Position paper

Management of chronic peripheral artery disease patients with indication for endovascular revascularization

A position paper by the European Society of Vascular Medicine

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Summary: With an increasing global burden of patients with chronic peripheral artery disease (PAD) the safe and effective provision of lower limb revascularisation is a growing medical need. Endovascular procedures for the treatment of PAD have become a crucial cornerstone of modern vascular medicine, and the first line revascularisation approach if technically feasible and taking patient choice into consideration. With the increasing age of patients with PAD and the increasing number of comorbidities open vascular surgery is also often not feasible. We outline a framework of key messages, endorsed by the board of the European Society of Vascular Medicine for pre-, peri- and post procedural management of patients requiring endovascular arterial procedures of the lower limbs. These key messages emphasize the important and increasing role of interventional vascular physicians.

Keywords: Peripheral artery disease, treatment guidelines, vascular medicine

Introduction

This position statement provides an evidence-based framework for specialised physicians involved in the management of patients with symptomatic peripheral artery disease, having a potential indication for endovascular lower extremity arterial revascularisation. It has been endorsed by the board of the *European Society of Vascular Medicine* and reviewed by the UK based vascular charity organisation the *Circulation Foundation*. It aims to optimise pre-, peri- and post-interventional management by reducing unwarranted variation in care for the benefit of this growing and vulnerable patient population highlighting the key role of vascular physicians [1].

The burden of PAD is steadily increasing worldwide. While it was estimated that in 2010 202 Million people lived with PAD, this number increased to 237 Million in 2015 and this may be due in part to the global diabetes pandemic and also to an ageing population [2, 3, 4]. PAD is very common in people with diabetes, and increases the risk of non-healing ulcers, amputation, and mortality [5, 6, 7, 8]. So the increasing numbers of PAD are likely driven by growing numbers of people with diabetes, which were estimated at 422 Million in 2014 and increase to 578 Million by 2030 according to the WHO. PAD is the most common initial manifestations of cardiovascular disease in type 2 diabetes [9]. Mortality after diabetes-related amputation exceeds 70% at 5 years [10]. Hospital admissions for diabetic foot ulcers are higher than those for congestive heart failure, renal disease, depression, and most forms of cancer [11]. In the UK, diabetic foot care costs are rising. In 2010–11 they were estimated at £580M (~0.6% NHS expenditure) with more than half spent on ulcer care in primary community care and increased to £837–946 M (0.8–9% NHS expenditure) in 2014–2015 [12, 13, 14]. Optimal therapy and smoking cessation can decrease the risk by 40%, and timely revascularization promotes wound healing and prevents amputation [15]. Revascularization is a huge untapped potential for saving healthcare costs and improving wellbeing.

The patient profile of increasing age, high prevalence of co-morbidities and large variety of often complex vascular lesion morphologies makes endovascular revascularisation in most cases the first and sometime also the only choice, chosen over the more invasive surgical option. Mortality in the postoperative period is about 4% before hospital discharge and 5.5% in the first year [16, 17]. The probability of death increases with age, major surgery, severe comorbidities and if postoperative complications occur. While many call for randomized controlled trials comparing the outcome after surgical to endovascular revascularisation like the BASIL trial, this is becoming increasingly difficult as for a growing number of patients complex surgical procedures are not possible, do often not reflect patient choice and cannot be delivered at the scale required [18]. Overall, endovascular revascularisation is inherently less invasive than surgery, cheaper and associated with lower peri-procedural complication rates with similar or better amputation free survival [18, 19, 20, 21]. However, more repeat procedures particularly in patients with diabetes or severe renal disease may be required. In most cases endovascular procedures do not jeopardise surgical options in the future.

Key messages

- Growing global burden of PAD
- Need for provision of timely, safe and effective revascularisation at scale
- Endovascular revascularisation in most cases the first choice (from a patient, medical and economic perspective)

Pre-interventional

General considerations about indications, risks and benefits

The technical progress in interventional material and techniques, and the growing know-how of interventionalists make even complex endovascular procedures in the majority of cases safe and effective [21]. Nevertheless, the patients are becoming older and the occurrence of obesity, hypertension and diabetes is growing. Parallel to this, co-morbidities including polyvascular disease and clinically relevant renal impairment are more frequent and patients are often on a complex medication regime. All these factors need to be considered to allow safe and effective procedures. The social perspective and the importance of taking patient choice into account must be also recognised.

Ahead of any intervention there must be a detailed discussion with the patient, evaluating all revascularization possibilities. The individual risk factors have to be identified and mitigated and risks clearly balanced against the expected benefits and technical feasibility of the intervention. In all cases, the medication needs to be reviewed and the periprocedural changes in the medication should be explained to the patient and documented in the notes. This discussion should be documented in detail during the informed consent process, which has at the end to be signed by the patient and the interventionalist, who will perform the procedure. In elective cases, this discussion should be performed at least 24 hours before the intervention.

Nowadays peripheral endovascular procedures can also be performed on a day case basis. Advantages are cost-effectiveness and patient preference. Main concerns relate to safety, as patients with PAD are generally a higher risk population. While no risk scores for complications exist, several studies have shown that complication rates in selected patients are low [22]. Typical inclusion criteria for day case based angioplasty are body mass index <35 kg/m^2, low perioperative risk (e.g. ASA <4), sufficient kidney function (e.g. chronic kidney disease <4), sheath size $\leq$7F needed for procedure, not socially isolated with <1 h drive to hospital, telephone available with responsible adult present overnight, and no anti-coagulation requiring bridging. While the use of arterial occlusion systems should be used, if possible, haemostasis with manual compression does not preclude same day discharge [23]. Accordingly, the day case treatment should be reserved for low-risk patients, and effective post-procedural care, optimal medical management and follow-up needs to be in place.

Key messages

- Catheter interventions are in experienced hands increasingly safe and effective for many patients
- Expectations of the individual patients are growing, parallel with the technical possibilities and the

medical know-how in catheter interventions and need to be considered (Patient choice)
- Endovascular revascularisation procedures are in most cases feasible and effective but should be performed under clearly defined conditions and need timely individual planning
- The personal communication between patient and interventionalist (with information about all aspects of the planned procedure) at least 24 h prior the procedure is, besides medico-legal aspects, crucial for a good patient-doctor relationship and contributes to therapeutical success

Pre-interventional assessment and workup

Assessment of case severity

As the foremost goal of revascularization is to improve blood flow to the foot, it is important to assess the severity of PAD including degree of ischaemia, pattern and extent of lesions, severity of symptoms, likelihood of symptomatic improvement and limb salvage [5, 24]. Of note, while chronic critical lower limb ischaemia (CLI) has been defined as ischaemia that endangers the leg there is no consensus on its definition in terms of haemodynamics and most of the existing classifications are not based on evidence [24]. Consequently, diagnostic tests such as ABI or toe pressure (TBI) can only help to evaluate the degree of ischaemia to a certain degree and the absolute values need to be evaluated together with symptoms. In this context, it is important to appreciate that the vascular pathophysiology of PAD is complex, in particular in patients with diabetes and CKD as these not only lead to macrovascular atherosclerosis (intimal plaques) that can be treated with angioplasty but also arteriosclerosis (media sclerosis) and microvascular disease. In addition, vascular calcifications make revascularisations more difficult and may limit long term patency [25]. The likelihood of obtaining technical success with acceptable long-term outcome and expected symptomatic or prognostic benefits have to be balanced against potential procedural risk associated with the particular lesion complexity and co-morbidities. While no dedicated risk scoring framework exists, it is clear that endovascular revascularisations pose lower risk for coronary or cerebrovascular peri-procedural events and access site related complications, when compared to surgery [19, 21, 26, 27, 28].

The vascular medicine team needs to decide based on the clinical severity of PAD on the indication for revascularization, evaluate the peri-procedural global and cardiovascular risks, and propose a method for revascularization. Joint discussion in a multidisciplinary team including vascular surgeons is often useful during this process. Patient pre-procedural evaluation addresses PAD itself, coronary and cerebrovascular clinical conditions, global patient risk, but also focuses on the technical feasibility including best choice of the arterial access site, and potential patient-specific risks related to the diagnostic procedure and interventional therapy.

Assessment for PAD revascularization also needs to be fully supported by complete clinical evaluation (history and physical examination). This will also help to define the clinical goal of a procedure and manage expectations, as only ischaemia related symptoms are likely to improve by revascularisation. Therefore, symptoms related to venous disease, neuropathy or musculoskeletal issues need to be considered for final decision making. When debridement or minor amputations are planned, revascularisation should be performed prior to this to support optimal wound healing. Patient's history will reveal date of claudication start, walking perimeter evolution, duration since rest pain started, duration since trophic changes appeared and their evolution, need for analgesics for pain relief and response to previous medication. History also should focus on previous coronary and cerebrovascular events, mainly angina pectoris, arrythmia, acute coronary syndromes, transient cerebral ischemic attacks, stroke and neurologic sequala. Physical evaluation should include inspection, pulses palpation and artery auscultation. This not only grades PAD ischaemia severity and supports the presence of associated arterial stenosis in remote areas (e.g., carotids, subclavian arteries), but also helps to identify available sites for arterial access (e.g., femoral or radial). The full extent of cardiovascular risk factors (e.g., hypertension, diabetes, dyslipidaemia, obesity, smoking) presence and degree of control under therapy, needs to be evaluated, as well as the presence of coexistent renal, respiratory, haematologic, aortic or other organ disorders.

