Chapter 8

General discussion
The general aim of this thesis was to expand the knowledge on the effectiveness of custom-made footwear to prevent plantar foot ulcer recurrence in diabetic patients, by applying objective measurements of offloading. The specific objectives in this thesis were (1) to determine the required minimum number of footsteps for reliable and valid in-shoe plantar pressure data, (2) to assess the offloading efficacy of custom-made footwear, (3) to assess the value of using in-shoe plantar pressure assessment for evaluating, improving and preserving the offloading properties of newly prescribed custom-made footwear, (4) to assess the effects of footwear modifications on in-shoe plantar pressure, (5) to assess the perceived usability of custom-made footwear, and (6) to evaluate the effectiveness of offloading-improved footwear to prevent recurrence of diabetic foot ulcers. In this Chapter, the main findings of the presented studies are discussed and issues concerning the methodology are critically reviewed. The implications of the findings for clinical practice are discussed and, finally, recommendations for further research are made.

**MAIN FINDINGS**

For assessing in-shoe plantar pressure data in diabetic patients, no guidelines were available on the minimum number of footsteps required to obtain valid and reliable in-shoe plantar pressure data. Few collected footsteps might be insufficient to assure high data quality while a large number of collected footsteps might unnecessarily increase patient’s burden and analysis time. By comparing pressures from an iterative number of steps with a reference number of 20 steps, it was shown in Chapter 2 that the required minimum number of footsteps for representative in-shoe plantar pressure data was twelve.

Conflicting results were published concerning the clinical effectiveness of custom-made footwear in the prevention of diabetic foot ulcers. A lack of adequate offloading efficacy of the footwear could play a role in this. In Chapter 3, an evaluation of in-shoe plantar pressures measured in newly delivered custom-made footwear of 171 diabetic patients with neuropathy and previous foot ulceration, showed that 39% of feet, particularly those with forefoot deformity, were not sufficiently offloaded (in-shoe plantar pressure ≥200 kPa). These results indicated that the offloading efficacy of custom-made footwear is not sufficient in many cases and should be improved.

It was demonstrated in Chapter 4 that the offloading properties of custom-made footwear could be improved, for which the use of in-shoe plantar pressure analysis was a valuable tool to guide footwear modifications. With this approach, in 85 diabetic patients at high risk for ulceration in-shoe peak pressure was reduced at high-risk foot locations with peak in-shoe pressure ≥200 kPa between 15% and 23%. Furthermore, the study showed that this improved offloading could be successfully preserved over 12 months. However, when peak
pressures were already <200 kPa, no further improvement in offloading was achieved. The described method might be of high clinical relevance as lower peak pressure reduces the risk for foot ulceration.\textsuperscript{8-10}

The offloading effect of the applied footwear modifications, described in Chapter 4, was analyzed in Chapter 5. All studied footwear modifications resulted in a significant peak pressure reduction at their target region. Combining footwear modifications generally led to larger pressure reduction than single modifications with the best result achieved for the replacement of the top cover of the insole for softer material combined with a trans-metatarsal bar in the insole. Based on the findings, an offloading effect-matrix was created that provided data-driven directions for effective footwear modification and design.

Next to adequate offloading, adherence to wearing custom-made footwear is essential in the prevention of foot ulcers in diabetic patients. However, low footwear use was reported in this patient population.\textsuperscript{11, 12} The role of the perception of the patient of their footwear might be important in this regard.\textsuperscript{13, 14} In Chapter 6 it was shown that high-risk diabetic patients perceived the usability of their custom-made footwear mostly as positive, although individual scores and priorities in usability varied considerably. Nevertheless, footwear use turned out to be low and was shown in a logistic regression analysis to be determined only by how patients perceived the benefit of their footwear.

In the Diabetic Foot Orthopedic Shoe (DIAFOS) trial, a multicenter randomized controlled trial on the effectiveness of offloading-improved custom-made footwear, presented in Chapter 7, it was shown that plantar foot ulcer recurrence after 18 months follow-up was not significantly lower when patients had improved-offloading footwear compared to usual care (no in-shoe pressure guided offloading). However, in a subgroup analysis of patients that wore their footwear in >80% of steps taken, improved-offloading footwear resulted in a significant 46% reduction in ulcer recurrence risk, indicating that offloading improved footwear could be effective if worn as recommended.

