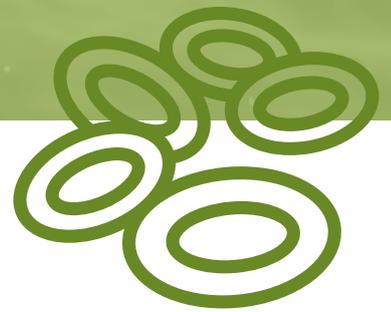


IWGDF Guideline on diagnosis, prognosis and management of peripheral artery disease in patients with a foot ulcer and diabetes



Part of the 2019 IWGDF Guidelines
on the Prevention and Management
of Diabetic Foot Disease

AUTHORS

Robert J. Hinchliffe¹, Rachael O. Forsythe²,
Jan Apelqvist³, Ed J. Boyko⁴, Robert FitrIDGE⁵,
Joon Pio Hong⁶, Konstantinos Katsanos⁷,
Joseph L. Mills⁸, Sigrid Nikol⁹, Jim Reekers¹⁰,
Maarit Venermo¹¹, R. Eugene Zierler¹²,
Nicolaas C. Schaper¹³ on behalf of the International
Working Group on the Diabetic Foot (IWGDF)

INSTITUTIONS

¹Bristol Centre for Surgical Research,
University of Bristol, Bristol, UK

²British Heart Foundation / University of Edinburgh
Centre for Cardiovascular Science, University of
Edinburgh, Edinburgh, Scotland, UK

³Department of Endocrinology, University Hospital
of Malmö, Sweden

⁴Seattle Epidemiologic Research and Information
Centre-Department of Veterans Affairs Puget
Sound Health Care System and the University of
Washington, Seattle, Washington, USA

⁵Vascular Surgery, The University of Adelaide,
Adelaide, South Australia, Australia

⁶Asan Medical Center University of Ulsan,
Seoul, Korea

⁷Patras University Hospital School of Medicine,
Rion, Patras, Greece

⁸SALSA (Southern Arizona Limb Salvage Alliance),
University of Arizona Health Sciences Center,
Tucson, Arizona, USA

⁹Asklepios Klinik St. Georg, Hamburg, Germany

¹⁰Department of Vascular Radiology, Amsterdam
Medical Centre, The Netherlands

¹¹Helsinki University Hospital, University of
Helsinki, Finland

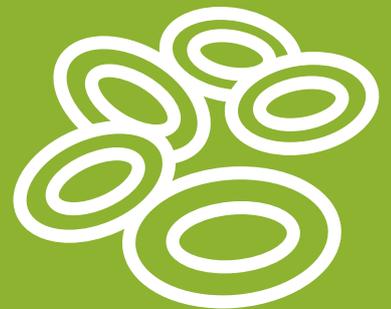
¹²Department of Surgery, University of Washington,
Seattle, Washington, USA

¹³Div. Endocrinology, MUMC+, CARIM and CAPHRI
Institute, Maastricht, The Netherlands

KEYWORDS

diabetic foot; foot ulcer; guidelines; peripheral
artery disease; surgery; diagnosis; prognosis;
vascular disease

www.iwgdfguidelines.org





ABSTRACT

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers and diabetes and updates the previous IWGDF guideline.

Up to 50% of patients with diabetes and foot ulceration have concurrent peripheral artery disease (PAD), which confers a significantly elevated risk of adverse limb events and cardiovascular disease. We know that the diagnosis, prognosis and treatment of these patients are markedly different to patients with diabetes who do not have PAD and yet there are few good quality studies addressing this important sub-set of patients.

We followed the GRADE methodology to devise clinical questions and critically important outcomes in the PICO format, to conduct a systematic review of the medical-scientific literature, and to write recommendations and their rationale. The recommendations are based on the quality of evidence found in the systematic review, expert opinion where evidence was not available, and a weighing of the benefits and harms, patient preferences, feasibility and applicability, and costs related to the intervention. We here present the updated 2019 guidelines on diagnosis, prognosis and management of PAD in patients with a foot ulcer and diabetes, and we suggest some key future topics of particular research interest.



RECOMMENDATIONS

1. Examine the feet of all patients with diabetes annually for the presence of peripheral artery disease, even in the absence of foot ulceration. At a minimum, this should include taking a relevant history and palpating foot pulses. (Strength of the recommendation: Strong; Quality of the evidence: Low)
2. Clinically examine (by relevant history and palpation of foot pulses) all patients with diabetes and foot ulceration for the presence of peripheral artery disease. (Strong; Low)
3. As clinical examination does not reliably exclude peripheral artery disease (PAD) in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement. No single modality has been shown to be optimal and there is no definite threshold value above which PAD can reliably be excluded. However, PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥ 0.75 and triphasic pedal Doppler waveforms. (Strong; Low)
4. Perform at least one of the following bedside tests in a patient with a diabetic foot ulcer and peripheral artery disease, any of which increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a transcutaneous oxygen pressure (TcPO₂) ≥ 25 mmHg. (strong; moderate)
5. Use the WIfI (Wound/Ischaemia/foot Infection) classification system as a means to stratify amputation risk and revascularisation benefit in a patient with a diabetic foot ulcer and peripheral artery disease. (Strong; Moderate)
6. Always consider urgent vascular imaging, and revascularisation, in a patient with a diabetic foot ulcer and an ankle pressure < 50 mmHg, ABI < 0.5 , a toe pressure < 30 mmHg or a TcPO₂ < 25 mmHg. (Strong; Low)
7. Always consider vascular imaging in patients with a diabetic foot ulcer, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite good standard of care. (Strong; Low)
8. Always consider revascularisation in a patient with a diabetic foot ulcer and peripheral artery disease, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite optimal management. (Strong; Low).
9. Do not assume diabetic microangiopathy, when present, is the cause of poor healing in patients with a diabetic foot ulcer, therefore always consider other possibilities for poor healing. (Strong; Low)
10. Use any of the following modalities to obtain anatomical information when considering revascularising a patient's lower extremity: colour Duplex ultrasound; computed tomographic angiography; magnetic resonance angiography; or, intra-arterial digital subtraction angiography. Evaluate the entire lower extremity arterial circulation with detailed visualisation of below-the-knee and pedal arteries, in an anteroposterior and lateral plane. (Strong; Low)
11. When performing revascularisation in a patient with a diabetic foot ulcer, aim to restore direct blood flow to at least one of the foot arteries, preferably the artery that supplies the anatomical



- region of the ulcer. After the procedure, evaluate its effectiveness with an objective measurement of perfusion. (Strong; Low)
12. As evidence is inadequate to establish whether an endovascular, open or hybrid revascularisation technique is superior, make decisions based on individual factors, such as morphological distribution of peripheral artery disease, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)
 13. Any centre treating patients with a diabetic foot ulcer should have expertise in, and rapid access to facilities necessary to diagnose and treat, PAD, including both endovascular techniques and bypass surgery. (Strong; Low)
 14. Ensure that after a revascularisation procedure in a patient with a diabetic foot ulcer, the patient is treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)
 15. Urgently assess and treat patients with signs or symptoms of peripheral artery disease and a diabetic foot infection, as they are at particularly high risk for major limb amputation. (Strong; Moderate)
 16. Avoid revascularisation in patients in whom, from the patient's perspective, the risk–benefit ratio for the probability of success of the procedure is unfavourable. (Strong; Low)
 17. Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia and treatment with a statin drug as well as low-dose clopidogrel or aspirin. (Strong; Low)

INTRODUCTION

The global burden of diabetes has increased rapidly over the past decade and many international bodies now consider diabetes a public health emergency. Health professionals and patients are becoming increasingly aware of the seriousness of diabetes-related complications. Yet despite substantial increase in awareness, the introduction of dedicated screening programmes and specialised interdisciplinary care teams in many developed countries, the number of people with diabetes has quadrupled since 1980 and the pooled estimate of worldwide prevalence of diabetes and foot ulceration is approximately 3%¹ in community-based cohorts, with a wide variation in rates of major amputation across the world².

