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

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Summary

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 – June 2014. 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 56 papers 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.

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

Abbreviations: ABI: ankle-brachial pressure index; AHA: American Heart Association; AKA: above knee amputation; ARF: acute renal failure; AT: anterior tibial artery; BKA: below knee amputation; CAD: coronary artery disease; CBA: control before and after (study design); 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 design); 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 artery disease; PT: posterior tibial artery; PTA: percutaneous transluminal angioplasty; RCT: randomised 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; UT: University of Texas (wound classification system).

Introduction

In 2012 a multidisciplinary group of experts of the International Working Group on the management of the Diabetic Foot (IWDGF) published a systematic review on the effectiveness of revascularisation 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].

PAD 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% to 40% in the general population of patients with diabetes have been reported [5,6,7,8]. In large observational studies PAD, ranging from relatively mild disease with limited effects on wound healing to severe limb ischemia with delayed wound healing, was present in up to 50% of the patients with a diabetic foot ulcer [9,10,11]. The relatively poor outcome of ischemic 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, 9,12,13,14] 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 glycemic control, microvascular dysfunction, impaired formation of collateral vessels, increased mechanical loading of the ulcer region and comorbidities mentioned above[16].

PAD in patients with diabetes has a number of 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 revascularisation 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 ischemic 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 – June 2014 (Appendix 1). Due to 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 MRA). 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, 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 revascularisation technology with another (for example 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 which resulted

in a systemic disturbance of the patient or prolonged hospitalisation (or as defined by the reporting study).

Patient demographics that were assessed included age, sex, ethnicity and comorbidities (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. TASC[20] or Bollinger systems[21]). Objective assessment of perfusion was reported when possible, which included ankle-brachial pressure index (ABI), toe pressure and transcutaneous oxygen concentration ($TcpO_2$). We made no distinction among various endovascular techniques (e.g. angioplasty, stenting, subintimal angioplasty, 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 PRISMA 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 was 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), Level 2 includes studies with case-control, cohort, controlled-before-after (CBA) or interrupted time series (ITS) design. Studies were rated as: ++ (high quality with low risk of bias), + (well conducted with low risk of bias) and – (low quality with higher risk of bias), according to the SIGN methodological quality score[23]. Level 3 studies, i.e. those without a control group, such as case series, were not rated. Pooling of data (and therefore weighting of studies) was not possible due to study heterogeneity and the generally low quality of evidence (see below). When several studies reported on a specific item we have summarised the data of these separate studies as inter-quartile ranges and median. It should be noted that these figures are not weighted means.

Results

After the identification and screening phase 958 articles were assessed for eligibility 57 papers were finally selected for full text review. These articles described revascularisation of

the ulcerated foot in 9029 patients with diabetes and PAD (Table 1). There were no randomised controlled trials but there were four non-randomised 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 revascularisation, 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 papers were case series (SIGN 3). Studies reported bypass surgery, endovascular therapy or both techniques used in combination. Although most reports adequately presented patient demographics and comorbidities, a major limitation was that few studies adequately reported or categorized either baseline foot lesions or PAD severity. A number of studies were reported from the same institution and it is likely that some patients were reported more than once.

Patient demographics and comorbidities

The median reported proportion of males in the included studies was 66% (inter-quartile ranges 60-74%), and the median reported age was 69 years (inter-quartile ranges 65-71 years). Patients with diabetes, PAD and foot ulcers had a prevalence of comorbidities. Specifically, the prevalence of coronary artery disease was reported as 38% – 59% (inter-quartile ranges) with a median of 47%, of cerebrovascular disease as 18% – 23% with a median of 21% and of end-stage renal disease as 11% – 41% with a median of 20% (although the definition varied form study to study and in some studies was only reported as renal impairment). Eight studies did not report any data on comorbidity and data on severity of comorbidities (e.g. NYHA 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 pre-defined 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 revascularisation (scoring of anatomical distribution was not given)[65, 30, 39]. In one of these studies, a large series of 993 consecutive patients with diabetes hospitalised with foot ulcer or ischemic rest

pain and PAD, percutaneous angioplasty (PTA) was technically not feasible in 16% of the patients due to 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 infra-inguinal 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 to the other series[65].

Crural vessel angioplasty

Crural PTA employed as a revascularisation 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 inter-quartile range of 85–98% at one year, a median of 88.5 (81.3–82.3%) at three years and 78% (78– 82.3%) at five years. However, the numbers available for follow-up at three and five years were low; the distribution / severity of PAD and the type of foot lesion were poorly reported.

Angiosome directed therapy

Five retrospective studies with a high risk of bias analysed the outcome of revascularisation 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 revascularisation results in a restoration of pulsatile blood flow through a feeding artery to the area where the ulcer is located, while with indirect revascularisation flow is restored through collateral vessels deriving from neighbouring angiosomes[80]. In these studies post-procedural angiograms were scored as either direct flow to site of the ulcer by a feeding artery (direct revascularisation) or indirect flow through collaterals (indirect revascularisation). Three studies reported significantly higher limb salvage rate after direct revascularisation[75-77], while in two no differences were observed[78,79]. Ulcer healing was also reported to be significantly higher after direct revascularisation 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 vs. indirect revascularisation: 69% vs. 47% after 1 year, respectively, but without any difference in limb salvage[78]. Acin et al further divided the patients with indirect revascularisation in two groups: those with indirect flow through collaterals and those with indirect flow but no visible collaterals[76]. The latter group had the poorest results, with ulcer healing rate of only 7% after 1 year and limb salvage rate of 59% after 2 years. The direct and indirect through collaterals revascularisations 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 ischemic ulcer is pivotal, with similar results of flow through medium or large size collaterals or via the feeding artery.

Infection

Only two studies specifically reported the outcomes of a revascularisation procedure in patients presenting with foot infection, PAD and diabetes[62, 61]. In these studies the mortality rates at one 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 end-stage renal disease (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% (inter-quartile range 2.6% – 8.8%) but one year mortality was high at 38% (inter-quartile range 25.5–41.5%). In survivors, one year limb salvage rates were a median of 70% (inter-quartile range 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 56%[58] and at 5 years 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

30-day or in-hospital mortality was described in 33 studies. The peri-operative mortality in the two types of procedures were similar: following open surgery it was reported in 23 studies with an inter-quartile range of 1-5%, with a median of 2%; in endovascular procedures the interquartile range 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 comorbidities frequently was not stated it was difficult to infer the effect of comorbidity on outcomes.

Mortality

Mortality at one year or longer following intervention was reported more frequently in studies describing open surgery. Morality at one year follow-up reported in these studies (n=15) had an inter-quartile range 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 one-year follow-up of patients undergoing endovascular procedures with mortality rates of median 7% (inter-quartile ranges 5.0%-10.0); five year follow-up mortality rate was reported in only two studies and varied widely (5% and 74%).

Limb salvage and Amputation

After five years the median limb salvage rate was of 77.5% (inter-quartile range 72% – 82.5%). Following an endovascular procedure the limb salvage rates within 1 year had an interquartile rage of 70%–89%, with a median of 78%, (7 studies); 3 years data were reported in 4 studies with an inter-quartile range of 63% – 80.0% and a median of 77%. After five 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 inter-quartile range of 80–90%, with a median of 85%; after 3 years these figures were 71%-90% and 80% (9 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% CI 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% (inter-quartile range 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% (inter-quartile range 23–57%) and those for endovascular studies had a median of 38% (inter-quartile range 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 revascularisation of the ulcerated foot in patients with diabetes and PAD. Up to 50% of the patients with diabetes and a foot ulcer have signs of PAD, which can have a major impact on ulcer healing and the risk for lower leg amputation[3, 81, 82] . Early reports on the effectiveness of revascularisation in patients with diabetes and PAD were not encouraging and led some to suggest that diabetes was associated with a characteristic occlusive small vessel arteriopathy, consequently leading to a nihilistic attitude toward revascularisation. However, subsequent studies indicated that revascularisation can have good results in patients with diabetes and an ischemic 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 8 additional studies. The quality of studies included in this review was frequently low. As there are no studies in which patients with an ischemic foot ulcer were randomised into either revascularisation or conservative treatment, it remains difficult to determine the effectiveness of revascularisation 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 CLI who were **not** revascularized, the limb salvage rate was 54% at one 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 etiologic factors, and the situation is compounded by the presence and severity of PAD[2]. Although the current data indicate that revascularisation should always be considered in a patient with diabetes, foot ulceration and severe ischemia, it still remains unclear if such procedures have an added value in cases of mild-moderate perfusion deficits. There was 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 vs. endovascular revascularisation techniques in diabetic patients with an ischemic foot ulcer. However, broadly speaking the major outcomes appeared similar across all studies where revascularisation 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 is revascularized that directly supplies the area of ulceration 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 drawing firm conclusions[75-79]. Moreover, due to the high variability in populations and the lack of a clear definition angiosome we do not believe that the results cannot be pooled. In contrast, a recent meta-analysis concluded that the angiosome approach may improve in ischemic 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 revascularisation procedure[89,90].

The variability in outcomes after revascularisation 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 ischemia, infection and multiple comorbidities. In particular, end-stage renal disease 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 revascularisation procedure. However, our data indicate that even in these patients favourable results can be obtained. The majority of studies reported 1-year limb salvage rates of 65-75% after revascularisation in survivors.

Although peri-operative mortality rates were generally low, given associated comorbidities, 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 revascularisation procedure per se. Reported morbidity or mortality between open and endovascular techniques were similar. Intermediate and long-term mortality rates during follow-up of studies were high; over 10% of patients were dead at one year and almost half were dead at five years. Patients with diabetes and a foot ulcer should be optimised prior to revascularisation 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 anatomical distribution pattern of the PAD, ABI, toe-pressure or $TcPO_2$ measurements, wound characteristics were reported poorly, although prospective studies have shown the impact 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 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 ischemia 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 revascularisation 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 high risk of selection and publication bias. 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. Due to heterogeneity we could not pool the data. For ease of data presentation we provided the median and interquartile ranges of the results of the studies we selected, but this did not correct for number of patients, severity of disease and comorbidities. Due to these limitations we cannot give reliable estimates of expected outcome. Clearly, there is an urgent need for properly controlled studies with a well described population and outcomes which are relevant to patients with diabetes.

