 mmol/l [2]. In high-risk diabetics, i. e., those with an extremity at risk of amputation, an LDL cholesterol level of < 55 mg/dl is recommended [13].

For Ezetrol, there are no robust statistics available on PAC.

Fibrates

Technically, fibrates lower triglycerides and increase HDL cholesterol more than statins. Subgroup analyses (tertiary endpoint), e. g., of the FIELD study, show an absolute reduction of the microcirculation-related amputation rate by a relative 36 % in people with diabetes mellitus. The rate of major amputations and in patients with macroangiopathy was not different [19].

Proprotein convertase subtilisin/kexin type 9 inhibitors

Subgroup analyses of the FOURIER study show a 42 % reduction in PAD-related events (acute limb ischaemia, amputation, or urgent peripheral revascularisation) for patients with or without PAD at the beginning of the study [20]. This allows PCSK-9 inhibitors to be used in patients with progressive PAD on statin therapy or in patients with statin intolerance within the scope of the statutory health insurance funds' prescription ability and subject to the proviso of high therapy costs.

FACIT

- In the case of confirmed PAD, a statin therapy with the maximum tolerable dosage for the patient (both with and without existing coronary heart disease) should be chosen to reduce the amputation and mortality risks.
- Target values for PAD: LDL cholesterol < 70 mg/dl or lowering by more than 50 % (with an initial LDL cholesterol level of 70–135 mg/dl).

Antidiabetics for PAD

Biguanide

Metformin is also the oral antidiabetic of choice for people with diabetes and PAD. This is true even though the data is meagre in this respect. A recently-published study again proves the positive effect on CV survival, but not on salvaging extremities and openness rate after peripheral revascularisation [21].

Sulfonylureas and glinides

For both substance groups, no robust statistics on PAD are available. They should generally only be used in justified exceptional cases when costs determine the therapy. Due to the relatively high risk of hypoglycaemia and the presumably unfavourable effects in patients with pre-existing coronary heart disease, these substance groups are of little relevance [22].

Thiazolidinediones (PPAR-γ agonists)

For the only thiazolidinedione (TZD) pioglitazone still available in Germany, positive endpoint studies for cardiovascular survival in patients with type 2 diabetes and prediabetic patients are available with the PROACTIVE and IRIS studies [23–27]. In the PROACTIVE study, amputations were also considered a primary endpoint. However, no significant advantage over the control group could be observed here. TZDs are contraindicated for existing heart failure.

Dipeptidyl peptidase-4 inhibitors

The cardiovascular endpoint studies SAVOR-Timi 53, EXAMINE, TECOS and CAROLINA show a non-inferiority of DPP-4 inhibitors to the investigated endpoints cardiovascular death, non-fatal myocardial infarction or stroke compared to placebo or glimepiride. In the SAVOR-Timi-53 study, however, significantly more frequent hospitalisation with saxagliptin due to heart failure was observed, which is why this substance should be used with caution in patients with known heart failure. Cardiovascular superiority or advantages in cases of simultaneous PAD have not been proven [28–32].

Glucagon-like peptide-1 agonists

It was possible to demonstrate the positive effect of liraglutide, dulaglutide and semaglutide on cardiovascular events such as fatal and non-fatal myocardial infarction and nonfatal stroke compared to placebos in endpoint studies [33–35]. However, semaglutide in combination with insulin shows an increased rate of microvascular eye complications, which is why this GLP-1 agonist should not be used in patients with uncontrolled diabetic retinopathy in combination with insulin for the time being [34]. With regard to PAD, however, no endpoint data is available for this substance group either.

Sodium-glucose Cotransporter-2 inhibitors

The EMPAREG-outcome study, the DECLARE-TIMI study and the CANVAS study provide data on the positive influence of the substances empagliflozin, dapagliflozin and canagliflozin on cardiovascular endpoints such as cardiovascular death, fatal and non-fatal myocardial infarction and stroke [36–39]. The EMPAREG outcome study and the DECLARE-TIMI study showed no increased amputation rate. For canagliflozin, which is not on the market in Germany, the amputation rate was significantly increased in the CANVAS study. In the recently published CREDENCE study, however, this was not observed [40]. The use of canagliflozin in patients with type 2 diabetes and PAD is not currently recommended.

