The intersocietal IWGDF, ESVS, SVS guidelines on peripheral artery disease in people with diabetes mellitus and a foot ulcer.

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Abstract:

Diabetes-related foot complications have become a major cause of morbidity and are implicated in most major and minor amputations globally. Approximately 50% of people with diabetes and a foot ulcer have peripheral artery disease (PAD) and the presence of PAD significantly elevates the risk of adverse limb and cardiovascular events.

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the management and prevention of diabetes-related foot complications since 1999. This guideline is an update of the 2019 IWGDF guideline on the diagnosis, prognosis and management of peripheral artery disease in people with diabetes mellitus and a foot ulcer. For this updated Guideline the IWGDF, the European Society for Vascular Surgery and the Society for Vascular Surgery decided to collaborate to develop a consistent suite of recommendations relevant to clinicians in all countries.

This guideline is based on three new systematic reviews. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework clinically relevant questions were formulated, and the literature was systematically reviewed. After assessing the certainty of the evidence, recommendations were formulated which were weighed against the balance of benefits and harms, patient values, feasibility, acceptability, equity, resources required, and when available, costs.

Through this process five recommendations were developed for diagnosing PAD in a person with diabetes, with and without a foot ulcer or gangrene. Five recommendations were developed for prognosis relating to estimating likelihood of healing and amputation outcomes in a person with diabetes and a foot ulcer or gangrene. Fifteen recommendations were developed related to PAD treatment encompassing prioritisation of people for revascularisation, the choice of a procedure and post-surgical care. In addition, the Writing Committee has highlighted key research questions where current evidence is lacking.

The Writing Committee believes that following these recommendations will help healthcare professionals to provide better care and will reduce the burden of diabetes-related foot complications.

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Keywords Peripheral artery disease; chronic-limb threatening ischaemia; critical limb ischemia; diabetes mellitus; diabetes-related foot ulcer; endovascular intervention; bypass surgery; practice guideline

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ABBREVIATIONS

ABI	Ankle-brachial index
ADA	American Diabetes Association
AP	Ankle pressure
CDUS	Colour Duplex ultrasound
CLTI	Chronic limb-threatening ischaemia
CTA	Computed tomography angiography
CWD	Continuous-wave Doppler
DFU	Diabetes-related foot ulcer
DSA	Digital subtraction angiography
EASD	European Association for the Study of Diabetes
ESVS	European Society for Vascular Surgery
HbA1c	Haemoglobin A1c
IWGDF	International Working Group on the Diabetic Foot
LDL	Low density lipoproteins
MAC	Medial arterial calcification
MRA	Magnetic resonance angiography
PAD	Peripheral artery disease
PECO	Population, Exposure, Comparison, Outcome
PICO	Population, Intervention, Comparison, Outcome
SPP	Skin perfusion pressure
SVS	Society for Vascular Surgery
TBI	Toe-brachial index
$TcPO_2$	Transcutaneous oxygen pressure
TP	Toe pressure
WIfI	Wound/Ischaemia/foot Infection

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LIST OF RECOMMENDATIONS

DIAGNOSIS

Recommendation 1

In a person with diabetes without a foot ulcer, take a relevant history for peripheral artery disease, examine the foot for signs of ischaemia and palpate the foot pulses at least annually, or with any change in clinical status of the feet. (Strong, low)

Recommendation 2

In a person with diabetes without a foot ulcer, if peripheral artery disease (PAD) is suspected, consider performing pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI). No single modality has been shown to be optimal for diagnosis of PAD and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥0.70; and triphasic or biphasic pedal Doppler waveforms. (Conditional, low)

Recommendation 3

In a person with diabetes with a foot ulcer or gangrene, take a relevant history for peripheral artery disease, examine the person for signs of ischaemia and palpate the foot pulses. (Strong, low)

Recommendation 4

In a person with diabetes with a foot ulcer or gangrene, evaluate pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI) measurements to identify the presence of peripheral artery disease (PAD).

No single modality has been shown to be optimal for diagnosis of PAD, and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥0.70; and triphasic or biphasic pedal Doppler waveforms. (Strong, low)

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Recommendation 5 - Best Practice Statement

In a person with diabetes without a foot ulcer in whom a non-emergent invasive foot procedure is being considered, peripheral artery disease should be excluded by performing assessment of pedal Doppler waveforms in combination with ankle-brachial index and toe-brachial index.

PROGNOSIS

Recommendation 6

In a person with diabetes and a foot ulcer, or gangrene, consider performing ankle pressures and ankle-brachial index (ABI) measurements to assist in assessment of likelihood of healing and amputation.

Ankle pressure and ABI are weak predictors of healing. A low ankle pressure (e.g. < 50 mmHg) or ABI (e.g. < 0.5) may be associated with higher likelihood of impaired healing and higher likelihood of major amputation. (Conditional, low)

Recommendation 7

In a person with diabetes and a foot ulcer or gangrene consider performing a toe pressure measurement to assess likelihood of healing and amputation.

A toe pressure ≥30 mmHg increases the pre-test probability of healing by up to 30% and a value < 30mmHg increases the pre-test probability of major amputation by approximately 20%. (Conditional, low)

Recommendation 8

In a person with diabetes and a foot ulcer or gangrene, if toe pressure cannot be performed, consider performing a transcutaneous oxygen pressure ($TcPO_2$) measurement or a skin perfusion pressure (SPP) to assess likelihood of healing.

A $TcPO_2$ ≥25 mmHg increases the pre-test probability of healing by up to 45% and value < 25 mmHg increases the pre-test probability of major amputation by approximately 20%. An SPP ≥40mmHg, increases the pre-test probability of healing by up to 30%. (Conditional, low)

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Recommendation 9

In a person with diabetes and a foot ulcer or gangrene we suggest the presence of peripheral artery disease and other causes of poor healing should always be assessed. Diabetes-related microangiopathy should not be considered the primary cause of foot ulceration, gangrene or poor wound healing without excluding other causes. (Conditional, low)

Recommendation 10

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, consider using the Wound/Ischaemia/foot Infection (WIfI) classification system to estimate healing likelihood and amputation risk. (Conditional, low)

TREATMENT

Recommendation 11 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who is being considered for revascularisation, evaluate the entire lower extremity arterial circulation (from aorta to foot) with detailed visualization of below-the knee and pedal arteries. Modalities that can be used to obtain anatomical information include: arterial colour duplex ultrasound, computed tomographic angiography, magnetic resonance angiography, or intra-arterial digital subtraction angiography (including anteroposterior and lateral views of the foot).

Recommendation 12 - Best Practice Statement

In a person with diabetes, peripheral artery disease, a foot ulcer and clinical findings of ischaemia, a revascularisation procedure should be considered. Findings of ischaemia include absent pulses, monophasic or absent pedal Doppler waveforms, ankle pressure <100 mm Hg or toe pressure <60 mm Hg. Consult a vascular specialist unless major amputation is considered medically urgent.

Recommendation 13 - Best Practice Statement

In a person with diabetes, peripheral artery disease, a foot ulcer, and severe ischaemia i.e., an ankle-brachial index <0.4, ankle pressure <50mmHg, toe pressure <30mmHg or transcutaneous oxygen

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pressure <30mmHg or monophasic or absent pedal Doppler waveforms, urgently consult a vascular specialist regarding possible revascularisation.

Recommendation 14 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer with infection or gangrene involving any portion of the foot, urgently consult a vascular specialist in order to determine the timing of a drainage procedure and a revascularisation procedure.

Recommendation 15 - Best Practice Statement

In a person with diabetes and a foot ulcer, when the wound deteriorates or fails to significantly improve (e.g. a less than 50% reduction in wound area within 4 weeks) despite appropriate infection and glucose control, wound care, and offloading, conduct further assessment of the vascular status and consult with a vascular specialist regarding possible revascularisation.

Recommendation 16 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, avoid revascularisation when the risk–benefit ratio for the probability of success of the intervention is unfavourable.

Recommendation 17

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who has an adequate single segment saphenous vein in whom infrainguinal revascularisation is indicated and who are suitable for either approach, consider bypass in preference to endovascular therapy (Conditional, moderate)

Recommendation 18 - Best Practice Statement

A person with diabetes, peripheral artery disease (PAD) and a foot ulcer or gangrene, should be treated in centres with expertise in, or rapid access to, endovascular and surgical bypass revascularisation. In this setting, consider making treatment decisions based on the risk to and

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preference of the individual, limb threat severity, anatomic distribution of PAD, and the availability of autogenous vein.

Recommendation 19 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, revascularisation procedures should aim to restore in-line blood flow to at least one of the foot arteries.

Recommendation 20

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene undergoing an endovascular procedure, consider targeting the artery on angiography that supplies the anatomical region of the ulcer, when possible or practical. (Conditional, very low)

Recommendation 21 - Best Practice Statement

In a person with diabetes and either a foot ulcer or gangrene who has undergone revascularisation, objectively assess adequacy of perfusion e.g. using non-invasive bedside testing.

Recommendation 22 - Best Practice Statement

A person with diabetes, peripheral artery disease and either a foot ulcer or gangrene should be treated by a multidisciplinary team as part of a comprehensive care plan.

Recommendation 23 - Best Practice Statement

In a person with diabetes and peripheral artery disease the following target levels should be :

- HbA1c < 8% (< 64 mmol/mol), but higher target HbA1c value can be necessary depending on the risk of severe hypoglycaemia.
- Blood pressure < 140/ 90 mmHg but higher target levels can be necessary depending on the risk of orthostatic hypotension and other side-effects.
- Low density lipoprotein target of < 1.8 mmol/l (<70 mg/dl) and reduced by at least 50% of baseline. If high intensity statin therapy (with or without ezetimibe) is tolerated, target levels < 1.4 mmol/l (55 mg/dl) are recommended.

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Recommendation 24 - Best Practice Statement

A person with diabetes and symptomatic peripheral artery disease:

- should be treated with single antiplatelet therapy,
- treatment with clopidogrel may be considered as first choice in preference to aspirin
- combination therapy with aspirin (100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for people without a high bleeding risk.

Recommendation 25 - Best Practice Statement

In a person with type 2 diabetes and peripheral artery disease:

- with an eGFR > 30 ml/min/1.73m2, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit should be considered, irrespective of the blood glucose level.
- SGLT-2 inhibitors should not be started in drug-naïve people with a diabetes-related foot ulcer or gangrene and temporary discontinuation should be considered in people already using these drugs, until the affected foot is healed.

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EXTERNAL EXPERTS, PATIENT REPRESENTATIVES AND REVIEW PROCESS

The review process had several steps, in which six external experts, four patient representatives and guideline reviewers of the International Working Group for the Diabetic Foot (IWGDF), European Society for Vascular Surgery (ESVS) and Society of Vascular Surgery (SVS) were involved. The external experts and patient representatives were from various countries and continents (Singapore, Japan, South Africa, China, Hong Kong, Colombia, Bulgaria, Australia, England, the United States of America). The process started with review of the clinical questions that the Writing Committee proposed to address, which were subsequently adjusted and which formed the basis of the guideline development. The first preliminary version of the guideline was reviewed by the IWGDF, ESVS and members of SVS Document Oversight Committee. The revised text was then reviewed by the external experts and patient representatives, and subsequently a new version was submitted for review to the three organisations. The Writing Committee met for the first time in late 2020 and the first draft of the guideline was sent out for review in December 2022.

METHODOLOGY

This guideline is also part of a set of guidelines (and their supporting systematic reviews) of the IWGDF on the management of diabetes-related foot ulcers, which all used the same GRADE methodology. These guidelines address the other aspects of management and are published separately. The IWGDF editorial board had the task of ensuring that there would not be too much overlap between these documents and that they were consistent with each other. The ESVS and SVS Executive Board agreed with this approach. The methodology used is described in detail in a separate IWGDF document (link here); here a summary is provided (1).

In brief, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was followed (2, 3). GRADE is structured by the development of clinical questions and selection of critical outcomes which are subsequently translated in the PECO (Population, Exposure, Comparison, Outcome) format for the selection of diagnostic and prognostic studies and the PICO (Population, Intervention, Comparison, Outcome) format for the selection of intervention studies. The Writing Committee developed the clinical questions to be investigated after consultation with the external experts and patient representatives. Critically important outcomes for clinical questions were voted upon by the Writing Committee members. Subsequently, the PECOs and PICOs were created and voted on for inclusion by Writing Committee members. The PECOs and PICOs to be included were then reviewed by the external experts, patient representatives and the guideline committee of the societies involved.