It is estimated that in middle and high income countries up to 50% of patients with diabetes and foot ulceration have underlying peripheral artery disease (PAD)^{3 4}, whereas neuropathic ulcers are possibly more prevalent in low income countries^{5 6}. In patients with diabetes, PAD may remain undiagnosed until the patient presents with (severe) tissue loss, as many patients typically lack the classic preceding clinical symptoms of PAD such as claudication or rest pain^{7 8}. Diagnostic tests may be less reliable due to the presence of peripheral neuropathy, medial arterial calcification⁹ and peripheral oedema. However, it is important to identify PAD in patients with diabetic foot ulceration (DFU) at the earliest possible stage, as the presence of PAD is associated with increased risk of non-healing ulcers, infection and major limb amputation, as well as an elevated risk of cardiovascular morbidity and overall mortality



^{10 11 12 13 14}. The prognosis of a patient with diabetes, PAD and foot ulceration requiring amputation is worse than many common cancers – up to 50% of patients will not survive 5 years ^{4 15}.

There are several guidelines for the management of patients with PAD and chronic limb threatening ischaemia (CLTI). However, most studies reporting on PAD outcomes fail to include a diabetes sub-group, although it is likely that many of the included patients actually have diabetes. Moreover, many studies reporting on PAD and diabetes include only patients with intact feet, or do not adequately describe the presences of neuropathy, ulcer, infection or other contributing factors to poor outcomes ¹⁶.

There is no doubt that patients with diabetes and PAD represent a special sub-group. They tend to have a different clinical presentation, natural history and outcomes. Patients frequently present with severe tissue loss without significant symptoms, which may rapidly progress to limb loss; further characteristics are described in Table I. As such, there is clearly a need for further research into this unique sub-group of patients with diabetes, foot ulceration and PAD in order that we may improve outcomes around the world.

Table I. ⁷⁴

Characteristics of PAD in people with diabetes (compared to people without diabetes)
More common
Affects younger individuals
Multi-segmental and bilateral
More distal
More medial calcification
Impaired collateral formation
Faster progress with higher risk of amputation

This guideline is an update of the previous IWGDF Guideline on PAD ¹⁷, and is part of the IWGDF Guidelines on the prevention and management of diabetic foot disease. We aim to provide evidence-based recommendations on the diagnosis, prognosis, and management of PAD in patients with a foot ulcer and diabetes.

METHODS

In this guideline we have followed the GRADE methodology, which is structured around clinical questions in the PICO-format (Patient-Intervention-Comparison-Outcome), systematic searches and assessment of the available evidence, followed by developing recommendations and their rationale ^{18 19}.

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which were revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and



other health care professionals in providing useful information on the diagnosis, prognosis and management of peripheral artery disease in persons with diabetes and a foot ulcer. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate et al. ¹⁶ as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as 'high', 'moderate' or 'low'. The systematic review(s) supporting this guideline are published separately ^{20 21 22}.

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic review(s) ^{20 21 22}, expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method ^{18 19}. Based on these factors, we graded the strength of each recommendation as 'strong' or 'weak', and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the 'IWGDF Guidelines development and methodology' document ²³.

DIAGNOSIS

PICO: In a person with diabetes and no foot ulceration, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude peripheral artery disease?

Recommendation I: Examine the feet of all patients with diabetes annually for the presence of peripheral artery disease, even in the absence of foot ulceration. At a minimum, this should include taking a relevant history and palpating foot pulses. (Strong; Low)

Rationale: This recommendation is in line with other (inter)national guidelines on the management of diabetes, recommending yearly screening for PAD in subjects with diabetes ^{24 25 26}. In addition to absent foot pulses, specific clinical findings that alert the healthcare professional to the presence of PAD include the presence of femoral bruits and a slow venous filling time ^{27 8}. 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 ²⁸, however classical signs may be absent in patients with PAD and a DFU. Patients with diabetes and these signs of PAD should therefore be reviewed more frequently. Moreover, individuals with PAD have an elevated risk of other cardiovascular diseases, necessitating strategies to address these problems as well ²⁹.



PICO: In a person with diabetes and a foot ulcer, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude peripheral artery disease?

Recommendation 2: Clinically examine (by relevant history and palpation of foot pulses) all patients with diabetes and foot ulceration for the presence of peripheral artery disease. (Strong; Low)

Rationale: Few data exist about the accuracy of symptoms or clinical examination for the identification of PAD in patients with diabetes and foot ulceration. 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 in all patients. Many patients with diabetes and PAD have few or atypical symptoms⁷ and in our experience, patients can have severe tissue loss with limited symptoms. The paucity of symptoms may be related to the presence of co-existing neuropathy and loss of pain sensation. Foot temperature may be unreliable due to arterio-venous shunting resulting in a relatively warm foot³⁰. The palpation of foot pulses should form a key part of the initial clinical examination, however the presence of palpable foot pulses cannot be used in isolation to reliably exclude PAD. For example, in a screened primary care population of patients > 50 years more than two thirds of patients with PAD had a detectable pulse³¹. Even in the hands of a skilled examiner, palpable pulses may be present despite the presence of significant ischaemia³². Therefore, a more objective evaluation should be performed in all patients with a foot ulcer.

PICO: In a person with diabetes and a foot ulcer which 'bedside' diagnostic procedure, alone or in combination, has the best performance in diagnosing or excluding peripheral artery disease?

Recommendation 3: As clinical examination does not reliably exclude peripheral artery disease (PAD) in most persons with diabetes and a foot ulcer, evaluate pedal Doppler arterial waveforms in combination with ankle systolic pressure and systolic ankle brachial index (ABI) or toe systolic pressure and toe brachial index (TBI) measurement. No single modality has been shown to be optimal and there is no definite threshold value above which PAD can reliably be excluded. However, PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥ 0.75 and triphasic pedal Doppler waveforms. (Strong; Low)

Rationale: In addition to clinical history and examination, an objective evaluation should be performed in all patients with a foot ulcer. As discussed in our systematic review²⁰, an ABI (< 0.9) is a useful test for the detection of PAD. However, an ABI > 0.9 does not rule out PAD. The majority of patients with PAD and a foot ulcer will have (autonomic) peripheral neuropathy, which is associated with medial wall calcification (Mönckeberg sclerosis) of the arteries in the lower leg, resulting in rigid arteries and an elevated ABI, adversely affecting the utility of the test⁹. It should be noted that medial calcification does not necessarily cause arterial stenosis and reduced blood flow^{33 29}. The detection of a triphasic pedal Doppler arterial waveform with a handheld Doppler appears to provide stronger evidence for the absence of PAD. The same applies for measurement of a toe brachial index, which makes the presence of PAD unlikely if it is ≥ 0.75 ²⁰ and provides additional information compared to the ABI, particularly in patients with severe PAD below the ankle³⁴. Unfortunately, toe pressures may also be falsely elevated by the same factors that affect ABI (including digital artery calcification). There is insufficient evidence to



support the use of a single bedside diagnostic test for PAD that may be used for all patients with diabetes and foot ulceration³⁵. However recent studies suggest that TBI and tibial waveforms (measured at the level of the medial malleolus, the dorsalis pedis and in the mid-calf for the peroneal artery) are the most useful non-invasive tests to select patients for diagnostic imaging^{36 37}. Using more than one test in parallel certainly improves diagnostic accuracy^{35 38 39}.