In conclusion, studies reported herein appear to demonstrate improved rates of limb salvage associated with revascularisation compared to the results of 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 optimisation and long-term medical management of patients' diabetes and comorbidities. Overall, there were insufficient data to recommend one method of revascularisation over another. There is need for standardised reporting of baseline demographic data, comorbidity, severity of disease and outcome reporting in this group of patients. A standardised 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 standardise and improve outcome reporting, which should

include wound healing, and it is important to move away from procedure specific outcomes to disease specific outcomes in this cohort of patients.

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Appendix 1: Medline via OvidSP

Date of search: June 2014

File searched: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R); 1948 to Present

1. diabet*.ti,ab.
2. exp Diabetes Mellitus/
3. 1 or 2
4. (lower adj1 extremit*).ti,ab.
5. (lower adj5 limb*).ti,ab.
6. limb*.ti,ab.
7. leg*.ti,ab.
8. (foot or feet).ti,ab.
9. toe*.ti,ab.
10. Lower Extremity/
11. Leg/
12. Foot/
13. Toes/
14. Extremities/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. peripheral vascular disease*.ti,ab.
18. peripheral arterial disease*.ti,ab.
19. (pvd or povd).ti,ab.
20. (pad or paod or poad).ti,ab.
21. exp Peripheral Vascular Diseases/
22. (claudication or claudicant*).ti,ab.
23. exp Intermittent Claudication/
24. exp Arterial Occlusive Diseases/
25. exp Graft Occlusion, Vascular/
26. exp Saphenous Vein/
27. exp Femoral Artery/
28. exp Popliteal Artery/
29. 26 or 27 or 28
30. occlus*.ti,ab.
31. stenosis.ti,ab.
32. 30 or 31
33. 29 and 32
34. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 33
35. 15 and 34
36. 16 or 35
37. perfusion.ti,ab.
38. reperfusion.ti,ab.
39. exp Reperfusion/
40. (odema or edema or oedema).ti,ab.
41. exp Edema/
42. (swelling* or swollen).ti,ab.
43. inflamed.ti,ab.
44. inflammation.ti,ab.
45. (flow or flux).ti,ab.

46. exp Blood Flow Velocity/
47. capillar*.ti,ab.
48. exp Capillaries/
49. (ischem* or ischaem*).ti,ab.
50. exp Ischemia/
51. (by-pass or by-pass).ti,ab.
52. percutaneous.ti,ab.
53. angioplast*.ti,ab.
54. exp Angioplasty/
55. (ballon adj1 dilation).ti,ab.
56. (ballon adj1 dilatation).ti,ab.
57. exp Balloon Dilatation/
58. endotherapy.ti,ab.
59. endovascular.ti,ab.
60. evt.ti,ab.
61. (revascularization or revascularisation).ti,ab.
62. (endoscopic adj1 therapy).ti,ab.
63. exp Endoscopy/
64. atherectom*.ti,ab.
65. endarterectom*.ti,ab.
66. artherosclerosis.ti,ab.
67. exp Atherectomy/
68. stent*.ti,ab.
69. exp Stents/
70. patency.ti,ab.
71. exp Vascular Patency/
72. (limb adj1 salvage).ti,ab.
73. exp Limb Salvage/
74. subintimal.ti,ab.
75. surg*.ti,ab.
76. su.fs.
77. pta.ti,ab.
78. 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
79. 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77
80. 36 and 78 and 79
81. (letter or comment or editorial or case reports).pt.
82. 80 not 81
83. limit 82 to humans

Appendix 2: Embase via OvidSP
Date of search: June 2014;
Database file searched: Embase 1980 to present

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

Table 1: Evidence table

Reference	Study design	Population (age, sex, number with diabetes)	PAD (distribution and severity)	Foot lesion	Comorbidities	Intervention and control management	Outcomes	Comment	Opinion
AhChong 2004[24]	Case series 265 consecutive infrainguinal bypasses with outcomes described diabetes versus no diabetes	DM patients 176 No DM 89 Age median 74 (45-94) yrs versus 75 (29-94) no DM gender: 50% (88) male DM, 45 (51%) no DM (P=NS)	Distribution: NR Severity: ABI 0.43 Median toe pressure 26mm Hg (0-57) No scoring system used	Tissue loss 158 (90%) DM No DM 70 (79%) tissue loss (P=0.014) Ulcer score: NR Infection: NR	CAD 48% CVD 26% ESRD NR	Bypass graft to DM patients Fem-pop 44% Crural 40% Pedal 16% Autogenous vein 66% No DM Fem-pop 56% Crural 35% Pedal 9% (P=NS) Autogenous vein 63%	Median f/u 19months Mortality 30days 8% DM versus 1% No DM (P=0.04) Cardiovascular complications 9% v 4% (P=NS) Overall graft patency 1yr 63% Graft patency 4yrs 46% DM versus 34% no DM (P=0.19) Survival rate at 1,3,5 yrs 80%, 57%, 33% Ulcer healing: NR Limb salvage overall at 1 yr 83% for both groups and 5yrs 78% DM v 81% no DM (P=0.79)	Chinese population may differ from Western world Limited information about patient management	Early graft failure 6% 65 grafts failed overall during total study

							Major amputation: NR Minor amputation: NR Complications: 8% peri-op		
Alexandrescu 2009 [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 classificaion reported	Wagner classification grade 2-4 in 104 limbs (59%) or as isolated calf ulcers in 42 cases (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)	Mean f/u 22 (SD 1) months Ulcer healing: 129 (73%) before end of study, Limb salvage: 12, 24, 36 and 48 month limb-salvage proportions: 89%, 83%, 80% and 80%. In a intention-to-treat analysis, the cumulative primary and secondary patency at 12, 24, 36 and 48 months were 62%, 45%, 41% and 38%, together with 80%, 69%, 66% and 66%, respectively. Major amputation: 24 (13%) during f/u		Level of intervention not described in all patients. Approximately 50% infrapopliteal or crural 70% neuropathy

							Minor amputation: 67 (38%) 30-day mortality: 1% 1 and 2 year mortality: 7% and 19 % Major complication: 5%		
Bargellini 2008 [26]	Prospective case series of multilevel subintimal PTA in patients deemed not fit for surgical bypass	DM patients: 60 age: 69,4 (SD 9,4) gender: 68% (41) males	Distribution: NR Severity: NR	Fontaine: 100% Fontaine IV Infection: NR	CAD 42% CVD 25%	Subintimal PTA in patients not suitable for surgical bypass: Fem-pop level 56.7% (34) Infra-popliteal level 25% (15) Both levels combined 18,3% (11)	Mean follow-up 23 months (range, 0–48 months) Ulcer healing: 75% (45/60) Limb salvage: 93.3% (56/60) Major amputation: 3 within 30 days and 4 within 16 months Minor amputation: NR Complications: Peri-procedural mortality was 5% (3/60) Mortality at 1yr, 3yr 10%, 17%	How follow-up was performed, was not defined Long term mortality low for a „high risk" population medically unfit for bypass surgery	

Davidson 1993 [27]	Retrospective case series Bypass below knee case series	54 DM patients (total population 70) age 55-95; gender: 54% (38) men (total population)	Distribution: majority infra-popliteal severity: no information No score of distirbution	gangrene 56%, ulcer 28% (of total population) Infection: NR Ulcer score: NR	CAD 55%, CVD 27%, hemodialysis 7% (total population)	Vein graft below knee (57% to foot)	Limb salvage 90% at 12months and 86% at 24 months Major complications: 9/70 Early graft failure n=3 (4.2%) Patency 93% 1yr and 85% 2yrs Mortality: NR	Follow-up duration was variable and after 1 year 29 limbs out of 58 limbs were available for evaluation and after 3 years 6 limbs out of 58.	
Dosluoglu 2008 [28]	Case series A comparison of peroneal to other run-off vessels after PTA	80 DM patients out of 111 age: NR gender: NR	Distribution: infrapopliteal Severity: NR TASC classification provided	All tissue loss Infection: NR	NR	Infrapopliteal PTA	F/U mean 19,2 (SD 13,4) months Ulcer healing: NR Limb salvage rate 75% in 24 months in diabetic patients with peroneal run-off and in run-off in other vessels 76% No other data on the diabetes sub-group divided		Strengths and weaknesses: No data on patient, leg or ulcer characteristics in DM patients provided. Study with less than 80% with diabetes but limb salvage was reported separately for the diabetes patients in both groups
Dorweiler 2002 [29]	Case series of pedal	DM patients 46	Distribution: crural	All (100%) tissue loss	CAD 46% ESRD 13%	Pedal bypass with vein graft	F/U median 28 (1-70) months	No data on severity of	

	bypass grafts	age: median 69yrs gender :78% (36) male	occlusions Severity: NR	Ulcer score: NR Infection: NR			Ulcer healing: NR Limb salvage: 30 days 98%, 87% at 2 years Major amputation: 4 (3 within 30 days) Minor amputation: 70% Complications: peri-operative mortality 2% One patient failed graft within 30days Mortality at end of study 21/46 (47%)	PAD. No specific data on foot lesions Drop out and loss to f/u NR Well defined study	
Faglia 2002 [19]	Case series Mixed series of PTA	All DM patients 221 age: NR gender: NR	Distribution: 11 patients ilio/femoral/popliteal axis 81 exclusively infrapopliteal 127 femoropopliteal and infrapopliteal Severity: TcpO2 21 (30 SD) mm Hg in 180 cases.	Wagner grade ulceration I – 19% II – 25% III – 17% IV – 38% V – 1%	CAD 55% ESRD 4%	PTA of stenoses greater than 50% diameter infra-inguinal	Median f/u 12 (5-30) months Ulcer healing: see opinion Limb salvage: NR Major amputation: 5% Minor amputation: 38% (83)		Probably significant amount of the data is also reported in Faglia 2009 221 had angio but 2 had no significant stenoses therefore 219 reported 28 subjects PTA not possible (9