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The systematic reviews of the literature to address the clinical questions were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (4).The process of identifying and evaluating the available evidence, with its main conclusions, resulted in three systematic reviews on Diagnosis, on Prognosis and on Management, of Peripheral Arterial Disease in Diabetes Mellitus. These systematic reviews are published separately (insert link here). The population of interest was people with diabetes mellitus (with or without a foot ulcer or gangrene, depending on the clinical question). For the PECOs assessment was any non-invasive bedside test and the comparator an objective imaging study; for the PICOs the interventions were bypass (open) and direct revascularisation and the comparators endovascular and indirect revascularisation respectively. The primary outcomes were wound healing, minor and major amputation and adverse events, limb salvage and wound healing. After the literature search all abstracts and subsequently selected articles were reviewed by two authors, as described in our systematic reviews. We included studies in which at least 80% of participants had diabetes or in which the results of the participants with diabetes were reported separately. All included studies were assessed for quality and risk of bias with the following instruments, depending on the type of study: Quality in Prognosis Studies (QUIPS) , the revised quality appraisal tool for studies of diagnostic reliability (QUADAS-2), ROBINS-I (for assessing risk of bias in non-randomised studies of interventions) , and Newcastle-Ottawa Scale (for non-randomised studies, including observational and cohort studies where details regarding allocation to intervention groups were not provided, and the Cochrane risk of bias 2 tool for randomised-controlled trials (5-10). For each PECO and PICO the quality of evidence was graded for risk of bias, inconsistency, imprecision, publication bias and overall quality. The certainty of the evidence was then rated as “high,” “moderate,” “low” or “very low”.

The GRADE evidence to decision approach was subsequently used for the development of the recommendations during online discussions of our Writing Committee (which were all recorded and available for later review from the Secretary). In developing each recommendation and its strength the following aspects were taken into account: benefits, harms, effect size and certainty; balance of benefits and harms; resource use; acceptability; feasibility; equity. The strength of each recommendation was graded as “Strong” or “Conditional” . All Writing Committee members voted on each recommendation, for a ‘Strong” recommendation at least 75% and for a “Conditional” recommendation at least 60% had to agree. After each recommendation, a rationale is provided for how we determined each recommendation (1, 11).

There were situations where we could not identify sufficient direct evidence supporting the formulation of a recommendation, but performing the actions recommended would very likely result in clear benefit or not performing the test or intervention in marked harm. In these situations, we

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formulated an ungraded Best Practice Statement with a rationale explaining how we came to this statement and we considered GRADE criteria for developing such a statement, as advised in a recent publication of the GRADE group on this topic (12). According to GRADE such recommendations should be formulated as actionable statements when they are deemed necessary for practice and when the desirable effects of an intervention clearly outweigh its undesirable effects. Although in these cases direct evidence is lacking, they should be supported by indirect evidence.

For the clinical question on the use of current medical therapies to reduce cardiovascular risk or lower limb events in people with diabetes and symptomatic peripheral artery disease (PAD) we did not perform a systematic review or develop graded recommendations, as recent high-quality guidelines on these topics already exist (13-20). However, in order to give the reader a complete overview we created a summary of these existing guidelines, where relevant for our clinical question and adapted these to the person with diabetes mellitus and symptomatic PAD. These recommendations were also formulated as Best Practice Statements. We do acknowledge that for certain recommendations high quality evidence exists, as summarised in other guidelines of organisations such as ESVS, SVS and American Diabetes Association, but for others there is only lesser quality evidence. In order not to repeat all these evidence-based guidelines already developed by other relevant organisations we chose to make in this area ungraded Best Practice Statements, with references provided to the relevant guidelines. Finally, the Writing Committee considered topics for future research and voted to focus on 5 key topics which are discussed at the end of the guideline.

The recommendations and corresponding rationales were reviewed by the same international external experts and committees responsible for guideline development of the three aforementioned societies. Further details are provided in the IWGDF guidelines methodology document (1). The background materials we developed, i.e. the three systematic reviews, the relevant evidence tables for each of the systematic reviews as well as the summary of judgements tables that were the basis for formulating each recommendation and Best Practice Statement, can be found in the Supplementary Materials of this article (link here). These systematic reviews provide the evidence for the graded recommendations made in this Guideline.

TARGET POPULATION AND TARGET AUDIENCE

Poorly healing foot ulcers or gangrene in people with diabetes mellitus are frequently caused by several factors acting in concert. The primary target population of this guideline is people with diabetes mellitus with a foot ulcer or gangrene on any portion of the foot (with or without neuropathy) in whom the presence of PAD could have contributed to the development of the ulcer and/or its poor

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healing potential. The secondary target group was people with diabetes mellitus in whom the presence of PAD was considered or needed to be excluded. People with pure venous ulcers, ulcers above the ankle , acute limb ischemia, embolic disease, and non-atherosclerotic chronic vascular conditions of the lower extremity were excluded.

The primary target audience of this guideline are vascular specialists and all other health care professionals who are involved in the diagnosis, management and prevention of diabetes-related foot ulcers and gangrene, who work in primary, secondary and tertiary care.

Once the guidelines are approved, the patient representatives will be approached to discuss which elements of the guideline should be included in the "Information for Patients". This will result in a list of items that should be addressed in this information. Given cultural and language differences , the final text should be produced on a national/local level.

GUIDELINE WRITING GROUP CONFLICT OF INTEREST POLICY

The three organizations participating in these guidelines are committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI) members of the Writing Committee were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the Writing Committee, members were asked to report any COI in writing. In addition, at the beginning of each meeting this question was also asked and if answered yes, the members were asked to submit an updated COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included: ownerships of stocks/ options or bonds of a company; any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the three organisations and these can be found at IWGDFguidelines.org/

No company was involved in the development or review of the guidelines. Nobody else involved in the guideline received any payment or remuneration of any costs.

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DEFINITIONS AND TERMINOLOGY AS USED IN THIS DOCUMENT

The definitions and criteria for diabetes-related foot disease were standardised by the IWGDF and in parallel to this guideline an update is published (21). In addition, in this guideline we used the following terminology:

Bedside testing: any non-invasive test assessing for PAD in the lower limb using a measure of blood flow that could be conducted at the bedside.

Chronic Limb Threatening Ischaemia: a clinical syndrome defined by the presence of peripheral artery disease in combination with rest pain, gangrene or foot ulcer of at least 2 weeks duration. Venous, embolic, non-atherosclerotic and traumatic aetiologies are excluded.

Diabetes-related microangiopathy: pathological structural and functional changes in the microcirculation of people with diabetes mellitus, that can occur in any part of the body as a consequence of the disease.

Diabetes-related foot ulcer: A break of the skin of the foot that involves as a minimum the epidermis and part of the dermis in a person with diabetes and usually accompanied by neuropathy and/or PAD in the lower extremity.

Diabetes-related foot gangrene: A condition that occurs when body tissue dies because of insufficient blood supply, infection or injury.

Foot perfusion: Tissue perfusion strictly means the volume of blood that flows through a unit of tissue and is often expressed in ml blood/100 gm of tissue. With respect to clinical assessment of the foot, perfusion is traditionally measured by the surrogate markers of systolic arterial pressure at the level of the ankle and toe arteries. Pressure measurements may be misleading in people with diabetes due to the frequent presence of medial calcinosis. This has led to the development of a number of alternative, clinically utilized means of assessing tissue perfusion, including $TcPO_2$ (transcutaneous pressure of Oxygen), SPP (skin perfusion pressure), PAT (pedal acceleration time) and near-infrared spectrophotometry (NIRS).

Multidisciplinary team: A grouping of people from relevant clinical disciplines, whose interactions are guided by specific team functions and processes to achieve team- and person-defined favourable outcome.

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Peripheral artery disease (PAD): Obstructive atherosclerotic vascular disease of the arteries from aorta to foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities.

INTRODUCTION

The incidence of diabetes continues to increase in all countries. Recent estimates are that 537 million people are affected by diabetes (1 in 11 adults worldwide) and that 783 million individuals will be affected by 2045 (22). Diabetes is associated with significant risk of foot complications including ulceration, gangrene and amputation. Development of diabetes-related foot ulceration (DFU) precedes up to 85% of non-traumatic amputations with an annual incidence of ulceration of approximately 2% and lifetime incidence of DFU up to 34% (23). Diabetes-related complications in the lower limb including peripheral neuropathy and peripheral artery disease (PAD) typically precede the development of DFU (24). Collectively these complications are a leading global cause of disability, hospitalisation and amputation, with high mortality following amputation (25).

Diabetes is a significant risk factor for the development of PAD. In a recent systematic review, Stoberock et al. (26) found that the prevalence of PAD was 10-26% in the general adult population and 20-28% in those with diabetes . In those with DFU, the prevalence of PAD was 50% which is consistent with the findings of the multicentre Eurodiale study (26, 27). PAD in people with diabetes is characterised by a disease pattern that is frequently multi-segmental and bilateral with impaired collateral formation, often long segment tibial artery occlusions, and is more distally distributed in the lower limb including frequent presentation of infragenicular arterial occlusive disease (28-30), with an increased risk of amputation. The diagnosis of PAD and chronic limb-threatening ischaemia (CLTI) is frequently complicated by the absence of classical symptoms of PAD such as intermittent claudication and rest pain, probably due to factors such as sedentary lifestyle and loss of pain sensation due to, diabetes-related peripheral neuropathy, which is present in the majority of people with an (ischaemic) DFU (27, 29). Co-existent medial artery calcification (MAC), which is also associated with peripheral neuropathy, is common and can affect the accuracy of non-invasive tests such as the ankle-brachial index (ABI) by causing elevation of ankle and, to a lesser extent, digital pressures (31).

In people with diabetes early diagnosis of PAD is essential (26). The disease process is associated with greater likelihood of delayed or non-healing of DFU, gangrene and amputation in addition to elevated rates of cardiovascular morbidity and mortality (32). The prognosis of a person with diabetes, PAD, and foot ulceration requiring amputation is worse than many common cancers—up to 50% of people will not survive 5 years (23, 33). PAD places the person at very high risk of adverse cardiovascular events and thus optimal medical management of cardiovascular risk factors should be ensured (29).

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Early and adequate assessment of foot perfusion is necessary to ensure that the elevated risk of delayed or poor wound healing and amputation are identified early so that they can be addressed without treatment delay.

Despite the severity of the outcomes of PAD in people with diabetes, and particularly for those with DFU, there are few practice guidelines that specifically address the diagnosis and management of PAD in this population. Formulating recommendations for this specific population should take into account the multi-system nature of diabetes and the impact of other diabetes complications on the utility of diagnostic tests, wound healing, amputation and survival outcomes. One of the guidelines that specifically addressed these topics have been those of the IWGDF, with the last version produced in 2019 (34). Instead of making a new updated version, the IWGDF together with the ESVS and the SVS decided to collaborate in writing this new, intersociety, practice guideline on PAD in diabetes mellitus, with emphasis on people with diabetes-related foot ulcers or gangrene. We aim to provide evidence-based recommendations on the diagnosis, prognosis (i.e. the prognostic value of different non-invasive tests), and treatment of PAD in people with a foot ulcer and diabetes. Each of these topics is discussed in the different sections below. It is not our intention to detail the specific roles, tasks and responsibilities of each medical specialty involved as these vary markedly between and within countries and this guideline is a multinational initiative. However, we do emphasize which expertise should be present, in terms of knowledge, skills and competence, in order to manage the people according to the expected standards of care.

Related guidelines

This guideline is also part of the IWGDF Guidelines on the prevention and management of diabetes-related foot disease. Management of PAD in these people without addressing the other aspects of DFU treatment will frequently result in suboptimal outcomes. The reader is therefore referred to the other IWGDF Guidelines for these aspects. This IWGDF, ESVS, SVS Intersocietal guideline on PAD in people with diabetes mellitus is also part of the IWGDF guidelines on the management of diabetes-related foot complications with additional chapters on Classification (ref/link), Prevention (ref/ link), Offloading (ref/ link), Infection (ref/link) Charcot (ref/link)and Wound healing (ref/link). These guidelines are summarised for daily clinical use in the Practical Guidelines on the prevention and management of diabetes-related foot disease (ref/link). This guideline builds upon a previous version of the IWGDF guideline on peripheral artery disease in patients with foot ulcers and diabetes, and integrates with the Global Vascular Guidelines on the management of Chronic Limb-threatening Ischaemia (17, 34)

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DIAGNOSIS

Clinical question

In a person with diabetes with or without a foot ulcer does medical history and clinical examination (including pulse palpation) compared to a reference test (imaging- digital subtraction angiography [DSA], magnetic resonance angiography [MRA], computed tomography angiography [CTA], colour Duplex ultrasound [CDUS]) accurately identify PAD and reliably diagnose PAD?

Clinical question

In a person with diabetes with or without a foot ulcer, which non-invasive bedside testing alone or in combination compared to reference tests (imaging- digital subtraction angiography [DSA], magnetic resonance angiography [MRA], computed tomography angiography [CTA], colour Duplex ultrasound [CDUS]) should be performed to accurately and reliably diagnose PAD?

Recommendation 1

In a person with diabetes without a foot ulcer, take a relevant history for peripheral artery disease, examine the foot for signs of ischaemia and palpate the foot pulses at least annually, or with any change in clinical status of the feet. (Strong, low)

Recommendation 2

In a person with diabetes without a foot ulcer, if peripheral artery disease (PAD) is suspected, consider performing pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI).

