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SPECIAL ARTICLE

Treatment of peripheral arterial disease in diabetes: A consensus of the Italian Societies of Diabetes (SID, AMD), Radiology (SIRM) and Vascular Endovascular Surgery (SICVE)

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Abstract Diabetic foot (DF) is a chronic and highly disabling complication of diabetes. The prevalence of peripheral arterial disease (PAD) is high in diabetic patients and, associated or not with peripheral neuropathy (PN), can be found in 50% of cases of DF. It is worth pointing out that the number of major amputations in diabetic patients is still very high. Many PAD diabetic patients are not revascularised due to lack of technical expertise or, even worse, negative beliefs because of poor experience. This despite the progress obtained in the techniques of distal revascularisation that nowadays allow to reopen distal arteries of the leg and foot. Italy has one of the lowest prevalence rates of major amputations in Europe, and has a long tradition in the field of limb salvage by means of an aggressive approach in debridement, antibiotic therapy and distal revascularisation. Therefore, we believe it is appropriate to produce a consensus document concerning the treatment of PAD and limb salvage in diabetic patients, based on the Italian experience in this field, to share with the scientific community.

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Diabetic foot (DF) is a chronic and highly disabling complication of diabetes that affects patients with peripheral neuropathy (PN) and/or peripheral arterial disease (PAD). It has been traditionally considered that DF is caused by PN, but epidemiological data have shown that the prevalence of PAD is high in diabetic patients [1,2] and, associated or not with PN, can be found in 50% of cases with lower limb lesions [3]. The presence of PN may mask the typical clinical symptoms of PAD, such as claudication and pain at rest, and so an ulcer that fails to heal and/or more or less extensive gangrenous areas of the foot may be the first signs of previously unknown PAD.

DF generally affects patients with long duration of the disease and, as they may also be affected by various co-morbidities, they may be particularly fragile and difficult to manage clinically. The high rate of (especially cardiovascular) co-morbidities means that attention should not be exclusively focussed on the foot with an ulcer, but takes into account the patient as a whole and the various clinical conditions that can jeopardise his or her life and have a negative impact on treatment. It would be a mistake to consider the foot separately from the rest of the body because DF is a local manifestation of a systemic condition.

Another aspect that needs to be considered is the complexity of the manifestations of DF, which include ischaemia, neuropathy, biomechanical problems, infection, wound healing and so on. This complexity practically rules out any single specialist approach and requires the assistance of a multidisciplinary team capable of guaranteeing functional rehabilitation of the foot and, whenever possible, optimising the patient's clinical condition. The team should include a diabetologist, a vascular surgeon, an interventional radiologist, an orthopaedic surgeon, a specialist in infectious diseases, a cardiologist, an orthopaedic technician and a podiatrist. A multidisciplinary approach has proved to be the winning formula in many published experiences [4,5].

The high prevalence of PAD in diabetic patients in general [1–3,6,7] is due to the nature of the disease itself, but other factors such as the longer average life span, a longer disease duration and (in diabetics with end-stage renal failure) the role of dialytic treatment should not be underestimated [8]. This indicates the burden that the complication may have for individual patients and society as a whole, given its chronic nature and the relatively frequent recourse to major lower limb amputations. However, it is worth pointing out that, despite the progressive increase in the prevalence of PAD in diabetic patients, the number of major amputations has decreased because of the growing use of distal revascularisation [9].

At this point, it is worth remembering that:

- there is a long tradition in the field of distal revascularisation in Italy, which is one of the few countries where revascularisation is routinely used to treat diabetic patients [10–13];
- Italy has one of the lowest prevalence rates of major amputations in Europe which is 3.1/100,000 inhabitants [9]; and
- Eurodiale data (obtained from 14 European reference centres) show that the participating Italian centres are among the first in terms of clinical outcome, with the highest rate of wound healing and the lowest rates of major amputations [3,14].

On the basis of these considerations, we believe it is appropriate to produce a consensus document concerning the treatment of PAD and limb salvage in diabetic patients that is based on the Italian experience, to share with the scientific community. In drawing up this document, we have referred to the international literature published over the past 20 years, especially the one produced by Italian groups because of their increasingly greater use of endovascular treatment and the large number of treated patients [10–13,15–17].

Epidemiology and prevalence

The published prevalence rates of PAD vary widely between studies. A recent review by Jude indicates that its prevalence among diabetics is 8–30% [18]; Faglia estimates a prevalence of about 22% in patients with newly diagnosed type 2 diabetes [2], and Prompers a prevalence of about 50% in diabetic patients with foot ulcers [3].

Characteristics of PAD in diabetic patients

PAD in diabetic subjects is a systemic, obstructive atherosclerotic disease with some particular histopathological characteristics, especially the higher incidence of vascular calcifications [19–24]. In comparison with non-diabetics, diabetic patients with PAD are generally younger, have a higher body mass index (BMI), are more often neuropathic and have more cardiovascular co-morbidities [25].

The clinical peculiarities of obstructive arteriopathy in diabetic patients are its rapid progression and prevalently distal and bilateral topographical expression. Furthermore, the arterial walls are often calcified and occlusions are more frequent than stenoses. The natural adaptive response to reduced flow inside an artery is neoangiogenesis, but this and the capacity to generate compensatory collateral circulations are reported to be reduced in diabetic subjects [26–33], even if a recent observation shows better collateral development towards the culprit vessel at least in the coronary artery disease [34].

Anatomical characteristics

The anatomical distribution of PAD is different in the diabetic and non-diabetic populations. In diabetic subjects, PAD more frequently affects below-the-knee vessels such as the tibial and peroneal arteries and is symmetric and multi-segmental, and the collateral vessels can also be affected by stenosis [35,36].

The severity of the lesions is also different in the two populations, with diabetic subjects having a larger number

of stenoses/obstructions of the deep femoral, popliteal, peroneal, anterior and posterior tibial and even the plantar arteries [37,38].

It is essential to define the type and extent of PAD when deciding the clinical prognosis because infra-popliteal involvement is associated with a high risk of major amputation in diabetic subjects who have not undergone distal revascularisation [39]:

- PAD is a common complication of diabetes and affects more than 50% of the patients with ulcers.
- Its localisation is predominantly distal and symmetrical, and it is rapidly progressive.

Evolution and prognosis

The initial clinical picture is rarely symptomatic (claudication may be absent because of concomitant PN) and more frequently characterised by the ischaemic lesions and gangrene typical of more advanced disease stages. For this reason, the current clinical classifications of PAD are not really applicable in the presence of diabetes and foot ulcers, and it is more appropriate to use the University of Texas Wound Classification System [40]. PAD is present in 50% of diabetic patients with ulcerative wounds and is a widely recognised risk factor for major amputations.

The negative prognosis of ischaemic ulcerative lesions in diabetic patients is probably related to the co-existence of factors such as the anatomical distribution of PAD, infection, neuropathy and renal insufficiency and the concomitant presence of other coronary and cerebral vascular manifestations. About 27% of diabetic subjects with PAD experience progressive disease in the following 5 years, and 4% undergo major amputation; about 20% manifest a cardiovascular event (myocardial infarction or stroke). The prognosis of diabetic patients with critical limb ischaemia (CLI) is even more serious as 30% may require a major amputation and 20% die of cardiovascular disease within 1 year [41].

Non-revascularisation of PAD diabetic patients is an independent predictive factor of amputation [16] and also an independent determinant of poor survival [18].

The risk of co-existing ischaemic heart disease in diabetic patients with PAD is 50% [42–44]. The simultaneous presence of silent and non-silent myocardial ischaemia is significantly more frequent in diabetic than in non-diabetic subjects [45,46], which means that all diabetic patients with PAD should undergo diagnostic investigations of the coronary district in order to identify any previously unknown coronary disease.

Diabetic patients with PAD have frequently a concomitant chronic renal insufficiency (CRI) requiring haemodialysis, which means that the vascular damage is more severe and progresses more rapidly than in diabetic patients without end-stage renal disease. Renal disease is one of the most important factors underlying the unfavourable course of an ulcerative lesion, and dialysis is one of the main risk factors for ulceration and amputation in diabetic patients [3,47].

Distal revascularisation in dialysed patients is a challenge because they are more susceptible to infections, uraemia further hinders the healing of ulcerative lesions and PAD is complicated by the presence of marked calcifications of the vessel walls. Furthermore, the risk of major amputation is 4.7 times higher than in non-dialysed subjects [8].

Diabetic subjects with renal insufficiency also experience more perioperative complications such as sepsis and heart failure, and there is a high rate of mortality due to surgical revascularisation (2.4–13%) [8].

However, despite the complexity of the local and general management of diabetic PAD patients undergoing dialysis, recent data show that 1-year limb salvage can be as high as 65–75%. [48]

- Diabetic patients rarely experience the early symptomatic manifestation of PAD (claudication) because of the frequent concomitance of sensitive motor neuropathy.
- The current classifications of PAD in non-diabetic patients do not apply to diabetics.
- Ischaemic wounds, ulcers and gangrene are frequent initial signs of PAD in diabetic patients.
- It is appropriate to use the University of Texas Wound Classification System.
- Fifty percent of diabetic patients with PAD also have possibly silent ischaemic heart disease: a thorough diagnosis is needed that also includes the coronary and carotid regions.
- Diabetic patients with CLI undergoing dialysis have a more serious and rapidly progressive form of PAD that is very difficult to treat.

Assessing impaired perfusion in a DF

In the case of suspected PAD, a number of examinations need to be carried in order to assess the severity of the clinical picture. Centres that mainly screen and manage less complex wounds should non-invasively determine whether the patient is ischaemic or not and, above all, evaluate whether the ischaemia has any negative effect on the evolution of the ulcerative lesion.

