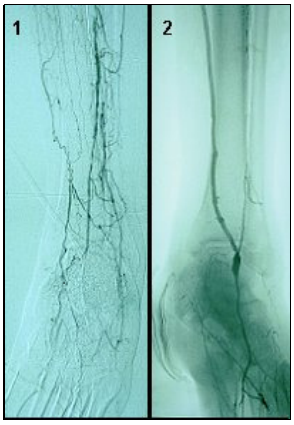

Peripheral arterial disease and diabetes

General introduction

In 2007 the IWDGF produced a consensus document on peripheral arterial disease (PAD) in diabetes. In recent years new techniques and technologies have been introduced in treating PAD, which might be relevant for the patient with diabetes and a poorly healing ischemic foot ulcer. The editorial board of International Working Group on the Diabetic Foot (IWDGF) therefore established in 2009 a multidisciplinary working group. This working group included specialists in vascular surgery, interventional radiology, cardiology, internal medicine and epidemiology on the diagnosis and treatment of PAD in diabetic patients with a foot ulcer. The aims of this multidisciplinary working group was to produce a systematic review on the efficacy of revascularization procedures in diabetic patients with a foot ulcer and PAD. This document was approved by all representatives but one of the IWDGF in 2011. Moreover a short progress report on diagnosis and prognosis was produced by the working group. Based on these documents the working group formulated specific guidelines. In this electronic document of the IWDGF the following texts on diabetes and PAD can be found:

I. Peripheral arterial disease and diabetes: International Consensus 2007
II. A Systematic Review of the Effectiveness of Revascularization of the Ulcerated Foot in Patients with Diabetes and Peripheral Arterial Disease (2011).
III. Diagnosis and treatment of PAD in the diabetic patient with a foot ulcer. A progress report (2011).
In this document the IWDGF working group on PAD and diabetes gives an updated overview on the management of a patient with diabetes and a foot ulcer, based on the above described systematic review and supplemented with expert opinions.
IV. Specific guidelines on diagnosis and treatment of PAD in the diabetic patient with a foot ulcer (2011).

I. Peripheral arterial disease and diabetes: International Consensus 2007

Contents

1. Key messages

- Peripheral arterial disease (PAD) is the most important factor relating to the outcome of a diabetic foot ulcer.
- PAD often can be recognized by simple clinical examination: colour and temperature of the skin, palpation of pedal pulses, ankle blood pressure measurement.
- The probability of a diabetic foot ulcer healing can be estimated using non-invasive vascular tests. Ankle, and occasionally, toe blood pressure

readings may be falsely elevated due to medial sclerosis.

- Rest pain due to ischaemia may be absent in people with diabetes - probably due to peripheral neuropathy.
- Micro-angiopathy should never be accepted as the primary cause of an ulcer.
- Conservative approaches should involve a walking programme (if no ulcer or gangrene is present), appropriate footwear, cessation of smoking, and aggressive treatment of hypertension and dyslipidaemia.
- Patency rates and limb-salvage rates after revascularization do not differ between people with or without diabetes. Therefore, diabetes is not a reason to withhold this treatment.

The management of foot disease in diabetes remains a major therapeutic challenge throughout the world. The International Working Group of the Diabetic Foot (IWGDF) has issued guidelines on management since 1999, but good evidence is still required to substantiate the roles of particular interventions.

It is for this reason that from 2005 the IWGDF established working groups to undertake a series of systematic reviews into aspects of prevention and management of foot disease, including off-loading [1], osteomyelitis [2] and chronic ulceration [3]. At the invitation of the IWGDF Editorial Board the IWGDF working group on wound healing has already started six years ago therefore to undertake a systematic review of the evidence in order to inform protocols for routine care and to highlight areas which should be considered for further study. This evidence-based guideline was developed by a multidisciplinary group of clinicians and scientists working in the field of wound healing for the diabetic foot. The working group had worked on it between November 2005 and May 2007 to select the interventions of interest, discuss the methodology of literature search and grading, carry out the methodological assessment of the literature, agree on the results, and wrote the guideline, which was approved by the IWGDF Editorial board and launched at the 5th International Symposium on the Diabetic Foot in 2007. The documents were published in 2008[3]. The same working group reports now on papers published since 2006 on the interventions to improve the healing of chronic ulcers.

2. Introduction

Peripheral arterial disease (PAD) causing arterial insufficiency is the most important factor relating to the outcome of a diabetic foot ulcer. In people with diabetes, atherosclerosis and medial sclerosis are the most common arterial diseases. Atherosclerosis causes ischaemia by arterial narrowing and blockage. Medial sclerosis (Moenckeberg sclerosis) is calcification of the tunica media producing rigid conduit arteries - without encroachment on the arterial lumen. Thus medial sclerosis, which is frequently associated with neuropathy, does not cause ischaemia, but the rigid arterial tube may severely interfere with indirect measurement of arterial blood pressure. Finally, micro-angiopathy should not be accepted as the primary cause of a skin lesion.

3. Characteristics

The prevalence of PAD in people with diabetes is probably high, and ranges from 10% to 40% depending on the definition used; in patients with foot ulcers 50% have signs of PAD. There are no peripheral arterial lesions specific to diabetes, but the pattern of atherosclerosis is somewhat different. The characteristics of these lesions, according to expert opinion, are listed in Table 1.

Table 1:

Characteristics of atherosclerosis in people with diabetes as opposed to people without diabetes

- More common

- Affects younger individuals
- No sex difference
- Faster progress
- Multi-segmental
- More distal (aorto-iliac arteries less frequently involved)
- More aggressive

4. Pathophysiology

The presence of PAD in people with diabetes is related to older age, HbA_{1c}, smoking, and hypertension. Based on studies in people without diabetes, dyslipidaemia and end-stage renal disease are also probably risk factors. In patients with diabetes, for every 1% increase in HbA_{1c}, there is a corresponding 26% increase risk of PAD. Accumulation of cholesterol within the vessel wall is the cardinal step in atherogenesis. During this process, intimal plaques are formed, which can ulcerate with subsequent thrombosis. This narrows and occludes the arteries, reducing blood flow and perfusion pressure in the peripheral tissues. The process is mostly segmental, leaving distal segments, for instance, of the crural or pedal arteries - open and accessible for vascular reconstruction. Following arterial obstruction, local microcirculatory changes occur unless the obstruction is compensated by collateral vessels.

PAD can be regarded as a sign of general atherosclerotic disease. Therefore, the heart and carotid arteries should also be examined in patients with PAD. Precisely why people with diabetes are more prone to develop atherosclerotic vascular disease is still unclear, but it is likely that changes in circulating lipoproteins result in a more atherogenic lipid profile, with low HDL-cholesterol and elevated triglycerides. The role of hyperglycaemia in atherogenesis is less clear, however, and still open to debate. Within the diabetic population, nephropathy is a marker for generalized vascular disease, and it is likely - but not proven - that these people are more prone to develop PAD.

5. Symptoms

When adequate collateral vessels compensate for arterial occlusion, there may be no symptoms at rest, but when the demand for blood-flow increases, for example during walking, intermittent claudication may occur. However, less than 25% of individuals with PAD and diabetes report intermittent claudication, which means that 75% of people with diabetes have so-called 'asymptomatic' disease. End-stage symptoms are rest pain - particularly at night - and ulceration/gangrene. Also, many of these patients have few symptoms, despite extensive tissue loss - probably due to peripheral neuropathy.

6. Identifying PAD

Experts recommend that the vascular status in people with diabetes should be examined on an annual basis, with particular attention to:

1. A history of intermittent claudication or ischaemic rest pain, to be distinguished from pain caused by peripheral neuropathy.
2. Palpation of pulses in the posterior tibial and dorsalis pedis arteries is mandatory. Detection of foot pulses by palpation is affected by room temperature and the skill of the examiner. If a pulse is absent, popliteal and femoral pulsations should be examined. The dorsalis pedis artery may be congenitally absent. If foot pulses are present, significant vascular disease is unlikely. Some experts advise that when pedal pulses are absent in an asymptomatic patient, ankle blood pressure should be measured with a

hand-held ultrasound Doppler device. An ankle brachial pressure index (ABI - systolic ankle blood pressure divided by systolic arm blood pressure, both measured with the patient in the supine position) of below 0.9 indicates occlusive arterial disease. If pedal pulses are absent in a patient with a foot ulcer, further non-invasive investigation is mandatory.

3. Potential signs of critical ischaemia are: blanching of the feet on elevation, dependent rubor, ulceration, skin necrosis or gangrene. However, due to peripheral neuropathy, the critically ischaemic foot maybe relatively warm, with little discoloration. Finally, critical ischaemia can sometimes be confused with infection, as local erythema may be observed in the ischaemic foot.

7. Chronic critical ischaemia

Critical ischaemia indicates risk of amputation of a major part of the limb, unless reversed by a revascularization procedure. Definition and guidelines for the treatment of acute ischaemia are beyond the scope of this document. Chronic critical ischaemia has been defined by either of the two following criteria: persistent ischaemic rest pain requiring regular analgesia for more than two weeks; ulceration or gangrene of the foot or toes - both associated with an ankle systolic pressure of <50 mmHg or a toe systolic pressure of <30-50 mmHg.

These criteria are based on the assumption that there are no differences between people with or without diabetes concerning critical ischaemia. However, studies in patients with diabetes with foot ulcers suggest that these cut-off pressure levels are either too low or inaccurate, as described below.