			ABI in 128 cases 0.53 (0.15)				Mortality 30days: 0% Mortality 5.3% at f/u Complications: n=1 (transient renal failure)		surgery and 19 no candidate for any revasc) All ulcers healed with medical dressings of the 190 patients – nothing more specific
Faglia 2005 [30]	Retrospective case series Consecutive series of diabetic foot patients hospitalised. PTA as first choice revascularisation	DM patients 993 age: 65.5 (9.4) gender: 67% (663) male	7% ilio-femoral 61% femoro-popliteal /crural 32% crural Severity: tcpO2 17,0 (11,9)	88% tissue loss Texas classification 0 – 12% I – 16% II – 19% III- 53%	CAD 62% ESRD 5%	PTA 68% procedures in crural arteries	Mean f/u 26 (15.1) months Ulcer healing: 862/868 wounds healed Limb salvage: 98,3% during f/u Major amputations 2% during f/u Minor amputation: 48% Complications: 3.4% Mortality 30-day 0,1% Primary patency at 5yrs 88% (SD 9%) Mortality at 1 yr 6,7 % and 20,1% at 3 yrs	good wound description at presentation, level of disease : treated was well described some f/u data was obtained by treating physician telephone interview	Possibly some patients reported elsewhere Of the 993 treated with PTA only 10 did not manage to successfully get one vessel in line flow to the foot

							(extrapolated from Kaplan-Meier curve)		
Faglia 2009 [31]	Cohort with follow up 5,9 year (SD 1,28) Follow up study of 564 diabetic patients with „CLI" referred for angiography, patients with obstruction more than 50% underwent PTA, when possible as first choice	PTA: 413 DM patients age:69,7 (SD 9,5) gender: 64.6% 267) males Bypass group: 114 DM patients age: 69.9 (SD 9.4) gender: 69,3% (79) males No revasc group: 27 DM patients age: 76.7 (SD 10.4) gender: 51,9% (14) males	Distribution: PTA: Iliac - femoral-popliteal axis in 28 patients (6,8%) Infra-popliteal in 137 patients (32,2%) Combination of both in 248 patients (60%) Bypass: NR No revasc: NR Severity: PTA: tcpO2 15,3 (11,9) Bypass: tcpO2 10,2 (10,3) No revasc: tcpO2: 7,0 (8,1) Scoring: NR	PTA: No lesion 62 (16%), rest Wagner 1-4 Infection: 65% Bypass: No lesion 16 (14%), rest Wagner 1-4 Infection 63% No revasc: No lesion 3 (11%), rest Wagner 1-4 Infection: 63%	PTA: Dialysis 24 (5,7%) CAD 225 (54,8%), CVD 53 (19%) Bypass: Dialysis 8 (7%); CAD 64 (59%), CVD 18 (15,8%) No revasc: Dialysis NR, CAD 24 (88,9%), CVD 9 (33,3%)	PTA, all stenoses > 50% were treated (see PAD distribution) Iliac-femoral-popliteal axis in 28 patients (6,8%) Infra-popliteal in 137 patients (32,2%) Combination of both in 248 patients (60%) Bypass, femoro-popliteal 58 Fem-infrapopliteal 55 Other 1	Mean f/u 5,93 (SD 1,28) years of total cohort. No f/u data on the 3 subgroups PTA: Ulcer healing: NR Limb salvage: NR Major amputation: 1 month 2,3%; 8% at end of follow up Minor amputation: NR Complications: NR Bypass: Ulcer healing: NR Limb salvage: NR Major amputation: 1 month 5,4%; 21% at end of follow up Minor amputation: NR Complications: NR 32% primary bypass failures	In addition authors analyzed their data as a 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-Meijer data are incomplete: number at risk at time points are missing. The study cannot used as a cohort study comparing PTA vs bypass, it does however give information about the results of PTA and information of the revascularised vs non-revascularised patients Baseline characteristics of the groups

							No revascularisation: Ulcer healing: NR Limb salvage: NR Major amputation: 59% at end of follow up Minor amputation: NR Complications:NR PTA vs. bypass p < 0,001 SIGN 2-		are different and therefore confounding was induced.
Ferraresi 2009 [32]	Case series Long-term outcome of BK PTA in diabetes	101 DM patients and 107 legs age: 66 (SD 9,4) gender: 84% (85) males	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	Mean f/u 2.9 (SD 1,4) years Ulcer healing: NR Limb salvage: 93% during f/u Major amputation: 7% Minor amputation: 64% Complications: NR Mortality 30 day: NR Mortality during f/u 9%	This case series is a sub analysis of a larger study	Strengths: Treated lesions clearly defined and standardised Patients with marked tissue loss Weaknesses: 1 and 3 year leg salvage and survival data are not provided, hindering interpretation.

Gargiulo 2008 [33]	Prospective case series Outcome of successful tibial PTA in „CLI"	74 DM patients out of 87 total population age: 72 (SD 8,8) gender: 56% males	Distribution: NR Severity: NR	92% Fontaine IV Ulcer classification: University of Texas Infection: NR	CAD 53% ESRD 28%	infrapopliteal PTA"s (100%) combined with fem-pop angiopolasty in 63% and in 3 (3,4%) patients combined with open revascularisation	Mean f/u 10,9 months (range 2 days-29 months) Ulcer healing: 74,9% at 1 year Limb salvage: 92,7% at 18 months Major amputation: 6,9% during f/u Minor amputation: NR Complications: No early perioperative complications	Only technically successful PTA included in the analysis	Strengths and weaknesses: Strengths: well performed prospective study with complete data set, provides relevant information on wound healing Weakness: the shortest follow-up data was 2 days, a Kaplan Meijer that includes duration of follow-up is missing, hampering interpretation
Gibbons 1995 [34]	Retrospective case series Infra-inguinal bypass series Six months all patients were asked to fill in questionnaires on health related quality of life	259 DM patients (total population 318) age: mean age 66years gender: 62.3% males	Distribution: Multilevel disease Severity: no information No score anatomical distribution	237/318 (74.8%) ulcer or gangrene Infection: NR Ulcer score: NR	No information	infra-inguinal open revascularisation fempop 84 (26.4%) femtibial / peroneal 132 (41.5%) fempedal / plantar 100 (31.4%)	F/u 6 months Ulcer healing: NA Limb salvage: 97% at 6 months Minor amputation: NA 93% primary graft patency at 6months and secondary 97%	Walking devices used at start of study 63% and at end of 6months 74% 38% more active at f/u 32.5% about the same and 29.5% worse.	Selected group of patients: primarily HRQOL study

	(HRQOL)						Complications: morbidity peri-op 21%	Less than half back to normal at 6months (47.4%)	
Hering 2010 [35]	Prospective case series of crural PTA in patients with diabetes and an(neuro-) ischemic foot ulcer	44 DM Age 72 (42-88yrs) Gender 75% (33) male	Distribution: NR Severity: NR	Wagner grade I – 0 II – 6 (14%) III (30 (68%) IV – 8 (18%) Infection: NR	CAD 77% CVD 52% ESRD 16%	Peroneal PTA	Mean F/u 23 (5-45) months Ulcer healing: 59% Limb salvage: 81%, 71% and 63% at 6, 12 and 18 months Mortality 30days: 9.1% Minor amputation: NR Complications: 1 renal failure		A prognostic study of doppler waveform patterns predicting outcome of peroneal PTA Overall 50% had a restenosis or occlusion of peroneal artery
Hertzer 2007 [36]	Case series Mixed case series of bypass grafts	312 DM patients out of 650 (48%) age: NR gender: 62% males	Distribution: NR Severity: NR	71% ulceration or gangrene Ulcer score: NR Infection: NR	NR	infrainguinal bypass grafts for occlusive disease	Median follow-up 4yrs Ulcer healing: NR Limb salvage: 73% (95% CI 67 – 78) at 5 years, 15 years 51% (38 – 64) Major amputation: 29 amputations in 201 diabetic patients		Strengths and weaknesses: very long follow up time limited specific data on diabetics

							Minor amputation: NR Mortality 6.7% 30 days Mortality at end of study 83% at median 4yrs Complications: not reported separately for diabetes		
Hughes 2004 [37]	Retrospective case series Series of pedal bypasses	DM patients 82 (84%), total 98 age: 68 (SD12) gender: 83% (81) male	Distribution: Crural Severity: NR No scoring	93 (95%) tissue loss Infection: NR Ulcer classification: NR	CAD 40% ESRD 4%	Bypass to plantar and tarsal arteries with vein graft (one prosthetic) Popliteal inflow 72%	Duration of f/u median 9 (1-112)months Ulcer healing: NR Mortality 30 days 1/98 total Complications: 124 peri-op complications Mortality at 1yr 9%, 5yrs 37% Limb salvage 75% 1yr, 69% 5yr Secondary patency 70% 1yr	Primary patency 41% and secondary patency of 50% at 5yrs Consecutive series of all revascularisations Excluded lost to f/u cases from analysis (n=26)	No differences in outcome between tarsal/plantar and dorsalis pedis bypass
Isaksson 2000 [38]	Retrospective case	DM patients 43 (48 legs)	Distribution: NR	7 (15%) rest pain	Prev MI 11 (26%), angina	Pedal bypass with vein	F/U up to 1yr	Short follow-up –	

	series Pedal bypass graft case series	age: 74 (40-84) gender: 37 % (16) males	Severity: ABPI median 0.47 (0 – 2.14) Score: NR	All others (85%) tissue loss Ulcer score: NR Infection: NR	6 (14%)	(proximal anastomosis femoral artery 20 (42%) and popliteal artery or below 28 (58%))	Ulcer healing: Limb salvage: 1yr 85% Minor amputation: NR Complications at 30 days 2 died (4%), 1 patient MI Mortality rate at 1yr 14% Patency at 1yr 83%	early results only	
Jamsen 2002 [39]	Retrospective case series Outcome of consecutive series of 100 infra-inguinal PTA considered suitable for PTA first approach	100 patients (116 limbs) 76 (76%) DM patients age: 72 (38-90)yr total population gender: 40% (40) total population males	Distribution: NR Severity: ankle systolic pressure <50mm Hg Scoring system not used	Rest pain 23 (20%), ulcer 50 (43%), gangrene 43 (37%) Wound classification: NR Infection: NR	CAD 47%, CVD 28%	Angioplasty Femoropopliteal 54% Crural 17% Multilevel 29%	Median f/u 25months. Intention to treat analysis 1yr 67%, 3yr 63%, 5yr 56%, 8yr 45% limb salvage Ulcer healing: NR Limb salvage for endovascular treatments at 2, 3, and 5 years was 74%, 65% and 60% Major amputation:	11 required bypass for PTA failure. . Validity of 5 and 10 year questionable – very small numbers available after 3 years Pre selected to PTA first approach	