No single modality has been shown to be optimal for diagnosis of PAD, and there is no value above which PAD can be excluded. However, PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥0.70; and triphasic or biphasic pedal Doppler waveforms. (Conditional, low)

Rationale:

Diagnosis and treatment of PAD is critical due to the increased risk of developing DFU as well as elevated rate of complications from co-existent cardiovascular disease including myocardial infarction and stroke (32, 35). Evidence for the diagnostic accuracy of pulse palpation for PAD in people with diabetes without DFU is limited with two studies of low quality demonstrating that although presence

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of pulses does not exclude disease , there is a small increase in ability to rule disease in where a foot pulse is absent or weak (positive likelihood ratio [PLR]1.84 to 2.46) (36, 37). (The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the negative likelihood ratio [NLR] expresses a change in odds of experiencing an outcome if the test is negative. A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful diagnostic test). However, it is important to recognise that pulse palpation should therefore be performed, and results considered in the context of other clinical examinations that may be associated with PAD including hair loss, muscle atrophy and reduced peripheral skin temperature. It should be noted that these clinical examinations are highly subjective and such findings may also be associated with neuropathy. PAD may also be asymptomatic or have an atypical presentation in people with diabetes as in other elderly or at-risk populations (24, 38, 39). For example, peripheral neuropathy can mask pain symptoms and autonomic neuropathy can result in a warm foot, meaning that the widely recognised signs and symptoms of PAD may not be present (40).

These recommendations are applicable to all people with diabetes. When DFU is absent, but there are clinical signs and symptoms of PAD or PAD is suspected, for example due to long-standing diabetes, chronic hyperglycaemia, other diabetes complications such as peripheral neuropathy or presence of atherosclerotic disease in other vascular beds, more frequent screening vascular assessment including additional bedside testing is necessary. These recommendations are consistent with other (inter)national guidelines on the management of diabetes, endorsing annual clinical assessment for PAD (and for other foot complications) in people with diabetes (41-44).

Although based on low quality evidence, data demonstrating increased likelihood of PAD in those with weak or absent pulses and elevated risk of cardiovascular morbidity and mortality support the preference of a person with diabetes for clinical examination including pulse palpation to be performed (32, 45). The non-invasive nature of clinical examination and pulse palpation suggest these assessments would be valued by people with diabetes as initial diagnostic tests. As equipment is not required, the Writing Committee considered pulse palpation and other forms of clinical examination have low resource requirements, can be applied on a broad scale by a range of practitioners, and offer a method to increase equity of health care access that is both feasible for health care providers and acceptable for people with diabetes. We therefore made this a strong recommendation based on low certainty of evidence and expert opinion.

Bedside testing techniques that provide objective measurement of peripheral blood flow in the lower extremity (e.g., ankle-brachial index [ABI], toe-brachial index [TBI] and pedal Doppler waveforms) have been shown to be useful as a means to diagnose and exclude PAD in people with diabetes. Our

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systematic review demonstrates that multiple bedside testing techniques that offer objective measurement of the peripheral circulation in the lower limb are useful as a means to rule disease in or out for people with diabetes without a DFU but who are suspected of having PAD (45).

We identified forty studies investigating the diagnostic accuracy of non-invasive bedside tests in populations with diabetes (45). Twenty-five of the studies were prospective, two cross sectional and the remainder retrospective. Overall, the studies were of low quality and evidence was judged as being of low certainty. Although we could not identify the absolute threshold or 'normal' values of bedside tests, we suggest that PAD is a more likely to be present in this population with an ABI <0.9 or >1.3, a TBI <0.70, and presence of one or more monophasic Doppler waveforms from assessment of pedal arteries with continuous wave Doppler (CWD) (45). In people without DFU, an ABI of <0.90 is associated with a moderate to large increase in likelihood of PAD with PLRs ranging from 2.1 to 19.9, however the ability to rule disease out is limited (NLR 0.29 to 0.84). A TBI <0.70 has a moderate ability to diagnose and exclude PAD (PLRs 2.0 to 3.55, NLRs 0.25 to 0.44) and the presence of a visual monophasic pedal Doppler waveform has a moderate ability to diagnose and exclude PAD (PLR 7.09, NLR 0.19). Non-invasive tests are therefore likely to be beneficial for people without a DFU, however high quality studies of diagnostic accuracy are required. A summary of results is provided in Supplementary Table 1.

When calculating the ABI in the leg of a person with and without DFU for the purposes of diagnosing PAD we advise to use the lower systolic blood pressure of either the dorsal pedis or posterior tibial artery as this improves the diagnostic accuracy of the test (45). For PAD affecting arteries below the knee this calculation method identifies the most severe disease while using the higher pressure identifies the least affected artery. We also recommend using the three tests (ABI, TBI and pedal Doppler waveforms). This is due to the fact that the accuracy of the tests may be affected by the presence of other diabetes-related complications.

Due to the use of bedside measures to monitor PAD status over time, reliability (or reproducibility) of the tests is important to determining their clinical effectiveness. Our systematic review showed the reliability of both the ABI and TBI was good to excellent, however these tests are limited by wide margins of error which affect the amount of change required for this to be considered a true change rather than related to error in the measurement. For example, an ABI measured by the same rater requires a change of 0.15 to be considered a true change (46). Therefore, care should be taken in performing the measure to control for factors that may introduce measurement error including incorrect positioning of the person being tested (this should be horizontal supine) and incorrect testing procedures (e.g. pre-test exercise, caffeine consumption etc).

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Our recommendation identifies the need to perform bedside testing in people with diabetes in whom PAD is suspected. In people with diabetes without a DFU, the presence of PAD will increase the risk of a future DFU and amputation, its presence will therefore influence the frequency of screening and the measures that can be safely taken to reduce the risk of amputation, as described in the Prevention Guidelines of the IWGDF (link here). It is therefore critical that apart from the history and foot examination, risk factors for PAD are also considered such as long standing or poorly controlled diabetes or diagnosis of atherosclerosis in other vascular beds Considering the benefits and harms of this recommendation we judge it essential to diagnose or exclude PAD in this population given the large impact of untreated disease, the low burden of the tests to the person undergoing testing and the high likelihood that diagnosis will be valued by them. All aforementioned bedside tests (ABI, TBI, CWD) should be performed by trained health care professionals in a standardized manner and these tests can be applied by a wide range of practitioners, after having received adequate training. From the perspective of middle or high income countries the resources required to undertake bedside testing are relatively low in comparison to other methods of diagnosing PAD such as CDUS, CTA, MRA and angiography. It is likely that many people will value the knowledge that their feet need more intensive care to prevent amputation, but this has not been studied in a sufficiently large cohort. Based on the uncertainty of the evidence we made a conditional recommendation for additional non-invasive testing in this group of people with asymptomatic disease. The role of additional testing in those with intermittent claudication is outside the scope of these guidelines.

Recommendation 3

In a person with diabetes with a foot ulcer or gangrene, take a relevant history for peripheral artery disease, examine the person for signs of ischaemia and palpate the foot pulses. (Strong, low)

Recommendation 4

In a person with diabetes with a foot ulcer or gangrene, evaluate pedal Doppler waveforms in combination with ankle-brachial index (ABI) and toe-brachial index (TBI) measurements to identify the presence of peripheral artery disease (PAD).

No single modality has been shown to be optimal for diagnosis of PAD, and there is no value above which PAD can be excluded. However PAD is less likely in the presence of ABI 0.9-1.3; TBI ≥0.70; and triphasic or biphasic pedal Doppler waveforms. (Strong, low)

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Rationale:

PAD is present in approximately half of the people with a DFU (26, 27). Therefore, in any person with diabetes and a foot ulcer or gangrene, PAD should be considered and should be excluded with the appropriate diagnostic strategies. Subsequently, once diagnosed the second question is whether the PAD is of sufficient severity to contribute to delayed wound healing and increased risk of amputation. This will inform whether further investigation or intervention is required. In addition, although cardiovascular risk factor modification is always indicated in people with diabetes, those with symptomatic PAD (i.e., also those with a DFU) belong to the very high cardiovascular risk category and need more intensive risk treatment, as described in the Treatment Section.

Apart from taking a clinical history, all people with a DFU or gangrene should undergo a complete physical examination, including palpation of the lower limb pulses which can help to determine the likely presence of arterial disease (47). In our systematic review on diagnosis, we identified one study of low quality, that assessed the diagnostic accuracy of pedal pulse assessment in people with a DFU (48). Pulse palpation had a PLR of 1.38 and a NLR 0.75 for PAD in people presenting with a foot ulcer (48). These likelihood ratios represent a very small ability of the test to identify or exclude disease. Pulse palpation should be seen as the first step in a systematic evaluation of the affected limb and foot, but when DFU is present further diagnostic procedures should be performed with non-invasive bedside testing techniques as clinical examination is not sufficient to exclude PAD. Although of limited value it should not be discarded as in the early phase of management other tests are sometimes unavailable, or findings may be difficult to interpret. The evidence base is small with low certainty but as previously discussed this form of testing has low resource requirements, can be applied on a broad scale by a range of practitioners, is feasible and may increase equity of health care access. We therefore made this a strong recommendation based on low certainty of evidence and expert opinion. However, a systematic foot examination for signs of ischaemia should be the starting point of a systematic evaluation, as failure to diagnose and treat this condition may have dire consequences in many people. When DFU is present further diagnostic testing using bedside testing techniques in the first instance should performed as palpation of foot pulses and clinical examination alone are not sufficient to exclude PAD.

Our systematic review identified eight studies (48-55) of diagnostic accuracy of bedside testing that included participants with active DFU, with the proportion of the study population affected ranging from 6.6% to 100% (48, 49). One study demonstrated a visual pedal Doppler waveform evaluation to be diagnostic (PLR≥10), with a moderate ability of the test to exclude PAD. In a second study ~40% of the participants having a foot ulcer, the PLR was lower (3.04) and the NLR similar (0.35) (53). In studies in which the majority of the study population had DFU an ABI <0.90 increased the pre-test probability

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of disease by a small amount (PLR: 1.69 to 2.40) with limited ability of the test to exclude disease (NLR: 0.53 to 0.75) (48, 51, 54, 55). Similarly, data for the TBI were limited and variable with the PLR-in both mixed populations (with and without DFU) and DFU only, ranging from 1.62 (indicating limited ability to diagnose disease) to being diagnostic (PLR ≥10) and indicating the test has small to moderate ability to exclude disease (NLR 0.30 to 0.47) (48, 51, 53, 54).

All aforementioned non-invasive tests (ABI, TBI, CWD) can be applied by a wide range of practitioners, in particular in settings where people are treated in secondary care or specialised outpatient foot clinics. These tests have low resource requirements relative to other methods of diagnosing PAD such as CDUS and angiography. These factors are likely to increase equity in health care access and make the tests feasible and acceptable for both the person having the tests and health care providers. Given the large potential beneficial effect and its impact on subsequent treatment we made a Strong recommendation for this population, although we acknowledge the limitations of the evidence base.

Recommendation 5 - Best Practice Statement

In a person with diabetes without a foot ulcer in whom a non-emergent invasive foot procedure is being considered, peripheral artery disease should be excluded by performing pedal Doppler waveforms in combination with ankle-brachial index and toe-brachial index.

Rationale:

Except when required as an emergency to control severe infection, all people with diabetes who require foot surgery should have vascular testing consisting of pedal Doppler waveforms in combination with ABI and TP or TBI. Non-emergent invasive procedures, such as elective surgery, may be indicated in people with diabetes without a DFU with the intent to address painful foot conditions. Particularly in those with peripheral neuropathy (56), prophylactic procedures could be considered to address risk factors for foot ulceration, such as foot deformity and elevated localised plantar pressures. Prior to any surgical procedure on the foot in a person with diabetes, PAD status should be established and this finding should contribute to determination of suitability of an individual for the procedure. The decision to perform the elective surgery should be made in a shared decision-making process that will be influenced by balancing the benefit of the operation versus the potential harm, such as the risk of poor wound healing based on the non-invasive assessments.

As discussed above bedside testing generally has moderate ability to diagnose PAD or to exclude this disease in people with diabetes mellitus. Any abnormal test result should be considered indicative of

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PAD. Therefore, we suggest this recommendation will reduce the risk of undiagnosed severe PAD which would potentially negatively affecting post-surgical outcomes and it is likely that people will value this approach. Feasibility and the impact of these tests on resource use are discussed in recommendation 4. No randomised controlled trials (due to ethical reasons) or observational studies of sufficient quality have been performed on the added value of performing bedside tests prior to any surgical procedure in the foot. Given the indirect evidence discussed above, the major clinical implications of missing the diagnosis of PAD and the limited harm and additional costs, a "Best Practice Statement" was made.

PROGNOSIS

Clinical question

In a person with diabetes, suspected PAD and a foot ulcer or gangrene, which non-invasive bedside tests, alone or in combination, at any time point (including after revascularisation procedures), predict DFU healing, healing after minor amputation, and major amputation?

Recommendation 6

In a person with diabetes and a foot ulcer, or gangrene, consider performing ankle pressures and ankle-brachial index (ABI) measurements to assist in assessment of likelihood of healing and amputation.

Ankle pressure and ABI are weak predictors of healing. A low ankle pressure (e.g. <50 mmHg) or ABI (e.g. <0.5) may be associated with higher likelihood of impaired healing and higher likelihood of major amputation.(Conditional, low)

Recommendation 7

In a person with diabetes and a foot ulcer or gangrene, consider performing a toe pressure measurement in order to assess likelihood of healing and amputation.

A toe pressure ≥30 mmHg increases the pre-test probability of healing by up to 30% and a value <30mmHg increases the pretest probability of major amputation by approximately 20%. (Conditional, low)

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Recommendation 8

In a person with diabetes and a foot ulcer or gangrene, if toe pressure cannot be performed, consider performing a transcutaneous oxygen pressure ($TcPO_2$) measurement or a skin perfusion pressure (SPP) to assess likelihood of healing.