8. Non-invasive vascular investigation

Given the uncertainties of history and clinical examination, more objective measurements of skin perfusion are frequently needed. Commonly used techniques include ankle pressure, toe pressure and (less frequently) transcutaneous oxygen pressure (TcPO2) measurements. These non-invasive vascular tests can be used for:

- diagnosis and quantification of PAD
- predicting wound healing of a diabetic foot ulcer
- follow-up and control of treatment.

The most widely used method for the diagnosis and quantification of PAD is the measurement of ankle pressure, as described above. Ankle pressures may be falsely high (due to medial sclerosis), and an ABI above 1.3 is unreliable. It has been suggested that in this situation ankle perfusion pressure can be estimated with the 'pole-test', which records the disappearance of the ultrasound signal as the leg is elevated. However, ankle pressures are not accurate predictors of wound healing. Therefore, experts suggest that in a patient with a foot ulcer, these measurements should, if possible, be supplemented with a more peripheral measurement.

Several studies have been published on the ability of these techniques to predict the probability of wound healing. A schematic estimate of probability of healing for foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure and transcutaneous oxygen pressure measurements (TcPo2), based on selected reports, is given in Figure 1. It should be noted that diagnostic specificity can not be ascertained from these curves.

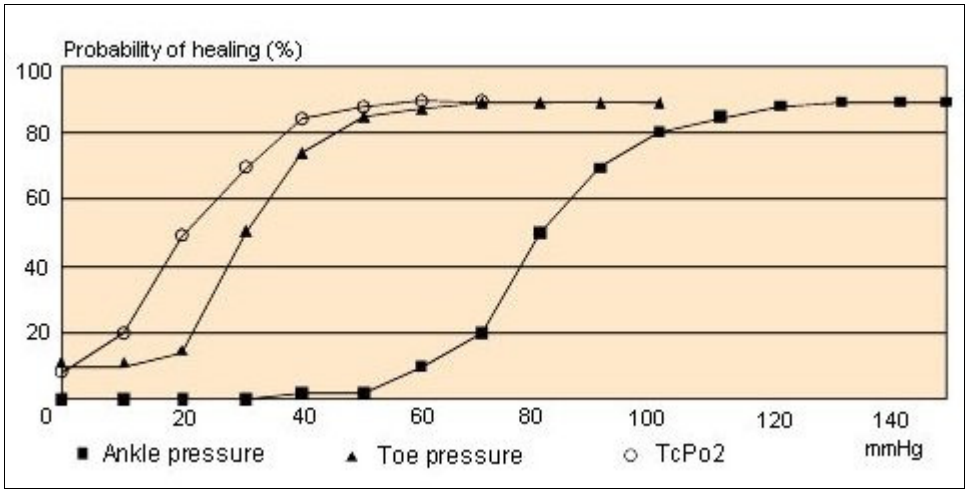

Figure 1: Non-invasive evaluation and an estimate of probability of healing

In a recent study comparing different methods for PAD screening in people with diabetes, the sensitivity of ABI in neuropathic patients was only 53%; in a patient with a non-healing ulcer, significant peripheral vascular disease should always be considered - even if clinical signs of PAD are absent and non-invasive testing is not clearly abnormal. In these patients, repeated evaluation may be necessary, and, according to experts, angiography should be considered in a chronic non-healing ulcer after 6 weeks of optimal treatment.

9. Treatment

Revascularization

In a patient with a foot ulcer, an estimate of the probability of wound healing should be based on clinical examination and, if possible, the non-invasive vascular tests described above. If the probability of healing is deemed to be too low (see Figure 1), or if the patient has persistent ischaemic rest pain, revascularization should always be considered. A second indication for revascularization can be intermittent claudication. In all of these cases, the arterial tree of the lower extremity, including the pedal arteries, must be visualized. Several techniques can be used. Arteriography of the lower extremity can be performed using the Seldinger technique - with or without digital subtraction angiography. If there are no signs of more proximal vascular disease, the examination can be restricted to one leg, with puncture of the femoral artery to limit the amount of contrast medium. This technique can be replaced or supplemented by magnetic resonance angiography (MRA), CT-angiography, or duplex (echo-Doppler) examinations. To avoid contrast nephropathy, adequate hydration and blood glucose control are mandatory before, during, and after angiography.

Arterial reconstruction can be performed through open procedures such as a bypass or, more rarely, via a thromboendarterectomy or an endovascular procedure - such as a balloon dilatation (percutaneous transluminal angioplasty, PTA) or an endovascular (subintimal) recanalization. In general, when endovascular revascularization and open repair or bypass of a specific lesion give equivalent results, endovascular techniques should be used first, given their lower risks and costs. Traditionally, endovascular procedures were reserved for short proximal arterial lesions, and bypass surgery was usually required for long and distal occlusions. However, based on recent reports, and according to the experience of experts, endovascular techniques can also be used in long lesions in the lower leg, with good healing rates of (neuro-)ischaemic ulcers. If bypass surgery is performed, the great saphenous vein is superior to synthetic graft material. Most recent reports suggest that durability is of the same order of magnitude in people with or without diabetes.

A revascularization procedure is technically possible in most patients suffering from critical ischaemia. Because excellent results have been published on distal reconstructions in patients with diabetes, a more aggressive approach to revascularization procedures should be promoted. Whenever a major amputation is under consideration, the option of revascularization should always be considered first. Pharmacological therapy to maintain patency after vascular reconstruction is controversial, although aspirin is used by the majority of vascular surgeons.

According to the recent TASC II Guidelines, patients should participate in a clinical surveillance programme after bypass surgery, which should be performed in the immediate post-operative period and at regular intervals (usually every 6 months) for at least 2 years.

Risk-factor modification

Cardiovascular morbidity and morality are markedly increased in patients with PAD. Treatment of neuro-ischaemic ulcers should therefore not be solely focused at the foot, but should also aim to reduce this poor survival. In patients without diabetes, cessation of smoking has been shown to decrease the risk of developing intermittent claudication and decrease the subsequent risk of amputation. Moreover, patency rates for vascular reconstruction are higher, and the risk of death is lower, if the patient stops smoking. Although there are no studies which demonstrate that treating hypertension and dyslipidaemia has any beneficial effect on ischaemic foot problems, experts strongly advise that these factors be treated aggressively. In addition, patients with PAD should be treated with low-dose aspirin to reduce vascular co-morbidity.

Placebo-controlled trials have demonstrated that pharmacological treatment can be of some value in improving peripheral perfusion in patients with critical ischaemia. However, at present, there is not sufficient evidence of efficacy to advocate the routine use of any drug for this purpose.

Walking programmes have been shown to improve intermittent claudication in people with diabetes. Proper footwear is essential, and cardiac function should be assessed before a walking programme is initiated. Expert opinion is that walking programmes should not be initiated in case of ulceration or gangrene.

Lumbar sympathectomy is an obsolete procedure for the treatment of intermittent claudication and critical ischaemia in patients with diabetes.

10. Further reading

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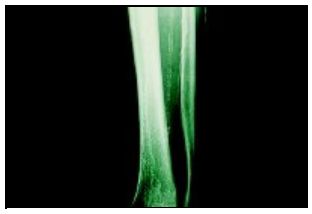
11. Peripheral vascular disease

Peripheral vascular disease



Mediasclerosis of the artery leading to incompressible crural vessels.

Pre-gangrenous fourth toe due to ischemia.

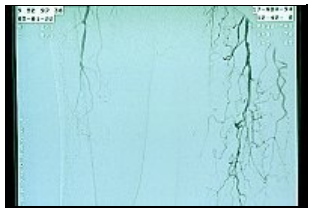
(Minor) gangrene of the fourth toe.

(Major) gangrene of the forefoot.

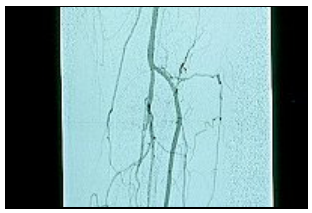
12. Angioplasty

Angioplasty

69-year old male with a history of a resection of the second through fourth toe with subplantar abscess underwent angiography.



Angiography showed short segment occlusion of the superficial femoral artery and multiple crural occlusions.



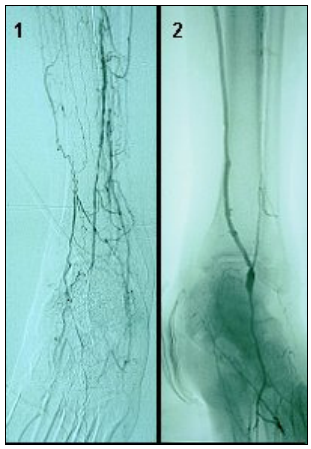
Percutaneous transluminal angioplasty (PTA) of the distal superficial femoral artery was performed.

Wound healing after successful PTA.

13. Bypass surgery

Angioplasty

Bypass surgery



1) Angiography showed multiple crural occlusions.

2) Because of the non-healing defect a popliteal-pedal bypass from the infragenual popliteal artery to the pedal artery was performed.

Secondarily healed defect after successful reconstructive revascularisation.