As introduced in Chapter 1, evidence for the effectiveness of custom-made footwear to prevent ulcer recurrence was meagre and conflicting results were presented in the literature.\textsuperscript{1-5} Well-designed prospective trials in which offloading was measured and the role of both offloading and adherence to wearing offloading footwear was determined were in our view needed to better inform clinical practice.\textsuperscript{15-17} It was furthermore suggested from previous work that the use objective measurements of offloading such as in-shoe pressure analysis were useful to obtain improved offloading.\textsuperscript{9, 18} In this view, the DIAFOS trial was designed and showed, together with the supportive studies, the need for offloading improvement in custom-made footwear, ways to improve and preserve offloading, and finally it was shown that offloading-improved custom-made footwear was not clinically benefi-
cial unless footwear was worn as recommended. Overall, it was concluded that adequate offloading of at-risk location and adherence to wearing footwear both are factors of paramount importance in the prevention foot ulceration. Recommendations for improvement of these factors were formulated. These findings contribute to the existing knowledge based on custom-made footwear effectiveness to prevent ulcer recurrence, and support the use of objective measurements for evaluation of prescription footwear in clinical practice.

**METHODOLOGICAL CONSIDERATIONS**

In the studies described in this thesis, with the exception of Chapter 2, use was made of data collected in the DIAFOS trial. Relevant issues regarding the methodology, strengths and weaknesses of the performed studies will be discussed in this section.

**Recruitment of high-risk diabetic patients**

In the DIAFOS trial, the included diabetic patients were at high risk for ulcer recurrence, because they had peripheral neuropathy and a recent history of plantar foot ulceration. Only a limited number of exclusion criteria were formulated. This resulted in patients with severe foot deformity such as Charcot foot and partial foot amputations being included in the study. We aimed to also include these patients because for them custom-made footwear is of paramount importance to protect their feet which cannot be fitted in off-the-shelf footwear. In several previous studies on the effectiveness of custom-made footwear, such patients were excluded, probably because the tested footwear also included standard footwear. Our results were considered as representative for at-risk diabetic patients for which preventive custom-made footwear is recommended and typically prescribed. This improved the external validity of the study results.

**Sample size**

One hundred and seventy-one patients were included in the trial, which was extensive compared to other footwear trials. This large number of patients allowed the analysis of data from subgroups for specific research questions described in Chapter 3, 4 and 6. However, due to an unexpected low number of eligible patients, the recruitment rate was lower than the anticipated 240 patients. To increase recruitment, two additional hospitals were added to the study and patient recruitment was extended with 12 months. The dropout rate was lower than the expected 20%, only 6% in 18 months, which is low compared to other footwear trials. This might result from the fact that the trial was embedded in the clinical practice of dedicated diabetic foot clinics together with intensive monitoring, and the frequent contact between the patients and the investigators.
Based on the intention-to-treat analysis in which also dropouts were analyzed, the study was slightly underpowered with a power of 0.76 (one-sided) and 0.65 (two-sided), because the targeted number of patients was not achieved. However, because of the lower than expected effect-size, together with the large impact found for footwear adherence on study outcomes, inclusion of the originally intended number patients would probably not have changed the conclusions drawn from the trial (Chapter 7). Concerning the analyses of footwear efficacy described in Chapter 3 and offloading improvement described in Chapter 4 and 5, data from the left and right foot of the patient and multiple shoe pairs per patient were pooled to increase statistical power. With this we disregarded potential interdependence between observations. Although this does not comprise an ideal approach, the large number of patients needed to obtain independent observations could not be realized. Pooling of data was therefore chosen to improve statistical power.

**(Blinded) assessment of the primary outcome**

To assure independent assessment of the primary outcome of the trial, proper blinding was considered essential. To assess presence of plantar foot ulcers, photographs that were taken of the plantar side of the foot during every visit or when an ulcer developed in-between visits, were scored by three to five independent diabetic foot experts, a method that was further refined based on the trial by Reiber et al. on footwear effectiveness. These experts were instructed about the operational definition of a foot ulcer and were blinded for treatment allocation. Although scoring of foot ulcers on photographs could introduce limitations compared to *in-vivo* evaluation, for example regarding information on skin color and foot temperature, this procedure, involving independent and multiple judgments was considered a strength of this study compared to earlier studies. For example, in one study, ulcer recurrence was assessed based on patient’s self-reports. In another study, outcome assessment was performed by the investigators, who were not blinded for treatment allocation. In other cases, the method of scoring ulcers was not reported. Moreover, in most of these studies, the definition of a foot ulcer was not clearly stated, leaving room for interpretation, or conservative definitions were used, which complicates comparison of ulcer recurrence rates between studies.

