DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2012; **28**(Suppl 1): 179–217.
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2249

REVIEW ARTICLE

A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease†

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†Published on behalf of the International Working Group on the Diabetic Foot.

Received: 1 October 2011
Accepted: 1 October 2011

Summary

In several large recent observational studies, peripheral arterial disease (PAD) was present in up to 50% of the patients with a diabetic foot ulcer and was an independent risk factor for amputation. The International Working Group on the Diabetic Foot therefore established a multidisciplinary working group to evaluate the effectiveness of revascularization of the ulcerated foot in patients with diabetes and PAD. A systematic search was performed for therapies to revascularize the ulcerated foot in patients with diabetes and PAD from 1980–June 2010. Only clinically relevant outcomes were assessed. The research conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the Scottish Intercollegiate Guidelines Network methodological scores were assigned. A total of 49 papers were eligible for full text review. There were no randomized controlled trials, but there were three nonrandomized studies with a control group. The major outcomes following endovascular or open bypass surgery were broadly similar among the studies. Following open surgery, the 1-year limb salvage rates were a median of 85% (interquartile range of 80–90%), and following endovascular revascularization, these rates were 78% (70.5–85.5%). At 1-year follow-up, 60% or more of ulcers had healed following revascularization with either open bypass surgery or endovascular revascularization. Studies appeared to demonstrate improved rates of limb salvage associated with revascularization compared with the results of medically treated patients in the literature. There were insufficient data to recommend one method of revascularization over another. There is a real need for standardized reporting of baseline demographic data, severity of disease and outcome reporting in this group of patients. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords diabetic foot; ulcer; peripheral arterial disease; amputation; diabetes

Abbreviations: ABI, ankle-brachial pressure index; AHA, Americal Heart Association; AKA, above-knee amputation; ARF, acute renal failure; AT, anterior tibial artery; BASIL, bypass versus angioplasty in severe ischaemia of the leg; BKA, below-knee amputation; CAD, coronary artery disease; CBA, controlled 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; NYHA, New York Heart Association; PAD, peripheral arterial disease; PT, posterior tibial artery; PTA, percutaneous transluminal angioplasty; RCT, randomized 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).

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, in every 20 s, a leg is lost in our world as a result of diabetes [1,2]. Peripheral arterial 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 10–40% in the general population of patients with diabetes have been reported [5–7]. Moreover, in comparison with 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 ischaemia with delayed wound healing and a high risk of amputation. In several large observational studies, PAD was present in up to 50% of the patients with a diabetic foot ulcer (DFU) and was an independent risk factor for amputation [9–11]. 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 such as infection, neuropathy and renal failure and the presence of abnormalities in other vascular territories, such as the coronary or cerebral arteries [7,9,12–14] The mortality of patients with PAD and a DFU 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 patients with diabetes and a foot ulcer will therefore relate in part to its severity and extent and 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 patients with diabetes and ankle-brachial pressure index (ABI) < 0.5 underwent adequate vascular evaluation and subsequent revascularization, 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 that 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 revascularization 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, ulceration or gangrene are usually the result of several interacting factors in patients with diabetes, 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 ischaemic 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, internal medicine and epidemiology to evaluate the effectiveness of revascularization of the ulcerated foot in patients with diabetes and PAD. The aim of this multidisciplinary working group was to produce a systematic review on the efficacy of (endovascular and surgical) revascularization procedures and medical therapies in diabetic patients with a foot ulcer and PAD. With this review, supplemented with expert opinion if necessary, practical guidelines were formulated. These documents were commented upon and subsequently approved by the members of the IWDGF. In this article, we report the results of the systematic review on revascularization techniques. The consensus practical guidelines are published elsewhere in this issue.

Materials and methods

The MEDLINE and Embase databases were searched for therapies to revascularize the ulcerated foot in patients with diabetes and PAD from 1980–June 2010, (Appendix A). Searches excluded studies before 1980 because of

DOI: 10.1002/dmrr

the changing nature of interventions for PAD and improving technology.

Peripheral arterial disease 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 (e.g. angiography or magnetic resonance angiography).

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. Many studies in PAD are not exclusively on patients with diabetes, and the outcome of the patient with diabetes and PAD and a foot ulcer cannot be assumed to behave in a similar way in patients without diabetes. We reported studies where >80% of patients of the population studied had diabetes in studies 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 subgroup 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 revascularization 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 that resulted in a systemic disturbance of the patient or prolonged hospitalization (or as defined by the reporting study). Target lesion revascularization was not considered.

Patient demographics that were assessed included patient age, gender, ethnicity and co-morbidities [cardiovascular, renal and cerebrovascular disease]. 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 DFU scoring system. The anatomical distribution of PAD was extracted according to the site of the disease; standard reporting systems were included where possible (e.g. TASC/Bollinger systems [18,21]). Objective assessment of perfusion was reported when possible, which included ABI, toe pressure and transcutaneous oxygen concentration ($TcPO_2$). We made no distinction between various endovascular techniques (e.g. angioplasty, stenting, subintimal angioplasty and atherectomy), all being referred to as 'endovascular therapy'. Similarly, no distinction was made between various bypass techniques (e.g. *in situ versus* reversed venous bypass).

The systematic search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [22]. Two reviewers assessed studies for inclusion on the basis of titles; two reviewers then excluded studies on the basis of 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 randomized controlled trials (RCTs). Level 2 includes studies with case–control, cohort, controlled before and after or interrupted time series 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 (e.g. 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 because of study heterogeneity and the generally low quality of evidence (see following discussion). When several studies reported on a specific item, we have summarized the data of these separate studies as interquartile ranges (IQRs) and median. It should be noted that these figures are not weighted means.

Results

After the identification and screening phase, 865 articles were assessed for eligibility and 49 papers were finally selected for full text review. These articles described revascularization of the ulcerated foot in 8290 patients with diabetes and PAD (Table 1). There were no RCTs, but there were three nonrandomized 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 co-morbidities, 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.

Co-morbidity and patient demographics

Overall, the proportion of men in each study varied from 37–96% with mean or median ages of individual studies

