DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2016; **32**(Suppl. 1): 84–98.
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2701

SUPPLEMENT ARTICLE

Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review

J. J. van Netten[1]*
P. E. Price[2]
L. A. Lavery[3]
M. Monteiro-Soares[4]
A. Rasmussen[5]
Y. Jubiz[6]
S. A. Bus[7]
on behalf of the International Working Group on the Diabetic Foot (IWGDF)

[1]*Diabetic Foot Clinic, Department of Surgery, Ziekenhuisgroep Twente, Almelo and Hengelo, The Netherlands*

[2]*Vice Chancellors' Office, Cardiff University, Cardiff, Wales, UK*

[3]*Department of Plastic Surgery, University of Texas Southwestern Medical Centre, Dallas, TX, USA*

[4]*CIDES/CINTESIS – Health Information and Decision Sciences Department (U753-FCT), Oporto Faculty of Medicine, Oporto, Portugal*

[5]*Steno Diabetes Centre A/S, Gentofte, Denmark*

[6]*Diabetic Foot Unit, Colombian Diabetes Association, Bogotá, Colombia*

[7]*Department of Rehabilitation Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands*

*Correspondence to: Jaap J. van Netten, Diabetic Foot Clinic, Department of Surgery, Ziekenhuisgroep Twente, Almelo and Hengelo, Zilvermeeuw 1, 7609 PP Almelo, The Netherlands.
E-mail: jv.netten@zgt.nl

Abstract

Background Prevention of foot ulcers in patients with diabetes is extremely important to help reduce the enormous burden of foot ulceration on both patient and health resources. A comprehensive analysis of reported interventions is not currently available, but is needed to better inform caregivers about effective prevention. The aim of this systematic review is to investigate the effectiveness of interventions to prevent first and recurrent foot ulcers in persons with diabetes who are at risk for ulceration.

Methods The available medical scientific literature in PubMed, EMBASE, CINAHL and the Cochrane database was searched for original research studies on preventative interventions. Both controlled and non-controlled studies were selected. Data from controlled studies were assessed for methodological quality by two independent reviewers.

Results From the identified records, a total of 30 controlled studies (of which 19 RCTs) and another 44 non-controlled studies were assessed and described. Few controlled studies, of generally low to moderate quality, were identified on the prevention of a first foot ulcer. For the prevention of recurrent plantar foot ulcers, multiple RCTs with low risk of bias show the benefit for the use of daily foot skin temperature measurements and consequent preventative actions, as well as for therapeutic footwear that demonstrates to relieve plantar pressure and that is worn by the patient. To prevent recurrence, some evidence exists for integrated foot care when it includes a combination of professional foot treatment, therapeutic footwear and patient education; for just a single session of patient education, no evidence exists. Surgical interventions can be effective in selected patients, but the evidence base is small.

Conclusion The evidence base to support the use of specific self-management and footwear interventions for the prevention of recurrent plantar foot ulcers is quite strong, but is small for the use of other, sometimes widely applied, interventions and is practically nonexistent for the prevention of a first foot ulcer and non-plantar foot ulcer. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords diabetes mellitus; diabetic foot; foot ulcer; prevention; self management; shoes; podiatry; home monitoring; surgery; systematic review

Abbreviations IWGDF, International Working Group on the Diabetic Foot; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SIGN, Scottish Intercollegiate Grouping Network

Introduction

Foot ulcers are a major complication of diabetes mellitus, with high morbidity, mortality and resource utilization [1–3]. Yearly incidence is estimated to be around 2%, and lifetime incidence lies between 15 and 25% [1]. Treatment of these foot ulcers is challenging because of their multifactorial aetiology, and it places a high burden on patients, healthcare systems and society [1]. Even when an ulcer is successfully healed, risk for recurrence is high, with reported rates between 30 and 40% within the first year [4,5]. Therefore, prevention of foot ulcers is of paramount importance and has long been recognized as a priority by the International Working Group on the Diabetic Foot (IWGDF).

Not all patients with diabetes are at risk for ulceration. Based on a large number of retrospective and prospective studies, risk factors for ulceration are defined in a variety of risk classification systems [1,6–9]. The key factors that are present in each of these include peripheral neuropathy, foot deformity, peripheral vascular disease, previous foot ulceration and previous amputation of (a part of) the foot or leg. In general, patients without any of these risk factors are considered not to be at risk for ulceration. The classification systems show similar diagnostic/prognostic results (such as sensitivity, specificity, predictive values and likelihood ratios) in predicting ulceration [10]. Despite the popularity and common use of these systems, the evidence base for their use is small, with little validation of their predictive ability [10]. A recent meta-analysis of prognostic factors for ulceration may help to improve the level of evidence of risk classification for foot ulceration [11].

To prevent foot ulcers, various interventions have been studied and are used in clinical practice. The effectiveness of some of these interventions has been systematically reviewed, that is, on complex interventions [12], patient education [13], interventions studied in randomized controlled trials [14], population-based screening [15], podiatry [16], therapeutic footwear [17], footwear and offloading interventions [18], insoles [19], flexor tenotomy [20] and cost-effectiveness of interventions [21]. However, all these reviews have used different inclusion criteria for their study selection, non-uniform patient populations and a variety of outcomes, which limits comparison. Furthermore, none conducted a comprehensive analysis of all reported preventative measures. Such an analysis is needed to properly inform caregivers about effective preventative treatment. The aim of this systematic review was to investigate the effectiveness of interventions to prevent first and recurrent foot ulcers in persons with diabetes who are at-risk for ulceration and do not have a current foot ulcer. This systematic review forms the basis of the IWGDF guidance on prevention of foot ulcers in at-risk patients with diabetes [22].

Methods

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The systematic review was prospectively registered in the PROSPERO database for systematic reviews (CRD42014012964).

The population of interest for this systematic review was persons with type 1 or 2 diabetes mellitus who are at risk for foot ulceration. In accordance with the IWGDF definition, 'at-risk' was defined as 'presence of peripheral neuropathy, with or without a foot deformity or peripheral artery disease, or a history of foot ulcer(s) or amputation of (a part of) the foot or leg' [1]. Primary outcomes were first diabetic foot ulcer and recurrent diabetic foot ulcer. A diabetic foot ulcer was defined as a 'full thickness lesion of the skin distal to the malleoli in a person with diabetes mellitus' [1]. 'First ulcer' was the first-ever recorded diabetic foot ulcer in a patient. 'Recurrent ulcer' was any foot ulcer after successful healing of a previous one, irrespective of which foot or at what location on the foot the ulcer recurred. We have reported first and recurrent ulcer separately because patients with a previous ulcer are considered at higher risk compared with those without [1,6], and consequently, these patients require more preventative foot care. If a study included both patients with and without a previous ulcer and results were not presented separately for first and recurrent ulcers, the primary outcome was 'first/recurrent ulcer'.

Original research studies were included that reported on interventions that had the goal to prevent a first or recurrent foot ulcer in the population of interest. We defined three groups of interventions *a priori* and systematically reviewed the literature for each group separately in order to structure the literature search and to distribute assignments among reviewers.

1. Care: interventions aimed at improvements in care, such as with podiatry, chiropody, multidisciplinary care, integrated foot care, screening interventions to detect and treat patients at risk for diabetic foot ulceration, or interventions aimed at education of health care professionals.
2. Self-management: interventions aimed at the self-management of patients, such as patient education, home monitoring of foot status, or lifestyle interventions.
3. Medical: generally hospital-based interventions, such as surgery and therapeutic footwear.

We excluded studies on healthy subjects, on persons with diseases other than diabetes or on persons with diabetes who are not at risk for foot ulceration. We only included studies of persons with active ulcers when these studies reported outcomes on ulcer recurrence after

DOI: 10.1002/dmrr

healing of the active ulcer. We excluded studies on interventions with surrogate outcomes related to ulcer prevention, for example, studies with results on foot care behaviour, knowledge, and awareness, quality of life, preulcerative lesions, plantar pressure or amputation only. We included systematic reviews and meta-analyses, randomized controlled trials, non-randomized controlled trials, case–control studies, cohort studies, (controlled) before-and-after studies, interrupted time series, prospective and retrospective non-controlled studies, cross-sectional studies and case series. We excluded case reports.

Before performing the systematic search of the literature, we created validation sets of approximately 20 publications for each group of interventions. Each publication in the sets had to be identified in the literature search. The validation set was created by first including key publications known to the authors that fit the scope of this systematic review. Secondly, reference lists in these publications and references to these publications were checked and key publications were included in the validation set. Finally, the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) (http://apps.who.int/trialsearch/default.aspx) was searched using the search string (Diabet* AND ulcer* OR diabet* AND reulcer* OR diabet* AND amput). We screened identified trials for relevance in relation to the scope of this review and searched trial numbers and authors of relevant trials in PubMed to identify publications to be added to the validation set.

The literature search was performed on 24 July 2014, covered publications in all languages and was not restricted by date. The following databases were searched: PubMed, Excerpta Medica Database (EMBASE) via Ovid SP, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effect and Cochrane Central Register of Controlled Trials. We prepared the search strings (online Appendix 1–4) for each database with the help of a clinical librarian.