A $TcPO_2$ ≥25 mmHg increases the pre-test probability of healing by up to 45% and value <25 mmHg has been shown to increase the pre-test probability of major amputation by approximately 20%. An SPP ≥40mmHg increases the pre-test probability of healing by up to 30%. (Conditional, low)

Rationale:

The presence of PAD constitutes a significantly increased risk of failure to heal and major lower limb amputation for people with a diabetes-related foot ulcer or gangrene. Bedside testing results are an integral component of determining the severity of ischaemia and, to that end, to determine the need for, and urgency of, further investigations. Non-invasive bedside tests including AP, ABI and TP should be performed in a person with a DFU or gangrene to guide further management as they can help to predict the chance of healing and/or major amputation. $TcPO_2$ and skin perfusion pressure (SPP) give additional information on healing potential and are useful for measuring perfusion following forefoot amputations when TP are no longer possible. However, in our opinion these are secondary tests due to greater expense and less availability of the equipment and the time and expertise required to apply them.

Assessment of the pedal arterial Doppler waveforms combined with measurement of the AP and subsequent calculation of the ABI, are usually the first steps in the assessment of PAD. Although relevant for its diagnosis, as discussed in the Rationales of Recommendations 1 and 2, we could not identify sufficient data on the capacity for Doppler arterial waveform analysis to predict wound healing in populations with DFU (45). We did identify two studies of low quality that concluded that abnormal or absent Doppler waveforms were associated with a small (15%) increase in the likelihood of major amputation (57, 58), further limiting its use. Similarly there are currently insufficient data to support the use of TBI to predict healing or amputation outcomes, however TP (as a component of TBI) has been more widely investigated and is therefore included in our recommendation.

The predictive capacity of APs and ABI for wound healing was inconsistent in the 15 studies included in our systematic review (45). We could not identify thresholds for AP and ABI which were associated with increased probability of healing, however a very low ankle pressure (e.g. <50 mmHg) or ABI (e.g. < 0.5) was associated with a higher likelihood of delayed healing and according to current guidelines revascularisation should be considered when such values are measured in people with PAD and an

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ulcer or gangrene (17). AP and ABI values above 50 mmHg or above 0.5, should not be used in isolation to predict likelihood of ulcer healing given their uncertainty, but detailed clinical examination and further vascular testing is needed, as stated in recommendation 6. Regarding amputation risk, the probability of major amputation was increased by approximately 45% with an ABI <0.4 based on one study in people who had undergone transmetatarsal amputation however an ABI threshold <0.9 was not associated with any increase (45, 59).Thresholds used for AP were highly variable in the literature and we were unable to determine which threshold was optimal (45). Other research has demonstrated an elevated ABI (>1.3) is associated with both higher likelihood of amputation and worse amputation free survival outcomes and therefore should be recognised as a risk factor for poor DFU outcomes. The same observations were made in people without diabetes and an elevated ABI is therefore seen as a marker for more severe cardiovascular disease with an elevated risk of amputation (60, 61).

TP and TBI can assess blood flow distal to the forefoot and toes, where most DFUs occur (62).Based on ten studies of low quality we found that with TP of ≥30 mmHg the pretest probability of healing was increased by up to 30% (63). Regarding major amputation, a value <30 mmHg increases the probability of major amputation by approximately 20%, which suggests a (somewhat) lower predictive capacity compared to the ABI. In the three studies identified, there was inconsistent and insufficient evidence for the use of the TBI to predict either healing or major amputation.

$TcPO_2$ and SPP are additional tests that have the advantage of measuring perfusion at tissue level and therefore reflect both macrovascular and microvascular function. In our systematic review the majority of available studies (n=7) which were of low quality, reported that $TcPO_2$ can be used to predict the likelihood of DFU healing, (63-72) although there is variability in thresholds used. With a $TcPO_2$ ≥25 mmHg the pretest probability of healing is increased by up to 45%, which was higher than reported for the other tests in the studies we included. Regarding amputation, a value < 25 mmHg increases the probability of major amputation by approximately 20%, a predictive value that seems lower than that of the ABI when we compared the different studies. A SPP (≥40mmHg) was shown to increase the pre-test probability of healing by up to 30% in one study of low quality (73). There are insufficient data investigating the relationship between SPP and amputation outcomes to formulate a recommendation.

In summary, when comparing different studies, the ABI seemed to have the best predictive capacity for major amputation, while the TP and $TcPO_2$ seemed to have a better predictive capacity for wound healing. It was noteworthy that there was insufficient evidence for the use of the TBI to predict either healing or amputation outcomes. The number of prospective studies and the number of participants

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included in the aforementioned studies were relatively small, the populations studied differed and results of the tests performed were frequently not blinded. Moreover, comparison of studies was hampered by the fact that different studies used different thresholds for disease and thus combining data for analysis was not possible.

When bedside testing is not performed the risks of a poor clinical outcome or unnecessary, more costly, investigations are large. As discussed earlier the majority of bedside tests are of low burden to both the person and the health care system although training and expertise are necessary. If these tests are not performed, the clinician has to rely only on clinical judgement and on imaging investigations. Although imaging will provide details of the arterial anatomy, the non-invasive tests will inform the clinician about the perfusion in the foot. However, absolute perfusion thresholds applicable for all people cannot be provided as the outcome of the DFU is not only determined by the degree of ischaemia. Other factors such as infection, extent of tissue loss and ulcer depth, can have a major effect on healing potential and amputation risk, as discussed below. For this reason and the uncertainty of the evidence, we made Conditional recommendations for use of AP, ABI and TP to predict the likelihood of healing and amputation.

$TcPO_2$ and SPP tests require more expensive equipment and greater expertise for application than other bedside testing which may be a barrier for centres in low- or middle-income countries. Although health care expenditures may increase with each of these measurements, incorrect assessment of the severity of PAD can result in inadequate treatment and poorer outcomes with ultimately an increase in costs. Importantly all the aforementioned bedside tests have varying capacity to predict likelihood of healing and of amputation, as summarised in our systematic review(74). Based on current evidence no test has convincingly been shown to perform better than other tests as a prognostic indicator of both healing and amputation. In the opinion of the Writing Committee multiple tests should be used. Given the limited available evidence on $TcPO_2$ and SPP and their higher costs we made a conditional recommendation on these two tests.

Recommendation 9:

In a person with diabetes and a foot ulcer or gangrene we suggest the presence of peripheral artery disease and other causes of poor healing should always be assessed. Diabetes-related microangiopathy should not be considered the primary cause of foot ulceration, gangrene or poor wound healing without excluding other causes. (Conditional, low)

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Rationale:

The definition of microvascular disease in DFU and its role in wound healing are not well understood. Many clinicians have assumed that microvascular disease is present in a high proportion of people with DFU and that it is a major cause of delayed wound healing- often despite a lack of thorough investigation of large vessel arterial disease. As discussed elsewhere in this guideline, people with diabetes and a DFU frequently have distal, lower leg obstructive atherosclerotic disease often with involvement of the pedal arteries, which due to their smaller size can be difficult to image. However, advances in imaging and technology have shown that tibial and pedal arteries are potentially treatable by endovascular and open surgical techniques.

The term "microvascular" disease describes abnormalities affecting the arteriolar, capillary and venular vessels. Several studies have reported microvascular abnormalities in the skin and subcutaneous tissues in people with diabetes. These abnormalities can be structural, i.e. occlusive disease and alterations in the blood vessel wall, and functional, such as impaired vasodilatory responses to endogenous or noxious stimuli (75). However, in our systematic review on this topic we could not identify studies of sufficient quality showing that such abnormalities contribute to impaired wound healing (76). One prospective study did report that microvascular changes observed in skin-biopsies in the feet in people with diabetes and neuro-ischemia were associated with poorer wound healing after revascularisation (77). However, both these microvascular changes and poorer wound healing could be due to tissue damage caused by ischaemia and not by pre-existent diabetes-related microangiopathy.

If perfusion of the foot ulcer is adequate but the ulcer fails to heal, other causes of poor wound healing should be sought and treated, such as infection, insufficient protection from biomechanical stress, oedema, poor glycaemic control, poor nutritional state and underlying co-morbidities (78). Based on the lack of studies showing that diabetes-related micro-angiopathy contributes to poor wound healing in DFU and the potential harm if this is assumed, we made a conditional recommendation based on low certainty of evidence.

Recommendation 10

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, consider using the Wound/Ischaemia/foot Infection (WIfI) classification system to estimate healing likelihood and amputation risk. (Conditional, low)

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Rationale:

The Wound, Ischaemia and Foot infection (WIfI) classification system was developed to guide the clinician in estimating the risk of amputation and potential benefit of revascularisation in people with a foot ulcer or gangrene and is recommended by the Global Vascular Guideline for limb staging (relating to severity of limb threat) in people with chronic limb threatening ischaemia (CLTI) (17). This system was developed by an interdisciplinary panel of experts and stages the limb based on the presence of, and severity of, the foot wound, ischaemia and infection. A Delphi consensus process was used to allocate these combinations into 4 clinical stages based on very low (stage 1), low (stage 2), moderate (stage 3) and high (stage 4) predicted one-year risk of major amputation. Consistent with all other commonly used limb staging systems, co-morbidities of individuals which are likely to influence wound healing and amputation risk are not incorporated into WIfI. A second distinct aspect of the WIfI system is the predicted likelihood of benefit from revascularisation (79).

A recent systematic review concluded that in people undergoing a revascularisation procedure, the likelihood of an amputation after one-year increases with higher WIfI stages. The estimated one-year major amputation rates from four studies comprising 569 participants were 0%, 8% (95% CI 3-21%), 11% (95% CI 6-18%) and 38% (95% CI 21-58%), for WIfI clinical stages 1-4, respectively (80). For the population of people with a DFU, the WIfI system was evaluated in the IWGDF systematic review on classification systems, that is published in parallel to this guideline. In summary, in people with diabetes, PAD and a foot ulcer this systematic review identified seven studies, with low certainty evidence, demonstrating that a high WIfI limb clinical stage is associated with longer time to healing and increased likelihood of non-healing at 6 and 12 months (81-87). Higher WIfI clinical stages are also associated with increased likelihood of major amputations with one study reporting amputation rate of 64% for stage 4 (88). Similarly, higher WIfI clinical stages have been linked to high rates of minor amputation and lower rates of amputation free survival at 12 months (83, 84, 87, 89-94). For prediction of revascularisation benefit there are few data available and inadequate evidence to determine if WIfI revascularisation benefit staging predicts healing or amputation outcomes in people undergoing revascularisation.

The WIfI tool (Table 1) has demonstrated predictive capacity for the key outcomes of wound healing and amputation in people with DFU (83, 84, 87, 89-94). It uses clinical grading of infection and wound characteristics in combination with non-invasive bedside testing to determine severity of ischaemia and it has wide availability, also as an online tool (https://apps.apple.com/us/app/svs-ipg/id1014644425). Moreover, it can be used by a wide range of practitioners making application in clinical practice feasible, its costs are relatively limited, and it is expected to be acceptable to practitioners as well as being of value to people receiving the care. It is likely to stimulate a

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standardised access to a form of vascular assessment, which is also relevant for low-income countries where invasive testing may not be a widely available. Due to the observational and often retrospective nature of most of the current evidence, this recommendation was made conditional.

TREATMENT

Clinical question

In which persons with diabetes, PAD and a foot ulcer or gangrene using clinical findings, perfusion test findings, and/or classification systems, should revascularisation be considered?

Recommendation 11 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who is being considered for revascularisation, evaluate the entire lower extremity arterial circulation (from aorta to foot) with detailed visualization of below-the-knee and pedal arteries. Modalities that can be used to obtain anatomical information include arterial colour duplex ultrasound, computed tomographic angiography, magnetic resonance angiography, or intra-arterial digital subtraction angiography (including anteroposterior and lateral views of the foot).

Rationale:

As per our recommendations 1-4 clinical examination and bedside testing should be the first line testing undertaken to diagnose the presence of PAD. When a revascularisation is being considered further anatomical information on the arteries of the lower limb should be obtained to assess the presence, severity, and distribution of arterial stenoses or occlusions. In this process, adequate imaging of the tibial and pedal vessels is of critical importance, particularly in planning intervention in people with diabetes and a foot ulcer (17). The Writing Committee considered that each of the imaging techniques have their advantages and disadvantages and their use will depend heavily on the availability of equipment and local expertise, preferences of the individual and associated costs. For these reasons a Best Practice statement was formulated. Regarding their use in people with diabetes, the utility of some these techniques, such as CDUS and CTA, can be affected by (severe) MAC, which is frequently present in the smaller arteries of the leg in people with DFU. MRA images are incapable of defining the extent of calcification which may be important when planning revascularisation (17). Finally, as stated in the Global Vascular Guidelines, catheter digital subtraction angiography (DSA), represents the gold standard imaging technique, especially for below the knee and foot arteries (17).

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In many centres DSA is typically used when MRA or CTA are not available, fail to adequately define the arterial anatomy, or when an endovascular intervention is planned. Arterial imaging should allow complete anatomic staging from aorta to foot using, for example, TASC for aorto-iliac disease and the Global Anatomic Staging System (GLASS), described in the Global Vascular Guidelines, for infrainguinal and pedal disease (17).

