Custom-made footwear in diabetes: Offloading, usability and ulcer recurrence
Arts, Marc

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 7

Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial

Diabetes Care. DOI: 10.2337/dc13-0996

© Reprinted with permission from the American Diabetes Association

SA Bus
R Waaijman
MLJ Arts
M de Haart
TE Busch-Westbroek
JG van Baal
F Nollet
ABSTRACT

Objective
Custom-made footwear is the treatment of choice to prevent foot ulcer recurrence in diabetes. This footwear 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 (relative risk -11%, odds ratio 0.80, 95% confidence interval [0.44; 1.47], p = 0.48). Ulcer-free survival curves were also not significantly different between groups (p = 0.40). 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 (relative risk -46%, odds ratio 0.38, 95% confidence interval [0.15; 0.99], p = 0.045).

Conclusions
Offloading-improved custom-made footwear does not significantly reduce the incidence of plantar foot ulcer recurrence in diabetes compared to custom-made footwear that does not undergo such improvement unless it is worn as recommended.
INTRODUCTION

Every 30 seconds a limb is lost somewhere in the world due to diabetes. These amputations are nearly always preceded by a foot ulcer, which has a lifetime risk of 15-25% in patients with diabetes. Foot disorders, including ulcers, are a leading cause of hospitalization and high treatment costs in patients with diabetes. 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. Therefore, to reduce risk of ulceration, relief of mechanical pressure (also called ‘offloading’) is indicated. For this purpose, custom-made therapeutic footwear is recommended by international guidelines and is the standard of care in the Netherlands for patients with foot deformity and a history of ulceration.

Despite widespread prescription of custom-made footwear, foot ulcers often recur. A limited number of randomized trials have shown inconsistent results on custom-made footwear efficacy to prevent ulcer recurrence in diabetes. These studies varied considerably in 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. Footwear cannot be effective if not worn, and adherence is known to be low in diabetic patients. Observational studies and one randomized trial show that only 22-29% of patients wear their prescription footwear more than 80% of daytime. High quality randomized trials are needed to better inform clinical practice about effective footwear designs and the importance of adherence in footwear effectiveness.

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. 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. 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 criteria were: age 18 or above, confirmed type 1 or 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 tarsometatarsal joint, the use of walking aids that offload the foot, severe illness that would make 18 months survival unlikely (as judged by the patients’ physician), 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 a) custom-made footwear of which the offloading properties were improved and subsequently preserved based on in-shoe plantar pressure measurement and analysis or b) custom-made footwear that did not undergo improvement based on in-shoe pressure measurement (i.e. usual care). At footwear delivery, the study investigator randomly assigned subjects using an online accessible computer-generated allocation sequence 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. Caregivers 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**
All patients received their new prescription custom-made footwear at study entry. This footwear consisted of custom-made insoles worn in custom-made shoes (i.e. fully-customized footwear, 85.4% of patients) or custom-made insoles worn in off-the-shelf (extra depth) shoes (i.e. semi-customized footwear, 14.6% of patients). Any additional pair of custom-
made footwear that patients already possessed at study entry (i.e. earlier prescriptions) or were prescribed during follow-up was included in the study. Plantar pressures were measured inside this additional footwear and, if indicated, the footwear was modified in the intervention group. In each center the local specialist in physical and rehabilitation medicine prescribed the footwear and the local orthopedic shoe technician manufactured the footwear; both professionals were experienced in diabetic foot care. There was no cross training between centers in footwear prescription or modification.

Although not enforced by any protocol, footwear design generally resembled design recommendations from a previously published algorithm. Shoe lasts for the fully customized shoes were generally created based on plaster cast molding of the foot and in some cases