II. A Systematic Review of the Effectiveness of Revascularisation of the Ulcerated Foot in Patients with Diabetes and Peripheral Arterial Disease

Contents

Chapters

Appendices

I. Abbreviations

ABI	ankle:brachial pressure index
AHA	Americal Heart Association
AKA	above knee amputation
ARF	acute renal failure
AT	anterior tibial artery
BKA	below knee amputation
CAD	coronary artery disease
CBA	control before and after (study)
CFA	common femoral artery
CIA	common iliac artery
CKD	chronic kidney disease
CLI	critical limb ischaemia
CVD	cerebrovascular disease
DFU	diabetic foot ulcer
DM	diabetes mellitus
DP	dorsalis pedis artery
IQR	interquartile range
ITS	interrupted time series (study)
ITT	intention to treat (analysis)
IWGDF	International Working Group on the Diabetic Foot
MI	myocardial infarction
MRA	Magnetic Resonance Angiography
NA	not available
NPWT	negative pressure wound therapy
NR	not reported
PAD	peripheral artery disease
PT	posterior tibial artery
PTA	pecutaneous transluminal angioplasty
RCT	randomised controlled trial
SD	standard deviation
SFA	superficial femoral artery
SIGN	Scottish Intercollegiate Guidelines Network
TASC	The Inter-Society Consensus for the Management of Peripheral Arterial Disease
TBI	toe-brachial pressure index
$TcpO_2$	transcutaneous oxygen tension
UT	University of Texas (wound classification system)

II. Introduction

An amputation of the leg or foot is one of the most feared complications of diabetes mellitus and it is has been calculated that at this moment every 20 seconds a leg is lost in our world due to diabetes [1, 2]. Peripheral artery disease (PAD) and infection are the major causes of lower leg amputation in diabetes and >80% of these amputations are preceded by a foot ulcer [3, 4]. Diabetes is a risk factor for PAD and depending on the definitions used, prevalence rates of 10 to 40% in the general population of patients with diabetes have been reported [5, 6, 7]. Moreover, in comparison to subjects without diabetes, PAD is more likely to progress in patients with diabetes[8]. A substantial number of individuals with a foot ulcer will therefore have PAD, ranging from relatively mild disease with limited effect on wound healing to severe limb ischemia with delayed wound healing and a high risk of amputation. In several large observational studies PAD was present in recent series in up to 50% of the patients with a diabetic foot ulcer and was an independent risk factor for amputation [9, 10, 11]. The relatively poor outcome of ischaemic foot ulcers in diabetes is probably related to a combination of factors, such as the anatomic distribution of the vascular lesions rendering them more difficult to treat, the association with other abnormalities like infection,

neuropathy and renal failure and the presence of abnormalities in other vascular territories, such as the coronary or cerebral arteries[7, 9, 12, 13, 14] The mortality of patients with PAD and a diabetic foot ulcer is high with 50% of patients dead at 5 years[15]; the results are worse after major amputation with a 50% mortality after 2 years. In addition, wound healing can be further disturbed by a complex interplay of several other factors such as poor glycaemic control, microvascular dysfunction, impaired collateral formation, abnormal mechanical loading of the ulcer and co-morbidities. The effect of PAD on wound healing in diabetic patients with a foot ulcer will therefore relate in part to its severity and extent but also to these other factors[16].

Clearly, early recognition of PAD, an accurate estimation of its severity and prompt institution of effective treatment in cases of severe disease would seem to be a logical approach to reduce the high number of amputations. However, as shown in the Eurodiale cohort, less than 50% of the diabetic patients with ABI<0.5 underwent adequate vascular evaluation and subsequent revascularisation, suggesting that there is ample room for improvement in the delivery of care[14]. PAD in patients with diabetes has a number of important characteristics which renders it more difficult to treat. The atherosclerotic lesions are multilevel and particularly severe in tibial arteries, with a high prevalence of long occlusions[17]. The predilection for multiple crural vessel involvement combined with extensive arterial calcification increases the technical challenges associated with revascularisation using either open bypass or endovascular techniques.

The term critical limb ischaemia (CLI) is frequently used in the PAD literature but may not be particularly relevant for patients with diabetes. The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) document suggests that the term "should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease"[18]. However, in diabetic patients ulceration or gangrene are usually the result of several interacting factors, with neuropathy playing a central role in most patients in combination with varying degrees of PAD and therefore confusion may exist in reporting outcomes in the literature.

Updated guidelines on the diagnosis and treatment of PAD have been provided in 2007 by TASC II, but evidence based guidelines on the treatment of PAD in patients with diabetes and ischaemic foot ulcers are currently lacking[18]. In recent decades new techniques and technologies have been introduced in treating PAD, which might be relevant for the patient with diabetes and a poorly healing ischemic foot ulcer. In particular interesting results have been reported on endovascular approaches in the leg and the field is rapidly evolving[19, 20]. The International Working Group on the Diabetic Foot (IWDGF) therefore established a multidisciplinary working group, including specialists in vascular surgery, interventional radiology, cardiology, internal medicine and epidemiology to evaluate the effectiveness of revascularisation of the ulcerated foot in patients with diabetes and PAD. The aims of this multidisciplinary working group was to produce a systematic review on the efficacy of (endovascular and surgical) revascularisation procedures and medical therapies in diabetic patients with a foot ulcer and PAD. Based on this review and supplemented with expert opinion if necessary, practical guidelines were formulated These documents were commented upon and subsequently approved by all members (n=xx) of the IWDGF and in this article we report the results of the systematic review on revascularisation techniques and the consensus practical guidelines.

III. Materials and methods

The Medline and Embase databases were searched for therapies to revascularise the ulcerated foot in patients with diabetes and PAD from 1980 - June 2010 respectively (Appendix 1). Searches excluded studies pre-1980 due to the changing nature of interventions for PAD and improving technology. PAD was defined for the purpose of this systematic review as any flow limiting atherosclerotic lesion of the arteries below the inguinal ligament. All patients included had to have objective evidence of PAD (eg angiography or MRA).

It was felt that studies on patients with less severe PAD (resulting in claudication, rest pain or unspecified 'critical ischaemia') were not really of great importance as the aim was to determine the effects of vascular intervention in patients with PAD, diabetes and a foot ulcer. We therefore

restricted the studies to those with patients with tissue loss and studies were only included if greater than 80% of patients had evidence of tissue loss (defined as any lesion of the skin breaching the epithelium / ulceration / gangrene). The diagnosis of diabetes was made according to the individual publication. Because many studies in PAD are not exclusively on patients with diabetes and because the outcome of the patient with diabetes and PAD and a foot ulcer can not be assumed to behave in a similar way to patients without diabetes. We reported studies where >80% of patients of the population studied had diabetes were compromised of more than 40 patients. If a smaller proportion of patients had diabetes we included them only if the outcomes of that cohort were specifically reported as a separate sub-group and the results of at least 30 patients were reported. We excluded studies solely reporting interventions on aortic and iliac arterial disease, studies that had only data on health related quality of life or costs and studies examining the diagnosis and prognosis of PAD in diabetes. Studies reporting medical therapy or local / topical therapy to improve tissue perfusion or to increase oxygen delivery were excluded (for example prostaglandin or hyperbaric oxygen therapy) as well as studies comparing one form of revascularisation technology with another (for example various atherectomy devices).

Only studies reporting ulcer healing, limb salvage, major amputation and survival as the primary outcome measures were included in the review. Early morbidity or mortality was considered within 30 days or within the first hospital admission. A major complication was defined as any which resulted in a systemic disturbance of the patient or prolonged hospitalisation (or as defined by the reporting study). Target lesion revascularisation was not considered.

Patient demographics that were assessed included patient age, gender, ethnicity and co-morbidities (cardiovascular, renal and cerebrovascular). The specifics of the foot lesions were reported where possible, such as site on the foot, depth, presence of infection and stratified when possible according to any previously reported / validated diabetic foot ulcer scoring system. The anatomical distribution of PAD was extracted according to the site of the disease; standard reporting systems were included where possible (eg TASC / Bollinger systems[18, 21]). Objective assessment of perfusion was reported when possible, which included ankle-brachial pressure index (ABI), toe pressure and transcutaneous oxygen concentration (TcpO2). We made no distinction between various endovascular techniques (eg angioplasty, stenting, subintimal angioplasty, atherectomy), all being referred to as 'endovascular therapy' and similarly no distinction was made between various bypass techniques (eg in situ versus reversed venous bypass).

The systematic search was performed according to PRISMA guidelines[22]. Two reviewers assessed studies for inclusion based on titles; two reviewers then excluded studies based on review of the abstract; and then finally, a full text review was performed of selected articles. Studies were assessed for methodological robustness. To do this the Scottish Intercollegiate Guidelines Network (SIGN) instrument was used as follows: Level 1 includes meta-analyses and RCTs, Level 2 includes studies with case-control, cohort, controlled-before-after (CBA) or interrupted time series (ITS) design. Studies were rated as: ++ (high quality with low risk of bias), + (well conducted with low risk of bias) and - (low quality with higher risk of bias), according to the SIGN methodological quality score[23]. Level 3 studies were studies without a control group (eg case series), these studies were not rated. Data were extracted into evidence tables by pairs of reviewers and then reviewed by the whole group. Pooling of data (and therefore weighting of studies) was not possible due to study heterogeneity and the generally low quality of evidence (see below). When several studies reported on a specific item we have summarised the data of these separate studies as inter-quartile ranges and median. It should be noted that these figures are not weighed means.

IV. Results

After the identification and screening phase 866 articles were assessed for eligibility and total of 49 papers described revascularisation of the ulcerated foot in 8,290 patients with diabetes and PAD (PRISMA diagram). These 49 studies were selected for full text review and are summarised in table 1. There were no randomised controlled trials but there were three non-randomised studies with an intervention and control group[31, 47, 57]. These were all of low quality and potentially subject

to significant bias (SIGN 2-). The remaining 46 papers were case series (SIGN 3). Studies reported bypass surgery, endovascular therapy or both techniques used in combination. Although most reports adequately presented patient demographics and comorbidities, a major limitation was that few studies adequately reported or categorized either baseline foot lesions or PAD severity. A number of studies were reported from the same institution and it is likely that some patients were reported more than once.

