

REVIEW ARTICLE

Chronic Critical Limb Ischemia

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SUMMARY

Background: Some 40 000 lower limb amputations are performed in Germany each year, 70% of them in diabetics. About 80% of all major amputations may be preventable with the use of new interventional and vascular surgical procedures, particularly on the arteries of the leg and foot. We present the current state of the art in revascularization techniques and evaluate their usefulness for preservation of the lower limb.

Methods: This overview is based on the guidelines for the diagnosis and treatment of peripheral artery disease (PAD) and diabetic foot syndrome (DFS) that have been issued by the American Heart Association (AHA), the American College of Cardiology (ACC), the German Society of Angiology (DGA), the Trans-Atlantic Intersociety Consensus (TASC II), the German Society of Vascular Surgery (DGG), and the German Diabetes Society (DDG). A selective search in PubMed for relevant articles that appeared from 2000 to 2011 was conducted with the search terms “pedal bypass,” “vascular intervention crural pedal,” and “crural-pedal revascularization.”

Results: Most of the data on crural and pedal revascularization are derived from small-scale studies. The few comparative studies of interventional treatments and bypass surgery have not revealed any significant differences in outcome, but all studies of revascularization have shown good success rates for lower limb preservation.

Conclusion: Though the data are still sparse, the high reported rates of limb preservation imply that peripheral revascularization techniques can play a major role in the treatment of chronic critical limb ischemia (CLI). Therefore, these techniques are recommended without exception by the current guidelines.

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The greatest challenge in the treatment of patients with peripheral arterial disease (PAD) and diabetic foot syndrome (DFS) is avoiding major amputation. Over 40 000 such amputations of the lower limb are carried out each year in Germany; 70% of the patients are diabetics (1–3). Impaired arterial perfusion is the principal cause of poor wound healing and refractory rest pain. Arteries of the pelvis, upper leg and proximal lower leg used to be the main target vessels for bypass surgery and catheter interventions, but nowadays arteries right down to the foot can be successfully revascularized. Our intention here is to review the prospects for limb preservation and healing of chronic wounds by means of this approach. The data we present were gleaned from a selective search of publications in the period from 2000 to 2011 and from current guidelines for the treatment of PAD (4–6, e5) and DFS (7).

Indications

Some 1.8 million people in Germany have symptomatic PAD, and each year 50 000 to 80 000 of them develop chronic critical limb ischemia (CLI) (6). The prevalence of diabetes mellitus in the German population is 7%, and around 90 000 people suffer from DFS with angiopathic component (7).

CLI and DFS are the only confirmed indications for crural and pedal revascularization, and the decision to undertake such treatment should be arrived at jointly by angiologists, radiologists, and vascular surgeons. Apart from determination of the appropriate technique for revascularization—surgical or interventional—the timing is crucial: soon after failure of conservative treatment, not when advanced infection and spreading necrosis of the foot already make amputation unavoidable.

In deciding whether revascularization should be achieved by surgical or interventional means, we adhere to the TASC II criteria, in the knowledge that these recommendations were actually formulated for the iliac and femoropopliteal vessels. There are as yet inadequate comparative data for crural and pedal vascular interventions, so no guidelines are available. While at the claudication stage the sole criterion of success is the long-term patency rate after revascularization, the primary treatment goal in CLI is limb preservation.

Depending on the method used, timely revascularization achieves 1-year limb preservation rates of 70% to 90% (8, 9). Statistics on long-term patency and limb preservation following revascularization are of limited relevance, because the mortality of CLI is >20% at 1 year and 55% after 5 years. Only 8% of the patients survive 10 years (5).