DOI: 10.1002/dmrr

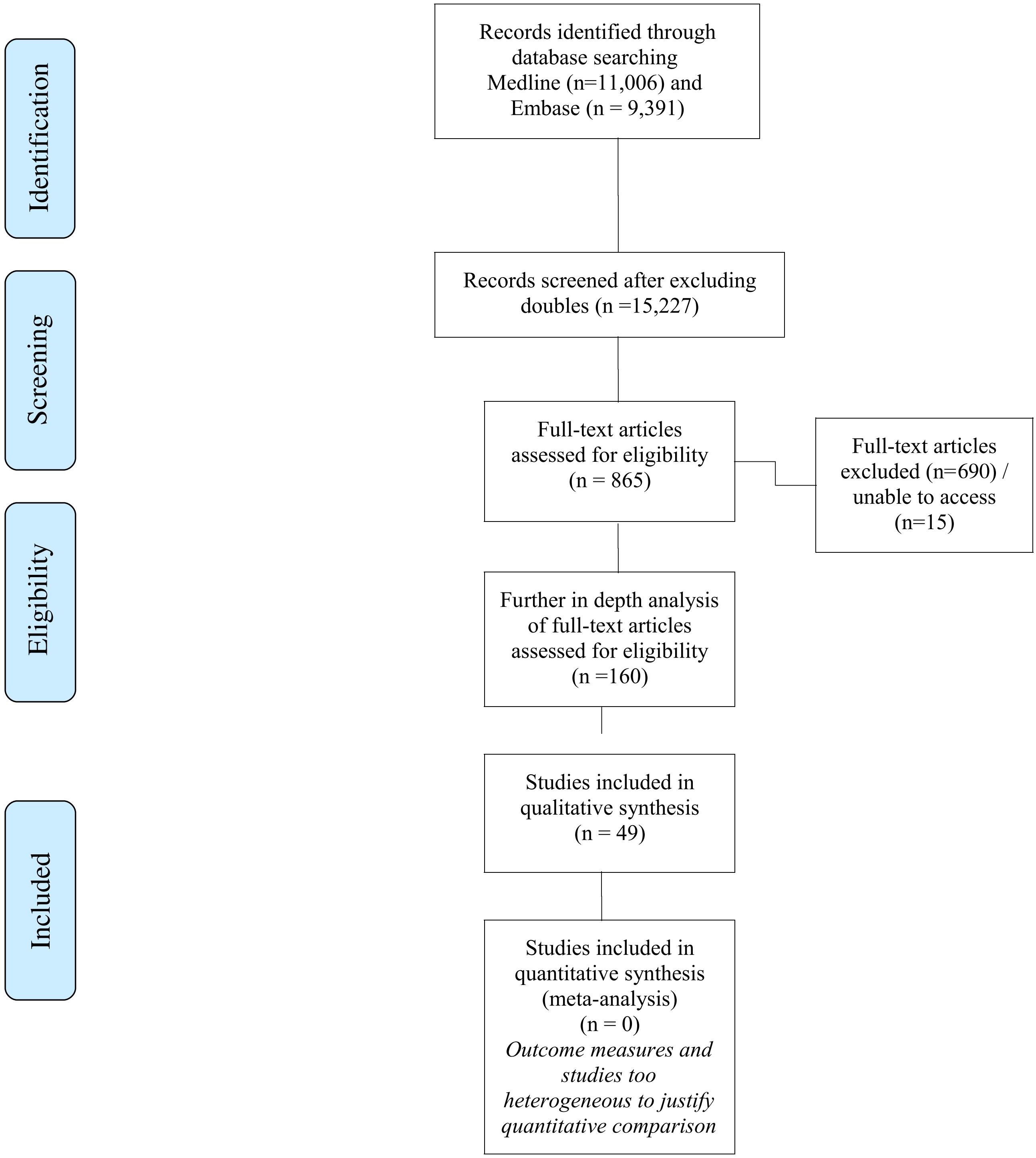

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

varying from 36 to 74 years. Patient with diabetes, PAD and foot ulcers had significant co-morbidity with a relatively large proportion of patients having cardiovascular, CVD or renal disease. The prevalence of coronary artery disease was reported as 40–60% (IQRs) with a median of 50%, of CVD as 18–24% with a median of 20% and of end-stage renal disease (ESRD) as 11–48% with a median of 20% (although the definition varied from 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 (e.g. New York Heart Association classifications).

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.

Perioperative mortality

Thirty-day or in-hospital mortality was described in 30 studies. The perioperative mortality following open surgery was reported in 20 studies and had an IQR 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.

Mortality

Mortality at 1 year or longer following intervention was reported more frequently in studies describing open surgery. Morality at 1-year follow-up reported in these studies had an IQR of 11.3–21.8% with a median of 13.5% and at 5 years an IQR of 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 1-year follow-up of patients undergoing endovascular procedures with mortality rates of 10% in two studies and 29% in another; 5-year follow-up mortality rate was reported in two studies and varied widely (5 and 74%).

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 1-year limb salvage rates had an IQR of 80–90% with a median of 85% in the 19 studies with 1-year data. Following endovascular revascularization, these rates were 70.5–85.5% (IQR) with a median of 78%. At 3 and 5 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 3 years following endovascular procedures, the limb salvage rate was 72–78.5% (IQRs) with a median of 76% in four studies. At 5 years, limb salvage was 56 and 77% in the two studies that reported it. Wound healing was reported in seven studies [25,30,33,35,59,65,66]. Only one defined wound healing at a predefined 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.

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 IQR 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 focused 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 endpoint 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 [24,28–30,32,39,41,43,49,65,66]. Over the study periods, minor amputation was reported a median of 38% (IQR 23–59%). However, there was great variation with studies reporting a range of 12–91.7%. 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% (IQR 19–70%) and angioplasty studies 43% (IQR 38–53%); however, the number of studies was small and the demographics heterogeneous.

Infection

Only two studies specifically reported the outcomes of patients presenting with foot infection, PAD and diabetes [61,62]. Mortality at 1 year was 5 and 19%. Limb outcomes were poorly described but limb salvage was 98% in one study at 1 year [61].

End-stage renal disease

Patients with 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% (IQR 2.6–8.8%), but 1-year mortality was high with 38% (IQR 25.5–41.5%) of patients perishing. One-year limb salvage rates were 70% (IQR 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].

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 revascularization (scoring of anatomical distribution was not given) [30,39,65]. In one of these studies, a large series of 993

DOI: 10.1002/dmrr

consecutive patients with diabetes hospitalized with foot ulcer or ischaemic rest pain and PAD, percutaneous transluminal angioplasty (PTA) was technically not feasible in 16% of the patients because of 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 infrainguinal 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 were 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 with the other series.

Crural vessel angioplasty

Crural PTA employed as a revascularization technique in isolation was reported in four studies [27,32,35,67,69]. Studies variously reported limb salvage outcomes, all of which exceeded 63% at 18 months (up to 93% at 35 months).

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 IQR of 85–98%, with a median of 86% at 1 year, 88.5% (81.3–82.3%) at 3 years and 78% (78–82.3%) at 5 years. However, the numbers available for follow-up at 3 and 5 years were low; the distribution/severity of PAD and the type of foot lesion were poorly reported.

Discussion

This systematic review examines the evidence to support the effectiveness of revascularization 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 patients with diabetes 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 revascularization in patients with diabetes and PAD were not encouraging and led some to suggest that diabetes was ssociated with a characteristic occlusive small vessel arteriopathy, consequently leading to a nihilistic attitude toward revascularization. Subsequent laboratory studies and clinical results well summarized by the Beth Deaconess group suggested that revascularization was possible [74]. It has become increasingly recognized that patients with diabetes and an ischaemic foot ulcer represent a unique problem among patients with PAD. Consequently, the number of studies reporting a population or subgroup 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 that were not clinically relevant (e.g. target lesion revascularization) or that compared specific techniques (such as atherectomy *versus* transluminal *versus* subintimal angioplasty).

Although the quality of studies included in the review was frequently low, there were a surprising number reporting on the effectiveness of revascularization in patients with diabetes, PAD and tissue loss. The interpretation of the effectiveness of revascularization 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 CLI according to a standard definition (although not necessarily limited to those patients with tissue loss or ulceration) do, however, exist. In one study that reported the outcomes of patients with diabetes and CLI who were not revascularized, the limb salvage rate was 54% at 1 year [75]. This rate would appear much lower than in the series presented here where limb salvage rates in the majority of studies reported were between 78 and 85%. In a study by Marston in which patients with PAD and ulceration of the foot were treated without revascularization (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 periprocedural mortality and morbidity as any event occurring during a 30-day hospitalization period. Although perioperative mortality rates in this review were generally low given associated co-morbidities, perioperative major systemic complications were significant in the region of 10%. It is possible that part of these major complications was not related to the revascularization procedure *per se* but was 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 revascularization for PAD should be optimized if possible prior to revascularization. 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 previously, 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 1 year, and almost half were dead at 5 years. These results are similar to those reported in patients presenting with a foot ulcer of any origin, with 5-year mortality rates around 44% [15]. It was difficult to establish whether early aggressive and successful revascularization reduced mortality in the long term. Lepantalo also found that patients with diabetes

DOI: 10.1002/dmrr

and CLI appear to be at particularly high risk of death compared with those without diabetes [75]. However, patients in whom successful revascularization is performed appear to do better than those who undergo major amputation, half of whom are dead within 3 years [77,78]. These findings underscore the importance of the severity and systemic nature of vascular disease in patients with diabetes. Patients with diabetes and 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 patient with diabetes and ulceration of the foot, the pathways to ulceration may differ (e.g. neuropathy and altered biomechanics) as well as the predominant factors affecting outcome (e.g. PAD, infection and co-morbidities). Although the current data indicate that revascularization should always be considered in a patient with diabetes, foot ulceration and severe ischaemia, it still remains unclear if such procedures have an added value in cases of mild to moderate perfusion deficits. There was 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 (anatomical distribution and degree of perfusion) and the characteristics of the foot wound itself.

End-stage renal disease is a strong risk factor for both foot ulceration and amputation in patients with diabetes [79]. These patients are frequently difficult to treat, and long-term mortality is high, which might negatively influence the decision to perform a revascularization 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 revascularization.

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 $TcPO_2$ measurements and the anatomical distribution pattern of the PAD were usually not reported, and our review indicates that all future reports on revascularization in patients with diabetes and an ischaemic ulcer should include objective measurements of the severity of PAD, including both anatomical and functional measurements, such as toe-pressure and/or $TcPO_2$ measurements. Wound characteristics were also 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 standardized wound classification system should be part of all future studies [80]. Moreover, there is a clear need for studies on the role of early revascularization in patients with diabetes, 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 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 revascularization in diabetic patients with PAD.

There are currently no RCTs directly comparing open *versus* endovascular revascularization techniques in patients with diabetes with an ischaemic foot ulcer. Therefore, there was 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 revascularization 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 the two studies of consecutive patients with diabetes where angioplasty was the preferred first-line option for revascularization, 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 subgroup 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 is 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-recognized expert centres in revascularization 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 revascularization 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 offloading 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

DOI: 10.1002/dmrr

studies reported validated foot ulcer scoring systems and the indications for amputation were rarely reported. As discussed previously, 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 case series with high risk of selection and publication bias. Moreover, case series comparing bypass surgery and endovascular treatment are difficult to compare because of indication bias. Several studies included in this review were retrospective analyses containing a small number of patients. Because of 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 co-morbidities. Because of 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 that are relevant to patients with diabetes.