Key messages

- PAD patients have in general a high cardiovascular risk
- But the peri-procedural cardiovascular risk is lo
- Pre-interventional assessment of technical feasibility, individual risks, treatment goals and patient choice are integral parts of the decision making

Standard pre-interventional diagnostic investigations

If there is a clinical suspicion of symptomatic PAD including typical claudication, tissue loss (ulcers or gangrene) or rest pain, a complete physical exam with peripheral pulse status, measurement of ankle brachial index (ABI) and duplex ultrasound scan of aorta, pelvic and limb arteries should be performed (Figure 1). If ABI is less or equal to 0.9 together with typical symptoms and concordant pathological wave forms such as monophasic signals, the diagnosis of PAD is confirmed. If there is discordance of examination results, further non-invasive evaluation of ischaemia severity needs to be performed. In people with diabetes and renal failure medial sclerosis can lead to false

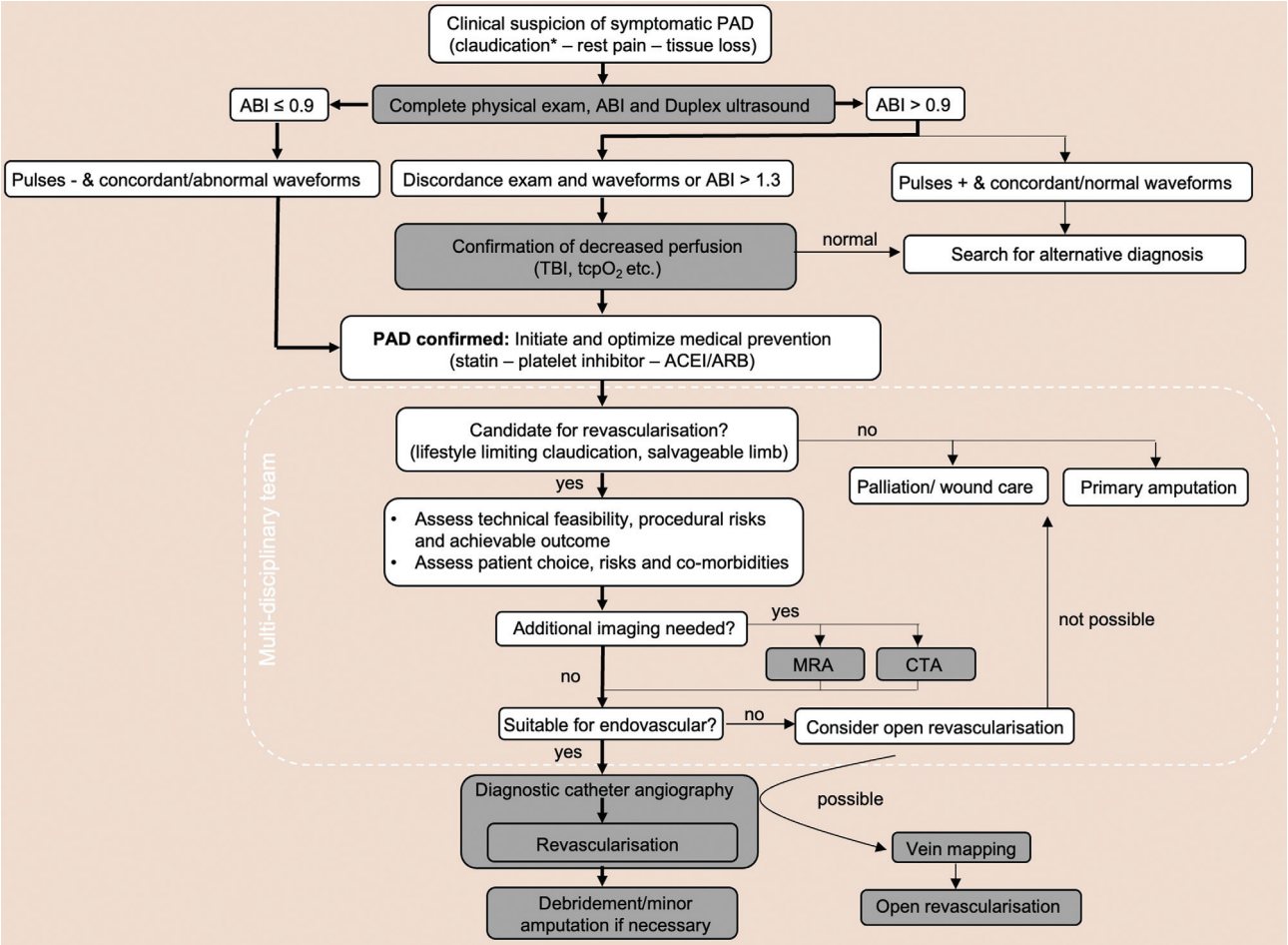

Figure 1. Schematic diagram of workflow.

normal or increased ABI due to medial sclerosis. Toe brachial pressure (TBI), transcutaneous oxygen pressure or oscillometric ABI measurement can help to confirm or reject a PAD diagnosis. Measuring the extent of ischaemia is useful for the decision on revascularisation. If possible it should be assessed by TBI in particular when there are discordant exams. Ultrasound, performed by a skilled vascular medicine physician, nurse or technician, is useful for the identification of arterial lesions topography and type of distal flow, including collateral flow, but also for the characterization of arterial wall morphology (e.g. plaques, calcifications, dissections and reference vessel diameter) of the target lesion and proposed access sites [29]. The analysis of the distal Doppler waveform during duplex exam and also during ABI measurement can be used to detect impaired blood flow characteristics. In some centres computed tomography angiography (CTA) or magnetic resonance angiography (MRA)are standard of care prior to intra-arterial angiography as qualified sonographers are not available and this may bring useful additional anatomic information, e.g. for procedure planning and can uncover clinically relevant extravascular incidental findings, particularly malignancies [30].

Cardiological workup in high-risk patients

Cardiac status of a PAD patient with an indication for revascularization is ideally evaluated prior to intervention. A history of acute coronary syndrome, heart failure or ventricular arrhythmias, as well as clinical signs of multisite atherosclerosis, even more justify such an approach. In these high-risk patients, ECG and echocardiography may be mandatory in particular if surgical revascularisation is planned. As endovascular therapy carries a low procedural risk, a limb saving procedure should be performed as soon as possible, especially in CLI patients [28]. CLI patients undergoing revascularisation exhibit better short and long term outcome than without [31]. If angiography leads to an indication for surgical revascularization, surgical risk needs to be further evaluated. Prior to surgical arterial revascularization, identification of myocardial ischaemia requires an ECG, which is routine, even in asymptomatic coronary patients. In high-risk patients, Holter ECG or stress tests like myocardial scintigraphy or dobutamine stress echocardiography may be indicated to evaluate myocardial ischaemia. Patients with a history of acute coronary syndromes or previous myocardial infarction on the ECG may require coronary angiography evaluation of their cardiac risk, as they may benefit from coronary revascularization especially if surgical revascularisation is required. Echocardiography brings data on cardiac structure and function (systolic and diastolic), valve disorders or pulmonary pressure. Low ejection fraction, presence of heart failure clinical signs and pulmonary hypertension, segmental myocardial contractility

abnormalities and significant valvular heart disease represent markers of surgical risk. These conditions need to be addressed and improved, as much as possible, before surgical revascularization. The priority and timing of cardiac and peripheral procedures needs to be evaluated on an individualized level and decision made together with a multi-disciplinary team and the patient.

Key messages

- The more elective and riskier the planned interventional or surgical procedures are, the more the diagnostic cardiovascular risk workup should be performed in advance and possible risk factors for the intervention should be excluded or at least mitigated

Pre-interventional laboratory analyses

Preprocedural laboratory tests mainly serve the purpose of identifying risks to allow risk mitigation and optimizing medical prevention as well as cardiovascular risk factor modification. The tests include identification of potential anaemia (haemoglobin, haematocrit), inflammation (leukocyte count, CRP), coagulation and thrombosis unbalance (INR, aPTT, platelet count), renal impairment (urea, creatinine), electrolyte changes (sodium, potassium), thyroid function (TSH), glucose (HbA1c, fasting glucose) and lipid panel. As a minimum requirement INR, eGFR and whole blood count should be obtained within 3 weeks prior to the procedure, while ideally within the last 72 hours before the intervention.

Endovascular interventions could be considered as outpatient procedures in the absence of significant anaemia, renal impairment or coagulation and thrombosis unbalance. Aetiology of a significant or recently aggravating anaemia must be investigated in any case before revascularization as otherwise peri-procedural anticoagulation with heparin and post-procedural single or especially dual platelet inhibition may pose additional bleeding risks. Low platelet count may prompt to in-hospital procedures and monitoring, as well as to single antiplatelet therapy post-procedurally. Low eGFR should lead to the use of contrast agents with lower nephrotoxicity and in smaller volumes, as well as to post-procedural search for contrast associated nephropathy which occurs typically only at day 2 or 3 after a procedure.

Key messages

- Chemical and haematological laboratory analyses give important information about the general state of the patient's health and offer ways to improve the patient condition prior the intervention
- Minimum required blood tests in most centres include INR, eGFR, (TSH), Hb and full blood count obtained within 3 weeks, ideally within 72 h before procedure

Peri-interventional management of anticoagulation

Oral anticoagulants may in most cases be stopped before interventions. In this context the indication for chronic anticoagulation should be reviewed. Individual decisions are made together with the patient and ideally involving a multi-disciplinary team on whether interrupting anticoagulation is safe and provide a plan how to stop, how to restart and if necessary how to bridge [32]. In most cases, interventions can and should be done without bridging as the risks of bleeding increase without significantly lowering embolic/stroke/PE risk [32]. INR is used to monitor oral anticoagulation with vitamin K antagonists (VKA). Depending on the planned procedure, indication for and degree of anticoagulation, VKA should be stopped 2–3 days and revascularization performed when an INR target (typically 1.5–2.0) defined by the team is reached. DOACs are to be stopped before interventions depending on kinetics of individual drugs, age and renal function to achieve 3–4-fold half-life reductions of activity of the DOAC. INR evaluation under DOAC therapy is in any way not reliable and not recommended [33].

Bridging for oral anticoagulants may be needed in a minority of patients, particularly in high-risk patients (e.g., mechanical valves or recent thromboembolic events). This is usually performed with intravenous heparin and in patients with heparin induced thrombocytopenia with lepirudin, argatroban, fondaparinux or danaparoid [34]. Many procedures can be safely performed under therapeutic anticoagulation using adequate techniques.