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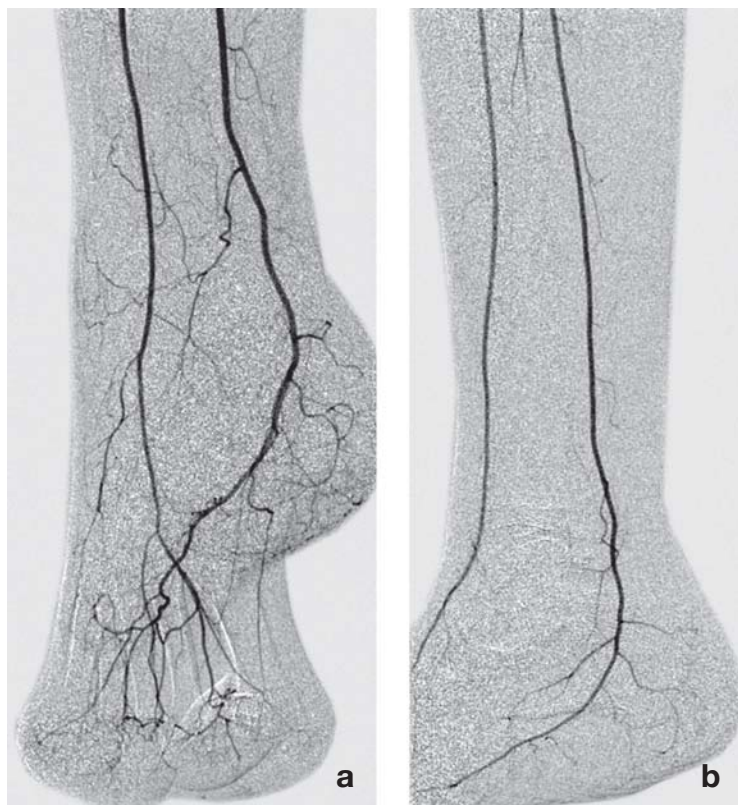


Figure 1: Digital subtraction angiography of the arteries of the foot (a, anteroposterior; b, lateral)

Diagnostic imaging

Basic non-invasive angiological investigations (pulse, Doppler blood pressure measurement, oscillography) can confirm the diagnosis of PAD and supply information on location and severity, but alone do not permit a decision regarding the appropriate technique of revascularization in crural and pedal arteries. The essential requirements for the data to be provided by diagnostic imaging are laid down in the standards of TASC II. The relevant aspects are the length and sequence of stenosed segments, differentiation of occlusion from stenosis, and the length of the occluded segment (6).

Duplex sonography is valuable particularly in the diagnostic imaging of the pelvic region and the femoropopliteal arteries. However, its usefulness is restricted by attenuation phenomena in the leg in this predominantly multimorbid group of patients (diabetes mellitus, renal failure) (4).

After localization of the site of impaired perfusion by means of clinical examination and non-invasive techniques, particularly in patients with renal failure, primary digital subtraction angiography (DSA) preparatory to intervention can render other diagnostic investigations (CTA, MRA) unnecessary. Precise delineation of all crural and pedal arteries, also in the late phase, is important (*Figure 1*). Even in patients with pronounced calcifications, the very high spatial and

temporal-dynamic resolution permit diagnosis and treatment in one single step. In the case of impaired renal function (glomerular filtration rate [GFR] <60 mL/min/1.73 m²), it may be best to restrict diagnostic DSA to the crural level. Moreover, nephroprotective measures (NaCl 0.9 i.v. 10 mL/kg BW 12 h before and up to 12 h after administration of contrast medium [CM], ACC 2×600 mg i.v. or p.o. on the day before administration of CM and on the day of examination, discontinuation of diuretics and non-steroidal antirheumatics [NSAR] 24 h before examination) are advisable (4) (*Table*).

Magnetic resonance angiography (MRA) visualizes the whole vascular tree with clarity comparable to that achieved with DSA. The method is non-invasive and uses gadolinium-containing CM that are non-nephrotoxic, carry a tenfold lower risk of allergy than iodine-containing CM, and also have no impact on thyroid function. Disadvantages of MRA are overestimation of the degree of stenosis, signal extinction by stents, failure to visualize vessel wall calcifications, venous superimposition by AV shunts in the lower leg in the presence of CLI (13, 14), and artifacts caused by turbulent or slow blood flow (6). Venous superimposition can be minimized by dynamic MRA with imaging every 2 s for 30 s. However, it often necessitates administration of a second dose of gadolinium to depict the arteries of the pelvis and upper leg. Resolution, particularly of the arteries of the foot, is reduced. These methodological limitations can be partially overcome by the use of 3-T MR devices and CM that do not permeate the vascular lumen (11).

