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SUPPLEMENT ARTICLE

Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review

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Abstract

Symptoms or signs of peripheral artery disease (PAD) can be observed in up to 50% of the patients with a diabetic foot ulcer and is a risk factor for poor healing and amputation. In 2012, a multidisciplinary working group of the International Working Group on the Diabetic Foot published a systematic review on the effectiveness of revascularization of the ulcerated foot in patients with diabetes and PAD. This publication is an update of this review and now includes the results of a systematic search for therapies to revascularize the ulcerated foot in patients with diabetes and PAD from 1980 to June 2014. Only clinically relevant outcomes were assessed. The research conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, and Scottish Intercollegiate Guidelines Network methodological scores were assigned. A total of 56 articles were eligible for full-text review. There were no randomized controlled trials, but there were four 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% (70–89%). At 1-year follow-up, 60% or more of ulcers had healed following revascularization with either open bypass surgery or endovascular techniques. Studies appeared to demonstrate improved rates of limb salvage associated with revascularization compared with the results of conservatively 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 © 2015 John Wiley & Sons, Ltd.

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

Abbreviations ABI, ankle brachial pressure index; AHA, American Heart Association; AT, anterior tibial artery; CAD, coronary artery disease; CKD, chronic kidney disease; CLI, critical limb ischaemia; CVD, cerebrovascular disease; DM, diabetes mellitus; DP, dorsalis pedis artery; IQR, interquartile range; MI, myocardial infarction; NA, not available; NR, not reported; PAD, peripheral artery 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 Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Artery Disease; TBI, toe brachial pressure index; $TcpO_2$, transcutaneous oxygen tension

Introduction

In 2012, a multidisciplinary group of experts of the International Working Group on the Management of the Diabetic Foot published a systematic review on the effectiveness of revascularization in patients with a diabetic foot ulcer and peripheral artery disease (PAD) [1]. Since this publication, several new studies on this topic have been published, and this current review is an update of the 2012 publication; using the same search strategy, we added new information to the original publication with shortening of some sections of the first publication. This systematic review is also the basis for our guidance document on the diagnosis, prognosis and interventions for patients with PAD and diabetic foot ulceration, which is published separately in this journal [2].

Peripheral artery disease and infection are the major causes of lower-leg amputation in persons with diabetes [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 [5–8]. In large observational studies, PAD, ranging from relatively mild disease with limited effects on wound healing to severe limb ischaemia with delayed wound healing, was present in up to 50% of the patients with a diabetic foot ulcer [9–11]. The relatively poor outcome of ischaemic foot ulcers in diabetes is probably related to a combination of factors, including the anatomic distribution of the vascular lesions, rendering them more difficult to treat; the association with other abnormalities like infection, neuropathy and renal failure; and the presence of abnormalities in other vascular territories, such as the coronary or cerebral arteries [7,9,12–14]. The mortality of these patients is high with 50% of patients dead at 5 years [15]. The effect of PAD on wound healing will relate in part to its severity and extent but also on other factors such as poor glycaemic control, microvascular dysfunction, impaired formation of collateral vessels, increased mechanical loading of the ulcer region and co-morbidities mentioned earlier [16].

Peripheral artery disease in patients with diabetes has a number of characteristics that render 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. In the last decades, new techniques and technologies have been introduced for treating PAD, which might be relevant to the patient with diabetes and a poorly healing ischaemic foot ulcer. In particular, encouraging results have been reported on endovascular approaches, and the field is rapidly evolving [18,19].

Materials and Methods

We searched the Medline and Embase databases for articles related to therapies to revascularize the ulcerated foot in patients with diabetes and PAD published from January 1980 to June 2014 (Online Appendix S1). Because of the changing nature of interventions for PAD and improving technology, we excluded studies before 1980. PAD was defined for the purpose of this systematic review as any flow limiting atherosclerotic lesion of the arteries below the inguinal ligament. All patients included had to have objective evidence of PAD (e.g. angiography or magnetic resonance angiography). We only included studies in the English language.