It is important to emphasise the need to transfer ischaemic patients to a specialised, multidisciplinary centre as soon as possible [49]. Published data show that ischaemic lesions are less likely to heal, and that the onset of infection can transform an originally mild lesion into gangrene. This risk increases with the duration of the lesion and the continuation of ineffective treatment without appropriate revascularisation.

PAD should be sought in all diabetic subjects with foot ulcers. The evaluation begins with a search for arterial pulses (femoral, popliteal, posterior tibial and dorsalis pedis) but, despite this being essential in the case of epidemiological investigations, it has some limitations when it comes to verifying the presence of an ischaemic component in patients affected by ongoing ulcers. In particular, the dorsalis pedis pulse may be absent in up to

30% of patients free of vascular disease, is poorly reproducible and may sometimes be detected even in the presence of ischaemia. The posterior tibial pulse seems to be more reliable and provides more certain information concerning the presence or absence of ischaemic condition. It needs to be underlined that the obstruction of one tibial artery (or only the plantar arch in diabetics) can lead to an ischaemic ulcer, and so the presence of a single well-palpated tibial pulse does not exclude it. However, the greatest limitation of using pulses to evaluate ischaemia is the fact that an absent pulse does not provide any information concerning perfusion deficit and therefore the healing potential of the lesion itself [50]. In a large-scale survey of diabetics with an ulcer and peripheral ischaemia, Apelqvist found that >50% of the patients would not have been classified as ischaemic if they had not undergone an instrumental evaluation [51].

Furthermore, the semiotic methods that are widely used when diagnosing non-diabetics, such as the search for femoral pulse or position-related changes in foot colour, can be influenced by many confounding factors and so using them alone to diagnose PAD in diabetic subjects is considered not sufficient [52].

It is clear that the presence of an ulcer requires a more objective evaluation, not least because this can guide therapeutic decision-making, particularly the need for revascularisation.

Diabetic patients with limb ischaemia can be non-invasively evaluated in different ways but, as each of them has different advantages, disadvantages and limitations, it is often necessary to integrate them.

The ankle/brachial pressure index (ABI) is the ratio of the systolic pressure in the ankle to that in the arm and is considered a reference test insofar as it is reproducible, sensitive and specific in detecting PAD. In diabetics, it should be calculated using whichever is the lower of the systolic pressure in the anterior and posterior tibial arteries [53]. The American Diabetes Association recommends using the ABI to screen all diabetics aged >50 years and all insulin-dependent diabetics regardless of age in the presence of other cardiovascular risk factors. On the basis of the ABI, it is possible to define the entity of peripheral vascular impairment: 0.91–1.30 = normality; 0.70–0.90 = mild; 0.40–0.69 moderate; and <0.40 = severe [54]. From the clinical point of view, in the presence of an ulcer, an ABI of >0.7 is indicative of reduced perfusion but it is still sufficient to ensure healing. In any case, a reduced ABI is an important predictor of cardiovascular events and premature death [55]. An ABI of >1.30 indicates that the arteries are scarcely compressible because of the presence of extended calcification of the walls, but does not exclude the presence of PAD [56]. This value has negative prognostic implications *per se* insofar as it correlates with PN [57] and is a risk factor for cardiovascular events [58], but is non-diagnostic in the case of PAD. The same calcifications may sometimes lead to a falsely normal ABI, but the search for pulses can help in diagnosing PAD [59,60]. Wall calcifications are common in subjects with long-lasting diabetes, those undergoing dialysis (particularly if diabetic) and the elderly.

One test that is currently used to overcome the problem of calcifications is to measure toe systolic pressure and calculate the ratio between it and brachial systolic pressure (the toe/brachial index, TBI) [61]. This is possible because toe vessels are generally free of calcifications. Under normal conditions, the pressure of the hallux is about 30 mm Hg less than that of the ankle, and the TBI is >0.71. A TBI of <0.71 is indicative of PAD, but absolute values of >50 mm Hg indicate sufficient perfusion to guarantee ulcer healing in diabetic patients, whereas values of <50 mm Hg indicate critical ischaemia and values of <0.3 insufficient perfusion for healing [62]. This test is impossible in patients with digital gangrene.

Transcutaneous oximetry ($TcPO_2$) measures the transcutaneous partial pressure of oxygen, and is indicated for diabetic patients with ulcerative or gangrenous lesions, claudication or pain at rest insofar as it is a measure of the presence and severity of PAD and can provide information concerning the healing potential of a lesion [63]. The reference value is 50 mm Hg, whereas values of <30 mm Hg indicate little healing potential. The relationship between $TcPO_2$ and perfusion is not linear because values equal to zero do not really indicate the absence of flow but a state of severe ischaemia in which all of the available oxygen is consumed by the tissues. There are a number of conditions under which the test value should be considered cautiously: for example, the presence of peripheral oedema or widespread cellulitis that can influence the measurements and lead to unreliable values. $TcPO_2$ is also used to define amputation levels as values of >50 mm Hg predict a good likelihood of surgical wound healing, whereas healing is uncertain at values of 30–50, and improbable at values of <30 [64].

Duplex ultrasonography (echo Doppler) allows the morphological/functional study of the vascular tree [65]. According to some experts, the information provided by duplex scans is sufficient to indicate which patients should undergo revascularisation, but others believe further diagnostic evaluations such as magnetic resonance (angio-MR) or computed tomography angiography (angio-CT) are necessary. It needs to be underlined that the American College of Cardiology/American Heart Association guidelines recommend the use of angio-MR rather than angio-CT because it allows better definition and leads to fewer technique-related risks [66].

Invasive arteriography is never considered a diagnostic technique *per se*, but represents the first step in endovascular therapy; it can only be proposed for diagnostic purposes in cases in which the other methods have failed to define the extent and topography of stenotic/obstructive arterial disease.

Diagnostic evaluation before revascularisation

The preoperative evaluation of diabetic patients at risk of limb loss is a much-debated subject because the need to characterise the arterial bed of patients with advanced vasculopathy in a detailed manner conflicts not only with the need to be as uninvasive as possible but also with the

high costs of the most advanced diagnostic techniques. Furthermore, despite the tumultuous progress of vascular imaging techniques, none can be considered a gold standard that satisfies all diagnostic needs.

The correct evaluation of patients with PAD cannot be limited to the lower limbs but should also include the aortic vessels, abdominal aorta and renal arteries because this would reduce the number of co-morbidities associated with revascularisation.

The techniques currently used for vascular studies are duplex ultrasonography, angio-CT and angio-MR.

Duplex ultrasonography is considered to be the most important and, in many centres, is the only technique used before revascularisation procedures. One of its main advantages is that it provides information concerning the haemodynamics of the obstructive arteriopathy and the state of run-off [67]. However, it has often been limited by its operator dependence and the patient's condition [68], although these factors certainly have less impact in centres that carry out a large number of examinations. Nevertheless, a complete evaluation including the renal arteries, the abdominal aorta, the iliac axes, the femoro-popliteal axis and leg vessels takes a long time.

The use of angio-CT and angio-MR has made it possible to obtain repeatable and panoramic images that not only assist the planning of the revascularisation procedure but also allow the simultaneous evaluation of any other area of vascular disease in just a few minutes [69]. However, they have the drawbacks of being expensive and not widely available. Among other things, angio-MR is playing an increasingly important role in pre-revascularisation assessments of the vascular tree because the new-generation coils make it possible to obtain panoramic views from the intracranial circulation to the plantar arch and avoid the use of nephrotoxic contrast media. MR is highly sensitive and specific in the various vascular districts, and its performance is similar to that of standard angiography at the level of the iliac aorta, the femoro-popliteal axis and the renal and carotid arteries. Its main limitations are related to venous contamination of the foot, the lack of information concerning the type of plaque causing the stenosis/obstruction (calcified, lipid or fibrous), the absence of signal in the presence of ferromagnetic artefacts (metal stents and arthroprostheses) and the general contraindications to MR such as pacemakers, claustrophobia, etc [70].

Multilayer angio-CT is currently considered the gold standard in most vascular districts, where its sensitivity and specificity are similar to those of arteriography. It optimally characterises the type of plaque causing the stenosis/obstruction and therefore makes it possible to choose the most suitable technique and material for each individual procedure, and it provides more information than MR concerning the surrounding parenchyma and the presence of associated co-morbidities. Furthermore, technological advances have reduced acquisition times to a minimum (a few seconds) and reduced the radiation dose to acceptable levels. The main limitation of angio-CT is the use of the iodinated contrast media: these may be nephrotoxic in this category of patients, especially as it is followed by endovascular treatment using arteriography, which uses the same type of contrast [71,72].

- PAD should be suspected and assessed in all diabetic subjects with foot ulcers.
- ABI and TBI are good screening tests.
- A semiological diagnosis of PAD is not reliable in diabetics.
- The non-invasive evaluation of PAD requires the integration of various tests.
- $TcPO_2$ can predict the healing potential of ischaemic or ulcerative lesions.
- Doppler ultrasonography provides morphological and functional information with a good degree of sensitivity and specificity.
- Angio-MR or angio-CT is used when further diagnostic details are required.
- Arteriography should never be considered an exclusively diagnostic test.

Medical therapy

There are currently no published data concerning any medical treatment of PAD other than revascularisation. However, it is important to correct any modifiable risk factors for cardiovascular disease, especially perioperatively and during the follow-up.

Vasodilators

Prostanoid treatment (i.e., the intravenous infusion of a stable prostacyclin (PGI_2) analogue such as iloprost/Alprostar for 3–4 weeks) is not an alternative to peripheral revascularisation in diabetic patients with PAD [73]. For ethical reasons, no randomised clinical trials have been carried out in order to compare the efficacy of prostanoid treatment with that of surgery in patients with critical ischaemia. However, it is important for relieving pain while awaiting surgical revascularisation, improving post-revascularisation perfusion and improving the patients' quality of life [74].