Key messages

- In most cases anticoagulation 'bridging' is not required
- In certain situation with strong indication for anticoagulation, bridging strategies should be considered and planned respecting the patient's individual risk and preference

Considerations about pre-interventional platelet inhibition

There is agreement that patients with symptomatic PAD should be treated with anti-platelet drugs. This should be, preferably clopidogrel, or if there is low bleeding risk, dual-pathway inhibition (DPI) with aspirin and rivaroxaban at 2.5 mg BID (COMPASS study) [35]. Antiplatelet therapy should be in place to prevent major cardiovascular events and major limb events (see further discussion below under *Post-procedural medication strategy*) [5, 36]. Anti-platelet therapy should not be stopped to perform interventions, based on less data and extrapolation from studies in cardiology, there is also agreement that after interventions dual-anti platelet therapy (DAPT) should be installed temporarily (1–3 months) in order to improve patency. Longer term DAPT may have benefits but carries increased bleeding risk

[37]. There is uncertainty which patients may benefit from DAPT or DPI, how long it should be maintained for which devices, at which time DAPT should be initiated and if clopidogrel loading dose of 300 mg or 600 mg should be given. While most agree that DES or covered stents require rather 3 months DAPT and 1 month for DCB and BMS is sufficient some believe that plain balloon angioplasty only requires SAPT. Some studies start DAPT as early as 1 week before a planned intervention, some start after the intervention. One advantage of starting DAPT before the procedure is that this allows time to test if DAPT effectively blocks platelet reactivity. High on treatment platelet reactivity has been shown to be a major determinant of late procedural failure that could be overcome by adapting therapy [38, 39]. Potential disadvantages maybe related to a higher risk of bleeding complication if procedures are performed on effective DAPT. If DAPT is in place in particular for other indications such as myocardial infarction or previous coronary interventions, it should not be stopped [32].

More recently and based on the VOYAGER PAD study, DPI may be initiated after interventions to improve outcome [40]. In this study, rivaroxaban was stopped if re-interventions were performed while continuing aspirin. Therefore, if patients are on DPI before the procedure, the low dose rivaroxaban but not aspirin should be paused peri-interventionally.

Key messages

- As a minimum single platelet inhibition with aspirin or preferably clopidogrel should be in place before intervention
- Rivaroxaban (2.5 mg BID) should be paused peri-interventionally while continuing aspirin
- DAPT inhibition should not be stopped for interventions in particular if there is a cardiological indication

Management of patients with relevant renal impairment

In patients with reduced kidney function exposure to iodinated contrast media may lead to so-called contrast-associated acute kidney injury (CA-AKI). Although the true risk of CA-AKI remains uncertain for patients with severe kidney disease, prophylaxis with intravenous normal saline is indicated for patients who have AKI or an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 who are not undergoing maintenance dialysis. In individual high-risk circumstances, prophylaxis may be considered in patients with an estimated glomerular filtration rate of 30–44 ml/min/1.73 m^2 at the discretion of the ordering clinician [42]. The ideal timing, volume, and rate of volume expansion is uncertain. Typical volume expansion regimens begin 1 hour before and continue 3–12 hours after contrast media administration, with typical doses ranging from fixed (e.g., 500 ml before and after) to weight-based volumes (1–3 ml/kg per hour). The amount of sodium chloride loaded by the infusion should not be neglected, because it can make the blood pressure management more difficult and may not be tolerated well in patients with concomitant heart failure. So limited infusion volume combined with sufficient oral water intake seems more reasonable. In addition, cessation of nonessential nephrotoxic medications may decrease the risk of CA-AKI and is recommended when feasible.

To decrease or avoid usage of iodinated contrast medium in patients with renal impairment [41]. and much more seldom iodine contrast intolerance CO_2 gas can be used as an adjuvant or sole contrast agent for intra-arterial angiography [42, 43]. In general the legs should be positioned slightly upwards to avoid CO_2 to reach to the abdominal or cerebral vessels. As CO_2 gas may lead to permanent cerebral damage, a patent foramen ovale or significant right-left shunt should be excluded before application of this technique. To improve image quality, butylscopolamine iv can decrease bowel movement. For these procedures antegrade access is favourable. Especially the group with severely impaired but not preterminal renal function is good for the CO_2 technique. This group still tolerates much better the gas injection, because their blood buffering capacity is still sufficient so that the produced carbon acid does not cause a longer lasting pain in the vessel wall. In patients with preterminal renal function we recommend the procedure under sedation and anaesthesia because of the strong and longer lasting pain caused by the carbon acid.

Key messages

- CA-AKI prophylaxis with sodium chloride infusion in patients with <30 ml/1.73 m^2 is recommended and should be considered in high-risk constellation (CAVE: volume overload with risk of heart failure)
- Carbon dioxide angiography is an option for patients with impaired renal function and/or contra-indications for iodinated contrast agents. In very severe renal impairment, the pain caused by the persistent effect of the carbon acid on the vessel wall has to be considered and potentially procedure performed under general anaesthesia

Peri-interventional management

Evidence-based data on peri-interventional management are scarce. Hence, the following section is in part based on recommendations from interventional experts.

Imaging

Prior to each peripheral arterial revascularization procedure, comprehensive vascular imaging should be

conducted including the abdominal aorta, the iliac arteries of both limbs and the infrainguinal arteries of the target limb. Pre-interventional imaging modalities comprise duplex ultrasound (DUS), CTA and MRA [44, 45]. In PAD patients scheduled for revascularization, DUS should be considered as first non-invasive imaging approach, while its reliability depends on the individual sonographer's expertise [5, 46]. Applied by experienced sonographers, additional pre-interventional imaging modalities are not mandatory [47, 48, 49, 50]. However, in patients with complex multisegmental disease, especially when involving the aorto-iliac arteries, complementary CTA or MRA should be considered for procedure planning [51].

Vascular access

Both safety and efficacy considerations need to be taken into account during the procedure. In any circumstances, one always has to balance risks and benefits of different procedural strategies. Periinterventional complications often arise from access site related bleeding complications. Major risk factors for puncture site complication in patients with lower extremity endovascular procedures are, manual compression, age, procedure duration >45 minutes, crural procedures, uncontrolled hypertension, and impaired coagulation but also obesity can be challenging, in particular when planning antegrade groin access [27]. To reduce bleeding risk, the smallest sheath diameter sufficient for the planned procedure should be used.

Pre-interventional duplex-imaging of possible puncture sites should be considered for procedure planning. In case of common femoral artery obstructions alternative puncture sites should be considered.

For aortoiliac procedures an ipsilateral retrograde access, a contralateral retrograde cross-over access, a transbrachial or transradial arterial access, or a combination of these access sites is suitable. For infrainguinal interventions, either an ipsilateral antegrade access or a contralateral retrograde cross-over access – especially for combined treatment of aortoiliac and infrainguinal lesions or even crural lesions to establish straight line flow to the foot – can be applied. In complex procedures, especially in chronic occlusions, additional access sites, such as a pedal, tibial, popliteal or distal femoral access may be required.

Ultrasound guided puncture of the artery should be used whenever possible to reduce the risk of puncture-site associated complications [52, 53].

Regarding the most commonly used inguinal femoral access, the recommended puncture level is the middle of the femur head which guarantees the optimal efficacy of compression and haemostasis after sheath removal [54]. Especially in older patients as well as in patients after orthopaedic hip surgery, the preferred puncture site should be in the lower half of the femur head to reduce risk of bleeding.

Vascular closure devices have shown marked improvement in patients' comfort and satisfaction as well as in time to haemostasis and ambulation after percutaneous vascular procedures. However interventionalists have to ensure suitability of device deployment (not calcified, no plaque, vessel diameter >5 mm), be aware of potential device failure and specific device-related complications [55]. Especially, in case of transbrachial, distal femoral or popliteal vascular access, options for vessel closure and haemostasis have to be considered during procedure planning.

Key messages

- Considerations about the appropriate access site and the correct puncture technique are crucial for a successful and safe procedure
- Image guided puncture is recommended in all cases
- Closure devices are very useful tools in daily practice, but they may have limitations and complications
- The complication rate of these devices can be reduced by considering the application and suitable access site during the planning of the procedure

Fasted or non-fasted?

Classically strict fasting was advised to prevent potential aspiration in case of emergency and allowed direct transfer to the operation theatre. However, as these complications are rare in specialists' hands, insisting on strict fasting is becoming rarer but rather ask for a small breakfast at least 4 h before procedures. Independent of this the usual medication in particular blood pressure lowering with the exception of diuretics and analgesic medication should be taken as usual. In patients with diabetes, one has to take potential diabetic gastroparesis and prolonged gastric emptying time into account, along with medications associated with a risk of hypoglycaemia [56]. Although metformin is not directly nephrotoxic, it has been postulated that it can impair gluconeogenesis from lactate, which may lead lactate to be accumulated under circumstances such as contrast-associated acute kidney injury. Nevertheless, while the risk of developing *metformin-associated lactic acidosis* is low when GFR is >60 ml/min/1.73 m^2, many interventionalist paused it prior to a contrast exposure [57]. Pausing long acting insulin on the day of the procedure should be considered to prevent hypoglycemia.

Key messages

- Strict fasting is not required and in particular usual blood pressure lowering and analgesic medication should be taken on the day of the procedure
- Medication that can cause hypoglycaemia should be stopped on the day of the procedure
- Pausing metformin should be considered in particular in patients with renal function impairment

Management of anaesthesia and sedation

The vast majority of interventions can be done under local anaesthesia of the access site, for instance by local injection

of 10 ml 2% lidocaine during ultrasound or fluoroscopy guided puncture on the anterior side of the artery and on demand sedation by iv benzodiazepines. Patients with severe renal insufficiency or with groins already often punctured or surgically treated need a higher dose of local anaesthesia because of impaired spreading of the drug or impaired efficiency caused by the higher tissue acidity in patients with severe renal insufficiency. Procedures lasting longer than an hour may require an additional dose of local anaesthesia before sheath removal because the effect of the initial dose may have faded. Patients with uncontrollable pain, with mental or neurological disorders are candidates for general anaesthesia or analgosedation [51, 56]. This can be either provided by a trained interventionalist or it can be delegated to the anaesthesiology team, which potentially increases patients' safety since it enables the interventionalist to pay full attention to the procedure itself [51].

