DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2013; **29**: 183–193.
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2386

REVIEW ARTICLE

Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis

Judy K. Morona[1]*
Elizabeth S. Buckley[1]
Sara Jones[2]
Edith A. Reddin[1]
Tracy L. Merlin[1]

[1]*Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health, University of Adelaide, Adelaide, South Australia, Australia*

[2]*School of Health Sciences, Division of Health Sciences, University of South Australia, Adelaide, South Australia, Australia*

*Correspondence to: Judy Morona, Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, School of Population Health, The University of Adelaide, Mail Drop DX 650 545, Adelaide, South Australia 5005, Australia.
E-mail: judy.morona@adelaide.edu.au

Received: 6 August 2012
Revised: 15 November 2012
Accepted: 7 December 2012

Summary

Effective off-loading is considered to be an important part of the successful clinical management of diabetic foot ulcers. The aim of this systematic review is to investigate the safety and effectiveness of different off-loading devices for the treatment of diabetic foot ulcers. The medical literature was extensively searched from January 1966 to May 2012. Systematic reviews and controlled studies that compared the use of different off-loading devices formed the evidence base. Studies were critically appraised to determine their risk of methodological bias, and data were extracted. Results were pooled using random effects meta-analysis and tested for heterogeneity. When compared with removable devices, non-removable off-loading devices were found, on average, to be more effective at promoting the healing of diabetic foot ulcers ($RR_p = 1.43$; 95% CI 1.11, 1.84; $I^2 = 66.9\%$; $p = 0.001$; $k = 10$). Analysis, stratified by type of removable device, did not detect a statistically significant difference between non-removable off-loading devices and removable cast walkers; however, on average non-removable off-loading devices performed better than therapeutic shoes at promoting the healing of diabetic foot ulcers ($RR_p = 1.68$; 95% CI 1.09, 2.58; $I^2 = 71.5\%$; $p = 0.004$; $k = 6$). The two types of non-removable off-loading devices i.e. total contact casts and instant total contact casts (removable cast walker rendered irremovable by securing with bandage or lace), were found to be equally effective ($RR_p = 1.06$; 95% CI 0.88, 1.27; $I^2 = 3.3\%$; $p = 0.31$; $k = 2$). In conclusion, non-removable off-loading devices regardless of type, are more likely to result in ulcer healing than removable off-loading devices, presumably because patient compliance with off-loading is facilitated. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords neuropathic diabetic foot; plantar ulcer; off-loading; total contact cast; removable cast walker; therapeutic shoe

Introduction

Neuropathic and neuroischaemic foot ulcers are the leading causes of diabetes-related amputations of the lower extremity worldwide [1,2]. Between 15% and 25% of people with diabetes will suffer from a foot ulcer during their lifetime, and 70% of these patients will have recurrent lesions within 5 years [3]. Even with comprehensive treatment programmes, neuropathic lesions may take weeks or months to heal or may not heal at all [4,5]. Developing effective treatment programmes are further complicated by the presence of ischaemia in the affected limb, which can be caused by either atherosclerosis or peripheral arterial disease.

Patients with neuroischaemic diabetic foot ulcers have a worse prognosis than those with neuropathic ulcers in terms of ulcer healing and have a much higher probability of amputation [1]. Effective off-loading to relieve pressure in the ulcer area is an important part of successful treatment programmes [6].

Non-weight-bearing strategies such as bed rest and the use of a wheelchair or crutches are the most effective methods of off-loading but are not practical because of the limitations on the patient's autonomy and their quality of life [6,7]. Consequently, clinicians favour the use of off-loading orthotic devices that allow the patient greater mobility [8].

Traditionally, the total contact cast (TCC), made of plaster of Paris bandages and/or fibreglass bandages, is considered to be the 'gold standard' for the treatment of neuropathic plantar ulcers as it is moulded to the lower limb with the aim of redistributing pressure over the plantar aspect of the diabetic foot and thus reducing pressure at the site of ulceration [9,10]. The TCC is thought to heal a higher proportion of wounds in a shorter amount of time than other off-loading devices and results in fewer infections, even though it has been associated with numerous side effects, such as abrasions around bony prominences, fungal infections on the digits and worsening of occult osteomyelitis [11,12]. However, TCCs are underutilized in clinical practice as they are technically difficult and time consuming to apply, relatively expensive and have low patient tolerance [8,9]. As a result, only 1.7% of US treatment centres used a TCC to treat the majority of diabetic foot ulcers in their clinic, and 45.5% of centres did not use TCCs at all [8]. Their use is also contraindicated in patients with infected or ischaemic ulcers [13].

Clinicians generally prefer to prescribe off-loading devices that are easy to apply, with most (95%) treatment centres using removable cast walkers (RCWs) or therapeutic shoes to treat at least some of the patients with diabetic foot ulcers in their clinics [8]. RCWs are made from various rigid materials that provide similar whole-foot load reduction as the TCC but with a greater degree of flexibility to reduce the incidence of side effects [14,15]. They are also designed to be removed to allow for easy access for dressing changes if required. Therapeutic shoes have been produced using a variety of techniques and materials, including felted foam, rubber, cork and leather, with or without a rigid rocker-bottom sole. They are removable and supposedly more acceptable to patients [7,16]. Half shoes that only provide a rear foot platform or offer heel relief have also been used [6,17].

To date, no meta-analysis has been conducted on available data to compare the effectiveness of different off-loading devices in patients with diabetic foot ulcers. Mason *et al.* [18], Spencer [19], Bus *et al.* [20], Hunt [21] and Ndip *et al.* [22] conducted systematic reviews of randomized controlled trials (RCTs) evaluating pressure relieving interventions in either the prevention or the treatment of diabetic foot ulcers. However, no meta-analysis was conducted in any of these reviews.

The aim of this review was to determine the relative safety and effectiveness of different off-loading devices in the treatment of neuropathic foot ulcers in people with diabetes. The principal hypothesis to be tested was that non-removable off-loading devices (NRDs) are more effective than removable off-loading devices in treating neuropathic diabetic foot ulcers.

Methods

The original systematic literature search, over the period from January 1966 to November 2009, was conducted as part of a larger search to evaluate all interventions used to treat diabetic foot ulcers. The search was conducted using the bibliographic databases listed in Table 1. A further search of the grey literature including government documents and Health Technology Assessment websites was also conducted. Reference lists of included publications (primary studies and reviews) were scanned for further potential relevant citations. This search was updated to include articles published between November 2009 and 19 May 2012, using the search terms listed in Table 1. Reference lists of all newly identified relevant publications (primary studies and systematic reviews) were also scanned for further potentially relevant citations.

Criteria for including studies in this systematic review were based on the PICO structure – population, intervention

Table 1. PubMed search strategy for updating systematic review search terms

Databases searched	CINAHL (1983–5/2012); Embase.com (including Embase and Medline 1974–5/2012); PubMed (2012); the Cochrane Library including Cochrane Databases of Systematic Reviews, Database of Abstracts of Review of Effects, the Cochrane Central Register of Controlled trials (CENTRAL), the Health Technology Assessment Database and the NHS Economic Evaluation Database (1966–5/2012); Web of Science – Current Contents and Science Citation Index Expanded (1995–5/2012)
PubMed search terms	
Population	((Diabetes Mellitus, Type 1 [MeSH] OR Diabetes Mellitus, Type 2 [MeSH] OR "NIDDM" OR (("type1" OR "type 2") AND diabet*) AND foot) OR diabetic foot OR neuro* OR Arthropathy, Neurogenic [MeSH] OR ((Diabet* OR Charcot*) AND (neuroarthropath* OR arthropath* OR neuroosteoarthropath*)) OR (Charcot* AND (joint OR foot)))
Intervention	Shoes [MeSH] OR shoe* OR "footwear" OR "off loading" OR Weight-Bearing [MeSH] OR Orthotic Devices [MeSH] OR Stockings, Compression [MeSH] OR Casts, Surgical [MeSH] OR "total contact casting" OR "cast"
Limits	Human; 2009–September 2011

DOI: 10.1002/dmrr

(treatment), comparator (against which an intervention's effectiveness is measured) and outcomes of interest. Systematic reviews and controlled studies that were published in English and provided data on patients older than 18 years with clinically documented diabetes and a foot ulcer were eligible for inclusion. The papers needed to describe the use of various orthotic devices in the treatment of chronic neuropathic ulcers. The primary outcomes for assessing safety were any adverse events or complications, such as infection. Comparative effectiveness was assessed by the proportion of ulcers healed, the time to healing, change in ulcer size and differences in the number of amputations required.

The appraisal of study quality was undertaken using a checklist for the appraisal of RCTs and non-RCTs developed by the Scottish Intercollegiate Guidelines Network [23]. Data were extracted from the included articles by one of two researchers and confirmed by an independent assessor, using tables and outcome definitions developed *a priori* for patient characteristics at baseline and for all safety and effectiveness outcomes. Katz *et al*. [24] reported only the percentage of patients with ulcers that healed using both intention-to-treat (ITT) and per-protocol analyses, so the absolute number of patients for each intervention had to be inferred.

All statistical calculations were undertaken using the biostatistical computing software package, STATA version 12 [25]. Meta-analyses were conducted using the metan command, with ITT data being entered into random effects models using the method of DerSimonian and Laird [26], with the estimate of heterogeneity taken from Mantel–Haenszel mixed effects models.

Results

Details of included studies

Of an initial total of 10 595 citations identified by the original non-specific search, 1003 studies were retrieved for full-text review. After the application of inclusion criteria, eight RCTs and two non-randomized studies comparing different orthotic devices were included (Table S2, Supporting information). Three RCTs and the two non-randomized studies compared NRDs with therapeutic shoes [7,27–30], one RCT compared removable and non-removable cast devices [9], one RCT compared a TCC, a RCW and half shoes [14], two RCTs compared two different NRDs [24,31], and one RCT compared a felted foam off-loading dressing with a therapeutic half shoe [32].

The updated search identified an additional 2520 citations, of which 55 articles involving off-loading devices were retrieved for full-text review. After the application of inclusion criteria and pearling of relevant references, three additional RCTs that compared a removable and non-removable cast device in the treatment of diabetic foot ulcers were included [15,33,34]. The PRISMA flowchart detailing the results of the study selection process is shown in Figure 1.

No systematic reviews that met the inclusion criteria were included for further analysis. The systematic reviews by Mason *et al*. [18] and Spencer [19] only included one published study by Mueller *et al*. [29], and the systematic review by Ndip *et al*. [22] identified only the systematic review by Spencer [19] as providing evidence that TCCs are effective in healing ulcers and, therefore, provided no additional information. Although

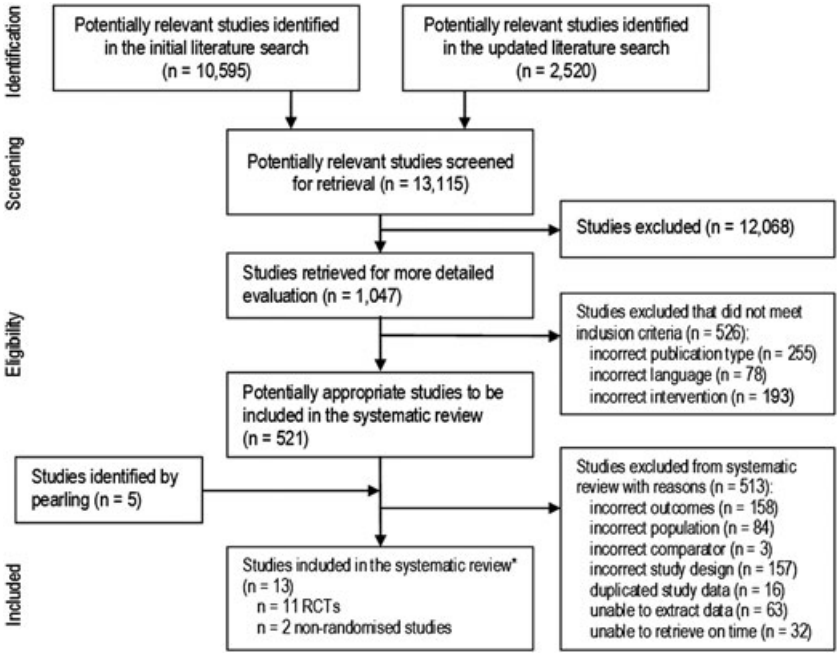

Figure 1. PRISMA flowchart. A summary of the process used to identify and select studies for the review of safety and effectiveness of different off-loading devices in the treatment of neuropathic foot ulcers in diabetic patients. Adapted from Liberati *et al*. (2009)

the systematic reviews by Bus *et al*. [20] and Hunt [21] included several RCTs comparing the effectiveness of various off-loading devices in treating diabetic foot ulcers, they provided only a narrative review of the data and were therefore also excluded. All the studies in the published systematic reviews were identified for this review. The 13 included studies are listed in Table S2.

Methodological quality

All included studies were of average quality and gave reasonable descriptions of the intervention, comparator and main outcomes (Table S2). Although important to minimize information bias, blinding of the intervention to subjects and health care professionals was not feasible for these studies. Blinded assessment of ulcer healing was possible (i.e. assessors are unable to determine the type of off-loading device used by the patients with the plantar ulcer) but only occurred in two trials [30,32]. All studies gave details of patients lost to follow-up and any adverse events that occurred in the studies. The data were analysed by the authors according to ITT in all but four studies [14,30,33,34].

Seven trials enrolled either consecutive patients or all patients attending the relevant clinic(s) that met the inclusion criteria and had given informed consent [7,24,30–34]. The other five studies did not comment on the proportion of the clinic population screened for inclusion [9,14,15,27–29]. Randomization occurred via a computer-generated randomization schedule in four studies [9,14,15,31], a pre-prepared random number table in two studies [7,24] and opaque sealed envelopes in one study [30], but details as to how allocation was implemented were not provided. Three studies gave no details about the randomization method used [29,32,33]. In the two non-randomized studies, patients who met the inclusion criteria were allocated to study groups on the basis of the duration of their ulcer [28] or at the discretion of the clinician [27].

The baseline characteristics for the randomized groups were similar, with no clinically or statistically significant differences between groups. All studies enrolled patients with neuropathic plantar ulcers, three of which included 100% patients with a forefoot ulcer location [31,32,34]. Five studies included mostly (at least 75%) patients with forefoot plantar ulcers [15,24,28–30], and the remaining five studies did not report data on the location of the plantar ulcers [7,9,14,27,33].

Four studies [9,14,28,34] only included patients with University of Texas Diabetic Foot Wound Classification grade 1, stage A ulcers (grade 1 = superficial wounds not involving tendon, capsule or bone; stage A = free of infection and/or ischaemia) [35]. Two trials included patients with University of Texas Diabetic Foot Wound Classification grade 1 or 2 ulcers (stage A), which included wounds penetrating to the tendon or capsule [24,31]; however, the proportion of patients with either grade 1 or 2 ulcers was not reported. Four trials included patients with Wagner grade 1 (superficial) or 2 (deep to tendon, capsule or bone) ulcers [36]; 30% of patients in the study by Mueller *et al*. [29] had grade 2 ulcers, 70% of patients in the study by Van De Weg *et al*. [30] and 90% of patients in the study by Zimny *et al*. [32]. The proportion of Wagner grade 1 and grade 2 ulcers in the study by Gutekunst *et al*. [15] was not reported. The study by Agas *et al*. [27] included patients with Wagner grade 2 or 3 ulcers, but the proportions were not reported. The severity or classification of the ulcers belonging to patients in the RCTs by Caravaggi *et al*. [7,33] were not reported.

Van De Weg *et al*. [30] observed baseline differences, likely due to chance, with respect to mean ulcer surface area; as the ulcers in the TCC group were 29% [95% CI −19, 76] larger than in the therapeutic shoe group. Even though this difference was not statistically significant (likely due to the small sample size), the authors sensibly adjusted for the imbalance when calculating the primary outcome of reduction in wound surface area. However, the influence of the difference in wound surface area at baseline on the proportion of ulcers that eventually healed in each group was not considered.

Caravaggi *et al*. [33] did not provide any details on patient characteristics except ulcer size but stated that the patients' age, sex, type of diabetes and duration of diabetes were comparable for the two groups. Despite the lack of statistically significant differences in the mean size of ulcers in most of the studies, imbalances between groups occurred in five RCTs because of their small size, involving 18-30 patients in each group. Ulcers in the NRD group were 13% [95% CI −30, 56] and 26% [95% CI 1, 52] larger at baseline than in the removable device group in Caravaggi *et al*. [33] and Armstrong *et al*. [9], respectively. Conversely, ulcers in the NRD group were 27% [95% CI −22, 75], 36% [95% CI −12, 86] and 36% [95% CI −32, 104] smaller than in the removable device group in three trials [7,29,34]. Gutekunst *et al*. [15] did not report on the size of the ulcers included in the study.

The ulcer baseline characteristics in the non-randomized studies also differed between the two groups. The ulcers in the study by Agas *et al*. [27] were 20% [95% CI −39, 79] smaller and of 23% [95% CI -126, 171] shorter duration in the TCC group compared with those in the therapeutic shoe group, potentially overestimating any treatment benefits favouring the TCC. In the study by Ha Van *et al*. [28], the ulcers were significantly different between the two groups for width and depth of the wound, ulcer duration and ulcer site. This is not surprising as TCC treatment was offered to patients with ulcers that had failed to heal in the previous 6 months and patients with Charcot foot, whereas therapeutic shoes were offered to patients with ulcers of less than 6 months duration. Thus, ulcers in the TCC group were 43% [95% CI 28, 59] larger in area (mean length × mean width) and 38% [95% CI 5, 70] deeper than those in the therapeutic shoe group, and there was a higher risk of confounding. As a result, any benefits with TCC treatment compared with therapeutic shoe treatment were likely to be underestimated. The authors adjusted for patient age in the analysis to offset the confounding effect of age on healing outcomes.

DOI: 10.1002/dmrr

NRDs compared with off-loading with therapeutic shoes

Six studies (four RCTs and two prospective non-randomized studies) compared the effectiveness of NRDs with the use of therapeutic shoes for treatment of diabetic neuropathic ulcers. Five studies used standard wound care, which consisted of sharp debridement, cleansing of the wound and dressing changes as required, in conjunction with the off-loading device (Table S2). The sixth study, by Agas *et al*. [27], also treated the ulcers in both groups with Regranex gel, which contains platelet derived growth factor. Three studies used a standard non-removable TCC [14,29,30], and three used a TCC with a window cut out to expose the ulcer [7,27,28]. These were compared with half shoes [14,28], accommodative footwear such as a healing shoe or sandal, or extra-depth shoe with plastazote insert [27,29], cloth shoe with a rigid rocker-bottom sole and cushioned alkaform insoles [7] or custom-made temporary footwear [30].

All six studies reported the proportion of ulcers that healed completely during the study period (Table S2). Three studies found that there were significantly more patients with ulcers that healed in the NRD groups than in the therapeutic shoe groups [7,27,29]. The other three studies found no statistically significant difference in the number of ulcers healed between the two groups [14,28,30], although two studies showed a trend favouring NRDs. This outcome was predictable for the non-randomized study, as patients selected for treatment using a therapeutic shoe had ulcers that were significantly smaller in area (43% [95% CI 28, 59]), shallower (3.4 ± 3.2 *versus* 5.4 ± 5.4 mm; $p = 0.03$) and of shorter duration (134 ± 272 days *versus* 395 ± 560 days; $p = 0.0078$) compared with patients selected for treatment with an NRD, potentially underestimating any treatment benefits associated with the NRD.

Meta-analysis of the results of these studies show that on average, NRDs are more effective at achieving complete healing of diabetic foot ulcers than therapeutic shoes ($RR_p = 1.68$ [95% CI 1.09, 2.58]; Figure 2). Substantial between-study heterogeneity was observed ($I^2 = 71.5\%$; $p = 0.004$).

Five of the six studies reported that the time taken for ulcers to heal was shorter with NRDs than for therapeutic shoes. The mean difference for time to healing was statistically significant in four studies [14,27–29] but not in the study by Van De Weg *et al*. ($p = 0.11$) [30].

Mueller *et al*. [29] reported fewer adverse events in patients using a TCC than in patients using therapeutic shoes. Five patients (26%) in the therapeutic shoe group required hospitalization due to infection and two subsequently required amputations. No patients with TCC were hospitalized during the 12-week study period, although three patients (14%) did experience an adverse event. Agas *et al*. [27] reported that five patients (24%) using a therapeutic shoe required an amputation compared with no patients using a TCC. Ha Van *et al*. [28] found that patients with a TCC were less likely to develop secondary osteomyelitis compared with those using a half shoe ($RR = 0.37$ [95% CI 0.013, 0.88], $p = 0.03$). However, five patients (12%) using a TCC developed a new ulcer (caused by the fibreglass TCC) during the study period compared with no patients in the half shoe group ($p = 0.01$).

Van De Weg *et al*. [30] reported that five patients (22%) had complications in the TCC group, leading to discontinuation of treatment in two cases (one resulting in amputation). For therapeutic shoes, two patients (10%) suffered minor abrasions that did not necessitate a cessation of treatment, but this difference was not statistically significant ($p = 0.2$). The remaining two studies reported that no device-related adverse events occurred [7,14].

Felted foam off-loading dressing compared with therapeutic shoes

One RCT compared a non-removable, felted foam off-loading dressing with a Thanner pressure relief half shoe [32]. Zimny *et al*. [32] found that the mean difference for time to healing was statistically significant, favouring the felted foam off-loading dressing (75.2 days [95% CI 67–84] compared with85.2 days [95% CI 79–92] for

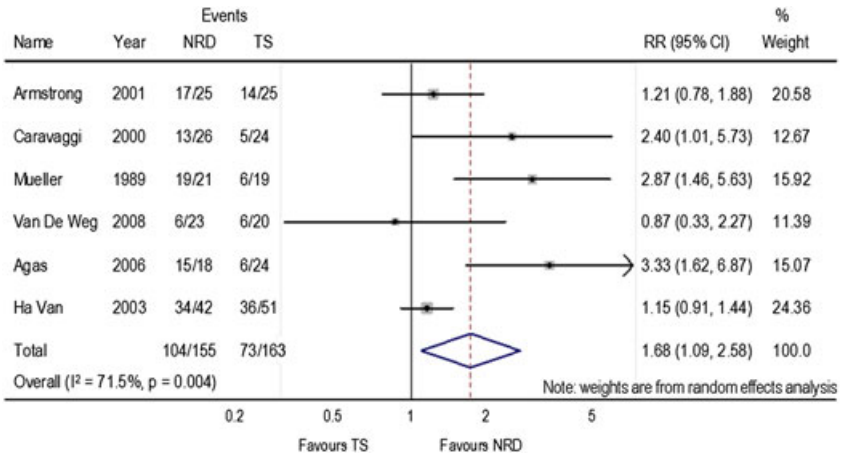

Figure 2. Forest plot showing meta-analysis of NRDs *versus* therapeutic shoes for ulcer healing. TS, therapeutic shoes; NRD, non-removable off-loading devices

DOI: 10.1002/dmrr

the half shoe, $p = 0.03$). The mean wound radius reduction decreased by 0.48 mm (95% CI 0.42–0.56) per week in the felted foam group and by 0.39 mm (95% CI 0.35–0.42) per week in the therapeutic shoe group ($p = 0.005$). The authors also reported that the frequency of soft tissue infections did not differ between the two treatment groups (25% felted foam NRD group, 23% half shoe group; $p > 0.05$) [32].

NRDs compared with RCWs

Five RCTs compared an NRD with an RCW for the treatment of neuropathic plantar ulcers in patients with diabetes. Four studies used a TCC [14,15,33,34], and one study used an instant TCC (iTCC) devised by wrapping an RCW, the Active Off-loading Walker (Royce Medical, Camarillo, CA), with a cohesive bandage to prevent patients from being able to remove it [9]. The effectiveness of these NRDs in treating neuropathic plantar ulcers were compared with three different RCWs: Armstrong *et al.* [14] used the Aircast diabetic RCW (Aircast, Summit, NJ), Caravaggi *et al.* [33] used the Aircast Pneumatic Walker (XP Diabetic Walker) and Faglia *et al.* [34] used the Stabil-D RCW (Podartis, Montebelluna, Treviso, Italy). The Active Off-loading Walker (Royce Medical) used by Armstrong *et al.* [9] and the DH Pressure Relief Walker used by Gutekunst *et al.* [15] (Össur, Foothill Ranch, CA, USA) are the same device.

Results for the number of ulcers that healed for the individual studies are given in Table S2. Meta-analysis of these five studies did not detect a statistically significant difference between the devices in terms of complete healing of the ulcers ($RR_p = 1.23$ [95% CI 0.96, 1.58]; Figure 3). Although there was a moderate level of between-study heterogeneity, it was not statistically significant ($I^2 = 51.1\%$; $p = 0.085$).

Armstrong *et al.* [9] and Caravaggi *et al.* [33] reported a significant difference between the two treatments in favour of NRDs for time to healing ($p = 0.02$ and $p < 0.005$, respectively). Armstrong *et al.* [14] and Faglia *et al.* [34] also reported a mean difference in time to healing that favoured NRDs, but the difference was not statistically significant ($p = 0.07$ and $p = 0.71$, respectively). There was no difference in the time to healing ($p = 0.95$) between the two treatment arms in the study by Gutekunst *et al.* [15].

Armstrong *et al.* [9] reported that the patients with an NRD had a statistically significant higher rate of peri-wound maceration (68.2%) than patients with an RCW (37.5%; $RR = 1.96$ [95% CI 1.09, 3.43]), and they also developed fewer soft tissue infections (27.3% compared with 41.7%; $p = 0.40$). Armstrong *et al.* [14] and Gutekunst *et al.* [15] reported no adverse events, and Caravaggi *et al.* [33] reported no difference in the number of serious infections between the two groups (17.2% compared with 20.1%; $p = 0.74$). Faglia *et al.* [34] found twice as many adverse events occurred when using an RCW compared with an NRD (8.7% compared with 4%; $RR = 0.46$ [95% CI 0.06, 3.40]).

TCC compared with iTCC

Two RCTs provided evidence regarding the comparison of two NRDs, TCCs and iTCCs. Katz *et al.* [24] compared the Royce DH RCW (Royce Medical), rendered irremovable by fibreglass casting material, with a standard TCC. The authors found that the use of an iTCC was comparable with a TCC in terms of proportion of ulcers healed and median time to healing (Table S2). Further, the number of adverse events were reduced using the iTCC, although this positive trend was not statistically significant and the study may have been underpowered for this outcome (38% compared with 65%; $p = 0.09$).

Piagessi *et al.* [31] also compared a TCC with an iTCC, constructed using the Optima Diab RCW (Molliter, Civitanova Marche, Italy) rendered irremovable by the use of a plastic lace. The proportion of ulcers healed, median time to healing and number of adverse events were comparable for both devices (Table S2). Meta-analysis of the data from these two studies showed TCCs and iTCCs to be equally effective at achieving complete healing of diabetic foot ulcers ($RR_p = 1.06$ [95% CI 0.88, 1.27], $I^2 = 3.3\%$, $p = 0.31$; Figure 4).

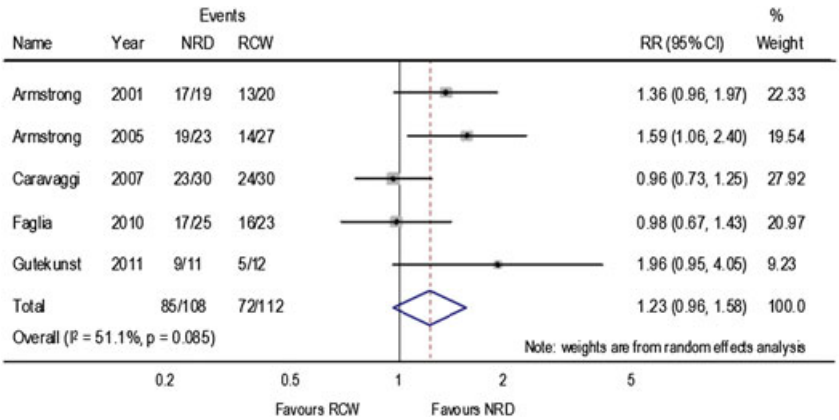

Figure 3. Forest plot showing meta-analysis of NRDs *versus* RCWs for ulcer healing. RCW, removable cast walker; NRD, non-removable off-loading devices

DOI: 10.1002/dmrr

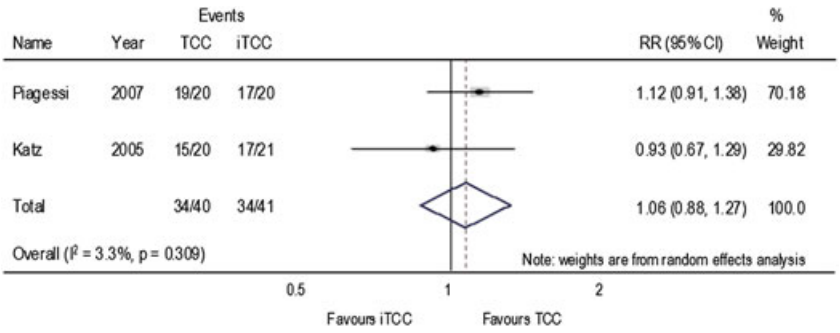

Figure 4. Forest plot showing meta-analysis of TTCs *versus* iTCCs for ulcer healing. The absolute numbers of patients with ulcers that healed in the study by Katz *et al*. [24] were inferred from the percent of patients reported to have ulcers that healed using both ITT and per-protocol analysis. iTCC, instant total contact cast; TCC, total contact cast

NRDs compared to removable off-loading devices

Meta-analysis of all studies comparing all types of non-removable devices (TCCs and iTCCs) with all types of removable devices (therapeutic shoes and RCWs) showed that, on average, there was a statistically significant difference in treatment effect (Figure 5). A significantly greater proportion of patients had ulcers that healed whilst using an NRD when compared with those using removable devices ($RR_p = 1.43$ [95% CI 1.11, 1.84]; $k = 10$). There was considerable between-study heterogeneity ($I^2 = 66.9\%$; $p = 0.001$).

Discussion

NRDs compared with off-loading with therapeutic shoes

NRDs are considered to be more effective off-loading devices than therapeutic shoes; on the basis of mechanical pressure measurements, NRDs provide 25–50% greater pressure relief to the ulcerated area than therapeutic shoes [16]. However, therapeutic shoes are easily removed, and patient non-compliance may further reduce their off-loading potential. Meta-analysis of studies that compared the use of NRDs to off-load diabetic plantar ulcers with therapeutic shoes showed that on average, there is a statistically significant difference favouring NRDs over therapeutic shoes in achieving complete ulcer healing. However, there was substantial heterogeneity between studies in the extent of treatment benefit observed (Figure 2). Patient compliance was not factored into this result, as ITT data were used in the analysis. Although the NRD used in all five studies was a TCC (with or without a window exposing the ulcer), each study used a different therapeutic shoe. Whereas a TCC has been shown to provide 80–90% peak pressure reduction compared with pressures exerted on the plantar surface of the foot in normal footwear or when barefoot [10,15], therapeutic shoes reduce peak pressure by between 38% and 64% compared with control [16,37]. Thus, it is possible that the off-loading performance of the various therapeutic shoes may have differed sufficiently to be a source of heterogeneity. However, it is more likely that the underlying cause of the observed heterogeneity was

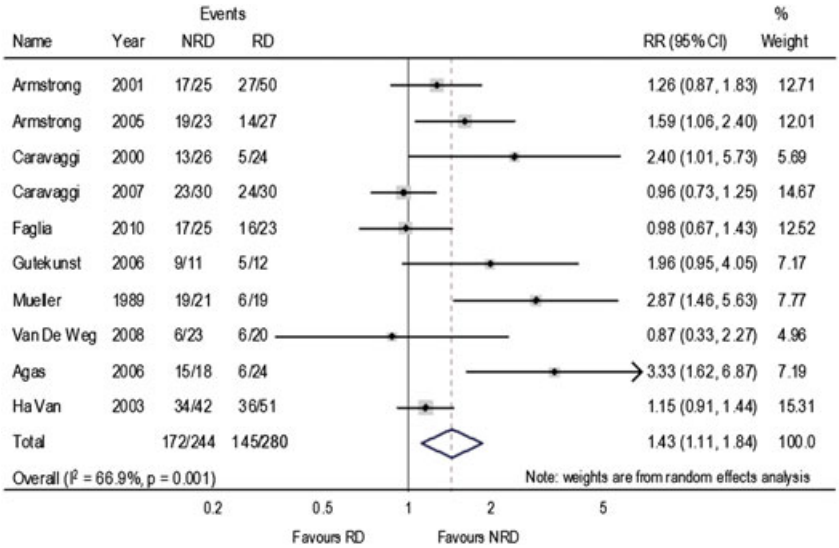

Figure 5. Forest plot showing meta-analysis of NRDs *versus* removable devices for ulcer healing. RD, removable device; NRD, non-removable device

DOI: 10.1002/dmrr

due to the characteristics of the patients involved in these studies and/or their ulcers.

The ability of a chronic wound, such as a diabetic foot ulcer, to heal depends not only on the treatment provided but also on a number of other factors, including the severity of contributing underlying disease (especially diabetes, neuropathy and peripheral arterial disease), age, obesity, nutrition, smoking, alcoholism, and compliance, as well as the duration, size, depth and grade of the ulcer [4,38–40]. The duration and size of the ulcer are most likely a reflection of the general state of health of the patient; those with poorly controlled diabetes and smokers are likely to heal more slowly. Hence, their ulcers would be expected to be larger and present for a longer duration. As the depth and grade of the ulcer increases, the likelihood of a favourable healing outcome decreases and the risk of amputation increases [4]. Systematic imbalances between trial arms on any one of these factors – particularly given the small sample sizes of these trials – could have confounded the results. However, all of the larger studies consistently showed results that favoured NRDs; so even if the magnitude of the effect has been influenced by confounding, it is probable that the direction of the effect is real.

Only one study reported on patient compliance; Ha Van *et al.* [28] found that less than half of the patients complied with the instructions for use of a half shoe, compared with almost total 'enforced' compliance in the non-removable TCC group (41% *versus* 98%; $p = 0.001$). Interestingly, Caravaggi *et al.* [7] reported that there was no significant difference in patient acceptance levels for treatment using either a TCC or a cloth shoe (88.33 ± 17.3 in the TCC group *versus* 91.15 ± 9.9 in the cloth shoe group; $p > 0.05$). It is possible that other factors affecting compliance also varied between studies.

The study by Van De Weg *et al.* [30] was the only study to include patients with infected ulcers, and nearly half the patients were receiving antibiotics in both groups, although patients who had ulcers with serious infections such as osteomyelitis (as determined by X-ray) were excluded. According to the American Diabetes Association consensus position, TCC is contraindicated for patients with infected ulcers [13], so the observed poorer outcome in patients treated with a TCC compared with those using a therapeutic shoe could be expected (26% *versus* 30% of patients with ulcers that healed, $p = 0.78$). However, a prospective cohort study by Nabuurs-Franssen *et al.* [41] found infected neuropathic ulcers treated with oral antibiotics healed almost as effectively when using a TCC for off-loading as uninfected neuropathic ulcers (87% of infected ulcers healed in 29 days compared with 90% without infection in 18 days). Thus, the overall contribution of infection to the poor outcome for patients treated with a TCC for up to 90 days in the study of Van De Weg *et al.* [30] cannot be determined.

A *post hoc* analysis by Armstrong *et al.* [14] noted that the wounds that healed within the study period were smaller at baseline than those that did not (1.1 ± 1.0 cm^2 *versus* 1.9 ± 1.3 cm^2, $p = 0.02$). In this study, there was no difference in mean wound size between the two groups at baseline and no significant difference in the proportion of patients with ulcers that healed within the 12-week study period (68% *versus* 56%, $p = 0.38$; Table S2). There were differences in ulcer size between groups in the other studies; however, as the standard deviations for ulcer size were very large in all of the studies, there were no statistically significant differences in ulcer size for any study except for Ha Van *et al.* [28]. Therefore, any variations in the proportion of large and small ulcers between groups in these studies, and the associated potential for underestimating or overestimating any treatment benefits, cannot be evaluated without individual patient data. Likewise, treatment effects associated with the location of the plantar ulcer and the suitability of specific off-loading devices for ulcers in different areas of the plantar surface cannot be evaluated. No data were available on healing outcomes with respect to plantar ulcer location in any of the included studies. However, the cohort study by Nabuurs-Franssen *et al.* [41] reported a lower percentage of healing with a cast for ulcers located at the heel compared with those located elsewhere on the plantar surface of the foot, suggesting that ulcer location may be important when selecting an off-loading device.

Felted foam off-loading dressing compared with therapeutic shoes

Zimny *et al.* [32] used a 0.158-cm layer of felt adhered to 0.635-cm thick rubber foam cut to allow clear visualization of the ulcer and to fit the plantar aspect of the foot and which was held in place with a gauze bandage. This dressing was designed to enable patients to retain a minimum of physical activity. The felted foam dressing was replaced every 3 days as a previous study showed that the felted foam effectively reduced peak plantar pressure at the ulceration site by approximately 70% for 3 days but lost its ability to provide pressure relief on day 4 [42]. This is comparable with a good therapeutic shoe, which can reduce peak pressure by up to 64% [35]. The authors found that the rate of ulcer healing favoured the felted foam off-loading dressing compared with the therapeutic shoe ($p = 0.005$). They concluded that the felted foam technique appeared to be as effective as therapeutic shoes for pressure relief and may be a useful treatment option for neuropathic diabetic foot ulcers, especially in patients who are not able to reliably avoid weight bearing.

NRDs compared with off-loading with RCWs

In theory, as the level of pressure relief offered by an NRD and an RCW are similar, their effectiveness as off-loading devices should also be similar [14]. Meta-analysis of the studies that compared the use of an NRD with RCW showed a trend favouring NRDs (Figure 3). Patient compliance is predicted to play a large role in the relative effectiveness of an NRD compared with an RCW. Armstrong

DOI: 10.1002/dmrr

et al. [43] conducted a study to evaluate the compliance and activity level of patients with diabetic foot ulcers who used an RCW for off-loading and found that the RCW was used for only 28% of total daily activity (873.7 ± 828.0 compared with 345.3 ± 219.1 daily steps with RCW; $p = 0.01$). Although the included studies that compared the use of an NRD with RCW did not report on patient compliance, Faglia *et al*. [34] suggested that the reason why the RCW was as effective as the TCC in their study was the previous ulcer history of the population making the patients more compliant in wearing the RCW. Armstrong *et al*. [14] used a pedometer to measure the difference in activity level of patients with diabetic foot ulcers and found that patients using an NRD took 22% fewer daily steps than those using an RCW (600.1 ± 320.0 compared with 767.6 ± 563.3 daily steps; $p = 0.67$) and 59% fewer steps than patients using a therapeutic shoe (600.1 ± 320.0 compared with 1461.8 ± 452.3 daily steps; $p = 0.04$). Reduced activity increases the off-loading effect of the NRD compared with removable devices; it has been previously documented that resting, with the affected limb completely off-loaded, is the most effective treatment for diabetic foot ulcers [6]. In fact, when the RCW was made irremovable, its effectiveness in treating diabetic plantar ulcers was similar to a TCC in terms of the number of ulcers healed and in time to healing ($RR_p = 1.06$ [95% CI 0.88, 1.27]) [24,31]. Thus, these studies add weight to the importance of patient compliance in effective off-loading with a removable device.

However, several practical advantages for RCWs were identified, when compared with TCCs. Rather than having the whole cast removed and replaced at each assessment, it can simply be reapplied after inspection by the health professional. Financial saving such as a plaster technician's time to put on a new cast and the cost of materials are also significantly reduced when a cast can be easily reused [34]. Some of these problems can be addressed by using a TCC with a window exposing the ulcer for easy treatment, thus negating the need for removing the cast at every assessment. Ha Van *et al*. [28] found that using a windowed TCC reduced the direct cost of TCC treatment such that the mean total cost was less than the mean total costs for treatment with the therapeutic shoe. An iTCC in which the RCW is rendered irremovable by use of some form of binding also has some advantages over a TCC. Katz *et al*. [24] and Piagessi *et al*. [31] reported that the iTCC was less expensive, faster and easier to apply and remove than a TCC as it did not require a trained cast technician (Table S2).

NRDs compared with off-loading with removable devices

Meta-analysis of the studies that compared the use of all types of NRDs (TCCs and iTCCs) with all types of removable devices (therapeutic shoes and RCWs) indicates that on average, there is a statistically significant difference favouring NRDs (Figure 4). Substantial heterogeneity was also associated with this analysis, so it is possible that the magnitude of benefit varies according to patient compliance, ulcer size or other clinical characteristics, as discussed earlier.

The prevalence of neuroischaemic foot ulcers among diabetic patients has been increasing over the past decade, currently 40–50% of all diabetic foot ulcers have a neuroischaemic aetiology compared with 35% being neuropathic [1,41]. Ischaemia in the limb as a result of either atherosclerosis or peripheral arterial disease complicates the treatment of these ulcers. However, most studies investigating the effectiveness of ulcer treatments, including those investigating off-loading devices, excluded patients with significant peripheral arterial disease [1]. Thus, treatment effectiveness outcomes for patients with neuroischaemic ulcers are largely unknown. One prospective cohort study by Nabuurs-Franssen *et al*. [41] did investigate the effectiveness of TCCs in healing diabetic foot ulcers in patients with polyneuropathy, with or without moderate peripheral arterial disease but without signs of critical limb ischaemia. Although the authors found that fewer neuroischaemic ulcers healed compared with neuropathic ulcers (69% compared with 90%, $p < 0.01$), and took longer to heal (42 days, range 14–65 days, compared with 18 days, range 10–41 days; $p < 0.05$), they concluded that casting was still an effective off-loading treatment for neuroischaemic ulcers. Thus, in addition to informing decisions on off-loading treatments as part of the clinical management of neuropathic foot ulcers, the findings in this review may provide some guidance for the use of off-loading devices in the clinical management of neuroischaemic ulcers in daily practice. Nevertheless, further studies investigating the effectiveness of off-loading devices in the treatment of neuroischaemic foot ulcers to determine their importance as part of a comprehensive treatment programme are warranted.

There is little evidence to support the supposition that TCCs are associated with more side effects, such as abrasions or ulcers caused by friction of the cast on bony protrusions, and joint rigidity and muscular atrophy caused by prolonged immobilization, and fewer infections including osteomyelitis [12]. Data that compared the use of TCC with off-loading devices made with more flexible materials found that there were no significant differences in the number of side effects or adverse events between the study groups [7,14,29,30,34]. Only Ha Van *et al*. [28], who compared a TCC (constructed using fibreglass bandages with a window exposing the ulcer) with a half shoe, reported statistically significant differences between groups. The TCC was associated with significantly more new ulcers and significantly fewer cases of osteomyelitis than the half shoe. Given this was not replicated in the other studies, it is possible that there were differences in the construction materials and designs of the TCCs and removable off-loading devices used or the technical expertise of the casting technician.

DOI: 10.1002/dmrr

Conclusions

Meta-analysis indicates that the use of NRDs results in a higher proportion of healed diabetic neuropathic plantar ulcers than removable off-loading devices. However, this result is associated with some uncertainties, particularly regarding the magnitude of effect and whether it is associated with patient compliance or certain clinical characteristics. A large RCT, with *a priori* subgroup analyses based on ulcer size, location on the plantar surface and patient compliance, is needed to lend support to the results of this meta-analysis.

Although there is some evidence to suggest that an RCW that is rendered irremovable is as effective as a TCC for treating diabetic foot ulcers, this is limited to two small RCTs. Thus, an adequately powered RCT to confirm that an RCW that is rendered irremovable and a TCC are equally effective off-loading devices as adjuncts to SWC in treating diabetic neuropathic foot ulcers should be undertaken.

There was little evidence to support the supposition that TCCs and other NRDs are associated with a higher incidence of side effects and a lower incidence of infections than removable devices.

Acknowledgements

Part-funding was provided by the Australian Government Department of Health and Ageing. Prior to this update, the original review was carried out in collaboration with Baker IDI and the George Institute. We would like to thank George Mnatzaganian and Benjamin Ellery for their help with study selection and data extraction.

Conflict of interest

The authors have no conflicts of interest.

Supporting information

Supporting information may be found in the online version of this article.

References

1. Armstrong DG, Cohen K, Courric S, Bharara M, Marston W. Diabetic foot ulcers and vascular insufficiency: our population has changed, but our methods have not. *J Diabetes Sci Technol* 2011; **5**: 1591–1595.
2. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* 1990; **13**: 513–521.
3. Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med* 1993; **233**: 485–491.
4. Armstrong DG, Lavery LA. Evidence-based options for off-loading diabetic wounds. *Clin Podiatr Med Surg* 1998; **15**: 95–104.
5. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. *N Engl J Med* 1994; **331**: 854–860.
6. Levin ME. Preventing amputation in the patient with diabetes. *Diabetes Care* 1995; **18**: 1383–1394.
7. Caravaggi C, Faglia E, De Giglio R, *et al*. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. *Diabetes Care* 2000; **23**: 1746–1751.
8. Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG. Use of pressure off-loading devices in diabetic foot ulcers: do we practice what we preach? *Diabetes Care* 2008; **31**: 2118–2119.
9. Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. *Diabetes Care* 2005; **28**: 551–554.
10. Lavery LA, Vela SA, Lavery DC, Quebedeaux TL. Reducing dynamic foot pressures in high-risk diabetic subjects with foot ulcerations: a comparison of treatments. *Diabetes Care* 1996; **19**: 818–821.
11. Cavanagh PR, Ulbrecht JS, Caputo GM. Biomechanical aspects of diabetic foot disease: aetiology, treatment, and prevention. *Diabet Med* 1996; **13**(Suppl 1): S17–22.
12. Sinacore DR. Total contact casting for diabetic neuropathic ulcers. *Phys Ther* 1996; **76**: 296–301.
13. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts: Diabetes Care 22:1354-1360, 1999.
14. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 2001; **24**: 1019–1022.
15. Gutekunst DJ, Hastings MK, Bohnert KL, Strube MJ, Sinacore DR. Removable cast walker boots yield greater forefoot off-loading than total contact casts. *Clinical Biomechanics.* 2011; **26**: 649–654.
16. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *J Vasc Surg* 2010; **52**: 37S–43S.
17. Schaff PS, Cavanagh PR. Shoes for the insensitive foot: the effect of a "rocker bottom" shoe modification on plantar pressure distribution. *Foot Ankle* 1990; **11**: 129–140.
18. Mason J, O'Keeffe C, Hutchinson A, McIntosh A, Young R, Booth A. A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. II: treatment. *Diabet Med* 1999; **16**: 889–909.
19. Spencer SA. *Pressure relieving interventions for preventing and treating diabetic foot ulcers. Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd: Chichester, UK, 2000.
20. Bus SA, Valk GD, van Deursen RW, *et al*. The effectiveness of footwear and off-loading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. *Diabetes Metab Res Rev* 2008; **24**: S162–S180.
21. Hunt D. Diabetes: foot ulcers and amputations. *Clin Evid (Online)*. 2011; **2011**.
22. Ndip A, Ebah L, Mbako A. Neuropathic diabetic foot ulcers – evidence-to-practice. *Int J Gen Med.* 2012; **5**: 129–134.
23. SIGN. SIGN 50 – A guideline developer's handbook. January 2008 edn: Scottish Intercollegiate Guidelines Network, 2008.
24. Katz IA, Harlan A, Miranda-Palma B, *et al*. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care* 2005; **28**: 555–559.
25. Stata Corporation. *Intercooled Stata 12.0 for Windows*. Stata Corporation: College City, Texas, 2011.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
27. Agas CM, Bui TD, Driver VR, Gordon IL. Effect of window casts on healing rates of diabetic foot ulcers. *J Wound Care* 2006; **15**: 80–83.
28. Ha Van G, Siney H, Hartmann-Heurtier A, Jacqueminet S, Greau F, Grimaldi A. Non-removable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance. *Diabetes Care* 2003; **26**: 2848–2852.
29. Mueller MJ, Diamond JE, Sinacore DR, *et al*. Total contact casting in treatment

of diabetic plantar ulcers. Controlled clinical trial. *Diabetes Care*. 1989; **12**: 384–388.
30. Van De Weg FB, Van Der Windt DA, Vahl AC. Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration. *Prosthet Orthot Int* 2008; **32**: 3–11.
31. Piaggesi A, Macchiarini S, Rizzo L, *et al*. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. *Diabetes Care* 2007; **30**: 586–590.
32. Zimny S, Schatz H, Pfohl U. The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers. *Diabet Med* 2003; **20**: 622–625.
33. Caravaggi C, Sganzaroli A, Fabbi M, *et al*. Nonwindowed nonremovable fiberglass off-loading cast versus removable pneumatic cast (AircastXP Diabetic Walker) in the treatment of neuropathic noninfected plantar ulcers. *Diabetes Care* 2007; **30**: 2577–2578.
34. Faglia E, Caravaggi C, Clerici G, *et al*. Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. *Diabetes Care* 2010; **33**: 1419–1423.
35. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *The Journal of Foot and Ankle Surgery*. 1996; **35**: 528–531.
36. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. *Foot & Ankle* 1981; **2**: 64–122.
37. Bus SA, van Deursen RWM, Kanade RV, *et al*. Plantar pressure relief in the diabetic foot using forefoot offloading shoes. *Gait & Posture* 2009; **29**: 618–622.
38. Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res* 2010; **89**: 219–229.
39. Margolis D, Kantor J, Santanna J, Strom B, Berlin J. Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. *Arch Dermatol* 2000; **136**: 1531–1535.
40. Oyibo SO, Jude EB, Tarawneh I, *et al*. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med* 2001; **18**: 133–138.
41. Nabuurs-Franssen MH, Sleegers R, Huijberts MS, *et al*. Total contact casting of the diabetic foot in daily practice. *Diabetes Care* 2005; **28**: 243–247.
42. Zimny S, Reinsch B, Schatz H, Pfohl M. Effects of felted foam on plantar pressures in the treatment of neuropathic diabetic foot ulcers. *Diabetes Care* 2001; **24**: 2153–2154.
43. Armstrong DG, Lavery LA, Kimbriel HR, Nixon BP, Boulton AJM. Activity patterns of patients with diabetic foot ulceration. *Diabetes Care* 2003; **26**: 2595–2597.