Anti-platelet agents/anticoagulants

In relation to anti-thrombotic/anticoagulant treatment for the primary and secondary prevention of PAD, we recommend following the ninth edition (2012) of the guidelines of the American College of Chest Physicians and other recent reviews [75–78].

Diabetic patients aged >50 years who are asymptomatic for PAD should undergo primary prevention using long-term daily aspirin monotherapy (75–100 mg), as in the case of cardiovascular events.

In the case of secondary prevention, various stages need to be distinguished:

- Symptomatic PAD (intermittent claudication): aspirin (75–100 mg day^{-1}) or clopidogrel (75 mg day^{-1}).

Dual anti-platelet and anticoagulant treatment is not advisable.

- PAD with intermittent claudication and reduced physical exercise capacity (without lesions): cilostazol (100–200 mg day^{-1}) in addition to aspirin (75–100 mg day^{-1}) or clopidogrel (75 mg day^{-1}).

Pentoxifylline, heparinoids and prostanoids are not advisable.

- Chronic limb ischaemia or symptomatic PAD and critical ischaemia/pain at rest/ischaemic lesions awaiting revascularisation: aspirin (75–100 mg day^{-1}) or clopidogrel (75 mg day^{-1}).
- Before and after percutaneous transluminal angioplasty (PTA): dual anti-platelet treatment with aspirin (75–100 mg day^{-1}) and clopidogrel (75 mg day^{-1}) for 1 month, followed by long-term single anti-platelet therapy.
- The guidelines of the European Society of Vascular Surgery state that the use of oral anticoagulants during the first 6 months after surgical revascularisation increases the primary patency of the graft, although it is not highly recommended. [79]

The role of the more recent anticoagulants has yet to be evaluated especially in terms of their cost/efficacy ratio and the risk of bleeding in relation to the obvious advantage of less frequent blood chemistry checks.

- There is no evidence concerning the use of PAD treatments other than revascularisation in diabetic patients.
- It is essential to correct risk factors perioperatively and during follow-up.
- Vasodilators are not indicated for the treatment of PAD in diabetic subjects.
- Anti-platelet therapy is always indicated in diabetics with PAD.

Non-revascularisable patients or candidates for primary amputation

Primary amputation is a demolitive operation that is not preceded by any attempt at revascularisation, and it is considered primary therapy only in some cases of DF. Major amputations (above the ankle) are necessary when there is a life-threatening infection that cannot be controlled by antibiotics. In this context, amputation is indicated on the basis of the patient's general condition and the fact that any delay could affect patient survival.

The next aspect to consider is the residual function of the limb during the post-reparative phase: necrosis extending to most of the foot will surely prevent functional recovery and therefore it is unnecessary to proceed to revascularisation.

Some patients have a functional deficit that is independent of the foot lesion (sequelae of a stroke, the position of the limb in flexion, etc.) and it effectively prevents deambulation. In such cases, a major amputation does not alter the patient's quality of life and may even lead to an improvement because it allows the prompt resolution of a major clinical problem such as infection or pain.

The primary aim of an amputation is to heal the leg as distally as possible. The energy spent on deambulation increases with level of the amputation. Preservation of the knee and a significant part of the tibia allows the use of a light prosthesis, as well as the early and independent deambulation of old or debilitated patients. In brief, the ideal level of amputation is the most distal level that has a possibility of healing, which is about 90% in the case of above-the-knee amputation and 80% if the joint is preserved. In clinical practice, healing capacity at a certain level can be predicted on the basis of $TcPO_2$.

The return to deambulation plays an essential role in the quality of life, and major advances in the fields of prosthetics and rehabilitation now mean that this is a real possibility in 50% of cases.

- Primary amputation is indicated in the case of life-threatening infection or extensive necrosis of the foot.

Indications for revascularisation

PAD is a risk factor for amputation [51,80] and needs to be diagnosed early in order to be able to take all of the therapeutic measures necessary to avoid it as soon as possible.

In the case of a foot ulcer in a diabetic patient with PAD, it is first necessary to evaluate the usefulness of revascularisation and then choose the method of revascularisation on the basis of the following clinical criteria: the healing potential of the ulcer; the local condition of the foot and its residual function after the healing process; the condition of the vascular tree; and finally the general condition of the patient.

Healing potential refers to the real possibility of healing on the basis of foot perfusion. Transcutaneous oximetry and evaluating the pressure of the toe may be helpful because, in addition to stenoses and obstructions, they can determine whether distal blood flow is sufficient to guarantee tissue healing. According to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) document [81], foot lesions generally heal if toe pressure is >50 mm Hg and $TcPO_2$ >50 mm Hg, whereas healing is a remote possibility if both are <30 mm Hg. However, it must be pointed out that TASC II does not specifically refer to diabetics but also includes the non-diabetic population.

In a critical review of $TcPO_2$ levels, Faglia considers values of <34 mm Hg an absolute indication for revascularisation, with an 85% probability of amputation in the case of no revascularisation; values of 34–40 mm Hg represent a less impelling indication for revascularisation, but there is still a considerable probability of amputation (about 20%). In the case of values of >40 mm Hg, revascularisation can be considered if the tissue loss is significant and there is a need to accelerate healing, or in the

presence of osteomyelitis for which conservative treatment is preferred [82].

In any case, once a perfusion deficit has been identified, revascularisation should always be considered. [83].

Another possible situation is one in which the limb is apparently perfused ($TcPO_2$ >40 mm Hg or toe pressure >50 mm Hg) but, despite optimal local treatment, the lesion shows no signs of healing. After having excluded general negative factors such as malnutrition or underlying osteomyelitis, it is necessary to consider the possibility that the non-invasive evaluations have overestimated peripheral perfusion and that there may be undetected ischaemia. In the presence of an ulcer that does not evolve positively within 4–6 weeks, an ischaemic component should always be suspected.

The condition of the foot and its potential functional recovery may above all condition the therapeutic choice of limb salvage or primary amputation. Gangrene may be the first sign of PAD in diabetic patients, and this may give rise to a false conviction that it is too late for revascularisation [84] and amputation is the only alternative. However, it should always be remembered that the local clinical picture may appear to be more compromised than it actually is because it may be greatly affected by an infection that can be cured with appropriate therapy, and so it may be possible to save a limb that at first sight seems definitely lost.

There are also situations in which the involvement is such that there is no possibility of saving the foot and major amputation is unavoidable. However, even in these cases (as in the case of partial amputation), it is essential to investigate the vascular tree because correcting underlying ischaemia may allow a more distal amputation and the more rapid healing of the amputated stump.

Even if a lesion is so large that limb salvage seems impossible or so small that it seems hardly worthy of a thorough diagnosis, the local condition of the foot should never condition therapeutic choices in absolute terms, although various studies have shown that a large ulcer is a risk factor for healing failure and major amputation [3,13].

The apparently obvious observation that a large ulcer implies an increased risk of major amputation disguises an extremely important aspect of managing DF: foot lesions are never large at the beginning but become so because of inadequate (and therefore ineffective) treatment or, even worse, the picture has been completely underestimated and inappropriate treatment has been continued for a long time. The concept of 'time is tissue' also applies to the foot, and so delayed or inadequate treatment leads to the irreversible loss of portions of foot tissue [85]. In particular, it has been demonstrated that, if a patient with an acutely phlegmonous foot is immediately referred to a tertiary centre [49], the outcome in terms of amputation is surely better than when he or she is first referred to a less suitable hospital because, in order to be effective, the necessary treatment (adequate surgical debridement and distal vascularisation) needs to be performed in a timely manner [86,87].

Another factor capable of significantly conditioning the choice and method of revascularisation is the involvement of the vascular tree. In order to define the type of intervention, it is important to assess the condition of the common iliac and femoral arteries, and equally important to evaluate distal run-off. There is no way that even optimal revascularisation will last over time without sufficient downstream blood flow: whether endoluminal or performed by means of bypass surgery, the revascularisation must allow the restoration of direct flow up to the dorsalis pedis or plantar arch [88].

One further aspect that needs to be considered is the patient's general condition. The most important of the many factors to consider are life expectancy and the presence of co-morbidities, particularly heart failure and CRI. The supporters of bypass peripheral revascularisation require a minimum life expectancy of 2 years for a surgical approach, whereas neither technique is considered suitable if life expectancy is <6–12 months [89]. It is probably better not to generalise but to evaluate the situation from time to time, also considering the improved quality of life that comes from pain control when the ischaemia is removed. In terms of co-morbidities, the entire vascular tree needs to be carefully assessed: half of the patients with PAD may have concomitant coronary disease, one-third concomitant carotid disease and about 15–20% both [90], and this has both diagnostic and therapeutic implications.

In terms of diagnosis, diabetic patients should never undergo distal revascularisation without having undergone at least a cardiological evaluation (haemodynamic status and possibly coronary reserve) and an echo Doppler examination of the upper aortic trunks in the search for a haemodynamically significant plaque in the territory of the internal carotid artery. It is clear that priority should be given to the treatment of any coronary instability and/or significant carotid stenosis.

Diabetes and end-stage renal disease are independent risk factors for PAD. It has been reported that the prevalence of PAD among patients with end-stage renal disease is as high as 77% [91], and renal insufficiency is an independent predictor of the non-healing of ischaemic and neuro-ischaemic ulcers and major amputations [92,93].

Between 22% and 44% of dialysed patients undergo primary amputations because of ischaemic lesions. These patients are difficult to treat and their high short-term mortality rate (3–17%) and low long-term survival rate (45%) can negatively influence the decision to undertake revascularisation [94–98].