There are no definitive data on the absolute threshold or 'normal' values of non-invasive tests for people with diabetes and foot ulceration. Previous studies examining the use of bedside tests to diagnose PAD have used pre-determined threshold values, however there is no information available about other thresholds that may be of interest. We suggest that PAD is a less likely diagnosis in the presence of ABI 0.9-1.3, toe brachial index ≥ 0.75 and triphasic pedal Doppler waveforms, however this should be complimented by definitive imaging where uncertainty remains.

All bedside techniques should be performed by trained healthcare professionals in a standardised manner. There is insufficient evidence to confidently recommend the use of any of the aforementioned bedside non-invasive diagnostic modalities over another for the detection of PAD. 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.

PROGNOSIS

PICO: In a person with diabetes foot ulceration and PAD, which clinical signs, symptoms or non-invasive bedside tests may predict ulcer healing and amputation?

Recommendation 4: Perform at least one of the following bedside tests in a patient with a diabetic foot ulcer and peripheral artery disease, any of which increases the pre-test probability of healing by at least 25%: a skin perfusion pressure ≥ 40 mmHg; a toe pressure ≥ 30 mmHg; or, a transcutaneous oxygen pressure (TcPO₂) ≥ 25 mmHg. (strong; moderate)

Recommendation 5: Use the WIfI (Wound/Ischaemia/foot Infection) classification system as a means to stratify amputation risk and revascularisation benefit in a patient with a diabetic foot ulcer and peripheral artery disease. (Strong; Moderate)

Recommendation 6: Always consider urgent vascular imaging, and revascularisation, in a patient with a diabetic foot ulcer and an ankle pressure < 50 mmHg, ABI < 0.5 , a toe pressure < 30 mmHg or a TcPO₂ < 25 mmHg. (Strong; Low)

Recommendation 7: Always consider vascular imaging in patients with a diabetic foot ulcer, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite good standard of care. (Strong; Low).



Recommendation 8: Always consider revascularisation in a patient with a diabetic foot ulcer and peripheral artery disease, irrespective of the results of bedside tests, when the ulcer is not healing within 4-6 weeks despite optimal management. (Strong; Low).

Recommendation 9: Do not assume diabetic microangiopathy, when present, is the cause of poor healing in patients with a diabetic foot ulcer, therefore always consider other possibilities for poor healing. (Strong; Low)

Rationale: In our systematic review, the most useful tests for predicting healing in an ulcerated foot were skin perfusion pressure (≥ 40 mmHg), toe pressure (≥ 30 mmHg) and TcPO₂ (≥ 25 mmHg)²¹. 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 failure to heal, of a diabetic foot ulcer should be taken in the context of the quality of the published literature, which is limited.

Most available data in the literature are based on univariable analysis, and these PAD measures should all be interpreted in the context of other determinants of outcome. Given the relatively poor chance of healing and the increased risk of amputation in patients with a toe pressure < 30 mmHg or a TcPO₂ < 25 mmHg, we suggest imaging and consideration of revascularisation in these patients. The ABI has very little value in predicting ulcer healing⁴⁰, but an ABI < 0.5 and/or an ankle pressure < 50 mmHg does confer a higher risk of amputation. 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 area⁴¹. A recent study has suggested that perfusion angiography may predict early major amputation but this needs further confirmation⁴². Finally, in light of their limited diagnostic and prognostic utility, none of the tests described earlier 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. In an observational study, shorter time to revascularisation (< 8 weeks) was associated with a higher probability of healing of ischaemic foot ulcers⁴³. Additionally, a recent retrospective study demonstrated that patients with diabetes who experienced a delay of greater than 2 weeks from presentation to revascularisation were at a significantly increased risk of limb loss⁴⁴. These studies suggest that an aggressive approach with early revascularisation might improve outcome but these procedures are not without risk as summarised below²². The zealous approach of 'the sooner the better' may be tempting, however this should be also mitigated by the finding that up to 50% of patients with DFU and PAD who do not undergo revascularisation may be expected to heal their foot ulcers¹⁰. There is therefore no 'one size fits all approach' and each case should be evaluated on an individual basis.

We recommend considering revascularisation in all patients with diabetes, PAD and a foot ulcer, irrespective of the results of bedside tests, when the ulcer does not improve within 4-6 weeks despite optimal management. Due to the multiple factors contributing to non-healing, it is impossible to determine the optimal duration of a trial of conservative management before considering imaging and



vascular intervention. A post hoc analysis of a clinical trial suggested that a 4-week period is sufficient in patients with uncomplicated neuropathic foot ulcers to assess the likelihood of healing ⁴⁵. For pragmatic reasons, based on expert opinion, we suggest considering vascular imaging and subsequent revascularisation in neuro-ischaemic ulcers that do not improve within 6 weeks and have no other likely cause of poor wound healing.

Healing is related to the interplay of the severity of the perfusion deficit with other characteristics of the foot and the patient, such as amount of tissue loss, presence of infection, mechanical load on the ulcer, comorbidities such as heart failure and end-stage renal disease ⁴⁶. As discussed in our IWGDF classification guideline ⁴⁷, the Wound, Ischemia and Foot infection (WIFI) classification system can guide the clinician in estimating the risk of amputation and potential benefit of revascularisation. This system categorises the patient's ulcer, severity of ischaemia based on non-invasive tests and the severity of infection based on the IWGDF/IDSA classification. The WIFI system was generated from expert consensus and subsequently validated in diabetes and non-diabetes populations⁴⁸. The scoring system is summarised in Table 2, is discussed in our classification guideline, and is freely available to download as a calculator tool ^{47 49}. Finally, the chance of healing will be related to the subsequent quality of care, which should address any of these aforementioned problems.

Table 2. ⁴⁸

Wound Grade	DFU	Gangrene
0	No ulcer <i>Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.</i>	No gangrene
1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx <i>Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.</i>	No gangrene
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement <i>Clinical description: major tissue loss salvageable with multiple (≥ 3) digital amputations or standard transmetatarsal amputation (TMA) \pm skin coverage.</i>	Gangrenous changes limited to digits
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer \pm calcaneal involvement <i>Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect</i>	Extensive gangrene involving forefoot and /or midfoot; full thickness heel necrosis \pm calcaneal involvement



Ischemia			
Grade	Ankle-Brachial Index	Ankle systolic pressure (mmHg)	Toe Pressure, Transcutaneous oxygen pressure (mmHg)
0	≥ 0.80	> 100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

Foot Infection	
Grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least 2 of the following items: <ul style="list-style-type: none"> • Local swelling or induration • Erythema >0.5 to ≤2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
2	Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: <ul style="list-style-type: none"> • Temperature >38°C or <36°C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO₂ <32 mm Hg • White blood cell count >12,000 or <4000 cu/mm or 10% immature (band) forms

SIRS = systemic inflammatory response signs

In the past, 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 remains the most important cause of impaired perfusion of the foot in a patient with diabetes⁵⁰. 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 a decrease in tissue oxygenation, and these should all be treated appropriately^{51 52}.