In conclusion, studies reported herein appear to demonstrate improved rates of limb salvage associated with revascularization compared with the results of medically treated patients with diabetes, PAD and ulceration previously reported in the literature. High perioperative morbidity and long-term mortality rates underline the importance of perioperative optimisation and long-term medical management of patients' diabetes and co-morbidities. Overall, there were insufficient data to recommend one method of revascularization over another. There is a real need for standardized 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 standardize 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.

Conflict of interest

None declared.

Appendix A
MEDLINE and Embase search strings

MEDLINE diabetes treatments final search
Date of search: 2 June 2010
Search platform: OvidSP

File searched: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 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: 30 June 2010
Platform: OvidSP
Database file searched: Embase 1980 to present 30 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

Appendix B

Evidence tables

Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
AhChong [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) years *versus* 75 (29–94) years no DM gender: 50% (88) male DM, 45 (51%) no DM ($P = \text{NS}$)	Distribution: not reported (NR) Severity: ABI 0.43 Median toe pressure 26 mmHg (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	Coronary artery disease (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% ($P = \text{NS}$) Autogenous vein 63%	Median follow-up 19 months Mortality 30 days 8% DM *versus* 1% no DM ($P = 0.04$) Cardiovascular complications 9 *vs* 4% ($P = \text{NS}$) Overall graft patency 1 year 63% Graft patency 4 years 46% DM *versus* 34% no DM ($P = 0.19$) Survival rate at 1,3 and 5 years 80, 57, and 33%, respectively Ulcer healing: NR Limb salvage overall at 1 year 83% for both groups and 5 years 78% DM *vs* 81% no DM ($P = 0.79$) Major amputation: NR Minor amputation: NR Complications: 8% mortality perioperative	Chinese population may differ from Western world Limited information about patient management	Early graft failure 6% 65 grafts failed overall during total study

DOI: 10.1002/dmrr

Alexandrescu [25]	Case series A retrospective case series of subintimal PTA and PTA in 161 patients with diabetes and ischaemic wound, PTA-first approach	161 DM patients Age: >70 years 41% Gender: NR	Distribution: majority multilevel disease Severity: NR TASC classification reported	Wagner classification grade 2–4 in 104 limbs (59%) or as isolated calf ulcers in 42 subjects (24%). In 30 (17%) limbs, complex below-the-knee trophic lesions were noted. Infection: NR	CVD 40 (22%) CAD 122 (69%) ESRD 33 (18%) dialysis	161 procedures majority multilevel with 124 subintimal PTA (26 had single subintimal PTA)	Ulcer healing: 129 (73%) before end of study, mean follow-up 22 (1) months Limb salvage: 12, 24, 36 and 48-month limb-salvage proportions: 89, 83, 80 and 80%, respectively. In an 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 follow-up Minor amputation: 67 (38%) 30-day mortality: 1% 2-year mortality: 19 % Major complication: 4		Level of intervention not described in all patients. Approximately 50% infrapopliteal or crural 70% neuropathy
Bargellini [26]	Prospective case series of multilevel subintimal PTA in patients deemed not fit for surgical bypass	DM patients: 60 Age: 69.4 years (SD 9.4)Gender: 41 male	Distribution: NR Severity: NR	Fontaine: 100% Fontaine stage IV Infection: NR	CAD 42% CVD 25%	Subintimal PTA in patients not suitable for surgical bypass: Fem-pop level 56.7% (34)	Mean follow-up 23 months (range, 0–48 months) Ulcer healing: 75% (45/60)	How follow-up was performed, was not defined Long-term mortality low for a 'high risk'	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
						Infrapopliteal level 25% (15) Both levels combined 18.3% (11)	Limb salvage: 93.3% (56/60) Major amputation: 3 within 30 days and 4 within 16 months Minor amputation: Complications: Periprocedural mortality was 5% (3/60) Mortality at 1 and 3 years, 10 and 17%, respectively	population medically unfit for bypass surgery	
Davidson [27]	Retrospective case series Bypass below knee case series	54 DM patients (total population 70) Age: 55–95 years; 38 men (total population)	Distribution: majority infrapopliteal Severity: no information No score of distribution	Gangrene 56%, ulcer 28% (of total population) Infection: NR Ulcer score: NR	CAD 55%, CVD 27%, haemodialysis 7% (total population)	Vein graft below knee (57% to foot)	Limb salvage: 90% at 12 months and 86% at 24 months Major complications: 9/70 Early graft failure $n = 3$ (4.2%) Patency 93% 1 year and 85% 2 years Mortality: NR	Follow-up duration was variable, and after 1 year, 29 of 58 limbs were available for evaluation and, after 3 years, 6 of 58 limbs.	
Dosluoglu [28]	Case series A comparison of peroneal to other run-off vessels after PTA	80 of 111 DM patients 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 76% in other run-off vessels		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 diabetic patients in both groups

							No other data on the diabetes sub-group divided		
Dorweiler [29]	Case series of pedal bypass grafts	DM patients 46	Distribution: crural occlusions	All (100%) tissue loss	CAD 46%	Pedal bypass with vein graft	Follow-up median 28 (1–70) months	No data on severity of PAD.	
		Age: median 69 years Gender: 36/46 (78%) male	Severity: NR	Ulcer score: NR Infection: NR	ESRD 13%		Ulcer healing: NR Limb salvage: 30 days 98% and 87% at 2 years Major amputation: 4 (3 within 30 days) Minor amputation: 32/46 Complications: perioperative mortality 2% One patient failed graft within 30 days Mortality at end of study 21/46 (47%)	No specific data on foot lesions Drop out and loss to follow-up: NR Well-defined study	
Faglia [19]	Case series	All DM patients 221	Distribution:	Wagner grade ulceration	CAD 55%	PTA of stenoses greater than 50% diameter infrainguinal	Median follow-up 12 (5–30) months		Probably significant (>80%??) of the data is a duplication of PDF 117, data reported in DE 117
	Mixed series of PTA	Age: NR	11 patients ilio/femoral/popliteal axis	I – 19%	ESRD 4%		Ulcer healing:		221 had angioplasty but 2 had no significant stenoses, therefore 219 reported
		Gender: NR	81 exclusively infrapopliteal	II – 25%			Limb salvage:		28 subjects PTA not possible (9 surgery and 19 no candidate for any revascularization)
			127 femoropopliteal and infrapopliteal	III – 17%			Major amputation: 10 (5%)		Of the 190 patients, all ulcers healed with medical dressing – nothing more specific
			Severity: TcPO2 21 (30 SD) mmHg in 180 cases.	IV – 38%			Minor amputation: 83 (38%)		