1. Co-morbidity and patient demographics

Overall the proportion of males in each study varied from 37% - 96% with mean or median ages of individual studies varying from 36 - 74 years. Patient with diabetes, PAD and foot ulcers had significant comorbidity with a relative large proportion of patients having cardiovascular, cerebrovascular or renal disease. The prevalence of coronary artery disease was reported as 40 - 60% (interquartile ranges) with a median of 50%, of cerebrovascular disease as 18 - 24% with a median of 20% and of end-stage renal disease as 11 - 48% with a median of 20% (although the definition varied form study to study and in some studies was only reported as renal impairment). Eight studies did not report any data on co-morbidity and data on severity of co-morbidities was sparse (eg NYHA classifications).

2. Early complications

Methods for reporting early complications were varied. Major systemic complications were frequent in both patients undergoing bypass surgery and endovascular procedures with the majority of studies reporting major systemic complications in the region of 10% with similar rates for endovascular and bypass surgery.

3. Peri-operative mortality

30-day or in-hospital mortality was described in 30 studies. The peri-operative mortality following open surgery was reported in 20 studies and had an interquartile range of 0.8-3.7%, with a median of 1.4% and was comparable in endovascular procedures: 0 - 4.3% with a median of 0.5%. In both open and endovascular series there were several outlying studies with either no mortality or a mortality rate of 9% or greater. It was not clear why these results were so different. As the severity of co-morbidities frequently was not stated it was difficult to infer the effect of co-morbidity on outcomes.

4. Mortality

Mortality at one year or longer following intervention was reported more frequently in studies describing open surgery. Morality at one year follow-up reported in these studies had an inter-quartile range of 11.3 - 21.8%, with a median of 13.5% and at five years: 36 - 52.3% with a median of 46.5%. There was a paucity of long-term follow-up data in patients having undergone endovascular procedures. Three studies reported on one-year follow-up of patients undergoing endovascular procedures with mortality rates of 10% in two studies and 29% in another; five year follow-up mortality rate was reported in two studies and varied widely (5% and 74%).

5. Limb salvage and wound healing

Limb salvage data were reported in the majority of studies, however in almost all studies it was not clearly defined. Following open surgery, the one-year limb salvage rates had an inter-quartile range of 80 - 90% with a median of 85% in the 19 studies with one year data. Following endovascular revascularisation these rates were 70.5 - 85.5% (inter-quartile ranges) with a median of 78%. At three and five years following open surgery these figures were 79.5 - 90% with a median of 82% and 74 - 78% with a median of 78%, respectively. At three years following endovascular procedures the limb salvage rate was 72 - 78.5% (inter-quartile ranges) with a median of 76% in four studies. At five years limb salvage was 56% and 77% in the two studies which reported it. Wound healing was reported in seven studies[25, 30, 33, 35, 59, 65, 66]. Only one defined wound healing at a pre-defined time point of 12 months[59]. However, overall the seven studies following endovascular and two following bypass surgery demonstrated an ulcer healing rate of 60% or more at 12 months follow-up.

6. Amputation

Major amputation was reported by 30 studies. The definition of major amputation was not always specified and sometimes differed between studies. Major amputations within 30 days were reported in three studies and varied from 2.1%, 3.5% and 5%. Only two studies reported amputations at 12 months[29, 63]. The amputation rates within 24 months following open surgery had an inter-quartile range of 12.8 - 22.8%, with a median of 17.3% and following an endovascular procedure these figures were 5.4 - 12.5% and 8.9%, respectively. The study by Malmstedt was an interpretation of the Swedish national vascular registry, Swedvasc and therefore represents the results of a number of different vascular centres rather than those simply focussed on distal bypass procedures[44]. A composite outcome of amputation and death (median follow-up 2.2 years) was given in the registry. The rate of ipsilateral amputation or death per 100 person years was 30.2 (95% CI 26.6 - 34.2). The median time to reach this end-point in patients with diabetes and PAD undergoing bypass surgery (82% for ulceration) was 2.3 years.

Minor amputation rates varied widely in the 11 studies reporting on this complication[24, 28, 29, 30, 32, 39, 41, 43, 49, 65, 66]. Over the study periods minor amputation was reported a median of 38% (inter-quartile range 23 - 59%). However there was great variation with studies reporting a range of 12% to 91.7%. It was not clear whether patients received one or more minor amputations in any particular study. The rates of minor amputations varied between open surgery studies 26% (inter-quartile range 19 - 70%) and angioplasty studies 43% (inter-quartile range 38 - 53%), however the numbers of studies was small and the demographics heterogeneous.

7. Infection

Only two studies specifically reported the outcomes of patients presenting with foot infection, PAD and diabetes[62, 61]. Mortality at one year was 5% and 19%. Limb outcomes were poorly described but limb salvage was 98% in one study at one year[61].

8. End-stage renal disease

Patients with end-stage renal disease (ESRD) were identified in six studies[40, 43, 47, 52, 58, 67]. The definition of ESRD varied and included patients both prior to and on dialysis and those with functioning renal transplants. Thirty day mortality was 4.6% (inter-quartile range 2.6 - 8.8%) but one year mortality was high with 38% (interquartile range 25.5 - 41.5%) of patients perishing. One year limb salvage rates were 70% (inter-quartile range 65 - 75%) in survivors. Long-term outcomes were also poor. Reported mortalities at 2 years were 48%[43] and 72%[40], at 3 years 56%[58] and at 5 years 91%[47].

9. Angioplasty first strategy

Three studies, with a mean follow-up of 20, 25 and 26 months reported on an angioplasty first strategy, where angioplasty was the preferred fist-line option for revascularisation (scoring of anatomical distribution was not given)[65, 30, 39]. In one of these studies, a large series of 993 consecutive patients with diabetes hospitalised with foot ulcer or ischemic rest pain and PAD. PTA was technically not feasible in 16% of the patients due the complete calcified occlusion of the vessel which did not permit balloon catheter passage[30]. PTA did not establish in line flow to the foot in only 1%. The second study was a consecutive series of 100 patients considered suitable for an infra-inguinal PTA first approach and 11% of the patients required bypass surgery for a failed PTA[39]. In the third study, a consecutive series of 534 patients were recruited from a tertiary referral hospital. Of these, data was available on 510. Angioplasty was attempted in 456 (89.4%). Angioplasty was a technical failure in 11%[65]. Mortality and limb salvage rates were comparable to the other series.

10. Crural vessel angioplasty

Crural PTA employed as a revascularisation technique in isolation was reported in four studies[27, 32, 35, 67, 69]. Outcomes were variously on limb salvage, all of which exceeded 63% at 18 months (up

to 93% at 35 months).

11. Pedal bypass grafts

Ten studies reported the results of pedal bypass grafting (one of which focused on outcomes in patients with ESRD). Studies reported limb salvage rates following pedal bypass grafting with an inter-quartile range of 85 - 98%, with a median of 86% at one year, 88.5 (81.3 - 82.3%) at three years and 78% (78 - 82.3%) at five years. However, the numbers available for follow-up at three and five years were low; the distribution / severity of PAD and the type of foot lesion were poorly reported.

V. Discussion

This systematic review examines the evidence to support the effectiveness of revascularisation of the ulcerated foot in patients with diabetes and PAD. This is timely because the proportion of patients with diabetes and an ischaemic component to their ulcer is increasing. Recent reports suggest that up to 50% of the diabetic patients with a foot ulcer have signs of PAD, which had a major impact on ulcer healing and the risk for lower leg amputation[3, 72, 73]. Early reports on the effectiveness of revascularisation in patients with diabetes and PAD were not encouraging and led some to suggest that diabetes was associated with a characteristic occlusive small vessel arteriopathy, consequently leading to a nihilistic attitude toward revascularisation. Subsequent laboratory studies and clinical results well summarised by the Beth Israel-Deaconess group suggested that revascularisation was possible[74]. It has become increasingly recognised that patients with diabetes and an ischemic foot ulcer represent a unique problem among patients with PAD. Consequently the numbers of studies reporting a population or sub-group of patients with PAD, diabetes and ulceration is increasing and more than 50% of the studies included in this systematic review were published after 2001. We specifically did not include studies reporting either outcomes which were not clinically relevant (eg target lesion revascularisation) or that compared specific techniques (such as atherectomy versus transluminal versus subintimal angioplasty).