Key message

- The vast majority of interventions can be done under local anaesthesia of the access site

Monitoring and pharmacology

Anticoagulation

On table monitoring of anticoagulation in PAD patients is not routine practice. In most cases there will be a single intraarterial dose of heparin at the beginning of the procedure (3000–5000 U unfractionated heparin) [58, 59]. In case of heparin induced thrombocytopenia (HIT) alternative drugs such as fondaparinux can be used [60, 61]. When guiding catheters are used within the procedure, the flushing of heparin via the guiding catheter offers a potential advantage, because the inner surface of the catheter is then also covered by heparin and reduces the risk of clotting activation during the procedure.

One option to control the intra-interventional heparinisation is the bedside measurement of activated clotting time (ACT). In longer interventional procedures repeated administration of unfractionated heparin including ACT measurements with a target ACT of 200–250 seconds should be considered [51].

Cardiovascular monitoring by pulse oximetry or continuous ECG

We recommend pulse oximetry in addition to continuous ECG for the non-invasive monitoring because pulse oximetry controls not only the heart rate but also blood flow and respiration. Deterioration of the patients' cardiorespiratory state will be recognized earlier in pulse oximetry than on the ECG. ECG monitoring is useful though, especially in procedures, which have the risk of provoking arrhythmias for example transbrachial procedures with passage of the aorta – In these cases also a device for defibrillation should be available.

Blood pressure monitoring and hypertension management

Patients require blood pressure monitoring during the procedure. This can be accomplished by upper arm cuffs set to 5 min intervals or by connecting invasive blood pressure with statham element to the sheath. In general, patients should take their regular antihypertensive medication in the morning of the procedure. Nevertheless, the unfamiliar situation in the angio-suite and the upcoming intervention could raise the blood pressure. Low dose sedation with iv benzodiacepines could have a positive effect on anxiety and blood pressure. On-table monitoring of blood pressure by non-invasive techniques is recommended and especially useful at the end of the procedure to diagnose any bleeding in particular if manual compression of the puncture site is required. The blood pressure at sheath removal should not exceed 160/80 mmHg – but fast acting blood pressure lowering medication should be used very cautiously in particular in older patients.

On table sedation and pain management

Many even younger patients complain about back pain when lying on the fluoroscopy table. Low dose benzodiazepine like 1–2 mg of midazolam iv is often sufficient to control this situation for about 45 minutes. After that time an additional same dose is often necessary. For back pain, 1 g iv of paracetamol is another good initial choice [51].

In CLI patients, benzodiazepines are often not sufficient. Patients with rest pain on the table need sufficient pain control (e.g., fentanyl in 25 ug steps iv or morphine with an initial dose of 3–5 mg iv.) to be able to cooperate or they need general anaesthesia for the interventional procedure.

Key messages

- In most cases procedures can be done without on table coagulation monitoring
- Pulse oximetry, ECG and non-invasive blood pressure monitoring are adequate for peri-procedural hemodynamic monitoring
- Defibrillator needs to be available when there is increased risk of arrythmia
- Consider sedation to positively affect anxiety and raised blood pressure
- Consider careful blood pressure lowering in particular if manual compression is needed

Interventional procedure

In the treatment of aorto-iliac lesions stent implantation is superior over balloon angioplasty [62, 63, 64]. The decision for self-expanding vs. balloon expandable stents should be made upon lesion characteristics [56]. Covered stents may reduce the procedural risk of vessel rupture and the mid-term risk of restenosis [65]. Whether and to which extend covered stents affect clinical outcome is still matter of discussion.

Common femoral artery lesions are commonly treated by open surgery [66, 67]. In frail and high surgical risk patients endovascular therapy by stent placement or a combination treatment of atherectomy and drug-coated balloon (DCB) angioplasty could be an adequate alternative [67, 68, 69].

In the femoropopliteal segment the application of antiproliferative agents by using drug-coated balloons (DCB) or drug-eluting stents (DES) potentially contribute to a reduction of the risk of restenosis [70]. Heavy vessel calcification potentially impairs the transmission and efficacy of antiproliferative drugs as well as lumen gain during interventional procedures [71]. Different interventional strategies, such as atherectomy or lithotripsy, might be useful for intraprocedural vessel preparation [70, 72, 73, 74]. Stent placement should be minimized, however, it should not be withheld if necessary [75].

Infrapopliteal disease is often characterized by complex and heavily calcified lesions [76]. Up to now, the most effective endovascular strategy for infrapopliteal arteries is matter of discussion. DES placement appears to be superior over plain balloon angioplasty and bare metal stent implantation [77, 78]. The role of DCB in this segment remains debatable due to a lack of sufficient data [73, 79]. According to the potential limitations in achieving long-term patency, revascularization procedures of infrapopliteal arteries should be reserved for patients with clear indication for infrapopliteal treatment, such as patients with CLI. In patients with CLI angiosome-oriented direct revascularization appears to be beneficial over indirect revascularization [80, 81]. According to the complexity of lesions, however, the angiosome concept cannot always be taken into account in daily practice [81]. The overall goal is to create a straight direct flow to the foot [82].

Key messages

- The indication for revascularization as well as the decision on specific revascularization techniques should be based on the stage of PAD, lesion morphology and patients' individual risk profile
- An "endovascular first" approach is often the most appropriate according to the frailty of patients with advanced PAD or CLI if technically feasible

Radiation exposure

Interventionalists should pay special attention to radiation exposure during peripheral vascular revascularization procedures for both patient and interventionalist. The degree of interventionalists' radiation exposure depends on the patients' treated anatomic region (higher estimated dose of scattered radiation in aortoiliac interventions), the patients' habitus (higher radiation exposure in obese patients), fluoroscopy times, angulation as well as the interventionalists' experience and the use of protective clothing and devices [83, 84].

Observation period in angio-suite

The observation period in the angio-suite is influenced by multiple factors varying from patient to patient and institution facilities/practise [51]. The stay in the angio-suite should last until haemostasis at the puncture site is achieved and the patient is in a hemodynamically stable condition. Under these circumstances the further surveillance can also be made in a daycare ward or comparable surveillance options which offer a regular hemodynamic and puncture site control for the further stay of the patient. Before demission to home, there should be a final check of the puncture site and a short evaluation of the general perfusion of the treated limb by the interventionalist.

Key message

Surveillance of haemodynamics and puncture site by experienced staff in the early postprocedural period is mandatory

Pre-discharge assessment

To evaluate the clinical success, exclude complications and ideally ensure hemodynamic success, it is recommended that focused exams are performed prior to discharge patients after angioplasty. This should include physical exam and duplex ultrasound of access site, as well as the target lesion(s). The physical exam should include peripheral pulses, abdominal palpation, sensation, and motor strength of the legs as retroperitoneal bleeding usually leads to abdominal pain and neurological symptoms of the legs. Ideally, ABI/TBI should be performed to document immediate hemodynamic success and detect early signs of revascularisation failure as well as a duplex ultrasound of the target lesion to document the early target lesion outcome.

Access site related bleeding complications including haematomas and false aneurysms are the most frequent complications [85]. In addition, rare complications like early thrombosis, thromboembolism, dissections are possible. Active bleeding, hematomas and false aneurysms should be treated in the first instance by prolonged manual compression with or without ultrasound guidance followed by bed rest with monitoring of haemoglobin/ haematocrit, vital signs, sensation, and motor function of legs. Ultrasound guided thrombin injection is a safe and effective strategy for closing false aneurysms if the anatomy is suitable. The shunt volume of AV fistulas should be estimated by ultrasound. Small AV fistulas (<500 ml/min) usually close spontaneously, larger ones may require interventional or open repair to avoid ischaemia to the leg (steal) or the development of cardiac high output failure [86].

Key messages

- Prior discharge of the patient a check of the general physical condition and a brief evaluation of the pro-

cedural success (pedal pulses, ultrasound of access site and treated vascular segment, ABI) should be made
- The most frequent complications are access site-related bleeding or a false aneurysm and should be successfully treated prior the discharge of the patient

Post-interventional surveillance and medication

Considerations for intermediate and long-term surveillance

While the early technical success rate of peripheral interventions in terms of angiographic patency is usually over 95%, the intermediate and long-term effectiveness/benefit of procedures can be limited by procedure related complications, remaining flow limiting lesions, re-stenosis/re-occlusion, and atherosclerotic disease progression. Post interventional surveillance aims at addressing these points to optimize results, preventing both MALE and MACE [87]. The frequency and scope of follow-up may differ according to indication and the type of revascularisation as well as patient's physical condition. The surveillance should include assessment of the access site, of the entire revascularized limb as well as the contralateral one. General and vascular physical examination, as well as specific vascular exams including Duplex and Doppler tests are recommended during follow up (Figure 2).

The frequency of follow-up exams depends on the individual medical and vascular condition of the patient. In general, revascularized patients should be followed-up at 2–6 weeks, 3–6 months, 1 year, and then annually to assess vascular patency, detect re-stenosis-occlusion, and ensure optimal PAD management. During follow-up visits, medical therapy is further adjusted, and continued need for DAPT is assessed. In case of revascularisation failure, a repeat procedure can be planned in accordance with the clinical presentation and clinical need of the patient. Follow-up visits should be carried out by vascular physicians however, in some healthcare systems surveillance is performed by primary care doctors. Nonetheless, particularly in patients with ulcers, these should be seen by a vascular specialist at least until wounds have healed. It is a matter of debate if vascular diagnostic tests are required during 6 months, 1 year and yearly follow-ups if wounds are healed and symptoms resolved. We propose that a specific history with regard to re-occurence or new symptoms, current medication and smoking status, physical exam to detect new tissue loss and risk factor assessment in particular blood pressure, cholesterol and glucose is sufficient as this would trigger change in management. Re-occurrence of or new symptoms may trigger further vascular exams such as ABI or imaging. To determine a >80% in-stent stenosis, combining a PSV >275 cm/s and a ratio >3.5 is highly specific and predictive [88]. In patients with high amputation risk including people with diabetes and those requiring haemodialysis shorter 3–6 month intervals may be required. While surveillance can improve early detection of revascularisation failure, progressive intimal hyperplasia allowing early re-intervention, efficacy and cost-effectiveness of such programs have still not been systematically evaluated. However, PAD being a chronic disease with frequent severe co-morbidities and high CV mortality follow-up of patients is necessary to ensure appropriate disease management and secondary CV prevention.