For each of the three groups of interventions, two members of the working group independently reviewed publications by title and abstract for eligibility to be included in the analysis, based on four criteria: population; study design; outcomes; and intervention. Cohen's kappa was calculated for agreement between reviewers. Reviewers discussed and reached consensus on any disagreement on inclusion of publications. Publications identified in more than one intervention group were discussed between all reviewers and further analysed within the intervention group for which the study best fitted. Subsequently, the same two reviewers independently assessed full-paper copies of included publications on the same four criteria for final eligibility. Conference proceedings, if included after assessment of title and abstract, were used to search for full-paper publications. If no full-paper copy of the study was found, we contacted the authors for more information, to assess for any possible publication bias or selective reporting of results. Tracking of references of included publications was not performed.

To further assess for possible publication bias or selective reporting of results, the WHO-ICTRP trial registry (http://apps.who.int/trialsearch/default.aspx) was searched on 30 July 2014. The Clinicaltrials.gov registry was also searched separately (https://clinicaltrials.gov) on 31 July 2014 (Appendix 5). Two reviewers independently assessed identified trials for eligibility based on three criteria: patient group; outcomes; and intervention. Reviewers retrieved the status of eligible trials ('completed', 'ongoing' or 'not yet started') from the databases. Cohen's kappa was calculated for agreement. Reviewers solved disagreement concerning eligibility by discussion, until consensus was reached. Any relevant publication related to a completed trial was searched for in the same databases as for the literature search. If no publications were identified, the principal investigator of the trial was contacted for more information.

We used the Scottish Intercollegiate Grouping Network (SIGN) algorithm for classifying study design for questions of effectiveness (http://www.sign.ac.uk/pdf/studydesign.pdf) to classify the study design for each publication. The same two reviewers per intervention group independently assessed included publications with a controlled study design for methodological quality (i.e. risk of bias), using scoring sheets developed by the Dutch Cochrane Centre (www.cochrane.nl). Reviewers resolved disagreement regarding risk of bias by discussion, until consensus was reached. The SIGN level of evidence was determined for each publication [24]. Level 1 refers to randomized controlled trials and Level 2 refers to case–control, cohort, controlled before-and-after designs or interrupted time series. Risk of bias was scored for each study as ++ (very low risk of bias), + (low risk of bias) or – (high risk of bias). Data were extracted from each included publication with a controlled study design and summarized in the evidence table. This table included patient and study characteristics, characteristics of the intervention and control conditions and primary and secondary outcomes. One of the reviewers extracted the data; the other reviewer checked this for content and presentation. All members of the working group thoroughly discussed the evidence table. Reviewers did not participate in the assessment, data extraction and discussion of publications of which they were a co-author, to prevent any conflict of interest.

Finally, the two reviewers per group drew conclusions for each intervention based on the strength of the available evidence. All members of the working group discussed these conclusions, until consensus was reached.

DOI: 10.1002/dmrr

Results

In the literature database search, we identified a total of 3061 publications for intervention group 1 (care), 2641 publications for group 2 (self-management) and 2793 publications for group 3 (medical), and we identified 556 trials in the trial registries search (Figure 1). Agreement between reviewers was fair to moderate, with Cohen's kappa values ranging from 0.314 to 0.604. Contacting authors of conference proceedings did not result in the addition of any publications. Based on the outcomes from the pooled publications of the original three intervention groups, we decided to identify five intervention groups for analysis in this systematic review: integrated foot care, self-management, patient education, therapeutic footwear, and surgical interventions. A total of 74 publications were included for qualitative analysis, of which 30 were controlled studies [19 randomized controlled trials (RCTs) and 11 non-randomized controlled studies]. Risk of bias was very low in 3 studies, low in 11 studies and high in 16 studies (Table 1). Results of the controlled studies are summarized in the evidence table (online Table 2). Narrative descriptions of the results of both controlled and non-controlled studies are presented per intervention group in the following paragraphs. Results are presented separately for outcomes of first ulcer, first/recurrent ulcer and recurrent ulcer.

Integrated foot care

We defined integrated foot care as care given by one or multiple collaborating professionals treating patients at multiple occasions with multiple interventions. We identified five controlled studies and five non-controlled studies on this topic.

First ulcer

One RCT with high risk of bias conducted in a Chinese minority group by Liang *et al.* found a significantly lower percentage of ulcers after 2 years for integrated foot care in addition to standard care provided by an endocrinologist and diabetes nurse, compared with standard care alone (i.e. 2 h of diabetes education): 0% *vs* 24.1%; $p = 0.014$ [25].

In a small non-controlled study of 24 patients who visited a multidisciplinary foot clinic for preventative care,

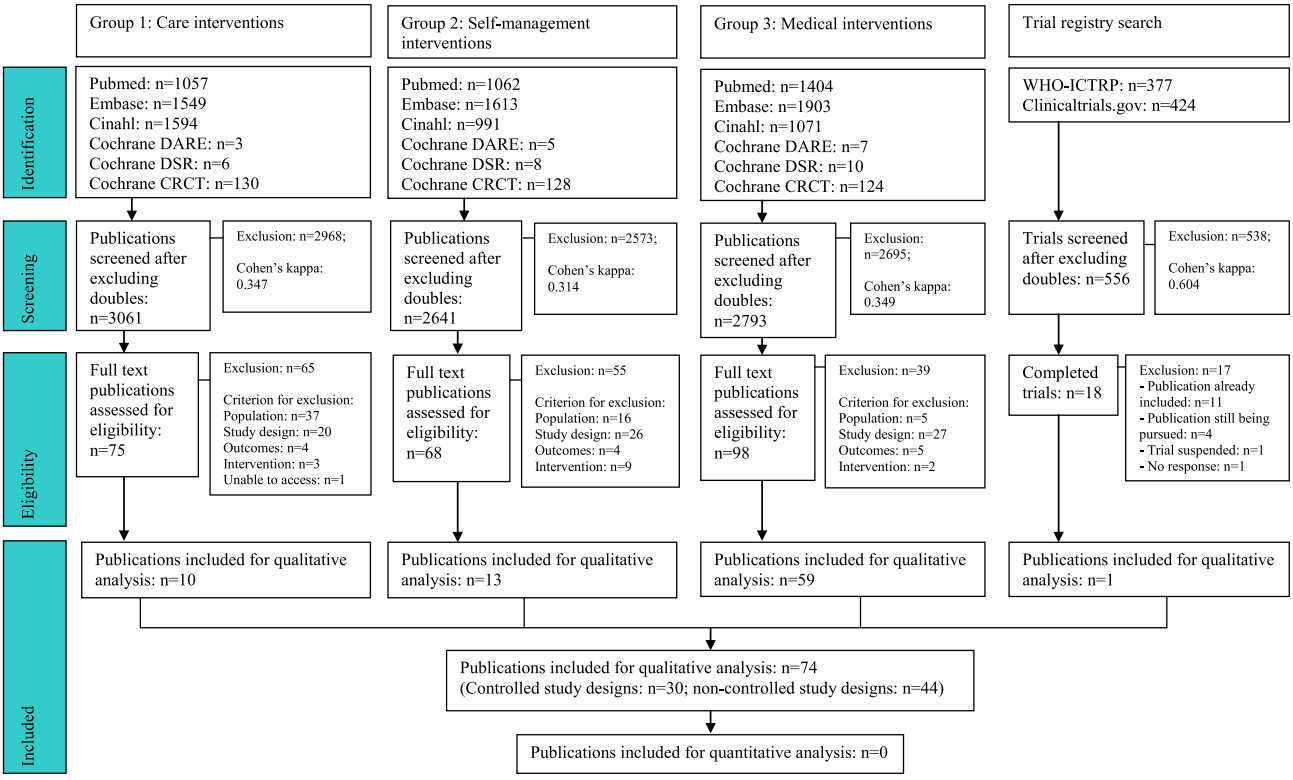

Figure 1. PRISMA flow diagram. DARE = Database of Abstracts of Reviews of Effects; DSR = Database of Systematic Reviews; CRCT = Central Register of Controlled Trials; WHO-ICTRP = World Health Organization International Clinical Trials Registry Platform. Note: publications could be identified in multiple groups; as such, the sum of the included publications in the four different groups exceeds the total number of publications included for qualitative analysis