Whilst the quality of studies included in the review was frequently low there were a surprising number reporting on the effectiveness of revascularisation in diabetic patients with PAD and tissue loss. The interpretation of the effectiveness of revascularisation on outcomes in these studies is difficult as none of the studies included a matched control group receiving non-interventional therapy and the natural history of patients with PAD and an ulcerated foot remains poorly defined. Data on the natural history of patients with PAD, diabetes and critical limb ischaemia (CLI (though not necessarily limited to those patients with tissue loss or ulceration) do, however, exist. In one study that reported the outcomes of diabetic patients with CLI who were not revascularised, the limb salvage rate was 54% at one year[75]. This rate would appear much lower than in the series presented here where limb salvage rates were the majority of studies reported limb salvage rates between 78% and 85%. In a study by Marston in which patients with PAD and ulceration of the foot were treated without revascularisation (70% diabetes) amputation was required in 23% at 12 months but complete wound closure was achieved in 52% in the same time period. ABI at presentation (<0.5) predicted limb loss and the only factor associated with healing was size of ulcer.[76]

We defined peri-procedural mortality and morbidity as any event occurring during a 30-day hospitalisation period. Although peri-operative mortality rates in this review were generally low given associated comorbidities, peri-operative major systemic complications were significant, in the region of 10%. It is possible that part of these major complications were not related to the revascularisation procedure per se, but were more related to the poor general health status of the patients. These major systemic complications were usually poorly defined and are therefore not reported separately in this systematic review. However, our review does indicate that patients with diabetes and a foot ulcer undergoing revascularisation for PAD should be optimised if possible prior to revascularisation. There did not appear to be major differences in morbidity or mortality between open and endovascular techniques, although the studies are difficult to compare as discussed above and we cannot exclude that there were major differences in patient

characteristics and severity of disease. Intermediate and long-term mortality rates during follow-up of studies in this systematic review were high. Over 10% of patients were dead at one year and almost half were dead at five years. These results are similar to those reported in patients presenting with a foot ulcer of any origin, with five year mortality rates around 44%[15]. It was difficult to establish whether early aggressive and successful revascularisation reduced mortality in the long-term. Lepantalo also found that patients with diabetes and CLI appear to be at particularly high risk of death compared to the others with CLI[75]. However, patients in whom successful revascularisation is performed appear to do better than those who undergo major amputation, half of whom are dead within three years [77, 78]. These findings underscore the importance of the severity and systemic nature of vascular disease in patients with diabetes. Diabetic patients with an ischaemic foot ulcer should therefore receive aggressive and appropriate medical management of risk factors to reduce their high long-term mortality.

Ulceration of the foot in diabetes is often a complex interplay of many aetiologic factors, and the situation is compounded by the presence and severity of PAD. In any diabetic patient with ulceration of the foot the pathways to ulceration may differ (eg neuropathy, altered biomechanics) as well as the predominant factors affecting outcome (eg PAD, infection, co-morbidities). Although the current data indicate that revascularisation should always be considered in a patient with diabetes, foot ulceration and severe ischemia, it remains still unclear if such procedures have an added value in cases of mild-moderate perfusion deficits. There are little data to inform on the indications or timing for either diagnostic angiography or intervention among the studies, which should be one of the important topics of future studies. These studies should probably revolve around the influence of patient co-morbidity, the severity of PAD (distribution and level of perfusion) and the characteristics of the foot wound itself.

End-stage renal disease (ESRD) is a strong risk factor for both foot ulceration and amputation in diabetic patients[79]. These patients are frequently difficult to treat and long-term mortality is high, as also exemplified in this systematic review, which might negatively influence the decision to perform a revascularisation procedure. However, our data indicate that even in these patients favourable results can be obtained, the majority of studies reported 1-year limb salvage rates of 65-75% after revascularisation.

Attempts have been made to categorize the distribution of PAD in patients with diabetes and correlate this with perfusion[17]. However, the severity of PAD was not well described in most studies. Results of ABI, toe-pressure or tcPO2 measurements and the anatomical distribution pattern of the PAD were usually not reported and our review indicates that all future reports on revascularisation in diabetic patients with an ischemic ulcer should include objective measurements of the severity of PAD, including both anatomical and functional measurements, such as toe-pressure and/ or TcpO2 measurements. Also wound characteristics were reported poorly, although prospective studies have shown the impact of factors such as size, depth or the presence of infection on healing and amputation rate. Clearly, a standardised wound classification system should be part of all future studies[80]. Moreover, there is a clear need for studies on the role of early revascularisation in diabetic patients with PAD and infected foot ulcers, as these patients are in particular at risk for a major amputation[3].

Standard reporting criteria exist for dealing with lower extremity ischaemia (Rutherford 1997) but are 15 years old and do not focus on factors that are specific to patients with diabetes[81]. Interestingly outcome measures such as major amputation and wound healing were less frequently reported and if reported variously defined in the studies reviewed. Given the difficulty in strictly defining limb salvage, we suggest that major amputation and wound healing should be used as the major endpoints in future reports on revascularisation in diabetic patients with PAD. A separate document on endpoints in studies reporting outcomes of patients with PAD, diabetes and ulceration of the foot will be published from the IWGDF.

There are currently no RCTs directly comparing open vs endovascular revascularisation techniques in diabetic patients with an ischemic foot ulcer. Therefore, there were insufficient data to demonstrate whether open bypass surgery or endovascular interventions were more effective in these patients. However, broadly speaking the major outcomes appeared similar across all studies

where revascularisation of the foot was successful. Two meta-analyses on the outcomes of pedal bypass grafting and crural angioplasty have been performed by the same group and the majority of patients in these two meta-analyses had diabetes[82, 83]. Although the inclusion criteria were different (many of the studies included did not specifically report on patients with diabetes or tissue loss) from our systematic review, limb salvage rates of pedal bypass grafting and crural angioplasty appeared to be equivalent to the results of our systematic review and no major differences were reported between the two techniques. In contrast, primary and secondary patency rates were better after bypass surgery. In two studies of consecutive diabetic patients where angioplasty was the preferred first-line option for revascularisation favourable results were obtained and bypass surgery was only required in a minority of these patients[31, 40]. It is not possible to infer data from the BASIL trial that compared endovascular and bypass surgery in PAD, because it only included 42% of patients with diabetes and no sub-group analysis was performed[84]. However, the results of both open and endovascular procedures will greatly depend upon the expertise in a given center. Clearly further data are required to establish specifically which technique should be preferred taking patient characteristics, severity and distribution of PAD, and wound characteristics into account. Many of the studies reported herein were from well recognised expert centres in revascularisation techniques for patients with diabetes, which bias the results towards more favourable outcomes. Moreover, in some instances there was probably significant overlap in the larger series of patients from certain centres. The data from the Swedvasc registry would suggest that it is possible to attain good outcomes when revascularisation techniques are applied outside centres of expertise[44]. However, such a procedure should not be performed in isolation but should always be part of an integrated multifactorial approach that should include aggressive treatment of infection, debridement and off-loading to protect the wound from repetitive biomechanical stress.

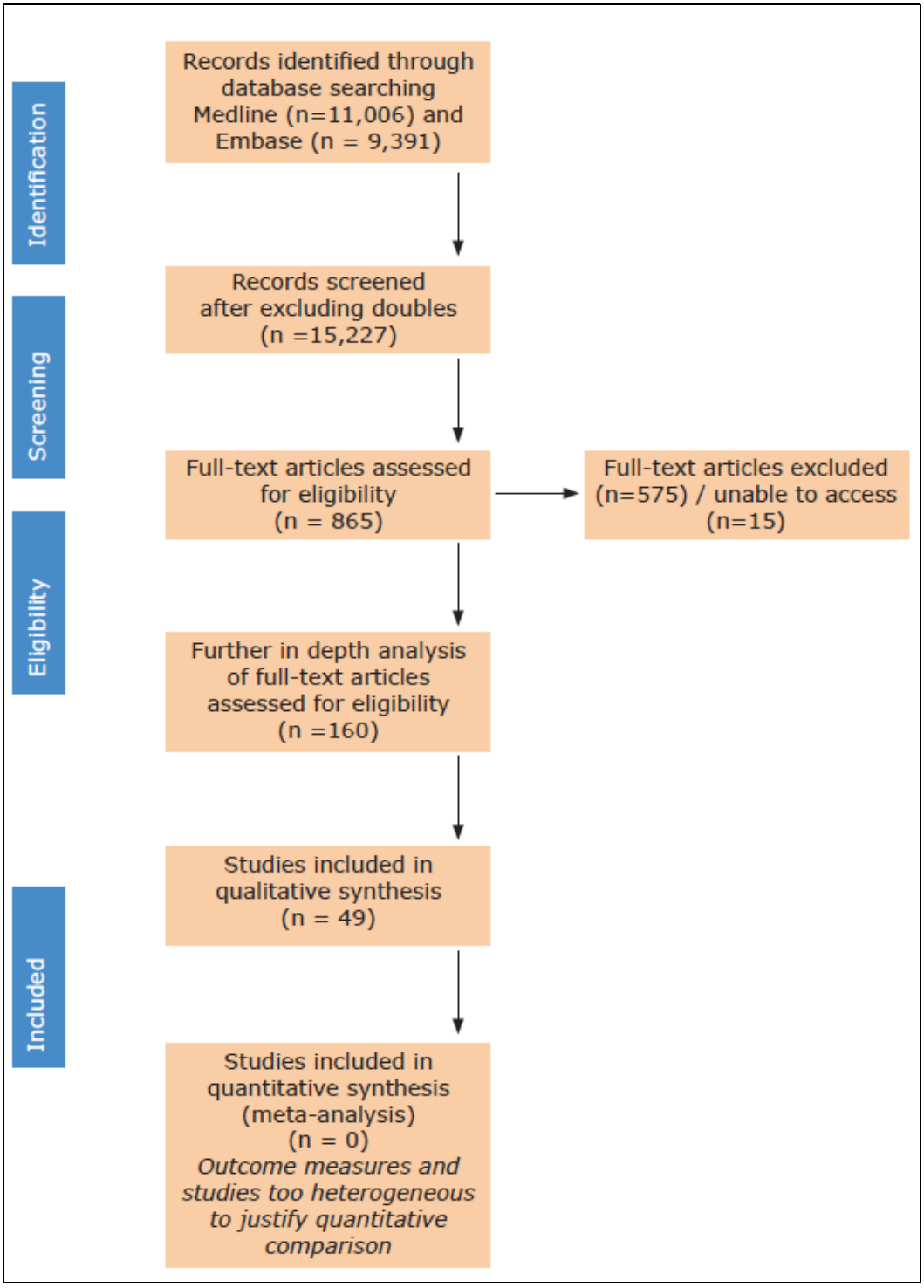
There were significant variations in the proportion of patients undergoing minor amputations. It is difficult to speculate why these rates may vary especially because few studies reported validated foot ulcer scoring systems and the indications for amputation were rarely reported. As discussed above, healing of an ulcer with an intact foot should be one of the primary endpoints of future studies but healing was, if reported, poorly defined in almost all studies. Where healing is only defined as intact skin, an apparently high proportion of patients with healed wounds can be reported if many patients undergo a minor amputation combined with primary wound closure. Clearly this is also an area for future reporting standards.