We only selected studies in which >80% of patients had evidence of tissue loss (defined as any lesion of the skin breaching the epithelium or ulceration or gangrene). The diagnosis of diabetes was made according to the individual publication. We included studies of more than 40 patients where >80% of the population had diabetes or when the results of at least 30 patients with diabetes were reported separately. Studies solely reporting interventions on aortic and iliac arterial disease were excluded because the treatment of supra-inguinal disease in people with diabetes does not differ markedly from that in non-diabetic individuals. We also excluded studies that had only data on quality of life, on costs and on diagnosis and prognosis of PAD; that were only concerned with medical or topical therapy or on improvement of oxygen delivery; and that compared one form of revascularization technology with another (e.g. various atherectomy devices). Only studies reporting ulcer healing, limb salvage, major amputation or 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).

Patient demographics that were assessed included age, sex, ethnicity and co-morbidities (cardiovascular, renal and cerebrovascular). We extracted the specifics of the foot lesions where possible, such as site on the foot, depth, presence of infection and stratified when possible according to any previously reported and validated diabetic foot ulcer scoring system. The anatomical distribution of PAD was extracted according to the site of the disease; standard reporting systems were included where possible (e.g. the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Artery Disease [20] or Bollinger systems [21]). Objective assessment of perfusion was reported when possible, which included ankle brachial pressure index, toe pressure and transcutaneous oxygen tension. We made no distinction among various endovascular techniques (e.g. angioplasty, stenting,

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subintimal angioplasty and atherectomy), all being referred to as 'endovascular therapy' or various bypass techniques (e.g. *in situ versus* reversed venous bypass).

The systematic search was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [22]. Two reviewers assessed studies for inclusion based on titles; two reviewers then excluded studies based on review of the abstract and reviewed the full text of selected articles for quality rating; the data for the evidence table were extracted by one author. Studies were assessed for methodological robustness, using the Scottish Intercollegiate Guidelines Network (SIGN) instrument as follows: level 1 includes meta-analyses and randomized controlled trials (RCTs), and level 2 includes studies with case–control, cohort, controlled before–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, that is, those without a control group, such as case series, were not rated. Pooling of data (and therefore weighting of studies) was not possible because of study heterogeneity and the generally low quality of evidence. 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, 958 articles were assessed for eligibility; 57 articles were finally selected for full-text review (Figure 1). These articles described revascularization of the ulcerated foot in 9029 patients with diabetes and PAD (online Table 1). There were no RCTs, but there were four nonrandomized studies with an intervention and control group [31,47,57,72]. These were all of low quality and potentially subject to significant bias (SIGN 2−). Moreover, there were five recent studies comparing the effect of the direct and indirect revascularization, according to the angiosome concept [75–79]. Also, these studies had a high risk of bias and were graded as SIGN 2−. The remaining 56 articles 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.

Patient demographics and co-morbidities

The median reported proportion of men in the included studies was 66% (IQRs 60–74%), and the median