Dialysed patients treated with bypass surgery generally experience worse outcomes than those undergoing PTA [99], as has also been confirmed in a recent Japanese case series [100].

In relation to the endovascular treatment of diabetic patients with renal insufficiency, Lepantolo [8] says "that although there is no evidence supporting endovascular treatment over open by-pass surgery in these high-risk patients, endoluminal revascularisation seems to be attractive as a first option provided that the area of the ulcer can be provided with an adequate blood flow." Rabellino et al.[101] used the endovascular technique and

achieved a limb salvage rate of 58.6% after a mean follow-up of 15 months, and Graziani [48] a salvage rate of 80% in a series of dialysed patients, about half of whom were diabetics. Finally, in another recent study of diabetics with PAD and severe foot lesions [13], outcomes were clearly worse in the patients on dialysis, although a 1-year limb salvage rate of 57% was reached in a subsequent series of unselected patients [102].

Although it is a non-modifiable risk factor, patient age also needs to be considered. Adults up to the age of 65–70 years do not give rise to any age-related problems and treatment decisions can be made more freely when a patient's clinical and chronological age coincide, but the situation is different in the case of elderly patients with more severe co-morbidities. Studies of bypass surgery and angioplasty have shown that age is not an impediment to either, and even the elderly can benefit from revascularisation in terms of limb salvage even though it does not change their final life expectancy [103].

In brief, as in the case of non-diabetic patients, the indication for revascularisation in diabetics depends on their clinical picture. Revascularisation is indicated in patients with chronic obstructive arterial disease and:

- disabling claudication and/or pain at rest and
- a trophic lesion and foot $TcPO_2$ of <30 mm Hg or a trophic lesion that shows no sign of healing after being adequately treated for 1 month.

The (absolute or relative) exclusion criteria are a life expectancy of <6 months, psychiatric disorders, untreatable antalgic flexion of the leg on the thigh, chronic bed confinement and the absence of deambulation.

- Once a perfusion deficit has been diagnosed, revascularisation should always be considered.
- The surgical treatment of any coronary and/or carotid perfusion deficit has priority over peripheral revascularisation.
- Diabetic patients with end-stage renal disease treated by dialysis may be candidates for revascularisation if they have:
- chronic obstructive arterial disease,
- disabling claudication and/or pain at rest,
- a trophic lesion and a $TcPO_2$ of <30 mm Hg and
- an ulcer that shows no sign of healing after being adequately treated for 1 month.
- Exclusion criteria are:
- a life expectancy of <6 months,
- severe psychiatric disorders,
- absence of deambulation and
- untreatable flexion of the leg.

Choice of revascularisation technique

'Angioplasty first' strategy

Various studies have evaluated the role of PTA in diabetic patients with critical PAD, especially diseases of the infrapopliteal vessels [2,12,13,15,17,104–113], the overall results of which are favourable in terms of feasibility, technical efficacy, the reduced number of complications and limb salvage rates.

Although long-term patency is better after bypass surgery than after angioplasty, which is burdened by a high restenosis rate [114–117], angioplasty can also be proposed for patients who cannot be candidates for a bypass because of significant co-morbidities, a reduced life expectancy, infection or gangrene in the possible sites of distal anastomoses, the unavailability of suitable veins or the absence of an adequate 'landing zone' for the distal part of the bypass [2,13,15,103,111].

Many patients with critical ischaemia are elderly, affected by multiple co-morbidities and at high operative risk [30,118]. These are unsuitable for surgical revascularisation, but a percutaneous procedure (technically reduced to the minimum possible invasiveness) can still be considered in order to improve their quality of life. Angioplasty does not require general anaesthesia and can be carried out with few contraindications in cardio- and nephropathic subjects at high surgical and anaesthetic risk [2,15,111]. In complex cases, it can be divided into various steps in order to reduce stress and the volume of contrast medium administered, by evaluating the clinical result and renal function after each step. In this way, more aggressive revascularisation can be restricted to the patients who really need it and whose renal function has not worsened.

Angioplasty can be easily repeated in the case of restenosis or reocclusion or be performed after the failure of bypass surgery [2,119–121].

The considerable industrial effort that has been made to create new instruments (very long, low-profile balloons, drug-eluting balloons, atherotomes, medicated and non-medicated stents, etc.) means that angioplasty can be increasingly proposed even in extreme situations and assures the better long-term patency of the treated vessels [121–126].

When patients can be treated either surgically or percutaneously, the fundamental rule of an 'angioplasty first strategy' is to respect the so-called surgical 'landing zones'. It can generally be said that the failure of angioplasty does not preclude subsequent bypass surgery [127], but there are reports indicating that a distal bypass procedure is more difficult after the failure of percutaneous revascularisation and associated with more complications and failures [128,129]. It is therefore imperative that percutaneous revascularisation procedures be carried out by experts capable of correctly identifying and technically respecting the 'landing zones' required for a subsequent distal bypass salvage operation. It is also necessary to use stents very carefully because any restenosis/reocclusion makes subsequent (surgical or percutaneous) treatment difficult or impossible.

By the same token, the use of open surgery should not compromise the possibility of future percutaneous treatment: for example, ligation of the superficial femoral artery makes it impossible to perform a subsequent percutaneous intervention to restore its patency in the case of bypass failure.

Even in the context of an 'angioplasty first' approach, there are some forms of vascular obstruction that should preferentially be treated surgically. Obstructive disease of the common femoral artery and its bifurcation are generally not related to diabetic arterial disease [130], and can be resolved by means of relatively trauma-free surgery requiring little anaesthesia in almost all cases. Another example is an extremely long occlusion of the femoro-popliteal and infra-popliteal axes, although there is no consensus concerning the length of the obstruction and local expertise is particularly important: the percutaneous treatment of such lesions is currently burdened by a high incidence of restenosis and repeat procedures [115,130,131], whereas a distal bypass in an autologous vein is a more effective and longer-lasting solution [114,115,132].

Surgical revascularisation by means of a bypass should be performed after having visualised the vascular tree by means of Doppler ultrasonography, angio-CT, angio-MR or angiography, and considered a series of important variables that condition the success of the procedure and its complications (see flow chart in Fig. 1).

The patient's general clinical condition: The risks associated with bypass surgery (the type of bypass and the type of anaesthesia) should be evaluated in relation to the patient's clinical condition (age, co-morbidities and life expectancy).

Foot lesions: Percutaneous revascularisation can be proposed for substantially any type of foot lesion, but bypass surgery requires a careful evaluation of the site of distal anastomosis, which may be more or less affected by tissue alterations. Both methods should also be evaluated on the basis of the type of orthopaedic surgical correction programmed for the type of lesion: forefoot amputations can interrupt vascular connections between the dorsal and plantar systems making their respective vascularisations functionally 'terminal'.

The type of 'bypass' (prosthesis/vein): It is necessary to consider the type of bypass (proximal/distal), the availability of a vein and its quality.

Vessel destined for distal anastomosis: The characteristics of the vessel used to receive the distal anastomosis of the bypass should be evaluated: its diameter, the presence of disease/calcifications, the site of the ischaemic lesion and the presence of small distal vessel disease causing a poor distal run-off [133,134]. While bypass surgery can be applied only when a suitable distal target vessel is recognised at some level in the vascular tree of the leg, angioplasty can be extended to the foot vessels, opening and improving the foot distribution system in the case of very distal disease [135–137]. The pedal–plantar loop technique can often restore a direct arterial inflow from both tibial arteries achieving a complete below-the-knee and below-the-ankle revascularisation and providing a high rate of acute success, intended as the ability to cross the lesions and inflate the balloon, achieving adequate angiographic results, without periprocedural complications [138–141].

- PTA in diabetic patients with PAD is feasible and technically efficient, reduces the number of complications and increases limb salvage rates because it can be applied in patients unsuitable for bypass surgery.

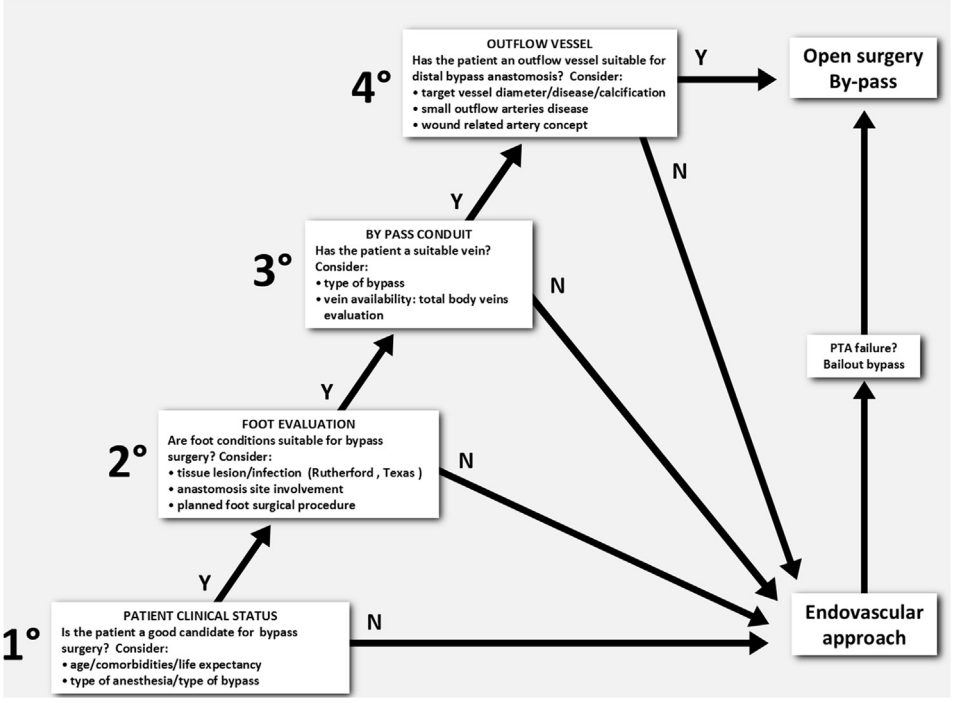

Figure 1 Revascularisation strategy in diabetic patients with critical limb ischaemia due to extensive disease of the femoro-popliteal axis and/or infrapopliteal vessels.