Recent advances in magnetic resonance imaging (MRI) (e.g., improved data acquisition, new coil technology) permit high-quality visualization of the whole vascular tree even in the presence of marked calcifications (12). An additional significant contraindication to MRI in patients with GFR <30 mL/min/1.73 m² has emerged with the recognition of nephrogenic systemic fibrosis (NSF) caused by gadolinium in patients with renal failure (German Federal Institute for Drugs and Medical Devices [BfArM]: over 500 cases worldwide up to October 2008) (15). Time-of-flight sequences avoid this problem by enabling visualization of vessels without CM, but they have poor resolution and have not yet been validated for the crural level. Multislice computed tomography angiography (MS-CTA) with multirow CT scanners (≥16 detector rows) is superior to MRI for portrayal of calcifications and in-stent stenoses. The improved image quality comes at the price of higher radiation exposure of the patient than is the case for DSA (10). CO₂ angiography, although it is not listed in the current guideline recommendations for diagnosis, has experienced a renaissance since the recognition of NSF in connection with the administration of gadolinium-containing CM in patients with advanced renal failure. It does not attain the image quality of the other imaging procedures, but features none of the risks associated with CM. The combination of duplex sonography at the pelvic level and DSA of the arteries of the leg—alternatively, in the presence of

advanced renal failure, CO₂ angiography of the crural and pedal arteries—represents a diagnostic algorithm that delivers all the information required to decide on the appropriate treatment while minimizing the risks of CM administration (Table).

Conservative treatment

Conservative treatment has three different functions in patients with CLI.

Preparation for planned crural/pedal bypass surgery

Multimorbid patients must first be rendered operable. To this end, decompensating cardiopulmonary disorders must be recompensated. Local conditions at the operation site often have to be dealt with before bypass surgery can be carried out, for example skin infections in the area of the planned anastomosis or ischemic or lymphogenic edema, which if left untreated predisposes to postoperative disturbance of wound healing.

Postoperative treatment after bypass implantation

The aim of postoperative conservative treatment is prevention of early bypass malfunction. This includes optimal local treatment of the surgical wounds and timely manual lymph drainage to deal promptly with the frequent postoperative lymphedema. Particularly in the case of reduced arterial flow, the perfusion pressure in the vessels is so low that any additional increase in pressure by interstitial edema formation can endanger bypass function. The edema can be treated by compression only if the Doppler pressure reading is clearly above the pressure of 40 to 50 mm Hg caused by a compression bandage.

Of course, depending on the bypass situation, postoperative treatment includes administration of thrombocyte aggregation inhibitors or anticoagulants, with corresponding instruction of the patient.

Measures to deal with the cardiovascular risk factors form part of the conservative treatment in every stage of PAD. Because of the often simultaneous occurrence of coronary heart disease and cerebral arteriovenous disease in the stage of CLI, the same strict treatment goals apply as for cardiology patients (4).

Conservative treatment when intervention and bypass surgery are not possible

In the absence of a suitable peripheral target vessel for intervention or bypass surgery, the prospects for success of conservative treatment alone are at best limited. The first-line option in these circumstances is PGE1 infusion, but cardiac adverse effects mean that this treatment is occasionally not tolerated (4–6). Intra-arterial infusion at reduced dosage may be helpful in such cases. However, 40% of exclusively conservatively treated patients have to have a major amputation within 6 months (6).

Conservative treatment also includes adequate oxygenation of the blood (compensation of cardiopulmonary diseases, compensation of anemia with hemoglobin under 9 g/dL) and connective tissue massage,

TABELLE

Recommendations for diagnostic imaging in CLI, depending on renal function

Stage of renal failure	Diagnostic strategy
GFR >60 mL/min/1,73 m ²	DSA of pelvic and lower limb arteries with visualization of pedal arteries
GFR 30–60 mL/min/1,73 m ²	Duplex sonography of pelvic arteries + DSA of the arteries of the affected leg, including the foot (fine-needle angiography) 12 h before and after administration of CM: – NaCl 0.9% 10 mL/kg BW i.v. – ACC 600 2 × 1 i.v. or p.o. – Discontinue diuretics 24 h before CM – Discontinue NSAR 24 h before CM
GFR <30 mL/min/1,73 m ²	Duplex sonography of pelvic arteries + CO ₂ angiography of the arteries of the affected leg right down to the foot

CLI, chronic critical limb ischemia; CM, contrast medium; DSA, digital subtraction angiography; GFR, glomerular filtration rate; NSAR, non-steroidal antiinflammatories