Figure 7.1. Study flow diagram.
### Table 7.1. Baseline characteristics of the subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Improved footwear</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6 ± 10.2</td>
<td>63.9 ± 10.1</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>82.3</td>
<td>82.6</td>
</tr>
<tr>
<td>Caucasian ethnicity (%)</td>
<td>97.6</td>
<td>93.0</td>
</tr>
<tr>
<td>Diabetes type 2 (%)</td>
<td>67.1</td>
<td>75.6</td>
</tr>
<tr>
<td>Diabetes duration (years) (n=169)</td>
<td>19.9 ± 15.1</td>
<td>14.7 ± 11.2*</td>
</tr>
<tr>
<td>Glycated haemoglobin (% (mmol/mol)) (n=162)</td>
<td>7.5 ± 1.4 (58.9 ± 15.5)</td>
<td>7.6 ± 1.5 (59.9 ± 16.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.9 ± 6.4</td>
<td>30.4 ± 4.9</td>
</tr>
<tr>
<td>Loss of protective sensation (%)†, based on:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal SW monofilament</td>
<td>94.1</td>
<td>91.9</td>
</tr>
<tr>
<td>Vibration perception threshold &gt;25V</td>
<td>85.2</td>
<td>85.9</td>
</tr>
<tr>
<td>Vibration perception threshold (V) †</td>
<td>50.0 (11.1)</td>
<td>50.0 (9.0)</td>
</tr>
<tr>
<td>Peripheral arterial disease (%) (n=160)‡</td>
<td>28.8</td>
<td>37.5</td>
</tr>
<tr>
<td>Foot deformity (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>4.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Mild</td>
<td>31.8</td>
<td>32.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>49.4</td>
<td>40.7</td>
</tr>
<tr>
<td>Severe</td>
<td>14.1</td>
<td>24.4</td>
</tr>
<tr>
<td>Location of most recently healed foot ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallux / Digits 2-5</td>
<td>15 / 19</td>
<td>26 / 15</td>
</tr>
<tr>
<td>Metatarsal 1 / Metatarsals 2-5</td>
<td>22 / 27</td>
<td>22 / 17</td>
</tr>
<tr>
<td>Midfoot</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Custom-made footwear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully customized footwear (%)¶</td>
<td>85.9</td>
<td>84.9</td>
</tr>
<tr>
<td>First time users (%)</td>
<td>51.3</td>
<td>50.6</td>
</tr>
<tr>
<td>No. of pair per patient</td>
<td>2.06 ± 0.70</td>
<td>1.49 ± 0.63</td>
</tr>
<tr>
<td>No. of visits to a foot-care provider in-between 3-month follow-ups (n=142)¶</td>
<td>4.1 ± 2.1</td>
<td>3.5 ± 2.5</td>
</tr>
<tr>
<td>Barefoot peak pressure at baseline (kPa)#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At the previous ulcer location (n=147)</td>
<td>675 ± 392</td>
<td>780 ± 396</td>
</tr>
<tr>
<td>At the highest pressure location (n=167)</td>
<td>934 ± 294</td>
<td>1025 ± 286*</td>
</tr>
<tr>
<td>In-shoe peak pressure at footwear delivery (kPa)††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At all regions of interest &gt;200 kPa (n=564)</td>
<td>269 ± 62</td>
<td>273 ± 56</td>
</tr>
<tr>
<td>Previous ulcer location &gt; 200 kPa (n=90)</td>
<td>281 ± 68</td>
<td>316 ± 87*</td>
</tr>
<tr>
<td>Previous ulcer location &lt; 200 kPa (n=139)</td>
<td>124 ± 44</td>
<td>126 ± 40</td>
</tr>
</tbody>
</table>
Prevention of foot ulcer recurrence in diabetes

from 3D digital scans of a fiberglass cast of the foot. Insoles for these shoes consisted of multi-layered materials, generally with a cork base added with micro-cork and a mid layer of ethylene vinyl acetate-based multiform. Insoles for the semi-customized shoes were mostly manufactured by attaching a thermoplastic polyurethane-based material to a positive plaster cast of the foot that was created from static impressions of the foot in a foam box. A multiform or cork base was then added. In a minority of cases, insoles for semi-customized shoes were created from stock multiform insoles, which were individually adapted. For both footwear types, static foot pressure prints on carbon paper sheets were used to identify locations that guided any placement of a metatarsal pad or bar or additional medial arch support. Areas of interest (e.g. Charcot deformity, previous ulcer location) were regularly targeted by applying a softer, more cushioning, material at the corresponding location in the insole or by trimming the insole to create more support around the location. The insoles were finished with a Plastazote (60.8% of insoles), leather (29.3%), or PPT (9.9%) top cover. The stiffened rubber or Poron shoe outsole had a roller configuration with in the majority of cases a 1-2 cm toe-spring and a pivot point location just proximal to the offloading target. Geometric foot measures (length, circumference, instep height) were obtained and used to help obtain appropriate fit of the shoes. Patients’ preferences about style and color of the shoes were taken into account as long as biomechanical function was not jeopardized.
Chapter 7