Blinding of the patients, although attempted, was not optimal because no sham or placebo intervention could be performed in this RCT. We therefore evaluated whether patients were aware of treatment allocation. Seventy-one of the 74 patients, when asked at the moment of ulceration or at the final follow-up moment at 18 months, did not know if they were allocated to the intervention group or not. This suggested that patient blinding was successful. The investigators and care providers were not blinded for treatment allocation. Therefore, great care was taken to blind the primary outcomes assessment (as shown above).
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Clinical setting
Data collection was performed in a clinical setting, mostly during regular outpatient visits and the study findings therefore reflected current clinical practice in the Netherlands. Additionally, the substantial offloading improvement achieved while using in-shoe plantar pressure measurements, without a strict protocol for footwear modification, emphasized the applicability and value of such an objective evaluation tool. Moreover, previous data showed that the offloading efficacy of custom-made footwear could be markedly improved within (on average) 53-minute testing sessions and the approach was found to be feasible in clinical practice.

However, such a setup inevitably has some limitations. First, the targeted minimum plantar pressure reductions were not always met within the maximum three rounds of footwear modifications, because the shoe technician was out of options to further modify the shoes, or because of time constraints in a busy clinic. Second, time constraints sometimes forced shoe technicians to choose quick and easy to apply modifications instead of more elaborate, probably more effective, modifications. As a consequence, several more rigorous (combinations of) modifications were applied infrequently (less than 10 times) in the study, and could therefore not be evaluated with respect to their effectiveness (Chapter 5).

Offloading improvement
Based on a proof-of-principle study, a minimum of 25% reduction in peak pressure was set out in the trial to assure sufficient contrast in pressure between the intervention and control group. To avoid a learning-effect, meaning that during the study, shoe technicians altered their way of working in the usual care group from their experiences in the intervention group, shoe technicians were not informed about the offloading effects of their last modifications made. Moreover, in the usual care group only a limited number of footwear modifications were performed in-between study visits. Finally, each of the 10 involved shoe technicians only modified the footwear of their own patients, which was a relatively low number, limiting the chance to gain and apply experience on footwear modifications per technician. It was therefore assumed that study outcomes were not affected by potential cross-over effects.

Despite the goal to improve peak pressure with 25%, only around 20% pressure relief was achieved in the trial. This reduced offloading efficacy could be due to several factors. First, 61% of prescribed footwear was already considered efficacious (peak pressure <200 kPa) at delivery (Chapter 3). This limited the room to make major improvements in offloading. Next, over time, in-shoe pressures in the intervention group often followed a ‘saw-tooth pattern’ (Figure 4.2). This could be a consequence of wear-out effects of the used materials, in particular the soft foam products (Chapter 5). Such an effect, however, was not seen in the
usual care group. Possibly, compared to the improved-offloading group, the present leather top covers in the usual care group were not replaced for a softer material due to which less wear-out effects might be expected. However, no information on peak pressure of in-between visits was available to characterize this saw-tooth pattern in relation to footwear design and should be the focus of future research (also see below).

**Subjective assessment of footwear use**
In the study described in Chapter 6, as well as in comparable studies 39, 40, footwear use was assessed based on patient reports. This could have introduced some inaccuracy as such subjective methods lack sensitivity and increase the risk of reporting bias and missing data 41-43. Moreover, some patients may have given socially desired answers to questions about footwear use 44. During the course of the trial, a temperature sensor (the @monitor) was developed to objectively assess footwear use, and was used in the RCT (Chapter 7) 45, 46. The different timing of the objective assessments of footwear use and perceived usability questionnaire restricted synchronizing these data, and therefore only the subjective data on footwear use was used in Chapter 6. The correlation between the outcomes for adherence based on the subjective and objective assessments was significant but not very strong (R = 0.377, p < 0.001), and showed slightly higher footwear use in the subjective data, confirming the presence of inaccuracy (unpublished data). The primary aim in Chapter 6, however, was to compare perceived usability scores between low-to-moderate users and scores of frequent users, instead of comparing the absolute amount of footwear use between those groups. The distribution of footwear use between low-to-moderate users and frequent users seemed to be quite similar for the objective and subjective data. These findings suggest that the study outcomes and drawn conclusions in Chapter 6 would not have been different if objective adherence data would have been used.

**CLINICAL IMPLICATIONS**
The implications of the findings for clinical practice are summarized in Textbox 8.1 and will be discussed in this section.