							32% during total f/u Minor amputation: 12% Major complications:11% Mortality at 1,5 and 10 yrs 18%, 74%, 86%		
Johnson 1995 [40]	Restrospective case series Retrospective review of popliteal distal bypass grafts in patients with ESRD	43 DM patients In total population 53 age: 59 (total population) gender: 46% (27) males (total population)	Distribution: NR Severity: in general toe pressures <40, ABI <0.5 (or incompressable) Scoring NR	69 limbs (53 with tissue loss) Ulcer score: NR	43 ESRD (kidney transplant 10) CAD 38% CVD 15%	Total population 69 venous bypasses: Fem-pop 19 Crural 50	Mean f/u 14 (range 3-96) months Ulcer healing: NR Limb salvage: 1yr 65% and 62% at 18 months Major amputation: 22 („foot amputations") Minor amputation: NR Peri-op mortality 10% 1yr mortality 42%, 2yr mortality 72%	59% „foot amputations" performed with patent graft	Amputation can be related not only to occlusion but also to other factors like infection.

Kalra 2001 [41]	Retrospectiv ecase series Series of pedal bypass grafting using vein	DM patients 191 (75%), total population 256, 280 procedures age: median 70 (30-91)yrs total population gender: 68% (174) male total population Long grafts (prox anastomosis above popliteal) 130 (46%) of total population Short grafts (prox anastomosis at or below popliteal) 150 (54%) of total population	Distribution: NR Severity: tcpO2 < 20mmHg in 88% and ABI =0.44 (38% incompressible) in 150 limbs Scoring system: NR	90% tissue loss total population Infection: NR Wound classification: NR	CAD 132 (52%), CVD 54 (21%), ESRD 19 (7%)	All vein bypass grafts to pedal vessels	Median f/u 2.0 (range 0,1-10,1) years Cumulative limb salvage rates at 1, 3, and 5 years were 85% (95% CI, 80.3-89.5), 79% (95% CI, 73.9-85.1), and 78% (95% CI, 71.7-83.7), respectively Ulcer healing: NR Major amputation: 15% at 2.7years mean f/u Minor amputation: 12.4% Complications: 1.6% peri-op mortality Long-term mortality 1,3,5 yr = 13%, 24%, 40% Secondary patency at 1yr 78%, 3yr 72%, 5yr 71%	Survival rate was 65% if had patent graft at 5 yrs versus 26% if leg off 57% of patients had one or more secondary interventio ns for pedal graft	

Kandzari 2006 [42]	Case series Endovascular revascularisation using catheter based plaque excision	52 DM patients out of total pop of 69 age: 70 (SD 12) (total pop) gender: 49% males	Distribution: 154/160 lesions infrainguinal 43% crural Severity: ankle pressure < 50 mmHg	93% Ruth 5 7% Ruth 6 (total pop) No ulcer classififcation	CAD 57% CVD 23% Infection: NR	endovascular plaque excision	F/u 6 months Ulcer healing: NR Limb salvage: NR Major amputation: 20% diabetes versus 18% no diabetes (p=0.86) at 6 months Minor amputation: NR Complications: major adverse events (26.7% diabetes versus 22.2% no diabetes, p=0.72).		Data reported comparing patients with and without diabetes however very little information given
Leers 1998 [43]	Retrospective case series Pedal bypass grafts in ESRD	DM patients 31 (91%) 34 total age: 64 (39-85)yrs total population gender: male 59% total population	Distribution: infrapopliteal in 23 legs and infrainguinal in 13 legs of total population Severity (only in 16 patients): ABI 0.48 (0-0.95) mean, toe pressure 18 (0-78)	probably > 90% had tissue loss although this was not explicitly stated in the article Wound classification: NR Infection: NR	CAD: 28 (82%) ESRD: 100% (29 haemodialysis and 2 transplants)	Pedal venous bypass 88% total population	Average follow-up 13.5 (1-84) months Ulcer healing: NR Cumulative assisted primary patency at 1yr, 2ys 62% and 62% Limb salvage: 56% at 1yr and at 2yrs 50%	Retrospective, some data were obtained from family or dialysis institutions Data difficult to interpret – self reported data	

							Major amputation: 16 (39%) at 13.5months average f/u Minor amputation: 51 (26%) total population at 1yr Complications: Survival 64% at 1yr 1 periop death (2%) Mortality 36% at 1yr and 48% at 2yrs		
Malmstedt 2008 [44]	part of country wide observational data base (Swedvasc) Outcome after bypass surgery in diabetics	742 DM patients age: 74 (SD 9,8) gender: 58% male	Distribution: NR Severity: NR Infection: NR	82% tissue loss Ulcer classification: NR	CAD 65% CVD 19% ESRD defined as creatinine 150 umol/L 20%	261 femoral-popliteal bypasses 481 infra-popliteal bypasses	Mead f/u 2,2 years Ulcer healing: NR Limb salvage: NR Major amputation: NR Minor amputation: NR Complications: NR		Composite primary endpoint was: amputation or death The rate of ipsilateral amputation or death was per 100 person years 30,2 (95% CI 26,6-34,2) Median time to life or limb loss was 2,3 years (CI 1,9-2,8) The use of the composite end-point renders

									interpretation very difficult.
Mills 1994 [45]	Retrospective case series of patients with popliteal distal vein bypass grafts	46 DM patients (total population 53) age: 62,4 (total population) gender: 80% (37) men (total population)	Distribution: infra-popliteal Severity: NR Scoring distribution: NR	52 tissue loss Infection: NR Ulcer score: NR	CAD 57%; ESRD 28%	Infra-popliteal vein bypass All crural bypass	Mean f/u 12,5 (range 1-66) months Ulcer healing: NR Limb salvage: 85% after 1 year (22 limbs out of 56 legs available at 1 year). Minor amputation: NR Complications: Peri-operative mortality: 2 out 53 (3,6%) Within 30 days 2 graft occlusions with subsequent 2 major amputations Mortality 1yr 13%, and 2yr 29%		Strength: well defined cohort Weaknesses: high rate withdrawal rate, probably combination of short duration and lost-to-follow-up (not reported separately) Paper is an example of the confusion between the total population, number of diabetics, number of extremities and number of procedures.
Mohan 1996 [46]	Case series Pedal bypass graft case series	All DM patients 32 Mean age: 60 (range 42-84)yrs gender: 50%	Distribution: popliteal artery inflow AK pop 9 BK pop 26 Severity: NR	NR 18 (51%) ulcers 15 (43%) gangrene 2 (6%) patients rest pain	CAD 47% Chronic renal failure 28%	Popliteal to distal artery bypass PT 9 AT 8 DP 10 Peroneal 8 All vein grafts	Mean follow-up 24 (1-72) months Ulcer healing: NR 30day mortality	Small study population and no information regarding drop-out rate	

		males		Ulcer score: NR Infection: NR			0% Limb salvage: 90% at 1yr, 82% at 3 years Major amputation:5 within 20 months Minor amputation: NR Patency 1, 3yr 95%, 89% Complications: 4 failing grafts surgery revised. 3 bypass occlusions of which 2 resulted in major amputation 3 additional amp due to infection Mortality (longterm): NR		
Owen 2007 [47]	Cohort study According to 4 different levels of kidney disease	CKD 4 (eGFR 15-29): 25 DM patients out of 32 (total cohort) age: 67,5 (SD 11,5) gender: 76% (19) males (total cohort)	Distribution: infra-inguinal, no further data given Severity: NR	CKD 4 (eGFR 15-29): 84% foot lesions CKD 5 (eGFR < 15 and HD): 90% foot lesions	CKD 4 (eGFR 15-29): CAD: 23 (71,9%) CKD 5 (eGFR < 15 and HD): CAD: 44 (61,1%)	Infra-inguinal bypass	Mean f/u 69,2 (SD 28,5) months CKD 4 (eGFR 15-29): Ulcer healing: NR Limb salvage: at 5 year 77 (Sd14) Minor		A study that provides relevant data on CKD in severe forms as a prognostic factor. Infra-inguinal bypass, outflow data not provided

		CKD 5 (eGRF < 15 and HD): 60 DM patients out of 72 (total cohort) age: 65 (SD 11) gender: 53% (38) males (total cohort)		Ulcer score: NR Infection: NR			amputation: NR Complications: 30 day mortality 3,1% CKD 5 (eGFR < 15 and HD): Ulcer healing: NR Limb salvage: at 5 year 50 (Sd 12) Minor amputation: NR Complications: 30 day mortality 4,2% CKD 5 mortality at 1yr 46%, 91% at 5yr SIGN 2-		This study was reported as a case series Probably only sufficient data on CKD 5 patients Difficult to use patency data because mortality very high
Panneton 2000 [48]	Retrospective case series Pedal bypass graft series	DM patients 157 age: 66 (30-78)yrs gender: 71% (111) males	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 2.7yrs Ulcer healing: NR Limb salvage: 1yr 86%, 5yr 78% Minor amputation: NR Complications: 30-day mortality	A sub group of a series comparing diabetics versus no diabetics in which no differences were observed between the two groups	Comparison of diabetes and no diabetes