DOI: 10.1002/dmrr

Table 1. Risk of bias of included publications

Randomized controlled trials

Reference	Randomization	Independent assignment	Similarity groups	Patient blinded	Care provider blinded	Outcome assessor blinded	Withdrawal / drop-out acceptable (<20%)	Intention-to-treat	Patients treated equally except for intervention	Score
Foot care programmes										
Liang *et al.* [25]	?	?	+	–	–	?	+	–	+	3/9
Van Putten *et al.* [28]	+	+	+	–	–	–	+	–	+	5/9
Cisneros *et al.* [29]	?	?	+	–	–	?	–	-	+	2/9
Plank *et al.* [31]	+	+	+	–	?	?	+	+	?	5/9
Self-management										
Armstrong *et al.* [35]	+	+	+	–	?	?	?	+	+	5/9
Armstrong *et al.* [36]	+	+	+	–	+	+	?	?	+	6/9
Lavery *et al.* [37]	?	?	+	–	+	?	+	+	+	5/9
Lavery *et al.* [38]	+	+	+	–	+	?	+	+	+	7/9
Patient education										
Gershater *et al.* [42]	+	+	+	–	–	–	–	-	+	4/9
Lincoln *et al.* [43]	+	+	+	–	?	?	+	+	+	6/9
Footwear and orthoses										
Scire *et al.* [53]	+	?	+	–	–	+	+	+	+	6/9
Lavery *et al.* [54]	?	?	+	–	+	–	–	+	+	4/9
Rizzo *et al.* [55]	+	?	+	–	–	–	–	–	+	3/9
Ulbrecht *et al.* [57]	+	+	+	+	–	+	–	+	+	7/9
Bus *et al.* [5]	+	+	+	–	–	+	+	+	+	7/9
Reiber *et al.* [58]	+	?	+	–	–	+	+	?	+	5/9
Uccioli *et al.* [61]	+	?	+	–	–	–	?	?	+	3/9
Surgical interventions										
Mueller *et al.* [70]	+	+	+	–	–	?	+	–	+	5/9
Armstrong *et al.* [80]	+	?	+	+	–	+	+	+		6/8
Piaggesi *et al.* [78]	+	?	+	–	–	–	+	+	+	5/9

Cohort studies

Reference	Study groups defined	Selection bias avoided/ excluded	Intervention clearly defined	Outcome clearly defined	Outcome assessed blind for exposure	Withdrawal/ drop – out acceptable (<20%)	Selective loss to follow-up excluded	Major confounders / prognostic factors identified and controlled	Score
Foot care programmes									
Dargis *et al.* [32]	+	+	?	+	–	+	?	–	4/8
Footwear and orthoses									
Viswanathan *et al.* [62]	?	–	+	–	–	?	?	–	1/8
Busch and Chantelau [63]	+	–	+	–	?	+	+	?	4/8
Reike *et al.* [64]	+	–	+	+	–	–	?	–	3/8
Surgical interventions									
Aszmann *et al.* [65]	–	–	–	–	–	–	–	–	0/8
Nickerson and Rader [66]	–	–	+	?	–	–	?	–	1/8
Faglia *et al.* [79]	+	–	+	+	–	–	?	–	3/8
Armstrong *et al.* [81]	+	–	+	+	?	?	?	–	3/8
Armstrong *et al.* [87]	+	–	–	+	?	–	?	–	2/8
Vanlerberghe *et al.* [90]	–	?	+	–	–	+	+	?	3/8

no ulcers were presented in a 20-month retrospective analysis (3.46 consultations per patient) and an ulcer in 16.7% of patients in a 20-month prospective analysis (0.23 consultations per patient) [26]. In 308 patients who were followed for a mean 4.6 years, a significantly lower ulcer incidence was present for those patients adherent to integrated foot care compared with those who were not adherent: 0.2% *vs* 4.4% ($p < 0.01$) in a lower-risk category and 0.5% *vs* 4.3% ($p < 0.01$) in a higher-risk category of patients [27].

First/recurrent ulcer
An unpublished RCT with low risk of bias in 569 neuropathic patients without a foot ulcer in the previous 12 months by Van Putten *et al.* found that podiatric treatment given at least twice a year in addition to standard care did not significantly reduce ulcer incidence in 3 years over standard care alone: 10% *vs* 11%; $p = 0.89$ [28]. However, the podiatric care group had significantly less infected or deep ulcers (11% *vs* 37%; $p \leq 0.03$) and treatment costs in the podiatric group were 25% of costs in the control group. Cisneros *et al.*, in a small RCT with high risk of bias in 53 patients, found after 24 months of integrated foot care, a lower but not significantly reduced ulcer incidence compared with that of standard care: 38.1% *vs* 57.1%; $p = 0.317$ [29].

The implementation of the IWGDF 'Step by Step' programme, aimed at ulcer prevention in lower-income countries, showed in one non-controlled study to lower ulcer incidence in one centre when compared with pre-implementation data [30].

Recurrent ulcer
One RCT with low risk of bias by Plank *et al.* investigated in 93 patients four-weekly chiropody treatments free of charge in addition to standard care, in comparison with standard care alone [31]. They presented after 2 years no significant difference in ulcer incidence between groups in the 'per patient' analysis (38% *vs* 57%; $p = 0.09$), but significant differences in favour of chiropody in the 'per foot' analysis (22% *vs* 38%; $p = 0.03$). In a prospective cohort study with high risk of bias in 145 neuropathic patients, Dargis *et al.* found that multidisciplinary foot care given at least once every 3 months resulted in significantly less ulcers than standard foot care after 2 years: 30.4% *vs* 58.4%; $p < 0.001$ [32].

In a 20-month prospective non-controlled study, higher adherence to multidisciplinary care showed a 2.5-fold reduced ulcer recurrence rate [26]. In another non-controlled study, patients who were adherent to once every 1–2 months preventative care in a multidisciplinary diabetes clinic for 3 years had a lower ulcer recurrence percentage than non-adherent patients: 5.4% *vs* 81.8% ($p < 0.0001$) [33]. In a case series of patients who received integrated foot care by a trained diabetes nurse, 8% ulcer recurrence per year was found [34].

Self-management

We identified four RCTs on this topic.

First ulcer
No studies were identified.

First/recurrent ulcer
One RCT with low risk of bias by Armstrong *et al.* instructed patients to apply on a daily basis topical antifungal nail lacquer as a way to increase frequency of foot self-inspection, but found no benefit after 12 months compared with standard care: (5.9% *vs* 5.6% ulcer incidence; $p = 0.9$) [35]. Two RCTs with low risk of bias assessed the preventative effect of daily foot skin temperature measurements, in which patients contacted a research nurse and dosed their activity when abnormal left to right temperature differences were measured [36,37]. When compared with standard care, Armstrong *et al.*, studying 225 patients, found significantly fewer ulcers after 18 months (4.7% *vs* 12.2%; $p = 0.038$), and Lavery *et al.*, studying 85 patients, after 6 months (2.4% *vs* 16.0%; $p < 0.05$).

Recurrent ulcer
In another RCT on daily foot skin temperature monitoring and subsequent preventative actions, with very low risk of bias, Lavery *et al.* showed in 173 patients significantly fewer recurrent ulcers after 15 months (8.5%) compared with either standard care plus instructions to perform daily foot inspection (30.4%, $p = 0.0061$) or to standard care alone (29.3%, $p = 0.008$) [38]. Additionally, patients who were less adherent to daily foot skin temperature measurements had substantially higher ulcer recurrence risk (OR 50.0; $p < 0.001$).

Patient education

We identified two RCTs and three non-controlled studies on this topic.

First ulcer
In a non-controlled study, of 318 neuropathic patients who underwent four 90–120 min foot educational sessions held during 1 week and were followed for at least 3 years, those adherent to the foot care habits as educated presented with a significantly lower percentage of ulceration than those not adherent: 3.1% *vs* 31.6%; $p < 0.001$ [40].

DOI: 10.1002/dmrr

First/recurrent ulcer
One non-controlled study of 3245 participants with diabetic neuropathy who were educated regarding diabetic foot disease and its complications presented an 18-month ulcer or infection incidence of 5.8%; those adherent to the advice at least 5 days a week presented with a lower incidence (5% *vs* 26%; $p < 0.0001$; [39]). In a non-controlled before-and-after design study of 185 patients, it was presented that intensive nursing education reduced ulcer incidence from 7.0 to 3.7 per 100 person-years ($p = 0.002$) [41].

Recurrent ulcer
In an RCT with high risk of bias, Gershater *et al.*found in 131 patients no benefit in ulcer recurrence after 6 months of one participant-driven 60-min patient education group session in addition to standard care, compared with standard care alone: 48% *vs* 38%; $p > 0.05$ [42]. Lincoln *et al.*, in an RCT with low risk of bias, found in 172 patients that a single 1-h education session, followed by a single phone call after 4 weeks, in addition to standard care, did not significantly improve ulcer recurrence at 12 months compared with standard care alone: 41.4% *vs* 41.2% [43].

Therapeutic footwear

We identified seven RCTs, three cohort studies, and nine non-controlled studies on this topic. Given the relatively large number of controlled studies, we decided not to discuss the non-controlled studies [44–52].

First ulcer
In an RCT with low risk of bias in 167 patients, Scire *et al.* showed significantly fewer ulcers and hyperkeratotic lesions at 3 months after the use of one of three types of custom-made digital silicon orthoses in addition to standard care, compared with standard care alone (i.e. sharp debridement, a 'soft' accommodating insole and extra depth footwear): 1.1% *vs* 15.4% for ulcers ($p < 0.001$) and 41% *vs* 84% for hyperkeratotic lesions, ($p = 0.002$) [53].

