IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

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IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

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Recommendations

Diagnosis

1. Examine a patient with diabetes annually for the presence of peripheral artery disease (PAD); this should include, at a minimum, taking a history and palpating foot pulses. (GRADE recommendation: strong; Quality of evidence: low)

2. Evaluate a patient with diabetes and a foot ulcer for the presence of PAD. Determine, as part of this examination, ankle or pedal Doppler arterial waveforms; measure both ankle systolic pressure and systolic ankle brachial index (ABI). (Strong; Low)

3. We recommend the use of bedside non-invasive tests to exclude PAD. No single modality has been shown to be optimal. Measuring ABI (with <0.9 considered abnormal) is useful for the detection of PAD. Tests that largely exclude PAD are the presence of ABI 0.9-1.3, toe brachial index (TBI) ≥0.75 and the presence of triphasic pedal Doppler arterial waveforms. (Strong; Low)

Prognosis

4. In patients with a foot ulcer in diabetes and PAD, no specific symptoms or signs of PAD reliably predict healing of the ulcer. However, one of the following simple bedside tests should be used to inform the patient and healthcare professional about the healing potential of the ulcer. Any of the following findings increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥40mmHg; a toe pressure ≥30mmHg; or, a TcPO2 ≥25 mmHg. (Strong; Moderate)

5. Consider urgent vascular imaging and revascularisation in patients with a foot ulcer in diabetes where the toe pressure is <30mmHg or the TcPO2 <25 mmHg. (Strong; Low)

6. Consider vascular imaging and revascularisation in all patients with a foot ulcer in diabetes and PAD, irrespective of the results of bedside tests, when the ulcer does not improve within 6 weeks despite optimal management. (Strong; Low)

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

7. Diabetic microangiopathy should not be considered to be the cause of poor wound healing in patients with a foot ulcer. (Strong; Low)

8. In patients with a non-healing ulcer with either an ankle pressure <50mmHg or ABI <0.5 consider urgent vascular imaging and revascularisation. (Strong; Moderate)

Treatment

9. Colour Doppler ultrasound, CT-angiography, MR-angiography or intra-arterial digital subtraction angiography can each be used to obtain anatomical information when revascularisation is being considered. The entire lower extremity arterial circulation should be evaluated, with detailed visualization of below-the-knee and pedal arteries. (Strong; Low)

10. The aim of revascularisation is to restore direct flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound, with the aim of achieving a minimum skin perfusion pressure ≥40mmHg; a toe pressure ≥30mmHg; or, a TcPO2 ≥25 mmHg (Strong; Low)

11. A centre treating patients with a foot ulcer in diabetes should have the expertise in and rapid access to facilities necessary to diagnose and treat PAD; both endovascular techniques and bypass surgery should be available. (Strong; Low)

12. After a revascularisation procedure for a foot ulcer in diabetes, the patient should be treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)

13. Do not use a nerve decompression procedure in an effort to prevent a foot ulcer in an at-risk patient. (Weak; Low)

14. Patients with signs of PAD and a foot infection are at particularly high risk for major limb amputation and require emergency treatment. (Strong; Moderate)

15. Avoid revascularisation in patients in whom, from the patient perspective, the risk-benefit ratio for the probability of success is unfavourable. (Strong; Low)

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

16. All patients with diabetes and an ischemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension and prescription of a statin as well as low-dose aspirin or clopidogrel. (Strong; Low)

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Introduction

Peripheral artery disease

Peripheral artery disease (PAD) is more common in patients with diabetes and around half of patients with a diabetic foot ulcer have co-existing PAD (1-3). PAD has been variously defined in the literature, but for the purposes of this guidance document it is defined as any atherosclerotic arterial occlusive disease below the level of the inguinal ligament resulting in a reduction in blood flow to the lower extremity. Aorto-iliac disease is not considered in the current guidance because the treatment of supra-inguinal disease in people with diabetes does not differ markedly from that in non-diabetic individuals. Peripheral arterial disease in diabetes is a condition predominantly of the infra-inguinal vasculature and is distinct from that in patients without diabetes in its characteristics, treatment and outcomes. Identifying PAD among patients with foot ulceration is important because its presence is associated with worse outcomes, such as a slower (or lack of) healing of foot ulcers, lower extremity amputations, subsequent cardiovascular events and premature mortality (4, 5). Diagnosing PAD is challenging in patients with diabetes, as they frequently lack typical symptoms, such as claudication or rest pain, even in the presence of severe tissue loss (1, 6, 7). Arterial calcification (8-10), foot infection, oedema and peripheral neuropathy, each of which is often present with diabetic foot ulceration, may adversely affect the performance of diagnostic tests for PAD.