Recommendation 12 - Best Practice Statement

In a person with diabetes, peripheral artery disease, a foot ulcer and clinical findings of ischaemia, a revascularisation procedure should be considered. Findings of ischaemia include absent pulses, monophasic or absent pedal Doppler waveforms, ankle pressure < 100 mm Hg or toe pressure < 60 mm Hg. Consult a vascular specialist unless major amputation is considered medically urgent.

Rationale:

The natural history of people with diabetes, PAD, and a DFU or gangrene remains poorly defined, but in two studies reporting the outcomes of participants with diabetes and limb ischaemia who were not revascularised, the limb salvage rate was around 50% at 1 year (65, 95). Our analysis of the evidence for revascularisation suggests that revascularisation in appropriately selected people with diabetes and hemodynamically significant PAD, can improve perfusion, expedite wound healing and reduce major limb amputations(74). After a revascularization procedure, most studies report limb salvage rates of 80% to 85% and ulcer healing in >60% at 12 months (96). On the other hand, performing a revascularisation is not without risks. As summarised in the systematic review performed by the IWGDF in 2019 (96), peri-operative or 30-day mortality was around 2% in people with diabetes undergoing either endovascular or surgical revascularisation (96). The highest risk group is people with end-stage renal disease, who have a 5% perioperative mortality, 40% 1-year mortality and 1-year limb salvage rates of around 70% (96).

People with signs of ischaemia, e.g., as defined by WIfI and the Global Vascular Guidelines; absent pulses and monophasic or absent pedal Doppler waveforms, ankle pressure < 100 mm Hg or toe pressure < 60 mm Hg, are very likely to have significant PAD that could impact wound healing potential and amputation risk (17, 79). We judged in our systematic review the certainty of the evidence on the effects of revascularisation on wound healing and amputation risk as low, as many important factors that can affect outcomes were not reported such as the availability of vein conduit, wound care, offloading and sufficient anatomic details about the extent and severity of lesions treated. Factors

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that influence the decision to revascularise include the degree of limb threat (e.g., WIfI classification), the amount of tissue loss, presence of infection, co-morbidities, feasibility of the different revascularisation options and their risk.

As discussed in other parts of the IWGDF Guidelines, restoration of perfusion in the foot is only part of the treatment required to optimise wound healing and to prevent or limit tissue loss, which should be provided by a multidisciplinary team (78). Any revascularisation procedure should 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, assessment and improvement of nutritional status, as well as treatment of oedema and co-morbidities (78). The decision to perform a revascularisation procedure and which procedure is preferable depends therefore on several factors and in each individual the balance should be made between expected benefits, potential risks, harms and costs, in a shared decision-making process. For these reasons we made a Best Practice Recommendation. The care of persons with a DFU is frequently managed by health care professionals who are not specifically trained in the treatment of PAD. Care for people with PAD is differently organised in many countries, with different medical disciplines involved, such as vascular surgeons, angiologists, interventional radiologists, nephrologists, cardiac surgeons and cardiologists. For this reason, we used the term “vascular specialist consultation” in our recommendation, but whatever the organisation of care all people with diabetes and PAD should have access to both bypass surgery and endovascular procedures.

Recommendation 13 - Best Practice Statement

In a person with diabetes, peripheral artery disease, a foot ulcer, and severe ischaemia i.e. an ankle-brachial index <0.4, ankle pressure <50mmHg, toe pressure <30mmHg or transcutaneous oxygen pressure <30mmHg or monophasic or absent pedal Doppler waveforms, urgently consult a vascular specialist regarding possible revascularisation.

Rationale:

Severe ischaemia is defined in The Global Vascular Guidelines (GVG) as an ABI <0.4, AP pressure <50mmHg, TP <30mmHg or $TcPO_2$ <30mmHg or monophasic or absent pedal Doppler waveforms (17, 79). Such perfusion deficits are, as also stated in the GVG, an indication for revascularisation, unless contra-indicated or technically not possible. There is retrospective evidence demonstrating that a delay in revascularisation of more than two weeks in people with diabetes results in increased risk of

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limb loss (97). This is supported by observational research demonstrating that a shorter time to revascularisation (<8 weeks) is associated with higher probability of DFU healing and lower likelihood of limb loss (66). As shorter time to revascularisation was associated with higher probability of DFU healing and lower likelihood of limb loss we made a Best Practice Statement supporting urgent referral for vascular consultation in people with DFU and evidence of severe ischaemia (Figure 1).

Recommendation 14 - Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer with infection or gangrene involving any portion of the foot, urgently consult a vascular specialist in order to determine the timing of a drainage procedure and a revascularisation procedure.

Rationale:

In the presence of PAD and infection or gangrene, an urgent revascularisation should be considered. In the prospective Eurodiale study participants with the combination of a foot infection and PAD had a 1-year major amputation rate as high as 44% (80). In addition, participants with higher WIfI infection grade had higher risk of amputation in several observational studies, as summarised in our systematic review on Classification Systems (98). Delay in treatment can lead to rapid tissue destruction and life-threatening sepsis as described in the IWGDF/IDSA Guidelines on Management of Diabetic Foot Infections (99). In a person with a foot abscess or infection of a deep foot compartment that needs immediate drainage, or where there is gangrene that must be removed to control the infection, immediate surgery should be considered first (99). This should be accompanied by broad-spectrum antibiotic therapy, which is subsequently tailored according to tissue culture results—"time is tissue" in these people. Once the sepsis is controlled and the person is stabilized, evaluation of the arterial tree should lead to consideration for prompt revascularisation (i.e. within a few days) in people with significant perfusion deficits. Once blood flow is improved and infection is controlled, a definitive operation may be required in order to create a functional foot, which may require soft tissue and bone reconstruction (100). Due to the risk of amputation in this clinical scenario, the likelihood that the person will value avoidance of amputation, and the need for appropriate prioritisation of intervention strategies to achieve this, the Writing Committee formulated a Best Practice Statement.

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Recommendation 15 - Best Practice Statement

In a person with diabetes and a foot ulcer, when the wound deteriorates or fails to significantly improve (e.g. a less than 50% reduction in wound area within 4 weeks) despite appropriate infection and glucose control, wound care, and offloading, conduct further assessment of the vascular status and consult with a vascular specialist regarding possible revascularisation.

Rationale:

Multiple factors may contribute to delayed or non-healing of DFU, including presence of infection, wound size and depth, elevated foot pressures at the wound site and inadequate wound care. A number of studies have demonstrated that a reduction in percentage of wound area of more than 50% by four weeks after presentation is predictive of healing at 12 weeks (101-104). This has been shown to be the case independent of the ulcer size at baseline and supports review of treatment protocols where adequate wound reduction is not being achieved in the four-week timeframe. Presence of suspected CLTI or a DFU that is failing to adequately heal despite best practice care requires prompt consultation with a vascular specialist and assessment of whether a revascularisation procedure is indicated. There is no direct evidence supporting our recommendation which is a pragmatic statement based on indirect evidence and expert opinion. Given the risk of poor outcomes when PAD is left untreated in a person with a poorly healing ulcer, we have made a Best Practice Statement.

Recommendation 16 – Best Practice Statement

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, avoid revascularisation when the risk–benefit ratio for the probability of success of the intervention is unfavourable.

Rationale:

Revascularisation should not be performed if there is no realistic chance of wound healing, when major amputation is inevitable, a functional foot is unlikely to be achieved, or when life expectancy is short and there is unlikely to be of benefit to the person. The Writing Committee considered that in such persons any revascularisation procedure is unlikely to be of benefit to the person and may cause harm. Many affected individuals pose high peri-procedural risk because of comorbidities. In particular, the following people may not be suitable for revascularisation: those who are very frail, have short life expectancy, have poor functional status, are bed bound, and/or have a large area of tissue destruction

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that renders the foot functionally unsalvageable and those who cannot realistically be expected to mobilize following revascularisation. There are occasional situations where an arterial inflow procedure is performed to improve the likelihood of healing of a below knee amputation, so as to avoid an above knee amputation.

There is evidence from several observational studies of a 50% healing rate for ischaemic DFU in people with diabetes unsuitable for revascularisation and this should also be considered in determining choice of care (66, 95). The decision to proceed to primary amputation, or to adopt a palliative approach, should be made in conjunction with the person and the multidisciplinary team (105) including a vascular specialist unless an emergent procedure is indicated as discussed earlier. The Writing Committee considered that in these circumstances where healing is improbable a person is unlikely to value the outcomes from revascularisation over no intervention. Similarly in such circumstances the benefit of revascularisation will not outweigh the potential harms.

Clinical question

In people with diabetes, PAD and either a foot ulcer or gangrene how does endovascular revascularisation compare to open or hybrid revascularisation?

Recommendation 17

In a person with diabetes, peripheral artery disease and either a foot ulcer or gangrene who have an adequate single segment saphenous vein in whom infrainguinal revascularisation is indicated and who are suitable for either approach, we suggest bypass in preference to endovascular therapy (conditional, moderate)

Recommendation 18- Best Practice Statement

A person with diabetes, peripheral artery disease (PAD) and a foot ulcer or gangrene, should be treated in centres with expertise in, or rapid access to, endovascular and surgical bypass revascularisation. In this setting, consider making treatment decisions based on the risk to and preference of the individual, limb threat severity, anatomic distribution of PAD, and the availability of autogenous vein.

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Rationale:

Once the decision to revascularise has been made, the next decision is whether an endovascular, an open (i.e., bypass or endarterectomy) procedure, or a combination of both (i.e. hybrid procedure) should be performed. Recommendation 18 highlights the complementary role of open and endovascular techniques in contemporary vascular practice. In particular, endovascular techniques have largely replaced open surgery in the management of aorto-iliac disease and also allow treatment of foot/ pedal arch disease.

The majority of studies we identified in our systematic review on endovascular and bypass surgical outcomes were observational and retrospective case series, with a high risk of bias (106). The BEST CLI trial was a large randomised clinical trial with low risk of bias comparing an endovascular first with a surgical first approach. People with CLTI who were deemed appropriate for revascularisation for infrainguinal arterial occlusive disease were included (107). The primary outcome was above-ankle amputation of the index limb or a major reintervention in the index limb (new bypass, vein graft interposition revision, thrombectomy or thrombolysis) or mortality. It was designed in two parallel-cohort trials: (Cohort 1) people who had adequate single segment great saphenous vein (GSV) available for use as a bypass conduit, and (Cohort 2) people without adequate single segment GSV who required use of an alternate conduit. Treatment with a GSV bypass first approach was superior to endovascular therapy first for the primary outcome (hazard ratio [HR], 0.68; 95% confidence interval [CI] 0.59-0.79; P <0.001). In Cohort 2 the primary outcomes were similar between the two groups. Subgroup analysis of people in Cohort 1 favoured surgery in people with diabetes (HR 0.72; CI 0.61-0.86) with benefit comparable to those without diabetes (HR 0.57; CI 0.41-0.78). At the time of writing this guideline, further results of this study have not been published. Of note whole group data for Cohort 1 demonstrated a higher rate of major amputation in those undergoing an endovascular procedure compared to those having surgery (Surgery:74/709 (10.4%) Endovascular:106/711 (14.9%). Further sub-analysis may demonstrate this is relevant to those with diabetes and therefore this may affect an individual's preference for intervention. From the perspective of the person receiving treatment, the difference in length of hospital stay should be taken into account, which in our systematic review was longer in the bypass publications than in endovascular publications. In addition, people might prefer to have an endovascular approach given the more invasive approach of bypass surgery. Considering costs there are probably no major differences except the length of hospital stay however this is yet to be determined and may be an additional outcome of the BEST-CLI study. Subsequent analyses are also awaited to shed more light on the anatomic patterns and extent of disease treated, as well as which patterns of disease were not well represented or excluded. As BEST-CLI is currently the only randomised controlled trial (RCT) in this area, the certainty of the evidence for our recommendation was moderate. Given the important differences in outcomes in the BEST-CLI

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trial we recommend considering bypass surgery as first option in people with a suitable saphenous vein. We acknowledge that this recommendation can lead to some major changes in the policy of the many centres who currently have an 'endovascular-first' approach for everyone.

Our recommendation may not be feasible in the short term in all countries due to the lack of equipment and expertise. Finally, it should be noted that in the BEST-CLI study, endovascular procedures could be performed in the iliac and common femoral artery to ensure optimal inflow into the bypass, emphasizing that a centre treating PAD in people with a DFU should have the expertise to perform both endovascular and bypass procedures. In addition, in some centres the immediate availability of an endovascular approach might be a reason to opt for this treatment when an urgent revascularisation is needed or when the surgical risk is deemed too high. For these reasons and the moderate certainty of the evidence we made a Conditional recommendation.

In people with diabetes in whom a revascularisation is considered but who do not have a suitable single segment great saphenous vein for bypass surgery, the results in BEST-CLI were similar for endovascular and surgical bypass. This statement is in line with the results of our systematic review, in which the non-randomised and observational studies showed that the evidence was inadequate to establish whether an endovascular, open, or hybrid revascularization technique is superior. 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, spinal or epidural anaesthesia is usually necessary and a suitable vein, as a bypass conduit, should be present, as in the BEST-CLI trial. 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 performed (108). Over the past few decades, there have been significant advancements in endovascular techniques; however, parallel to this, we have seen improvements in anaesthesia and perioperative care that have helped improve surgical outcomes. As there is no "one-fits-all" approach to treatment for people with diabetes, PAD and foot ulceration or gangrene, 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 techniques. We recommend that in each person requiring lower limb revascularization, all revascularisation techniques should be considered (Figure 2).