TREATMENT



PICO: In a person with diabetes and foot ulceration, which diagnostic imaging modalities to obtain anatomical information are most useful when considering revascularisation?

Recommendation 10: Use any of the following modalities to obtain anatomical information when considering revascularising a patient's lower extremity: colour Duplex ultrasound; computed tomographic angiography; magnetic resonance angiography; or, intra-arterial digital subtraction angiography. Evaluate the entire lower extremity arterial circulation with detailed visualisation of below-the-knee and pedal arteries, in an anteroposterior and lateral plane. (Strong; Low)

Rationale: Deciding who needs lower limb arterial revascularisation and determining what procedure is the most appropriate to achieve revascularisation requires appropriate imaging to guide therapy. It is unacceptable to rely on clinical examination alone prior to performing a revascularisation 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-the-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, magnetic resonance angiography, computed tomography angiography and digital subtraction angiography ⁵⁰.

Briefly, Colour Duplex ultrasound (CDUS) provides both anatomic details and a physiologic assessment of blood flow at specific arterial sites. By scanning sequentially from the abdominal to the tibial arteries, the entire lower extremity arterial circulation can be directly evaluated. However, diffuse multi-segmental involvement, calcification and oedema may hamper the investigation. CDUS has the advantage of being a non-invasive test but it requires sophisticated equipment and specialized expertise and is not appropriate as a routine screening test. In computed tomography angiography (CTA), an iodinated contrast medium is injected intravenously and the vascular tree from the level of the renal arteries down to the foot can be visualised. Severe calcification may hamper the evaluation of smaller arteries, especially in the lower leg. Further disadvantages are potential allergic reactions and the development of contrast-induced nephropathy, particularly in patients with pre-existing renal disease or cardiac failure. In contrast-enhanced magnetic resonance angiography (CE-MRA) gadolinium is used as contrast and with dedicated techniques images can be obtained from the abdominal aorta down to the foot. A major advantage of CE-MRA is the use of a contrast agent with low nephrotoxicity, disadvantages include the limited spatial resolution and artefacts because of previous stent placement. However, its use is limited in patients with implants, such as pacemakers and claustrophobia and in patients with severe renal insufficiency (creatinine clearance <30mL/min) use of gadolinium-containing contrast is (relatively) contraindicated because of the risk of developing nephrogenic systemic fibrosis. Newer non-gadolinium agents, such as ultrasmall superparamagnetic particles of iron oxide (which has a number of magnetic resonance applications), may be alternative and safer agents in patients with compromised renal function ⁵³.

Intra-arterial digital subtraction angiography is still regarded as the gold standard for arterial imaging because of its high spatial resolution. It has the advantage of allowing endovascular therapy during the same procedure but has the disadvantage of the use of an iodinated contrast medium and is an invasive procedure, associated with potential complications of arterial puncture.



Healthcare professionals should be aware of these techniques and of their limitations in individual patients. The decision on which imaging modality to use will depend upon patient contraindications as well as local availability and expertise.

PICO: What are the aims and methods of revascularisation and onward management in a person with diabetes, foot ulceration and PAD?

Recommendation 11: When performing revascularisation in a patient with a diabetic foot ulcer, aim to restore direct blood flow to at least one of the foot arteries, preferably the artery that supplies the anatomical region of the ulcer. After the procedure, evaluate its effectiveness with an objective measurement of perfusion. (Strong; Low)

Rationale: The natural history of patients with diabetes, PAD and an ulcerated foot remains poorly defined, but in two studies reporting the outcomes of patients with diabetes and limb ischaemia who were not revascularised, the limb salvage rate was around 50% at 1 year^{10 54}. After a revascularisation procedure, most studies report limb salvage rates of 80–85% and ulcer healing in >60% at 12 months²². The quality of evidence is generally low due to the poorly defined population cohorts, variability of indications for intervention and multiple potentially confounding factors. Patients undergoing revascularisation are at increased risk of peri-operative mortality and the highest risk group is those patients with diabetes, PAD and end-stage renal disease, who have a 5% peri-operative mortality, 40% 1-year mortality and 1-year limb salvage rates of around 70%²².

Historically, the aim of revascularisation in patients with PAD has been to achieve inline pulsatile flow to the foot, usually by targeting the best vessel available. However, more recently, the angiosome-directed approach has been advocated but remains a subject of much debate^{55 56}. According to this theory, the foot can be divided into three-dimensional blocks of tissue, each with its own feeding artery. Direct revascularisation would result in a restoration of pulsatile blood flow through the feeding artery to the area where the ulcer is located, while with indirect revascularisation flow is restored through collateral vessels deriving from neighbouring angiosomes. By targeting revascularisation at the vessel directly supplying the anatomical area (angiosome) of tissue loss, the theory is that this will be a more effective method of revascularisation than simply targeting the best vessel, which may not supply the area of tissue loss. A recent retrospective study of endovascular limb salvage attempts in patients with DFU suggested that indirect angiosome revascularisation was associated with poorer outcomes than direct revascularisation⁵⁷. However, due to lack of clear definitions and factors like selection bias, the effectiveness of the angiosome concept in patients with diabetes is unknown^{58 59 60 55}. Particularly in patients with diabetes who usually have poor collaterals, restoration of flow to an artery directly supplying the affected area seems the best approach during an endovascular procedure⁵⁶. Successfully opening one or more occluded vessels is not the same as a clinically successful procedure and before the procedure is terminated blood flow to the ulcer area should therefore be assessed. If feasible, opening multiple arteries may be useful provided at least one supplies the ischaemic area directly⁵⁵.

The effectiveness of a revascularisation procedure should preferably be evaluated with objective perfusion measurements. We have not provided target perfusion pressures in this recommendation, as



there is no robust evidence to support such an approach. We previously suggested revascularisation should achieve a minimum skin perfusion pressure of 40mmHg, toe pressure >30mmHg or TcPO₂ >25mmHg in order to be considered effective¹⁷. However, we now recommend that revascularisation should aim to improve perfusion to the foot *as much as possible*, which will vary according to the individual patient. As skin oxygen tension increases progressively in a period of several weeks after a successful PTA, TcPO₂ measurements should preferably be performed at least 1-3 weeks after the procedure⁶¹.