Basal insulin

There are no endpoint studies available for basal insulin therapy for patients with PAD. No reduction of cardiovascular endpoints could be demonstrated for insulin degludec or, in the ORIGIN study, for insulin glargine. However, there was no increased incidence of cardiovascular complications meaning that the therapy can be considered safe for the cardiovascular system [41, 42].

Insulin should be used in people with type 2 diabetes mellitus especially in the presence of cardiovascular complications – except in the initial adjustment phase – as far as possible, only after optimized oral or GLP-1-based subcutaneous antidiabetic therapy.

FACIT

- The data regarding antidiabetic therapy and PAD outcome is meagre.
- Metformin is also the oral antidiabetic of choice for people with diabetes and PAD.
- If PAD is confirmed, the next step should be to add an SGLT-2 inhibitor or a GLP-1 agonist.
- According to current data, the use of empagliflozin and dapagliflozin is safe. Canagliflozin, on the other hand, has shown an increased risk of amputation in a large outcome study (albeit in retrospective subgroup analysis).
- Therapy with basal insulin analogues is safe, but a reduction of cardiovascular events has not been proven.

Principles of interventional therapy

The interventional therapy of PAD depends on the stages of the disease and the affected vascular segments, which also applies for people with diabetes mellitus.

Intermittent claudication

In intermittent claudication, the therapy goal is an improvement of walking distance and quality of life. An initial intervention with subsequent structured walking training [44] has had the greatest success.

For aortoiliac disease, the primary openness rate 5 years after percutaneous intervention is – generally – stent implantation in over 90 % [45]. For iliofemoral lesions with involvement of the femoral artery, a hybrid procedure should be considered.

An intervention can also be considered even in femoropopliteal stenosis with lifestyle-limiting PAD, even if the restenosis rates are significantly higher. None of the guidelines recommend infrapopliteal, invasive therapy in the stage of intermittent claudication [46, 47].

Femoropopliteal surgery for short-stretch lesions with a length of less than 5 cm is still the indication for balloon dilatation only. Only from a lesion length of more than 10 cm do studies show a clear advantage of the additional implantation of self-expanding Nitinol stents [48]. Stents are also used in cases of recoil or dissection, even for shorter lesions. Paclitaxel-coated drug-eluting balloons (DEB) and stents (DES) showed a significant advantage over conventional PTA in multiple randomised controlled trials with postoperative monitoring periods of up to 5 years by reducing the restenosis rate [49, 50].

In December 2018, Katsanos published a meta-analysis using pooled data from 3 studies, including both DEB and DES, 2–5 years after implantation in which a statistically-significant higher all-cause mortality was determined compared to patients treated with uncoated systems [51]. In January 2019, for the first time, the US Food and Drug Administration (FDA) published recommendations in which it recommended preventive health protection by carefully weighing the benefits and risks of the use of paclitaxel-coated balloons and stents. It was strongly recommended to inform affected patients before the intervention that the use of paclitaxel-coated devices can lead to an increased probability of death as of 2 years after implantation. This recommendation was endorsed by both the Federal Institute for Drugs and Medical Products/Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and the affected German professional associations [52]. The most recent FDA publication on this subject appeared on August 7, 2019 [53]. Our own analyses also confirm the increased mortality signal after 5 years with the use of paclitaxel-coated balloons and stents. At the same time, the missing data on possible mechanisms, the weakness of meta-analyses of very different studies with limited case numbers and the high effectiveness of paclitaxel-coated balloons and stents in preventing restenosis are also pointed out. Most recently, a joint security notice was sent to users was in June 2020 by 9 participating companies

Critical limb ischaemia

If a circulatory disorder is present with acute danger to an extremity, initial revascularisation should be sought in addition to treating the accompanying infection. Here the "Endovascular first" strategy has gained in importance and is also recommended in the current German S3 guideline [46].

In the treatment of the aortoiliac and femoropopliteal segments, there is no difference in the intervention strategy compared to intermittent claudication.