							1.3%, MI 11 (7%), ARF 5 (3.2%), major amp 3 (1.8%)		
Pomposelli 1995 [49]	Case series Retrospective review of 367 consecutive patients undergoing 384 distal bypasses	350 DM patients, total population 367 age: 58 mean gender: male 69% (253)	Distribution: NR Severity: NR Scoring: NR	219 (72%) with ulcer; 47 (12%) of gangrene; 16% other indications Infection: 222 (55%) Ulcer classification: NR	Prior myocardial infarction 29%, CVD 12%, ESRD 5% (dialysis) of total population	Dorsalis pedis arterial bypass	Mean f/u 21 (range 2 -84) months Ulcer healing: NR Limb salvage: cumulative limb salvage rate 87% at 5 years. 1yr and 2yr estimated from K-M 90% and 85% Secondary patency rates 82% at 5yrs Major amputation: 13 (3,5%) within 30 days. Total number of major amputations 30 (8,1%) within the 5 year follow up. Minor amputation: 75 (19%) Complications: 30-day mortality 1.8% myocardial	Comorbidity 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 predifend problem; there is no drop out rate reported. Outcome lim salvage wasn"t defined any further.

							infarction 5.4%. graft failures 7.5% at 30 days, Mortality 43% after 5yrs		
Pomposelli 2003 [50]	Retrospective case series Pedal bypass graft series	865 total population 92% diabetes age: 67years gender: 69% male	Distribution: inflow vessel 41% BK pop 29% CFA 12% AK pop 11% SFA Severity: NR No scoring	78% ulcer Infection: NR Ulcer score: NR	CAD 47% ESRD 11% Of the total population	Sub group analysis of 1032 DP artery bypass All except 2 with vein	Mean f/u 23,6 (range 1-120) months Ulcer healing: NR Limb salvage: 78% at 5 yrs and 10yrs 58% Graft patency 85% 1yr Secondary patency at 5yrs 66% DM versus 56% no DM 51% and 76% mortality at 5 and 10yrs Minor amputation: NR Complications: 10 (1%) deaths within 30days 3% MI	43 (4.2%) failed within 30 days	Sub-group analysis of a large 3731 bypasses to 1032 to DP arteries of which some were diabetic (865)
Pua 2008 [51]	Case series	91% DM patients out	Distribution: NR	37/46 patients with	33% CAD 20% CVD	Mixed 25 5 crural	Mean f/u 13,3 (range 12-21)	5 technical failures	Limited information

	Consecutive patients receiving PTA for limb slavage	of 46 total age: NR gender: NR	Severity: NR No Score	foot lesions Ulcer score: NR Infection: NR		16 fem-pop 3 aortoiliac	months Ulcer healing: at 13months 66% patients with gangrene healed Limb salvage: 78% at 1 year. Mortality: NR Minor amputation: NR		regarding patient characteristics, comorbidity and selection procedures. Foot ulcers / gangrene are not specified any further.
Ramdey 2002 [52]	Prospective case series (registry) Infra-inguinal revascularisation	DM patients; 92% out of a total population of 146 age: 63 years (SD 13) (total population) gender:65 % (Total population)	Distribution: NR Severity: NR	Tissue loss: 91% (total population) Ulcer score: NR Infection: 48%	CAD 115 (65%) MI 64 (36%) CVD 27 (15%) ESRD: all patients	Artery Inflow Iliac or femoral 123 (70%) Suprageniculate popliteal 20 (11%) Infrageniculate popliteal 34 (19%) Outflow Iliac/femoral 1 (0.6%) Suprageniculate popliteal 17 (10%) Infrageniculate popliteal 28 (16%) Tibial 50 (28%) Dorsalis pedis 80 (45%) Tarsal 1 (0.6%)	Follow-up: no data provided Complications: 30 day morbidity 23% 30 day mortality 5% Ulcer healing: NR Patency 1,3yr: 85, 68% Limb salvage: 1 yr 80% and 3yrs 80% Major amputation: 21 Minor amputation: NR	Follow-up not specified	

							Survival 60% 1 year, 3yrs 18% and only 5% alive at 5yrs		
Reed 2002 [53]	Retrospective case series Case series of bypass grafts originating distal to the groin	DM patients 140, total population 217, 249 procedures age: 65 (30-90) gender: 69% (140)male	Distribution: NR Severity: NR Scoring system: NR	Necrosis 127 (80%), rest pain 27 (17%) Infection: NR Wound classification: NR	CAD 95 (60%), ESRD 53 (33%) with 35 (23%) on dialysis	Infra-inguinal vein bypass graft Pedal (35%), Crural (60%) Femoropopliteal (4%),	Mean f/u 27months (range 1-180 months) 30 day mortality 0.6% Complications: major post-op morbidity 16 (10%) Ulcer healing: NR Limb salvage rate was 84% (SD +/-4) at 5years Minor amputation: NR 5yr patient survival was 44 (+/-5)%	Data extracted out of a cohort study comparing diabetics with non diabetics 21% secondary procedures	Major amputation was required in 9 patients with a patent graft
Rosenbaum 1994 [54]	Retrospective case series Case series of infrapopliteal bypass	DM patients: 39 age:62.3 (45-78) gender: 85% (33) males	Distribution: NR Severity: NR Score: NR	100% tissue loss Ulcer score: Gibbons classification Infection: NR	NR	Peripheral bypass: 79% infra-popliteal Popliteal 19% Tibial/peroneal: 48% Dorsalis	Mean f/u 21,2 (2-64) months Ulcer healing: 40 limbs (of total 42 limbs) with or without foot surgery	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

	grafts					pedis/plantar artery: 31% Aotobifemoral 2%	Major amputation: 3% Minor amputation: NR Complications: NR Mortality 3% during f/u		
Saltzberg 2003 [55]	Retrospective case series Case series of mixed bypass grafts	DM patients: 96% of total population in 51 patients all younger than 40 years age: 36 (27-40 yrs) gender:49% male All data in this table as reported on total population	Distribution: 76 bypass procedures with inflow: Common Iliac 2.6% Femoral 67% Above knee popliteal 7,9% Below knee popliteal 21.1 % Tibial artery 1.3% Severity: NR	86% tissue loss Ulcer score: NR Infection: NR	CAD 37% ESRD (creat > 2 mg/dl, dialysis or transplant) 53% (of which dialysis 29%)	Venous (95%) or prosthetic (5%) bypass with outflow: Dorsalis Pedis: 30,3% Tibial artery: 18.4% Peroneal atery 3.9% Below knee popliteal: 23,7% Above knee popliteal: 11.8% Femoral artery: 3.9% Other: 7.9%	How follow-up was performed not described; no data on follow-up reported Patency 1yr,5yr 82,63% Ulcer healing: NR Limb salvage: 87% at 1 year and 77% at 5yrs Amputation: 23.5% required amp. level unspecified Minor amputation: see above Complications: 30 days mortality rate: 0%; postoperative	Unspecified follow-up	

							heart failure: 1.32% Mortality at 1yr 12%, at 5yrs 27%		
Schneider 1993 [56]	Case series of pedal bypass extracted from a cohort study that compares tibial with pedal	DM patients 45 of total population n=53 age: 67 (42-78)yrs total population gender: 73% (33) males of total population	Distribution: NR Severity: ABI 0.53 total population	77% tissue loss Ulcer score: NR Infection: NR	CVD NR CAD NR ESRD NR	All pedal bypass graft with vein	Mean f/u22.5months (SD 3.4) Ulcer healing: NR Patency 1yr,3,5yr 70, 58, 58% Limb salvage at 1,3,5yr: 98%, 98%,95% Minor amputation: NR Complications: Peri-op 9% mortalty Mortality 27%, 39%,50% at 1yr,3,5yr	Major amputation defined as amputation proximal to metatarsals Low numbers of patients (6) at 5yrs	
Schneider 2001 [57]	Retrospective cohort Revascularisation using either fem-distal bypass, combined SFA PTA and distal	SFA PTA plus short distal bypass DM patients 12 age: 70 (13)yrs gender: 83% male	Distribution: Combined: Below knee disease plus focal SFA disease (<3cm length) Severity ABPI 0.52 (0.19) Long distal	All gangrene Infection: NR Wound classification: NR	Combined CAD 33%, ESRD 58% Long distal CAD 38% ESRD 74% Short distal CAD 49%	Distal target vessels Combined Tibial – 25% Pedal 75% Long distal Tibial 57% Pedal 43%	Mean f/u 23 months Ulcer healing: NR Limb salvage at 2 years Combined 90 (9)% Long distal 78	Small sample Heterogeneous populations – different distribution of PAD Confoundin	

	bypass grafting or short distal bypass graft	Long distal bypass DM patients 46 age: 68 (11)yrs gender: 50% male Short distal bypass DM patients 52 age: 69 (11)yrs gender: 65% male	bypass: Extensive infra-inguinal disease involving fempop and infra-geniculate arteries Severity ABPI 0.42 (0.17) Short distal bypass: Severe infra-geniculate occlusive disease and patent fempop arteries Severity: ABPI 0.46 (SD 0.15) Scoring system: NR		ESRD 67%	Short distal Tibial 35% Pedal 65%	(9)% Short distal 98 (2)% Patency all procedures 78 (+/-5)% at 2yrs, 63 (8)% 5 yrs Minor amputation: NR Complications: NR Mortality: NR No differences between groups SIGN 2-	g by indication Drop out and loss to f/u not reported	
Sigala 2006 [58]	Case series Mixed bypass graft plus 50 PTA	All diabetics 97 with 121 procedures 66% male Mean age 68 (range 41 – 85)yrs	Distribution: Large variation Severity: NR	49 necrosis 32 gangrene, 24 ulcers, 16 rest pain, Ulcer score: NR Infection: NR	CAD 78% CVD 20% 100% ESRD	Infra-inguinal revascularisations Endovascular – 36% only 5% combination endo and open Bypass only 59% Crural artery 55% 10% crural artery only 28% femoropopliteal 18% ext iliac to femoropopliteal	Follow-up NR Ulcer healing: NR Limb salvage: 86% at 6 mo, 75% at 12, 56% 3 yrs Minor amputation: NR Complications 12/97 patients Mortality 30day 10%, 1yr 22%, 3yr 56%	Heterogeneous population of patients with wide variation of PAD distribution and revascularisation procedures All patients had ESRD Number of infections not stated in study but outcomes	