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
			ABI in 128 cases 0.53 (0.15)	V – 1%			Mortality 30 days: 0% Mortality 5.3% at follow-up Complications: $n = 1$ (transient renal failure)		
Faglia [30]	Retrospective case series	DM patients 993	7% iliofemoral	88% tissue loss	CAD 62%	PTA	Mean follow-up 26 (15.1) months	Good wound description at presentation, level of disease treated was well described	Possibly some patients reported elsewhere
	Consecutive series of diabetic foot patients hospitalized. PTA as first choice revascularization	age: 65.5 (9.4) gender: 663 (67%) male	61% femoropopliteal /crural 32% crural Severity: TcPO2 17.0 (11.9)	Texas classification 0 – 12% I – 16% II – 19% III – 53%	ESRD 5%	68% procedures in crural arteries	Ulcer healing: 862/868 wounds healed Limb salvage: NR 21/993 major amputations Minor amputation: 478 Complications: NR 3.4% Mortality 30-day 1/993 Primary patency at 5 years 88% (SD 9%) Mortality at 1 year 5% (extrapolated from Kaplan–Meier curve)	Some follow-up data were obtained by physician telephone interview	Of the 993 treated with PTA, only 10 did not manage to successfully get one vessel in-line flow to the foot
Faglia [31]	Cohort with follow-up 5.9 year (SD 1.28)	PTA:	Distribution:	PTA: No lesion 62 (16%), rest Wagner score 1–4	PTA: Dialysis 24 (5.7%) CAD 225 (54.8%), CVD 53 (19%)	PTA, all stenoses >50% were treated (see PAD distribution)	PTA:	In addition, the authors analyzed their data using a case–control 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–Meier data are incomplete: number of at risk at time points is missing. The study cannot be used as a cohort study comparing PTA and bypass. It does however give information about the results of PTA and information of the revascularized *versus* nonrevascularized patients
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	413 DM patients	PTA: Iliac–femoral–popliteal axis in 28 patients (6.8%)	Infection: 65%	Bypass: Dialysis 8 (7%); CAD 64 (59%), CVD 18 (15.8%)	Iliac–femoral–popliteal axis in 28 patients (6.8%)	Ulcer healing: NR	Baseline characteristics of the groups are different. Therefore, confounding was induced.
	Age: 69.7 years (SD 9.5)	Infrapopliteal in 137 patients (32.2%)	Bypass:	No revascularization: Dialysis: NR, CAD 24 (88.9%), CVD 9 (33.3%)	Infrapopliteal in 137 patients (32,2%)	Limb salvage: NR	
	Gender: 146 (35.4%) female	Combination of both in 248 patients (60%)	No lesion 16 (14%), rest Wagner 1-4		Combination of both in 248 patients (60%)	Major amputation: 1 month 6 (2,3%); 34 (8%) at end of follow-up	
	Bypass group:	Bypass: NR	Infection 63%		Bypass, femoropopliteal 58	Minor amputation: NR	
	114 DM patients	No revascularization: NR	No revascularization: no lesion 3 (11%), rest Wagner 1–4		Fem-infrapopliteal 55	Complications: NR	
	Age: 69.9 years (SD 9.4)	Severity:	Infection: 63%		Other 1	Bypass:	
	Gender: 35 (30.7%) female	PTA: TcPO2 15.3 (11.9)				Ulcer healing: NR	
	No revascularization group:	Bypass: TcPO2 10.2 (10.3)				Limb salvage: NR	
	27 DM patients	No revascularization: TcPO2: 7.0 (8.1)				Major amputation: 1 month 3 (5,4%); 24 (21%) at end of follow-up	
	Age: 76.7 years (SD 10.4)	Scoring: NR				Minor amputation:	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
		Gender: 13 (48,1%) female					Complications: NR 36 (32%) primary bypass failures No revascularization: Ulcer healing: NR Limb salvage: NR Major amputation: 16 at end of follow-up Minor amputation: NR Complications: NR PTA *versus* bypass $p < 0.001$ SIGN 2−		
Ferraresi [32]	Case series Long-term outcome of BK PTA in diabetes	101 DM patients and 107 legs Age: 66 (SD 9.4) years Gender: 16 female	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 follow-up 2.9 years Major amputation: 8/107 (7%) during mean follow-up 2.9 years Minor amputation: 64% Complications: NR Mortality 30 days: NR Mortality during follow-up: 9%	This case series is a sub-analysis of a larger study.	Strengths: Treated lesions clearly defined and standardized Patients with marked tissue loss Weaknesses: 1- and 3-year leg salvage and survival data are not provided, thus hindering interpretation.
Gargiulo [33]	Prospective case series Outcome of successful tibial PTA in 'CLI'	74 DM patients of 87 total population Age: 72 (SD 8.8) years Gender: 44% female	Distribution: NR Severity: NR	92% Fontaine stage IV Ulcer classification: University of Texas Infection: NR	CAD 53% ESRD 28%	Infrapopliteal PTAs (100%) combined with fem-pop angioplasty in 63% and in 3 (3.4%) patients combined with open revascularization	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: well-performed prospective study with complete data set, provides relevant information on wound healing Weakness: the shortest

							Minor amputation: NR Complications: No early perioperative complications		follow-up data were 2 days. A Kaplan–Meier that includes duration of follow-up is missing, hampering interpretation
Gibbons [34]	Retrospective case series	259 DM patients (total population 318)	Distribution:	237/318 (74.8%) ulcer or gangrene	No information	Infrainguinal open revascularization	Ulcer healing: NA	Walking devices used at start of study 63% and at end of 6 months 74%	Primarily health-related quality of life study
	Infrainguinal bypass series	Age: mean 66 years Gender: 62.3% male	Multilevel disease Severity: no information No score of anatomical distribution	Infection: NR Ulcer score: NR		Fem-pop 84 (26.4%) Fem-tibial/ peroneal 132 (41.5%) Fem-pedal/ plantar 100 (31.4%)	Limb salvage: 97% at 6 months Major amputation: NA Minor amputation: NA 93% primary graft patency at 6 months and secondary 97% Complications: perioperative morbidity 21%	38% more active at follow-up 32.5% about the same and 29.5% worse. Less than half back to normal at 6 months (47.4%)	
Hering [35]	Prospective case series	All diabetics 44	Distribution: NR	Wagner grade	CAD 77%	Peroneal PTA	Mean follow-up 23 (5–45) months		Really a prognostic study of Doppler waveform patterns predicting outcome of peroneal PTA
	Case series of crural PTA	Gender: 33 male Age: 72 (42–88) years	Severity: NR	I – 0 II – 6 (14%) III – (30 (68%) IV – 8 (18%) Infection: NR	CVD 52% ESRD 16%		Ulcer healing: 26/44 Limb salvage: 81% at 6, 71% at 12 and 63% at 18 months Mortality 30 days: 9.1% Major amputation: 5 (11%) Minor amputation: NR Complications: 1 renal failure		Overall, 50% had a restenosis or occlusion of peroneal artery
Hertzer [36]	Case series	312 DM patients of 650 (48%)	Distribution: NR	71% ulceration or gangrene	NR		Median follow-up 4 years		Strengths and weaknesses: very

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
	Mixed case series of bypass grafts	Age: NR Gender: 62 male	Severity: NR	Ulcer score: NR Infection: NR		Infrainguinal bypass grafts for occlusive disease	Ulcer healing: NR Limb salvage: 73% (95%CI 67–78) at 5 years, 51% (38–64) at 15 years Major amputation: 29 amputations in 201 diabetic patients Minor amputation: NR Mortality 6.7% 30 days Mortality at end of study 83% at median 4 years Complications: not reported separately for diabetes		long follow-up time-limited specific data on diabetic patients
Hughes [37]	Retrospective case series	DM patients 82 (84%), total 98	Distribution: crural	93 (95%) tissue loss	CAD 40%	Bypass to plantar and tarsal arteries with vein graft	Duration of follow-up median 9 (1–112) months	Primary patency 41% and secondary patency of 50% at 5 years	No differences in outcome between tarsal/plantar and dorsalis pedis (DP) bypass
	Series of pedal bypasses	Age: 68 (SD 12) years	Severity: NR	Infection: NR	ESRD 4%	(one prosthetic)	Ulcer healing: NR	Consecutive series of all revascularizations	
		Gender: 81/98 (83%) male	No scoring	Ulcer classification: NR		Popliteal inflow 72%	Mortality 30 days 1/98 total Complications: 124 perioperative complications Mortality at 1 year 9%, 5 years 37% Limb salvage 75% at 1 year, 69% 5 years Secondary patency 70% at 1 year	Excluded lost to follow-up cases from analysis ($n = 26$)	
Isaksson [38]			Distribution: NR	7 (15%) rest pain					

