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SUPPLEMENT ARTICLE

Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review

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Abstract

Prediction of wound healing and major amputation in patients with diabetic foot ulceration is clinically important to stratify risk and target interventions for limb salvage. No consensus exists as to which measure of peripheral artery disease (PAD) can best predict outcomes. To evaluate the prognostic utility of index PAD measures for the prediction of healing and/or major amputation among patients with active diabetic foot ulceration, two reviewers independently screened potential studies for inclusion. Two further reviewers independently extracted study data and performed an assessment of methodological quality using the Quality in Prognostic Studies instrument. Of 9476 citations reviewed, 11 studies reporting on 9 markers of PAD met the inclusion criteria. Annualized healing rates varied from 18% to 61%; corresponding major amputation rates varied from 3% to 19%. Among 10 studies, skin perfusion pressure ≥40 mmHg, toe pressure ≥30 mmHg (and ≥45 mmHg) and transcutaneous pressure of oxygen ($TcPO_2$) ≥25 mmHg were associated with at least a 25% higher chance of healing. Four studies evaluated PAD measures for predicting major amputation. Ankle pressure <70 mmHg and fluorescein toe slope <18 units each increased the likelihood of major amputation by around 25%. The combined test of ankle pressure <50 mmHg or an ankle brachial index (ABI) <0.5 increased the likelihood of major amputation by approximately 40%. Among patients with diabetic foot ulceration, the measurement of skin perfusion pressures, toe pressures and $TcPO_2$ appear to be more useful in predicting ulcer healing than ankle pressures or the ABI. Conversely, an ankle pressure of <50 mmHg or an ABI <0.5 is associated with a significant increase in the incidence of major amputation. Copyright © 2015 John Wiley & Sons, Ltd.

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

Abbreviations ABI, ankle brachial index; CDUS, colour duplex angiography; CTA, computed tomographic angiography; CV, cardiovascular; DM, diabetes mellitus; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; NLR, negative likelihood ratio; PAD, peripheral artery disease; PLR, positive likelihood ratio; PRISMA, preferred reporting items for systematic revie ws and meta-analyses; QUIPS, quality in prognostic studies; TBI, toe brachial index; $TcPO_2$, transcutaneous pressure of oxygen

Introduction

Convincing evidence suggests that peripheral artery disease (PAD), present in half of patients with diabetic foot ulcer [1], confers poorer outcomes. PAD is not only associated with failure to heal and amputation [2] but also poor quality of life [3], cardiovascular disease and premature mortality [4,5].

Comprehensive data outlining the adverse effects of PAD in the diabetic foot derive from the Eurodiale study, which enrolled 1229 patients presenting to 14 secondary care institutions with a new foot ulcer. Patients with PAD had healing rates of 69% *vs* 84% without PAD and major amputation rates of 8% *vs* 2%, respectively [2]. These data are supported by the various scoring systems that exist for the classification and prognosis of the diabetic foot, which almost invariably incorporate a component relating to ischemia [6]. A variety of definitions are used to describe the ischemia variable of each score, reflecting the problems associated with the nomenclature and classification of PAD in patients with diabetes. The clinical findings used as an expression of ischemia include gangrene [7,8], absence of pulses [9,10] and symptomatic PAD in combination with non-invasive testing criteria [11]. The lack of consistency in the clinical finding or investigation of PAD that is used to predict outcome underscores the paucity of data on which features of PAD are prognostically most important.

There is consensus that PAD is associated with poor outcome, but importantly, the aspect of PAD that correlates with outcome is unknown. PAD is a variable disease in terms of its distribution and severity. This is abundantly clear when the pattern of disease is compared between individuals with and without diabetes. The former have typically diffuse and distal disease with a greater prevalence of medial sclerosis (calcification of the tunica media) and poor collateral formation relative to their non-diabetic counterparts [12–14]. The clinically important question is whether it is possible to identify specific characteristics of PAD that predict poor outcome, the need for revascularization to prevent a poor outcome, or to identify those in whom an outcome is likely futile irrespective of revascularization strategy. The aim of this systematic review was to evaluate the usefulness of measures of PAD for the prediction of outcome among patients with diabetic foot ulcer.