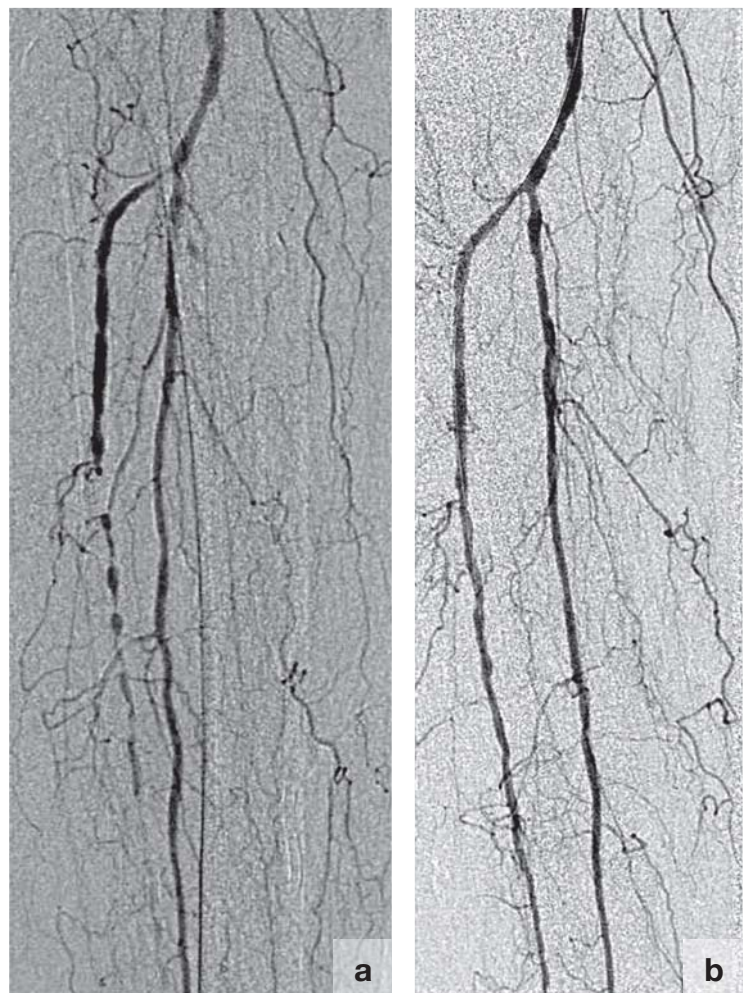
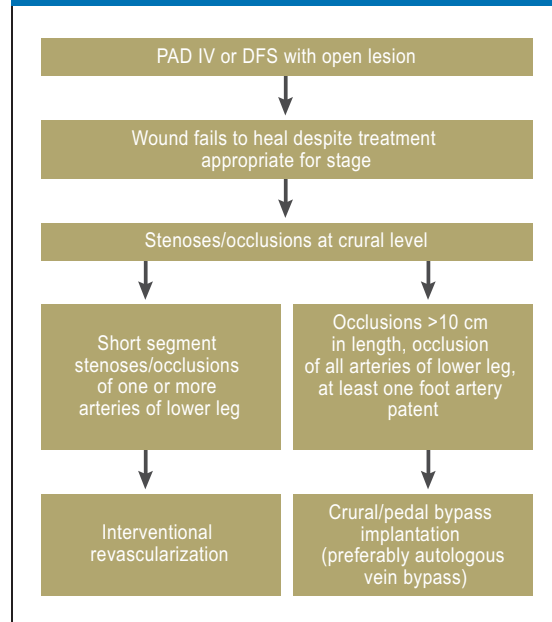


Figure 2: Crural intervention (a, before; b, after percutaneous transluminal angioplasty)

Figure 3: Digital subtraction angiography of a popliteo-pedal bypass from the popliteal artery (P3) to the dorsal artery of the foot



FIGURE 4



Indications for crural/pedal bypass implantation or intervention. PAD, peripheral arterial disease; DFS, diabetic foot syndrome

which leads to widening of peripheral vessels. Any infection requires systemic antibiotic treatment following swabbing or wound biopsy to determine the bacteria present and produce an antibiogram (4, 16).

Pain treatment to avoid stress-related vasoconstriction is particularly important. Spinal cord stimulation (SCS) is useful: It alleviates pain and has metabolic effects that help to improve the microcirculation (17, 18).

Lumbar sympathectomy is used in patients with endangiitis obliterans in whom there is no potential for revascularization, but is of no therapeutic benefit in diabetics because of the autonomic neuropathy associated with diabetes (19).