- PTA can also be proposed for patients with co-morbidities, a reduced life expectancy and significant tissue involvement.
- PTA should be carried out in such a way that it does not preclude subsequent bypass surgery.
- Classical surgery is indicated in the case of the involvement of the common femoral artery and its bifurcation, or extremely long occlusions (as judged by the surgeon) of the femoro-popliteal and infra-popliteal arteries.

Objectives of revascularisation

Correctly identifying the vascular anatomy of the patient in relation to his/her tissue lesions is fundamental for guiding decisions concerning the strategy of revascularisation.

- Complete revascularisation.

Peregrin analysed the clinical success rates of PTA in diabetic patients with CLI by considering the number of successfully treated infra-popliteal vessels [142]. The results showed that complete revascularisation is better than partial revascularisation: the 1-year limb salvage rate was 56% without any direct flow to the foot (no open infra-popliteal vessels) and, respectively, 73%, 80% and 83% with one, two and three open vessels. Faglia demonstrated that angioplasty of the tibial arteries led to better results in terms of limb salvage than the revascularisation of the peroneal artery alone [143].

- Wound-related artery

When it is not possible to obtain complete revascularisation for technical reasons or because of the need to reduce the duration of the procedure and the dose of contrast medium, efforts should concentrate on the wound-related artery, that is, the revascularisation should aim at reopening the artery irrigating the angiosome of the foot affected by the ischaemic lesion(s) [144,145]. Revascularisation of the wound-related artery is associated with higher limb salvage rates than revascularisation of the arteries running to other angiosomes [146,147]. Even in the case of surgical revascularisation by means of a bypass, Neville has shown that a direct bypass on the wound-related artery leads to higher limb salvage rates [134].

If tibial artery treatment is technically impossible, angioplasty of the distal perforating branches of the peroneal artery is a successful practicable option.

Neither complete nor wound-related artery revascularisation should be pursued uncritically, but both should be personalised on the basis of a realistic technical strategy, the type of tissue lesions and their orthopaedic surgical treatment and the patient's general clinical condition. [148]

- The main aim of revascularisation is to reopen all occluded arteries.
- In the case of technical impossibility, it is better to target the recanalisation of the wound-related artery in accordance with the concept of angiosomes.
- Revascularisation should be personalised on the basis of the overall clinical picture of the foot.

Follow-up of revascularised patients

There are currently no unequivocal criteria that define with certainty the most appropriate follow-up methods for patients who have undergone revascularisation because of ischaemic DF. This is probably due to the heterogeneity of patients with CLI: these may be relatively young with a good life expectancy and be suitable for the application of severe follow-up criteria that consider vascular, tissue and general aspects. However, there are also patients characterised by a 'terminal' picture of widespread atherosclerotic disease, who therefore have a very limited life expectancy in whom the follow-up should be less invasive.

Generally, the follow-up should be clinical, oximetric and/or ultrasonographic, and the examinations should take place 1, 3, 6 and 12 months after treatment, and every 12 months thereafter. However, just as the treatment of DF needing a multidisciplinary approach, we believe that the follow-up of revascularised patients should also be global, multidisciplinary and personalised, and take into account the following key elements.

Vascular follow-up criteria

The criteria indicating the purely haemodynamic success of revascularisation are primary and secondary patency, that is, the capacity of the revascularisation procedure to guarantee the continued patency of the treated vessel or bypass [41].

In the case of a bypass, the follow-up should include Doppler ultrasonography in order to detect any restenosis (generally of the anastomosis) or the upstream or downstream progression of bypass disease; the treatment of such obstructions is fundamental as it prolongs the life of the bypass itself [149]. Although randomised trials have not shown any real benefit of a close follow-up in vein bypasses [150–152], there is a clear benefit in the prosthetic or composite bypasses [153,154]. The recent guidelines of the European Society of Vascular Surgery recommend at least using the ankle brachial index to select patients who should be sent for a Doppler ultrasonography examination [155].

In the case of percutaneous revascularisation, the follow-up criteria are uncertain. Given that extreme revascularisation of the infra-popliteal arteries is burdened by early restenoses (70% after 3 months) [131], an exclusively vascular follow-up aimed at identifying and treating such restenoses could lead to an incessant re-treatment without reflecting the clinical reality. The occurrence of restenosis is not always an indication for re-treatment *per se*, but re-treatment should be considered in patients with

recurrent clinical symptoms or patients in whom the process of wound healing has been interrupted.

However, it is important to recognise that in some patients percutaneous revascularisation enables the reopening of extended segments of multi-level vessels, often with extreme difficulty. It allows the reconstruction of a fragile flow line up to the foot, to which the maintenance in time through a close vascular follow-up protocol, the same way as for distal bypasses, can be deemed necessary. A focal restenosis can be simply, rapidly and often lastingly treated, whereas its subsequent evolution into occlusion (and the consequent extension of the upstream and downstream thrombosis of the original lesion) needs more complex treatment, especially in the case of intra-stent occlusions, and is burdened by a high rate of recurrence.

A follow-up based on vascular criteria should therefore be personalised for each individual patient and based on the type of revascularisation.

Perfusional follow-up criteria

By 'perfusional criteria', we mean $TcPO_2$ measurements that indicate the real degree of tissue perfusion regardless of whether it occurs through patent native vessels, revascularised vessels or collateral circulation. Given the relationship between healing potential and oximetry values, periodic oximetric evaluations are surely helpful, especially in patients whose skin lesions show little sign of healing notwithstanding revascularisation. Oximetry values of <30 mm Hg are indicative of low tissue perfusion, but it might be useful to repeat the measurement after a few days before considering the revascularisation a failure because it has been observed that $TcPO_2$ values gradually increase 1 month after successful revascularisation, whereas they remain low in the case of ineffective revascularisation [156].

Clinical follow-up criteria

These criteria include limb salvage (the avoidance of major amputation of the leg or thigh), wound healing (the complete closure of skin lesions) and healing after 'minor amputation' of the toes, rays or tarsal region. Clinical criteria such as the healing time of foot lesions, the restoration of walking capacity and the time needed for this restoration (time to walking) are currently underestimated in the literature and should be reconsidered as primary criteria.

General follow-up criteria

One of the aspects that can never be emphasised enough is the close relationship between diabetes and cardiovascular diseases. If this is true for the diabetic population in general, it is even truer for those with ongoing vascular complications. About 50% of diabetic patients with PAD have an associated coronary disease, 30% have carotid artery disease and about 15–20% have both simultaneously. Recent data show that patients with PAD treated successfully by percutaneous lower extremity revascularisation have better cardiovascular outcomes than those treated by conservative medical therapy alone [157]. The known cardiovascular risk factors, such as hypercholesterolaemia, hypertension and smoking, are made more aggressive by the presence of diabetes, particularly if there is no metabolic compensation. Given the pathogenic role played by risk factors in the manifestation and rapid evolution of cardiovascular disease, it can be presumed that they can also significantly influence the results of revascularisation over time and the reparative response of tissue lesions.

1. Revascularisation should always be followed by a strict follow-up.
2. Periodic oximetric evaluations should be performed.
3. Clinical symptoms and ulcer evolution must be frequently monitored.
4. Cardiovascular risk factors must be corrected.

References

[1] Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes. Diabet Med 2010;27:4–14.

[2] Mingardi R, Morabito A, Piaggesi A, et al. SCAR (SCreening for ARteriopathy) Study Group. Screening for peripheral arterial disease by means of the ankle-brachial index in newly diagnosed type 2 diabetic patients. Diabet Med 2005;22:1310–4.

[3] Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. EURODIALE Study Diabetologia 2008;51:747–55.

[4] Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012 Jun;54(12):e132–73.

[5] Scatena A, Petruzzi P, Ferrari M, Rizzo L, Cicorelli A, Berchiolli R, et al. Outcomes of three years of teamwork on critical limb ischemia in patients with diabetes and foot lesions. Int J Low Extrem Wounds 2012 Jun;11(2):113–9.

[6] Monami M, Adalsteinsson JE, Desideri CM, Ragghianti B, Dicembrini I, Mannucci E. Fasting and post-prandial glucose and diabetic complication. A meta-analysis. NMCD 2013;23:591–8.

[7] Brevetti G, Schiano V, Chiariello M. Endothelial dysfunction: a key to the pathophysiology and natural history of peripheral arterial disease? Atherosclerosis 2008;197:1–11.

[8] Lepäntalo M, Fiengo L, Biancari F. Peripheral arterial disease in diabetic patients with renal insufficiency: a review. Diabetes Metab Res Rev 2012;28(Suppl. 1):40–5.

[9] Lombardo FL, Maggini M, De Bellis A, Seghieri G, Anichini R. Lower extremity amputations in persons with and without diabetes. Italy 2001-2010. PLOS ONE PONE-D- 13-17607R410.1371, 2014, EMID:c24139134c38c87a.

[10] Faglia E, Mantero M, Caminiti M, Caravaggi C, De Giglio R, Pritelli C, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med 2002;252:225–32.