Methods

Data search

A systematic search was performed according to the preferred reporting items for systematic reviews and meta-analyses guidance [15]. The MEDLINE and EMBASE databases were searched for English articles pertaining to the diagnosis of PAD among patients with diabetes from 1980 to June 2014. The results of two separate searches were combined. Firstly, a search undertaken for a previous systematic review from the International Working Group on the Diabetic Foot (IWGDF) on the effectiveness of revascularization of the ulcerated foot [16] was updated (Online Appendix A). In addition, a second search was performed with different search terms (Online Appendix B). The abstracts of identified studies were combined and evaluated for inclusion independently by two reviewers (R. J. H. and J. R. W. B.) with conflicts adjudicated by a third reviewer (N. C. S.). At a later stage, full-text manuscripts of the selected studies were evaluated by two reviewers.

Criteria for inclusion/exclusion

Studies evaluating ulcerated patients only were included; those evaluating the prognosis of the asymptomatic (intact) foot were excluded. Cohort studies involving patients undergoing revascularization were included, providing a risk ratio was reported, which was adjusted for revascularization. Studies eligible for inclusion included those evaluating outcome and those based on an index measure of PAD; the studies evaluating demographic factors and their association/predictive value for outcome were excluded.

Included were studies evaluating investigations of PAD/reduced perfusion and their level of abnormality that would predict healing or major amputation. Investigations considered included clinical examination findings, ankle and toe pressures/indices, Doppler waveform analyses, transcutaneous oxygen pressure ($TcPO_2$), laser Doppler imaging, pole test and objective measures of skin temperature. Gold standard tests used to diagnose PAD included magnetic resonance angiography, computed tomographic angiography and digital subtraction angiography and were considered if reported with a cut-off or threshold to predict outcome. Studies that excluded patients with PAD or those with insufficient information on the revascularization status of the cohort during follow-up were excluded. Only studies reporting separately on ≥30 patients with diabetic foot ulceration were considered. Where studies reported on mixed cohorts of patients with and without diabetes; those with a proportion of patients with diabetes of <80% were excluded. Studies that reported data in a fashion that did not permit the calculation of sensitivity and specificity values, and therefore likelihood ratios, were excluded. Also excluded were studies with unspecified or <6-month duration of follow-up.

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Data extraction and quality assessment

Data were extracted by one observer (J. R. W. B.) and independently verified by another reviewer (E. B.). Methodological quality of included studies was assessed independently by the same two reviewers against parameters included in the Quality in Prognosis Studies (QUIPS) tool [17,18]. There is no consensus as to deriving an overall score for quality from the QUIPS tool; studies were rated as low quality (0), in which case they were excluded, acceptable (+) or high quality (++). Overall ratings were based on the number of assessment criteria in QUIPS that each study met. If the majority of criteria were met with little or no risk of bias, a '++' rating was given; if most criteria were met but some flaws in the study carried an associated risk of bias, then a '+' rating was allocated. Studies in which most criteria were not met, with significant flaws in key aspects of the study design, including accounting for confounding and completeness of follow-up, were rated as '0' and excluded (Figure 1). Given the heterogeneity of populations studied in observational reports, the predictive values of test performance were reported separately where possible. For example, if a single study reported separate analyses on a cohort of patients with and without neuropathy, those separate groups are reflected in the evidence table. When not reported in the article, sensitivity, specificity and risk ratios (RR) were calculated from raw data, in addition to the positive likelihood (PLR) and negative likelihood ratios (NLR).

The PLR and NLR were the primary endpoints chosen for this systematic review. Likelihood ratios provide the most meaningful comparator for clinical decision-making [19]. A PLR is the number of times more likely a particular test result is present in a person with a particular outcome compared with the likelihood of this result in a person without the outcome. In contrast, a NLR is the likelihood of a negative test in an individual without the outcome compared with a person who experiences the outcome. A PLR ≥10 and a NLR ≤0.1 were considered markers of good test performance [20,21]. Where information on mortality was provided, the healing and amputation status of an individual at death defined their outcome. Given substantial heterogeneity in both the populations studied and the range of index PAD measures evaluated, a meta-analysis