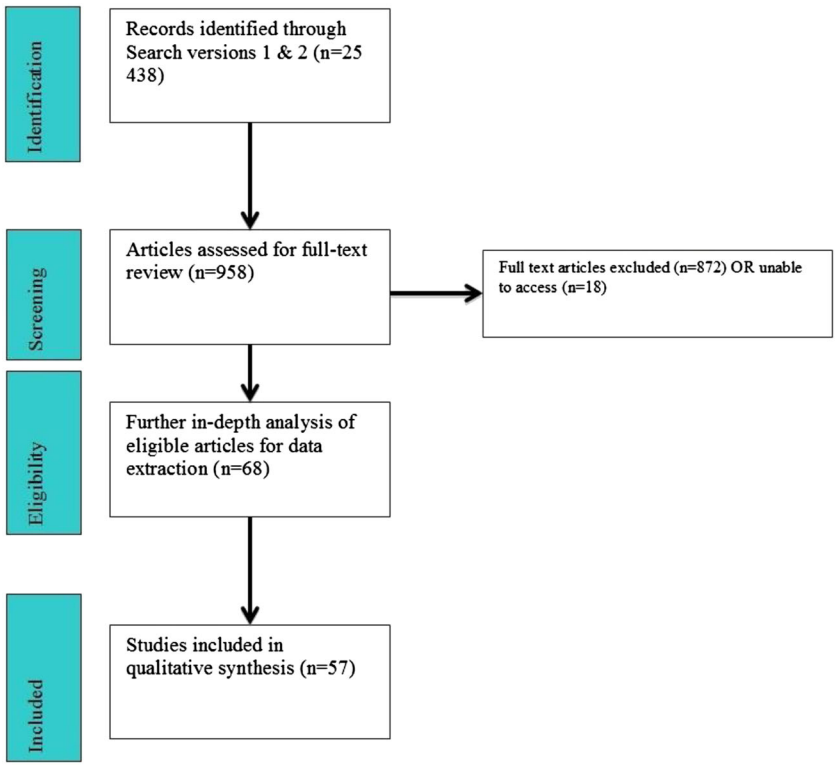

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram

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reported age was 69 years (IQRs 65–71 years). Patients with diabetes, PAD and foot ulcers had a prevalence of co-morbidities. Specifically, the prevalence of coronary artery disease was reported as 38–59% (IQRs) with a median of 47%, that of cerebrovascular disease as 18–23% with a median of 21% and that of end-stage renal disease (ESRD) as 11–41% 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 (e.g. New York Heart Association classifications) were sparse.

Wound healing

Wound healing was only reported in seven studies [25,30,33,35,59,65,66]. Only one study defined wound healing at a predefined time point of 12 months [59]. Overall, for the seven studies of endovascular and two of bypass surgery, the ulcer healing rate was 60% or more at 12 months' follow-up.

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) [65,30,39]. In one of these studies, a large series of 993 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 complete calcified occlusion of the vessel precluding balloon catheter passage [30]. PTA did not establish in-line flow to the foot in only 1% of patients. 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 from a tertiary referral hospital, angioplasty was attempted in 456 (89.4%) of 510 patients; it was a technical failure in 11%. Mortality and limb salvage rates were comparable with the other series [65].

Crural vessel angioplasty

Crural PTA employed as a revascularization technique in isolation was reported in five studies [27,32,35,67,69,72,73]. Studies variously reported limb salvage outcomes, all of which exceeded 63% at 18 months (and 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 in a median of 86% with an IQR of 85–98% at 1 year, a median of 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.

Angiosome-directed therapy

Five retrospective studies with a high risk of bias analysed the outcome of revascularization according to the angiosome concept, in which the foot can be divided into three-dimensional blocks of tissue, each with its own feeding artery. According to this concept, direct revascularization results in a restoration of pulsatile blood flow through a feeding artery to the area where the ulcer is located, while with indirect revascularization flow is restored through collateral vessels deriving from neighbouring angiosomes [80]. In these studies, post-procedural angiograms were scored as either direct flow to the site of the ulcer by a feeding artery (direct revascularization) or indirect flow through collaterals (indirect revascularization). Three studies reported significantly higher limb salvage rate after direct revascularization [75–77], while in two no differences were observed [78,79]. Ulcer healing was also reported to be significantly higher after direct revascularization in three studies [75,78,79]. Söderström *et al*. therefore analysed their data using propensity scores in order to reduce confounding and reported a significantly increased healing rate after direct *versus* indirect revascularization: 69% *vs* 47% after 1 year, respectively, but without any difference in limb salvage [76]. Acín *et al*. further divided the patients with indirect revascularization in two groups: those with indirect flow through collaterals and those with indirect flow but no visible collaterals [75]. The latter group had the poorest results, with an ulcer healing rate of only 7% after 1 year and a limb salvage rate of 59% after 2 years. The direct and indirect flow through collateral revascularizations had comparable outcomes with healing rates of 66% *vs* 68% and limb salvage rates of 89% *vs* 85%, respectively. These authors suggest that restoration of blood flow to an ischaemic ulcer is pivotal, with similar results of flow through medium-size or large-size collaterals or via the feeding artery.

Infection

Only two studies specifically reported the outcomes of a revascularization procedure in patients presenting with foot infection, PAD and diabetes [62,61]. In these studies,

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the mortality rates at 1 year were 5% and 19%, respectively. Limb outcomes were poorly described, but limb salvage was 98% in one study at one year [61].

End-stage renal disease

Patients with ESRD were identified in nine studies [40,43,47,52,58,67]. The definition of ESRD varied and included patients who were and who were not receiving renal dialysis and those with functioning renal transplants. The 30-day mortality in these patients was 4.6% (IQR 2.6–8.8%), but 1-year mortality was high at 38% (IQR 25.5–41.5%). In survivors, 1-year limb salvage rates were a median of 70% (IQR 65–75%). Long-term outcomes were also poor with reported mortalities (when available) at 2 years of 48% [43] and 72% [40], at 3 years of 56% [58] and at 5 years of 91% [47].

Early complications

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

Peri-operative mortality

Thirty-day or in-hospital mortality was described in 33 studies. The peri-operative mortality in the two types of procedures was similar: following open surgery, it was reported in 23 studies with an IQR of 1–5%, with a median of 2%; in endovascular procedures, the IQR was 0–5.5% with a median of 1%. 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. Mortality at 1-year follow-up reported in these studies ($n = 15$) had an IQR of 13–36% with a median of 20% and at five years 40.8–80.5% with a median of 50.5%. There was a paucity of long-term follow-up data in patients having undergone endovascular procedures. Seven studies reported on 1-year follow-up of patients undergoing endovascular procedures with mortality rates with a median of 7% (IQRs 5.0–10.0); 5-year follow-up mortality rate was reported in only two studies and varied widely (5% and 74%).

Limb salvage and amputation

After 5 years, the median limb salvage rate was of 77.5% (IQR 72–82.5%). Following an endovascular procedure, the limb salvage rates within 1 year had an IQR of 70–89%, with a median of 78% (seven studies); 3 years' data were reported in four studies with an IQR of 63–80.0% and a median of 77%. After 5 years, the limb salvage was 56% and 77% in the two studies in which it was reported.

Major amputation rates were reported by 37 studies. The definition of major amputation was not always specified and sometimes differed among studies. The median number of major amputations within 30 days was 3.5% (range 2–5%) based on five studies. The limb salvage rates within 12 months following open surgery were reported in 21 studies and had an IQR of 80–90%, with a median of 85%; after 3 years, these figures were 71–90% and 80% (nine studies). The study by Malmstedt was an interpretation of the Swedish national vascular registry, Swedvasc, and therefore represents the results of a number of different vascular centres rather than those simply focussed on distal bypass procedures [44]. The registry provided a composite outcome for ipsilateral amputation or death per 100 person years of 30.2 (95% confidence interval 26.6–34.2) at a median follow-up of 2.2 years. The median time to reach this end-point in patients with diabetes and PAD undergoing bypass surgery (82% for ulceration) was 2.3 years.

Minor amputation rates varied widely (from 12% to 92%) in the 12 studies reporting on this complication with a median of 38% (IQR 23–59%). It was not clear whether patients received one or more minor amputations in any particular study. The rates of minor amputations for open-surgery studies had a median of 36% (IQR 23–57%), and those for endovascular studies had a median of 38% (IQR 23–57%). However, the number of studies reporting this complication was small, and the demographics were heterogeneous.

Discussion

This systematic review is an update of our 2012 report. It examines the evidence to support the effectiveness of revascularization of the ulcerated foot in patients with diabetes and PAD. Up to 50% of patients with diabetes and a foot ulcer have signs of PAD, which can have a major effect on ulcer healing and the risk for lower-leg amputation [3,81,82]. Early reports on the effectiveness of revascularization in patients with diabetes and PAD were not encouraging and led

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some to suggest that diabetes was associated with a characteristic occlusive small-vessel arteriopathy, consequently leading to a nihilistic attitude towards revascularization. However, subsequent studies indicated that revascularization can have good results in patients with diabetes and an ischaemic foot ulcer [83], but these patients represent a unique problem among patients with PAD.

In our 1980–2010 review, 49 studies were identified fulfilling our selection criteria, and our current review resulted in eight additional studies. The quality of studies included in this review was frequently low. As there are no studies in which patients with an ischaemic foot ulcer were randomized into either revascularization or conservative treatment, it remains difficult to determine the effectiveness of revascularization in these patients. It is also unlikely that such a study will ever be performed. Also, the natural history of patients with PAD and an ulcerated foot remains poorly defined. But in two studies that reported the outcomes of patients with diabetes and critical limb ischaemia who were *not* revascularized, the limb salvage rate was 54% at 1 year [84,85] much lower than the 78% and 85% in the series presented here.

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 [2]. 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–moderate perfusion deficits. There were little data to inform on the indications or timing for either diagnostic angiography or intervention among the studies.

There are currently no RCTs directly comparing open *versus* endovascular revascularization techniques in diabetic patients with an ischaemic foot ulcer. However, broadly speaking, the major outcomes appeared similar across all studies where revascularization of the foot was successful. This conclusion is in line with two meta-analyses on the outcomes of pedal bypass grafting and crural angioplasty, although different inclusion criteria were used; the majority of patients in these two meta-analyses had diabetes [86,87]. In two studies of consecutive patients with diabetes included in our review where angioplasty was the preferred first-line option for revascularization, bypass surgery was only required in a minority [31,40]. However, the results of both open and endovascular procedures will greatly depend upon the expertise in a given centre.

Traditionally, revascularization of the lower limb is aimed at the best vessel supplying in-line flow to the foot [18]. Recent case series have tried to establish whether a new approach in which the angiosome that directly supplies the area of ulceration is revascularized will improve outcome. According to this theory, the foot can be divided into three-dimensional blocks of tissue, angiosomes, each with its own feeding artery. Restoration of pulsatile blood flow through this feeding artery is thought to have better results than when flow is restored through collaterals deriving from neighbouring angiosomes. We identified five studies with conflicting results and high risk of bias, precluding the drawing of firm conclusions [75–79]. Moreover, because of the high variability in populations and the lack of a clear definition of angiosome, we do not believe that the results can be pooled. In contrast, a recent meta-analysis concluded that the angiosome approach may improve in ischaemic foot ulcers' wound healing and limb salvage rates, compared with indirect revascularization [88]. This disparity will only be resolved by well-structured, prospective studies, in combination with new imaging techniques that enable objective evaluation of regional blood flow during a revascularization procedure [89,90].

The variability in outcomes after revascularization is probably related to the large variability of patients included in these observational studies, with some patients having only relative mild PAD and others having severe ischaemia, infection and multiple co-morbidities. In particular, ESRD is a strong risk factor for both foot ulceration and amputation in patients with diabetes [91]. 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 in survivors.

Although peri-operative mortality rates were generally low, given associated co-morbidities, peri-operative major systemic complications were around 10%. It is possible that part of these major complications were more related to the poor general health status of the patients rather than to the revascularization procedure *per se*. Reported morbidity or mortality between open and endovascular techniques was similar. Intermediate and long-term mortality rates during follow-up of studies were high; over 10% of patients were dead at 1 year and almost half were dead at 5 years. Patients with diabetes and a foot ulcer should be optimized prior to revascularization, and given the systemic nature of their vascular disease, they should also receive aggressive and appropriate medical management of risk factors to reduce their high long-term mortality.

Attempts have been made to categorize the distribution of PAD in patients with diabetes and correlate this with perfusion [17]. However, in most studies of the anatomical distribution pattern of the PAD, ankle brachial pressure index, toe pressure or transcutaneous oxygen tension measurements, wound characteristics were reported poorly, although prospective studies have shown the effect of these factors on healing or amputation rate. Also, many studies report major amputation or limb salvage as an outcome, but this is actually a treatment. The decision to

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perform such a procedure is likely to be influenced by factors such as infection, patient and doctor preferences as well as reimbursement. The standard reporting criteria for lower-extremity ischaemia are 15 years old and do not focus on factors that are specific to patients with diabetes [92]. Also, minor amputations are part of management, particularly in case of infection, and improving blood supply to the fore foot can help to limit tissue loss. But we found no studies of sufficient quality on amputation level selection.

Many of the studies reported herein were from well-recognized expert centres, biasing the results towards more favourable outcomes. Moreover, in some instances, there was probably substantial overlap in the larger series of patients from certain centres. The data from the Swedvasc registry suggest that it is possible to attain good outcomes when revascularization techniques are applied outside centres of expertise [44]. However, such procedures should always be part of an integrated multifactorial approach that should include treatment of infection, debridement and off-loading to protect the wound from repetitive biomechanical stress.

Almost all studies were cases series with a high risk of selection and publication bias. Case series comparing bypass surgery and endovascular treatment are difficult to conduct 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 provided the median and IQRs 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 non-revascularized patients with diabetes, PAD and ulceration previously reported in the literature. High peri-operative morbidity and long-term mortality rates underline the importance of peri-operative optimization 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 need for standardized reporting of baseline demographic data, co-morbidity, severity of disease and outcome reporting in this group of patients. A standardized wound classification system should be part of all future studies [93]. 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.

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Supporting information

Table 1 (evidence table) and the search strategy can be downloaded as supplements from the publisher's website.

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