Assessments

All study data were collected, post-processed, and entered into a database by three trained and centrally appointed researchers. 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\textsuperscript{e} testing \textsuperscript{5}. Peripheral arterial status was assessed based on the PEDIS classification \textsuperscript{21}. 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\textsuperscript{f} \textsuperscript{22}. 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\textsuperscript{1} that measured peak pressure distribution at 50Hz sampling rate at the sock-insole interface during comfortable walking \textsuperscript{23}. In the improved-footwear group the measured in-shoe plantar pressures guided the modification of footwear following a previously described protocol \textsuperscript{24}. In short, the previous ulcer location with peak pressure >200 kPa and, per foot, the two forefoot or midfoot locations that showed the highest peak pressures >200kPa were identified and targeted for pressure relief. The shoe technician modified the footwear until peak pressure at these regions of interest was reduced by 25% or below an absolute level of 200kPa (whichever was reached first), or until a maximum of three rounds of modifications and pressure evaluations were used \textsuperscript{19,25}. Choice of footwear modification was left to the shoe technician and multiple modifications were allowed within one round. At each 3-month follow-up visit, this offloading-improvement protocol was applied when the offloading criteria were not yet met at study entry or when peak pressure at the region of interest had increased ≥5% over time.

At least three months after randomization, footwear use was measured objectively during 7 consecutive days using a temperature-based monitor\textsuperscript{g} placed inside all custom-made shoes the patient had at the time of testing \textsuperscript{14,26}. Walking activity was measured simultaneously using a step activity monitor\textsuperscript{h} worn around the ankle. Both monitors produced valid and reliable data \textsuperscript{26,27}. Average daily step count and footwear adherence were calculated from these measurements. Footwear adherence was defined as the percentage of steps over seven days of recording that custom-made footwear was worn.

Subjects were followed for 18 months or until plantar foot ulceration, whichever came first. 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 \textsuperscript{21,28}. A panel of three (or, in case of disagreement, five) blinded and independently operating foot care specialists who were not directly involved in the study diagnosed the ulcer. Ulcer diagnosis was done from digital photographs of the plantar foot taken at each
follow-up visit, or in-between visits when the patient or treating physician reported the lesion, added with descriptions of the lesion. The same specialists classified ulcers using the University of Texas system. Non-ulcerative plantar lesions (i.e. hemorrhage, blister, abundant callus, or erythema) were also scored from these photographs by two teams of two blinded researchers who reached consensus on outcome. This scoring was done after the last study visit, not to influence treatment during the study.

Statistical analysis
Statistical analysis was performed after the last follow-up visit in April 2012 using SPSS, 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 footwear delivery, daily step count, and adherence were assessed using independent sample t-tests when data was normally distributed and Mann-Whitney U tests when data was not-normally distributed. In-shoe peak pressures over time were modeled by multilevel linear regression analysis using MLwiN software 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 group effects for in-shoe peak pressure over time, pressures were corrected for baseline values at study entry.

In an intention-to-treat analysis, the primary outcome was assessed using Pearson \( \chi^2 \) tests. Ulcer outcome data from patients who died during the study was based on outcome at moment of death (last observation carried forward). From patients who withdrew participation, information on ulcer outcome at 18 months 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. \( \chi^2 \) 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 to test for the percentage of patients with complicated foot ulcers (i.e. infected, ischemic). To assess the influence of footwear adherence on ulcer recurrence, \( \chi^2 \) tests compared ulcer recurrence between study groups in the subgroups of patients with high adherence and with low adherence. These subgroups were defined based on a pre-statistical-analysis defined cut-off of 80% adherence indicated from previous studies as being an appropriate cut-off to create similar-sized groups of high and low adherent patients.