Various techniques are available for infrainguinal endovascular recanalization. In principle, angioplasty is to be preferred in intraluminal procedures. In designated centres, an infrapopliteal leg salvaging rate of over 90 % can be achieved after percutaneous angioplasty [55].

Although a significant advantage of medicine-coated stents compared to balloon angioplasty could be demonstrated in small, randomised controlled trials in terms of amputation-free survival after 5 years, the benefit of medicine-coated balloons cannot yet be conclusively evaluated [56, 57].

In a 2020 paper, the Katsanos et al. group published another meta-analysis of randomised controlled trials on the mortality risk and amputation rates with the use of paclitaxel-coated balloons in the treatment of infrapopliteal arteries. Amputation-free survival was significantly worse in the group with paclitaxel-coated balloons than after treatment with uncoated balloons.

The rate of target lesion revascularisation (TLR) was significantly reduced when paclitaxel-coated balloons were used.

The results show a dose dependence with significance at a dose of paclitaxel classified as high (3.0–3.5 µg/mm) and lack of significance at a dose < 2.0 µg/mm). A non-target embolisation of paclitaxel is discussed as the cause [58].

A benefit assessment of DEB in PAD was performed in a 10/2020 report by the Medical Service of the Federal Health Insurance Funds [59]. In this assessment of the benefit and harm endpoints, the analysis for the infrapopliteal arteries showed no evidence of additional benefit of PTA with the use of a DEB compared to PTA alone with an uncoated balloon in the indication areas of de-novo stenoses and restenoses of the infrapopliteal arteries. This concerned, among others, the criteria of (major) amputations, mortality, and major adverse events. Also, with regard to quality of life at the time point 12 months after the procedure, there was neither an advantage nor a disadvantage of PTA with additional use of a DEB compared with PTA with a standard balloon alone. Data at longer time points is not available for any of these endpoints.

The detailed expert opinion is confirmed by an analysis of the different techniques for the treatment of infrapopliteal arteries, in which non-randomised studies were included because of the lack of randomised controlled trials to assess DES. No significant advantage of any method was found for the treatment of infrapopliteal arteries [60].

A further option is the possibility of gradual revascularisation [61]. Retrograde recanalization is successful in more than 80 % of cases of critical limb ischaemia without antegrade revascularisation [62]. However, these complex procedures increase the duration of the intervention and the radiation exposure for the patient and the examiner. The previously-prevailing opinion that the revascularisation results for diabetic foot are worse has been rendered obsolete. According to literature research, only the subgroup of people with diabetes mellitus requiring dialysis shows significantly poorer results both in the openness and the leg salvaging rate at each 50–70 % after 1 year, with a tendency towards a higher mortality rate [22]. In general, for people with diabetes mellitus and impaired kidney function as well as still-functioning residual renal function, CO_2 should be used as a negative intravascular contrast agent for angiography and interventional therapy for nephroprotection whenever possible [64].

Acute limb ischaemia

Interventional endovascular approaches are local catheterisation, mechanical thrombectomy by aspiration or special thrombectomy catheterisation. Modern concepts show 6-month amputation rates of less than 10 % with the best outcome at an occlusion duration of less than 14 days [45].

Care after vascular interventions

After peripheral vascular interventions, the administration of platelet aggregation inhibitors for secondary prophylaxis is absolutely necessary. Statins are also indicated for secondary prophylaxis (independent of the LDL cholesterol value). This not only improves clinical survival, but also significantly improves the bypass openness rate and walking ability.

The Voyager trial demonstrated that the administration of rivaroxaban at a dose of 2.5 mg twice daily in addition to aspirin 100 mg significantly reduced the risk of acute limb ischemia, major amputations due to vascular disease, myocardial infarction, stroke, and death due to cardiovascular disease in patients undergoing peripheral vascular procedures or surgery. This makes it the first ever large randomised trial to examine the benefit of platelet function inhibition or anticoagulation in patients after peripheral vascularisation. In particular, patients with an increased cardiovascular risk or increased risk of re-occlusion (long-distance recanalization) should therefore be offered this therapy. Additional administration of clopidogrel has no further benefit in this setting [69].

Structured vascular training improves walking ability and clinical outcome even after revascularizing procedures.