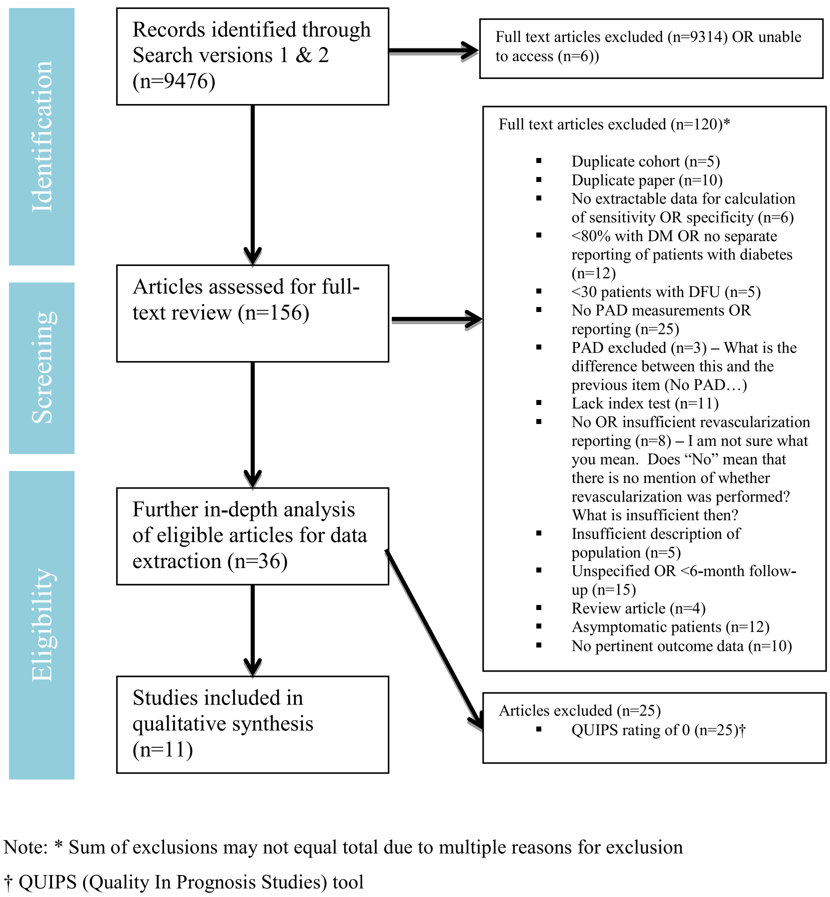

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram

was not performed. The median and range of summary statistics, including estimates of predictive performance, are presented, stratified by index test and population studied.

Results

Search strategy and study selection

From 9476 titles and abstracts, 156 articles were selected for full-text review (Figure 1). Of these, a total of 11 studies reporting on 5890 patients met the inclusion criteria and were included in the qualitative data synthesis (online Table 1, Appendix of the online data supplement) [22–32]. Most studies ($n = 7$) were prospective; [22–25,29–31] the remainder were retrospective ($n = 1$) [28], or did not specify ($n = 3$) [26,27,32].

Comorbidities and patient demographics

The mean or median age of cohorts studied ranged between 61 and 76 years; the proportion of men ranged between 59% and 74%. Seven studies reported on purely ulcerated patients [22–24,26,29–31], while two studies included patients with either active ulceration or gangrene at baseline. [27,32] One study investigated the prognostic performance of PAD measures in patients with foot infection and/or ischemia (Fontaine III/IV) [25]. Among studies involving patients with diabetic foot ulceration, a severity assessment was reported in five, and the proportion of patients with Wagner grade ≥3 ranged from 16% to 61% (median 51%) [23,24,28,30,31]. Five studies failed to report any indication of ulcer severity [22,26,27,29,32].

Revascularization

Three studies excluded patients undergoing revascularization [24,26,29]. Among the remaining studies, revascularization rates (including endovascular and surgical arterial reconstruction) ranged from 5% to 100% (median 44%). In studies where data were available on the revascularization strategy, angioplasty (794/2363, 34%) appeared to be more frequently performed than surgical bypass (496/2363, 21%) overall.

Prognostic markers

Five studies evaluated various thresholds of ankle pressure (>50, ≥70, ≥80 and ≥100 mmHg) for the prediction of outcome [25,27,28,31,32]. Some studies evaluated several different thresholds of the same PAD investigation enabling direct comparison of their performance. Other tests evaluated against an outcome of major amputation or healing included toe pressures ($n = 5$) [25,27,28,30,32], skin perfusion pressure ($n = 2$) [27,33], $TcPO_2$ ($n = 2$), [26,30] intermittent claudication [24], ankle brachial index (ABI) [31] and the presence of pedal pulses (all $n = 1$) [26]. The skin perfusion pressure is the blood pressure of the microcirculation in the skin required to restore flow following release of carefully controlled occlusion. Transcutaneous oxygen pressure is a recording of the partial pressure of oxygen at the skin surface. Using this technique, the amount of oxygen detected by an electrode is a balance between oxygen delivery and local physiological demands. One study investigated the prognostic performance of the fluorescein toe slope [27], derived from measuring the distribution of fluorescence in the skin after intravenous injection of fluorescein. It is thought to provide quantitative dynamic information about skin perfusion and its distribution. Six studies provided information on the prognostic performance of multiple modalities of PAD assessment or cut-off values enabling direct comparison of particular tests within the same cohort [24–27,29,31].