Basic treatment measures include foot-down positioning and strict relief of pressure on the affected foot, including the heel. Patients and their relatives must be shown how to inspect the foot every day and avoid pressure points. In addition to the acute treatment, referral of high-risk patients to specialized foot clinics can avoid future amputations (20).

Interventional treatment

The data on interventional revascularization of crural and/or pedal arteries in CLI are still too sparse to permit formulation of evidence-based guidelines. The indication criteria are oriented on the TASC II recommendations for treatment at the well-investigated femoropopliteal level: the shorter the stenoses/occlusions and the fewer arteries requiring treatment, the better the clinical outcome. The technical success rate of infragenicular interventions is 90% and the clinical success rate 70% to 90% (6, 21–23) (Figure 2). The restenosis

rate remains very high, however; 65% in the first 2 years after treatment. The rate of complications for therapeutic interventions in the leg is 2.4% to 17% (6).

Various new techniques (long balloons for diffuse long-segment stenoses, drug-eluting stents [DES], bare metal stents [BMS], drug-coated balloons, cutting balloons, laser angioplasty, atherectomy) are being investigated in studies (24, 25, e1–e4), but none can yet be recommended for routine clinical application. Early results indicate, however, that, in the leg, DES achieves better patency rates at one-year follow-up than balloon percutaneous transluminal angioplasty (PTA) or BMS (DES 81% to 85%, balloon PTA 58%, BMS 56%) (e12) (Scheinert D: Achilles study—randomized comparison of sirolimus eluting stents vs PTA for BTK obstructions. Presented at LINC 2011 Annual Meeting, 19 January 2011, Leipzig, Germany).

Surgical treatment

In line with the TASC II criteria for the femoropopliteal level, peripheral bypass surgery is also recommended for revascularization of long-segment occlusions of the crural and pedal circulation (4, 6, 7, e5).

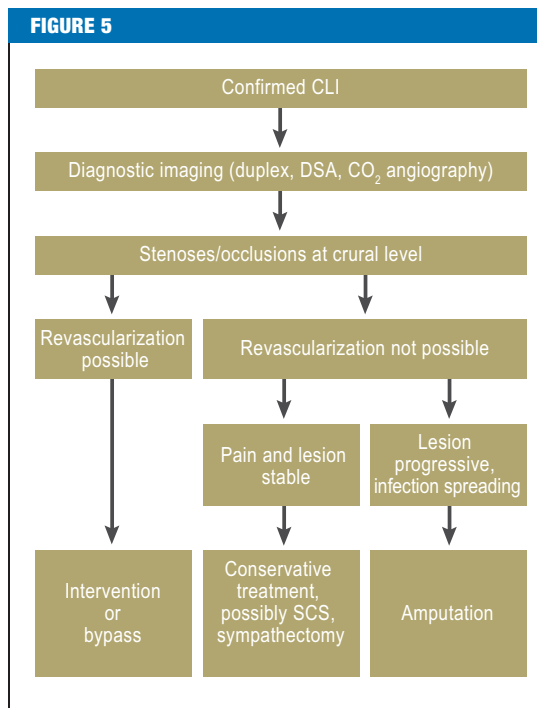
Autologous vein material should be preferred. One-year follow-up rates of 80% to 90% for bypass patency and 90% to 95% for limb preservation can be achieved by this method (6, e7). If no suitable vein is available, thin-walled polytetrafluoroethylene (PTFE) implants can be used; however, the secondary 5-year patency rate for PTFE implants is 35%, compared with 60% for venous bypasses (6).

The implanted bypass should be no longer than necessary. All variants (femoro-crural, popliteo-crural, popliteo/cruro-pedal) are technically feasible (Figure 3). The 5-year rates for bypass patency and limb preservation are approximately 60% and 80% respectively (6, e7). Bypasses can be implanted in all three arteries of the leg, with no differences in prognosis (e7, e8). There is also no significant difference in outcome between diabetics and non-diabetics (e9). The dorsal artery of the foot and the posterior tibial artery as far as the plantar artery are suitable for pedal reconstruction. Imaging of the vessels of the foot reveals amenable pedal arteries in around 90% of patients, particularly in diabetics (e9).

Postoperative wound healing is problematic in 15% to 25% of cases, and the rate of bypass infections is 1% to 3% (predominantly in artificial implants). The perioperative cardiovascular mortality is 1% to 2%, and 10% of patients have died by a year after operation (6). Cruro-pedal bypasses have to be monitored especially closely in the first year, with clinical examination at 3-month intervals. In our experience additional duplex sonography at each follow-up is beneficial, although the published data are contradictory (e10).