First/recurrent ulcer
An RCT with high risk of bias by Lavery *et al.* found in 299 patients, of whom 26% had prior ulcers, that insoles designed to reduce shear stress and were worn in extra-depth therapeutic shoes show a trend but do not significantly reduce ulcer incidence after 18 months compared with standard insoles: 2.0% *vs* 6.7% ($p = 0.08$) [54]. Another RCT with high risk of bias from Rizzo *et al.* [55] involved the initial randomization of 298 patients, 20% with previous ulceration, to intensive footwear therapy based on a prescription algorithm [56] or standard care consisting of footwear advice but no footwear prescription. Ulcer incidence at 1, 3 and 5 years was significantly lower in the intensive footwear group (11.5%, 17.6% and 23.5%, respectively) compared with standard care (38.6%, 61% and 72%, respectively, $p < 0.0001$), but there was a large attrition after 1 year. Some aspects of the methodology of this study are not clear (Table 2).

Recurrent ulcer
An RCT with very low risk of bias by Ulbrecht *et al.* randomized 130 patients with metatarsal head ulcer history to either shape and barefoot pressure-based custom-made insoles or to shape-based custom-made insoles, worn in extra-depth diabetic shoes [57]. While only a trend was found after 15 months follow-up in favour of the shape and pressure-based insoles for a composite outcome of plantar pre-ulcerative lesions and recurrent foot ulcer ($p = 0.13$), these insoles showed significantly less recurrent plantar foot ulcers than the shape-based insoles only (9.1% *vs* 25.0%, $p = 0.007$). An RCT with very low risk of bias by Bus *et al.* randomized 171 patients with plantar foot ulcer history to custom-made footwear with improved pressure-relieving properties guided by in-shoe pressure measurement or to the same custom-made footwear that did not undergo such improvement [5]. Overall, there was no significant difference in plantar foot ulcer recurrence after 18 months follow-up between the groups: 38.8% *vs* 44.2% ($p = 0.48$). However, in the 79 patients who wore their footwear for at least 80% of their measured activity, these authors showed a significantly lower ulcer recurrence incidence in the group with pressure-improved footwear than the control group: 25.7% *vs* 47.8% ($p = 0.045$). An RCT with low risk of bias by Reiber *et al.* randomized 400 patients to therapeutic shoes with customized inserts, therapeutic shoes with prefabricated inserts or the patient's own footwear [58]. No significant difference in proportion of persons with recurrent ulcer over a 2-year period was found between groups (15%, 14% and 17%; no *p*-value given). However, the methodological quality of this study has been debated [59,60]. An RCT with high risk of bias by Uccioli *et al.* in 69 patients found a significantly lower proportion of patients with a foot ulcer over a 1-year period in those who had worn therapeutic shoes compared with those who continued to use their own shoes: 27.7% *vs* 58.3%, $p = 0.009$ [61].

A cohort study with high risk of bias by Viswanathan *et al.* found in 241 patients significantly fewer recurrent ulcers in 9 months when using therapeutic sandals compared with using sandals with a hard leather board insole [62]. Another cohort study by Busch and Chantelau with high risk of bias found 15% ulcer recurrence over 12 months in 62 patients who were beneficiaries of prescribed diabetic footwear compared with 60% in 30 patients who were not reimbursed and therefore wore their own footwear ($p < 0.001$) [63]. Reike *et al.*, in a

DOI: 10.1002/dmrr

small cohort study with high risk of bias, found no benefit in ulcer recurrence at 2 years between patients accepting the prescription of orthopaedic footwear and patients who did not accept the prescription and wore their own shoes [64]. In all three cohort studies, selection bias cannot be ruled out and may be an important determinant of outcome.

Surgical interventions

We identified nine controlled studies and 27 non-controlled studies on this topic. All studies evaluated the effect on ulcer recurrence, except for one study on nerve decompression.

Nerve decompression

One retrospective cohort study by Aszmann *et al.* with high risk of bias, in 50 patients with neuropathic pain without a previous ulcer, found a significantly lower ulcer and amputation incidence over a mean 4.6 years follow-up in the affected leg treated with decompression of the peroneal nerve than the contralateral control leg: 0 versus 15 events (12 ulcers and three amputations); $p < 0.001$ [65]. A retrospective cohort study with high risk of bias by Nickerson and Rader, which assessed 42 patients with painful neuropathy and failed pharmacologic treatment for effect of nerve decompression in the previously ulcerated foot, found that over a mean 35.8 months follow-up, ulcer recurrence was significantly lower in the operated limb compared with the non-operated limb: 1.6 *vs* 7% per patient per year; $p = 0.048$ [66]. One retrospective and two prospective non-controlled studies presented low percentages of recurrent ulcers (2.6–4.3% per patient year) after 1 to 5.5 years follow-up with decompression of the peroneal and tibial nerves in diabetic patients with (symptomatic) peripheral neuropathy and a previous ulcer [67–69].

Achilles tendon lengthening

An RCT with low risk of bias from Mueller *et al.* found that patients who were treated with Achilles tendon lengthening, in addition to total contact casting to heal their forefoot ulcer, had significantly less recurrence at 7 months follow-up than patients treated with total contact casting alone for their active ulcer: 15% *vs* 59%, $p = 0.001$ [70]. This difference persisted at 2 years (38% *vs* 81%, $p = 0.002$).

One non-controlled retrospective study compared 138 patients treated with Achilles tendon lengthening with that of a historic cohort of 149 patients treated with wound closure surgery for ulcer healing and presented at a mean 3-year follow-up significantly fewer recurrences in the Achilles tendon lengthening group (2% *vs* 25%, $p < 0.001$), but significantly more transfer lesions (12% *vs* 4%, $p = 0.001$) [71]. Several other non-controlled studies presented few recurrent ulcers (0–20%) during 17–48 months follow-up after successful healing of a neuropathic ulcer with Achilles tendon lengthening [72–77].

Single or pan metatarsal head resection

An RCT with low risk of bias by Piaggesi *et al.* assessed ulcer recurrence at 6 months follow-up in 41 patients who were treated for ulcer healing with either removal of bone segments underlying the lesion or conservative treatment, that is, relief of weight-bearing and regular dressing [78]. They found significantly fewer ulcers in the surgical group: 14% *vs* 41%, $p < 0.01$. In a retrospective cohort study with high risk of bias, Faglia *et al.* found in 207 patients no significant differences in recurrence rates after a mean 40.6 months follow-up between those patients treated for their ulcers with surgical bone removal of the toe or metatarsal head, or with minor amputation of the toe or ray [79]. A retrospective cohort study from Armstrong *et al.* [80], with low risk of bias, found in 92 patients fewer recurrent ulcers at 1 year in patients treated with pan metatarsal head resection compared with those conservatively treated for their plantar forefoot ulcers (15.2% *vs* 39.1%, $p = 0.02$). Moreover, fewer infections were found in the surgical group (35.5% *vs* 64.5%, $p = 0.047$). A retrospective cohort study from Armstrong *et al.* [81], with high risk of bias, found significantly lower recurrence rates at 6 months follow-up after healing in those patients treated with single metatarsal head resection compared with those treated with conservative offloading treatment: 5% *vs* 28% ($p = 0.04$). One prospective and four retrospective non-controlled studies on the effects of pan-metatarsal head resection, including between 10 and 119 patients, presented between 0 and 41% recurrent ulcers after a mean 13.1 to 74 months follow-up [82–86].

Metatarsophalangeal joint arthroplasty

One retrospective cohort study by Armstrong *et al.* with high risk of bias in 41 patients, found that metatarsophalangeal joint arthroplasty of the great toe resulted in significantly fewer recurrent ulcers at 6 months follow-up than a total contact casting group, as a method to primarily treat plantar foot ulcers (5% *vs* 35%, $p = 0.02$) [87].

Two small non-controlled studies presented no recurrent ulcers at either 26 months or 2 to 5 years follow-up after primary healing in patients who underwent either inter-phalangeal joint arthroplasty or resection of the proximal phalanx of the great toe [88,89].

Osteotomy

A retrospective cohort study by Vanlerberghe *et al.* found that osteotomy plus arthrodesis, primarily applied to heal metatarsal head ulcers, found a significantly lower rate of combined recurrence and amputation when compared with conservative treatment (7.5% *vs* 35.5%, $p = 0.0013$), although data on recurrent ulcers alone were not significantly

DOI: 10.1002/dmrr

different between groups (7.5% *vs* 18%, $p = 0.14$) [90]. One non-controlled study presented no recurrent ulcers during 13 months follow-up in 21 patients who underwent osteotomy for healing of forefoot ulcers [91].

Digital flexor tendon tenotomy
Seven retrospective case series of percutaneous digital flexor tendon tenotomies performed in patients to heal apex toe ulcers presented a recurrence rate between 0 and 20% over a mean follow-up between 11 and 36 months in a total of 231 treated patients [92–98]. Four of the seven studies also assessed effects of digital tenotomy of a toe where no ulcer was present at the time of the procedure, in a cumulative total of 58 patients with impending ulcers (i.e. abundant callus on tip of the toe or thickened nails) and presented no ulcer occurrence in a mean 11–31 months follow-up [91,92,94,95].