Event rates

Online table 1 presents the clinical outcomes by study. The rate of primary healing varied between 36% and 71%. Rates of major amputation varied between 5% and 35% and were greatest (35%) in the study by Tsai *et al.*, [28] involving a high-risk cohort with diabetic foot ulceration and dialysis dependent end-stage renal failure. Annualized event rates could not be calculated in six studies owing to a lack of information on precise follow-up duration [25–28,31,32].

Test parameters and likelihood ratios for healing

Because many factors influence the likelihood of healing and major amputation, the data were analysed as univariate associations (of PAD markers with outcome). The importance of potential confounders in the outcome of diabetic foot ulcers is well understood; however, we lacked individual participant data from which to perform adjusted analyses to determine the associations between PAD markers and outcomes adjusted for potential confounding factors. Ten out of eleven studies used healing as an outcome measure (online Table 1). Generally, the predictive performance of PAD measures for healing was poor.

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Ankle pressures

When examining studies using ankle pressure for the prediction of healing, a pressure >50 mmHg gave a PLR between 1.08 and 1.46, associated with changes in the pre-test probability <15% [33]. An ankle pressure threshold ≥70 or ≥80 mmHg produced a PLR of 2.52–3.24 corresponding to approximate changes in the probability of healing between 15% and 25%. On the other hand, an ankle pressure ≥70 mmHg achieved a NLR ≤0.1 in one study, that is, the chance of not healing was low when these values are measured. One study only examined the performance of ABI measures; [30] an ABI between 0.9 and 1.3 was similarly not strongly predictive of healing (PLR 2.61, NLR 0.92).

Toe and skin perfusion pressures

A toe pressure threshold ≥30 mmHg resulted in a PLR of between 1.12 and 5.00 and ≥45 mmHg between 2.88 and 4.30. In comparison, a skin perfusion pressure using a ≥40 mmHg cut-off showed moderately good performance for predicting healing in two small studies, [26,32] with PLR between 4.86 and 6.40 and corresponding NLRs of 0.03–0.40. A toe pressure ≥30 mmHg demonstrated a significant association with healing in two studies (RR 1.85–2.43) and a non-significant association with healing in one further study (online Table 2).

Intermittent claudication

One study examined the impact of the presence of intermittent claudication on healing, finding that rates of primary healing or healing following a minor amputation were greater among patients with intermittent claudication than those without [23]. Despite this, the presence of intermittent claudication was not a useful prognostic measure with a PLR of 1.59 and NLR 0.81

Pulse palpation

Palpable pedal pulses in the presence of foot infection were associated with healing (RR 2.26, 95% CI 2.05-2.49) in one study [25]. The specificity and sensitivity of palpable pedal pulses for the correct prediction of healing were 35% and 100%, respectively. The PLR could not be calculated because the specificity was 100%; the NLR was 0.65.

Test parameters and likelihood ratios for major amputation

Four studies examined the accuracy of PAD measures for the prediction of major amputation (online Table 3) [27,28,30,31]. Overall, the PAD measures examined in these studies had poor accuracy for predicting major amputation with no single modality achieving a PLR ≥10 or a NLR ≤0.1. No two measures across these four studies were alike, so no pooled comparisons were possible.

Ankle pressures

Three different ankle pressure thresholds were evaluated across two studies [27,31]. In the same cohort, ankle pressure thresholds <50 mmHg and <80 mmHg were compared. Although improvement in the specificity was observed with the lower threshold (84% *vs* 79%), this was at the cost of a significant reduction in sensitivity (20% *vs* 39%). Accordingly, the lower <50 mmHg threshold performed worst (PLR 1.25, NLR 0.95); however, both measures performed poorly for the prediction of major amputation. A further study evaluating an ankle pressure threshold <70 mmHg reported improved performance with a PLR of 4.28 corresponding to an increase in the likelihood of major amputation by 25% or more. Of interest, the combination of ankle pressure <50 mmHg or ABI <0.5 was the most accurate predictor of events, with a PLR of 8.24 corresponding to around a 40% approximate change in the pre-test probability [19]. A parallel combination of these measures demonstrated a powerful association with major amputation with a RR of 25.0 (95% CI 13.5–41.9).