Almost all studies were cases series with high risk of selection and publication bias. Moreover, cases series comparing bypass surgery and endovascular treatment are difficult to compare because of indication bias. Several studies included in this review were retrospective analyses of small number of patients. Due to heterogeneity we could not pool the data. For ease of data presentation we could only provide the median and (interquartile) ranges of the results of the studies we selected, but this did not correct for number of patients, severity of disease and comorbidities. Due to these limitations we cannot give reliable estimates of expected outcome. Clearly, there is an urgent need for properly controlled studies with a well described population and outcomes which are relevant to patients with diabetes.

In conclusion, studies reported herein appear to demonstrate improved rates of limb salvage associated with revascularisation compared to the results of medically treated patients with diabetes, PAD and ulceration previously reported in the literature. High peri-operative morbidity and long-term mortality rates underline the importance of peri-operative optimisation and long-term medical management of patients' diabetes and co-morbidities. Overall, there were insufficient data to recommend one method of revascularisation over another. There is a real need for standardised reporting of baseline demographic data, severity of disease and outcome reporting in this group of patients. These standards should take into account both the specific characteristics of the PAD and of the wound in these patients. Further efforts are also required to standardise and improve outcome reporting, which should include wound healing, and it is important to move away from procedure specific outcomes to disease specific outcomes in this cohort of patients.

VI. PRISMA Flow Diagram

Fig 1 Open in new window



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Appendix

A. Medline and Embase search strings

Medline Diabetes Treatments Final Search
Date of search: 2nd June 2010
Search Platform: OvidSp,
File searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present

1. diabet*.ti,ab.
2. exp Diabetes Mellitus/
3. 1 or 2
4. (lower adj1 extremit*).ti,ab.
5. (lower adj5 limb*).ti,ab.
6. limb*.ti,ab.
7. leg*.ti,ab.
8. (foot or feet).ti,ab.
9. toe*.ti,ab.
10. Lower Extremity/
11. Leg/
12. Foot/
13. Toes/
14. Extremities/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. peripheral vascular disease*.ti,ab.
18. peripheral arterial disease*.ti,ab.
19. (pvd or povd).ti,ab.
20. (pad or paod or poad).ti,ab.
21. exp Peripheral Vascular Diseases/
22. (claudication or claudicant*).ti,ab.
23. exp Intermittent Claudication/
24. exp Arterial Occlusive Diseases/
25. exp Graft Occlusion, Vascular/
26. exp Saphenous Vein/
27. exp Femoral Artery/
28. exp Popliteal Artery/
29. 26 or 27 or 28
30. occlus*.ti,ab.

31. stenosis.ti,ab.
32. 30 or 31
33. 29 and 32
34. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 33
35. 15 and 34
36. 16 or 35
37. perfusion.ti,ab.
38. reperfusion.ti,ab.
39. exp Reperfusion/
40. (odema or edema or oedema).ti,ab.
41. exp Edema/
42. (swelling* or swollen).ti,ab.
43. inflamed.ti,ab.
44. inflammation.ti,ab.
45. (flow or flux).ti,ab.
46. exp Blood Flow Velocity/
47. capillar*.ti,ab.
48. exp Capillaries/
49. (ischem* or ischaem*).ti,ab.
50. exp Ischemia/
51. (by-pass or by-pass).ti,ab.
52. percutaneous.ti,ab.
53. angioplast*.ti,ab.
54. exp Angioplasty/
55. (ballon adj1 dilation).ti,ab.
56. (ballon adj1 dilatation).ti,ab.
57. exp Balloon Dilatation/
58. endotherapy.ti,ab.
59. endovascular.ti,ab.
60. evt.ti,ab.
61. (revascularization or revascularisation).ti,ab.
62. (endoscopic adj1 therapy).ti,ab.
63. exp Endoscopy/
64. atherectom*.ti,ab.
65. endarterectom*.ti,ab.
66. artherosclerosis.ti,ab.
67. exp Atherectomy/
68. stent*.ti,ab.
69. exp Stents/
70. patency.ti,ab.
71. exp Vascular Patency/
72. (limb adj1 salvage).ti,ab.
73. exp Limb Salvage/
74. subintimal.ti,ab.
75. surg*.ti,ab.
76. su.fs.
77. pta.ti,ab.
78. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
79. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77
80. 36 and 78 and 79
81. (letter or comment or editorial or case reports).pt.
82. 80 not 81
83. limit 82 to humans

Embase Diabetes Treatments Final Search

Date of search: 30th June 2010

Platform: OvidSP

Database file searched: Embase 1980 to present 30th June

1. diabet*.ti,ab.
2. exp Diabetes Mellitus/
3. exp Diabetic Foot/
4. 1 or 3
5. (lower adj1 extremit*).ti,ab.
6. (lower adj1 limb*).ti,ab.
7. limb*.ti,ab.
8. leg.ti,ab.
9. (foot or feet).ti,ab.
10. exp Lower Extremity/
11. Leg/
12. Foot/
13. Toes/
14. toe*.ti,ab.
15. Extremities/
16. or/5-15
17. 4 and 16
18. peripheral vascular disease*.ti,ab.
19. peripheral arterial disease*.ti,ab.
20. (pvd or povd).ti,ab.
21. (pad or paod or poad).ti,ab.
22. exp peripheral vascular disease/
23. (claudication or claudicant).ti,ab.
24. exp intermittent claudication/
25. exp peripheral occlusive artery disease/
26. exp graft occlusion/
27. exp saphenous vein/
28. exp femoral artery/
29. exp popliteal artery/
30. 27 or 28 or 29
31. occlu*.ti,ab.
32. stenosis.ti,ab.
33. 31 or 32
34. 30 and 33
35. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 34
36. 16 and 35
37. 17 or 36
38. perfusion.ti,ab.
39. reperfusion.ti,ab.
40. exp reperfusion/
41. (odema or edema or oedema).ti,ab.
42. exp edema/
43. (swelling* or swollen).ti,ab.
44. inflamed.ti,ab.
45. inflammation.ti,ab.
46. (flow or flux).ti,ab.
47. exp blood flow velocity/
48. capillar*.ti,ab.
49. exp capillaries/
50. (ischemi* or ischaemi*).ti,ab.
51. exp ischemia/
52. or/38-51
53. (by-pass or bypass or by pass).ti,ab.
54. percutaneous.ti,ab.

55. angioplast*.ti,ab.
56. exp angioplasty/
57. (ballon adj1 dilation).ti,ab.
58. (balllon adj1 dilatation).ti,ab.
59. exp balloon dilatation/
60. endotherapy.ti,ab.
61. endovascular.ti,ab.
62. revasculari#ation.ti,ab.
63. (endoscopic adj1 therapy).ti,ab.
64. exp endoscopy/
65. artherosclerosis.ti,ab.
66. exp atherectomy/
67. stent*.ti,ab.
68. patency/
69. exp vascular patency/
70. exp stents/
71. patency.ti,ab.
72. (limb adj1 salvage).ti,ab.
73. exp limb salvage/
74. subintimal.ti,ab.
75. surg*.ti,ab.
76. su.fs.
77. pta.ti,ab.
78. or/53-77
79. 37 and 52 and 78
80. (Letter or Editorial).pt.
81. 79 not 80
82. limit 81 to human

B. Evidence tables

Open in new window

Reference	Study design	Population (age, sex, comorbidity, number with diabetes)	PAD (distribution and severity)	Foot Lesion	Comorbidity	Intervention and control management	Outcomes	Comment	Opinion
AhChong 2004 [24]	Case series 265 consecutive infrainguinal bypasses with outcomes described diabetes versus no diabetes	DM patients 176 No DM 89 Age median 74 (45-94) yrs versus 75 (29-94) no DM gender: 50% (88) male DM, 45 (51%) no DM (P=NS)	Distribution: NR Severity: ABI 0.43 Median toe pressure 26mm Hg (0-57) No scoring system used	Tissue loss 158 (90%) DM No DM 70 (79%) tissue loss (P=0.014) Ulcer score: NR Infection: NR	CAD 48% CVD 26% ESRD NR	Bypass graft to DM patients Fem-pop 44% Crural 40% Pedal 16% Autogenous vein 66% No DM Fem-pop 56% Crural 35% Pedal 9% (P=NS) Autogenous vein 63%	Median f/u 19months Mortality 30days 8% DM versus 1% No DM (P=0.04) Cardiovascular complications 9% v 4% (P=NS) Overall graft patency 1yr 63% Graft patency 4yrs 46% DM versus 34% no DM (P=0.19) Survival rate at 1,3,5 yrs 80%, 57%, 33% Ulcer healing: NR Limb salvage overall at 1 yr 83% for both groups and 5yrs 78% DM v 81% no DM (P=0.79) Major amputation: NR Minor amputation: NR Complications: 8% mortality peri-op	Chinese population may differ from Western world Limited information about patient management	Early graft failure 6% 65 grafts failed overall during total study
Alexandrescu 2009 [25]	Case series A retrospective case series of subintimal PTA and PTA in 161 patients with diabetes and ischaemic wound,	161 DM patients age: > 70 years 41% gender	Distribution: majority multilevel disease Severity: NR TASC	Wagner classification grade 2-4 in 104 limbs (59%) or as isolated calf ulcers in 42 cases (24%).	CVD 40 (22%) CAD 122 (69%) ESRD 33 (18%)	161 procedures majority multilevel with 124 subintimal PTA (26 had single subintimal	Ulcer healing: 129 (73%) before end of study, mean f/u 22 (1) months Limb salvage: 12, 24, 36 and		Level of intervention not described in all patients. Approximately 50% infrapopliteal or crural 70% neuropathy