Tendon transfer and fascia release
Two non-controlled studies from the same research group, one on the effects of plantar fascia release in 60 patients with forefoot ulcers and one on the effect of flexor hallucis longus tendon transfer in nine patients with plantar heel ulcers, presented no ulcer recurrence after 24 months follow-up [99,100].

Discussion

In this systematic review, we searched the literature for publications on interventions to prevent first and recurrent foot ulcers in persons with diabetes who are at risk for ulceration, without limits on publication date, language or study design (except for case reports). The systematic review was not limited to specific categories of interventions, to enable optimal comparison between interventions and provide a comprehensive overview of the evidence in this important field of diabetic foot care. Thirty controlled studies, including nineteen RCTs, were reviewed. A further 44 non-controlled studies were additionally described. The methodological quality of the controlled studies assessed varied, with 13 studies with (very) low risk of bias and 17 studies with high risk of bias. The evidence base to support some interventions is quite strong and based on several high-quality RCTs, whereas more high-quality controlled studies are required for other interventions.

Integrated foot care

In most studied integrated foot care programmes, the key responsible professional was a podiatrist or chiropodist, who worked alone or in a multidisciplinary setting [25,28,29,31,32]. Integrated foot care differed between studies, but always included callus removal, nail trimming, patient education, prescription of therapeutic footwear and advice on how to use the footwear. Frequency of professional foot treatment varied from once per month to once per 6 months.

Only one study of low quality was found on the prevention of a first foot ulcer [25]; no relevant conclusions can therefore be drawn. No evidence was found to support integrated foot care to prevent a combination of first and recurrent ulcers, with two RCTs showing no effectiveness [28,29]. However, adherence to the integrated foot care provided was not taken into account in the two RCTs, while non-controlled studies have shown that risk of ulceration is lower when patients are more adherent [26,27]. To prevent a recurrent ulcer, two controlled and three non-controlled studies all reported lower ulcer percentages in patients who followed an integrated foot care programme compared with those who did not, although one study only in a 'per-foot' analysis [26,31–34]. This suggests that integrated foot care can effectively prevent ulcer recurrence.

All reported integrated foot care programmes lacked sufficient detail on the treatment given, which limits reproducibility of the study findings, translation to other settings than those studied and analysis of the part(s) of the care that drive the outcomes. Additionally, limited description of patient education and therapeutic footwear hinders comparison with studies on these specific topics [5,43]. Future studies should describe integrated foot care in more detail.

Self-management

Self-management is important in the context of foot ulcer prevention, as foot ulcers nearly always develop outside the clinical setting. However, only four controlled studies on self-management were identified, all aimed at improving daily foot care behaviour [35–38]. We found no support for the daily use of antifungal nail lacquer as a surrogate to help improve frequency of foot inspection and early recognition of foot problems to prevent foot ulcers [35]. In contrast, we found strong support for the home-monitoring of foot skin temperature, with subsequent preventative actions taken when abnormal temperatures are recorded, to prevent first or recurrent foot ulcers. This is based on the results of three high-quality RCTs from the same research group that were conducted in three different clinical settings [36–38]. Foot temperature monitoring provides instantaneous and clinically meaningful feedback on the risk of ulceration. Patient adherence to the daily measurement of foot temperature proved to be an important component in clinical outcome

DOI: 10.1002/dmrr

[38], and therefore should be monitored adequately in studies. These positive findings require confirmation in well-designed studies by other research groups in other regions of the world, in which cost-effectiveness and feasibility of implementation are also addressed, as this approach is currently not implemented in foot care. Technological advancements in the monitoring of foot temperature that reduce the user burden, such as with automatic detection of impending problems, may improve practical use of the approach.

Patient education

The two RCTs and three non-controlled studies on the effect of patient education do not provide evidence to support a single session of patient education for foot ulcer prevention [39–43]. Patient education can have many forms, with different methods (e.g. individual or group sessions), different intervals (e.g. single session or weekly meetings), length of treatment, and different educators (e.g. nurses, podiatrists and doctors). The best setup for patient education to be beneficial in prevention may yet have to be investigated. Furthermore, many educational interventions focus primarily on improving self-management behaviour [101–104]. This may be beneficial in itself for diabetic foot patients, but we did not fully consider this within the scope on ulcer prevention in the current review. We did find two non-controlled studies that showed a decrease in ulcer risk in patients who were adherent to change in behaviour after an educational intervention [39,40]. More evidence from well-designed studies is needed on this topic. These studies should investigate different forms of patient education and account for adherence to changes in behaviour.

Therapeutic footwear

Studies on the specific role of therapeutic footwear in preventing a first foot ulcer in at-risk patients with diabetes are lacking, and are therefore urgently needed. One RCT was undertaken on the use of a toe orthosis to prevent a first foot ulcer, but focussed exclusively on toe ulcers, which were a secondary outcome in the study [53]. Several recently published high-quality RCTs indicate that specific modalities of therapeutic footwear can be effective in the prevention of a recurrent plantar foot ulcer compared with more standard of care therapeutic footwear [5,55,57]. These RCTs suggest some underlying principles that can guide footwear prescription. Prescription according to a structured consensus-based algorithm resulted in fewer ulcers than no footwear prescription [55]. While this is something that most clinicians will find obvious, there is at least evidence that now supports this basic tenet of foot care. Two RCTs with very low risk of bias found that, in contrast to using just foot shape and clinical opinion in footwear prescription, directly measuring the plantar pressure under the foot can improve the efficacy of the resulting footwear [5,57]. In one case, an algorithm based on foot shape and barefoot plantar pressure was used in shoe insole design [57], while in the second study, in-shoe plantar pressure was used to guide the adjustment of the foot–shoe interface to lower pressure in key 'at-risk' regions of the foot, which proved effective if the footwear was worn by the patient for most of their steps during the day [5].

Surgical interventions

With only few exceptions, surgical interventions are primarily studied in the context of ulcer treatment. However, because surgery most often changes foot structure, it may have an enduring preventative effect after primary healing. From the limited number of controlled studies, Achilles tendon lengthening, single or pan-metatarsal head resection and metatarsophalangeal joint arthroplasty appear to reduce ulcer recurrence risk in selected patients with initially non-healing ulcers when compared with non-surgical treatment [70,78,80,81,87]. Osteotomy also appears to reduce risk of ulcer recurrence, but it is not clear in comparison with what form of standard care [88,89]. Several other surgical offloading procedures such as tendon transfer, plantar fascia release and digital flexor tendon tenotomy may be promising procedures to prevent ulcer recurrence. Based on the results of a few case series, flexor tenotomy may even have value in preventing a first foot ulcer in patients with abundant callus on the tip of their toes or thickened nails. These outcomes require confirmation in well-designed controlled studies. However, with any surgical intervention, the possible benefits should be considered with respect to the possible harms. Achilles tendon lengthening can negatively influence locomotion, and may, as other procedures do, increase risk of transfer ulcers [70,105].

As a separate group of surgical interventions, studies on nerve decompression have presented low ulcer incidence rates over extended follow-up periods in patients both with or without a prior foot ulcer experiencing neuropathic pain [65,66]. However, risk of bias in these studies was high, and study design was not always appropriate, lacking comparison with standard of care conservative treatment. Efficacy has not yet been assessed within an RCT design, and most studies performed are from the same research group. Therefore, the evidence to support this intervention is limited.

We realize that studies on surgical interventions with the appropriate design are not always easy or ethical to

DOI: 10.1002/dmrr

perform, as surgery is sometimes a last-resort approach after failed conservative treatment, without a possibility to randomize patients. Nevertheless, more controlled, high-quality studies are needed before definitive statements can be made about the safety and efficacy of surgical interventions to prevent ulcer recurrence.

Other considerations

Several issues related to this systematic review need to be considered.

First, the population of interest was persons with diabetes *at-risk* for foot ulceration, because these patients are entitled to preventative foot care in most countries with developed healthcare systems and are expected to benefit more from preventative interventions than patients who are not at risk [1,6]. Studies were excluded if information on clinical presentation to define 'at-risk' was insufficient or if the 'at-risk' population was not specifically analysed. For example, the article on patient education by Malone *et al.* [106] provided no information on ulcer healing in their study population of patients with an active foot ulcer, yet this information is essential to adequately assess ulcer recurrence. Another example is the study on foot screening and treatment by McCabe *et al.* [107]. This study provides no information on the number of high-risk patients in the control group, and outcomes are not presented specifically for persons at risk. Other studies focused on a population with specific comorbidities, such as chronic kidney disease requiring dialysis treatment [108,109]. Even though foot ulcer risk is high in this population [110,111], the lack of specific reporting of findings for the patients at risk limits assessment of effectiveness of an intervention for at-risk patients. For similar reasons, we did not assess the efficacy of lifestyle interventions [112] or intensified glucose treatment [113], as they target a general population of patients with diabetes mellitus. We strongly advocate for the reporting of results in intervention studies that are specific for the population at risk.