								reported in K-M relative to infection	
Soderstrom 2008 [59]	Prospective case series Healing of ischaemic ulcers after infra-inguinal bypass surgery	74 DM patients out of 148 total population age: NR gender: NR	Distribution: NR Severity: ABI < 0,5, systolic toe pressure < 30 mmHg. Fontaine 4 Classification: NR	Classification provided: All Fontaine IV ulcers Infection: NR	NR	Infra-inguinal bypass in all subjects, with 13 PTA inflow procedures (total population)	F/u 1 year 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 which 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 1991 [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) gender: reported as male:female ratio 5:1	Distribution: tibial Severity: NR Scoring: NR	non-healing 65 (52%), gangrene 20 (16%) infection: 40 (32%) foot abscess 2 (1.6%) osteomyelitis 6 (5%) Ulcer score: NR	CAD 32% ESRD 15%	Pop-distal by-pass graft (129 procedures)	Mean f/u 13 (range 1-66) months Ulcer healing: NR Limb salvage: NR Major amputation: 8 during mean f/u 13months: minor amputation: 34 Complications: operative mortality 0.8 %,		Non data about inclusion criteria according to PAD severity.

							1yr and 3yr secondary patency rates 92% and 89%		
Tannenbaum 1992 [61]	Retrospective case series Case series of pedal bypass	DM patients 53 age: NR gender: 64% (34) male	Distribution: NR Severity: NR Score: NR	73% ulcers, Infection: 45% cellulitis, 29% osteomyelitis, 20% gangrene, 2% abscess 11 minor amps performed pre bypass	NR	DP bypass with vein	Mean f/u 25 (SD 14) months 10 patients lost to f/u Limb salvage 1,2,3yr 98%, 98%, 95% Major amputation: NR Minor amputation: NR Patency 1,2,3yr 95%, 95%, 95% Complications: NR Mortality rate 1,2,3yr 5%,16%,16%	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%	
Taylor 1987 [62]	Retrospective case series Case series of 114 patients with infection, 43 of whom revascularis	DM patients 114 patients with a foot infection (138 limbs): 43 (48 limbs) with ischaemia and 71	Distribution: NR Severity: NR But ischemia was defined as absent pulses + ABI < 0.6 or TBI < 0,4 and abnormal wave forms	All infected ulcers Ulcer score: NR	NR	Peripheral bypass undefined	Mean f/u 3yrs (1-11yrs) Ulcer healing: NR Limb salvage: 2yrs 87%, 4yrs 73%	17 lost to follow-up No data on lost to follow up on revasc patients Much	

	ed	without ischaemia age: NR gender: NR	Score: NR				Major amputation: 9 (19%) at 3yr mean f/u Minor amputation: NR Complications: NR Mortality rate at 1,3,5yr 19, 62, 84%	important data missing 4/9 amputations due to infection	
Toursarkissian 2002 [63]	Primarily a prognostic study of the use of duplex as a predictor of bypass graft failure in diabetics	DM patients 65 age: 61yrs gender: 40/64 (63%) males	Distribution: NR Severity: toe brachial index 0.2 Score: NR	61 (94%) tissue loss Infection: NR Ulcer score: NR	CAD 38%, ESRD 16%	68 limbs Femoral to distal bypass 42 BK pop distal 16 Fem pop 10 All vein bypass	Mean f/u 12 (SD 6months) Ulcer healing: NR Limb salvage: 80% at 1 yr Major amputation: 8/68 limbs at 12months (SD 6months) Minor amputation: NR Graft patency assisted primary 75% at 1 yr (estimate of Kaplan-Meiier) Complications: nil Mortality: NR		86% Hispanic population
Toursarkissian	Case series of pedal	135 patients 144	Distribution: NR	96% tissue loss	CAD 62% ESRD 20%	Dorsalis pedis bypass grafts	Median f/u 8 (1-62) months	82% hispanics	

2002 [64]	bypass	procedures all DM patients age: 62 (SD 11)yrs gender: 78% males	Severity: NR	Ulcer score: NR Infection: NR			Ulcer healing: NR Limb salvage: 83% at 30months Major amputation: 19% at total f/u (mean 8months) Minor amputation: 36% Patency : 70% 1yr, 68% 30months Complications: 25 peri-op complications Mortality 30day 1.5% Mortality at end of study 10%	Study comparing outcome in various ethnic groups (hispanics versus no hispanics). Higher amp rate in hispanics	
Uccioli 2010[65]	Retrospective case series of patients with diabetes and CLI and tissue loss treated using an endovascular first approach in	DM patients: 510 (100%) (total population 534 but 24 lost) age: 70 (0.8) gender: 64% male	Distribution: NR Severity: tcpO2 16mm Hg +/-0.8 Score: NR	100% tissue loss Ulcer score: All class C/D and grade 2-3 of the Texas wound classification Infection: 79%	CAD 42% CVD 23% ESRD 13%	456/510 (89%) underwent attempted PTA 34%, 35%, 31% AK, BK, AK+BK PTA 1.8 (0.04) vessels treated per limb (total number of	Mean f/u 20 (13) months Ulcer healing: 61% at 9.4 (0.5) months and 7% at 23months Major amputation 15% during f/u	Good description of cohort. Outcomes better reported using K-M analysis. Of the 89.4% of	

	a tertiary care clinic					arterial stenoses 2.6 (0.06) per limb)	Minor amputation: 54% Complications: NR Mortality 30d NR Mortality: 16% at 9 months	consecutive patients who were able to be treated using a PTA first approach, 11% had technical failure. 23% of PTA subintimal	
Verhelst 1997 [66]	Retrospective case series Case study of pedal and crural bypass graft	DM patients: 33 (92% of total population n=36) age:62 (29-78) gender: 81% (29) males All data in this table as reported on total population	Distribution: NR Severity: tcpO2 18 mmHg +/- 7 Score: NR	89% tissue loss Ulcer score: NR Infection: NR	CAD 44% Dialysis 4%	Popliteal-to-Distal venous Bypass Grafts (n=44): Posterior tibial: 13 Anterior tibial: 10 Peroneal: 6 Dorsalis pedis/plantar: 23	Mean f/u 27 (1-65) months Ulcer healing: in 33/36 patients complete healing of skin lesions and that includes minor amputations. Limb salvage: 90, 82, 77% at 1, 3 and 5 years. Minor amputation: 92% Patency 1,3yr 87%, 74% Complications: MI 1 Heart failure 1 Post-operative bypass	Confusion between patients/extremities. Small study. Mixture of vascular interventions. Started treating 33 patients – No standard error in curve and therefore high likelihood of significantly small numbers during follow-up	

							occlusion and major amputation 3 Mortality 30days 0% Deaths: 4 during following follow-up		
Werneck 2009 [67]	Case series Tibial PTA in patients with „CLI" at „high risk" restrospective case series	40 DM patients (total population 49) age:70 gender: 71% males	Distribution: All had „severe" tibial disease, "some also had femoropopliteal PAD" Severity: NR TASC reported:	Classification: 20% Ruth 4 80% Ruth 5* Infection: NR	CAD 69% ESRD 73% of the total population	Tibial angioplasty in all and in 45% multilevel (fempop segment)	Mean f/u 7,7 (range 1-61,5) months Ulcer healing: NR Limb salvage: 76% after mean f/u 8months Cumulative limb salvage rate in tibial PTA only after 1yr: approx 70% estimated from Kaplan-Meier Minor amputation: NR Complications: major complications occurred in 6.1% 30day mortality 2%	Angiographic success rate was 84%.	Number of pts with surgery vs. PTA not given. There were 10 amputations in patients with diabetess. However, it is unclear how many vases were in the PTA group.

							Mortality after 1yr 10%		
Woelfle 1993 [68]	Retrospective case series Case study of mixed bypass grafts	DM patients: 72 age: 70.5 gender: NR	Distribution: Isolated Tibioperoneal Vessel Occlusive Disease Severity: NR	All with minor tissue loss Ulcer score: NR Infection: NR	CAD 57% Symptomatic carotid disease: 21% ESRD (creat > 2 mg/dl): 25%	Distal Vein Graft Reconstruction: Proximal anastomosis: Below knee popliteal: 56 Anteriot tibial: 18 Distal anastomosis: ATA 10 DPA 37 PTA 13 Peroneal: 12 Plantar 3	Follow-up: no information provided how this was performed or data reported Ulcer healing: Limb salvage: at 30 days 93%, at 1 year 81%, 5yr 72% Patency: 30days 97%, 1yr 86%, 5yr 75% Minor amputation: NR Complications: mortality within 30 days 1,3% 23 patients died during follow-up (including post-op mortalty)	ulcer healing not reported; total number of BK amputations not reported. No data on follow-up	
Wolfle 2000 [69]	Retrospective case series of two different procedures Bypass crural versus PTA crural	Bypass DM patients 125 (130 grafts) age: 70 (50-87)yrs	Bypass Distribution: Crural Severity: NR PTA Distribution:	Bypass 127 tissue loss PTA 84 tissue loss	Bypass CAD 57% CVD 18% ESRD 25% PTA CAD 48% CVD 17%	Vein to DP in 63 or ant tibial artery in 20 and PT in 28 and in peroneal in 19 Angioplasty crural arteries	Average follow-up probably 24months Bypass Limb salvage 80% 1yr, 73% at 3yrs and 69% at	Poor information on loss to follow-up and drop out. Retrospecti	

		gender: NR Distal PTA DM patients 74 (89 limbs), 84 total age: 68 (48-89) gender: NR	Crural Severity: tcpO2 6.7 (0-29) Score: AHA	Ulcer score: NR Infection: NR	ESRD 42%	AHA classification (1994) 1 - 8 2 - 28 3 - 26 4 - 27	6yrs 2.3% 30day mortality Patency 1,3,5yr = 76%, 70%, 60% 30 major amputation at 24months Minor amputations: NR 64 died during f/u PTA Limb salvage 1yr 82%, 77% at 3yrs and 77% at 5 years 30day mortality 6% 17 major amputations during 24months Minor amputations: NR 26 deaths died during f/u Complications: Major haematoma 3 patients	ve case series of two different procedures and not a controlled study	