Recommendation 12: As evidence is inadequate to establish whether an endovascular, open or hybrid revascularisation technique is superior, make decisions based on individual factors, such as morphological distribution of peripheral artery disease, availability of autogenous vein, patient co-morbidities and local expertise. (Strong; Low)

Recommendation 13: Any centre treating patients with a diabetic foot ulcer should have expertise in, and rapid access to facilities necessary to diagnose and treat, PAD, including both endovascular techniques and bypass surgery. (Strong; Low)

Recommendation 14: Ensure that after a revascularisation procedure in a patient with a diabetic foot ulcer, the patient is treated by a multidisciplinary team as part of a comprehensive care plan. (Strong; Low)

Recommendation 15: Urgently assess and treat patients with signs or symptoms of peripheral artery disease and a diabetic foot infection, as they are at particularly high risk for major limb amputation. (Strong; Moderate)

Rationale: There is still no consensus on the most appropriate approach to revascularisation in a patient with diabetes and foot ulceration. In our systematic review, we found that the major outcomes of wound healing and amputation were broadly similar between endovascular and open interventions²². Each of these techniques has its advantages and disadvantages. A successful distal venous bypass can result in a marked increase of blood flow to the foot but general anaesthesia is usually necessary and a suitable vein, as a bypass conduit, should be present. An endovascular procedure has several logistical advantages but sometimes very complex interventions are necessary to obtain adequate blood flow in the foot and a failed endovascular intervention may lead to worse outcomes when an open procedure is subsequently performed⁶². Over the past few decades, there have been significant advancements in endovascular techniques, however parallel to this, we have seen improvements in anaesthesia and peri-operative care that have helped improve surgical outcomes. Whilst the BASIL trial is often quoted as a guide to revascularisation of patients with limb ischaemia⁶³, the cohort included a small proportion of patients with diabetes, of which there was no sub-group analysis, and was not focused on patients with ulceration. Therefore, we cannot extrapolate these findings to our patients with diabetes, foot ulceration and PAD. Finally, it is becoming increasingly common to adopt a combined open and endovascular (hybrid) approach. Therefore, we recommend that in each patient requiring lower-limb revascularisation, an endovascular, an open procedure and a hybrid procedure should be considered. As



there is no 'one-fits-all' approach to treatment for patients with diabetes, foot ulceration and PAD, it is important that a treating centre has the expertise and facilities to provide a range of treatment options with availability of both endovascular and open methods.

As discussed in other parts of the IWGDF Guidance, restoration of perfusion in the foot is only part of the treatment, which should be provided by multi-disciplinary care team ⁶⁴. Any revascularisation procedure should therefore be part of a comprehensive care plan that addresses other important issues including: prompt treatment of concurrent infection, regular wound debridement, biomechanical off-loading, control of blood glucose and treatment of co-morbidities ⁶⁴. In particular, patients with a foot infection are at high risk for limb loss and should be treated as a medical emergency. The 1-year major amputation rate for such patients has been reported to be as high as 44% ⁶⁵ and delay in treatment can lead to rapid tissue destruction and life-threatening sepsis ⁶⁶ as described in our guidelines on infection. In patients with deep infection, such as a foot abscess, infection of deep a foot compartment that needs immediate drainage or extensive tissue loss/ gangrene that must be removed to control the infection, immediate drainage should be considered first, in order to control sepsis ¹⁴. As described in our Infection Guidelines, this should be accompanied by aggressive antibiotic therapy, initially broad-spectrum, and rationalised according to tissue culture ¹⁴ - 'time is tissue' in these patients. Once the sepsis is controlled and the patient is stabilised, evaluation of the arterial tree should lead to consideration for prompt revascularisation (ie within a few days). Once blood flow is improved and infection is treated, a definitive operation may be required in order to create a functional foot, which may require soft tissue and bone reconstruction. In patients with severely impaired perfusion and severe tissue loss, but without infection, extensive debridement or amputation of part of the foot should preferably not be performed until perfusion is restored.

PICO: In a patient with a diabetic foot ulcer and PAD are there any circumstances in which revascularisation should not be performed?

Recommendation 16: Avoid revascularisation in patients in whom, from the patient's perspective, the risk-benefit ratio for the probability of success of the procedure is unfavourable. (Strong; Low)

Rationale: Revascularisation should not be performed if there is no realistic chance of wound healing, or when major amputation is inevitable. Many patients pose high anaesthetic risk due to comorbidities and major reconstructive surgery confers significant risk of peri-operative complications. In particular, the following patients may not be suitable for revascularisation: those who are very frail, have short life expectancy, poor functional status, are bed bound, have a large area of tissue destruction that renders the foot functionally unsalvageable, and those who cannot realistically be expected to mobilise following revascularisation. The decision to proceed to primary amputation, or to adopt a palliative approach, should be made in conjunction with the patient and a multi-disciplinary team that includes a vascular surgeon or another specialist with expertise in vascular interventions ⁶⁷.

In those patients in whom the risk-benefit ratio of revascularisation is unclear, it should be taken into account that some severely ischaemic ulcers heal without revascularisation - two observational studies



demonstrated healing rates of around 50% (with or without minor amputations) in patients unsuitable (either because they were deemed too frail or where revascularisation was not technically possible) for revascularisation ¹⁰.

There are several other techniques that have been investigated for patients with diabetes, PAD and ulceration in whom there are no options for revascularisation. These include venous arterialisation and intermittent pneumatic compression therapy. ^{68 69}. However, there are insufficient data to provide any recommendation on their utility in patients where no revascularisation option exists.

PICO: In patients with diabetes, foot ulceration and PAD, is it possible to reduce the risk of future cardiovascular events?

Recommendation 17: Provide intensive cardiovascular risk management for any patient with diabetes and an ischaemic foot ulcer, including support for cessation of smoking, treatment of hypertension, control of glycaemia and treatment with a statin drug as well as low-dose clopidogrel or aspirin. (Strong; Low)

Rationale: Patients with diabetes, PAD and ulceration have an overall 5-year mortality of around 50% due to the markedly increased risk of cardiovascular events ⁷⁰. In line with other guidelines ^{26 25}, we recommend prompt and thorough management of other cardiovascular risk factors in patients with diabetes and PAD.

Patients should receive support to stop smoking and should maintain their blood pressure and blood glucose according to hypertension and diabetes guidelines recommendations. In addition, all patients should be prescribed a statin and anti-platelet therapy. This strategy has been shown to reduce the 5-year mortality in patients with neuro-ischaemic ulcers ⁷¹. There is no specific evidence supporting the most appropriate anti-platelet agent in patients with diabetes, PAD and ulceration, however a number of recent guidelines have favoured clopidogrel over aspirin in the management of patients with PAD ²⁶. A sub-analysis of a recent trial of anti-platelets and anti-coagulation suggested that the combination of aspirin and the direct oral anticoagulant rivaroxaban was more effective at reducing major limb events when compared to aspirin alone in patients with PAD, however this strategy was at the expense of an increase in (non-fatal) bleeding events ⁷². Although 45% had diabetes, no information was provided about the presence of a foot ulcer and the outcomes of these patients were not reported separately. It should be noted that we did not address the effect of lipid lowering therapies, blood glucose lowering medication or anticoagulant therapies on wound healing and amputation, as we felt that the evidence in these areas is still too limited.



FUTURE RESEARCH PRIORITIES

Our systematic reviews have demonstrated that there is a paucity of contemporary high-quality data concerning the specific sub group of patients with diabetes, ulceration and PAD.⁷³ Further research is required in order to address the issues surrounding the appropriate management, including diagnosis, prognosis and deciding whether, when and how to revascularise. The IWGDF and EWMA published in 2016 the core details required in the planning and reporting of intervention studies in the prevention and management of diabetic foot ulcers, including those with PAD¹⁶. These guidelines can serve as a roadmap to increase the quality of studies published in this area.