Risk-factors & Interventions

When clinicians diagnose PAD they should consider its potential adverse effects on ulcer healing and risk of amputation. For each patient, the clinician should estimate the potential for infection resolution, wound healing and avoidance of amputation by balancing the severity of the perfusion deficit and the perfusion required for good outcomes (11). The amount of blood flow required is affected by factors such as the presence of infection, extent of tissue loss and abnormal mechanical loading of the foot during walking. A revascularisation procedure can have several aims, such as promotion of wound healing, helping to resolve infection and avoiding or limiting the level of amputation. But, it is currently unclear how to identify those patients with PAD and a diabetic foot ulcer (DFU) who are most likely to benefit from revascularisation. Furthermore, there is debate about the selection of the correct revascularisation technique such as when to choose an endovascular approach or a surgical bypass.

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

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Formulation of recommendations

This guidance document has been prepared by a working group of experts of the International Working Group on the Diabetic Foot (IWDGF) and was subsequently reviewed, revised and approved by the Editorial Board and members of the IWDGF. It is based on three systematic reviews on diagnosis, prognosis and treatment (endovascular or bypass) of PAD in a patient with diabetes and a foot ulcer, which are separately published in this journal (12-14). For each of these topics, we offer recommendations and a rationale of how we arrived at these, as well making a grading according to the GRADE system.[1] For several topics we did not perform a systematic review (e.g., the value of history taking in diagnosing PAD or its medical treatment) and our recommendations for these are based on expert opinion, supported by the available literature.

[1] Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (37). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence based on: the risk of bias of included studies, effect sizes, and expert opinion, and to rate the quality of evidence as 'high', 'moderate', or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harm, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Diagnosis

Which 'bedside' diagnostic procedure, alone or in combination, has the best performance in diagnosing or excluding PAD in an asymptomatic person with diabetes?

Recommendation 1:
Examine a patient with diabetes annually for the presence of PAD; this should include, at a minimum, taking a history and palpating foot pulses. (GRADE recommendation: strong; Quality of evidence: low)

Recommendation 2:
Evaluate a patient with diabetes and a foot ulcer for the presence of PAD. Determine, as part of this examination, ankle or pedal Doppler arterial waveforms; measure both ankle systolic pressure and systolic ABI.(Strong; Low)

Rationale 1&2:
These recommendations are in line with other (inter)national guidelines on the management of diabetes, recommending yearly screening for PAD in subjects with diabetes (15). In addition to absent foot pulses, specific clinical findings that alert the healthcare professional to the presence of PAD include the presence of a cool lower limb, femoral bruits and a slow venous filling time (16). Symptoms and signs of PAD, such as claudication, absent pulses and a low ABI, were identified as predictors of future ulceration in a recent systematic review (17). Patients with diabetes and these signs of PAD should be reviewed on a regular basis by a member of a specialist foot care team. Moreover, individuals found to have PAD have an elevated risk of other cardiovascular diseases, necessitating strategies to address these problems as well (18).

As discussed above, up to 50% of the patients with diabetes and a foot ulcer have PAD, and these patients have been consistently shown to be at increased risk for failure to heal the ulcer and lower limb loss (4, 19). Few data exist about the accuracy of symptoms or clinical examination for the identification of PAD in patients with a foot ulcer. However, it would seem appropriate that these patients should be initially assessed in a similar manner to the patient with a non-ulcerated (intact) foot. Identification of the patient with PAD is essential to optimise management of the foot ulcer and in undertaking other measures to mitigate cardiovascular risk (20). Patients should be informed that they have PAD and that it confers an increased risk to their foot.