	PTA first approach		classificaion reported	In 30 (17%) limbs, complex below-theknee trophic lesions were noted. Infection: NR	dialysis		48 month limb-salvage proportions: 89%, 83%, 80% and 80%. In a intention-to-treat analysis, the cumulative primary and secondary patency at 12, 24, 36 and 48 months were 62%, 45%, 41% and 38%, together with 80%, 69%, 66% and 66%, respectively. Major amputation: 24 (13%) during f/u Minor amputation: 67 (38%) 30-day mortality: 1% 2 year mortality: 19% Major complication: 4		
Bargellini 2008 [26]	Prospective case series of multilevel subintimal PTA in patients deemed not fit for surgical bypass	DM patients: 60 age: 69,4 (SD 9,4) gender: 41 males	Distribution: NR Severity: NR	Fontaine: 100% Fontaine IV Infection: NR	CAD 42% CVD 25%	Subintimal PTA in patients not suitable for surgical bypass: Fem-pop level 56.7% (34) Infrapopliteal level 25% (15) Both levels combined 18,3% (11)	Mean follow-up 23 months (range, 0-48 months) Ulcer healing: 75% (45/60) Limb salvage: 93.3% (56/60) Major amputation: 3 within 30 days and 4 within 16 months Minor amputation: Complications: Peri-procedural mortality was 5% (3/60) Mortality at 1yr, 3yr 10%, 17%	How followup was performed, was not defined Long term mortality low for a 'high risk' population medically unfit for bypass surgery	
Davidson 1993 [27]	Retrospective case series Bypass below knee case series	54 DM patients (total wpopulation 70) age 55-95; 38 men (total population)	Distribution: majority infra-popliteal severity: no information No score of distribution	gangrene 56%, ulcer 28% (of total population) Infection: NR Ulcer score: NR	CAD 55%, CVD 27%, hemodialysis 7% (total population)	Vein graft below knee (57% to foot)	Limb salvage 90% at 12months and 86% at 24 months Major complications: 9/70 Early graft failure n=3 (4.2%) Patency 93% 1yr and 85% 2yrs Mortality: NR	Follow-up duration was variable and after 1 year 29 limbs out of 58 limbs were available for evaluation and after 3 years 6 limbs out of 58. Strengths	
Dosluoglu 2008 [28]	Case series A comparison of peroneal to other run-off vessels after PTA	80 DM patients out of 111 age: NR gender: NR	Distribution: infrapopliteal Severity: NR TASC classification provided	All tissue loss Infection: NR	NR	Infrapopliteal PTA	Ulcer healing: NR Limb salvage rate 75% in 24 months in diabetic patients with peroneal run-off and in run-off in other vessels 76% No other data on the diabetes sub-group divided		Strengths and weaknesses: No data on patient, leg or ulcer characteristics in DM patients provided. Study with less than 80% with diabetes but limb salvage was reported separately for the diabetes patients in both groups
Dorweiler 2002 [29]	Case series of pedal bypass grafts	DM patients 46 age: median 69yrs gender: 36/46 (78%) male	Distribution: crural occlusions Severity: NR	All (100%) tissue loss Ulcer score: NR Infection: NR	CAD 46% ESRD 13%	Pedal bypass with vein graft	F/U median 28 (1-70) months Ulcer healing: Limb salvage: 30 days 98%, 87% at 2 years Major amputation: 4 (3 within 30 days) Minor amputation: 32/46 Complications: peri-operative mortality 2% One patient failed graft within 30days Mortality at end	No data on severity of PAD. No specific data on foot lesions Drop out and loss to f/u NR Well defined study	

							of study 21/46 (47%)		
Faglia 2002 [19]	Case series Mixed series of PTA	All DM patients 221 age: NR gender: NR	Distribution: 11 patients ilio/ femoral/popliteal axis 81 exclusively infrapopliteal 127 femoropopliteal and infrapopliteal Severity: TcpO2 21 (30 SD) mm Hg in 180 cases. ABI in 128 cases 0.53 (0.15)	Wagner grade ulceration I - 19% II - 25% III - 17% IV - 38% V - 1%	CAD 55% ESRD 4%	PTA of stenoses greater than 50% diameter infrainguinal	Median f/u 12 (5-30) months Ulcer healing: Limb salvage: Major amputation: 10 (5%) Minor amputation: 83 (38%) Mortality 30days: 0% Mortality 5.3% at f/u Complications: n=1 (transient renal failure)		Probably significant (> 80%??) of the data is a duplication of Pdf 117, data reported in DE 117 221 had angio but 2 had no significant stenoses therefore 219 reported 28 subjects PTA not possible (9 surgery and 19 no candidate for any revasc) All ulcers healed with medical dressings of the 190 patients - nothing more specific
Faglia 2005 [30]	Retrospective case series Consecutive series of diabetic foot patients hospitalised. PTA as first choice revascularisation	DM patients 993 age: 65.5 (9.4) gender: 663 (67%) male	7% ilio-femoral 61% femoropopliteal /crural 32% crural Severity: tcpO2 17,0 (11,9)	88% tissue loss Texas classification 0 - 12% I - 16% II - 19% III- 53%	CAD 62% ESRD 5%	PTA 68% procedures in crural arteries	Mean f/u 26 (15.1) months Ulcer healing: 862/868 wounds healed Limb salvage: NR NR 21/993 major amputations Minor amputation: 478 Complications: NR 3.4% Mortality 30-day 1/993 Primary patency at 5yrs 88% (SD 9%) Mortality at 1 yr 5% (extrapolated from Kaplan-Meier curve)	good wound description at presentation, level of disease : treated was well described some f/u data was obtained by treating physician telephone interview	Possibly some patients reported elsewhere Of the 993 treated with PTA only 10 did not manage to successfully get one vessel in line flow to the foot
Faglia 2009 [31]	Cohort with follow up 5,9 year (SD 1,28) Follow up study of 564 diabetic patients with 'CLI' referred for angiography, patients with obstruction more than 50% underwent PTA, when possible as first choice	PTA: 413 DM patients age:69,7 (SD 9,5) gender: 146 (35,4%) females Bypass group: 114 DM patients age: 69.9 (SD 9.4) gender: 35 (30.7%) females No revasc group: 27 DM patients age: 76.7 (SD 10.4) gender: 13 (48,1%) females	Distribution: PTA: Iliac -femoral-popliteal axis in 28 patients (6,8%) Infra-popliteal in 137 patients (32,2%) Combination of both in 248 patients (60%) Bypass: NR No revasc: NR Severity: PTA: tcpO2 15,3 (11,9) Bypass: tcpO2 10,2 (10,3) No revasc: tcpO2: 7,0 (8,1) Scoring: NR	PTA: No lesion 62 (16%), rest Wagner 1-4 Infection: 65% Bypass: No lesion 16 (14%), rest Wagner 1-4 Infection 63% No revasc: No lesion 3 (11%), rest Wagner 1-4 Infection: 63%	PTA: Dialysis 24 (5,7%) CAD 225 (54,8%), CVD 53 (19%) Bypass: Dialysis 8 (7%); CAD 64 (59%), CVD 18 (15,8%) No revasc: Dialysis NR, CAD 24 (88,9%), CVD 9 (33,3%)	PTA: Ulcer healing: NR Limb salvage: NR Major amputation: 1 month 6 (2,3%); 34 (8%) at end of follow up Minor amputation: NR Complications: NR Bypass: Ulcer healing: NR Limb salvage: NR Major amputation: 1 month 3 (5,4%); 24 (21%) at end of follow up Minor amputation: Complications: NR 36 (32%) primary bypass failures No revascularisation: Ulcer healing: NR Limb salvage: NR Major amputation: 16 at end of follow up Minor amputation: NR Complications: NR PTA vs. bypass p < 0,001 SIGN 2-	In addition authors analyzed their data as a a case control study	No data on severity of PAD. No specific data on foot lesions Drop out and loss to f/u NR Well defined study	The groups are the result of a stepwise treatment approach Statistical analyses do not seem systematically performed and analyses are missing. In particular, Kaplan-Meijer data are incomplete: number at risk at time points are missing. The study cannot used as a cohort study comparing PTA vs bypass, it does however give information about the results of PTA and information of the revascularised vs nonrevascularised patients Baseline characteristics of the groups are different and therefore confounding was induced.
Ferraresi 2009 [32]	101 DM patients and 107 legs age: 66 (SD 9,4) gender: 16 females	Distribution: Infrapopliteal Severity: tcpO2 18.1 (SD 11,2) Infection: NR	34 ulcers, 74 gangrene Rutherford classification	CAD 28% CVD 4% ESRD 3% (dialysis)	PTA infrapopliteal		Ulcer healing: NR Limb salvage: 93% during mean f/u 2.9yrs Major amputation: 8/107 (7%) during mean f/u 2.9yrs Minor amputation: 64% Complications: NR Mortality 30 day: NR Mortality during f/u 9%	This case series is a sub analysis of a larger study	Strengths: Treated lesions clearly defined and standardised Patients with marked tissue loss Weaknesses: 1 and 3 year leg salvage and survival data are not provided, hindering interpretation.
Gargiulo 2008 [33]	Prospective case series Outcome of successful tibial PTA in 'CLI'	74 DM patients out of 87 total population age: 72 (SD 8,8) gender: 44%	Distribution: NR Severity: NR	92% Fontaine IV Ulcer classification: University of Texas Infection: NR	CAD 53% ESRD 28%	infrapopliteal PTA's (100%) combined with fem-pop angiopolasty in 63% and in 3 (3,4%) patients combined with open revascularisation	Ulcer healing: 74,9% at 1 year Limb salvage: 92,7% at 1 year Major amputation: NR	Only technically successful PTA included in the analysis	Strengths and weaknesses: Strengths: well performed prospective study with complete data set, provides relevant information on wound healing