Key messages

- Following revascularization patients should be followed-up at 2–6 weeks, 3–6 and 12 months after the procedure and then annually. Patients with diabetes and those requiring haemodialysis should be followed-up at shorter 3–6 month intervals
- Following revascularization, patients with wounds also need intensified surveillance with a frequency every 2–4 weeks until wounds are healed
- Follow-up visits should be standardized comprising vascular exams and medical treatment (pharmacological and lifestyle) optimization

Post-procedural medication strategy

Medical therapy is aimed at secondary prevention of CV events in patients with symptomatic PAD in general and improvement of patency after intervention [89]. It should include antithrombotic therapy, lipid modification, blood pressure and glucose control, but also facilitate smoking cessation, healthy diet, weight management and exercise [90]. Unfortunately, the adherence to evidence based optimal medical therapy is still sub-optimal in this patient population [91]. Nevertheless the therapy should be reviewed and optimised before discharge. Patients should leave the hospital with an optimized medical regimen, instruction on what to do if a complication occurs and a follow-up appointment in 2–6 weeks. At this point, the success of medication optimisation can be confirmed and potentially DAPT de-escalated.

Antithrombotic therapy. There is agreement that patients with symptomatic PAD should be treated with a single anti-platelet drug, preferably clopidogrel, or if there is low bleeding and high CV risk (polyvascular disease), dual-antithrombotic treatment with aspirin and rivaroxaban at 2.5 mg BID (COMPASS study) should be in place to prevent major cardiovascular events and major limb events [5, 35, 36, 92]. A recent meta-analysis indicates that more intense antithrombotic therapy reduces the risk of limb amputation and revascularization as well as stroke but with an increase in the risk of bleeding events [37]. As endovascular interventions go along with vascular injury, endothelial denudation and exposure of tissue factor, current treatment guidelines recommend temporary dual anti-platelet

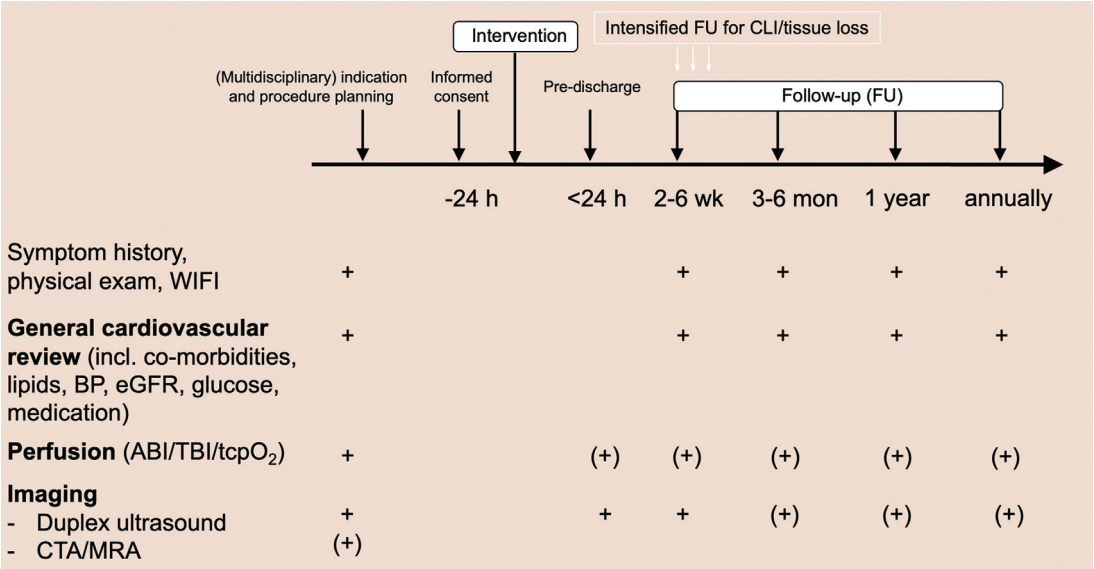

Figure 2. Schematic of follow up.

therapy for 1–3 months after interventions followed by de-escalation to single anti-platelet therapy with clopidogrel preference thereafter [5, 93]. The data supporting the common practice of prescribing dual platelet inhibition with aspirin and clopidogrel are sparse and are historically based on data from coronary interventions [94]. There was only one RCT comparing aspirin alone with aspirin and clopidogrel after lower limb angioplasty (MIRROR study) [95]. While at 6 months the target lesion revascularisation rate was lower in patients with DAPT, after de-escalation to aspirin monotherapy after this point the 12 month TLR was not significantly different [96]. Of note 32% of patients had clopidogrel resistance and TLR was not the primary endpoint the study was powered on. However, several real world studies indicate that temporal post procedural DAPT is effective to improve patency without increasing bleeding [97, 98, 99]. For instance, the Swedish national vascular registry suggest that the subgroups of people such as people with diabetes receiving stents for CLI may benefit from dual platelet inhibition [97]. This may be due to the higher rate of low responsiveness to aspirin, clopidogrel, or both in PAD with high on treatment platelet reactivity associated with major adverse limb events (MALE) [97]. Indeed, high on-treatment platelet reactivity including clopidogrel and aspirin resistance are frequent in PAD patients and are associated with a worse outcome, indirectly supporting the efficacy in patients with adequate response to DAPT [38]. A personalized platelet inhibition regimen may be the way forward in the future to prevent early revascularisation failure due to thrombosis. More recently the VOYAGER PAD study, showed that in patients with PAD, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin started after lower-extremity revascularization of mainly femoro-popliteal region was associated with a moderate yet significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone (19.9% vs 17.3% at 3 years) [40]. This was primarily driven by a significant decrease in acute limb ischaemia (6.9% vs 4.7%). The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone (5.9% vs 4.1% at 3 years). In half of the patients clopidogrel was also given and a recent analysis showed that this did not affect the efficacy or safety if only given for less than 30 days after the index procedure [100]. Taken together, patients should receive anti-thrombotic therapy after endovascular revascularisation, either DAPT for 1–3 months or DPI long-term. DAPT is typically only installed for 1 month after angioplasty, drug-coated balloons or bare metal stents. Drug eluting stents, long segment recanalisations or re-occlusions may require longer DAPT for at least 3 months with the rationale that re-endothelialisation may take longer. Ticagrelor should be given as an alternative in case of clopidogrel resistance [5]. Longer term DAPT may have benefits but carries increased bleeding risk [37]. DPI is an alternative currently reserved for patients with low-bleeding risk and without contraindications which may be as little as 10% [101].

Cholesterol lowering. Statin treatment significantly impacts the outcome. A recent comprehensive systematic review and meta-analysis investigated the impact of statins on MACCE including all-cause death, composite CV endpoints, CV death, stroke, and MALE including amputation and graft occlusion/revascularization in PAD patients including patients with stable claudication, CLI, and patients undergoing lower extremity revascularization [102]. A total of 51 studies with 138,060 PAD patients were included, of whom 48,459 (35.1%) were treated with statins. The analysis included 2 randomized controlled trials, 20 prospective, and 29 retrospective studies. Overall, 21,624 deaths, 4,852 composite CV endpoints, 4,609 CV deaths, 860 strokes, and 11,396 MALE events were used for the analysis. Statins reduced all-cause mortality by

39%, CV death by 41%, composite CV endpoints by 34%, ischemic stroke by 28%, MALE incidence by 30% and amputations by 35%. Another systematic review and meta-analysis focusing on CLI has included nineteen studies including 26,985 patients with CLI [103]. Among patients with known data on statin status, 12,292 (49.6%) were on statins versus 12,513 (50.4%) not on statins. Patients treated with statins were 25% less likely to undergo amputation and 38% less likely to have a fatal event. Statin therapy was also associated with increased overall patency rates and lower incidence of MACE. In the pooled analysis among the seven studies that reported any type of patency, patients treated with statins had 20% lower rates of loss of patency. In summary, all patients with symptomatic PAD should receive statins at the highest tolerable dose. The LDL cholesterol target is a decrease by at least 50% or absolute value of 1.4 mmol/l. Ezetimibe can be added to reach this target. PCSK9 inhibitors are indicated if targets cannot be reached with this. See our recent guideline on lipid management [104].

Blood pressure control. Optimal blood pressure control is a cornerstone of PAD management and a meta-analysis confirms that blood pressure lowering can improve walking distance [105]. Few studies exist that evaluated the effect of blood pressure lowering specifically on mortality [106]. A recent trial indicates that interventions in particular of proximal flow limiting stenoses or occlusions can significantly decrease central and peripheral blood pressure [107]. This underscores a potential important role of revascularisation on blood pressure control and warrants that blood pressure is checked before discharge and medication adapted. The recommended blood pressure target is 130 / 80 mmHg [5].