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Which symptoms and signs (clinical examination) should clinicians examine for in a patient with diabetes mellitus in order to identify or exclude PAD?

Recommendation 3:

We recommend the use of bedside non-invasive tests to exclude PAD. No single modality has been shown to be optimal. Measuring ABI (with <0.9 considered abnormal) is useful for the detection of PAD. Tests that largely exclude PAD are the presence of ABI 0.9-1.3, TBI ≥0.75 and the presence of triphasic pedal Doppler arterial waveforms. (Strong; Low)

Rationale 3:

Although a properly performed medical history and clinical examination can suggest the presence of PAD in a patient with a foot ulcer, their sensitivity is too low to rule out PAD. Even in the hands of a skilled examiner, palpable pulses may be present despite the presence of significant ischemia (21). Therefore, a more objective evaluation should be performed in all patients. As discussed in our systematic review (12), an ABI (<0.9) is a useful test for the detection of PAD in asymptomatic diabetic subjects who do not have peripheral neuropathy. Peripheral neuropathy is associated with medial wall calcification (Mönckeberg sclerosis) of the arteries in the lower leg, which may result in rigid arteries and an elevated ABI, adversely affecting the test. However, medial calcification does not necessarily cause arterial stenosis and reduced blood flow (8, 9, 18). The exclusion of patients with incompressible arteries (defined by an ABI ≥1.3), a factor known to be associated with poorer outcome in patients with limb ischemia, in a number of published studies makes it increasingly difficult to evaluate its diagnostic utility (12, 22). In contrast, detection of a triphasic pedal Doppler arterial waveform with a hand-held Doppler appears to provide stronger evidence for the absence of PAD. The same applies for measurement of a toe brachial index (TBI), which makes the presence of PAD unlikely if it is ≥0.75 (12).
Toe pressures may be falsely elevated by the same factors that affect ABI (including digital calcification). All of the bedside techniques should be performed in a standardised manner by trained healthcare professionals. There is insufficient evidence to support selecting any one of the bedside non-invasive diagnostic modalities for the detection of PAD across a spectrum of patients with diabetes. Healthcare professionals should be aware of the limitations of each modality and must decide which, either singly or in combination, to use, given their local expertise and test availability.

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Prognosis

In patients with diabetes and a foot ulcer, which symptoms, signs or bedside tests of PAD or reduced perfusion, and at what level of abnormality, will predict ulcer healing?

Recommendation 4:
In patients with a foot ulcer in diabetes and PAD, no specific symptoms or signs of PAD reliably predict healing of the ulcer. However, one of the following simple bedside tests should be used to inform the patient and healthcare professional about the healing potential of the ulcer. Any of the following findings increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥40mmHg; a toe pressure ≥30mmHg; or, a TcPO2 ≥25 mmHg. (Strong; Moderate)

Recommendation 5:
Consider urgent vascular imaging and revascularisation in a patient with afoot ulcer in diabetes where the toe pressure <30mmHg or a TcPO2 <25 mmHg. (Strong; Low)

Recommendation 6:
Consider vascular imaging and revascularisation in all patients with a foot ulcer in diabetes and PAD, irrespective of the results of bedside tests, when the ulcer does not improve within 6 weeks despite optimal management. (Strong; Low).

Recommendation 7:
Diabetic microangiopathy should not be considered to be the cause of poor wound healing in patients with a foot ulcer. (Strong; Low)

Rationale 4-7:
In our systematic review, the most useful tests for predicting healing in an ulcerated patient were skin perfusion pressure (≥40mmHg), toe pressure (≥30mmHg) and TcPO2 (≥25 mmHg) (13). All increased the pre-test probability of healing by at least 25% in one or more study. Given the variability of PAD in terms of its distribution, severity, and symptoms, it is unsurprising that no single measure performed with consistent accuracy for the prediction of healing. Interpretation of the specific characteristics of PAD that predict healing, or

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

failure to heal, of a diabetic foot wound, should be taken in the context of the quality of the published literature, which is limited. In addition, predicting healing of a diabetic foot ulcer is a complex endeavour that is associated with several variables other than PAD, such as: amount of tissue loss; presence of infection; mechanical load on the ulcer; and, co-morbidities, such as heart failure and end-stage renal disease (23). Healing is therefore related to the interplay of the severity of the perfusion deficit with these other characteristics of the foot and the patient. Finally, the chance of healing will be related to the subsequent quality of care, which should address any of these aforementioned problems.