In addition, there are a number of other key areas of interest that deserve further attention:

- What is the natural history of the diabetic foot ulcer with PAD with optimal conservative treatment?
- What is the optimal combination of diagnostic tests to predict healing in patient with a diabetic foot ulcer and PAD
- What is the role of novel methods of perfusion assessment (including the microcirculation) to inform the decision to revascularise patients with diabetic foot ulceration and PAD?
- Is there any role for pre-emptive revascularisation in patients with diabetes with intact feet who are at high risk for ulceration / amputation?
- Is angiosome-directed revascularisation more effective than a best vessel approach in patients with diabetic foot ulceration?
- Is venous arterialisation effective in healing ulcers or preventing amputation in people who are not appropriate for standard revascularisation?
- Are novel medical therapies including stem cells or peripheral blood mononuclear cells effective in healing patients with DFU and PAD where standard revascularisation is inappropriate?



ACKNOWLEDGEMENTS

The authors would like to thank the following external expert reviewers for their review of our PICO and guideline for clinical relevance: Stephan Morbach (Germany), Heidi Corcoran (Hongkong), Vilma Urbančič (Slovenia), Rica Tanaka (Japan), Florian Dick (Switzerland), Taha Wassila (Egypt), Abdul Basit Pakistan), Yamile Jubiz (Colombia), Sriram Narayanan (Singapore), Eduardo Alvarez (Cuba).

CONFLICT OF INTEREST STATEMENTS

Production of the 2019 IWGDF Guidelines was supported by unrestricted grants from: Molnlycke Healthcare, Acelity, ConvaTec, Uro Medical, Edixomed, Klaveness, Reaplix, Podartis, Aurealis, SoftOx, Woundcare Circle, and Essity. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines, and have not seen any guideline or guideline-related document before publication.

All individual conflict of interest statement of authors of this guideline can be found at: www.iwgdfguidelines.org/about-iwgdf-guidelines/biographies.

VERSION

Please note that this guideline has been fully refereed and reviewed, but has not yet been through the copyediting, typesetting, pagination and proofreading process. Thus, it should not be considered the Version of Record. This guideline might still contain errors or otherwise deviate from the later published final version. Once the final version of the manuscript is published online, this current version will be replaced.



REFERENCES

- (1) Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med*. 2017;49(2):106-116. doi:10.1080/07853890.2016.1231932.
- (2) Narres M, Kvitkina T, Claessen H, Droste S, Schuster B, Morbach S, Rümenapf G, Van Acker K, Icks A. Incidence of lower extremity amputations in the diabetic compared with the non-diabetic population: A systematic review. Grabowski A, ed. *PLoS ONE*. 2017;12(8):e0182081. doi:10.1371/journal.pone.0182081.
- (3) Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggese A, Bakker K, Edmonds M, Holstein P, Jirkovska A, Mauricio D, Ragnarson-Tennvall G, Reike H, Spraul M, Uccioli L, Urbancic V, Van Acker K, Van Baal J, Van Merode F, Schaper N. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25. doi:10.1007/s00125-006-0491-1.
- (4) Morbach S, Furchert H, Groeblichhoff U, Hoffmeier H, Kersten K, Klauke G-T, Klemp U, Roden T, Icks A, Haastert B, Ruemenapf G, Abbas ZG, Bharara M, Armstrong DG. Long-Term Prognosis of Diabetic Foot Patients and Their Limbs. *Dia Care*. 2012;35(10):2021-2027. doi:10.2337/dc12-0200.
- (5) Rigato M, Pizzol D, Tiago A, Putoto G, Avogaro A, Fadini GP. Characteristics, prevalence, and outcomes of diabetic foot ulcers in Africa. A systemic review and meta-analysis. *Diabetes Research and Clinical Practice*. 2018;142:63-73. doi:10.1016/j.diabres.2018.05.016.
- (6) Younis BB, Shahid A, Arshad R, Khurshid S, Ahmad M, Yousaf H. Frequency of foot ulcers in people with type 2 diabetes, presenting to specialist diabetes clinic at a Tertiary Care Hospital, Lahore, Pakistan. *BMC Endocr Disord*. 2018;18(1):53. doi:10.1186/s12902-018-0282-y.
- (7) Dolan NC, Liu K, Criqui MH, Greenland P, Guralnik JM, Chan C, Schneider JR, Mandapat AL, Martin G, McDermott MM. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Dia Care*. 2002;25(1):113-120.
- (8) Boyko EJ, Ahroni JH, Davignon D, Stensel V, Prigeon RL, Smith DG. Diagnostic utility of the history and physical examination for peripheral vascular disease among patients with diabetes mellitus. *Journal of Clinical Epidemiology*. 1997;50(6):659-668. doi:10.1016/S0895-4356(97)00005-X.
- (9) Edmonds ME, Morrison N, Laws JW, Watkins PJ. Medial Arterial Calcification and Diabetic Neuropathy. *BMJ*. 1982;284(6320):928-930.
- (10) Elgzyri T, Larsson J, Thörne J, Eriksson K-F, Apelqvist J. Outcome of ischemic foot ulcer in diabetic patients who had no invasive vascular intervention. *Eur J Vasc Endovasc Surg*. 2013;46(1):110-117. doi:10.1016/j.ejvs.2013.04.013.
- (11) Spreen MI, Gremmels H, Teraa M, Sprengers RW, Verhaar MC, van Eps RGS, de Vries J-PPM, Mali WPTM, van Overhagen H, Grp PS, Grp JS. Diabetes Is Associated With Decreased Limb Survival in Patients With Critical Limb Ischemia: Pooled Data From Two Randomized Controlled Trials. *Dia Care*. 2016;39(11):2058-2064. doi:10.2337/dc16-0850.
- (12) Richter L, Freisinger E, Lueders F, Gebauer K, Meyborg M, Malyar NM. Impact of diabetes type on treatment and outcome of patients with peripheral artery disease. *Diab Vasc Dis Res*. 2018;15(6):504-510. doi:10.1177/1479164118793986.
- (13) Blinc A, Kozak M, Šabovič M, Božič Mijovski M, Stegnar M, Poredoš P, Kravos A, Barbič-Žagar B, Stare J, Pohar Perme M. Survival and event-free survival of patients with peripheral artery disease undergoing prevention of cardiovascular disease. *Int Angiol*. 2017;36(3):216-227. doi:10.23736/S0392-9590.16.03731-7.
- (14) Lipsky BA, Senneville E, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil J, et al. IWGDF Guideline on the Diagnosis and Treatment of Foot Infection in People with Diabetes. *Diab Metab Res Rev*, in press
- (15) Junrungsee S, Kosachunhanun N, Wongthanee A, Rerkasem K. History of foot ulcers increases mortality among patients with diabetes in Northern Thailand. *Diabet Med*. 2011;28(5):608-611. doi:10.1111/j.1464-5491.2011.03262.x.
- (16) Jeffcoate WJ, Bus SA, Game FL, Hinchliffe RJ, Price PE, Schaper NC, International Working Group on the Diabetic Foot and the European Wound Management Association. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol*. 2016;4(9):781-788. doi:10.1016/S2213-8587(16)30012-2.
- (17) Hinchliffe RJ, Brownrigg JRW, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, Reekers J, Shearman CP, Zierler RE, Schaper



- NC, International Working Group on the Diabetic Foot (IWGDF). IWGDF guidance on the diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes. *Diabetes Metab Res Rev*. 2015;32 Suppl 1:n/a–n/a. doi:10.1002/dmrr.2698.
- (18) Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH, Schunemann HJ, GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ : British Medical Journal*. 2016;353:i2089. doi:10.1136/bmj.i2089.
 - (19) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.
 - (20) Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. *Diab Metab Res Rev*, in press
 - (21) Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diab Metab Res Rev*, in press
 - (22) Hinchliffe RJ, Forsythe RO, Apelqvist J, Boyko EJ, Fitridge R, Hong JP, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diab Metab Res Rev*, in press.
 - (23) Bus SA, Van Netten JJ, Apelqvist J, Hinchliffe RJ, Lipsky BA, Schaper NC. Development and methodology of the 2019 IWGDF Guidelines. *Diabetes Metab Res Rev*.
 - (24) Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, Driver VR, Frykberg R, Carman TL, Marston W, Mills JL Sr., Murad MH. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *YMVA*. 2016;63(2):3S–21S. doi:10.1016/j.jvs.2015.10.003.
 - (25) Hart T, Milner R, Cifu A. Management of a Diabetic Foot. *JAMA*. 2017;318(14):1387-1388. doi:10.1001/jama.2017.11700.
 - (26) National Institute for Health, Excellence C. *NICE Guidelines [CG119] Diabetic Foot Problems*. 2011.
 - (27) McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia - A critical review. *Arch Intern Med*. 1998;158(12):1357-1364.
 - (28) Soares MM, Boyko EJ, Ribeiro J, Ribeiro I, Ribeiro MD. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28(7):574-600. doi:10.1002/dmrr.2319.
 - (29) Norgren L, Hiatt WR, Dormandy JA. Inter-society consensus for the management of peripheral artery disease (TASC II). *European Journal of Vascular and Endovascular Surgery*. 2007;33(1):S1-S75.
 - (30) Rayman G, Hassan A, Tooke JE. Blood-Flow in the Skin of the Foot Related to Posture in Diabetes-Mellitus. *BMJ*. 1986;292(6513):87-90.
 - (31) Collins TC, Suarez-Almazor M, Peterson NJ. An absent pulse is not sensitive for the early detection of peripheral artery disease. *Fam Med*. 2006;38(1):38-42.
 - (32) Andros G, Harris RW, Dulawa LB, Oblath RW, Sallescunha SX. The Need for Arteriography in Diabetic-Patients with Gangrene and Palpable Foot Pulses. *Arch Surg*. 1984;119(11):1260-1263.
 - (33) Chantelau E, Lee KM, Jungblut R. Association of Below-Knee Atherosclerosis to Medial Arterial Calcification in Diabetes-Mellitus. *Diabetes Research and Clinical Practice*. 1995;29(3):169-172.
 - (34) Randhawa MS, Reed GW, Grafmiller K, Gornik HL, Shishehbor MH. Prevalence of Tibial Artery and Pedal Arch Patency by Angiography in Patients With Critical Limb Ischemia and Noncompressible Ankle Brachial Index. *Circulation: Cardiovascular Interventions*. 2017;10(5). doi:10.1161/CIRCINTERVENTIONS.116.004605.
 - (35) Wukich DK, Shen W, Raspovic KM, Suder NC, Baril DT, Avgerinos E. Noninvasive Arterial Testing in Patients With Diabetes: A Guide for Foot and Ankle Surgeons. *Foot Ankle Int*. 2015;36(12):1391-1399. doi:10.1177/1071100715593888.
 - (36) Vriens B, D'Abate F, Ozdemir BA, Fenner C, Maynard W, Budge J, Carradice D, Hinchliffe RJ. Clinical examination



- and non-invasive screening tests in the diagnosis of peripheral artery disease in people with diabetes-related foot ulceration. *Diabet Med*. 2018;35(7):895-902. doi:10.1111/dme.13634.
- (37) Tehan PE, Barwick AL, Sebastian M, Chuter VH. Diagnostic accuracy of resting systolic toe pressure for diagnosis of peripheral artery disease in people with and without diabetes: a cross-sectional retrospective case-control study. *J Foot Ankle Res*. 2017;10(1). doi:10.1186/s13047-017-0236-z.
 - (38) Barshes NR, Flores E, Belkin M, Kougas P, Armstrong DG, Mills JLS. The accuracy and cost-effectiveness of strategies used to identify peripheral artery disease among patients with diabetic foot ulcers. *YMVA*. 2016;64(6):1682-. doi:10.1016/j.jvs.2016.04.056.
 - (39) Bunte MC, Jacob J, Nudelman B, Shishehbor MH. Validation of the relationship between ankle-brachial and toe-brachial indices and infragenicular arterial patency in critical limb ischemia. *Vasc Med*. 2015;20(1):23-29. doi:10.1177/1358863X14565372.
 - (40) Wang Z, Hasan R, Firwana B, Elraiyah T, Tsapas A, Prokop L, Mills JLS, Murad MH. A systematic review and meta-analysis of tests to predict wound healing in diabetic foot. *YMVA*. 2016;63(2):29S-U99. doi:10.1016/j.jvs.2015.10.004.
 - (41) Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. *Dia Care*. 2007;30(3):660-663. doi:10.2337/dc06-2043.
 - (42) Schreuder SM, Nieuwdorp M, Koelemay MJW, Bipat S, Reekers JA. Testing the sympathetic nervous system of the foot has a high predictive value for early amputation in patients with diabetes with a neuroischemic ulcer. *BMJ Open Diabetes Res Care*. 2018;6(1):e000592. doi:10.1136/bmjdr-2018-000592.
 - (43) Elgzyri T, Larsson J, Nyberg P, Thörne J, Eriksson K-F, Apelqvist J. Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. *Eur J Vasc Endovasc Surg*. 2014;48(4):440-446. doi:10.1016/j.ejvs.2014.06.041.
 - (44) Noronen K, Saarinen E, Alback A, Venermo M. Analysis of the Elective Treatment Process for Critical Limb Ischaemia with Tissue Loss: Diabetic Patients Require Rapid Revascularisation. *European Journal of Vascular and Endovascular Surgery*. 2017;53(2):206-213. doi:10.1016/j.ejvs.2016.10.023.
 - (45) Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Dia Care*. 2003;26(6):1879-1882. doi:10.2337/diacare.26.6.1879.
 - (46) Gershater MA, Londahl M, Nyberg P, Larsson J, Thörne J, Eneroth M, Apelqvist J. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia*. 2009;52(3):398-407. doi:10.1007/s00125-008-1226-2.
 - (47) Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate WJ, Mills JL, Morbach S, et al. IWGDF Guideline on the classification of diabetic foot ulcers. *Diab Metab Res Rev*, in press.
 - (48) Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G, Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI). *Journal of Vascular Surgery*. 2014;59(1):220-34.e1-2. doi:10.1016/j.jvs.2013.08.003.
 - (49) Alliance STSALS. <https://diabeticfootonline.com/2015/09/15/download-the-wifi-threatened-limb-score-theres-an-app-for-that/>.
 - (50) Schaper NC, Andros G, Apelqvist J, Bakker K, Lammer J, Lepäntalo M, Mills JL, Reekers J, Shearman CP, Zierler RE, Hinchliffe RJ. Diagnosis and treatment of peripheral artery disease in diabetic patients with a foot ulcer. A progress report of the International Working Group on the Diabetic Foot. Schaper N, Houtum WV, Boulton A, eds. *Diabetes Metab Res Rev*. 2012;28 Suppl 1(S1):218-224. doi:10.1002/dmrr.2255.
 - (51) Boyko EJ, Ahroni JH, Stensel VL, Smith DG, Davignon DR, Pecoraro RE. Predictors of transcutaneous oxygen tension in the lower limbs of diabetic subjects. *Diabet Med*. 1996;13(6):549-554. doi:10.1002/(SICI)1096-9136(199606)13:6<549::AID-DIA126>3.0.CO;2-R.
 - (52) Pinzur MS, Stuck R, Sage R, Osterman H. Transcutaneous Oxygen-Tension in the Dysvascular Foot with Infection. *Foot Ankle*. 1993;14(5):254-256.
 - (53) Lehrman ED, Plotnik AN, Hope T, Saloner D. Ferumoxytol-enhanced MRI in the peripheral vasculature. *Clin Radiol*.