Glucose control. Several trials have demonstrated that intensive glucose lowering can reduce MACE and MALE in patients with diabetes [90, 108]. Poor periinterventional glycaemic control is associated with a higher incidence of restenosis after infrapopliteal revascularization [109]. Newer drugs belonging to the sodium-glucose cotransporter (SGLT)-2 inhibitor and glucagon-like peptide (GLP)-1 receptor agonist classes have been shown to reduce cardiovascular events and mortality in high-risk patients with type 2 diabetes [110, 111, 112]. These drugs provide vasculoprotection beyond their effects on glucose or other classical cardiovascular risk factors [113]. However, the relative benefits and possible risks of SGLT-2 inhibitors and GLP-1 agonists on PAD are presently unclear. An increased rate of amputation – primarily toe and metatarsal level – was reported in a trial of the SGLT-2 inhibitor canagliflozin [114]. Risk factors for amputation in CANVAS included prior history of amputation, peripheral vascular disease and neuropathy [115]. A Food & Drug Administration Boxed Warning on increased risk of leg and foot amputations imposed in 2017 was removed in 2020 in response to safety information from additional clinical trials. In rescinding the Boxed Warning, the FDA stated that the risk of amputation, while still increased with canagliflozin, was lower than previously described, particularly when patients were appropriately monitored (https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin). The European Medicines Agency issued a safety warning for canagliflozin and amputation risk that extended to all SGLT-2 inhibitors reflecting uncertainty whether the increased risk of lower limb amputation with canagliflozin constituted a class effect [116]. The Summary of Product Characteristics for canagliflozin states:

> *'In a[nother] long-term clinical study in patients with type 2 diabetes and diabetic kidney disease [CREDENCE [117]], no difference in lower limb amputation risk was observed in patients treated with canagliflozin 100 mg relative to placebo. In [the CREDENCE] study, precautionary measures were applied. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown'.*

Observational data suggest reductions in MALE, driven largely by reduced amputations, in patients with type 2 diabetes treated with GLP-1 agonists vs. dipeptidyl peptidase (DPP)-4 inhibitors [113, 114, 116, 118].

Exercise. Recent meta-analysis confirmed that exercise programmes provided important benefit compared with placebo or usual care in improving both pain-free and maximum walking distance in people with leg pain from claudication who were considered to be fit for exercise intervention [119]. Exercise did not improve ABI, and there was no evidence of an effect of exercise on amputation or mortality. Exercise may improve quality of life when compared with placebo or usual care. A meta-analysis of 7 trials including 987 patients showed that those who underwent combined endovascular therapy and supervised exercise training, compared with those who underwent supervised exercise training alone, had significantly greater maximum walking distance, as well as a lower risk of revascularization or amputation over a median follow-up of 12.4 months [120]. In patients with ulcers certainly offloading is indicated prohibiting exercise training involving the legs. Arm ergometry training could be an option. In the future these patients may benefit from experimental treatments that mimic exercise without putting pressure on wounds such as repetitive remote occlusion or dietary bioactives [121, 122]. In summary, PAD patients without tissue loss that requires offloading having undergone revascularisation should be enrolled in a supervised exercise and smoking cessation program, if necessary, as there is an added benefit in combination with revascularization [123, 124].

Wound care and off-loading. To facilitate wound-healing in CLI regular wound dressings and off-loading need to be arranged for [125].

Key messages

- An individually tailored medication schedule at discharge is crucial for the short and intermediate

success rate of the procedures and the general outcome of the patient
- Keeping the high cardiovascular risk of PAD patients in mind, optimal medical therapy of the individual CV-risk factors including lipid control, sufficient blood pressure control preferably by ACEIs or ARBs and at least single anti-platelet inhibition, or dual pathway inhibition, need to be initiated and treated to target
- Smoking cessation should be strongly encouraged, and appropriate medication prescribed
- Lifestyle interventions are also important, especially a supervised exercise program, weight control

Open question and areas that need development

- Risk scores for local access site complications, especially looking at access way, sheath size, age, sex and BMI
- Risk score for thrombotic complications – high degree of thrombocyte and plasmatic system activation, and which is the best way to evaluate the activation state
- Risk scores for early restenosis/re-occlusion
- Risk score for bleeding risk assessment
- Evaluation and best treatment strategy of concurrent venous disease in mixed ulcers
- Case severity dependent optimal pre-interventional medication strategy, especially for DCB, stents and in case of a planned catheter thrombectomy with high thrombotic load
- Impact and optimal duration interval of preprocedural statin therapy
- Personalised antithrombotic management (platelet inhibition)
- Pre-procedural anti thrombotic management/Post procedural/Place of rivaroxaban/other DOACs
- Identification of optimal postprocedural (after a catheter intervention) patient groups for the DAPT or dual pathway inhibition with aspirin and rivaroxaban (2.5 mg BID)
- Socioeconomic impact of structured surveillance programs in different patient subgroups (different ethnics, smokers, diabetics, haemodialysis patients, patients with inflammatory vascular diseases), with individual cost effectiveness analyses
- Optimal strategies for prevention of contrast-associated acute kidney injury

References

1. Heiss C, Madaric J, Belch J, Brodmann M, Mazzolai L. The compelling arguments for the need of medical vascular physicians in Europe. VASA. 2019;48(6):487–91.
2. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019; 7(8):e1020–30.
3. Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. Circ Res. 2021;128(12): 1818–32.
4. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116(9):1509–26.
5. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. European Society of Vascular Medicine: Guideline on peripheral arterial disease. Vasa. 2019;48:1–79.
6. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59(1):220–34.e1-2.
7. Ward R, Dunn J, Clavijo L, Shavelle D, Rowe V, Woo K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIfI amputation scores. Ann Vasc Surg. 2017;38:84–9.
8. Agnelli G, Belch JJF, Baumgartner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review. Atherosclerosis. 2020;293:94–100.
9. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105–13.
10. Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, Boulton AJ. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care. 2010;33(11):2365–9.
11. Skrepnek GH, Mills JL, Lavery LA, Armstrong DG. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the US. Diabetes Care. 2017;40(7):936–42.
12. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the National Health Service in England. Diabet Med. 2014;31(12):1498–504.
13. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J 2007;4(4):286–7.
14. Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019;36 (8):995–1002.
15. Hinchliffe RJ, Brownrigg JR, Andros G, Apelqvist J, Boyko EJ, Fitridge R, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes Metab Res Rev. 2016;32(Suppl 1):136–44.
16. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet. 2012;380(9847):1059–65.
17. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005;100(1):4–10.
18. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg. 2010;51 (Suppl 5):5S–17S.
19. Lin JH, Brunson A, Romano PS, Mell MW, Humphries MD. Endovascular – First treatment is associated with improved amputation-free survival in patients with critical limb ischemia. Circ Cardiovasc Qual Outcomes. 2019;12(8):e005273.
20. Tsai TT, Rehring TF, Rogers RK, Shetterly SM, Wagner NM, Gupta R, et al. The contemporary safety and effectiveness of

lower extremity bypass surgery and peripheral endovascular interventions in the treatment of symptomatic peripheral arterial disease. Circulation. 2015;132(21):1999–2011.
21. Gray WK, Day J, Horrocks M. Outcomes for angioplasty and bypass lower limb revascularisation procedures for limb salvage in England: findings from the getting it right first time programme. Eur J Vasc Endovasc Surg. 2020;60(5): 711–9.
22. Rodway A, Stafford M, Wilding S, Ntagiantas N, Patsiogiannis V, Allan C, et al. Day case angioplasty in a secondary care setting – initial experience. VASA. 2021;50(3):202–8.
23. Kasthuri R, Karunaratne D, Andrew H, Sumner J, Chalmers N. Day-case peripheral angioplasty using nurse-led admission, discharge, and follow-up procedures: arterial closure devices are not necessary. Clin Radiol. 2007;62(12):1202–5.
24. Constans J, Bura-Riviere A, Visona A, Brodmann M, Abraham P, Olinic DM, et al. Urgent need to clarify the definition of chronic critical limb ischemia – a position paper from the European Society for Vascular Medicine. VASA. 2019;48(3): 223–7.
25. Giannopoulos S, Varcoe RL, Lichtenberg M, Rundback J, Brodmann M, Zeller T, et al. Balloon angioplasty of infrapopliteal arteries: a systematic review and proposed algorithm for optimal endovascular therapy. J Endovasc Ther. 2020;27(4):547–64.
26. Agarwal S, Sud K, Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003–2011. J Am Coll Cardiol. 2016;67(16):1901–13.
27. Hackl G, Gary T, Belaj K, Hafner F, Eller P, Brodmann M. Risk factors for puncture site complications after endovascular procedures in patients with peripheral arterial disease. Vasc Endovascular Surg. 2015;49(7):160–5.
28. Plaisance BR, Munir K, Share DA, Mansour MA, Fox JM, Bove PG, et al. Safety of contemporary percutaneous peripheral arterial interventions in the elderly insights from the BMC2 PVI (Blue Cross Blue Shield of Michigan Cardiovascular Consortium Peripheral Vascular Intervention) registry. JACC Cardiovasc Interv. 2011;4(6):694–701.
29. Kim ES, Sharma AM, Scissons R, Dawson D, Eberhardt RT, Gerhard-Herman M, et al. Interpretation of peripheral arterial and venous Doppler waveforms: A consensus statement from the Society for Vascular Medicine and Society for Vascular Ultrasound. Vasc Med. 2020;25(5):484–506.
30. Nourzaie R, Das J, Abbas H, Thulasidasan N, Gkoutzios P, Ilyas S, et al. Extravascular findings during upper limb computed tomographic angiography focusing on undiagnosed malignancy. World J Radiol. 2019;11(1):10–8.
31. Stella J, Engelbertz C, Gebauer K, Hassu J, Meyborg M, Freisinger E, et al. Outcome of patients with chronic limb-threatening ischemia with and without revascularization. VASA. 2020;49(2):121–7.
32. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: A report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69(7):871–98.
33. Samuelson BT, Cuker A. Measurement and reversal of the direct oral anticoagulants. Blood Rev. 2017;31(1):77–84.
34. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22): 3360–92.
35. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major adverse limb events and mortality in patients with peripheral artery disease: The COMPASS Trial. J Am Coll Cardiol. 2018;71(20):2306–15.
36. Aboyans V, Bauersachs R, Mazzolai L, Brodmann M, Palomares JFR, Debus S, et al. Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy. Eur Heart J. 2021;42(39):4013–24.
37. Savarese G, Reiner MF, Uijl A, D'Amario D, Agewall S, Atar D, et al. Antithrombotic therapy and major adverse limb events in patients with chronic lower extremity arterial disease: systematic review and meta-analysis from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy in Collaboration with the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases. Eur Heart J Cardiovasc Pharmacother. 2020;6(2):86–93.
38. Busch L, Stern M, Dannenberg L, Mourikis P, Grone M, Ozaslan G, et al. Impact of high on-treatment platelet reactivity after angioplasty in patients with peripheral arterial disease. Platelets. 2020;32(3):391–7.
39. Spiliopoulos S, Pastromas G, Katsanos K, Kitrou P, Karnabatidis D, Siablis D. Platelet responsiveness to clopidogrel treatment after peripheral endovascular procedures: the PRECLOP study: clinical impact and optimal cutoff value of on-treatment high platelet reactivity. J Am Coll Cardiol. 2013;61(24):2428–34.
40. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382(21):1994–2004.
41. Davenport MS, Perazella MA, Yee J, Dillman JR, Fine D, McDonald RJ, et al. Use of intravenous iodinated contrast media in patients with kidney disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2020;294(3):660–8.
42. Stegemann E, Tegtmeier C, Bimpong-Buta NY, Sansone R, Uhlenbruch M, Richter A, et al. Carbondioxide-aided angiography decreases contrast volume and preserves kidney function in peripheral vascular interventions. Angiology. 2016;67(9):875–81.
43. Diamantopoulos A, Patrone L, Santonocito S, Theodoulou I, Ilyas S, Dourado R, et al. Carbon dioxide angiography during peripheral angioplasty procedures significantly reduces the risk of contrast-induced nephropathy in patients with chronic kidney disease. CVIR Endovasc. 2020;3(1):9.
44. Collins R, Burch J, Cranny G, Aguiar-Ibanez R, Craig D, Wright K, et al. Duplex ultrasonography, magnetic resonance angiography, and computed tomography angiography for diagnosis and assessment of symptomatic, lower limb peripheral arterial disease: systematic review. BMJ. 2007;334(7606):1257.
45. Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. JAMA. 2009;301(4):415–24.
46. Ouwendijk R, de Vries M, Stijnen T, Pattynama PM, van Sambeek MR, Buth J, et al. Multicenter randomized controlled trial of the costs and effects of noninvasive diagnostic imaging in patients with peripheral arterial disease: the DIPAD trial. Am J Roentgenol. 2008;190(5):1349–57.
47. Ranke C, Creutzig A, Alexander K. Duplex scanning of the peripheral arteries: correlation of the peak velocity ratio with angiographic diameter reduction. Ultrasound Med Biol. 1992;18(5):433–40.
48. Schlager O, Francesconi M, Haumer M, Dick P, Sabeti S, Amighi J, et al. Duplex sonography versus angiography for assessment of femoropopliteal arterial disease in a "real-world" setting. J Endovasc Ther. 2007;14(4):452–9.
49. Langenberger H, Schillinger M, Plank C, Sabeti S, Dick P, Cejna M, et al. Agreement of duplex ultrasonography vs. computed tomography angiography for evaluation of native and in-stent SFA re-stenosis – findings from a randomized controlled trial. Eur J Radiol. 2012;81(9):2265–9.
50. Spronk S, den Hoed PT, de Jonge LC, van Dijk LC, Pattynama PM. Value of the duplex waveform at the common femoral