The available data in the literature is based on univariable analysis and these PAD measures should all be interpreted in the context of other determinants of outcome that make up a pre-test probability. Given the relatively poor chance of healing in patients with a toe pressure <30mmHg or a TcPO2 <25 mmHg, we suggest considering imaging and revascularisation in these patients. Urgent imaging and treatment should also be considered in patients with PAD and higher pressure levels, in the presence of other predictors of poor prognosis, including infection or large ulcer surface area (24). Finally, in light of their limited diagnostic and prognostic utility, none of the above described tests can completely rule out PAD as a cause of impaired wound healing in a foot ulcer that does not respond to optimal treatment. Vascular imaging should therefore be performed in these patients in order to determine if the patient would benefit from revascularisation.
A post-hoc analysis of a trial suggested that a 4-week period is sufficient to assess the likelihood of healing in patients with uncomplicated neuropathic foot ulcers (25). In an observational study, shorter time to revascularisation (<8 weeks) was associated with a higher probability of healing of ischemic foot ulcers (26).
For pragmatic reasons, we suggest to consider vascular imaging and subsequent revascularisation in neuroischemic ulcers that do not improve within 6 weeks and have no other likely cause of poor wound healing.
In the past, diabetic microangiopathy was thought to be an important cause of poor healing of a diabetic foot ulcer. However, there is currently no evidence to support this notion, and PAD is the most important cause of impaired perfusion of the foot in a patient with diabetes (27). However, it should be noted that PAD is not the only cause of reduced perfusion in a lower extremity because oedema and infection can also result in poorer tissue oxygenation and these should all be treated accordingly (28, 29).

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Which symptoms, signs or bedside tests of PAD, and at what level of abnormality, help predict the risk of future major amputation in patients with diabetes and a foot ulcer?

Recommendation 8:

In patients with a non-healing ulcer with either an ankle pressure <50mmHg or ABI <0.5 consider urgent vascular imaging and revascularisation. (Strong; Moderate)

Rationale 8:

In contrast to healing, accurate risk prediction for major amputation could help to identify patients who would benefit from early vascular imaging and revascularization in an attempt to salvage the limb. Informative tests for predicting major amputation include: ankle pressure (<50mmHg); fluorescein toe slope (indocyanine green fluorescence angiography) (30); and, most usefully the combined result of an ankle pressure <50mmHg or an ABI <0.5. Again, each of these tests increased the pre-test probability by greater than 25%; in the case of the combined tests interpreted serially (ankle pressure and ABI) this value rose to around 40% (13). In our systematic review we could not identify studies fulfilling our inclusion criteria that assessed the predictive value of TcPO2 for major amputation. The prediction of major amputation is difficult and dependent on many factors. No measure could be considered a marker of good predictive performance (positive likelihood ratio >10) (13), and the decision to perform a major amputation before any attempt at revascularization should not be made on the basis of a perfusion measure alone.

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Treatment

When considering a revascularisation, which imaging modalities should be used to obtain anatomical information?

Recommendation 9:
Colour Doppler ultrasound, CT-angiography, MR-angiography or intra-arterial digital subtraction angiography can each be used to obtain anatomical information when revascularisation is being considered. The entire lower extremity arterial circulation should be evaluated, with detailed visualization of below-the-knee and pedal arteries. (Strong; Low)

Rationale 9:
Deciding who needs lower limb arterial revascularisation and what procedure to use is complex and requires appropriate imaging to guide therapy. It is unacceptable to rely on clinical examination alone; prior to a revascularization procedure anatomical information on the arteries of the lower limb should be obtained to assess the presence, severity and distribution of arterial stenoses or occlusions. Obtaining detailed imaging of below-knee and pedal arteries, especially with a dedicated assessment of the pedal circulation, is critically important in patients with diabetes. Techniques to define the lower limb arterial system in patients with diabetes include duplex ultrasound, MR angiography, CT angiography and digital subtraction angiography. Each of these techniques has its advantages, disadvantages and contra-indications, as described in a previous "Progress Report" of our working group (27). Healthcare professionals should be aware of all these techniques and of their limitations in individual patients. The decision on which imaging modality to use will depend upon any patient contra-indications as well as local availability and expertise.