[11] Faglia E, Dalla Paola L, Clerici G, Clerissi J, Graziani L, Fusaro M, et al. Peripheral angioplasty as the first-choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005 Jun;29(6):620–7.

[12] Ferraresi R, Centola M, Ferlini M, Da Ros R, Caravaggi C, Assaloni R, et al. Long-term outcomes after angioplasty of isolated, below-the-knee arteries in diabetic patients with critical

limb ischaemia. Eur J Vasc Endovasc Surg 2009 Mar;37(3):336–42.
[13] Uccioli L, Gandini R, Giurato L, Fabiano S, Pampana E, Spallone V, et al. Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. Diabetes Care 2010 May;33(5):977–82.
[14] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med 2008 Jun;25(6):700–7.
[15] Caravaggi C, De Giglio R, Pritelli C, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med 2002;252:225–32.
[16] Gabrielli L, Losa S, Mantero M, et al. Long- term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. Diabetes Care 2009 May;32(5):822–7.
[17] Gargiulo M, Maioli F, Ceccacci T, et al. What's next after optimal infrapopliteal angioplasty? Clinical and ultrasonographic results of a prospective single-center study. J Endovasc Ther 2008 Jun;15(3):363–9.
[18] Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes – a review. Diabet Med 2010 Jan;27(1):4–14.
[19] Dybdahl H, Ledet T. Diabetic macroangiopathy. Quantitative histopathological studies of the extramural coronary arteries from type 2 diabetic patients. Diabetologia 1987;30:882–6.
[20] Rasmussen LM, Heickendorff L. Accumulation of fibronectin in aortas from diabetic patients. A quantitative immunohistochemical and biochemical study. Lab Invest 1989;61:440–6.
[21] Andresen JL, Rasmussen LM, Ledet T. Diabetic macroangiopathy and atherosclerosis. Diabetes 1996;45(Suppl. 3):S91–4.
[22] Lehto S, Niskanen L, Suhonen M, Ronnemaa t, Laakso M. Medial artery calcification: a neglected Harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. Arterioscler Thromb Vasc Biol 1996;16:978–83.
[23] Shanahan CM, Cary NR, Salisbury JR, Proudfoot D, weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Mönckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. Circulation 1999;100:2168–76.
[24] Olesen P, Ledet T, Rasmussen LM. Arterial osteoprotegerin: increased amounts in diabetes and modifiable synthesis from vascular smooth muscle cells by insulin and TNFalfa. Diabetologia 2005;48:561–8.
[25] Brevetti G, Laurenzano E, Giugliano G, Lanero S, Brevetti L, Luciano R, et al. Metabolic syndrome and cardiovascular risk prediction in peripheral arterial disease. Nutr Metab Card Dis 2010;20:676–82.
[26] Eryol NK, Unal S, Arinc H, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. Circulation 1999;99:2239–42.
[27] Ludwig LM, Chilian WM, Pagel PS, et al. Chronic hyperglycemia attenuates coronary collateral development and impairs proliferative properties of myocardial interstitial fluid by production of angiostatin. Circulation 2004;109:2343–8.
[28] Waltenberger J. Impaired collateral vessel development in diabetes: potential cellular mechanisms and therapeutic implications. Cardiovasc Res 2001;49:554–60.
[29] Chung Ada WY, Hsiang York N, Matzke Lise A, McManus Bruce M, Breemen Cornelis van, Okon Elena B. Reduced expression of vascular endothelial growth factor paralleled with the increased angiostatin expression resulting from the upregulated activities of matrix Metalloproteinase-2 and -9 in human type 2 diabetic arterial vasculature. Circ Res 2006;99:140–8.
[30] Boodhwani M, Sodha NR, Mieno S, Xu SH, Feng J, Ramlawi B. Functional, cellular, and molecular characterization of the angiogenic response to chronic myocardial ischemia in diabetes. Circulation 2007;116(11 Suppl.):I31–7.
[31] van Golde JM, Ruiter MS, Schaper NC, Xu SH, Feng J, Ramlawi B. Impaired collateral recruitment and outward remodeling in experimental diabetes. Diabetes 2008;57:2818–23.
[32] Ruiter MS, van Golde JM, Schaper NC, Stehouwer CD, Huijberts MS. Diabetes impairs arteriogenesis in the peripheral circulation: review of molecular mechanisms. Clin Sci 2010;119:225–38.
[33] Beckman JA, Creager MA, Libby P. Diabetes and Atherosclerosis. Epidemiology, Pathophysiology, and management. JAMA 2002;15:2570–81.
[34] Niccoli Giubilato S, Di Vito L, Leo A, Cosentino N, Pitocco D, Marco V, et al. Severity of coronary atherosclerosis in patients with a first acute coronary event: a diabetes paradox. Eur Heart J 2013;34:729–41.
[35] American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care 2003;26:3333–41.
[36] Jude EB, Oyibo SO, Chalmers N, Boulton AJM. Peripheral arterial disease in diabetic and nondiabetic patients. A comparison of severity and outcome. Diabetes Care 2001;24:1433–7.
[37] Ciavarella A, Silletti A, Mustacchio A, Gargiulo M, Galaverni MC, Stella A, et al. Angiographic evaluation of the anatomic pattern of arterial obstructions in diabetic patients with critical limb ischemia. Diabet Med 1993;19:586–9.
[38] Graziani L, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, et al. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. Eur J Vasc Endovasc Surg 2007;33:453–60.
[39] Faglia E, Favales F, Quarantiello A, Calia P, Paratore C, Brambilla G, et al. Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. Diabetes Care 1998;21:625–30.
[40] Armstrong DG, Peters EJ. Classification of wounds of the diabetic foot. Curr Diab Rep 2001 Dec;1(3):233–8.
[41] Norgren L, Hiatt WR, Nehler MR, Harris KA. Fowkes FGR.on behalf of the TASC II Working Group. J Vasc Surg 2007;45(1):S5A–67A.
[42] Ouriel K. Peripheral arterial disease. Review. Lancet 2001;358:1257–64.
[43] Leibson CL, Ransom JE, Olson W. Peripheral arterial disease, diabetes, and mortality. Diabetes Care 2004;27(12):2843–9.
[44] Norman PE, Davis WA, Bruce DG, Davis TM. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2006;29(3):575–80.
[45] Nesto RW, Watson FS, Kowalchuk GJ, Zarich SW, Hill T, Lewis SM, et al. Silent myocardial ischemia and infarction in diabetics with peripheral vascular disease: assessment by dipyridamole thallium-201 scintigraphy. Am Heart J 1990;120(5):1073–7.
[46] Zellweger MJ. Prognostic significance of silent coronary artery disease in type 2 diabetes. Herz 2006;31:240–5.
[47] Ndip A, Lavery LA, Boulton AJ. Diabetic foot disease in people with advanced nephropathy and those on renal dialysis. Curr Diab Rep 2010;10:283–90.
[48] Graziani L, Silvestro A, Bertone V, Manara E, Alicandri A, Parrinello G, et al. Percutaneous transluminal angioplasty is feasible and effective in patients on chronic dialysis with severe peripheral artery disease. Nephrol Dial Transplant 2007 Apr;22(4):1144–9.
[49] Apelqvist J, Bakker K, van Houtum WH, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) prepared by the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev 2007;24(S1):S181–7.
[50] Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation 1985;71:516–22.
[51] Apelqvist Jan, Elgzyri Targ, Larsson Jan, Löndahl Magnus, Nyberg Per, Thörne Johan. Factors related to outcome of neuroischemic/ischemic foot ulcer in diabetic patients. J Vasc Surg 2011;53:1582–8.
[52] Faglia E. Characteristics of peripheral arterial disease and its relevance to the diabetic population. Int J Low Extrem Wounds 2011;10(3):152–66.
[53] Tasci I. Best practice in ankle brachial index measurement. J Wound Ostomy Cont Nurs 2012 May-Jun;39(3):238.
[54] Orchard J, Strandness Jr DE. Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Heart Association and the American Diabetes Association. Diabetes Care 1993;16:1199–209.
[55] Wang Y, Mou Q, Zhao D, Xu Y, Hu D, Ma H, et al. Predictive value of ankle-brachial index and blood glucose on the outcomes of