Woefle 2001 [70]	Retrospective case series Case studies infra-popliteal bypass graft	DM patients: 135 (143 procedures) age:70 (50-89) gender: NR	Distribution: extensive intra-popliteal occlusions Severity: NR	Tissue loss in 140 limbs Ulcer score: NR Infection: NR	CAD 82 (61%), CVD 29 (20%), ESRD 43 (16%),	All venous bypass with proximal anastomosis: BK popliteal 113 ATA 29 PA 1 Distal anastomosis: ATA 21 DPA 71 PTA 29 Peroneal 22 PTA of SFA prior to surgery in 37	Follow-up duration not reported Ulcer healing: NR Patency 1yr 83%, 5yr 60%, 7yr 51% Limb salvage rates 30 days 94%, 1 yr 80%, 5 yrs 74%, 7 yrs 64% Major amputation: 35 during follow-up Minor amputation: NR Complications: 30 day mortality 8% Mortality 1yr 27%, 5yr 70%, 7yr 82%	No data on mean duration of follow-up or on severity of PAD	
Zayed 2009 [71]	Retrospective series Series of combined PTA and bypass surgery	DM patients: 312 age: 72 yrs (39-93) gender: males 60% (188)	Distribution: NR Severity: NR Classification: NR	93% tissue loss Ulcer score: NR Infection: NR	CAD 107 (34%) Dialysis: 33 (10.5%)	257 (82%) PTA, 55 (18%) surgical bypass open surgery 20 had combination of both procedures	Follow-up not defined and no data reported Ulcer healing: NR Limb salvage: NR Major amputation: 13	No data on follow-up PTA not specified, severity of PAD not described All amputation	

							cases (4,1%), of these 7 had PTA, 6 had reconstructive vasc surgery Minor amputation: NR Complications: NR	s above or through knee	
Rigatelli 2011 [72]	Retrospective case series Review of outcome of diabetic patients with PAD and treated with PTA	DM patients 220 age: 78.5 years (SD 15.8) gender: 51% male	Distribution: all infrapopliteal (with 52% triple vessel disease) 19% iliac, 42% femoral, 17% popliteal occlusive disease severity: ABI 0.29 (SD 0.6) TcPO2 16.5 mmHg (SD 10.6)	Fontaine IV 79.5% Fontaine III 20.5% Ulcer score: NR Infection: NR	CAD 39% Chronic renal failure (not specified) 21%	PTA, with immediate success (unspecified) in 95% Subintimal approach	Mean f/u 3.1 (SD 1.8) (range 1 to 5) years Ulcer healing: 92% Limb salvage: 98% Minor amputation: 15% Complications: 5% (including vessel rupture, AV fistula) Mortality: 12% during f/u Post PTA ABI: 0.82 (SD 0.2) Post PTA TcPO2: 35.3 mmHg (SD 14.5)		No description ulcer, outcome not defined, no survival analysis reported
Park	Retrospectiv	DM patients	Distribution: all	Rutherford 4:	CAD 27%	PTA, with	Mean f/u	Very few	Ulcer not

2013 [73]	e case series of consecutive patients who underwent below infrapopliteal PTA. Patients with concomitant above knee occlusive disease were excluded	49, with 64 limbs in which PTA was performed age: mean 67.4 years gender: male 78%	infrapopliteal severity NR	27% Rutherford 5: 45% Rutherford 6: 28% Ulcer score: NR Infection: NR	Chronic renal failure (not specified): 22%	immediate success (unspecified) in 94% CT-angiogram every 6 months during follow-up	19.3 (SD 13.4) months Ulcer healing: NR Limb salvage: 91% Minor amputation: NR Major amputation 9% at unspecified time points Complications: none except haematoma (n=2), pseudoaneurysm (n=1), both disappeared during follow-up Primary patency rates at 6 and 12-months were 75 and 59% Mortality: none	clinical data, patency rate oriented report.	described, loss to follow-up unclear, no actuarial analysis reported on limb salvage
Lejay 2013 [74]	Retrospective case series of consecutive below knee bypasses. Limbs were divided post-PTA, according	DM patients 54 in whom 58 bypass procedures were performed. DR group: 36 limbs IR group: 22 limbs	Distribution: all infra-popliteal Skin perfusion pressure: DR: 15 mmHg (SD 12) IR: 17 mmHg (SD 13)	Ulcer present: DR: 89% IR: 91% Ulcer score: DR: deep ulcers 58% IR: deep ulcers 18% (deep = two highest	DR CAD 53% CVD 11% ESRD 53% IR CAD 55% CVD 9% ESRD 55% No significant	See study design. Tibial artery as outflow artery: DR: 86% IR: 77%	Mean f/u all patients 20 months (SD 16), no data reported on DR/IR groups Median ulcer healing DR vs IR: 56 (SD 18) vs	Definition of ischemia unclear as technique of skin perfusion measurement not described	Conclusions are limited because of retrospective design, relative small number of patients and confounding by indication

	the angiosome concept, in those with 1) flow to site of the ulcer by a feeding artery (direct revascularisation, DR) 2) flow through collaterals (indirect revascularization IR)	age: DR: 68 years (SD 10) IR: 71 years (SD 10) gender: DR: male 69% IR: male 68%		grades of UT scoring system combined) p< 0.04 gangrene: DR: 11% IR: 9% Infection DR: 69.5% IR: 13.6 p< 0.02	differences		112 days (SD 45) (p<0.02) Limb salvage at 1 and 3 years DR vs IR: 91% vs 66% and 65% vs 24%, respectively(p<0.04) Minor amputations: DR 42%; IR 45% (ns) Complications: NR Mortality after 1 ,3 yrs DR 22% and 43 %; IR 35% and 75 % (ns) No difference in primary patency rates		
Acin 2014 [75]	Retrospective case series of consecutive infrapopliteal PTA (± supra-popliteal PTA) Limbs were divided post-PTA, according the	DM patients: 92 with 101 procedures Age: 72 years (range 64-77) Gender: 61% male ESRD: exclusion criterion	Distribution: see Intervention and control management ABI: 0.54 (0.4-0.67) Non compressible ABI 54% TASC B: 6 % TASC C: 15% TASC D: 79%	Ulcer: all patients Ulcer score: NR Infection: 37%	CAD: 30% CVD: 20%	Supra-popliteal PTA 55% Infra-popliteal PTA 100% Multiple tibial revascularization attempts in 52% DR: 54%; IR with flow through collaterals: 26%; IR without collaterals: 20%	Median follow-up 19 (9-38) months Lost to follow-up 11% Ulcer healing at 12 months: in DR 66%, in IR through collaterals 68%, IR no collaterals 7% (p< 0.01). Limb salvage	All patients had critical limb ischemia according TASC, but how this diagnosis was made, is not reported.	Multiple analyses were performed, without statistical correction, and it is unclear to which extent only hypotheses were tested that were a priori formulated.

	angiosome concept, in those with: 1) flow to ulcer by a feeding artery (direct revascularisation, DR) 2) flow through collaterals (indirect revascularization IR) 3) IR without collaterals						after 24 months in DR 89%, in IR through collaterals 85% and in IR no collaterals 59% (vs DR p< 0.05) Ulcer healing at 1 year 51% in single revascularisation attempts (SR) and 59% in multiple revascularizations (MR), ns. Limb salvage at 2 years SR 72% and MR 78%, ns Major adverse cardiovascular event at 30 days: SR 4.1%; MR 1.9%, ns Major amputation in total group at 30 days 2% Minor amputation in total group 28% Mortality: NR		Objective criteria for and data on observer variability in categorising post-PTA limbs in DR/IR categories are lacking
Söderström 2013 [76]	Retrospective case series of consecutive technically successful primary PTA Limbs were	DM patients 226, with 250 consecutive limbs in which a revascularisation was performed and whom	Distribution: see Intervention and control management DR ABI 0.73 (SD 0.33) Toe pressure 41	DR Heel ulcer 16% Extending to bone 60% Infection 38% IR Heel ulcer	DR CAD 57% CVD 24% GFR < 30mL/min/1.73m2 or dialysis 22 %	PTA all infrapopliteal Additional PTA popliteal or suprapopliteal DR 28% IR 31%	F/u 1 year DR Ulcer healing at 12 months: 72% (SD 5) IR Ulcer healing at	Indication for PTA unclear; no data on mean follow-up in both groups and drop outs,	Many aspects of the cohort well described. Objective criteria for and data on observer variability in

	divided post-PTA, according the angiosome concept, in those with 1) flow to site of the ulcer by a feeding artery (direct revascularisation, DR) 2) flow through collaterals (indirect revascularization, IR) A propensity score was used for adjustment of differences in pre-treatment covariables in multivariate analysis and for 1:1 matching.	were considered unfit for infrainguinal bypass surgery or autologous vein grafts DR (n=121) age 68 (SD 12) gender 64% male IR (n=129) age 74 (SD 11) gender : 55% male	mmHg (SD 21) IR ABI 0.64 (SD 0.29) Toe pressure 36 mmHg (SD 19)	18% Extending to bone 50% Infection 40%	IR CAD 70% CVD 19% GFR < 30mL/min/ 1.73m2 or dialysis 10% IR significantly older, more females, more frequently CAD but less frequently lower GFR		12 months: 46% (SD 6) With the propensity score 84 DR and IR pairs were matched, with respectively healing at 12 months 69% (SD 7) vs 47% (SD 7) (p< 0.03) with hazard ratio for healing in DR 1.97 (95% confidence interval, 1.34-2.90). Limb salvage in DR and IR 86% (SD 3) and 74% (SD 4), ns Mortality NR	but based on figure in article possibly without major differences	categorising post-PTA limbs in DR/IR categories are lacking Not reported if patients were lost to follow-up
Kabra 2013 [77]	Case series of a patients with CLI selected for analysis because they had one crural artery crossing the	DR patients (n=39) diabetes: 77% age: NR gender: male 82%	Distribution: NR ABI (n=58): 0.5 (SD 0.3)	DR ulcer 59% gangrene 64% site of ischemia heel 5% IR	DR CAD 18% IR CAD 52% (p< 0.01 vs. DR)	DR Open 62% Endovascular 33% Hybrid 5% IR Open 48% Endovascular	Follow-up 6 months, with 6 patients lost to follow-up Overall 30-day mortality 6% DR	Highly selected series of patients, the DR and IR patient groups were not comparabl	Results difficult to interpret as the DR and IR groups do not seem to be balanced in clinical presentation and type of