What are the aims, outcomes and complications of endovascular therapy and open vascular surgery in people with a foot ulcer in diabetes and PAD?

Recommendation 10:
The aim of revascularisation is to restore direct flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the wound, with the aim of achieving a minimum skin perfusion pressure ≥40mmHg; a toe pressure ≥30mmHg; or, a TcPO2 ≥25 mmHg. (Strong; Low)

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

Rationale 10:
Historically, revascularisation of the lower limb was aimed at using the best vessel supplying in-line flow to the foot (18). Recent case series have tried to establish whether revascularisation of the angiosome directly supplying the area of ulceration will improve outcome, i.e. hasten healing or prevent amputation. According to this theory, the foot can be divided into three-dimensional blocks of tissue, called angiosomes, each with its own feeding artery. Restoration of pulsatile blood flow through a feeding artery directly to the area where the ulcer is located has been postulated to have better results than when flow is restored through a collateral vessel deriving from neighbouring angiosomes (31). Unfortunately many of the case series describing the results of this approach are at high risk of bias with confounding by indication and no attempts being made to adequately adjust for ulcer duration or severity (14, 32). Furthermore questions remain about the applicability and feasibility of angiosome directed revascularisation in everyday clinical practice and the effect of diabetes on angiosomes. But, whatever the theoretical concept behind the intervention, it seems preferable to improve blood flow to the anatomical area where the ulcer is located, when that is feasible.

Recommendation 11:
A centre treating patients with a foot ulcer in diabetes should have the expertise in and rapid access to facilities necessary to diagnose and treat PAD; both endovascular techniques and bypass surgery should be available.

Recommendation 12:
There is inadequate evidence to establish which revascularisation technique is superior and decisions should be made in a multidisciplinary team on a number of individual factors, such as morphological distribution of PAD, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)

Recommendation 13:
After a revascularisation procedure for a foot ulcer in diabetes, the patient should be treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)

Rationale 11-13:
The natural history of patients with PAD and an ulcerated foot remains poorly defined, but in two studies that reported the outcomes of patients with diabetes and limb ischemia who were not revascularised, the limb salvage rate was around 50% at one year (5,33). After a revascularisation procedure, most studies report limb salvage rates of 80–85% and ulcer healing in >60% at 12 months (14). The quality of the evidence on which

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

revascularisation technique (angioplasty or bypass surgery) to perform in patients with severe PAD and a diabetic foot ulcer is low, due to varying indications for intervention, poorly defined cohorts and multiple potential confounders. In our systematic review the major outcomes of healing, amputation and complications appear broadly similar between the two techniques (14). Some experts have recommended that patients requiring lower limb revascularisation should always receive an angioplasty procedure prior to considering surgical revascularisation. However, there is no published evidence to support this approach and the results of both open and endovascular procedures will greatly depend upon the local availability and expertise in a given centre as well as the morphological distribution of PAD (27). Open and endovascular revascularisations are also increasingly combined and in each patient an individual choice should be made which approach fits best with the specific problems of the patient and the expertise of the vascular specialists. Patients should therefore be managed in centres able to offer both approaches, with determinants of selection of technique including the length of lesion, availability of autogenous venous conduit and patient co-morbidity.

The perioperative mortality rates of revascularisation procedures in patients with diabetes and an ischemic foot ulcer are <5% in most studies, but major systemic in-hospital complications have been observed in about 10% of the patients in both open and endovascular series, probably reflecting the poor general health of these patients (14). The outcomes in patients with diabetes and end-stage renal disease are worse, with a 5% perioperative mortality and 1-year mortality of approximately 40% (14). However, even in these patients, favourable results can be obtained, but the majority of studies report 1-year limb salvage rates of approximately 70% (14). Any revascularisation procedure should be part of a comprehensive care plan that should also include treatment of infection, frequent debridement, biomechanical offloading, blood glucose control and treatment of co-morbidities.