	Retrospective case series Pedal bypass graft case series	DM patients 43 (48 legs) Age: 74 (40–84) years Gender: females 27 (63%)	Severity: ABI median 0.47 (0–2.14) Score: NR	All others (85%) tissue loss Ulcer score: NR Infection: NR	Previous myocardial infarction (MI) 11 (26%), angina 6 (14%)	Pedal bypass with vein(proximal anastomosis femoral artery 20 (42%) and popliteal artery or below 28 (58%))	Follow-up up to 1 year Ulcer healing: Limb salvage: 1 year 85% Major amputation: NR Minor amputation: NR Complications at 30 days: two died (4%), one patient MI Mortality rate at 1 year 14% Patency at 1 year 83%	Short follow-up – early results only
Jamsen [39]	Retrospective case series	100 patients (116 limbs)	Distribution: NR	Rest pain 23 (20%), ulcer 50 (43%), gangrene 43 (37%)	CAD 47%,	Angioplasty	Intention-to-treat analysis 1 year 67%, 3 years 63%, 5 years 56%, 8 years 45% limb salvage	11 required bypass for PTA failure
	Outcome of consecutive series of 100 infrainguinal PTA considered suitable for PTA-first approach	76 (76%) DM patients	Severity: ankle systolic pressure <50 mmHg	Wound classification: NR	CVD 28%	Femoropopliteal 54%	Ulcer healing: NR	Median follow-up 25 months. Validity of 5 and 10 years questionable – very small numbers available after 3 years
		Age: 72 (38–90) years total population	Scoring system not used	Infection: NR		Crural 17%	Limb salvage for endovascular treatments at 3, 5 and 8 years was 65, 60 and 60%, respectively	Preselected to PTA-first approach
		Gender: 40 (40%) male total population				Multilevel 29%	Major amputation: 37 (32%) during total follow-up Minor amputation: 14 (12%) Major complications: 11%	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
							The survival rates of the present study are 72, 26 and 14% at 1, 5 and 10 years.		
Johnson [40]	Retrospective case series	43 DM patients	Distribution: NR	69 limbs	43 ESRD (kidney transplant 10)	Total population 69 venous bypasses:	Ulcer healing: NR	59% 'foot amputations' performed with patent graft	Amputation can be related not only to occlusion but also to other factors such as infection.
	Retrospective review of popliteal distal bypass grafts in patients with ESRD	In total population 53	Severity: in general, toe pressure < 40, ABI < 0.5 (or incompressible)	(53 with tissue loss)	CAD 38%	Fem-pop 19	Limb salvage: 1 year 65% and 62% at 18 months		
		Age: 59 years (total population)	Scoring: NR	Ulcer score: NR	CVD 15%	Crural 50	Major amputation: 22 (foot amputations)		
		Gender: 27 male (total population)					Minor amputation: NR Major complications: NR Perioperative mortality 10% 1-year mortality 42%, 2-year mortality 72%		
Kalra [41]	Retrospective case series	DM patients 191 (75%), total population 256; 280 procedures	Distribution: NR	90% tissue loss total population	CAD 132 (52%), CVD 54 (21%), ESRD 19 (7%)	All vein bypass grafts to pedal vessels	Ulcer healing:	Survival rate was 65% if had patent graft at 5 years *versus* 26% if leg amputation	
	Series of pedal bypass grafting using vein	Age: median 70 (30–91) years total population	Severity: TcPO2 < 20 mmHg in 88% and ABI = 0.44 (38% incompressible) in 150 limbs	Infection: NR			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.	57% of patients had one or more secondary interventions for pedal graft	
		Gender: 174 (68%) male total population	Scoring system: NR	Wound classification: NR			Ulcer healing: NR		
		Long grafts (proximal					Major amputation:		

		anastomosis above popliteal): 130 (46%) of total population Short grafts (proximal anastomosis at or below popliteal): 150 (54%) of total population					15% at 2.7 years mean follow-up Minor amputation: 12.4% Complications: 1.6% perioperative mortality Long-term mortality at 1, 3 and 5 years: 13, 24 and 40%, respectively Secondary patency at 1 year 78%, 3 years 72% and 5 years 71%		
Kandzari [42]	Case series Endovascular revascularization using catheter-based plaque excision	52 DM patients out of total population of 69 Age: 70 years (SD 12) (total population) Gender: 49% male	Distribution: 154/160 lesions infrainguinal; 43% crural Severity: ankle pressure $<$ 50 mmHg	93% Ruth 5 and 7% Ruth 6 (total population) No ulcer classification	CAD 57%CVD 23% Infection: NR	Endovascular plaque excision	Ulcer healing: NR Limb salvage: NR Major amputation: 20% with diabetes *versus* 18% with no diabetes ($p = 0.86$) at 6 months Minor amputation: NR Complications: major adverse events (26.7% with diabetes *versus* 22.2% with no diabetes, $p = 0.72$).		Data reported comparing patients with and without diabetes, however very little information given
Leers [43]	Retrospective case series Pedal bypass grafts in ESRD	DM patients 31 (91%) 34 total Age: 64 (39–85) years total population	Distribution: infrapopliteal in 23 legs and infrainguinal in 13 legs of the total population Severity (only in 16 patients): ABI 0.48	Probably, >90% had tissue loss. Although, this was not explicitly stated in the article. Wound classification: NR	CAD: 28 (82%) ESRD: 100% (29 haemodialysis and 2 transplants)	Pedal venous bypass 88% of the total population	Average follow-up 13.5 (1–84) months Ulcer healing: NR	Retrospective, some data were obtained from family or dialysis institutions Data difficult to interpret – self-reported data	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
		Gender: male 59% total population	(0–0.95) mean, toe pressure 18 (0–78)	Infection: NR			Cumulative assisted primary patency at 1 and 2 years: 62 and 62%, respectively Limb salvage: 56% at 1 year of the total population and at 2 years 50% Major amputation: 16 (39%) at 13.5 months average follow-up Minor amputation: 51 (26%) of the total population at 1 year Complications: survival 64% at 1 yearone perioperative death (2%) Mortality 36% at 1 year and 48% at 2 years		
Malmstedt [44]	Part of country-wide observational data base (Swedvasc)	742 DM patients	Distribution: NR	82% tissue loss	CAD 65%	261 femoral–popliteal bypasses	Ulcer healing: NR		Composite primary endpoint was amputation or death
	Outcome after bypass surgery in diabetics	Age: 74 years (SD 9.8)	Severity: NR	Ulcer classification: NR	CVD 19%	481 infrapopliteal bypasses	Limb salvage: NR		With a median follow-up of 2.2 years, the rate of ipsilateral amputation or death per 100 person years was 30.2 (95%CI 26.6–34.2)
		gender: 42% female	Infection: NR		ESRD defined as creatinine 150 umol/L 20%		Major amputation: NR		Median time to life or limb loss was 2.3 years (CI 1.9–2.8)

							Minor amputation: NR Complications: NR		The use of the composite endpoint renders interpretation very difficult.
Mills [45]	Retrospective case series of patients with popliteal distal vein bypass grafts	46 DM patients (total population 53)	Distribution: infrapopliteal	52 tissue loss	ESRD 28%; CAD 57%	Infrapopliteal vein bypass	Ulcer healing:		Strength: well-defined cohort
		Age: 62.4 years (total population)	Severity: NR	Infection: NR		All crural bypass	Limb salvage: 85% after 1 year (22 of 56 legs available at 1 year).		Weaknesses: high withdrawal rate, probably combination of short duration and lost to follow-up (not reported separately)
		Gender: 37 men (total population)	Scoring distribution: NR	Ulcer score: NR			Major amputation: NR Minor amputation: NR Complications: Perioperative mortality: 2 of 53 (3.6%); within 30 days, two graft occlusions with subsequent two major amputations Mortality 1 year, 13%		This paper is an example of the confusion between the total population, number of diabetic patients, number of extremities and number of procedures.
Mohan [46]	Case series	All DM patients 32	Distribution: popliteal artery inflow	NR18 (51%) ulcers15 (43%) gangrene2 (6%) patients rest pain	CAD 47%	Popliteal to distal artery bypass	Mean follow-up 24 (1–72) months	Small study population and no information regarding drop-out rate	
	Pedal bypass graft case series	Mean age: 60 (range 42–84) years	AK popliteal 9 BK popliteal 26	Ulcer score: NR	Chronic renal failure 28%	Posterior tibial (PT) 9	Ulcer healing: NR		
		Gender: 50% male	Severity: NR	Infection: NR		Anterior tibial (AT) 8 DP 10	30-day mortality 0% Limb salvage: 90% at 1 year and 82% at 3 years		
						Peroneal 8	Major amputation: 5 within 20 months		
						All vein grafts	Minor amputation: NR		

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DOI: 10.1002/dmrr

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
							Patency at 1 and 3 years: 95 and 89%, respectively Complications: four failing graft surgeries revised. Three bypass occlusions of which two resulted in major amputation Three additional amputation because of infection Mortality (long term): NR		
Owen [47]	Cohort study	Chronic kidney disease (CKD) 4 [epidermal growth factor receptor (eGRF) 15–29]:	Distribution:	CKD 4 (eGRF 15–29):	CKD 4 (eGRF 15–29):	Infrainguinal bypass	CKD 4 (eGRF 15–29):		A study that provides relevant data on CKD in severe forms as a prognostic factor.
	According to four different levels of kidney disease	25 DM patients of 32 (total cohort)	Infrainguinal, no further data given	84% foot lesions	CAD: 23 (71.9%)		Ulcer healing: NR		Infrainguinal bypass, outflow data not provided
		Age: 67.5 years (SD 11.5)	Severity: NR	CKD 5 (eGRF < 15 and HD):	CKD 5 (eGRF < 15 and HD):		Limb salvage: at 5 years 77 (SD 14)		This study was reported as a case series
		Gender: 19 men (59%)		90% foot lesions	CAD: 44 (61.1%)		Major amputation: NR		Probably only sufficient data on CKD 5 patients
		CKD 5 (eGRF < 15 and HD): 60 DM patients of 72 (total cohort) Age: 65 years (SD 11) Gender: 38 men (53%)		Ulcer score: NR Infection: NR			Minor amputation: NR Complications: 30-day mortality 3.1% CKD 5 (eGRF < 15 and HD): Ulcer healing: NR Limb salvage: at 5 years 50 (SD 12) Major amputation: NR		Difficult to use patency data because mortality is very high