artery for diagnosing obstructive aortoiliac disease. J Vasc Surg. 2005;42(2):236–42. discussion 42
51. Katsanos K, Tepe G, Tsetis D, Fanelli F. Standards of practice for superficial femoral and popliteal artery angioplasty and stenting. Cardiovasc Intervent Radiol. 2014;37(3):592–603.
52. Kalish J, Eslami M, Gillespie D, Schermerhorn M, Rybin D, Doros G, et al. Routine use of ultrasound guidance in femoral arterial access for peripheral vascular intervention decreases groin hematoma rates. J Vasc Surg. 2015;61(5):1231–8.
53. Lo RC, Fokkema MT, Curran T, Darling J, Hamdan AD, Wyers M, et al. Routine use of ultrasound-guided access reduces access site-related complications after lower extremity percutaneous revascularization. J Vasc Surg. 2015;61(2):405–12.
54. Bangalore S, Bhatt DL. Femoral arterial access and closure. Circulation. 2011;124(5):e147–56.
55. Noori VJ, Eldrup-Jorgensen J. A systematic review of vascular closure devices for femoral artery puncture sites. J Vasc Surg. 2018;68(3):887–99.
56. Rossi M, Iezzi R. Cardiovascular and Interventional Radiological Society of Europe guidelines on endovascular treatment in aortoiliac arterial disease. Cardiovasc Intervent Radiol. 2014;37(1):13–25.
57. Namazi MH, AlipourParsa S, Roohigilani K, Safi M, Vakili H, Khaheshi I, et al. Is it necessary to discontinue metformin in diabetic patients with GFR >60 ml/min per 1.73 m^2 undergoing coronary angiography: A controversy still exists? Acta Biomed 2018;89(2):227–32.
58. Wiersema AM, Watts C, Durran AC, Reijnen MM, van Delden OM, Moll FL, et al. The use of heparin during endovascular peripheral arterial interventions: A synopsis. Scientifica. 2016;2016:1456298.
59. Doganer O, Wiersema AM, Scholtes V, Blankensteijn JD, Yeung KK, Jongkind V. No concluding evidence on optimal activated clotting time for non-cardiac arterial procedures. Eur J Vasc Endovasc Surg. 2020;59(1):137–47.
60. Nilius H, Kaufmann J, Cuker A, Nagler M. Comparative effectiveness and safety of anticoagulants for the treatment of heparin-induced thrombocytopenia. Am J Hematol. 2021;96(7):805–15.
61. Linkins LA, Hu G, Warkentin TE. Systematic review of fondaparinux for heparin-induced thrombocytopenia: When there are no randomized controlled trials. Res Pract Thromb Haemost. 2018;2(4):678–83.
62. Bosch JL, Hunink MG. Meta-analysis of the results of percutaneous transluminal angioplasty and stent placement for aortoiliac occlusive disease. Radiology. 1997;204(1):87–96.
63. Ichihashi S, Higashiura W, Itoh H, Sakaguchi S, Nishimine K, Kichikawa K. Long-term outcomes for systematic primary stent placement in complex iliac artery occlusive disease classified according to Trans-Atlantic Inter-Society Consensus (TASC)-II. J Vasc Surg. 2011;53(4):992–9.
64. Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of TransAtlantic Inter-Society Consensus class C and D aorto-iliac lesions. J Vasc Surg. 2011;53(6):1728–37.
65. Mallory A, Giannopoulos S, Lee P, Kokkinidis DG, Armstrong EJ. Covered stents for endovascular treatment of aortoiliac occlusive disease: a systematic review and meta-analysis. Vasc Endovascular Surg. 2021;55(6):560–70.
66. Boufi M, Ejargue M, Gaye M, Boyer L, Alimi Y, Loundou AD. Systematic review and meta-analysis of endovascular versus open repair for common femoral artery atherosclerosis treatment. J Vasc Surg. 2021;73(4):1445–55.
67. Changal KH, Syed MA, Dar T, Mangi MA, Sheikh MA. Systematic review and proportional meta-analysis of endarterectomy and endovascular therapy with routine or selective stenting for common femoral artery atherosclerotic disease. J Interv Cardiol. 2019;2019:1593401.
68. Shammas NW, Shammas GA, Karia R, Khalafallah R, Jones-Miller S, Shammas AN. Two-year outcomes of endovascular interventions of the common femoral artery: a retrospective analysis from two medical centers. Cardiovasc Revasc Med. 2021;24:72–6.
69. Cioppa A, Franzese M, Gerardi D, Pucciarelli A, Popusoi G, Stabile E, et al. Three-year outcome of directional atherectomy and drug coated balloon for the treatment of common femoral artery steno-occlusive lesions. Catheter Cardiovasc Interv. 2021 [Epub ahead of print]
70. Zhou Y, Wang J, He H, Li Q, Li M, Li X, et al. Comparative effectiveness of endovascular treatment modalities for de novo femoropopliteal lesions in intermittent claudication: A network meta-analysis of randomized controlled trials. Int J Cardiol. 2021;343:122–30.
71. Fanelli F, Cannavale A, Gazzetti M, Lucatelli P, Wlderk A, Cirelli C, et al. Calcium burden assessment and impact on drug-eluting balloons in peripheral arterial disease. Cardiovasc Intervent Radiol. 2014;37(4):898–907.
72. Tepe G, Brodmann M, Werner M, Bachinsky W, Holden A, Zeller T, et al. Intravascular lithotripsy for peripheral artery calcification: 30-day outcomes from the randomized disrupt PAD III trial. JACC Cardiovasc Interv. 2021;14(12):1352–61.
73. Rastan A, Brodmann M, Bohme T, Macharzina R, Noory E, Beschorner U, et al. Atherectomy and drug-coated balloon angioplasty for the treatment of long infrapopliteal lesions: a randomized controlled trial. Circ Cardiovasc Interv. 2021;14(6).
74. Zeller T, Langhoff R, Rocha-Singh KJ, Jaff MR, Blessing E, Amann-Vesti B, et al. Directional atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis and maintain vessel patency: twelve-month results of the DEFINITIVE AR study. Circ Cardiovasc Interv. 2017;10(9):e004848.
75. Voute MT, Stathis A, Schneider PA, Thomas SD, Brodmann M, Armstrong EJ, et al. Delphi consensus study toward a comprehensive classification system for angioplasty-induced femoropopliteal dissection: The DISFORM study. JACC Cardiovasc Interv. 2021;14(21):2391–401.
76. Almasri J, Adusumalli J, Asi N, Lakis S, Alsawas M, Prokop LJ, et al. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg. 2019;58(1S):S110–S9.
77. Scheinert D, Katsanos K, Zeller T, Koppensteiner R, Commeau P, Bosiers M, et al. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES trial. J Am Coll Cardiol. 2012;60(22):2290–5.
78. Spreen MI, Martens JM, Hansen BE, Knippenberg B, Verhey E, van Dijk LC, et al. Percutaneous transluminal angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia (PADI) trial. Circ Cardiovasc Interv. 2016;9(2):e002376.
79. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. Circulation. 2013;128(6):615–21.
80. Jongsma H, Bekken JA, Akkersdijk GP, Hoeks SE, Verhagen HJ, Fioole B. Angiosome-directed revascularization in patients with critical limb ischemia. J Vasc Surg. 2017;65(4):1208–19.e1.
81. Stimpson AL, Dilaver N, Bosanquet DC, Ambler GK, Twine CP. Angiosome specific revascularisation: does the evidence support it? Eur J Vasc Endovasc Surg 2019;57(2):311–7.
82. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg. 2019;58(1S):S1–S109.e33.
83. Aurshina A, Victory J, Velez L, Kibrik P, Hingorani A, Marks N, et al. Physician impact on use of fluoroscopy during