six-year all-cause mortality and cardiovascular mortality in a Chinese population of type 2 diabetes patients. Int Angiol 2012; 31:586–94.
[56] Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. Diabetologia 1993;36:615–21.
[57] Jeffcoate WJ, Rasmussen LM, Hofbauer LC, Game FL. Medial arterial calcification in diabetes and its relationship to neuropathy. Diabetologia 2009;52:2478–88.
[58] Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Arterial calcification and its association with mortality and complications of diabetes. Diabetologia 1988;31:16–23.
[59] Ix JH, Miller RG, Criqui MH, Orchard TJ. Test characteristics of the ankle-brachial index and ankle-brachial difference for medial arterial calcification on X-ray in type 1 diabetes. J Vasc Surg 2012; 56:721–7.
[60] Aubert CE, Cluzel P, Kemel S, Michel PL, Lajat-Kiss F, Dadon M, et al. Influence of peripheral vascular calcification on efficiency of screening tests for peripheral arterial occlusive disease in diabetes-a cross-sectional study. Diabet Med 2013. http://dx.doi.org/10.1111/dme. 12309. published on line 11 sep. 2013.
[61] Park SC, Choi CY, Ha YI, Yang HE. Utility of toe-brachial Index for diagnosis of peripheral artery disease. Arch Plast Surg 2012 May; 39(3):227–31.
[62] Høyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. J Vasc Surg 2013;58: 231–8.
[63] Ballad JL, Eke CC, Bunt TJ, Killeen JD. A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. J Vasc Surg 1995;22:485–90.
[64] Faglia E, Clerici G, Caminiti M, Quarantiello A, Curci V, Somalvico F. Evaluation of feasibility of ankle pressure and foot oximetry values for the detection of critical limb ischemia in diabetic patients. Vasc Endovasc Surg 2010;44:184–9.
[65] 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;334:1257–66.
[66] ACC/AHA guidelines for the management of patients with peripheral arterial disease (Lower extremity, renal, mesenteric, and abdominal aortic). J Vasc Interv Radiol 2006;17:1383–98.
[67] Bradbury AW, Adam DJ. Diagnosis of peripheral arterial disease of the lower limb. BMJ 2007;334:1229–30.
[68] Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US: a meta-analysis. Radiology 2000;216:67–77.
[69] Hingorani A, Ascher E, Marks N. Preprocedural imaging: new options to reduce need for contrast angiography. Semin Vasc Surg 2007;20:15–28.
[70] Lapeyre M, Kobeiter H, Desgranges P, Rahmouni A, Becquemin JP, Luciani A. Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. Am J Roentgenol 2005 Dec;185(6):1641–50.
[71] 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;301:415–24.
[72] Thomsen Henrik S. Contrast media safety: an update. Eur J Radiol 2011;80:77–82.
[73] Ruffolo AJ, Romano M, Ciapponi A. Prostanoids for critical limb ischaemia. Cochrane Database Syst Rev 2010.
[74] Piaggesi A, Vallini V, Iacopi E, Tedeschi A, Scatena A, Goretti C, et al. Iloprost in the management of peripheral arterial disease in patients with diabetes mellitus. Minerva Cardioangiol 2011 Feb; 59(1):101–8.
[75] Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012 Feb;141(2 Suppl.): e669S–90S.
[76] Ferreiro JL, Angiolillo DJ. Challenges and Perspectives of antiplatelet therapy in patients with diabetes mellitus and coronary artery diseases. Curr Pharm Design 2012;18(33):5273–93.
[77] Balasubramaniam K, Viswanathan GN, Marshall SM, Zaman AG. Increased atherothrombotic burden in patients with diabetes mellitus and acute coronary syndrome: a review of antiplatelet therapy. Cardiol Res Pract 2012;2012:909154.
[78] Di Minno G. Aspirin resistance and platelet turnover: a 25-year old issue. Nutr Met Card Dis 2011;21:542–5.
[79] Dicka F, Riccob JB, Daviesc AH, Cao P, Setacci C, de Donato G, et al. Chapter VI: follow-up after revascularisation. Eur J Vasc Surg 2011 Dec:S75–90. Suppl. 2.
[80] McNeely MJ, Boyko EJ, Ahroni JH, Stensel VL, Reiber GE, Smith DG, et al. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration. How great are the risks? Diabetes Care 1995 Feb;18(2):216–9.
[81] Norgren L, Hiatt WR, Harris KA, Lammer J. TASC II Working Group TASC II section F on revascularization in PAD. J Endovasc Ther 2007 Oct;14(5):743–4.
[82] Faglia E, Clerici G, Caminiti M, Quarantiello A, Curci V, Morabito A. Predictive values recorded of transcutaneous oxygen tension for above-the-ankle amputation in diabetic patients with critical limb ischemia. Eur J Vasc Endovasc Surg 2007;33:731–6.
[83] ESC guidelines on diabetes, prediabetes and cardiovascular diseases. Eur Heart J 2013. http://dx.doi.org/10.1093/eurheartj/eht108.
[84] Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine 2012 Jun;41(3):384–97.
[85] Setacci C. Time is tissue. J Endovasc Ther 2012;19(4):515–6.
[86] Faglia E, Clerici G, Caminiti M, Quarantiello A, Gino M, Morabito A. The role of early surgical debridement and revascularization in patients with diabetes and deep foot space abscess: retrospective review of 106 patients with diabetes. J Foot Ankle Surg 2006 Jul–Aug;45(4):220–6.
[87] van Baal JG. Surgical treatment of the infected diabetic foot. Clin Infect Dis 2004 Aug 1;39(Suppl. 2):S123–8.
[88] Söderström MI, Arvela EM, Korhonen M, Halmesmäki KH, Albäck AN, Biancari F, et al. Infrapopliteal percutaneous transluminal angioplasty versus bypass surgery as first-line strategies in critical leg ischemia: a propensity score analysis. Ann Surg 2010 Nov;252(5):765–73.
[89] Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepantalo M, et al. International Working Group on Diabetic foot. Specific guidelines for the diagnosis and treatment of peripheral arterial disease in a patient with diabetes and ulceration of the foot. Diabetes Metab Res Rev 2012 Feb; 28(Suppl. 1):236–7.
[90] Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic). J Am Coll Cardiol 2006 Mar 21;47(6):1239–312.
[91] Schleiffer T, Hölken H, Brass H. Morbidity in 565 type 2 diabetic patients according to stage of nephropathy. J Diabetes Complications 1998;12(2):103–9.
[92] Lavery LA, Lavery DC, Hunt NA, La Fontaine J, Ndip A, Boulton AJ. Diabetic foot disease in people with advanced nephropathy and those on renal dialysis. Curr Diab Rep 2010 Aug;10(4):283–90.
[93] Ndip A, Rutter MK, Vileikyte L, Vardhan A, Asari A, Jameel M, et al. Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. Diabetes Care 2010 Aug;33(8):1811–6.
[94] Jaar BG, Astor BC, Berns JS, Powe NR. Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. Kidney Int 2004;65(2):613–20.
[95] Gershater MA, Löndahl M, Nyberg P, Larsson J, Thorne J, Eneroth M, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009;52(3):398–407.
[96] Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Fiedrichs S, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev 2012 Feb;28(Suppl. 1):179–217.
[97] Johnson BL, Glickman MH, Bandyk DF, Esses GE. Failure of foot salvage in patients with end-stage renal disease after surgical revascularization. J Vasc Surg 1995;22:280–5.
[98] Venermo M, Biancari F, Arvela E, Korhonen M, Söderström M, Halmesmäki K, et al. The role of chronic kidney disease as a