Recommendation 19- Best Practice Statement

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In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene, revascularisation procedures should aim to restore in-line blood flow to at least one of the foot arteries.

Rationale:

In people with diabetes and a foot ulcer or gangrene in whom revascularisation is required, optimising blood flow to the foot is important to optimise the chance of healing the foot and avoiding amputation. Incomplete revascularisation (including treating inflow disease when distal disease is present or bypassing into "blind segment" arteries with no runoff), can result in delayed (or non-) wound healing and significant risk of amputation.

Bypass surgery is ideally performed to an outflow vessel that runs into the foot. However, bypasses performed to the peroneal artery (which rely on collateralisation to the foot) are most effective when there is good collateralisation to the foot and a patent foot arch is present (94). Pedal arch patency also seems to be associated with improved wound healing and reduced risk of major amputation (109).

Recommendation 20

In a person with diabetes, peripheral artery disease and a foot ulcer or gangrene who are undergoing an endovascular procedure, consider targeting the artery on angiography that supplies the anatomical region of the ulcer, when possible or practical. (Conditional, very low)

Rationale:

Angiosomes are three-dimensional regions of tissue and skin supplied by a source artery. The six angiosomes of the foot and ankle are supplied by the posterior tibial artery (n=3), peroneal artery (n=2) and anterior tibial artery (n=1) (Figure 3). Communications between angiosomes include direct arterial-arterial connections, as well as "choke" vessels which link adjacent angiosomes (109-111). The effect/ influence of angiosome-based revascularisation on wound healing and prevention of amputation (major and minor) in the management of diabetes-related foot complications remains controversial.

Direct revascularisation involves revascularisation of the tibial artery supplying the angiosome in which the tissue loss has occurred. The alternative to this is indirect revascularisation where the tibial artery treated is the artery in which successful in-line flow to the foot is most likely to be achieved by endovascular techniques or is deemed the best tibial outflow vessel for anastomosis in bypass surgery

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but does not directly supply the affected area of tissue loss. Our systematic review found that open vascular reconstruction procedures were equally effective whether direct or indirect revascularisation to the affected foot angiosome was performed (106).

In addition, healing and amputation outcomes for direct and indirect endovascular revascularisation shows that if direct revascularisation is possible, DFU healing time and major amputation may be reduced compared to indirect revascularisation. There is inadequate evidence to determine if direct revascularisation is superior to indirect revascularisation to prevent minor amputation (112). Indirect revascularisation with collaterals was associated with wound healing and limb salvage outcomes which were similar to direct revascularisation outcomes and significantly better than the indirect without collateral cohorts (113-117).

The majority of included studies in our systematic review used endovascular procedures with data probably favouring direct revascularisation. For bypass procedures there was little difference in healing and amputation outcomes at 12 months between direct and indirect revascularisation (117-120). These studies had a high risk of bias, lacked randomisation (and it is unlikely that this will ever be possible) and were mostly retrospective. Baseline variables such as wound/foot staging (e.g. by WIfI) and extent of tissue loss were infrequently reported. Heterogeneity of the included studies was found to be high preventing meta-analysis of data. This is likely to be due to high variability in participants and wound stage (extent of tissue loss, severity of ischaemia, presence of infection). Comparison of primary outcomes (healing/ amputation) or adverse events is therefore problematic. Based on the available data it appears direct revascularisation may have improved outcomes and therefore we considered that this procedure is likely to be preferred by people receiving treatment to improve healing and prevent amputation. However, the Writing Committee considered there is likely to be important variability in patient values due to the lack of cear benefit of one approach over the other. Factors such as the severity of ischaemia and tissue loss (e.g. WIfI staging) and patient suitability for the procedure/presence of comorbidities, as well as availability of expertise and costs of the procedures (which may vary between locations/countries) drives decision making in relation to the type of procedure considered appropriate with these factors also impacting. Several studies have noted that only a minority of foot and ankle wounds in their series corresponded to one angiosome. Kret et al, (121) found that only 36% of wounds in their series corresponded to a single distinct angiosome. Similarly, Aerden et al, (122) found it difficult to allocate people to direct revascularisation versus indirect revascularisation due to the presence of multiple wounds and large wounds that had more than one angiosome supplying them. In such cases it is the opinion of the Writing Committee that the best quality artery should preferentially be targeted. Many clinicians will consider attempting

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to treat the second vessel supplying the wound as well, although there is a lack of evidence to support this approach (106).

Clinical question

In people with DFU do revascularisation perfusion outcomes predict healing, major amputation or the need for further revascularisation?

Recommendation 21-Best Practice Statement:

In a person with diabetes and either a foot ulcer or gangrene who has undergone revascularisation, objectively assess adequacy of perfusion e.g., using non-invasive bedside testing.

Rationale:

There are little available data examining the predictive capacity of post-revascularisation perfusion measures for healing or amputation outcomes or for the need for further revascularisation in people with diabetes. However, adequate perfusion is essential for wound healing and clinical examination is often too unreliable. Diabetes-related PAD is characterised by atherosclerotic plaque formation that is long and diffuse in nature and more likely to involve distal vascular beds. Frequently long-term patency is not achieved in endovascular treatment of tibial lesions (123).

Regular assessment of perfusion post-revascularisation should therefore be undertaken due to the risk of occlusion/ restenosis after intervention. This should be conducted in combination with regular assessment of the foot lesion to determine if healing is indeed taking place. We recommend that revascularisation should aim to improve perfusion to the foot as much as possible, which will vary according to the individual. Due to the lack of data available determining the optimum time frame for follow-up and the likelihood that this may vary depending on the testing method being used, we have made a Best Practice Statement based on indirect evidence and expert opinion.

Recommendation 22- Best Practice Statement

A person with diabetes, peripheral artery disease and either a foot ulcer or gangrene should be treated by a multidisciplinary team as part of a comprehensive care plan.

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Rationale:

As discussed in several parts of this guideline and in other IWGDF guidelines on the diagnosis and management of DFU, restoration of perfusion in the foot is only part of the treatment, which should be provided by multidisciplinary care team (78). Lack access to specialist care is associated with worse foot outcomes. In rural and remote locations and areas where specialist access is challenging referral pathways that address care access (e.g. through virtual referral pathways) are essential to establish to provide multidisciplinary care (124). Any revascularization 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 offloading, control of blood glucose, cardiovascular risk reduction, and treatment of co-morbidities (124). Moreover, once the ulcer has healed the risk of recurrence is up to 50% over five years in several studies so preventive measures need to be taken and many people need long-term follow-up by a dedicated foot complication prevention team (23).

Clinical question: In a person with diabetes, PAD, and a foot ulcer, which medical treatments should be advised to prevent major adverse cardiovascular events (MACE), major adverse limb events (MALE) and mortality?

* MACE is defined as a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death.

* MALE is defined as the development of severe lower leg ischaemia leading to a vascular intervention or a major lower leg amputation.

*These definitions vary slightly between studies.

People with diabetes and PAD (with or without a foot ulcer) are at a very high cardiovascular risk. Cardiovascular risk factor goals should always be individualised taking life-expectancy, expected benefit, treatment burden, potential drug interactions and undesirable treatment effects into account. While taking these considerations into account the Writing Committee suggests the following treatment targets to reduce the risk of future major adverse limb and cardiovascular events:

Recommendation 23 - Best Practice Statement

In a person with diabetes and peripheral artery disease the following target levels should be:

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- HbA1c < 8% (< 64 mmol/mol), but higher target HbA1c value can be necessary depending on the risk of severe hypoglycaemia
- Blood pressure < 140/ 90 mmHg but higher target levels can be necessary depending on the risk of orthostatic hypotension and other side-effects.
- Low density lipoprotein target of < 1.8 mmol/l (<70 mg/dl) and reduced by at least 50% of baseline. If high intensity statin therapy (with or without ezetimibe) is tolerated, target levels < 1.4 mmol/l (55 mg/dl) are recommended.

Recommendation 24 - Best Practice Statement

A person with diabetes and symptomatic peripheral artery disease:

- should be treated with single antiplatelet therapy,
- treatment with clopidogrel may be considered as first choice in preference to aspirin
- combination therapy with aspirin (100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for people without a high bleeding risk.

Recommendation 25 - Best Practice Statement

In a person with type 2 diabetes with peripheral artery disease:

- with an eGFR > 30 ml/min/1.73m2, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit should be considered, irrespective of the blood glucose level
- SGLT-2 inhibitors should not be started in drug-naïve people with a diabetes-related foot ulcer or gangrene and temporary discontinuation should be considered in people already using these drugs, until the affected foot is healed.

Rationale:

The Writing Committee decided to not write their own guidelines on pharmacological interventions in people with diabetes, PAD and a foot ulcer or gangrene in order to reduce cardiovascular risk or to prevent major limb events as defined above. There are already a number of guidelines on cardiovascular risk prevention in people with diabetes and cardiovascular disease, and thus another guideline would have little added value. We decided to base our Best Practice Statements on the

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Global Vascular Guidelines for CLTI produced by the ESVS, SVS and World Federation of Vascular Societies (WFVS) (17), as these address the specific population of people with CLTI. Many people with diabetes, PAD and a foot ulcer or gangrene will belong to this target population. However, we also felt that some of the recommendations of the CLTI guidelines should be adapted to the specific population of people with diabetes. When we felt it was applicable, we used the guidelines of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and other guidelines on peripheral artery disease (European Society of Cardiology [ESC]-ESVS, European Society of Vascular Medicine [ESVM], ESC-EASD, ESC- European Atherosclerosis Society [EAS]) (13-16, 18-20).

PAD runs a more aggressive course in those with diabetes mellitus compared to those without diabetes, with an elevated risk of lower leg amputation. In addition, the combination of diabetes and PAD is associated with a high risk of developing complications in other vascular beds. As discussed previously, persons with an ischaemic diabetes-related foot ulcer have an overall 5-year cardiovascular mortality around 50% (125). Therefore, according to international guidelines of several major vascular and diabetes associations, these individuals should be considered as having a very high cardiovascular risk and should be treated as such. On the other hand, they usually have, in addition to peripheral neuropathy, other diabetes-related complications as well as several co-morbidities, resulting in a high burden of diseases and multiple medications (27). Many affected persons are elderly, frail and are living in vulnerable socio-economic circumstances with a low quality of life (126, 127). It is therefore essential that cardiovascular risk factor management in these people should be individualised, tailored and should be part of a shared decision-making process, taking life-expectancy, diabetes-related complications/co-morbidities, expected benefit, treatment burden, drug interactions and undesirable treatment effects into account. This care should be provided by health care worker(s) with sufficient expertise in treating cardiovascular risk factors and glycaemia, preferably by person(s) who are part of the multidisciplinary team for diabetes-related foot care.

Glycaemic goals

As stated in the ADA and ESC-EASD guidelines, near-normal glycaemia with HbA1c level below 7.0% (53 mmol/mol) will decrease microvascular complications (15, 19). Tighter glucose control initiated early in the course of diabetes in younger individuals leads to a reduction in macrovascular complications, i.e. cardiovascular outcomes, over a 20 year timescale. Such glucose control can have beneficial effects on microvascular complications in a shorter period of time. However, when blood glucose lowering agents are used that have the risk of severe hypoglycaemia, this can increase the risk of cardiovascular events and mortality, as detailed in the ADA and ESC-EASD guidelines (15, 18). As many people with a DFU and PAD also have atherosclerotic disease in other vascular beds, tight

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glucose control can be harmful. The risk of hypoglycaemia is markedly lower when people are only treated with metformin, a sodium–glucose cotransporter 2 inhibitor or a glucagon-like peptide 1 receptor agonist. Tight glucose control is often not indicated in persons with PAD and a DFU due to risk of hypoglycaemia outweighing potential benefit. The ADA recommends in the 2022 Standards of Care to aim for an Hba1c < 8% (< 64 mmol/mol) in such persons and the ESC-EASD 2019 guideline for levels below 8- 9% (<64-75 mmol/l) (15, 18). However, the target chosen will depend on factors such as age, duration of diabetes, complications, co-morbidities and risk of hypoglycaemia. These target HbA1c levels are higher than the level formulated in the Global Vascular Guidelines for CLTI (< 7,0%, 53 mmol/mol), but as discussed above we concluded that the risk of such tight blood glucose control is too high in this specific population.

Blood pressure goals

The ESC-EASD guidelines state that RCTs have shown the benefit (reduction of stroke, coronary events, and kidney disease) of lowering systolic BP to <140 mmHg and diastolic BP to <90 mmHg (15). Usually, multiple drugs are necessary to reach these levels in people with diabetes. In younger people (e.g. younger than 65 years) level below 130/80 mmHg can be considered if there are no contra-indications for such tight blood pressure control and the risk of orthostatic hypotension is low. Both the ADA and ESC-EASD stress the importance of individualised treatment as too aggressive blood pressure lowering is not without risk in the usually elderly with a DFU and those with multiple diabetes-related complications and co-morbidities. Therefore, we recommend in these persons blood pressures < 140/90 mmHg, but in younger individuals (e.g. < 65 years) and with a small risk of adverse effects of the treatment, lower target levels might be considered.