Toe pressures

A direct (within-study) comparison of toe pressure thresholds <30 mmHg and <45 mmHg suggests they are broadly equivalent in predicting major amputation. Among 2511 patients in the study by Gershater *et al.*, [31] the PLRs were 2.64 and 2.05 respectively. A lower threshold, <20 mmHg, in a smaller study showed a slight improvement (PLR 3.18) relative to higher cut-offs [27]. Significant unadjusted associations were reported for each of the three thresholds with major amputation [27,31]. Increasing power of association was observed with progressively lower thresholds <45, <30 and < 20 mmHg giving RRs of 2.98 (95% CI 2.28–3.91), 3.24 (95% CI 2.48–4.24) and 3.48 (95% CI 1.65–7.32), respectively.

Fluorescein toe slope

The prognostic accuracy of the fluorescein toe slope in predicting major amputation was similar to that of ankle pressure <70 mmHg and toe pressure <20 mmHg in a direct comparison in a single study. The PLR for a toe slope <18 units was 4.04; the NLR was 0.49, increasing the likelihood of major amputation by around 25%.

Doppler waveform analysis

The absence of flow or a monophasic signal in the below-knee vessels increased the likelihood of a major amputation (PLR 2.18) but was not as informative as several other measures, including the fluorescein toe slope, toe pressure <20 mmHg and the combined test of ABI <0.5 or ankle pressure <50 mmHg. The NLR of 0.20 compared favourably with all other measures of PAD with the exception of the combination of ankle pressure <50 mmHg or ABI <0.5.

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This study included patients with end-stage renal failure only and as such represents a distinct and high-risk diabetic foot ulcer cohort as compared with the other studies evaluated [28]. A summary of all the data extracted is presented in the Evidence Table (online Table 4).

Discussion

In this systematic review, we evaluated the prognostic utility of six different markers of PAD severity in patients with diabetic foot ulceration. All are being applied in clinical practice for purposes of prognosis and to determine whether there is a need for further vascular assessment and possibly revascularization. Predicting good or bad outcome in diabetic foot disease is a complex endeavour. Many patient factors beyond PAD will influence the clinical course of a foot ulcer, and none in isolation, including measures of PAD severity, should be relied upon. The Eurodiale study demonstrated that in patients presenting with a new diabetic foot ulcer, male sex, end stage renal failure, non-ambulation and large ulcer surface area were all associated with failure to heal [2]. When analyses were confined to patients with PAD (defined as ABI <0.9 and/or absence of two foot pulses), infection emerged as a powerful predictor of poor outcome. Amputation and healing rates varied considerably among included studies, reflecting heterogeneity in the populations under investigation. In the present review, the lack of individual participant data precluded adjusted analyses; however, univariate associations of PAD markers in various populations are presented and remain useful for clinical decision-making.

The *a priori* focus of this review was the PLR for healing. A clinically useful prognostic test with a high PLR could indicate near certainty of healing when combined with a moderate pre-test probability of healing. A conservative strategy of optimal wound care could then be followed and further vascular imaging would be unnecessary. Similarly, a test with a very high PLR would be viewed as very useful in clinical circumstances where healing was uncertain, irrespective of the pre-test probability.

Given the variability of PAD in terms of its distribution, severity and symptoms, it is unsurprising that no single measure performed with consistent accuracy for the prediction of healing or major amputation endpoints. The most useful tests for predicting healing in an ulcerated patient were skin perfusion pressure ($\geq$40 mmHg), toe pressure ($\geq$30 mmHg and $\geq$45 mmHg) and $TcPO_2$ ($\geq$25 mmHg). All increased the pre-test probability of healing by at least 25% in one or more study. Informative tests for predicting major amputation included ankle pressure ($<$70 mmHg), fluorescein toe slope and most usefully the combination of ABI <0.5 or ankle pressure $<$ 50 mmHg. Again, all tests were able to alter the pre-test probability by greater than 25%; in the case of the combined tests (ABI and ankle pressure), this value rose to around 40%. The likelihood ratios reported here should be used in daily practice in the context of a pre-test probability, that is, the probability of the patient having PAD should first be based on sound clinical judgement; no PAD measure was sufficiently accurate to be used in isolation. Intermittent claudication was positively associated with a somewhat higher probability of healing, but the available data do not allow further explanation of this paradoxical association [23].