Second, risk factors for ulcer development and ulcer risk classification systems were not analysed and described in this systematic review on interventions. Despite the importance of this topic, ulcer risk classification is only considered an intervention when a classification is linked directly to a strategy based on referral of patients for treatment [114]. No studies on such an intervention in the at-risk diabetic patient were identified. It remains crucial to better understand if the way in which we classify risk is effective for ulcer prevention.

Third, clear definitions and assessment methods for our primary outcome 'first or recurrent ulcer' were lacking in many studies. The use and reporting of a standardized definition for diabetic foot ulcers, such as provided by the IWGDF [1], are strongly recommended, together with a clear description of methods for assessing outcomes. Furthermore, although a very important outcome, amputation was not considered as a primary outcome in this systematic review, because amputation is an elective procedure and not a natural outcome from an intervention. Amputation also depends largely on ulcer treatment, and is therefore not a specific outcome for prevention in the non-ulcerated foot. As a consequence, the existing population-based studies on the effect of a preventative foot care programme in a multidisciplinary foot clinic on amputation prevention (e.g. [115,116]) were not considered.

Fourth, a key aspect of prevention that plays a critical role in outcome is treatment adherence. Studies on different interventions assessed for this systematic review consistently report that those patients who do not adhere to an intervention present with significantly worse outcomes [5,26,27,33,38–40]. Future intervention studies should incorporate a measure of treatment adherence, preferably objective, and investigate ways to improve adherence.

Finally, the overall quality of studies on interventions to prevent a foot ulcer in at-risk patients with diabetes should further improve, so that stronger recommendations for clinical practice can be made. Studies should conduct a power analysis, ensure adequate blinding whenever possible and use intention-to-treat analysis. More clarity is required in description of study populations, interventions, outcomes and outcome assessment. In addition, more focus should be put on cost-effectiveness studies, as we continue to operate in financially challenging times.

Conclusions

This systematic review of the literature shows that the evidence base to support the use of interventions that aim to prevent a first foot ulcer in the at-risk patient with diabetes is practically nonexistent. More data are available on the prevention of a recurrent foot ulcer, with strong evidence supporting the home-monitoring of foot skin temperatures with subsequent preventative actions and the use of therapeutic footwear with demonstrated pressure-relieving effect that is consistently worn by the patient. Furthermore, there is some evidence to suggest that prevention of a recurrent foot ulcer by means of integrated foot care is effective. There is no evidence to support a session of patient education for the prevention of a recurrent foot ulcer. While a limited number of studies show a benefit of surgical intervention in the prevention of ulcer recurrence in selected patient groups, no

DOI: 10.1002/dmrr

definitive conclusions can yet be drawn about efficacy and safety. More high-quality controlled studies are needed in these areas, in particular related to prevention of a first foot ulcer, patient education, self-management and surgical interventions, so to better inform clinicians and practitioners about effective preventative treatment.

Acknowledgements

The authors gratefully acknowledge the help from Joost Daams, MA, clinical librarian from the Academic Medical Centre, Amsterdam, the Netherlands, for his help with designing the search strings and performing the literature search. The contribution of Matilde Monteiro-Soares has been sponsored by "Fundação para a Ciência e Tecnologia (FCT)", Portugal; Grant number: SFRH/BD/86201/2.

Author contributions

J. vN. designed the search strings, performed the literature search, assessed the literature, extracted data and drew conclusions within 'care interventions', checked and completed the evidence and risk of bias tables and wrote the manuscript. P. P. assessed the literature, extracted data and drew conclusions within 'self-management interventions' and critically reviewed and edited the manuscript. L. L. assessed the literature, extracted data and drew conclusions within 'care interventions' and critically reviewed the manuscript. M. M. assessed the literature, extracted data and drew conclusions within 'self-management interventions' and critically reviewed the manuscript. A. R. assessed the literature, extracted data and drew conclusions within 'medical interventions' and critically reviewed the manuscript. Y. J. assessed the literature, extracted data and drew conclusions within 'medical interventions' and critically reviewed the manuscript. S. B. designed the search strings, assessed the literature, extracted data and drew conclusions within 'medical interventions' and wrote the manuscript. J. vN. acted as the secretary of the working group, S. B. as the chair of the working group.

Conflict of interest

L. L. is on the speaker's bureau for Osiris, Integra, PamLabs, Smit&Nephew; consultant for KCI, PamLabs, Innovacyn; Stock ownership in Prizm Medical; received research grants from Osiris, MacroCure, ThermoTrek, Integra, GlaxoSmithKline, KCI, Cardinal, Dipexium; J. vN., P. P., A. R., M. M. S., Y. J., S. B.: none declared.

References

1. Schaper NC, Van Netten JJ, Apelqvist J, *et al*. Prevention and Management of Foot Problems in Diabetes: A Summary Guidance for Daily Practice Based on the 2015 IWGDF Guidance Documents. *Diab Metab Res Rev*. DOI: 10.1002/dmrr.2695
2. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the National Health Service in England. *Diabet Med* 2014; **31**(12): 1498–504.
3. Prompers L, Huijberts M, Apelqvist J, *et al*. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia* 2007; **50**(1): 18–25.
4. Pound N, Chipchase S, Treece K, Game F, Jeffcoate W. Ulcer-free survival following management of foot ulcers in diabetes. *Diabet Med* 2005; **22**(10): 1306–1309.
5. Bus SA, Waaijman R, Arts M, *et al*. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. *Diabetes Care* 2013; **36**: 4109–4116.
6. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med* 1998; **158**(2): 157–162.
7. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. American Diabetes Association. Preventive foot care in diabetes. *Diabetes Care* 2004; **1**: S63–4.
8. Leese GP, Reid F, Green V, *et al*. Stratification of foot ulcer risk in patients with diabetes: a population-based study. *Int J Clin Pract* 2006; **60**: 541–545.
9. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* 2006; **29**(6): 1202–1207.
10. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. *Diabetologia* 2011; **54**(5): 1190–1199.
11. Crawford F, Cezard G, Chappell FM, *et al*. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess* 2015; **19**(57): 1–210. DOI: 10.3310/hta19570.
12. Hoogeveen RC, Dorresteijn JA, Kriegsman DM, Valk GD. Complex interventions for preventing diabetic foot ulceration. *Cochrane Database Syst Rev* 2015 **8**: CD007610. [Epub ahead of print] Review.
13. Dorresteijn JA, Kriegsman DM, Assendelft WJ, Valk GD. Patient education for preventing diabetic foot ulceration. *Cochrane Database Syst Rev* 2014; **12**: CD001488. DOI: 10.1002/14651858.CD001488.pub5. Review.
14. Arad Y, Fonseca V, Peters A, Vinik A. Beyond the monofilament for the insensate diabetic foot: a systematic review of randomized trials to prevent the occurrence of plantar foot ulcers in patients with diabetes. *Diabetes Care* 2011; **34**: 1041–1046.
15. Ozdemir BA, Brownrigg J, Patel N, Jones KG, Thompson MM, Hinchliffe RJ. Population-based screening for the prevention of lower extremity complications in diabetes. *Diabetes Metab Res* 2013; **29**: 173–182.
16. Buckley CM, Perry IJ, Bradley CP, Kearney PM. Does contact with a podiatrist prevent the occurrence of a lower extremity amputation in people with diabetes? A systematic review and meta-analysis. *BMJ Open* 2013; **3**.