We anticipated an 18-month ulcer recurrence rate of 30% in the usual-care group based on estimates from the literature and 15% in the improved-footwear group based on what we considered a relevant risk reduction compared to usual care. Based on \( \alpha 0.05 \) (one-sided), power 0.80, \( \chi^2 \) 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
### Table 7.2: Clinical and biomechanical outcomes.

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

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) 29. Two patients were not classified, one in each study group.
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 7.1. The number of included subjects varied between six and 32 across participating centers. Baseline patient characteristics are shown in Table 7.1, and in an online supplementary table for those patients who were adherent to footwear use. For those patients lost to follow-up, 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. In a random sample of 74 patients surveyed at 18 months or at ulcer recurrence for success of patient blinding, 71 did not remember the existence of two study groups or to which study group they were allocated. There was no effect of sex or ethnicity on the primary and secondary outcome.

In-shoe pressures and footwear modifications
At footwear delivery and over time, in-shoe peak pressures were significantly lower in the improved-footwear group after modifying the footwear than in the usual-care group in regions with peak pressure >200 kPa (Figure 7.2, Table 7.2). 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 study visits the footwear of the improved-footwear group was not modified, while 33 modifications were made to the footwear in 20 out of 86 usual-care group subjects following normal clinical practice.

Ulcer recurrence
Seventy-one patients (42% of the total group) had a recurrent plantar foot ulcer in 18 months (Table 7.2). 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 7.3; \( p = 0.40 \)). The improved-footwear group showed significantly less complicated foot ulcers (i.e. Texas depth 3 or grade C, D ulcers) than the usual-care group.

Seventy-nine patients, 46% of the total group, were adherent to wearing their custom-made footwear. In this subgroup, 25.7% of patients with improved footwear had a recurrent ulcer (Table 7.2). This was significantly lower than the 47.8% recurrence in the usual-care group.
group (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 7.3; \( p = 0.046 \)).

**Adverse events and non-ulcerative lesions**

Thirty serious adverse events occurred during follow-up (four deaths, 26 hospital admissions), equally divided between groups. None of these events could be related to the intervention. No significant group differences were present for non-ulcerative lesions occurring during the study (Table 7.2). 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, \( p < 0.001 \)).

![Graph](image-url)

**Figure 7.2.** 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 round symbols, all previous ulcer locations with peak pressure <200 kPa in square symbols, and all regions of interest (ROI) with peak pressure >200 kPa in triangles 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.
Figure 7.3. Kaplan-Meier plots on cumulative survival of 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: patients who were adherent to wearing custom-made footwear (i.e. ≥80% of steps taken in custom-made footwear, n=79).
Chapter 7

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 custom-made footwear that did not undergo such improvement (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. In the subgroup of adherent patients, offloading-improved custom-made footwear significantly reduced plantar foot ulcer recurrence risk with 46% compared to non-improved custom-made footwear. This suggests that improved offloading makes a clinically important difference 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, this outcome implies a reduced risk for infection and amputation, reduced treatment costs, and preserved patient quality of life.

The incidence of plantar foot ulcer recurrence (42%) was higher than found in other footware trials, which suggests that we included patients who are more prone to develop recurrent foot ulcers. Reiber et al. showed 15% recurrence in two years in patients wearing therapeutic footwear. However, many of their patients had foot sensation. These authors used a more conservative classification for ulceration and they excluded moderate to severe foot deformity. These factors may explain the difference in recurrence rates with our study. Rizzo et al. reported 12% ulcer occurrence in 12 months, including patients with severe deformity. However, 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. This is indicated by the high prevalence of non-ulcerative lesions at study entry in patients who developed ulcer recurrence, and the quick drop in ulcer-free survival (Figure 7.3). Uccioli et al. found comparable recurrence rates 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 failed to identify what role pressure relief plays in ulcer prevention because they did not measure pressure. The non-significant relative risk reduction of 11% found in our study suggests that solely improving offloading to a ≈20% peak pressure difference compared with non-improved footwear is insufficient to reduce ulcer recurrence risk. As comparison, successful healing of plantar foot ulcers often occurs in devices that reduce peak pressure between 50% and 80% compared to a control.
Prevention of foot ulcer recurrence in diabetes

condition, but such offloading effects seem unachievable in custom-made footwear. More appropriate would be to target footwear adherence since the data suggests that moderate differences in offloading of ≈20% make a clinically and statistically important difference when footwear adherence is assured. These findings suggest that footwear effectiveness is a function of both offloading and adherence.