							Minor amputation: NR Complications: 30-day mortality 4.2% CKD 5 mortality at 1 year 46% and 91% at 5 years SIGN 2−		
Panneton [48]	Retrospective case series Pedal bypass graft series	DM patients 157 Age: 66 (30–78) years Gender: 111 men	Distribution: NR Severity: NR Scoring system: NR	93% tissue loss 53% gangrene Wound classification: NR Infection: 27%	CAD 80 (51%), ESRD 41 (26%)	Pedal bypass graft with vein	Mean follow-up 2.7 years Ulcer healing: NR Limb salvage: at 1 year 86% and at 5 years 78% Major amputation: NRMinor amputation: NR Complications: 30-day mortality 1.3%, MI 11 (7%), ARF 5 (3.2%), major amputation 3 (1.8%)	A subgroup of a series comparing diabetic patients and nondiabetic patients in which no differences were observed between the two groups.	Comparison of diabetes and no diabetes
Pomposelli [49]	Case series Retrospective review of 367 consecutive patients undergoing 384 distal bypasses	350 DM patients, total population 367 Age: 58 years mean Gender: 352 male; 114 female	Distribution: NR Severity: NR Scoring: NR	219 (72%) with ulcer; 47 (12%) with gangrene; 16% other indications Infection: 222 (55%) Ulcer classification: NR	Prior MI 29%, CVD 12%, ESRD 5% (dialysis) of the total population	DP arterial bypass	Ulcer healing: NR Limb salvage: cumulative limb salvage rate 87% at 5 years. At 1 and 2 years estimated from K-M 90 and 85%, respectively. Secondary patency rates 82% at 5 years Major amputation: 13 (3.5%) within 30 days. Total number of major amputations 30 (8.1%) within the 5-year follow-up.	Co-morbidity subdivided in various kinds of cardiovascular disease.	Large case series, long follow-up period (5 years). Outcome is rather thoroughly described. Retrospective evaluation; not based on predefined problem; there is no drop-out rate reported. Outcome limb salvage was not defined any further.

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
							Minor amputation: 75 (19%) Complications: 30-day mortality 1.8% MI 5.4%. Graft failures 7.5% at 30 days Mortality 43% after 5 years		
Pomposelli [50]	Retrospective case series Pedal bypass graft series	865 total population 92% diabetes Age: 67 years Gender: 69% male	Distribution: inflow vessel 41% BK popliteal 29% CFA 12% AK pop 11% superficial femoral artery (SFA) Severity: NR No scoring	78% ulcer Infection: NR Ulcer score: NR	CAD 47%; ESRD 11% of the total population	Subgroup analysis of 1032 DP artery bypass All except two with vein	Ulcer healing: NR Limb salvage: 78% at 5 years and 58% at 10 years Graft patency 85% at 1 year Secondary patency at 5 years 66% DM *versus* 56% no DM 51 and 76% mortality at 5 and 10 years, respectively Major amputation: NR Minor amputation: NR Complications: 10 (1%) deaths within 30 days; 3% MI	43 (4.2%) failed within 30 days	Subgroup analysis of a large 3731 bypasses to 1032 to DP arteries of which some were diabetic patients (865)
Pua [51]	Case series Consecutive patients receiving PTA for limb salvage	91% DM patients out of 46 total Age: NR Gender: NR	Distribution: NR Severity: NR No score	37/46 patients with foot lesions Ulcer score: NR Infection: NR	33% CAD 20% CVD	Mixed 25 Five crural 16 fem-pop Three aortoiliac	Ulcer healing: at 13 months 66% patients with gangrene healed Limb salvage: 78% at 1 year. Mortality: NR	Five technical failures	Limited information regarding patient characteristics, co-morbidity and selection procedures. Foot ulcer/ gangrene is not specified any further.

							Major amputation: NR Minor amputation: NR		
Ramdey [52]	Prospective case series (registry)	DM patients; 92% of a total population of 146	Distribution: NR	Tissue loss: 91% (total population)	CAD 115 (65%)	Artery inflow	Follow-up: no data provided	Follow-up not specified	
	Infrainguinal revascularization	Age: 63 years (SD 13) (total population)	Severity: NR	Ulcer score: NR	MI 64 (36%)	Iliac or femoral 123 (70%); suprageniculate popliteal 20 (11%)	Complications: 30-day morbidity 23%; 30-day mortality 5%		
		Gender: 65% (total population)		Infection: 48%	CVD 27 (15%)	Infrageniculate popliteal 34 (19%)	Ulcer healing: NR		
					ESRD: all patients	Outflow	Patency at 1 and 3 years: 85 and 68%, respectively		
						Iliac/femoral 1 (0.6%)	Limb salvage: 1 and 3 years 80% both		
						Suprageniculate popliteal 17 (10%)	Major amputation: 21		
						Infrageniculate popliteal 28 (16%) Tibial 50 (28%) DP 80 (45%) Tarsal 1 (0.6%)	Minor amputation: NR Survival 60% 1 year, 3 years 18% and only 5% alive at 5 years		
Reed [53]	Retrospective case series	DM patients 140, total population 217, procedures 249	Distribution: NR	Necrosis 127 (80%), rest pain 27 (17%)	CAD 95 (60%), ESRD 53 (33%) with 35 (23%) on dialysis	Infrainguinal vein bypass graft	30-day mortality 0.6%	Data extracted from a cohort study comparing diabetic with nondiabetic patients	Major amputation was required in nine patients with a patent graft.
	Case series of bypass grafts originating distal to the groin	Age: 65 (30–90) years	Severity: NR	Infection: NR		Pedal (35%),	Complications: major post-operative morbidity 16 (10%)	21% secondary procedures	
		Gender: 79 female	Scoring system: NR	Wound classification: NR		Crural (60%), femoropopliteal (4%)	Ulcer healing: NR Limb salvage rate was 84% (SD $\pm$ 4) at 5 years Major amputation: Minor amputation: 5-year patient survival was 44 ($\pm$5)%	Mean 27 months follow-up	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
Rosenbaum [54]	Retrospective case series	DM patients: 39	Distribution: NR	100% tissue loss	NR	Peripheral bypass: 79% infrapopliteal	Follow-up: Mean 21.2 (2–64) months	Data of this study may be included in other reports of this group	No life-table analysis, no information about healing time, small series; follow-up procedures unclear
	Case series of infrapopliteal bypass grafts	Age: 62.3 (45–78) years	Severity: NR	Ulcer score: Gibbons classification		Popliteal 19%	Ulcer healing: 40 limbs (of total 42 limbs) with or without foot surgery		
		Gender: 33 (85%) male	Score: NR	Infection: NR		Tibial/peroneal: 48%	Limb salvage:		
						DP/plantar artery: 31%	Major amputation: 1		
						Aotobifemoral 2%	Major amputation: 1 Complications: NR		
Saltzberg [55]	Retrospective case series	DM patients: 96% of total population in 51 patients all younger than 40 years	Distribution: 76 bypass procedures with inflow:	86% tissue loss	CAD 37%	Venous (95%) or prosthetic (5%) bypass with outflow:	How follow-up was performed not described; no data on follow-up reported	Unspecified follow-up	
	Case series of mixed bypass grafts	Age: 36 (27–40 years)	Common iliac 2.6%	Ulcer score: NR	ESRD (creatinine > 2 mg/dL, dialysis or transplant) 53% (29% of which dialysis)	DP: 30.3%	NR		
		Gender: 49% male	Femoral 67%	Infection: NR		Tibial artery: 18.4%	Patency at 1 and 5 years: 82 and 63%, respectively		
		All data in this table as reported on total population	Above-knee popliteal 7,9%			Peroneal artery 3.9%	Ulcer healing: NR		
			Below knee popliteal 21.1 %			Below knee popliteal: 23,7%	Limb salvage: 87% at 1 year and 77% at 5 years		
			Tibial artery 1.3%			Above-knee popliteal: 11.8%	Major amputation: 23.5% required amputation level unspecified (12/51)		
			Severity: NR			Femoral artery: 3.9%Other: 7.9%	Minor amputation: see previous entry Complications: 30-day mortality rate, 0%; post-operative heart failure, 1.32%.		