17. Maciejewski ML, Reiber GE, Smith DG, Wallace C, Hayes S, Boyko EJ. Effectiveness of diabetic therapeutic footwear in preventing reulceration. *Diabetes Care* 2004; **27**: 1774–1782.
18. Bus SA, Valk GD, van Deursen RW, *et al.* The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev* 2008; **24**(Suppl 1): S162–S180.
19. Paton J, Bruce G, Jones R, Stenhouse E. Effectiveness of insoles used for the prevention of ulceration in the neuropathic diabetic foot: a systematic review. *J Diabetes Complications* 2009; **25**: 52–62.
20. Roukis TS, Schade VL. Percutaneous flexor tenotomy for treatment of neuropathic toe ulceration secondary to toe contracture in persons with diabetes: a systematic review. *J Foot Ankle Surg* 2009; **48**(6): 684–689.
21. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Pmc2909081; Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes Care* 2010; **33**: 1872–1894.
22. Bus SA, Van Netten JJ, Lavery LA, *et al.* IWGDF Guidance on the prevention of foot ulcers in at-risk patients with diabetes. *Diabetes Metab Res Rev* 2015. DOI: 10.1002/dmrr.2696.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items ;or Systematic Reviews and Meta-Analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**(10): 1006–1012.
24. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; **323**(7308): 334–336.
25. Liang R, Dai X, Zuojie L, Zhou A, Meijuan C. Two-year foot care program for minority patients with type 2 diabetes mellitus of Zhuang tribe in Guangxi, China. *Can J of Dia* 2012; **36**: 15–18.
26. Hamonet J, Verdie-Kessler C, Daviet JC, *et al.* Evaluation of a multidisciplinary consultation of diabetic foot. *Ann Phys Rehabil Med* 2010; **53**: 306–318.
27. Calle-Pascual A, Duran A, Benedi A, *et al.* A preventative foot care programme for people with diabetes with different stages of neuropathy. *Diabetes Res Clin Pract* 2002; **57**: 111–117.
28. Van Putten MA, Leffers P, Schreuder FHBM, Schaper NC. The effectiveness of a preventive foot care program versus treatment as usual to reduce the number of ulcers in diabetic patients with polyneuropathy: a randomized controlled trial. ISRCTN50646165; DOI: 10.1186/ISRCTN50646165.
29. Cisneros LL. Evaluation of a neuropathic ulcers prevention program for patients with diabetes. *Rev Bras Fisioter* 2010; **14**: 31–37.
30. Abbas ZG, Lutale JK, Bakker K, Baker N, Archibald LK. The 'Step by Step' Diabetic Foot Project in Tanzania: a model for improving patient outcomes in less-developed countries. *Int Wound J* 2011; **8**: 169–175.
31. Plank J, Haas W, Rakovac I, *et al.* Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects. *Diabetes Care* 2003; **26**: 1691–1695.
32. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. *Diabetes Care* 1999; **22**: 1428–1431.
33. Armstrong DG, Harkless LB. Outcomes of preventative care in a diabetic foot specialty clinic. *J Foot Ankle Surg* 1998; **37**: 460–466.
34. Marcinia M, Chantelau E. Qualified podiatry for rehabilitation of patients with diabetic foot syndrome. A cohort study. *Diabetes Stoffwechsel* 1998; **7**: 81–85.
35. Armstrong DG, Holtz K, Wu S. Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? Results from a randomised controlled pilot study. *Int Wound J* 2005; **2**: 166–170.
36. Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* 2007; **120**: 1042–1046.
37. Lavery LA, Higgins KR, Lanctot DR, *et al.* Home monitoring of foot skin temperatures to prevent ulceration. *Diabetes Care* 2004; **27**(11): 2642–2647.
38. Lavery LA, Higgins KR, Lanctot DR, *et al.* Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. *Diabetes Care* 2007; **30**(1): 14–20.
39. Viswanathan V, Madhavan S, Rajasekar S, Chamukuttan S, Ambady R. Amputation prevention initiative in South India: positive impact of foot care education. *Diabetes Care* 2005; **28**: 1019–1021.
40. Calle-Pascual A, Duran A, Benedi A, *et al.* Reduction in foot ulcer incidence: relation to compliance with a prophylactic foot care program. *Diabetes Care* 2001; **24**: 405–407.
41. Ren M, Yang C, Lin DZ, *et al.* Effect of intensive nursing education on the prevention of diabetic foot ulceration among patients with high-risk diabetic foot: a follow-up analysis. *Diabetes Technol Ther* 2014.
42. Gershater MA, Pilhammar E, Apelqvist J, Alm-Roijer C. Patient education for the prevention of diabetic foot ulcers. Interim analysis of a randomised controlled trial due to morbidity and mortality of participants. *Eur Diab Nursing* 2011; **8**: 102–107b.
43. Lincoln NB, Radford KA, Game FL, Jeffcoate WJ. Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial. *Diabetologia* 2008; **51**: 1954–1961.
44. Frigg A, Pagenstert G, Schafer D, Valderrabano V, Hintermann B. Recurrence and prevention of diabetic foot ulcers after total contact casting. *Foot Ankle Int* 2007; **28**: 64–69.
45. Tazi O, Debure C. Preventing high-risk diabetic foot ulceration by a new method of custom-made shoes in high-risk patients. *J Mal Vasc* 2008; **33**: 191–195.
46. Albert SF, Chen WY. Rigid foot orthoses in the treatment of the neuropathic diabetic foot. *Lower Extrem* 1996; **3**: 97–105.
47. Baumann R. Efficacy of industrially produced protective footwear for the 'diabetic foot': an observational study. *Diabetes Stoffwechsel* 1996; **5**: 107–112.
48. Borssen B, Bergenheim T, Lithner F. Preventive treatment of foot deformities in type 1 diabetic patients aged 15–50 years – an epidemiological and prospective study. *J Intern Med* 1996; **240**: 219–225.
49. Fernandez ML, Lozano RM, Diaz MI, Jurado MA, Hernandez DM, Montesinos JV. How effective is orthotic treatment in patients with recurrent diabetic foot ulcers? *J Am Podiatr Med Assoc* 2013; **103**: 281–290.
50. Illgner U, Wuhr J, Rummler M, Drerup B, Wetz HH. Orthopedic made-to-measure shoes for diabetics. Long-term 5-year outcome. *Orthopade* 2009; **38**: 1209–1214.
51. Chantelau E, Kushner T, Spraul M. How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study. *Diabet Med* 1990; **7**: 355–359.
52. Striesow F. Special manufactured shoes for prevention of recurrent ulcer in diabetic foot syndrome. *Med Klin (Munich)* 1998; **93**: 695–700.
53. Scire V, Leporati E, Teobaldi I, Nobili LA, Rizzo L, Piaggesi A. Effectiveness and safety of using Podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. *J Am Podiatr Med Assoc* 2009; **99**: 28–34.
54. Lavery LA, LaFontaine J, Higgins KR, Lanctot DR, Constantinides G. Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. *Adv Skin Wound Care* 2012; **25**: 519–24 quiz 525–6.
55. Rizzo L, Tedeschi A, Fallani E, *et al.* Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. *Int J Low Extrem Wounds* 2012; **11**: 59–64.
56. Dahmen R, Haspels R, Koomen B, Hoeksma AF. Therapeutic footwear for