Preventative foot care should therefore focus on the combined improvement of footwear offloading and adherence. Footwear offloading can be improved under guidance of in-shoe pressure measurements or by using footwear design methods that have been proven to be effective in relieving pressure, even though more systematic and evidence-based approaches to footwear design are still needed. To improve adherence, the provision of offloading footwear specifically for indoor use may be effective since adherence in high-risk diabetic patients is much lower when patients are at home than away from home. Reported factors for low adherence include low perceived esthetics, comfort, and therapeutic benefit of the shoes, higher BMI, and less foot deformity. To a certain extent these factors can be managed. Suggestions made to improve adherence include a) creating an acceptable style and color of footwear, b) educating and motivating the patient to wear their prescription footwear, and c) introducing technology to alert patients when shoes are not worn. The effect of these interventions on adherence has yet to be investigated. The current data can help to convince patients of the therapeutic value of their prescription footwear. The relatively high prevalence of non-ulcerative lesions found at study entry in patients who re-ulcerated suggests that, additionally, early recognition and treatment of these lesions is important in preventative foot care.

In conclusion, our findings show that offloading-improved custom-made footwear does not significantly reduce the incidence of plantar foot ulcer recurrence in diabetic patients with high foot ulcer risk compared to custom-made footwear that does not undergo such improvement unless it is worn as recommended. Although future trials should confirm the positive effect of continuously worn and adequately offloaded 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

- TENALEA Clinical Trial Data Management System, National Cancer Institute, Amsterdam, the Netherlands
- Rhenoflex GmbH, Ludwigshafen am Rhein, Germany
- Zotefoams plc, Croydon, UK
- PPT; Professional Protective Technology, Langer, Inc., Deer Park, New York, USA
- Biomedical Instruments, Newbury, Ohio, USA
- Novel GmbH, Munich, Germany
- Department of Medical Technology and Innovation, Academic Medical Center, Amsterdam, the Netherlands
- Orthocare Innovations LLC, Oklahoma City, OK, USA
- SPSS Inc., version 19.0, an IBM company, Armonk, NY, USA
- MLwiN software, version 2.23, Institute of Education, University of London, London, UK

ACKNOWLEDGEMENTS

In the DIAFOS trial, the Academic Medical Center in Amsterdam collaborated with nine other hospitals and nine orthopedic footwear companies in the Netherlands. The authors acknowledge the contribution of Ms. R. Keukenkamp (Academic Medical Center, Amsterdam) in collecting data for the study, and the following persons in recruiting patients and modifying footwear: PJA Mooren (Academic Medical Center, Amsterdam); JWE Verlouw, MD, I Ruijs, H van Wessel (Maxima Medical Centre, Veldhoven); JPJ Bakker, MD, PhD, C van den Eijnde (Medical Center Alkmaar); D Wever, MD, H Wessendorf (Medisch Spectrum Twente, Enschede); R Dahmen, MD, B Koomen (Slotervaart Hospital, Amsterdam); R Haspels (Hospital group Twente, Almelo); J Harlaar, PhD, V de Groot, MD, PhD, J Pulles (VU Medical Center, Amsterdam); WP Polomski, MD, R Lever, G du Mont (Spaarne Hospital, Hoofddorp); HGA Hacking, MD, J de Bruin (St. Antonius Hospital, Nieuwegein); H Berendsen, MD, W Custers, and I Paardekoper (Reinier de Graaf Gasthuis, Delft). Furthermore, we acknowledge the contribution of RP Michels, MD, PhD, HA Manning, CEVB Hazenberg, MD, EJ Peters, MD, PhD, and NC Schaper, MD, PhD in assessing the primary outcome in the study, and members of the Trial Steering Committee (NC Schaper, MD, PhD, F Elferink, and AL de Lange, PhD) for their valuable advice.
REFERENCES