Surgical revascularisation

In addition to the "Endovascular first" strategy, surgical revascularisations are another essential component of the multimodal therapy concept. The international guidelines on critical leg ischaemia of the European Society for Vascular Surgery (ESVS), the American Society (SVS) and the World Federation of Vascular Societies (WFVS) were published in 2019. In 2020, the International Working Group of Diabetes additionally named criteria for the indication of surgical revascularisation as a complementary therapy alternative in a systematic review [65, 66].

Open surgical reconstruction procedures (bypass procedures) are therefore accepted treatment options in selected high-risk patients and in cases of critical limb ischaemia (Wound Ischemia and Infection Classification [= WIFI] stages 3 and 4 or WIFI ischaemia grades 2 and 3). An average operative risk exists with peri-procedural mortality > 5 % and an estimated 2-year survival rate > 50 %; a high operative risk exists with periprocedural mortality > 5 % and an estimated 2-year survival rate < 50 % [65].

A quality assurance study of the American Society of Vascular Surgery (SVS) from 2016 showed in 2566 patients that there was no significant difference between diabetic patients and non-diabetic patients with regard to primary openness rate, major amputation and mortality [67]. This applies to endovascular intervention as well as to bypass surgery. After appropriate risk adjustment, the 1-year results show no difference between intervention and bypass surgery. In conclusion, both endovascular intervention and open bypass surgery can be indicated and successfully performed in patients with critical limb ischaemia due to PAD with or without diabetes mellitus [67].

In the case of complex vascular pathologies, existing autologous vein (great saphenous vein) and so-called pedal "run-off" (open lower leg outflow into the foot), surgical treatment can be weighed against the endovascular procedure with the aim of improving inflow and outflow with justifiable surgical risk. Further indications for surgical revascularisation are unsuccessful endovascular recanalizations and repeated recurrent occlusions after previous endovascular interventions. So-called Hybrid procedures (combined open-endovascular) should be included in surgical planning and present another option for targeted surgical revascularisation. In the case of existing wounds, especially in the hindfoot and midfoot areas, angiosome-related revascularisation should be performed, especially if an existing target vascular segment is available. The preferred infrainguinal bypass material is the autologous vein. Preoperative vein mapping should always include the brachial veins in addition to the great saphenous and parietal veins and should be considered in surgical planning. After femoro-crural bypasses using autologous veins, openness rates of 82 % and leg preservation rates of 85 % at 1 year and 87 % at 2 years have been published. In centres with the appropriate expertise, the opening rate of foot bypasses is up to 79 % after 3 years; the leg preservation rate is up to 98 % after 1 year, 82 % after 3 years and 78–82 % after 5 years [66]. Non-autologous bypass material should only be used if no autologous material (leg or arm vein) is available and endovascular therapy options have been exhausted. If no suitable autologous bypass material (autologous vein) is available, even crural bypasses with heparin-coated PTFE grafts (PTFE: polytetrafluoroethylene) can be created with a secondary openness rate of 47.4 %, a leg preservation rate of 79.3 % and a survival rate of 64.6 % after 2 years without significant difference to results of venous bypasses [68].

Inguinal surgical revascularisation is required for at least 50 % haemodynamically-relevant stenosis of the common femoral ar-

tery and the profundal femoral artery. In these regions, endovascular recanalization should primarily be avoided.

In cases of extensive deep soft tissue infection (PEDIS classification stage 3 and 4), plantar abscess, moist gangrene and incipient sepsis, the primary procedure is urgent surgical sanitation of the infection. Major amputations should be avoided by abscess drainage, soft tissue debridement and, if necessary, minor resections. In these stages, at least one iliac and femoral inflow improvement is required as an additive measure.

Conflict of Interest

NM received lecture and travel fees from: Bayer Vital, BARD, Medtronic. HL received lecture fees and consultancy fees from Bayer Vital GmbH, Pfizer, medac. DB received lecture fees and consulting fees from Medtronic, W.L. Gore & Ass. and Siemens in the last 3 years. BB received speaker fees from Pfizer, which also sponsors training events. Company Amgen: only training courses. Company Abbott: formerly shares.

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