		female		237/318			Minor amputation: NR Complications: No early perioperative complications		Weakness: the shortest followup data was 2 days, a Kaplan Meijer that includes duration of follow-up is missing, hampering interpretation
Gibbons 1995 [34]	Retrospective case series Infrainguinal bypass series	259 DM patients (total population 318) age: mean age 66years gender: 62.3% males	Distribution: Multilevel disease Severity: no information No score anatomical distribution Distribution:	(74.8%) ulcer or gangrene Infection: NR Ulcer score: NR	No information	infra-inguinal open revascularisation fempop 84 (26.4%) femtibial / peroneal 132 (41.5%) fempedal / plantar 100 (31.4%)	Ulcer healing: NA Limb salvage: 97% at 6 months Major amputation: n/a Minor amputation: NA 93% primary graft patency at 6months and secondary 97% Complications: morbidity peri-op 21%	Walking devices used at start of study 63% and at end of 6months 74% 38% more active at f/u 32.5% about the same and 29.5% worse. Less than half back to normal at 6months (47.4%)	primarily HRQOL study
Hering 2010 [35]	Prospective case series Case series of crural PTA	All diabetics 44 Gender 33 male Age 72 (42-88yrs)	Distribution: NR Severity: NR	Wagner grade I - 0 II - 6 (14%) III (30 (68%) IV - 8 (18%) Infection: NR	CAD 77% CVD 52% ESRD 16%	Peroneal PTA	Mean F/u 23 (5-45) months Ulcer healing: 26/44 Limb salvage: 81%, 6, 71% 12, and 63% at 18 months Mortality 30days: 9.1% Major amputation: 5 (11%) Minor amputation: NR Complications: 1 renal failure		Really a prognostic study of doppler waveform patterns predicting outcome of peroneal PTA Overall 50% had a restenosis or occlusion of peroneal artery
Hertzer 2007 [36]	Case series Mixed case series of bypass grafts	312 DM patients out of 650 (48%) age: NR gender: 62 males	Distribution: NR Severity: NR	71% ulceration or gangrene Ulcer score: NR Infection: NR	NR	infrainguinal bypass grafts for occlusive disease	Median follow-up 4yrs Ulcer healing: NR Limb salvage: 73% (95% CI 67 - 78) at 5 years, 15 years 51% (38 - 64) Major amputation: 29 amputations in 201 diabetic patients Minor amputation: NR Mortality 6.7% 30 days		Strengths and weaknesses: very long follow up time limited specific data on diabetics
Hughes 2004 [37]	Retrospective case series Series of pedal bypasses	DM patients 82 (84%), total 98 age: 68 (SD12) gender: 81/98 (83%) male	Distribution: Crural Severity: NR No scoring	93 (95%) tissue loss Infection: NR Ulcer classification: NR	CAD 40% ESRD 4%	Bypass to plantar and tarsal arteries with vein graft (one prosthetic) Popliteal inflow 72% Pedal bypass	Mortality at end of study 83% at median 4yrs Complications: not reported separately for diabetes Duration of f/u median 9 (1-112)months Ulcer healing: NR Mortality 30 days 1/98 total Complications: 124 peri-op complications Mortality at 1yr 9%, 5yrs 37% Limb salvage 75% 1yr, 69% 5yr Secondary patency 70% 1yr	Primary patency 41% and secondary patency of 50% at 5yrs Consecutive series of all revascularisations Excluded lost to f/u cases from analysis (n=26)	No differences in outcome between tarsal/ plantar and dorsalis pedis bypass
Isaksson 2000 [38]	Retrospective case series Pedal bypass graft case series	DM patients 43 (48 legs) age: 74 (40-84) gender: females 27 (63%)	Distribution: NR Severity: ABPI median 0.47 (0 - 2.14) Score: NR	7 (15%) rest pain All others (85%) tissue loss Ulcer score: NR Infection: NR	Prev MI 11 (26%), angina 6 (14%)	with vein (proximal anastomosis femoral artery 20 (42%) and popliteal artery or below 28 (58%))	F/U up to 1yr Ulcer healing: Limb salvage: 1yr 85% Major amputation: NR Minor amputation: NR Complications at 30 days 2 died (4%), 1 patient MI	Short followup - early results only	

							Mortality rate at 1yr 14% Patency at 1yr 83%		
Jamsen 2002 [39]	Retrospective case series Outcome of consecutive series of 100 infrainguinal PTA considered suitable for PTA first approach	100 patients (116 limbs) 76 (76%) DM patients age: 72 (38-90)yr total population gender: 40 (40%) total population males	Distribution: NR Severity: ankle systolic pressure <50mm Hg Scoring system not used	Rest pain 23 (20%), ulcer 50 (43%), gangrene 43 (37%) Wound classification: NR Infection: NR	CAD 47%, CVD 28%	Angioplasty Femoropopliteal 54% Crural 17% Multilevel 29%	Intention to treat analysis 1yr 67%, 3yr 63%, 5yr 56%, 8yr 45% limb salvage Ulcer healing: NR Limb salvage for endovascular treatments at 3, 5, and 8 years was 65%, 60%, and 60%, Major amputation: 37 (32%) major amp during total f/u Minor amputation: 14 (12%) Major complications: 11% The survival rates of the present study 72%, 26%, and 14% at 1, 5, and 10 years	11 required bypass for PTA failure. Median f/u 25months. Validity of 5 and 10 year questionable - very small numbers available after 3 years Pre selected to PTA first approach	
Johnson 1995 [40]	Restrospective case series Retrospective review of popliteal distal bypass grafts in patients with ESRD	43 DM patients In total population 53 age: 59 (total population) gender: 27 males (total population)	Distribution: NR Severity: in general toe pressures <40, ABI <0.5 (or incompressable) Scoring NR	69 limbs (53 with tissue loss) Ulcer score: NR	43 ESRD (kidney transplant 10) CAD 38% CVD 15%	Total population 69 venous bypasses: Fem-pop 19 Crural 50	Ulcer healing: NR Limb salvage: 1yr 65% and 62% at 18 months Major amputation: 22 ('foot amputations') Minor amputation: NR Major complications: NR Peri-op mortality 10% 1yr mortality 42%, 2yr mortality 72%	59% 'foot amputations' performed with patent graft	Amputation can be related not only to occlusion but also to other factors like infection.
Kalra 2001 [41]	Retrospectivecase series Series of pedal bypass grafting using vein	DM patients 191 (75%), total population 256, 280 procedures age: median 70 (30-91)yrs total population gender: 174 (68%) male total population Long grafts (prox anastomosis above popliteal) 130 (46%) of total population Short grafts (prox anastomosis at or below popliteal) 150 (54%) of total population	Distribution: NR Severity: tcpO2 < 20mmHg in 88% and ABI =0.44 (38% incompressible) in 150 limbs Scoring system: NR	90% tissue loss total population Infection: NR Wound classification: NR	(52%), CVD 54 (21%), ESRD 19 (7%)	All vein bypass grafts to pedal vessels	Ulcer healing: Cumulative limb salvage rates at 1, 3, and 5 years were 85% (95% CI, 80.3-89.5), 79% (95% CI, 73.9-85.1), and 78% (95% CI, 71.7-83.7), respectively Ulcer helaing: NR Major amputation: 15% at 2.7years mean f/u Minor amputation: 12.4% Complications: 1.6% peri-op mortality Long-term mortality 1,3,5 yr = 13%, 24%, 40% Secondary patency at 1yr 78%, 3yr 72%, 5yr 71%	Survival rate was 65% if had patent graft at 5 yrs versus 26% if leg off 57% of patients had one or more secondary interventions for pedal graft	
Kandzari 2006 [42]	Case series Endovascular revascularisation using catheter based plaque excision	52 DM patients out of total pop of 69 age: 70 (SD 12) (total pop) gender: 49% males	Distribution: 154/160 lesions infrainguinal 43% crural Severity: ankle pressure < 50 mmHg	93% Ruth 5 7% Ruth 6 (total pop) No ulcer lassification	CAD 57% CVD 23% Infection: NR	endo-vascular plaque excision	Ulcer healing: NR Limb salvage: NR Major amputation: 20% diabetes versus 18% no diabetes (p=0.86) at 6 months Minor amputation: NR Complications: major adverse		Data reported comparing patients with and without diabetes however very little information given