In the setting of an incident foot ulcer, previous guidance from the IWGDF recommended a 6-week period of expectant management with optimal wound care for patients with perfusion measurements indicating mild PAD (ABI $\geq$0.6 or $TcPO_2$ $>$50 mmHg) [34]. These recommendations were based on expert opinion. An ABI threshold $\geq$0.6 was not specifically evaluated in any of the included studies. Based on the current findings, it would be reasonable to conclude that patients presenting with incident ulceration and skin perfusion pressure $\geq$40 mmHg, toe pressure $\geq$45 mmHg or $TcPO_2$ $\geq$25 mmHg have a higher likelihood of healing relative to counterparts with evidence of a more severe perfusion deficit. In combination with a high pre-test probability of healing, for example, in a younger patient, free of end-stage renal failure, with a small and non-infected ulcer, the clinician could be reasonably confident of a good outcome using these test criteria.

In contrast to healing, risk prediction for major amputation can help to identify patients who would benefit from early vascular imaging and revascularization in an attempt to salvage the limb. Again, the pre-test probability will have a major bearing on outcome, particularly where infection is present. IWGDF guidance stresses that 'time is tissue' and infected ischemic ulcers should be treated as a medical emergency. The study by Brechow *et al.* [30] would suggest the risk is particularly high in patients with severe ischemia as indicated by an ABI <0.5 or ankle pressure $<$50 mmHg. Urgent vascular imaging and revascularization, where technically feasible, would seem appropriate to prevent limb loss in this group. Ascertaining patients destined to lose a limb regardless of salvage efforts will be difficult based on the performance of perfusion measures evaluated in this study. No measure achieved a PLR of 10, considered a marker of good performance, and the decision to perform a major amputation before any attempt at revascularization should not be made on the basis of a perfusion measure alone.

There is a compelling need for a better understanding of which PAD measures and thresholds best predict outcome among patients with incident ulceration. There are few reliable natural history data to support specific thresholds of perfusion measurements that are associated with failure of an ulcer to heal. Recommendations in current consensus

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documents are predominantly based on poorly designed studies, and there are suggestions that these guidelines are poorly followed. In Eurodiale, vascular imaging was only performed in 40% of patients who failed to heal or underwent a major amputation during follow-up. Practice beyond the 14 specialist foot centres that enrolled patients into Eurodiale is likely to be far worse. The development of a registry and protocols to standardize data collection to address the poor quality of evidence available and better determine which demographic, comorbidity, ulcer-related and PAD factors predict failure to heal is one potential solution. Poor reporting was exemplified in the studies included in this review where infection rates were not consistently provided. The dramatic increase in the worldwide prevalence of diabetes, rise in foot-related complications and associated healthcare costs justify significant ongoing efforts directed towards identifying and treating PAD in patients with diabetes, to both prevent and treat diabetic foot disease. A registry with a minimum pragmatic dataset on comorbidities, ulcer characteristics and measures of PAD would provide important individual participant data. This would not only enable adjustment for factors that impact the pre-test probability of outcome measures but also allow the analysis of raw data with respect to perfusion measures. The use of thresholds or cut-offs appears to be less informative than absolute values for PAD measures.

Conclusions

Rates of both healing and major amputation are very variable among patients with incident diabetic foot ulceration. Adequate perfusion to the foot, as indicated by skin perfusion pressure ≥40 mmHg, toe pressure ≥45 mmHg or $TcPO_2$ ≥25 mmHg, is associated with higher chances of healing. Poorer perfusion, indicated by ankle pressure <70 mmHg, fluorescein toe slope <18 units and most usefully the combination of ABI <0.5 or ankle pressure <50 mmHg, is associated with higher risk of major amputation. These PAD measures should all be interpreted in the context of other determinants of outcome that make up a pre-test probability. The quality of studies evaluated was generally poor, and there is a pressing need for standardized individual participant data to provide data that can be combined across sites to maximize precision, examined for heterogeneity and adjusted for potential confounding factors.

Conflict of interest

None declared.

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Supporting information

All tables and the search strategy can be downloaded as supplements from the publisher's website.

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