Lipid goals

The ADA and EASD guidelines recommend in persons with diabetes and atherosclerotic cardiovascular disease an LDL target of < 1.8 mmol/l (70 mmol/l) (18). In line with the 'the lower the better' approach, recent trials suggest that lower levels of LDL of < 1.4 mmol/l (55 mg/dl) can be beneficial in persons with a very high cardiovascular risk. Therefore, the recent ESC-EASD and ESC-EAS guidelines recommend that such very low LDL levels should be the target in these individuals (15, 16). In those with recurrent events within 2 years, even LDL levels < 1.0 mmol/l (40 mg/dl) are suggested as target in ESC-EAS guidelines (16). With statin therapy such as rosuvastatin 20-40 mg or atorvastatin 40-80 mg, marked reductions of LDL cholesterol can be achieved if these relatively simple treatments are tolerated. When the target is not reached ezetimibe can be added, which is available in combination tablets with both statins. These treatments have limited side effects in most (but not all) people and are relatively inexpensive. According to the recent ESC-EASD and ESC-EAS guidelines, an LDL-level

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below 1.0 mmol/l (40 mg/dl) can be the target in people with recurrent cardiovascular events (within 2 years), based on a limited number of RCT's in which relatively few participants with CLTI and diabetes were included. In order to reach the aforementioned very low LDL levels additional treatment with a PCSK9 inhibitor will be necessary in a proportion of people. PCSK9 inhibitors are monoclonal antibodies which have limited side-effects but have the drawback of high costs, parental administration and at present there is very limited evidence of the costs-effectiveness of PCSK9 inhibitors in people with diabetes, PAD and a foot ulcer or gangrene. In addition, the use of these expensive drugs is a problem for many countries in the world, and for these reasons we did not include a recommendation on LDL-level below 1.0 mmol/l (40 mg/dl) for our specific population, but we acknowledge that in several countries PCSK9 inhibitors are used to reach these goals in those with recurrent cardiovascular events.

In line with the other cardiovascular risk reduction interventions in these usually frail, multimorbid individuals, treatment and its goals should be based on shared decision making and should be individualised after careful weighting the benefits, harms and costs. The LDL (and other) treatment targets in our recommendation should not be interpreted as absolute goals but more as desired goals. Even if the goal is only partially met, it can result in a marked reduction in cardiovascular events in these very high-risk people. Although very low LDL levels are perhaps not achievable in all, LDL reductions up to 50% can be possible in many with the aforementioned potent statins (and ezetimibe), with marked reduction in cardiovascular risk (13).

Additional therapies

Antiplatelet therapy

All guidelines strongly recommend treatment with a single antiplatelet agent in persons with cardiovascular disease -or more specifically chronic limb threatening ischemia (CLTI). These drugs reduce the risk of cardiovascular events; in case of increased risk of gastric bleeding in aspirin treated individuals a proton pump inhibitor as additional treatment should be considered. There is less consensus which drug to choose, clopidrogel or aspirin. The ADA and ESC-EASD guideline advise in persons with diabetes and a cardiovascular event aspirin as first choice, but did not specify for the presence of PAD (15, 18). In the recent ESVM, ESC-ESVS and GVG Guidelines, clopidrogel is considered as the antiplatelet agent of choice in those with PAD. This recommendation is in particular based on 'The Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE)' trial, in which clopidrogel was more effective in reducing cardiovascular risk without an increased risk of bleeding (128). It should be noted that only a subset of participants in this trial had PAD of which only 21% had diabetes. Also, a meta-analysis did not show any benefit from aspirin for those with PAD (129). Given

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the potential benefit, we suggest in a conditional recommendation that clopidogrel may be considered as first choice, in line with the aforementioned Guidelines.

As an additional alternative to single antiplatelet therapy, combination therapy with aspirin (100 mg once daily) plus low-dose rivaroxaban (2.5 mg twice daily) may be considered for persons with low bleeding risk to prevent cardiovascular events as well as lower extremity ischaemic events in those with CLTI, as suggested by the Global Vascular Guidelines, ESVM and the ESC-EASD guidelines (13) (17, 20). This suggestion is based on the COMPASS trial in which this combination therapy was more effective than aspirin but was also associated with an increase of risk of clinically relevant bleeding, mostly gastrointestinal (130). In this trial approximately 38% had diabetes mellitus and the benefit of the combination therapy seemed similar in those with and without diabetes. Given this limited evidence base and the added treatment burden for this frequently vulnerable cohort, we made a Best Practice Statement.

The ESVS antithrombotic guidelines recommend that those not at high risk of bleeding who undergo an endovascular intervention for lower extremity PAD be considered for a 1-6 month course of dual antiplatelet therapy (aspirin plus clopidogrel) to reduce the risk of MACE and MALE followed by single antiplatelet therapy (131). Similarly, those undergoing endovascular intervention who are not at high risk of bleeding should be considered for aspirin (75-100 mg daily) and low-dose rivaroxaban (2.5 mg twice daily) to reduce the risk of MACE and MALE (132, 133). If the bleeding risk is considered to be high, single antiplatelet therapy should be used post-intervention.

If clopidogrel is used in addition to aspirin and low-dose rivaroxaban after endovascular intervention, clopidogrel should ideally only be used for <30 days as with longer-term use the bleeding risk is likely to outweigh the benefit (134).

The ESVS antithrombotic guidelines recommend that persons undergoing infrainguinal endarterectomy or bypass surgery who are not at high risk of bleeding should be considered for aspirin (75-100 mg daily) and low-dose rivaroxaban (2.5 mg twice daily) to reduce the risk of MACE and MALE. Those persons undergoing infrainguinal bypass surgery with autogenous vein who are not at high bleeding risk may be considered for treatment with vitamin K antagonist to improve graft patency (133, 135).

Those undergoing infrainguinal bypass with prosthetic should be considered for single antiplatelet therapy. Persons at high risk of bleeding undergoing lower extremity bypass surgery using autogenous or prosthetic conduit may be considered for single antiplatelet therapy to improve graft patency (133).

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Arterial duplex scanning post-autologous vein bypass surgery is generally advised post-procedure to detect graft stenoses. The benefits of post-procedure surveillance following endovascular intervention remain uncertain; we suggest following local protocols.

Sodium–glucose cotransporter 2 inhibitors and a glucagon-like peptide 1 receptor agonists

In recent years it has become increasingly clear that several sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 receptor (GLP-1) agonists, which were originally developed to lower blood glucose levels, can have beneficial cardiovascular effects in persons with type 2 diabetes (18). These effects are independent of their blood glucose lowering effect. To what extent this benefit can also be observed in those with type 1 diabetes mellitus, in whom glucose management with these drugs only has a limited (SGLT-2 inhibitors) or no (GLP-1 agonists) role to play, remains to be established. In individuals with an eGFR < 30 ml/min/1.73m^2 these drugs are contra-indicated. Therefore, we advise to consider these drugs in type 2 diabetes mellitus and peripheral artery disease with an eGFR > 30 ml/min/1.73m^2 after careful review and possibly adjustment of other blood glucose lowering medication in order to prevent hypoglycaemia, but for SGLT2-inhibitors there are additional caveats.

The SGLT2-inhibitor canagliflozin was associated with an increased risk of amputation in an RCT. This was not a pre-specified endpoint and was not observed in the other SGLT2-inhibitors trials (136) or in long-term prospective studies, as concluded in the ADA-EASD 2022 consensus report (137). In addition, in post-hoc analyses, these drugs had beneficial cardiovascular and renal effects in persons with peripheral artery disease (138). However, individuals with foot ulcers were frequently excluded in SGLT2-inhibitor trials and there is a second caveat to be considered. Diabetes-related ketoacidosis is a rare but serious side effect of SGLT2-inhibitors and prolonged fasting, acute illness and the peri-operative period predispose to developing ketoacidosis. In these situations, the ADA-EASD recommend temporary discontinuation of the medication, i.e. 3 days prior to surgery (137). As those with PAD, a diabetes-related foot ulcer or gangrene have a high risk of developing a foot infection or to undergo one or more (urgent) surgical procedures, we suggest for pragmatic reasons that SGLT-2 inhibitors should not be started in drug-naïve individuals and that temporary discontinuation should be considered in those already using these drugs, until the affected foot is healed.

Postscript

The targets discussed in this text are based on reduction of cardiovascular events, but is should be noted that this is a composite end-point and the definition between trials differs. MALE is also

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sometimes differently defined and the evidence for reducing lower limb events in persons with diabetes, PAD and a foot ulcer by pharmacological treatment is scarce. For this reason we could not provide a specific recommendation on this topic.

FUTURE RESEARCH PRIORITIES

One of the main limitations of this Guideline is the lack of prospective randomized trials, inconsistency of classification and outcomes reported, and lack of separation of outcome for people with CLTI with and without diabetes. Data reporting on PAD in relation to diagnosis, prognosis and management overwhelmingly relate to the general population. There is a paucity of high-level evidence for diagnosis and management of those with DFU or gangrene with studies frequently including only persons with intact feet or inadequately detailing (or controlling for) confounding factors including presences of neuropathy, ulcer, infection, or other contributors to poor outcomes. Moreover, few studies in CLTI cohorts provide sub-analysis for those with diabetes although they are likely to make up the majority of the included population. As such, there is clearly a need for further research into this unique subgroup of individuals with diabetes, in order that we may improve outcomes around the world.

The Writing Committee considers there are a number of priority areas for future research. Our systematic review of the prognostic capacity of bedside vascular testing to predict DFU healing and amputation outcomes demonstrated a lack of investigations of sufficient quality for several widely available tests including TBI and $TcPO_2$, with inconsistent use of measurement thresholds and a lack of data examining the effect of combining test outcomes.

New technologies to develop optimal tools and measures of foot perfusion for people with DFU and PAD to guide revascularization therapies would be invaluable in guiding revascularisation strategies for individuals s and for determining when more aggressive strategies are indicated.

Further questions:

1. Which group of people with diabetes and a DFU, tissue loss or gangrene most benefit from urgent revascularisation, and who may benefit from an initial expectant management?

The working group has made a Best Practice Statement attempting to define which people are likely to benefit most from urgent vascular assessment and revascularisation. Further studies to clarify

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person- and limb-related factors are needed and such predictions may be facilitated by new prediction methods such as Machine Learning (139).

2. Do newer endovascular revascularisation adjuncts and techniques developed for infra-popliteal revascularisation positively impact on patency rates and person-centred endpoints (amputation-free survival, improved wound healing and health-related quality of life) in those with diabetes, PAD and a foot ulcer?

A number of new technologies have been developed to enhance patency of endovascular interventions, including drug-eluting balloons and stents, and bioresorbable vascular scaffolds/stents. Atherectomy and lithotripsy devices have been developed to deal with heavily calcified lesions. Venous arterialisation has also been introduced to attempt to revascularize those with “no option” for revascularisation (140, 141). The role and indications for these interventions in the general population with CLTI and in particular, those with diabetes, remains to be clarified.

3. Identify effective regenerative therapies (e.g. cell or gene-based) to improve foot perfusion in persons with DFU and PAD who are not candidates for standard revascularization.

Angiogenesis (formation of new blood vessels from existing ones) is important for the development of arterial collateral formation in response to arterial occlusion and also for wound healing. Diabetes (and hyperglycaemia) are associated with impaired angiogenesis. A number of cell-, gene- and protein-based therapeutic approaches have, and are, being trialled for both “no option” CLTI and wound healing in diabetes. There are currently no therapeutic therapies which have proven beneficial and trials are on-going (142).

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CONTRIBUTION OF AUTHORS

The Writing Committee was chaired by R.F. (on behalf of the IWGDF), with R.H. (on behalf of the ESVS) and J.L.M (on behalf of the SVS) as co-chairs and supported by NCS (on behalf of the IWGDF). V.C. acted as scientific secretary. The three organisations involved were each tasked to select six well recognised experts in order to create an international, multidisciplinary, writing committee of eighteen members in total. Care was taken to have a global, multidisciplinary group that included disciplines such as vascular surgery, angiology, interventional radiology, vascular medicine, endocrinology, epidemiology and podiatry.

All members of the Writing Committee were involved in summarising the available evidence in the supporting systematic reviews, that are published separately, and in writing this guideline. Several members (the chairs, scientific secretary, N.S, and M.S.C.) were assigned to write individual sections of the guideline, and all authors reviewed and discussed during group meetings the evidence obtained, the evidence to decision items according to GRADE and each recommendation. All authors reviewed and agreed with the final document before societal review and subsequent submission for endorsement. All members of the working group undertook Level 1 GRADE training and the several working group members undertook Guideline Methodology training (McMaster University).

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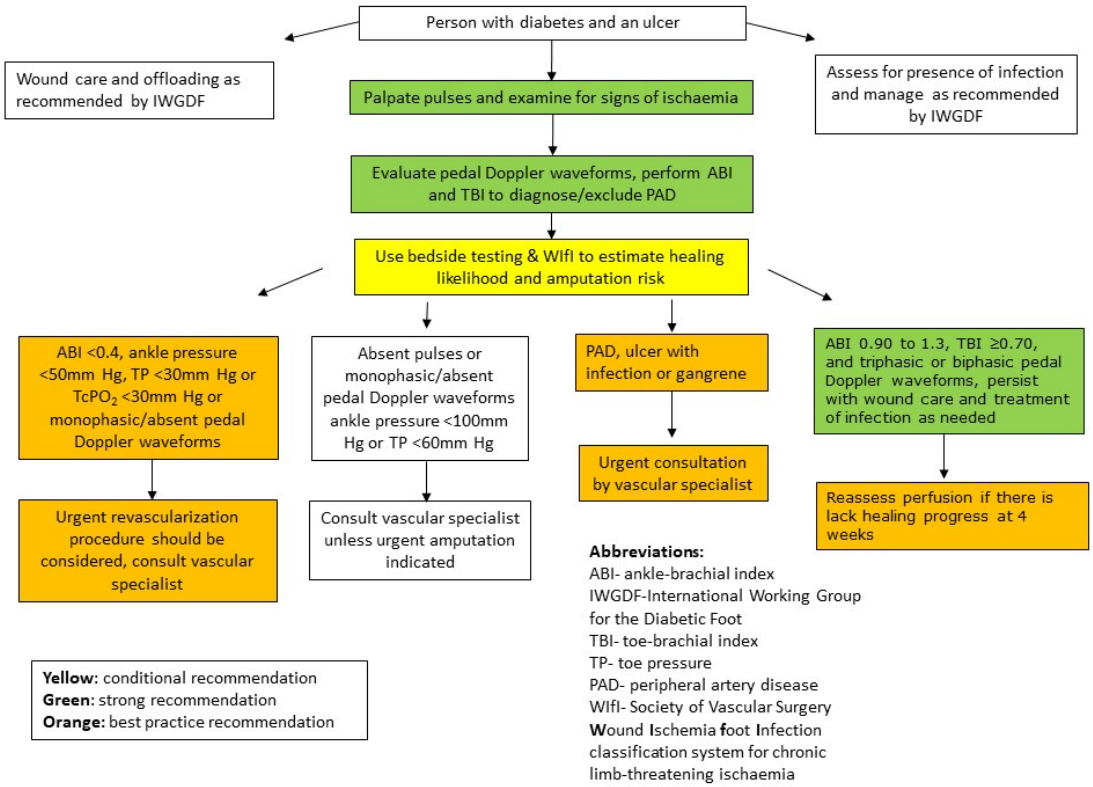

Figure 1: Assessment and management pathway for a person with diabetes, peripheral artery disease and a foot ulcer with findings of ischaemia, infection or gangrene. (Colour code: yellow=conditional recommendation, green=strong recommendation, orange= best practice recommendation)

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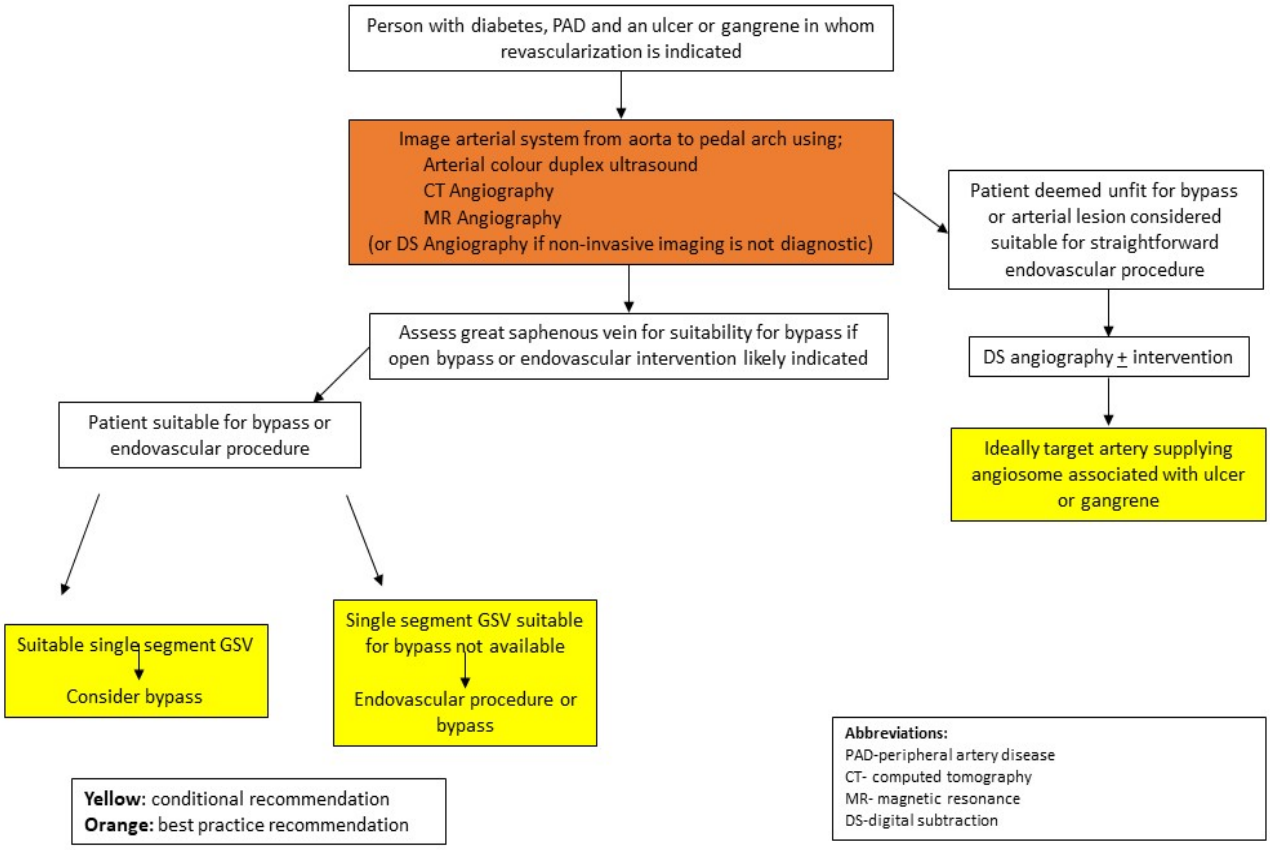

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1556 **Figure 2**: Approach to vascular intervention for a person with diabetes and a foot ulcer or gangrene.
1557 (Colour code: yellow=conditional recommendation, green=strong recommendation, orange= best
1558 practice recommendation)

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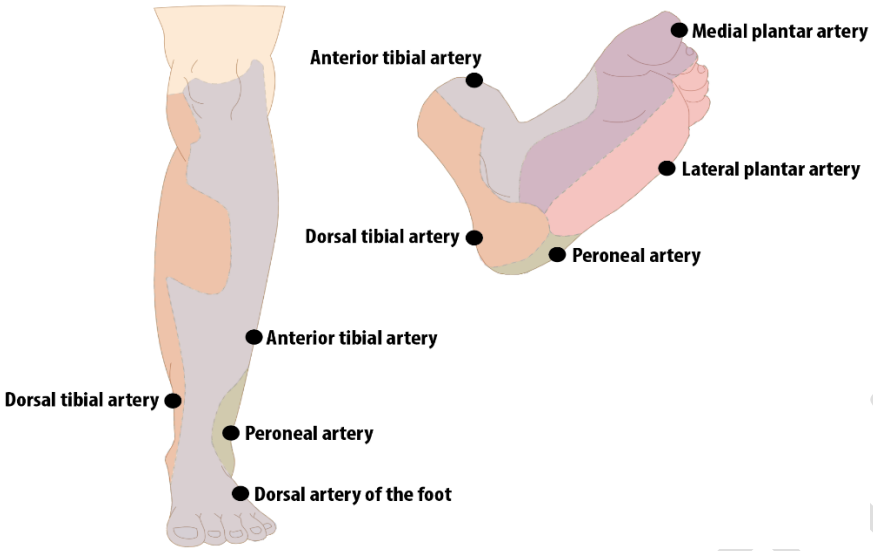

Figure 3: Angiosome distribution in the lower leg and foot

Dorsal tibial – posterior tibial

Dorsal artery- dorsalis pedis

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Grade	Clinical Description
0	Ischaemic rest pain; without frank ulcer or gangrene
1	Minor tissue loss: small shallow ulceration < 5 cm^2 on foot or distal leg **No gangrene.** ***Salvageable with simple skin coverage or <u>≤</u> 2 toe amputations***
2	Major tissue loss: deeper ulceration(s) with exposed bone, joint or tendon, ulcer 5-10 cm^2 not involving calcaneus; **gangrenous changes limited to digits.** ***Salvageable with extensive forefoot surgery***
3	Extensive ulcer/gangrene > 10 cm^2 involving forefoot or midfoot; full thickness heel ulcer > 5 cm^2 + calcaneal involvement. ***Salvageable only with complex foot reconstruction***

Table 1a) Wound Infection foot Ischaemia Classification System: **<u>W</u>**ound clinical category

Grade	ABI	Ankle SP (mmHg)	TP, $TcPO_2$ (mmHg)
0	≥0.8	≥100	≥60
1	0.6-0.79	70-99	40-59
2	0.40-0.59	50-69	30-39
3	<0.40	<50	<30

Table 1b) Wound Infection foot Ischaemia Classification System: **<u>I</u>**schaemia category

Grade	Clinical Description	IDSA	IWGDF Class
0	Wound without purulence or manifestations of infection	uninfected	1
1	>2 manifestations of infection, erythema (< 2cm), pain, tenderness, warmth or induration) no local complications or systemic illness	mild	2
2	Infection in patient who is systemically stable but has ≥ 1 of; cellulitis (>2 cm), lymphangitis, spread beneath fascia, deep tissue abscess, gangrene, muscle, tendon, joint or bone involvement	moderate	3
3	Infection in patient with systemic or metabolic toxicity (SIRS/ sepsis)	severe	4

Table 1c) Wound Infection foot Ischaemia Classification System: foot Infection category

	Ischemia – 0				Ischemia – 1				H	Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H		L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H		L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H		M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H		H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3		FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

Table 1d): Wound Infection foot Ischaemia Classification System: Estimate risk of amputation at 1 year

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

Table 1e): Wound Infection foot Ischaemia Classification System: Estimate likelihood of benefit of/requirement of revascularisation

Key:

Very Low = VL = Class or Clinical Stage 1
Low = L = Class or Clinical Stage 2
Moderate = M = Class or Clinical Stage 3
High = H = Class or Clinical Stage 4

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Supplementary Table 1: Summary of evidence for diagnostic and prognostic capacity of bedside tests at differing thresholds

Test	Threshold	Diagnosis No DFU		Diagnosis with DFU		Threshold	Prognosis - healing		Threshold	Prognosis - major amputation	
		PLR range	NLR range	PLR range	NLR range		PLR range	NLR range		PLR range	NLR range
ABI	**≤0.90**	1.28 to ≥10	0 to 0.56	2.18	0.75	**≥0.50**	2.0 to 4.0	0 to 0.12	**< 0.90**	1.1 to 1.3	0 to 0.92
	≤0.90 to ≥1.3	2.11 to ≥10	0.19 to 0.72	1.69 to 2.32	0.53 to 0.54	**>0.70**	4.59	0.23	**≤0.90 to ≥1.3**	2.3	0.64
						≥0.9	1.06 to 1.67	0.48 to 0.78			
AP	**<70mmHg**			2.25	0.67	**≥50mmHg**	1.08 to 1.12	0.34 to 0.48	**<50mmHg**	2.61	0.89
						≥70 mmHg	3.44	0.11	**<70 mmHg**	8.8	0.29
						≥80mmHg	1.27 to 1.5	0.32 to 0.47	**<80mmHg**	2.13	0.76
TBI	**<0.70**	2.0 to 3.55	0.28 to 0.44	1.62	0.24	**>0.65**	≥10	0.28			
	≤0.75	1.62 to 2.60	0.14 to 0.24			**≥0.75**	0.88	1.05	**<0.75**	1.44	0.61
Toe pressure	**<50mmHg**			17.55	0.56	**≥30mmHg:**	5.0 to 9.95	0.28 to 0.88	**<30mmHg**	2.90 to 3.24	0.1 to 0.75
	≤60mmHg	3.1	0.39			**≥45mmHg**	1.43 to 2.87	0.45 to 0.64	**<45mmHg**	2.14	0.67
$TcPO_2$	**<30mmHg**	2.66	0.40			**≥25mmHg**	5.0 to ≥10	0.09 to 0.14	**<20mmHg**	1.87	0.68
	<60mmHg			0.81	1.10	**>30mmHg**	1.24 to 1.60	0.29 to 0.47			
SPP						**≥30mmHg**	≥10	0.36			
						≥40mmHg	1.3 to 11.17	0.35 to 0.62			

ABI: Ankle -brachial Index, AP: ankle pressure, PLR: positive likelihood ratio, NLR: negative likelihood ratio, SPP: skin perfusion pressure, TBI: toe -brachial Index, $TcPO_2$: transcutaneous oxygen pressure. Ranges of numbers are provided were more than one study reported positive and negative likelihood ratios. Studies in mixed populations are not included.

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