	ankle after revascularisation, all other patients in the same time period were excluded. Patients were divided in those with 1) perfusion to the ischemic region by the source artery according the angiosome concept (direct revascularisation, DR) 2) perfusion by other artery (indirect revascularization IR)	IR patients (n=25) diabetes: 88% age: NR gender: male 84%		ulcer 88% (p < 0.2 vs DR) gangrene 20% (p< 0.001 vs DR) site of ischemia heel 40% (p< 0.001 vs DR)		48% Hybrid 4% No significant differences	Ulcer healing: 96% Major amputation: 13% Mortality: 4% Lost to follow-up: 5% IR Ulcer healing: 83% Major amputation: 16% Mortality: 20% Lost to follow-up: 16% Significantly higher ulcer healing rate at 6 months in DR (p< 0.03) Minor amputation :NR	e: in IR more heel ulcers (p<0.001) less ulcers (p< 0.02) but more gangrene (p<0.001). Definitions of ulcer and gangrene not given, no data on severity of PAD in the DR and IR patients	intervention (although for the latter statistically no differences were observed). No correction was made for these differences in prognostic factors Objective criteria for and data on observer variability in categorising limbs in DR/IR categories are lacking
Zhan 2012 [78]	Retrospective review in 85 consecutive diabetic patients comparing the hemodynamic response to either endovascula	Open (n=31) DM patients 100% age 71 years (SD 10) gender male 61% Endo (n=78) DM patients 100% age 68 years	Distribution: see intervention Open ABI baseline 0.5 (SD 0.2) Toe pressure 28.3 mmHg (SD 26.8) Endo ABI baseline	Open Rutherford 5-6 84% Endo Rutherford 5-6 85%	Open CAD 36% Creatinin > 133 mmol/l 18% Endo CAD 44% Creatinin > 133 mmol/l 35%	Open, level of intervention Aorta-iliac 10% Femoral-popliteal 35% Tibial 55% Endo, level of intervention Aorta-iliac 9% Femoral-popliteal 51%	Mean F/u Open 13 (SD 12) months and Endo 15 (SD 12 months: Open, post-intervention ABI 0.90 (SD 0.18) Toe pressure 62.7 mmHg (SD	Relative small numbers, selection bias likely as patients were not randomised, no data on PAD distribution; no data on	Results suggest that in selected patients the same short-term hemodynamic improvement in the foot can be improved with Endo as in Open.

	r (Endo) or open revascularisation (Open) procedures. 24 patients had multiple interventions and data were analysed per intervention (total n=109) ABI and toe pressure were measured directly before and within 6 weeks after the intervention	(SD 11) gender male 65% Patients with ABI > 1.3 excluded	0.51 (SD 0.27) Toe pressure 38.2 mmHg (SD 28.3) No significant differences		No significant differences	Tibial 40% 68% autologous venous material, 32% prosthetic material No significant differences in level of intervention	27.7) Endo, post-intervention ABI 0.86 (SD 0.26) Toe pressure 71.7 mmHg (SD 35.0) Major amputation rate in Open 11% and in Endo 11% No significant differences between Open en Endo Minor amputation:: NR Mortality: NR	ABI and toe-pressure > 6 weeks post-interventio n	No actuarial analysis performed
Alexandrescu 2011 [79]	Cohort of patients with diabetes treated with PTA according angiosome-targeted revascularization (ATR+) protocol which was compared with a historical control group treated	ATR+ 134 DM Age NR > 70 yrs 55% Gender NR ATR- 98 DM age NR > 70 yrs 51% Gender NR	PAD majority had multilevel disease, infrapopliteal lesions: ATR+ infrapopliteal lesions: TASC B 9% TASC C 32% TASC D 59% tcpO2 21.7 mmHg (range 19–39)	ATR+ Neuropathy 100% Cellulitis >2 cm 70% Deep ulcers 66% ATR – Neuropathy 100% Cellulitis >2 cm 66% Deep ulcers 64%	ATR+ CAD 88% CVD 23% ESRD 20% ATR- CAD 82% CVD 20% ESRD 15%	Below knee PTA in all subjects and above knee if indicated In 10% of the ATR+ patients the angiosome-oriented target artery could not be reopened and boundary vessels were treated	Overall 30-day mortality 2% ATR+ Mean f/u 54.7 (range 3–59) months Amputation at 1 yr 10%. During total follow-up HR for no amputation vs ARR- 2,32 (p<0.04) Limb salvage 97% Wound healing	Clinically well characterised cohorts, that seem well matched	Main weakness is the use of a historical control group. No actuarial analysis for wound healing and limb salvage Unusual definition of limb salvage (no major amputation + functional autonomy)

	before introduction of ATR protocol (ATR-)		ATR- infrapopliteal lesions: TASC B 7% TASC C 37% TASC D 54% tcpO2 25.1 mmHg (range 17–52)				73% Mortality at 1 and 3 years: 7% and 29% Minor amputation: NR ATR- Mean f/u 35.8 (range 1–68) months Amputation at 1 yr 16% Limb salvage 85% (p<0.03 vs ART+) Wound healing 68% Mortality at 1 and 3 years: 10% and 35% Minor amputation: NR		Definition amputation not given

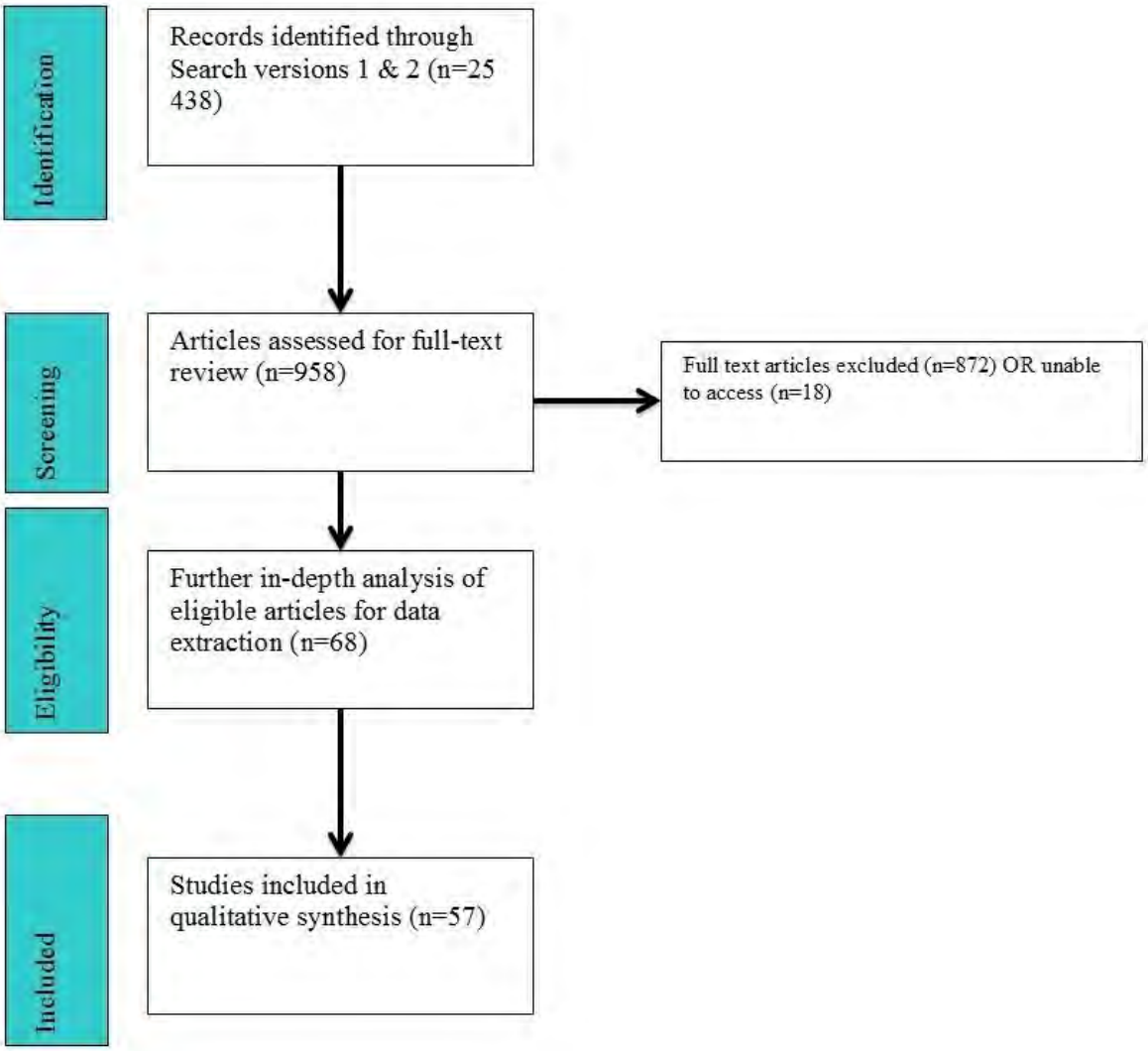

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram