Improving footwear to prevent ulcer recurrence in diabetes: Analysis of adherence and pressure reduction

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Publication date
2013

Citation for published version (APA):
Waaijman, R. (2013). *Improving footwear to prevent ulcer recurrence in diabetes: Analysis of adherence and pressure reduction*.

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Chapter 6

EFFECT OF CUSTOM-MADE FOOTWEAR ON FOOT ULCER RECURRENCE IN DIABETES: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

Submitted

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ABSTRACT

Objective: Custom-made footwear is the treatment of choice to prevent foot ulcer recurrence in diabetes, and primarily aims to offload plantar regions at high ulcer risk. However, ulcer recurrence rates are high. We assessed the effect of offloading-improved custom-made footwear and the role of footwear adherence on plantar foot ulcer recurrence.

Research design and methods: We randomly assigned 171 neuropathic diabetic patients with a recently healed plantar foot ulcer to custom-made footwear with improved and subsequently preserved offloading (≈20% peak-pressure relief by modifying the footwear) or to usual care (i.e. non-improved custom-made footwear). Primary outcome was plantar foot ulcer recurrence in 18 months. Secondary outcome was ulcer recurrence in patients with an objectively measured adherence ≥80% of steps taken.

Results: Based on intention-to-treat, 33 of 85 patients (38.8%) with improved footwear and 38 of 86 patients (44.2%) with usual care had a recurrent ulcer (effect size 11%, P =.48, odds ratio 0.80, 95% confidence interval [0.44; 1.47]). Ulcer-free survival curves were not significantly different between groups (P =.40). In the 79 patients (46% of total group) with high adherence, 9 of 35 patients (25.7%) with improved footwear and 21 of 44 patients (47.8%) with usual care had a recurrent ulcer (effect size 46%, P =.045; odds ratio 0.38, 95% confidence interval [0.15; 0.99]).

Conclusions: Offloading-improved custom-made footwear does not significantly reduce the incidence of plantar foot ulcer recurrence in diabetes. However, the results suggest that this footwear can be effective when adherence is assured, which needs confirmation in future trials.

INTRODUCTION

Every 30 seconds a limb is lost somewhere in the world due to diabetes[1]. These amputations are nearly always preceded by a foot ulcer, which has a lifetime risk of 15-25% in patients with diabetes[2, 3]. Foot disorders, including ulcers, are a leading cause of hospitalization and high treatment costs in patients with diabetes[4]. Therefore, prevention of ulceration is important to decrease the large patient and economic burden of diabetic foot disease.

About half of all diabetic foot ulcers occur on the plantar foot surface and are mainly caused by elevated levels of mechanical pressure acting on the foot during ambulation in the presence of loss of protective foot sensation due to peripheral neuropathy[5, 6]. Therefore, to reduce risk of ulceration, relief of mechanical pressure (also called 'offloading') is indicated. For this purpose, custom-made therapeutic footwear is recommended and the treatment of choice, in particular for patients with foot deformity and a history of ulceration [7].

Despite widespread prescription of custom-made footwear, foot ulcers often recur[8]. A limited number of randomized trials with moderate to high probability for bias have shown inconsistent results on custom-made footwear efficacy to prevent ulcer recurrence in diabetes[7, 9-11]. These studies varied considerably in used prescription methods and shoe designs, and foot pressure was not measured. To explain clinical outcome in footwear studies, an indication for effective pressure-relief seems important as well as an accurate estimate of patient adherence to wearing prescription footwear, which we know is low in these patients[12]. High quality randomized trials on this matter are needed to better inform clinical practice[13].

Within this context, the lack of existing evidence-based prescription guidelines and the proven variation in the offloading effect of custom-made footwear designs suggests that prescription footwear is sub-optimal in relieving pressure, and should be improved to increase clinical benefit[14-16]. We recently showed that evaluation of footwear using in-shoe plantar pressure measurements can effectively guide footwear modifications to improve pressure relief in each individual patient[17]. Significant reductions in peak pressure between 17% and 52% were achieved across patients. We hypothesized that with this approach ulcer recurrence can be reduced significantly, provided that pressure reduction is maintained over time. Therefore, the objective was to examine in an intention-to-treat analysis the effect of pressure-improved custom-made footwear in comparison with usual care (i.e. non-improved custom-made footwear) on plantar foot ulcer recurrence incidence in 18 months. In addition, we evaluated whether adherence to wearing custom-made footwear influences the outcomes on ulcer recurrence.

RESEARCH DESIGN AND METHODS

Study participants

We enrolled patients from the multidisciplinary outpatient diabetic foot clinics of two academic and eight large general public hospitals across the Netherlands. Inclusion cri-

teria were: age 18 or above, confirmed type 1 of type 2 diabetes mellitus, loss of protective foot sensation due to peripheral neuropathy, a healed plantar foot ulcer (i.e. full epithelialization without exudate) in the 18 months preceding randomization, and a new prescription of custom-made footwear. Exclusion criteria were bilateral amputation proximal to the tarso-metatarsal joint, the use of walking aids that offload the foot, unlikelihood to survive 18 months follow-up, and inability to follow the study instructions. Each subject provided written informed consent before inclusion.

Study design and randomization

In this investigator-initiated parallel-group study, we randomly assigned subjects between November 2007 and October 2010 in a balanced design to custom-made footwear of which the offloading properties were improved and subsequently preserved based on in-shoe plantar pressure measurement and analysis or custom-made footwear that were not improved based on in-shoe pressure measurement (i.e. usual care). At footwear delivery, subjects were randomly assigned by the study investigator using an online accessible computer-generated allocation sequence[a] that used the non-deterministic minimization method. The allocation sequence was prepared and managed by a non-involved investigator. Participating centre and gender were used as factors for stratification. Primary outcome assessors were blinded to group assignment. Care givers and investigators were not blinded to group assignment and were instructed not to communicate treatment allocation with patients. We attempted to blind patients by measuring in-shoe plantar pressures in both study groups at equal intervals and by evaluating and modifying the footwear outside the view of patients. The study was registered in the Dutch Trial Register (Study ID NTR1091) and was approved by the medical ethical committees of all ten participating centers.

Custom-made footwear

Footwear consisted of custom-made insoles worn in custom-made shoes or in off-the-shelf (extra depth) shoes. Additional custom-made footwear, that patients already possessed at study entry or were prescribed with during follow-up, was included in the study. All footwear was prescribed by a specialist in physical and rehabilitation medicine and manufactured by an orthopedic shoe technician, both experienced in diabetic foot care. Although not enforced by any protocol, footwear design generally resembled design recommendations from a previously published algorithm[18]. Shoe lasts were created based on plaster cast molding of the foot or on foam impressions including geometrical foot measures. Blueprints of the foot were used to specify at-risk regions to be targeted. Insoles consisted of multi-layered materials, with a cork base added with micro-cork and a mid layer of multiform (mix of ethylene vinyl acetate and polyethylene). The insoles were finished with a leather, PPT[b], or Plastazote[c] top cover. Local softening, metatarsal pads, or bars could be incorporated in the insoles. The stiffened rubber or Poron[b] shoe outsole had a roller configuration.

Assessments

All study data were collected, post-processed, and entered into a database by three trained researchers to minimize variation between assessments and centers. At baseline, data on demographics, diabetes, and foot complication history were collected. Loss

of protective sensation was assessed using 10g Semmes-Weinstein monofilament and Biothesiometer[e] testing[5]. Peripheral arterial status was assessed based on the PEDIS classification[19]. Presence of foot deformity was assessed from standardized digital photographs of the foot. Barefoot dynamic plantar pressure distribution was measured at 100Hz sampling rate using an Emed-X pressure platform[d, 20]. Regional mean peak pressures over 5 steps per foot were calculated and used for analysis. Each patient received written and verbal instructions on foot care and on proper use of footwear.

All footwear in both study groups was evaluated at delivery and at three-monthly follow-up visits using the Pedar-X in-shoe pressure measurement system[d] that measured peak pressure distribution at 50Hz sampling rate at the sock-insole interface during comfortable walking[21]. In the improved-footwear group, the measured in-shoe plantar pressures guided the modification of footwear, according to a previously described algorithm[22]. In short, the previous ulcer location and, per foot, the two highest forefoot or midfoot peak pressure locations above 200kPa were identified. The footwear was modified by the shoe technician with the goal to reduce peak pressure at these regions of interest with 25%, or below an absolute level of 200kPa[17, 23]. If these criteria were not met directly, a maximum of two further rounds of modifications and pressure evaluations were applied. The choice of footwear modifications was left to the shoe technician and multiple modifications were allowed at once. At each 3-month follow-up visit, the same protocol was applied when the offloading criteria were not yet met at footwear delivery or when peak pressure at the region of interest had increased ≥5% over time.

Footwear use was measured objectively during 7 consecutive days at least three months after randomization with a temperature-based monitor[f] placed inside the shoe[12, 24]. Walking activity was measured simultaneously using a step activity monitor[g] worn around the ankle. Both monitors produced valid and reliable data[24, 25]. Average daily step count and adherence, defined as the percentage of steps over seven days that custom-made footwear was worn, were calculated.

Subjects were followed for 18 months or until plantar foot ulcer recurrence. The primary outcome was the percentage of patients with a plantar foot ulcer in 18 months. Ulcers were defined as cutaneous erosions through the dermis without reference to time present[19, 26]. Ulcers were diagnosed by three (or by five in case of disagreement) blinded and independent foot care specialists, not directly involved in the study, from digital photographs taken at or in-between follow-up visits, added with descriptions of the lesion. These specialists classified ulcers using the University of Texas system[27]. Non-ulcerative plantar lesions (i.e. hemorrhage, blister, abundant callus, or erythema) were scored from the photographs by two teams of two blinded observers who reached consensus on outcome.

Statistical analysis

Statistical analysis was performed after the last follow-up measurement in April 2012 using SPSS[h], if not otherwise mentioned. All tests assessed group effects, were two-sided, using *P* < 0.05 for significance. Baseline patient characteristics, in-shoe peak pressures at delivery, daily step count, and adherence were assessed using independent sample t-tests when data was normally distributed and Mann-Whitney U tests when

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data was not-normally distributed. In-shoe peak pressures over time were modeled by multilevel linear regression analysis using MLwiN software[i] and nested at three levels: time, patient, and centre, to account for any dependency on these factors. Fixed factors were group, time, and group-time interaction. To analyze study group effects, pressures were corrected for baseline values at study entry.

In an intention-to-treat analysis, the primary outcome was assessed using Pearson χ^2 tests. Outcome data from patients who died during the study was based on outcome at moment of death. From patients who withdrew participation, 18-month outcome data was obtained with their consent from patient files. Survival of ulcer recurrence was assessed using Kaplan-Meier plots and log-rank testing using censored data for death. χ^2 tests were conducted to test for the percentage of patients who had ulcer recurrence at the previous ulcer location and the percentage of patients with non-ulcerative lesions. Fisher's exact test was conducted for the percentage of patients with complicated foot ulcers. To assess the influence of footwear adherence on ulcer recurrence, χ^2 tests compared the primary outcome between study groups in the subgroups of patients with high adherence and with low adherence. These subgroups were determined based on a pre-statistical-analysis defined cut-off point of 80% indicated from previous studies as being an appropriate cut-off point to create similar-sized groups of high and low adherent patients[12, 28].

We anticipated an 18-month ulcer recurrence rate of 30% in the usual-care group based on estimates from the literature[8-10, 29] and 15% in the improved-footwear group based on what we considered a relevant risk reduction compared to usual care. Based on α 0.05 (one-sided), power 0.80, χ^2 analysis, and anticipated loss to follow-up of 20%, we intended to include 240 patients. Due to a lower recruitment rate in the time available, actual sample size was 171. Based on the initially anticipated recurrence rates and intention-to-treat analysis, this sample size yielded a power of 0.76 (one-sided) and 0.65 (two-sided).

RESULTS

Study participants

A study flow diagram is shown in Figure 1. The number of included subjects varied between six and 32 across participating centers. Loss to follow-up was 6%. Causes of death and reasons given to withdraw were not related to the study intervention. Of all planned 3-monthly follow-up visits, 97% took place. Of the 77 patients who were surveyed at final visit for success in patient blinding, 74 did not know the existence of two study groups or to which study group they were assigned. Baseline patient characteristics are shown in Table 1. There was no effect of sex or ethnicity on the primary and secondary outcome.

Table 1. Baseline characteristics of the subjects.

Characteristic	Improved footwear	Usual care
No. of subjects	85	86
Age (years)	62.6±10.2	63.9±10.1
Male gender (%)	82.3	82.6
Caucasian ethnicity (%)	97.6	93.0
Diabetes type 2 (%)	67.1	75.6
Diabetes duration (years) (n=169)	19.9±15.1	14.7±11.2*
Glycated haemoglobin (mmol/mol) (n=162)	58.9±15.5	59.9±16.1
Body mass index (kg/m²)	30.9±6.4	30.4±4.9

Loss of protective sensation (%)†, based on:
    Abnormal SW monofilament
    Vibration perception threshold >25V
	
	94.1
	85.2
		
		91.9
		85.9

Vibration perception threshold (V)†	50.0 (11.1)	50.0 (9.0)
Peripheral arterial disease (%) (n=160)‡	28.8	37.5
Foot deformity (%)§		
Absent	4.7	2.3
Mild	31.8	32.6
Moderate	49.4	40.7
Severe	14.1	24.4
Fully custom-made footwear (%)‖	85.9	84.9
Barefoot peak pressure at baseline (kPa)¶		
At the previous ulcer location (n=147)	675±392	780±396
At the highest pressure location (n=167)	934±294	1025±286*
In-shoe peak pressure at footwear delivery (kPa)#		
At all regions of interest >200 kPa (n=564)	269±62	273±56
Previous ulcer location > 200 kPa (n=90)	281±68	316±87*
Previous ulcer location < 200 kPa (n=139)	124±44	126±40

Data are expressed as N, percentage (%), mean ± standard deviation for normally distributed data, or median (inter-quartile range) for not-normally distributed data, for the 171 analyzed patients if not specified differently.

† Loss of protective sensation was confirmed present in both feet by the inability to sense the pressure of a 10g Semmes Weinstein monofilament at any of three plantar foot sites (hallux, first and third metatarsal head) or a vibration of 25 Volts at the hallux from a Biothesiometer (maximum measurable value 50 Volts). In 12 patients the vibration perception threshold could only be measured in one foot due to hallux amputation.

‡ Peripheral arterial disease was confirmed present when pedal pulses were non-palpable and ankle-brachial index was <0.9 in the foot with the most recent episode of ulceration, according to the PEDIS classification [19]. In five cases, peripheral arterial disease could not be assessed and in six other cases data was missing.

§ Foot deformity was classified as "absent", "mild" (i.e. pes planus, pes cavus, hallux valgus or limitus, hammer toes, and lesser toe amputation), "moderate" (i.e. hallux rigidus, hallux or ray amputation, prominent metatarsal heads, claw toes), or "severe" (i.e. Charcot deformity, (fore)foot amputation and pes equines). The foot with the most severe deformity classification determined classification per patient.

‖ Fully custom-made footwear was custom-made insoles worn in custom-made shoes. All other subjects wore custom-made insoles in off-the-shelf (extra-depth) shoes.

¶ Barefoot pressure could not be measured in four patients. In 20 more patients, the previous ulcer location was not present due to amputation.

 # Cumulative numbers for the previous ulcer location (90 and 139) add up to more than 171 because many patients had more than one pair of custom-made shoes.
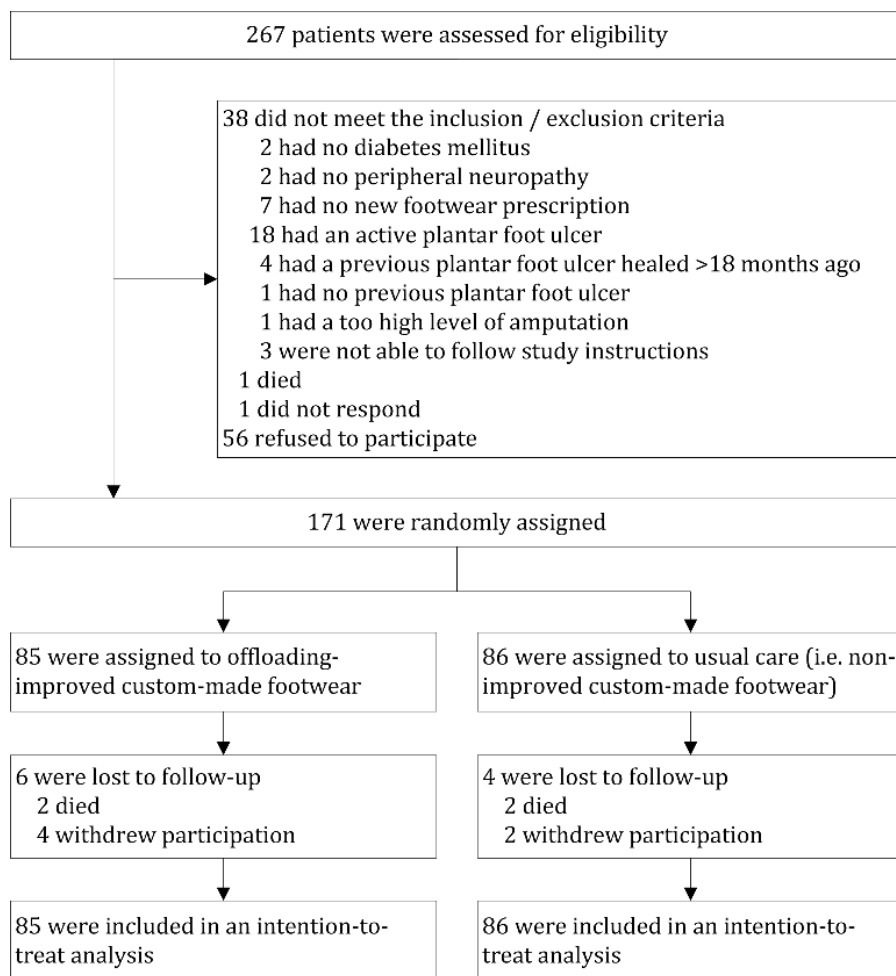
* Significantly different between groups, P < 0.05.

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┌─────────────────────────────────────────────────────────────────────┐
│                267 patients were assessed for eligibility             │
└─────────────────────────────────────────────────────────────────────┘

        ┌───────────────────────────────────────────────────────────────────┐
        │ 38 did not meet the inclusion / exclusion criteria                │
        │       2 had no diabetes mellitus                                  │
        │       2 had no peripheral neuropathy                              │
        │       7 had no new footwear prescription                          │
        │      18 had an active plantar foot ulcer                          │
        │       4 had a previous plantar foot ulcer healed >18 months ago   │
        │       1 had no previous plantar foot ulcer                        │
        │       1 had a too high level of amputation                        │
        │       3 were not able to follow study instructions               │
        │     1 died                                                        │
        │     1 did not respond                                             │
        │ 56 refused to participate                                         │
        └───────────────────────────────────────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────┐
│                     171 were randomly assigned                        │
└─────────────────────────────────────────────────────────────────────┘

┌────────────────────────────────┐      ┌────────────────────────────────┐
│ 85 were assigned to offloading-│      │ 86 were assigned to usual care │
│ improved custom-made footwear  │      │ (i.e. non-improved custom-made │
│                                │      │ footwear)                      │
└────────────────────────────────┘      └────────────────────────────────┘

┌────────────────────────────────┐      ┌────────────────────────────────┐
│ 6 were lost to follow-up       │      │ 4 were lost to follow-up       │
│   2 died                       │      │   2 died                       │
│   4 withdrew participation     │      │   2 withdrew participation     │
└────────────────────────────────┘      └────────────────────────────────┘

┌────────────────────────────────┐      ┌────────────────────────────────┐
│ 85 were included in an         │      │ 86 were included in an         │
│ intention-to-treat analysis    │      │ intention-to-treat analysis    │
└────────────────────────────────┘      └────────────────────────────────┘
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Figure 1. Study flow diagram.

In-shoe pressures and footwear modifications

At footwear delivery and over time, in-shoe peak pressures were significantly lower after modifying the footwear in the improved-footwear group when compared to the usual-care group in regions with peak pressure >200 kPa (Figure 2, Table 2). No time or group-time interaction effects were found. A total of 1183 footwear modifications in a mean 1.2 rounds of modifications per shoe pair per visit per patient were made in the improved-footwear group. In-between visits, no footwear modifications were made in the improved-footwear group. In 20 of 86 subjects from the usual-care group, a total of 33 footwear modifications were made in-between follow-up visits following usual care.

Ulcer recurrence

Of the 171 randomized patients, 71 had a recurrent plantar foot ulcer in 18 months (Table 2). In the improved-footwear group, 38.8% of patients had a recurrent ulcer,

which was not significantly different compared to the 44.2% recurrence in the usual-care group (relative risk reduction 11%, odds ratio 0.80, 95% confidence interval 0.44 to 1.47, $P = 0.48$). Ulcer survival curves were also not significantly different between study groups (Figure 3; $P = 0.40$). The improved-footwear group showed significantly less complicated foot ulcers (i.e. depth 3 or grade C, D ulcers according to Texas classification system) than the usual-care group.

Seventy-nine patients (=46% of the total group) were adherent to wearing their custom-made footwear, of which 35 were in the improved-offloading group and 44 in the usual-care group. No significant differences were found between the two study groups on baseline patient characteristics. In this subgroup of 79 adherent patients, 25.7% of patients with improved footwear had a recurrent ulcer. This was significantly lower than the 47.8% recurrence in with usual care (relative risk reduction 46%, odds ratio 0.38, 95% confidence interval 0.15 to 0.99, $P = 0.045$). Ulcer survival curves were also significantly different between study groups, in favor of the improved-footwear group (Figure 3; $P = 0.046$).
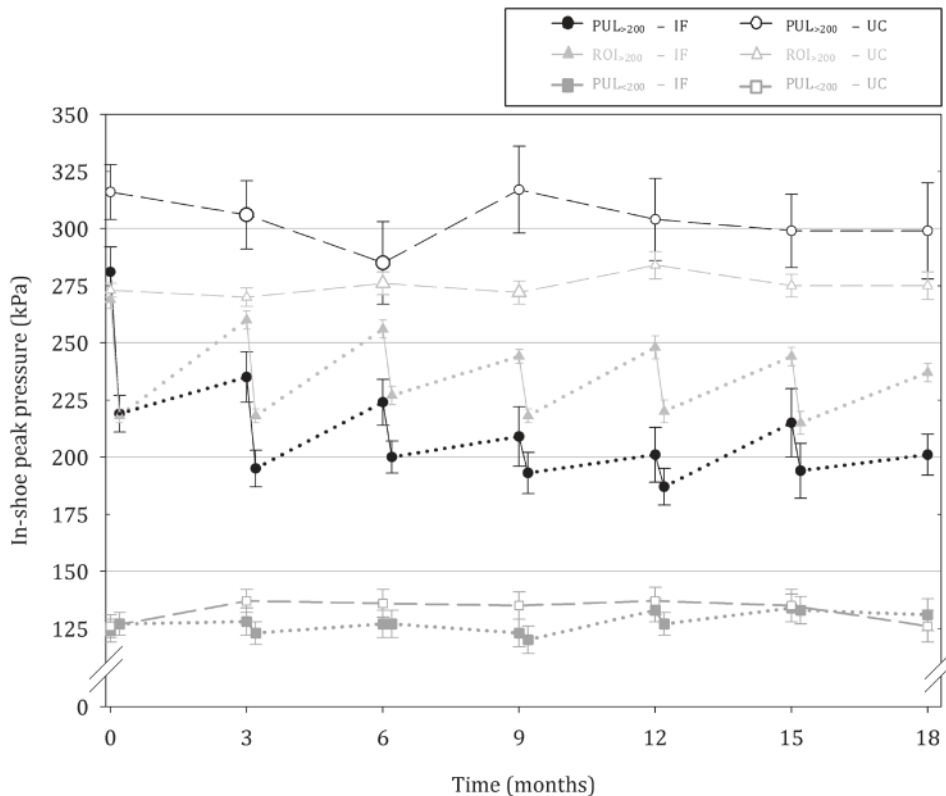
Figure 2. Mean in-shoe peak pressures over 18 months follow-up for all previous ulcer locations (PUL) with peak pressure at footwear delivery >200 kPa in black, all previous ulcer locations with peak pressure <200 kPa in dark grey, and all regions of interest (ROI) with peak pressure >200 kPa in light grey for both the improved-footwear group (IF, closed symbols) and usual-care group (UC, open symbols). Changes in peak pressure at each follow-up in the improved-footwear group are pressure changes after footwear modification. Error bars represent standard errors (SE) of the mean.

Table 2. Clinical and biomechanical outcomes.

Outcome parameter	Improved footwear	Usual care	P-value; Effect; [95%CI]†
In-shoe peak pressure at follow-up [kPa]			
All regions of interest >200 kPa (n=2648)	221±51	274±66	$P < 0.001$; β: -53; [-65; -42]
Previous ulcer locations >200 kPa (n=473)	200±47	304±101	$P < 0.001$; β: -69; [-89; -49]
Previous ulcer locations < 200 kPa (n=767)	127±44	133±42	$P = 0.17$; β: -6; [-14; 2]
Daily step count (n=157)	7287±3738	6171±3175	$P = 0.045$
Adherence (% of steps) (n=150) ‡	70.2±25.0	75.5±23.4	$P = 0.18$
Ulcer recurrence			
No. of patients with ulcer (%)	33 (38.8)	38 (44.2)	$P = 0.48$; OR: 0.80; [0.44; 1.47]
At previous ulcer location (%)	57.6	63.2	$P = 0.63$; OR: 0.79; [0.31; 2.07]
Complicated foot ulcers (%)§	0	16.2	$P = 0.027$; OR: 0.07; [0.00; 1.38]
Ulcer recurrence according to adherence‡			
No. of adherent patients	35	44	...
No. of adherent patients with ulcer (%)	9 (25.7)	21 (47.8)	$P = 0.045$; OR: 0.38; [0.15; 0.99]
No. of non-adherent patients	39	32	...
No. of non-adherent patients with ulcer (%)	16 (41.0)	11 (34.4)	$P = 0.57$; OR: 1.33; [0.50; 3.50]
Non-ulcerative lesions at follow-up			
No. of patients with a non-ulcerative lesion (%)	31 (36.5)	39 (45.3)	$P = 0.24$; OR: 0.69; [0.38; 1.28]
No. of non-ulcerative lesions	76	83	...

Data are expressed as N, percentage (%), mean ± standard deviation for normally distributed data, or median (inter-quartile range) for not-normally distributed data.
† Effect size from multi-level analysis; OR: odds ratio; CI: confidence interval.
‡ Footwear use was not measured in 21 patients because these patients dropped-out of the study before measurement (n=4), had a foot ulcer before measurement (n=5), refused measurement (n=7), or for other reasons (n=5). High adherence was a priori defined as ≥80% of steps in custom-made footwear, low adherence as <80% of steps in custom-made footwear.
§ University of Texas classification with complicated ulcers represented as depth 3 (i.e. bone contact) or grade C or D ulcers (ischemia with or without infection) [27]. Two patients were not classified, one in each study group.
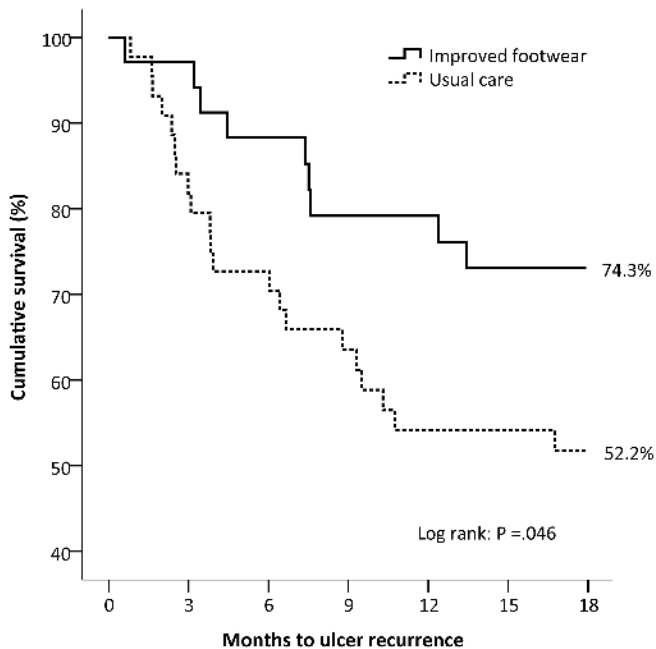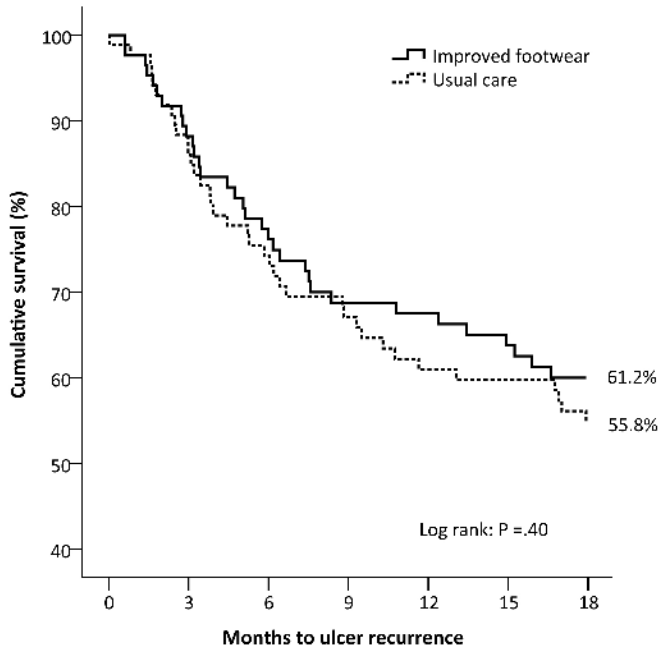
Figure 3. Kaplan-Meier plots of cumulative survival on plantar foot ulcer recurrence over 18 months follow-up with censored data for patients who died. Top diagram: intention-to-treat (N=171). Bottom diagram: the group of 79 patients (=46% of total) who were adherent to wearing custom-made footwear (i.e. ≥80% of steps taken in custom-made footwear).

Adverse events and non-ulcerative lesions

Thirty serious adverse events occurred during follow-up (four deaths, 26 hospital admissions), equally divided between groups, and none could be related to the intervention. No significant group differences were present for non-ulcerative lesions (Table 2). Of the 71 patients who reulcerated, 29 (=41%) had a non-ulcerative plantar lesion at study entry against 17 of the 100 patients (=17%) who did not reulcerate (odds ratio 3.4, 95% confidence interval 1.7 to 6.8, *P* < 0.001).

CONCLUSIONS

Among patients with diabetes, peripheral neuropathy, and a recently healed plantar foot ulcer, offloading-improved custom-made footwear showed no statistically significant protective effect against plantar foot ulcer recurrence over usual care. This unexpected outcome shows that better offloading in protective footwear is by itself not clinically beneficial. The intention-to-treat analysis was slightly underpowered, but we do not expect that inclusion of the originally anticipated number of patients would have given different outcomes. To understand (lack of) clinical success, we assessed the influence of footwear adherence, which was accurately measured using objective methods. Offloading-improved custom-made footwear significantly reduced plantar foot ulcer recurrence risk with 46% compared to usual care in the subgroup of 79 adherent patients. This suggests that improved offloading can be clinically beneficial when continuous pressure relief is guaranteed by assuring that custom-made footwear is worn. Although such a positive effect should be confirmed in future trials, for patient care this would imply a reduced risk for infection and amputation, reduced treatment costs, and preserved patient quality of life[4].

The incidence of plantar foot ulcer recurrence was higher than found in other footwear studies, confirming that we included high-risk patients who are prone to develop recurrent ulcers. Reiber et al.[10] showed 15% recurrence in two years in patients wearing custom-made footwear. However, many of their patients had foot sensation, they used a more conservative classification for ulceration, and they excluded moderate to severe foot deformity, which may explain the difference with our study. Rizzo et al.[11] reported 12% ulcer occurrence in 12 months, including patients with severe deformity, but only 20% of their studied patients had a prior foot ulcer. All patients in our study had a recently healed foot ulcer, which could leave the tissue more vulnerable for subsequent breakdown, as indicated by the high prevalence of non-ulcerative lesions at footwear delivery in patients who developed ulcer recurrence, and the quick drop in ulcer-free survival (Figure 3). Uccioli et al.[9] found comparable recurrence percentages to our study, but we assessed only plantar foot ulcers, whereas others including Uccioli et al. assessed all foot ulcers, regardless of location.

The primary goal of custom-made footwear is to protect the foot by reducing pressure at high-risk foot locations. Previous footwear trials did not identify whether intervention footwear relieved pressure more than control footwear and, therefore, what role pressure relief plays in ulcer prevention. The non-significant relative risk reduction of 11% found in our study suggests that ~20% improvement in offloading at selected regions of interest is insufficient to reduce ulcer recurrence risk. As comparison, devices found to

be successful in healing plantar diabetic foot ulcers can reduce peak pressure with more than 50% compared to a control condition[30]. Also the effect of the many repetitive cycles produced while walking unprotected on a deformed foot at high levels of barefoot pressure (see table 1 and 2 for data) may play a role. This combination of biomechanical and behavioral factors may counteract any beneficial effect that the footwear had and explain the high ulcer recurrence percentages and small effect size found. Identifying the exact cause of ulceration may shed more light on the relative role of these factors. This is difficult though. We collected data on ulcer cause from patient self-reports, but this data was not reliable enough to present and draw conclusions from.

The relative reduction of 46% in ulcer recurrence risk with using offloading-improved custom-made footwear in the group of adherent patients suggests that diabetic foot care should focus on the *combined* improvement of offloading and adherence. Footwear offloading can be improved under guidance of in-shoe pressure measurements or by using specific insole design methods[14, 15, 17, 22]. To improve adherence, the provision of offloading footwear specifically for indoor use may be effective since recent data shows that adherence in high-risk diabetic patients is much lower at home than away from home[12]. To date, patient education programs have failed to assess, let alone improve, footwear adherence and require further investigation[31]. The relatively high prevalence of non-ulcerative lesions found at footwear delivery in patients who re-ulcerated suggests that, additionally, the early recognition and treatment of these lesions could be an important contributor to prevention of ulcer recurrence.

In conclusion, our findings do not support the use of offloading-improved custom-made footwear as a single intervention to reduce the incidence of plantar foot ulcer recurrence in diabetic patients with high foot ulcer risk. However, the data suggests that a favorable and important clinical effect of offloading-improved custom-made footwear can be achieved when adherence to wearing this footwear is assured. Although future trials should confirm the positive effect of continuously worn offloading-improved footwear, based on the current findings we recommend the *combined* improvement of footwear offloading and adherence to reduce the risk of plantar foot ulcer recurrence in high-risk diabetic patients.

Suppliers

[a] TENALEA Clinical Trial Data Management System, National Cancer Institute, Amsterdam, the Netherlands

[b] PPT; Professional Protective Technology, Langer, Inc., Deer Park, New York, USA

[c] Zotefoams plc, Croydon, UK

[d] Novel, Munich, Germany

[e] Biomedical Instruments, Newbury, Ohio, USA

[f] Department of Medical Technology and Innovation, Academic Medical Center, Amsterdam, the Netherlands

[g] Orthocare Innovations LLC, Oklahoma City, OK, USA

[h] SPSS Inc., version 19.0, an IBM company, Armonk, NY, USA

[i] MLwiN software, version 2.23, Institute of Education, University of London, London, UK.

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Acknowledgements

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