Recommendation 14:
Patients with signs of PAD and a foot infection are at particularly high risk for major limb amputation and require emergency treatment. (Strong; Moderate)

Rationale 14:
As stated in our earlier “Progress Report”, “time is tissue” particularly in patients with infected ischemic diabetic foot ulcers (27). Patients with signs of PAD and a foot infection are at particularly high risk for extensive tissue loss and major limb amputation and they should be treated as a medical urgency. In one large observational

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

Prepared by the IWGDF Working Group on Peripheral Artery Disease

study the major and minor amputation rates after one year in these patients were 10% and 44%, respectively (4). Infection can spread extremely rapidly in the ischemic diabetic foot and may lead to life-threatening sepsis if treatment is delayed (34). In all patients with a deep foot infection consider immediate drainage with removal of all necrotic tissue and start intravenous antibiotic therapy after material is obtained for culture. At the same time, evaluate the vascular status and consider a revascularisation procedure once the infection is under control and the patient is stabilised. Once blood flow is restored to the foot and infection is treated, a final foot operation with soft tissue and skeletal reconstruction may be necessary to provide coverage and create a functional foot. However, in case of severe infection in the ischemic foot, especially in patients with systemic signs of sepsis (e.g. hemodynamic instability), immediate amputation may be the only option (27). In patients with a non-limb threatening infection and signs of PAD, the blood supply to the foot should be optimized before surgical debridement to ensure that potentially viable tissue is not unnecessarily removed (35,36).

Are there any patients with foot ulcers in diabetes and PAD in whom revascularisation interventions should not be performed?

Recommendation 15:
Avoid revascularisation in patients in whom, from the patient perspective, the risk-benefit ratio for the probability of success is unfavourable. (Strong; Low)

Rationale 15:
Revascularisation of the lower limb in patients with diabetes and PAD can be a particularly high-risk procedure. Patients with a diabetic foot ulcer and PAD have high rates of co-morbidities, such as cardiovascular and renal disease (1, 23). If there is no possibility of wound healing or when major amputation is inevitable, revascularisation should not be considered; an exception is when transtibial amputation is considered and there is no popliteal or femoral pulse, then investigation and vascular intervention should be considered. Because there is no reliable scoring system to identify these patients, clinical decision-making involving both patient and inter-disciplinary experts may be required. For instance, revascularisation may be inappropriate for patients who are severely frail, have a short life expectancy, who have poor functional status or are bed-bound or those with a large volume of tissue necrosis that renders the foot functionally unsalvageable.

In addition to patients where the risk of a revascularisation is clearly too high, there are also patients in whom the risk-benefit ratio of a revascularisation is unclear. In clinical decision making it should be taken into account that

even severely ischemic ulcers can heal without a revascularisation; as noted, two observational studies reported healing rates of about 50% (with or without minor amputations) (5,37).

Is risk reduction for future cardiovascular events feasible in patients with diabetes and an ischemic foot ulcer?

Recommendation 16:
All patients with diabetes and an ischemic foot ulcer should receive aggressive cardiovascular risk management including support for cessation of smoking, treatment of hypertension and prescription of a statin as well as low-dose aspirin or clopidogrel. (Strong; Low)

Rationale 16:
This question was not addressed in our systematic review (14), but this recommendation is in line with other guidelines in subjects with PAD (17, 36). Cardiovascular morbidity and mortality are markedly increased in patients with diabetes, a foot ulcer and PAD; these patients have an overall mortality at 5 years of approximately 50% (14). In one follow-up study in patients with a neuro-ischemic foot ulcer, introduction of aggressive cardiovascular risk management (i.e. antiplatelet agent, statin and antihypertensive medication when indicated) reduced 5-year mortality from 58% to 36% (20).

IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

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IWGDF Guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes

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