Discussion

Revascularization of crural or pedal arteries should be reserved for patients with CLI (Fontaine stage III and IV or Rutherford stage IV to VI). Infragenicular pro-



Treatment strategy in critical limb ischemia

(SCS, spinal cord stimulation)

cedures, whether surgical or interventional, are not indicated in intermittent claudication.

Duplex sonography (performed by an experienced examiner) and MRA have proved their worth in preoperative imaging. However, these procedures do not yield sufficient information in candidates for crural and pedal vascular reconstruction. These patients require visualization of vessels right down to the pedal arcade, so DSA still has a role in diagnosis. The combination of duplex sonography of the pelvic arteries with DSA of the arteries of the leg and foot (CO₂ angiography instead of DSA in patients with GFR <30 mL/min/1.73 m²) yields all the information needed for planning crural or pedal revascularization.

The decision whether revascularization should be carried out by interventional means or by open surgery is a matter for an interdisciplinary team. In the absence of adequate comparative data on crural and pedal interventions and bypasses, we are guided by the morphologically defined TASC II criteria for iliac and femoropopliteal procedures (Figure 4). Furthermore, a significant part is played by factors such as the patient's general health and fitness for anesthesia, the condition of the skin in the area of the planned anastomosis, and the experience of the team members.

Because surgical treatment is more invasive than a catheter intervention and the rates of both patency and limb preservation are comparable, intervention should be preferred, provided the anatomic preconditions are fulfilled (4).

Some new interventional procedures cannot yet be recommended for general use because of low case numbers and short observation periods. In general, one

should ensure in all peripheral vascular interventions that a distal segment of uninjured artery is left that can be used for a functioning bypass anastomosis.

Autologous veins should preferably be used for surgical revascularization of crural or pedal arteries. In the absence of suitable veins, composite or sequential bypasses can be created. Finally, an extra-anatomic bypass to the anterior tibial artery can be considered.

In cases of multilevel disease endovascular and surgical procedures can be combined; the flow of blood into or out of a bypass can be improved by interventional means.

If revascularization is no longer possible, infusion of PGE1 may alleviate pain and promote ulcer healing (Figure 5). If all options for revascularization and for conservative treatment have been exhausted, SCS may help to preserve the limb in selected cases.

No patient with CLI should be subjected to below-knee or above-knee amputation without the feasibility of crural and pedal revascularization being explored. Limb preservation must remain the foremost goal in order to preserve quality of life and avoid dependence on care. Crural and pedal revascularization, whether achieved by interventional means, open surgery, or a combination of both, achieves limb preservation rates of 90% to 95% after 1 year and 80% to 90% after 3 to 5 years.

Conflict of interest statement

Prof. Zeller acts as consultant to Cordis, Cook, ev3, and Medtronic. He has received lecture fees and reimbursement of training and accommodation costs from ev3, Cordis, Medtronic, Cook, Gore, Biotronik, Abbott, Vascular IDEV, and Straub Medical.

Dr. Eder has received reimbursement of costs for congress attendance and accommodation from Gore and Bard.

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The remaining authors declare that no conflict of interest exists.

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KEY MESSAGES

- Vascular reconstruction—crural or pedal, interventional or surgical—is indicated in peripheral arterial disease stage III or IV and in diabetic foot syndrome. These diseases are responsible for 40 000 major amputations each year in Germany.
- The primary aim of treatment for chronic critical limb ischemia is limb preservation. If all options for revascularization are exploited, this goal can be achieved in around 90% of cases.
- No amputation may be performed without previous diagnostic imaging of the arterial circulation down to and including the foot, followed by interdisciplinary discussion of the potential for revascularization.
- Duplex sonography, digital subtraction angiography, CT angiography, MR angiography, and in the case of advanced renal failure CO₂ angiography, singly or in combination, are suitable for diagnostic imaging of crural and pedal arteries.
- The long-term outcomes of interventional and operative cruropedal revascularization do not differ significantly. The complication rate for interventional procedures is 2.4% to 17%, while wound healing is problematic after 15% to 25% of bypass operations. If at all possible, the less invasive intervention method should be tried first, always leaving a distal segment of artery that can be used to create a bypass if necessary.

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