							Overall mortality 88 and 73% at 1 and 5 years, respectively	
Schneider 1993 [56]	Case series of pedal bypass extracted from an initial cohort study of diabetic *versus* nondiabetic patients, but this study compares tibial with pedal	DM patients 45 of total population *n* = 53	Distribution: NR	77% tissue loss	CVD NR	All pedal bypass graft with vein	Follow-up: 22.5 months (SD 3.4)	Major amputation defined as amputation proximal to metatarsals
		Age: 67 (42–78) years total population	Severity: ABI 0.53 total population	Ulcer score: NR	CAD: NR		Ulcer healing: NR	Low numbers of patients (6) at 5 years
		Gender: 33 men of total population		Infection: NR	ESRD: NR		Patency at 1, 3 and 5 years: 70, 58 and 58% years Limb salvage at 1, 3 and 5 years: 98, 98 and 95%, respectively Major amputation: NR Minor amputation: NR Complications: perioperative mortality 9% Mortality 27, 39 and 50% at 1, 3 and 5 years, respectively	
Schneider 2001 [57]	Retrospective cohort	SFA PTA plus short distal bypass	Distribution: Combined: Below knee disease plus focal SFA disease (<3 cm length)	All gangrene	Combined	Distal target vessels	Mean follow-up 23 months	Small sample
	Revascularization using either fem-distal bypass, combined SFA PTA and distal bypass grafting or short distal bypass graft	DM patients 12	Severity ABI 0.52 (0.19)	Infection: NR	CAD 33%, ESRD 58%	Combined	Ulcer healing: NR	Heterogeneous populations – different distribution of PAD
		Age: 70 (13) years	Long distal bypass: Extensive infrainguinal disease involving fem-pop and infrageniculate arteries	Wound classification: NR	Long distal	Tibial 25%	Limb salvage at 2 years	Confounding by indication
		Gender: 83% male	Severity ABI 0.42 (0.17)		CAD 38%	Pedal 75%	Combined 90 (9)%	Drop-out and loss to follow-up not reported
		Long distal bypass	Short distal bypass: Severe		ESRD 74%	Long distal	Long distal 78 (9)%	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
			infrageniculate occlusive disease and patent fem-pop arteries						
		DM patients 46	Severity: ABI 0.46 (SD 0.15)		Short distal	Tibial 57%	Short distal 98 (2)%		
		Age: 68 (11) years	Scoring system: NR		CAD 49%	Pedal 43%	Patency all procedures 78 (±5)% at 2 years, 63 (8)% at 5 years		
		Gender: 50% male			ESRD 67%	Short distal	Major amputation: NR		
		Short distal bypass				Tibial 35%	Minor amputation: NR		
		DM patients 52 Age: 69 (11) years Gender: 65% male				Pedal 65%	Complications: NR Mortality: NR No differences between groups SIGN 2−		
Sigala [58]	Case series	All diabetic patients 97 with 121 procedures	Distribution: Large variation	49 necrosis 32 gangrene, 24 ulcers, 16 rest pain,	CAD 78%	Infrainguinal revascularizations	Ulcer healing: NR	Heterogeneous population of patients with wide variation of PAD distribution and revascularization procedures	Sigala [58]
	Mixed bypass graft plus 50 PTA	66% male	Severity: NR	Ulcer score: NR	CVD 20%	Endovascular – 36% only	Limb salvage: 86% at 6 months, 75% at 12 months and 56% at 3 years	All patients had ESRD	PDF 845
		Mean age 68 (range 41–85) years		Infection: NR	100% ESRD	5% combination endovascular and open	Major amputation: NR	Number of infections not stated in study but outcomes reported in Kaplan–Meier relative to infection	
						Bypass only 59%	Minor amputation: NR		
						Crural artery 55%	Complications 12/97 patients		
						10% crural artery only 28% femoropopliteal 18% external iliac to femoropopliteal	Mortality 30 days 10%, 1 year 22% and 3 years 56%		
			Distribution: NR		NR				

Soderstrom [59]	Prospective case series Healing of ischaemic ulcers after infrainguinal bypass surgery	74 DM patients of 148 total population Age: NR Gender: NR	Severity: ABI < 0.5, systolic toe pressure < 30 mmHg. Fontaine stage IV Classification: NR	Classification provided: All Fontaine stage IV ulcers Infection: NR		Infrainguinal bypass in all subjects, with 13 PTA inflow procedures (total population)	Ulcer healing: 63% in 12 months in the diabetic patients Limb salvage: NR Major amputation: NR Minor amputation: NR Complications: NR Mortality: NR	Median time to achieve healing 213 days Diabetes was the only risk factor that delayed tissue healing (HR 0.5 95%CI 0.3–0.8 in multivariate analysis)	Arterial run-off for patients with diabetes not specified. No specific data on diabetic patients reported other than healing.
Stonebridge [60]	Case series Retrospective review of 117 diabetic patients with a popliteal artery (or below) to distal bypass	All DM patients (117) Age: 64 (27–92) years Gender: Male : female 5 : 1	Distribution: tibial Severity: NR Scoring: NR	Nonhealing 65 (52%), gangrene 20 (16%) Infection: 40 (32%) Foot abscess: 2 (1.6%) Osteomyelitis: 6 (5%) Ulcer score: NR	CAD 37/117 ESRD 17/117	Pop-distal bypass graft (129 procedures)	Ulcer healing: NR Limb salvage: NR Major amputation: 8 during mean follow-up 13 months: minor amputation: 34 Complications: operative mortality 0.8 %, 1 and 3 years secondary patency rates 92 and 89%, respectively		No data about inclusion criteria according to PAD severity.
Tannenbaum [61]	Retrospective case series Case series of pedal bypass	DM patients 53 Age: NR Gender: 34 male	Distribution: NR Severity: NR Score: NR	73% ulcers Infection: 45% cellulitis, 29% osteomyelitis, 20% gangrene and 2% abscess 11 minor amputations performed prebypass	NR	DP bypass with vein	Follow-up: average 25 (SD 14) months 10 patients lost to follow-up Limb salvage at 1, 2 and 3 years, 98, 98 and 95%, respectively Major amputation: NR Minor amputation: NR Patency at 1–3 years, all 95% Complications: NR	Study of acute sepsis in ischaemic diabetic feet Excellent limb survival and patient survival and healing No report on severity of PAD Wound infection 13%	

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
							Mortality rate at 1, 2 and 3 years, 5, 16 and 16%, respectively In the patients who did not die or had a major amputation, all ulcers healed during follow-up		
Taylor [62]	Retrospective case series	DM patients 114 patients with a foot infection (138 limbs):	Distribution: NR	All infected ulcers	NR	Peripheral bypass undefined	Mean follow-up 3 (1–11) years	17 lost to follow-up	
	Case series of 114 patients with infection, 43 of whom revascularized	43 (48 limbs) with ischaemia and 71 without ischaemia	Severity: NR	Ulcer score: NR			Ulcer healing: NR	No data on lost to follow-up on revascularized patients	
		Age: NR	But ischemia was defined as absent pulses +ABI < 0.6 or TBI < 0.4 and abnormal wave forms				Limb salvage: 2 and 4 years, 87 and 73%, respectively	Much important data missing	
		Gender: NR	Score: NR				Major amputation: 9 (19%) at 3 years mean follow-up Minor amputation: NR Complications: NR Mortality rate at 1, 3 and 5 years 19, 62 and 84%, respectively	4/9 amputations because of infection	
Toursarkissian [63]	Primarily a prognostic study of the use of duplex as a predictor of bypass graft failure in diabetic patients	DM patients 65	Distribution: NR	61 (94%) tissue loss	CAD 38%,	68 limbs	Duration of follow-up 12 months (SD 6 months)		86% Hispanic population
		Age: 61 years	Severity: TBI 0.2	Infection: NR	ESRD 16%	Femoral to distal bypass 42	Ulcer healing: NR		
		Gender: 40/64 (63%) male	Score: NR	Ulcer score: NR		BK pop distal 16	Limb salvage: whole group 80% at 1 year		
						Fem-pop 10	Major amputation: 8/68 limbs at		