- 2019;74(1):37-50. doi:10.1016/j.crad.2018.02.021.
- (54) Lepántalo M, Mätzke S. Outcome of unreconstructed chronic critical leg ischaemia. *European Journal of Vascular and Endovascular Surgery*. 1996;11(2):153-157. doi:10.1016/S1078-5884(96)80044-X.
 - (55) Stimpson AL, Dilaver N, Bosanquet DC, Ambler GK, Twine CP. Angiosome Specific Revascularisation: Does the Evidence Support It? *Eur J Vasc Endovasc Surg*. August 2018. doi:10.1016/j.ejvs.2018.07.027.
 - (56) Jongsma H, Bekken JA, Akkersdijk GP, Hoeks SE, Verhagen HJ, Fioole B. Angiosome-directed revascularization in patients with critical limb ischemia. *J Vasc Surg*. 2017;65(4):1208-1219.e1. doi:10.1016/j.jvs.2016.10.100.
 - (57) Lo ZJ, Lin Z, Pua U, Quek LHH, Tan BP, Punamiya S, Tan GWL, Narayanan S, Chandrasekar S. Diabetic Foot Limb Salvage-A Series of 809 Attempts and Predictors for Endovascular Limb Salvage Failure. *Annals of Vascular Surgery*. 2018;49:9-16. doi:10.1016/j.avsg.2018.01.061.
 - (58) Khor BYC, Price P. The comparative efficacy of angiosome-directed and indirect revascularisation strategies to aid healing of chronic foot wounds in patients with co-morbid diabetes mellitus and critical limb ischaemia: a literature review. *J Foot Ankle Res*. 2017;10(1). doi:10.1186/s13047-017-0206-5.
 - (59) Alexandrescu V, Hubermont G. The challenging topic of diabetic foot revascularization: does the angiosome-guided angioplasty may improve outcome. *J Cardiovasc Surg (Torino)*. 2012;53(1):3-12.
 - (60) Lejay A, Georg Y, Tartaglia E, Gaertner S, Geny B, Thaveau F, Chakfe N. Long-Term Outcomes of Direct and Indirect Below-The-Knee Open Revascularization Based on the Angiosome Concept in Diabetic Patients with Critical Limb Ischemia. *Annals of Vascular Surgery*. 2014;28(4):983-989. doi:10.1016/j.avsg.2013.08.026.
 - (61) Caselli A, Latini V, Lapenna A, Di Carlo S, Pirozzi F, Benvenuto A, Uccioli L. Transcutaneous oxygen tension monitoring after successful revascularization in diabetic patients with ischaemic foot ulcers. *Diabet Med*. 2005;22(4):460-465. doi:10.1111/j.1464-5491.2004.01446.x.
 - (62) Meecham L, Patel S, Bate GR, Bradbury AW. Editor's Choice - A Comparison of Clinical Outcomes Between Primary Bypass and Secondary Bypass After Failed Plain Balloon Angioplasty in the Bypass versus Angioplasty for Severe Ischaemia of the Limb (BASIL) Trial. *European Journal of Vascular and Endovascular Surgery*. 2018;55(5):666-671. doi:10.1016/j.ejvs.2018.02.015.
 - (63) Bradbury AW, Ruckley CV, Fowkes F, Forbes JF. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005. doi:10.1016/S0140-6736(05).
 - (64) Schaper NC, Van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA. IWGDF Practical Guidelines on the prevention and management of diabetic foot disease. *Diab Metab Res Rev*, in press.
 - (65) Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, Jirkovska A, Piaggese A, Ragnarson-Tennvall G, Reike H, Spraul M, Acker K, Baal J, Merode F, Ferreira I, Huijberts M. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral artery disease. The EURODIALE Study. *Diabetologia*. 2008;51(5):747-755. doi:10.1007/s00125-008-0940-0.
 - (66) Fisher TK, Scimeca CL, Bharara M, Mills JLS, Armstrong DG. A Stepwise Approach for Surgical Management of Diabetic Foot Infections. *Journal of the American Podiatric Medical Association*. 2010;100(5):401-405. doi:10.7547/1000401.
 - (67) Dunning T. Integrating palliative care with usual care of diabetic foot wounds. *Diabetes Metab Res Rev*. 2016;32 Suppl 1(3):303-310. doi:10.1002/dmrr.2758.
 - (68) Schreve MA, Vos CG, Vahl AC, de Vries JPPM, Kum S, de Borst GJ, Ünlü Ç. Venous Arterialisation for Salvage of Critically Ischaemic Limbs: A Systematic Review and Meta-Analysis. *European Journal of Vascular and Endovascular Surgery*. 2017;53(3):387-402. doi:10.1016/j.ejvs.2016.11.007.
 - (69) Moran PS, Teljeur C, Harrington P, Ryan M. A systematic review of intermittent pneumatic compression for critical limb ischaemia. *Vasc Med*. 2015;20(1):41-50. doi:10.1177/1358863X14552096.
 - (70) Hinchliffe RJ, Brownrigg JRW, Andros G, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, Reekers J, Shearman CP, Zierler RE, Schaper NC, International Working Group on the Diabetic Foot (IWGDF). Effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. *Diabetes Metab Res Rev*. 2015;32 Suppl 1:n/a-n/a. doi:10.1002/dmrr.2705.
 - (71) Young MJ, McCardle JE, Randall LE, Barclay JL. Improved survival of diabetic foot ulcer patients 1995-2008: possible



- impact of aggressive cardiovascular risk management. *Dia Care*. 2008;31(11):2143-2147. doi:10.2337/dc08-1242.
- (72) Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Aboyans V, Alings M, Kakkar AK, Keltai K, Maggioni AP, Lewis BS, Stoerk S, Zhu J, Lopez-Jaramillo P, O'Donnell M, Commerford PJ, Vinereanu D, Pogosova N, Ryden L, Fox KAA, Bhatt DL, Misselwitz F, Varigos JD, Vanassche T, Avezum AA, Chen E, Branch K, Leong DP, Bangdiwala SI, Hart RG, Yusuf S, Investigators C. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2018;391(10117):219-229. doi:10.1016/S0140-6736(17)32409-1.
- (73) Ali SR, Ozdemir BA, Hinchliffe RJ. Critical Appraisal of the Quality of Evidence Addressing the Diagnosis, Prognosis, and Management of Peripheral Artery Disease in Patients With Diabetic Foot Ulceration. *Eur J Vasc Endovasc Surg*. 2018;56(3):401-408. doi:10.1016/j.ejvs.2018.05.009.
- (74) Schaper NC, Kitslaar P. Peripheral vascular disease in diabetes mellitus, Chapter 84, 1515-1527. In: *International Textbook of Diabetes Mellitus*, Editors DeFronzo, Ferannini, Zimmet and Keen, John Wiley and Sons, 2004.