predictor of outcome after revascularisation of the ulcerated diabetic foot. Diabetologia 2011 Dec;54(12):2971–7.
[99] Leers SA, Reifsnyder T, Delmonte R, Caron M. Realistic expectations for pedal bypass grafts in patients with end-stage renal disease. J Vasc Surg 1998;28:976–80.
[100] Hoshino J, Fujimoto Y, Naruse Y, Hasegawa E, Suwabe T, Sawa N, et al. Characteristics of revascularization treatment for arteriosclerosis obliterans in patients with and without hemodialysis. Circ J 2010 Nov;74(11):2426–33.
[101] Rabellino M, Aragón-Sánchez J, González G, Zander T, Baldi S, Garcia-Nielsen L, et al. Is endovascular revascularisation worthwhile in diabetic patients with critical limb ischemia who also have end-stage renal disease? Diabetes Res Clin Pract 2010 Dec; 90(3):e79–81.
[102] Giurato L, Gandini R, Meloni M, Pampana E, Ruotolo V, Izzo V, et al. Percutaneous angioplasty in diabetic patients with critical limb ischemia and chronic kidney disease. Open J Endocr Metab Dis 2013;3:2008–12.
[103] Weis-Müller BT, Römmler V, Lippelt I, Porath M, Godehardt E, Balzer K, et al. Critical chronic peripheral arterial disease: does outcome justify crural or pedal bypass surgery in patients with advanced age or with comorbidities? Ann Vasc Surg 2011 Aug; 25(6):783–95.
[104] Jämsén T, Manninen H, Tulla H, Matsi P. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol 2002;13(5):455–63.
[105] Jacqueminet S, Hartemann-Heurtier A, Izzillo R, Cluzel P, Golmard JL, Ha Van G, et al. Percutaneous transluminal angioplasty in severe diabetic foot ischemia: outcomes and prognostic factors. Diabetes Metab 2005;31:370–5.
[106] Sigala F, Menenakos P, Sigalas P, Baunach CH, Langer ST, Papalambros E, et al. Transluminal angioplasty of isolated crural arterial lesions in diabetics with critical limb ischemia. VASA 2005;34:186–91.
[107] Bargellini I, Petruzzi P, Scatena A, Cioni R, Cicorelli A, Vignali C, et al. Primary infrainguinal subintimal angioplasty in diabetic patients. Cardiovasc Intervent Radiol 2008;31(4):713–22.
[108] Dosluoglu HH, Cherr GS, Lall P, Harris LM, Dryjski ML. Peroneal artery-only runoff following endovascular revascularizations is effective for limb salvage in patients with tissue loss. J Vasc Surg 2008;48(1):137–43.
[109] Graziani L, Piaggesi A. Indications and clinical outcomes for below knee endovascular therapy: review article. Catheter Cardiovasc Interv 2010;75(3):433–43.
[110] Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Long term prognosis of diabetic patients with critical limb ischemia: a population based cohort study. Diabetes Care 2009; 32(5):822–7.
[111] Werneck CC, Lindsay TF. Tibial angioplasty for limb salvage in high-risk patients and cost analysis. Ann Vasc Surg 2009;23(5):554–9.
[112] Alexandrescu V, Hubermont G, Philips Y, Guillaumie B, Ngongang Ch, Coessens V, et al. Combined primary subintimal and endoluminal angioplasty for ischaemic inferior-limb ulcers in diabetic patients: 5-year practice in a multidisciplinary 'diabetic-foot' service. Eur J Vasc Endovasc Surg 2009;37(4):448–56.
[113] Hering J, Angelkort B, Keck N, Wilde J,Amann B. Long-term outcome of successful percutaneous transluminal angioplasty of the fibular artery in diabetic foot syndrome and single-vessel calf perfusion depends on doppler wave pattern at the forefoot. Vasa 2010;39(1):67–75.
[114] Pomposelli FB, Kansal N, Hamdan AD, Belfield A, Sheahan M, Campbell DR, et al. A decade of experience with dorsalis pedis artery by-pass: analysis of outcome in more than 1000 cases. J Vasc Surg 2003;37:307–15.
[115] Pomposelli Jr FB, Marcaccio EJ, Gibbons GW, Campbell DR, Freeman DV, Burgess AM, et al. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. J Vasc Surg 1995;21(3):375–84.
[116] Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty. Factors influencing long-term success. Circulation 1991;83(2 Suppl.):170–80.
[117] Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg 2008;47(5):975–81.
[118] Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg 2006;32:484–90.
[119] Faglia E, Clerici G, Clerissi J, Caminiti M, Quarantiello A, Curci V, et al. Angioplasty for diabetic patients with failing bypass graft or residual critical ischemia after bypass graft. Eur J Vasc Endovasc Surg 2008;36(3):331–8.
[120] Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg 2007;45(4):751–61.
[121] Gandini R, Chiappa R, Di Primio M, Di Vito L, Boi L, Tsevegmid E, et al. Recanalization of the native artery in patients with bypass failure. Cardiovasc Intervent Radiol 2009;32(6):1146–53.
[122] White CJ, Gray WA. Endovascular therapies for peripheral arterial disease: an evidence-based review. Circulation 2007;116:2203–15.
[123] Schwarzwalder U, Zeller T. Below-the-knee revascularization. Advanced techniques. J Cardiovasc Surg (Torino) 2009;50(5): 627–34.
[124] Gandini R, Volpi T, Pampana E, Uccioli L, Versaci F, Simonetti G. Applicability and clinical results of percutaneous transluminal angioplasty with a novel, long, conically shaped balloon dedicated for below-the knee interventions. J Cardiovasc Surg (Torino) 2009;50(3):365–71.
[125] Ferraresi R, Centola M, Biondi-Zoccai G. Advances in below-the-knee drug-eluting balloons. J Cardiovasc Surg (Torino) 2012; 53(2):205–13.
[126] Gandini R, Del Giudice C, Merolla S, Morosetti D, Pampana E, Simonetti G. Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with ritical limb ischemia: a single-center, prospective, randomized study. J Endovasc Ther 2013;20(6): 805–14.
[127] Airoldi F, Vitiello R, Losa S, Tavano D, Faglia E. Retrograde recanalization of the anterior tibial artery following surgical vessel exposure: a combined approach for single remaining infragenicular vessels. J Vasc Interv Radiol 2010 Jun;21(6): 949–50.
[128] Spinelli F, Stilo F, Benedetto F, De Caridi G, La Spada M. Early and one-year results of infrainguinal bypass after failure of endovascular therapy. Int Angiol 2011;30:156–63.
[129] Nolan BW, De Martino RR, Stone DH, Schanzer A, Goodney PP, Walsh DW, et al. Vascular Study Group of New England. Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass. J Vasc Surg 2011;54(3):730–5.
[130] Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, et al. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. Eur J Vasc Endovasc Surg 2006;31:59–63.
[131] Schmidt A, Ulrich M, Winkler B, Klaeffling C, Bausback Y, Bräunlich S, et al. Angiographic patency and clinical outcome after balloon-angioplasty for extensive infrapopliteal arterial disease. Catheter Cardiovasc Interv 2010;76(7):1047–54.
[132] Gargiulo M, Giovanetti F, Bianchini Massoni C, Freyrie A, Faggioli G, Muccini N, et al. Bypass to the ankle and foot in the era of endovascular therapy of tibial disease. Results and factors influencing the outcome. J Cardiovasc Surg (Torino) 2012 Apr 20 [Epub ahead of print].
[133] Graziani L, Silvestro A, Bertone V, Manara E, Andreini R, Sigala A, et al. Vascular involvement in diabetic subjects with ischemic foot ulcer: a new morphologic categorization of disease severity. Eur J Vasc Endovasc Surg 2007;33:453–60.
[134] Neville RF, Attinger CE, Bulan EJ, Ducic I, Thomassen M, Sidawy AN. Revascularization of a specific angiosome for limb salvage: does the target artery matter? Ann Vasc Surg 2009;23: 367–73.
[135] Fusaro M, Dalla Paola L, Brigato C, Marangotto M, Nicolini S, Rripay R, et al. Plantar to dorsalis pedis artery subintimal angioplasty in a patient with critical foot ischemia: a novel technique in the armamentarium of the peripheral interventionist. J Cardiovasc Med (Hagerstown) 2007;8:977–80.
[136] Zhu YQ, Zhao JG, Liu F, Wang JB, Cheng YS, Li MH, et al. Subintimal angioplasty for below-the-ankle arterial occlusions in

diabetic patients with chronic critical limb ischemia. J Endovasc Ther 2009;16:604–12.
[137] Alexandrescu VA. Commentary: below-the-ankle subintimal angioplasty: how far can we push this application for lower limb preservation in diabetic patients? J Endovasc Ther 2009;16:617–8.
[138] Graziani L, Silvestro A. Alternative approaches in critical limb ischemia. London. UK: Gosling ed.; 2006. pp. 2–7. Clinical Vision;17.
[139] Fusaro M, Dalla Paola L, Biondi-Zoccai G. Pedal-Plantar LOOP Technique for a challenging below-the-knee chronic total occlusion: a novel approach to percutaneous revascularization in critical lower limb ischemia. J Invasive Cardiol 2007;19:E34–7.
[140] Manzi M, Fusaro M, Ceccacci T, Erente G, Dalla paola L, Brocco E. Clinical results of below-the-knee intervention using pedal-plantar loop technique for the revascularization of foot arteries. J Cardiovasc Surg 2009;50:331–7.
[141] Gandini R, Uccioli L, Spinelli A, Del Giudice C, Da Ros C, Volpi T, et al. Alternative techniques for treatment of complex below-the knee arterial occlusions in diabetic patients with critical limb ischemia. Cardiovasc Intervent Radiol 2013;29:377–83.
[142] Peregrin JH, Koznar B, Kovác J, Lastovicková J, Novotný J, Vedlich D, et al. PTA of infrapopliteal arteries: long-term clinical follow-up and analysis of factors influencing clinical outcome. Cardiovasc Intervent Radiol 2010;33:720–5.
[143] Faglia E, Clerici G, Clerissi J, Mantero M, Caminiti M, Quarantiello A, et al. When is a technically successful peripheral angioplasty effective in preventing above-the-ankle amputation in diabetic patients with critical limb ischaemia? Diabet Med 2007;24:823–9.
[144] Taylor GI, Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. Br J Plast Surg 1987;40(2):113–4.
[145] Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast Reconstr Surg 2006;117:261S–93S.
[146] Iida O, Nanto S, Uematsu M, Ikeoka K, Okamoto S, Dohi T, et al. Importance of the angiosome concept for endovascular therapy in patients with critical limb ischemia. Catheter Cardiovasc Interv 2010;75:830–6.
[147] Alexandrescu V, Vincent G, Azdad K, Hubermont G, Ledent G, Ngongang C, et al. A reliable approach to diabetic neuroischemic foot wounds: below-the-knee angiosome-oriented angioplasty. J Endovasc Ther 2011;18:376–87.
[148] Graziani L, Silvestro A, Monge L, Boffano GM, Kokaly F, Casadidio I, et al. Transluminal angioplasty of peroneal artery branches in Diabetics: initial technical experience. Cardiovasc Intervent Radiol 2008;31:49–55.
[149] Nguyen LL, Conte MS, Menard MT, Gravereaux EC, Chew DK, Donaldson MC, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. J Vasc Surg 2004;40:916–23.
[150] Ihlberg L, Luther M, Tierala E, Lepantalo M. The utility of duplex scanning in infrainguinal vein graft surveillance: results from a randomised controlled study. Eur J Vasc Endovasc Surg 1998;16:19–27.
[151] Ihlberg L, Luther M, Alback A, Kantonen I, Lepantalo M. Does a completely accomplished duplex-based surveillance prevent vein-graft failure? Eur J Vasc Endovasc Surg 1999;18:395–400.
[152] Davies AH, Hawdon AJ, Sydes MR, Thompson SG, VGST Participants. Is duplex surveillance of value after leg vein bypass grafting? Principal results of the vein graft surveillance randomised trial (VGST). Circulation 2005;112:1985–91.
[153] Brumberg RS, Back MR, Armstrong PA, Cuthbertson D, Shames ML, Johnson BL, et al. The relative importance of graft surveillance and warfarin therapy in infrainguinal prosthetic bypass failure. J Vasc Surg 2007;46:1160–6.
[154] Humphries MD, Pevec WC, Laird JR, Yeo KK, Hedayati N, Dawson DL. Early duplex scanning after infrainguinal endovascular therapy. J Vasc Surg 2011;53:353–8.
[155] Dick F, Ricco JB, Davies AH, Cao P, Setacci C, de Donato G, et al. Follow-up after revascularisation. Eur J Vasc Endovasc Surg 2011;42(Suppl. 2):S75–90.
[156] Caselli A, Latini V, Lapenna A, Di Carlo S, Pirozzi F, Benvenuto A, et al. Transcutaneous oxygen tension monitoring after successful revascularization in diabetic patients with ischaemic foot ulcers. Diabet Med 2005 Apr;22(4):460–5.
[157] Giugliano G, Di Serafino L, Perrino C, Schiano V, Laurenzano E, Cassese S, et al. Effects of successful percutaneous lower extremity revascularization on cardiovascular outcome in patients with peripheral arterial disease. Intern J Cardiol 2013;167:2566–71.