						All vein bypass	12 months (SD 6 months) Minor amputation: NR Graft patency assisted primary 75% at 1 year (estimate of Kaplan–Meier) Complications: nil Mortality: NR	
Toursarkissian [64]	Case series of pedal bypass	135 patients 144 procedures all DM patients	Distribution: NR	96% tissue loss	CAD 62%	DP bypass grafts	Median follow-up 8 (1–62) months	82% Hispanic
		Age: 62 (SD 11) years Gender: 78% male	Severity: NR	Ulcer score: NR Infection: NR	ESRD 20%		Ulcer healing: NR Limb salvage: 83% at 30 months Major amputation: 19% at total follow-up (mean 8 months) Minor amputation: 36% Patency: 70% at 1 year and 68% at 30 months Complications: 25 perioperative complications 30-day mortality 1.5% Mortality at end of study 10%	Study comparing outcome in various ethnic groups (Hispanic *versus* non-Hispanic). Higher amputation rate in Hispanic
Uccioli [65]	Retrospective case series of patients with diabetes and CLI and tissue loss treated using an endovascular-first approach in a tertiary care clinic	DM patients: 510 (100%) (total population 534 but 24 lost)	Distribution: NR	100% tissue loss	CAD 42%	456/510 (89%) underwent attempted PTA	Mean follow-up 20 (13) months	Good description of cohort
		Age: 70 (0.8) years	Severity: TcPO2 16 mmHg ±0.8	Ulcer score:	CVD 23%	34, 35 and, 31% respectively for AK, BK, AK + BK PTA	Ulcer healing: 61% at 9.4 (0.5) months and 7% at 23 months	Outcomes better reported using Kaplan–Meier analysis.
		Gender: 64% male	Score: NR	All class C/D and grades 2 and 3 of the Texas wound classification	ESRD 13%	1.8 (0.04) vessels treated per limb (total number of arterial stenoses 2.6 (0.06) per limb)	Major amputation 16% at 5 months	Of the 89.4% of consecutive patients who were able to be treated using a PTA-first approach, 11% had technical failure.

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DOI: 10.1002/dmrr

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
				Infection: 79%			Minor amputation: 54% Complications: NR 30-day mortality: NR Mortality: 16% at 9 months	23% of PTA subintimal	
Verhelst [66]	Retrospective case series	DM patients: 33 (92% of total population $n = 36$)	Distribution: NR	89% tissue loss	CAD 44%	Popliteal-to-distal venous bypass grafts ($n = 44$):	Meal follow-up 27 months (1–65)	Confusion between patients/extremities. Small study. Mixture of vascular interventions.	
	Case study of pedal and crural bypass graft	Age: 62 (29–78) years	Severity: TcPO2 18 mmHg ±7	Ulcer score: NR	Dialysis 4	PT: 13	Ulcer healing:	Started treating 33 patients – No standard error in curve and therefore high likelihood of significantly small numbers during follow-up	
		Gender: 29 male	Score: NR	Infection: NR		AT: 10	In 33/36 patients, complete healing of skin lesions and that includes minor amputations		
		All data in this table as reported on total population				Peroneal: 6	Limb salvage: 90, 82 and 77% at 1, 3 and 5 years, respectively.		
						DP/plantar: 23	Major amputation: occurred in follow-up period of 27 months Minor amputation: 35 Patency at 1 and 3 years 87 and 74%, respectively Complications: MI 1; heart failure 1; post-operative bypass occlusion and major amputation 3 30-day mortality 0% Deaths: 4 during following follow-up		

Werneck [67]	Case series	40 DM patients (total population 49)	Distribution: All had 'severe' tibial disease, 'some also had femoropopliteal PAD'	Classification: 20% Ruth 4	CAD 69%	Tibial angioplasty in all and in 45% multilevel (fem-pop segment)	Ulcer healing: NR	Angiographic success rate was 84%.	Number of patients with surgery *versus* PTA not given. There are ten amputations in diabetic patients. However, it is unclear how many cases were in the PTA group.
	Tibial PTA in patients with 'CLI' at 'high risk' retrospective case series	Age: 70 years	Severity: NR	80% Ruth 5*	ESRD 73% of the total population		Limb salvage: 76% after mean follow-up 8 months. Cumulative limb salvage rate in tibial PTA only after 1 year: approximately 70% estimated from Kaplan–Meier		
		Gender: 71% male	TASC reported:	Infection: NR			Major amputation: NR Minor amputation: NR Complications: major complications occurred in 6.1% 30-day mortality 2% Mortality after 1 year 10%		
Woelfle [68]	Retrospective case series	DM patients: 72	Distribution: Isolated tibioperoneal vessel; occlusive disease	All with minor tissue loss	CAD 41	Distal vein graft reconstruction:	Follow-up: no information provided or data reported on how this was performed	Ulcer healing not reported; total number of BK amputations not reported.	
	Case study of mixed bypass grafts	Age: 70.5 years	Severity: NR	Ulcer score: NR	ESRD (creatinine > 2 mg/dL): 18	Proximal anastomosis:	Ulcer healing: NR	No data on follow-up	
		Gender: NR		Infection: NR	Symptomatic carotid disease: 15	Below-knee popliteal: 56	Limb salvage at 30 days 93%, at 1 year 81% and 5 years 72%.		
						AT: 18	Patency: 30 days 97%, 1 year 86% and 5 years 75%		
						Distal anastomosis: ATA 10	Major amputation: NR Minor amputation: NR		
						DPA 37 PTA 13	Complications: Mortality within 30 days 1.3%		
						Peroneal: 12	23 patients died during follow-up		

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Reference	Study design	Population (age, sex, co-morbidity, number with diabetes)	PAD (distribution and severity)	Foot lesion	Co-morbidity	Intervention and control management	Outcome	Comment	Opinion
						Plantar 3	(including post-operative mortality)		
Wolfle [69]	Retrospective case series of two different procedures	Bypass	Bypass	Bypass	Bypass	Vein to DP in 63 or AT artery in 20 and PT in 28 and peroneal in 19	Average follow-up probably 24 months	Poor information on loss to follow-up and drop out.	
	Bypass crural *versus* PTA crural	DM patients 125 (130 grafts)	Distribution: crural	127 tissue loss	CAD 57%	Angioplasty	Bypass	Retrospective case series of two different procedures and not a controlled study	
		Age: 70 (50–87) years	Severity: NR	PTA	CVD 18%	Crural arteries	Limb salvage 80% at 1 year, 73% at 3 years and 69% at 6 years		
		Gender: NR	PTA	84 tissue loss	ESRD 25%	AHA classification (1994)	2.3% 30-day mortality		
		Distal PTA	Distribution: crural	Ulcer score: NR	PTA	1–8	Patency at 1, 3 and 5 years, 76, 70 and 60%, respectively		
		DM patients 74 (89 limbs), 84 total	Severity: TcPO2 6.7 (0–29)	Infection: NR	CAD 48%	2–28	30 major amputation at 24 months		
		Age: 68 (48–89) years	Score: AHA		CVD 17%	3–26	Minor amputations: NR		
		Gender: NR			ESRD 42%	4–27	64 died during follow-up		
							PTA		
							Limb salvage 82% at 1 year, 77% at 3 years and 77% at 5 years		
							30-day mortality 6%		
							17 major amputations during 24 months		
							Minor amputation: NR		
							26 died during follow-up		
Woefle [70]	Retrospective case series	DM patients: 135 (143 procedures)	Distribution: extensive	Tissue loss in 140 limbs	CAD 82 (61%)	All venous bypass with proximal anastomosis:	Follow-up duration not reported	No data on mean duration of	

			intrapopliteal occlusions					follow-up or on severity of PAD
	Case studies infrapopliteal bypass graft	Age: 70 (50–89) years	Severity: NR	Ulcer score: NR	ESRD 43 (16%)	BK popliteal 113	Ulcer healing: NR	
		Gender: NR		Infection: NR	CVD 29 (20%)	ATA 29	Patency at 1 year 83%, 5 years 60% and 7 years 51%	
						PA 1	Limb salvage: at 30 days 94%, 1 year 80%, 5 years 74% and 7 years 64%	
						Distal anastomosis:	Major amputation: 35 during follow-up	
						ATA 21	Minor amputation: NR	
						DPA 71 PTA 29	Complications: 30-day mortality 8%	
						Peroneal 22 PTA of SFA prior to surgery in 37	Mortality at 1 year 27%, 5 years 70% and 7 years 82%	
Zayed [71]	Retrospective series	DM patients: 312	Distribution: NR	93% tissue loss	CAD 107 (34%)	257 (82%) PTA,	Follow-up not defined and no data reported	No data on follow-up
	Series of combined PTA and bypass surgery	Age: Median 72 years (range 39–93 years)	Severity: NR	Ulcer score: NR	Dialysis: 33 (10.5%)	55 (18%) surgical bypass open surgery	Ulcer healing: NR	PTA not specified, severity of PAD not described
		Gender: 188 males (60%)	Classification: NR	Infection: NR		20 had combination of both procedures	Limb salvage: NR Major amputation: 13 cases (4.1%); of these, seven had PTA and six had reconstructive vascular surgery Minor amputation: NR Complications: NR	All amputations above or through knee

DOI: 10.1002/dmrr

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DOI: 10.1002/dmrr