endovascular procedures to improve radiation safety. J Vasc Surg. 2021;74(3):958–62.
84. Ketteler ER, Brown KR. Radiation exposure in endovascular procedures. J Vasc Surg. 2011;53(Suppl 1):35S–8S.
85. Hauguel A, Maurel B, Bague N, Gouaillier-Vulcain F, Costargent A, Chaillou P, et al. Management of ambulatory (day case) endovascular procedures for peripheral arterial disease. J Cardiovasc Surg. 2017;58(2):293–304.
86. Kelm M, Perings SM, Jax T, Lauer T, Schoebel FC, Heintzen MP, et al. Incidence and clinical outcome of iatrogenic femoral arteriovenous fistulas: implications for risk stratification and treatment. J Am Coll Cardiol. 2002;40(2):291–7.
87. Venermo M, Sprynger M, Desormais I, Bjorck M, Brodmann M, Cohnert T, et al. Editor's Choice – Follow-up of patients after revascularisation for peripheral arterial diseases: A consensus document from the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg. 2019;58(5):641–53.
88. Baril DT, Marone LK. Duplex evaluation following femoropopliteal angioplasty and stenting: criteria and utility of surveillance. Vasc Endovascular Surg. 2012;46(5):353–7.
89. Armstrong EJ, Chen DC, Westin GG, Singh S, McCoach CE, Bang H, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. J Am Heart Assoc. 2014;3(2):e000697.
90. Bonaca MP, Hamburg NM, Creager MA. Contemporary medical management of peripheral artery disease. Circ Res. 2021;128(12):1868–84.
91. Chan SL, Rajesh R, Tang TY. Evidence-based medical treatment of peripheral arterial disease: A rapid review. Ann Acad Med Singap. 2021;50(5):411–24.
92. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391(10117):219–29.
93. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763–816.
94. Robertson L, Ghouri MA, Kovacs F. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. Cochrane Database Syst Rev. 2012;2012(8):CD002071.
95. Strobl FF, Brechtel K, Schmehl J, Zeller T, Reiser MF, Claussen CD, et al. Twelve-month results of a randomized trial comparing mono with dual antiplatelet therapy in endovascularly treated patients with peripheral artery disease. J Endovasc Ther. 2013;20(5):699–706.
96. Tepe G, Bantleon R, Brechtel K, Schmehl J, Zeller T, Claussen CD, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy – The MIRROR study: a randomised and double-blinded clinical trial. Eur Radiol. 2012;22(9):1998–2006.
97. Thott O, Granath F, Malmstedt J, Wahlgren CM. Editor's Choice – Dual Antiplatelet Therapy Improves Outcome in Diabetic Patients Undergoing Endovascular Femoropopliteal Stenting for Critical Limb Ischaemia. Eur J Vasc Endovasc Surg. 2017;53(3):403–10.
98. Ipema J, Welling RHA, Bakker OJ, Bokkers RPH, de Vries JPM, Unlu C. Short-term clinical outcomes of single versus dual antiplatelet therapy after infrainguinal endovascular treatment for peripheral arterial disease. J Clin Med. 2020;9(11):3515.
99. Cho S, Lee YJ, Ko YG, Kang TS, Lim SH, Hong SJ, et al. Optimal strategy for antiplatelet therapy after endovascular revascularization for lower extremity peripheral artery disease. JACC Cardiovasc Interv. 2019;12(23):2359–70.
100. Hiatt WR, Bonaca MP, Patel MR, Nehler MR, Debus ES, Anand SS, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: Impact of concomitant clopidogrel on efficacy and safety. Circulation. 2020;142(23):2219–30.
101. Lapebie FX, Aboyans V, Lacroix P, Constans J, Boulon C, Messas E, et al. Editor's Choice – External Applicability of the COMPASS and VOYAGER-PAD Trials on Patients with Symptomatic Lower Extremity Artery Disease in France: The COPART Registry. Eur J Vasc Endovasc Surg. 2021;62(3):439–49.
102. Pastori D, Farcomeni A, Milanese A, Del Sole F, Menichelli D, Hiatt WR, et al. Statins and major adverse limb events in patients with peripheral artery disease: a systematic review and meta-analysis. Thromb Haemost. 2020;120(5):866–75.
103. Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, Katsaros I, Jawaid O, Jonnalagadda AK, et al. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: A systematic review and meta-analysis. Vasc Med. 2020;25(2):106–17.
104. Belch JJF, Brodmann M, Baumgartner I, Binder CJ, Casula M, Heiss C, et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease. VASA. 2021;50(6):401–11.
105. Thomas Manapurathe D, Krishna SM, Dewdney B, Moxon JV, Biros E, Golledge J. Effect of blood pressure lowering medications on leg ischemia in peripheral artery disease patients: A meta-analysis of randomised controlled trials. PLoS One. 2017;12(6):e0178713.
106. Sanchez Munoz-Torrero JF, Escudero-Sanchez G, Calderon-Garcia JF, Rico-Martin S, Robles NR, Bacaicoa MA, et al. Systolic blood pressure and outcomes in stable outpatients with recent symptomatic artery disease: a population-based longitudinal study. Int J Environ Res Public Health. 2021;18(17):9348.
107. Busch L, Heinen Y, Stern M, Wolff G, Ozaslan G, Tzetou K, et al. Angioplasty of flow-limiting stenosis reduces aortic and brachial blood pressure in patients with peripheral artery disease. J Am Heart Assoc. 2021;10(14):e019724.
108. Goldman MP, Clark CJ, Craven TE, Davis RP, Williams TK, Velazquez-Ramirez G, et al. Effect of intensive glycemic control on risk of lower extremity amputation. J Am Coll Surg. 2018;227(6):596–604.
109. Yap T, Silickas J, Weerakkody R, Lea T, Santhirakumaran G, Bremner L, et al. Predictors of outcome in diabetic patients undergoing infrapopliteal endovascular revascularization for chronic limb-threatening ischemia. J Vasc Surg. 2021. [Epub ahead of print]
110. Paul SK, Bhatt DL, Montvida O. The association of amputations and peripheral artery disease in patients with type 2 diabetes mellitus receiving sodium-glucose cotransporter type-2 inhibitors: real-world study. Eur Heart J. 2021;42(18):1728–38.
111. Dhatariya K, Bain SC, Buse JB, Simpson R, Tarnow L, Kaltoft MS, et al. The impact of Liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER Trial. Diabetes Care. 2018;41(10):2229–35.
112. Chang HY, Chou YY, Tang W, Chang GM, Hsieh CF, Singh S, et al. Association of antidiabetic therapies with lower extremity amputation, mortality and healthcare cost from a nationwide retrospective cohort study in Taiwan. Sci Rep. 2021;11(1):7000.
113. Bertoccini L, Baroni MG. GLP-1 receptor agonists and SGLT2 inhibitors for the treatment of type 2 diabetes: new insights

and opportunities for cardiovascular protection. Adv Exp Med Biol. 2021;1307:193–212.
114. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.
115. Matthews DR, Li Q, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, et al. Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS Program. Diabetologia. 2019;62(6):926–38.
116. Katsiki N, Dimitriadis G, Hahalis G, Papanas N, Tentolouris N, Triposkiadis F, et al. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) use and risk of amputation: an expert panel overview of the evidence. Metabolism. 2019;96:92–100.
117. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380 (24):2295–306.
118. Lin DS, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors. Diabetologia. 2021; 64(9):1949–62.
119. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev. 2017;12:CD000990.
120. Pandey A, Banerjee S, Ngo C, Mody P, Marso SP, Brilakis ES, et al. Comparative efficacy of endovascular revascularization versus supervised exercise training in patients with intermittent claudication: meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2017;10(7):712–24.
121. Schuler D, Sansone R, Nicolaus C, Kelm M, Heiss C. Repetitive remote occlusion (RRO) stimulates eNOS-dependent blood flow and collateral expansion in hindlimb ischemia. Free Radic Biol Med. 2018;129:520–31.
122. McDermott MM, Criqui MH, Domanchuk K, Ferrucci L, Guralnik JM, Kibbe MR, et al. Cocoa to improve walking performance in older people with peripheral artery disease: The COCOA-PAD pilot randomized clinical trial. Circ Res. 2020;126(5):589–99.
123. Minar E. Integrative therapy in patients with intermittent claudication. VASA. 2015;44(2):85–91.
124. Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. JAMA. 2015;314(18):1936–44.
125. Johnson DJ, Saar BJ, Shevitz AJ, Kim AH, Hammer L, Kendrick DE, et al. A total offloading foot brace for treatment of diabetic foot ulcers: results from a halted randomized controlled trial. Wounds. 2018;30(7):182–5.

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Conflict of interest
Dr. Heiss reports research grants from the Economic and Social Research Council outside the submitted work. Dr. Madaric reports research grants from Bayer and Pfizer and personal fees from Bayer, Pfizer, Medtronic and AlfaSigma outside the submitted work. Dr. Belch reports personal fees from Amgen, Bayer and Rexgenero outside the submitted work. Dr. Olinic reports grants from National Research Grant, Johnson & Johnson, Pfizer, Bayer and Behring personal fees from Astra Zeneca, Bayer, Pfizer and Sanofi, outside the submitted work. Dr. Brodmann reports personal fees from Biotronik, Medtronic, Philips, Bayer Healthcare, Boston Scientific, Cook Medical, Cagent, Reflow Medical, Shockwave, Surmodics and R3 Medical outside the submitted work. Dr. Krentz, Dr. Lichtenberg, Dr. Mazzolai, Dr. Schlager, Dr. Frank and Dr. Stanek have nothing to disclose related to the submitted work.

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