the neuropathic foot: an algorithm. *Diabetes Care* 2001; **24**(4): 705–709.
57. Ulbrecht JS, Hurley T, Mauger DT, Cavanagh PR. Prevention of recurrent foot ulcers with plantar pressure-based in-shoe orthoses: the careful prevention multicenter randomized controlled trial. *Diabetes Care* 2014; **37**: 1982–1989.
58. Reiber GE, Smith DG, Wallace C, *et al.* Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. *JAMA* 2002; **287**: 2552–2558.
59. Cavanagh PR, Boulton AJ, Sheehan P, Ulbrecht JS, Caputo GM, Armstrong DG. Therapeutic footwear in patients with diabetes. *JAMA* 2002; **288**(10): 1231 author reply 1232–3.
60. Chantelau E. Therapeutic footwear in patients with diabetes. *JAMA* 2002; **288**(10): 1231–2 author reply 1323–3.
61. Uccioli L, Faglia E, Monticone G, *et al.* Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care* 1995; **18**(10): 1376–1378.
62. Viswanathan V, Madhavan S, Gnanasundaram S, *et al.* Effectiveness of different types of footwear insoles for the diabetic neuropathic foot: a follow-up study. *Diabetes Care* 2004; **27**: 474–477.
63. Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. *Diabet Med* 2003; **20**: 665–669.
64. Reike H, Bruning A, Rischbieter E, Vogler F, Angelkort B. Recurrence of foot lesions in patients with diabetic foot syndrome: influence of custom-molded orthotic device. *Diabetes Stoffwechsel* 1997; **6**: 107–113.
65. Aszmann O, Tassler PL, Dellon AL. Changing the natural history of diabetic neuropathy: incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure. *Ann Plast Surg* 2004; **53**: 517–522.
66. Nickerson DS, Rader AJ. Nerve decompression after diabetic foot ulceration may protect against recurrence: a 3-year controlled, prospective analysis. *J Am Podiatr Med Assoc* 2014; **104**: 66–70.
67. Nickerson DS. Low recurrence rate of diabetic foot ulcer after nerve decompression. *J Am Podiatr Med Assoc* 2010; **100**: 111–115.
68. Dellon AL, Muse VL, Nickerson DS, *et al.* Prevention of ulceration, amputation, and reduction of hospitalization: outcomes of a prospective multicenter trial of tibial neurolysis in patients with diabetic neuropathy. *J Reconstr Microsurg* 2012; **28**: 241–246.
69. Nickerson DS, Rader AJ. Low long-term risk of foot ulcer recurrence after nerve decompression in a diabetes neuropathy cohort. *J Am Podiatr Med Assoc* 2013; **103**: 380–386.
70. Mueller MJ, Sinacore DR, Hastings MK, Strube MJ, Johnson JE. Effect of Achilles tendon lengthening on neuropathic plantar ulcers. A randomized clinical trial. *J Bone Joint Surg Am* 2003; **85-a**: 1436–1445.
71. Colen LB, Kim CJ, Grant WP, Yeh JT, Hind B. Achilles tendon lengthening: friend or foe in the diabetic foot? *Plast Reconstr Surg* 2012; **131**: 37e–43e.
72. Laborde JM. Midfoot ulcers treated with gastrocnemius-soleus recession. *Foot Ankle Int* 2009; **30**: 842–846.
73. Lin SS, Lee TH, Wapner KL. Plantar forefoot ulceration with equinus deformity of the ankle in diabetic patients: the effect of tendo-Achilles lengthening and total contact casting. *Orthopedics* 1996; **19**: 465–475.
74. Holstein P, Lohmann M, Bitsch M, Jorgensen B. Achilles tendon lengthening, the panacea for plantar forefoot ulceration? *Diabetes Metab Res* 2004; **20**(Suppl 1): S37–40.
75. Lee TH, Lin SS, Wapner KL. Tendo-Achilles lengthening and total contact casting for plantar forefoot ulceration in diabetic patients with equinus deformity of the ankle. *Oper Tech Orthop* 1996; **6**: 222–225.
76. Cunha M, Faul J, Steinberg J, Attinger C. Forefoot ulcer recurrence following partial first ray amputation: the role of tendo-achilles lengthening. *J Am Podiatr Med Assoc* 2010; **100**: 80–82.
77. Laborde JM. Neuropathic plantar forefoot ulcers treated with tendon lengthenings. *Foot Ankle Int* 2008; **29**: 378–384.
78. Piaggesi A, Schipani E, Campi F, *et al.* Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. *Diabet Med* 1998; **15**(5): 412–417.
79. Faglia E, Clerici G, Caminiti M, Curci V, Somalvico F. Feasibility and effectiveness of internal pedal amputation of phalanx or metatarsal head in diabetic patients with forefoot osteomyelitis. *J Foot Ankle Surg* 2012; **51**: 593–598.
80. Armstrong DG, Fiorito JL, Leykum BJ, Mills JL. Clinical efficacy of the pan metatarsal head resection as a curative procedure in patients with diabetes mellitus and neuropathic forefoot wounds. *Foot Ankle Spec* 2012; **5**: 235–240.
81. Armstrong DG, Rosales MA, Gashi A. Efficacy of fifth metatarsal head resection for treatment of chronic diabetic foot ulceration. *J Am Podiatr Med Assoc* 2005; **95**: 353–356.
82. Giurini JM, Basile P, Chrzan JS, Habershaw GM, Rosenblum BI. Panmetatarsal head resection. A viable alternative to the transmetatarsal amputation. *J Am Podiatr Med Assoc* 1993; **83**: 101–107.
83. Hamilton GA, Ford LA, Perez H, Rush SM. Salvage of the neuropathic foot by using bone resection and tendon balancing: a retrospective review of 10 patients. *J Foot Ankle Surg* 2005; **44**: 37–43.
84. Petrov O, Pfeifer M, Flood M, Chagares W, Daniele C. Recurrent plantar ulceration following pan metatarsal head resection. *J Foot Ankle Surg* 1996; **35**: 573–7 discussion 602.
85. Molines-Barroso R, Lazaro-Martinez J, Aragon-Sanchez J, Garcia-Morales E, Beneit-Montesinos J, Alvaro-Afonso F. Analysis of transfer lesions in patients who underwent surgery for diabetic foot ulcers located on the plantar aspect of the metatarsal heads. *Diabet Med* 2013; **30**: 973–976.
86. Griffiths GD, Wieman TJ. Metatarsal head resection for diabetic foot ulcers. *Arch Surg* 1990; **125**: 832–835.
87. Armstrong DG, Lavery LA, Vazquez JR, *et al.* Clinical efficacy of the first metatarsophalangeal joint arthroplasty as a curative procedure for hallux interphalangeal joint wounds in patients with diabetes. *Diabetes Care* 2003; **26**: 3284–3287.
88. Lin SS, Bono CM, Lee TH. Total contact casting and Keller arthoplasty for diabetic great toe ulceration under the interphalangeal joint. *Foot Ankle Int* 2000; **21**: 588–593.
89. Downs DM, Jacobs RL. Treatment of resistant ulcers on the plantar surface of the great toe in diabetics. *J Bone Joint Surg Am* 1982; **64**: 930–933.
90. Vanlerberghe B, Devemy F, Duhamel A, Guerreschi P, Torabi D. Conservative surgical treatment for diabetic foot ulcers under the metatarsal heads. A retrospective case–control study. *Ann Chir Plast Esthet* 2013.
91. Fleischli JE, Anderson RB, Davis WH. Dorsiflexion metatarsal osteotomy for treatment of recalcitrant diabetic neuropathic ulcers. *Foot Ankle Int* 1999; **20**: 80–85.
92. Tamir E, Vigler M, Avisar E, Finestone AS. Percutaneous tenotomy for the treatment of diabetic toe ulcers. *Foot Ankle Int* 2014; **35**(1): 38–43.
93. Rasmussen A, Bjerre-Christensen U, Almdal TP, Holstein P. Percutaneous flexor tenotomy for preventing and treating toe ulcers in people with diabetes mellitus. *J Tissue Viability* 2013; **22**: 68–73.
94. van Netten JJ, Bril A, van Baal JG. The effect of flexor tenotomy on healing and prevention of neuropathic diabetic foot ulcers on the distal end of the toe. *J Foot Ankle Res* 2013; **6**: 3.
95. Kearney TP, Hunt NA, Lavery LA. Safety and effectiveness of flexor tenotomies to heal toe ulcers in persons with diabetes. *Diabetes Res Clin Pract* 2010; **89**(3): 224–226.
96. Schepers T, Berendsen HA, Oei IH, Koning J. Functional outcome and patient satisfaction after flexor tenotomy for plantar ulcers of the toes. *J Foot Ankle Surg* 2010; **49**(2): 119–122.
97. Tamir E, McLaren AM, Gadgil A, Daniels TR. Outpatient percutaneous flexor tenotomies for management of

diabetic claw toe deformities with ulcers: a preliminary report. *Can J Surg* 2008; **51**(1): 41–44.
98. Laborde JM. Neuropathic toe ulcers treated with toe flexor tenotomies. *Foot Ankle Int* 2007; **28**(11): 1160–1164.
99. Kim JY, Hwang S, Lee Y. Selective plantar fascia release for nonhealing diabetic plantar ulcerations. *J Bone Joint Surg Am* 2012; **94**: 1297–1302.
100. Kim J, Lee I, Seo K, Jung W, Kim B. FHL tendon transfer in diabetics for treatment of non-healing planta heel ulcers. *Foot Ankle Int* 2010; **31**: 480–485.
101. Barth R, Campbell LV, Allen S, Jupp JJ, Chisholm DJ. Intensive education improves knowledge, compliance, and foot problems in type 2 diabetes. *Diabet Med* 1991; **8**: 111–117.
102. Rettig BA, Shrauger DG, Recker RR, Gallagher TF, Wiltse H. A randomized study of the effects of a home diabetes education program. *Diabetes Care* 1986; **9**: 173–178.
103. Corbett CF. A randomized pilot study of improving foot care in home health patients with diabetes. *Diabetes Educ* 2003; **29**: 273–282.
104. Borges WJ.The impact of a brief foot care intervention for persons with diabetes. University of Texas Health Science Center at Houston School of Nursing; 2004.
105. Salsich GB, Mueller MJ, Hastings MK, Sinacore DR, Strube MJ, Johnson JE. Effect of Achilles tendon lengthening on ankle muscle performance in people with diabetes mellitus and a neuropathic plantar ulcer. *Phys Ther* 2005; **85**(1): 34–43.
106. Malone JM, Snyder M, Anderson G, Bernhard VM, Holloway GA Jr, Bunt TJ. Prevention of amputation by diabetic education. *Am J Surg* 1989; **158**: 520–3 discussion 523–4.
107. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. *Diabet Med* 1998; **15**: 80–84.
108. McMurray SD, Johnson G, Davis S, McDougall K. Diabetes education and care management significantly improve patient outcomes in the dialysis unit. *Am J Kidney Dis* 2002; **40**: 566–575.
109. Lipscombe J, Jassal SV, Bailey S, Bargman JM, Vas S, Oreopoulos DG. Chiropody may prevent amputations in diabetic patients on peritoneal dialysis. *Perit Dial Int* 2003; **23**: 255–259.
110. Jones NJ, Chess J, Cawley S, Phillips AO, Riley SG. Prevalence of risk factors for foot ulceration in a general haemodialysis population. *Int Wound J* 2012.
111. Kaminski M, Frescos N, Tucker S. Prevalence of risk factors for foot ulceration in patients with end-stage renal disease on haemodialysis. *Intern Med J* 2012; **42**: e120–8.
112. Look AHEAD Research Group, Wing RR, Bolin P, *et al.* Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**(2): 145–154.
113. Rathsman B, Jensen-Urstad K, Nystrom T. Intensified insulin treatment is associated with improvement in skin microcirculation and ischaemic foot ulcer in patients with type 1 diabetes mellitus: a long-term follow-up study. *Diabetologia* 2014; **57**(8): 1703–1710.
114. Jeffcoate WJ. Stratification of foot risk predicts the incidence of new foot disease, but do we yet know that the adoption of routine screening reduces it? *Diabetologia* 2011; **54**(5): 991–993.
115. Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? *Diabet Med* 1995; **12**: 770–776.
116. Krishnan S, Nash F, Baker N, Fowler D, Rayman G. Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care* 2008; **31**: 99–101.

Supporting information

Table 2 (evidence table) and the search strategy can be downloaded as supplements from the publisher's website.

DOI: 10.1002/dmrr