**Need for better offloading footwear to prevent ulcer recurrence**
The ulcer recurrence rate reported in this thesis (42% overall and 44% in the usual care group of the DIAFOS trial) was larger than expected from published annual ulcer recurrence rates in footwear trials (=30%) 5, 11. All diabetic patients tested had peripheral neuropathy and a history of foot ulceration, but many also had (severe) foot deformity. For this reason, these patients were probably at higher risk than patients in other footwear trials, of which many have excluded patients with such complications 1, 4, 22, 23. This could explain the higher
ulcer recurrence rate found in our studied population. Nevertheless, the high ulcer recurrence rate should increase awareness with diabetic foot care providers and encourage them to find ways to reduce ulcer recurrence in diabetes, for example through targeted interventions aimed at improving footwear offloading efficacy and improving adherence to wearing custom-made footwear. Suggestions how to achieve this were formulated throughout this thesis.

Offloading was often not sufficiently achieved by the prescribed footwear (Chapter 3). It was therefore emphasized that current footwear provision should be improved when the focus is on offloading the foot, using a structured and data-driven approach. The offloading-effect matrix (Chapter 5) provided such an approach to improve the initial design of custom-made footwear and effective modification if needed. Moreover, most of the feet ulcerated during the first three months of the study, which emphasized that offloading should be adequate from the very first moment that the footwear is worn by the patient. In this regard, objective evaluation with in-shoe pressure measurements is recommended to assure that proper offloading is not only provided but also maintained over time.

**Implementation of in-shoe pressure assessments in daily clinical practice**

In the RCT it was suggested that offloading improved footwear could be clinically effective on condition that it was worn. Because the in-shoe plantar pressures were mostly measured in an outpatient setting, the described protocol for assessing and improving custom-made footwear was demonstrated to be feasible in daily clinical practice, facilitating the implementation of this procedure. Based on the guidelines on the minimum required number of steps for pressure analysis (Chapter 2), the time spent on collecting and analyzing pressure data is limited to on average 53 minutes. The use of the offloading effect-matrix (Chapter 5) may improve effectiveness and save time as it provides directions for better offloading initial footwear and is expected to result in a reduced number of required footwear modifications after delivery.

**Individual evaluation**

The tested group of patients in this thesis was considered a homogenous group, with all patients having diabetes, neuropathy, and a recently healed plantar foot ulcer, however, large inter-individual differences in offloading effects and footwear efficacy were found. Such large inter-subject variations are common in footwear studies among diabetic patients. In the studies described in this thesis, this variation may partly be explained by (1) the large variety in type of foot deformity present in the study group, (2) the differences in skills among shoe technicians in modifying footwear, and (3) the lack of a useful data-driven standardized approach to footwear prescription. Concerning these factors, each pair of custom-made footwear requires objective evaluation of its offloading properties to
assure adequate offloading in each individual patient. It may be expected that a more structured and data-driven approaches to footwear prescription in combination with objective evaluation of offloading as shown in this thesis will reduce variation in offloading efficacy among individual patients.

**Adherence to wearing custom-made footwear**
Offloading-improved footwear was by itself not beneficial in preventing foot ulcer recurrence in diabetic patients. Since adherence to footwear use was found to be an important factor, it is suggested that there is a great benefit of measuring footwear adherence in clinical practice, preferably with objective methods. Such measurements should include an assessment of the reasons for non-adherence with patients, and should result in targeted interventions that aim to increase footwear adherence. Several authors have shown that footwear adherence is much lower when patients are at home than when they are outdoors. Therefore, providing specific offloading shoes for indoor use to increase adherence at home could be an effective way to improve overall adherence.

Against expectations, the patients studied in this thesis were generally positive about the usability of their custom-made shoes. Furthermore, only the perceived benefit of using custom-made footwear was significantly associated with footwear use. These findings suggest that patients who perceive low benefit of their footwear should be informed more effectively about the therapeutic value of their shoes and should be motivated more effec-
tively to actually wear their shoes, preferably for each step taken. Although aspects such as aesthetics, comfort, and shoe weight are important as they determine overall perception, improving the perceived benefit of footwear should be given the highest priority.

If the gained knowledge is effectively implemented in diabetic foot care, the above clinical implications of the results from this thesis are expected to lead to a significantly reduction in recurrent foot ulcers in diabetic patients who are at high risk for ulceration. Such a reduction would substantially reduce treatment costs, and improve patient’s health-related quality of life.

**RECOMMENDATIONS FOR FURTHER RESEARCH**

In modifying the footwear of the patients tested in the RCT, many different methods and materials were used to reduce plantar peak pressure. Some (soft-foam) products such as Plastazote (Zotefoams plc, Croydon, UK), however, are subject to wear-out effects. Over time, pressure relief followed a saw-tooth pattern (Figure 4.2). This meant that footwear often had to be modified repeatedly to maintain pressure relief over time. Unfortunately, the interval in-between study visits was too large to describe exactly how the mechanical properties of materials changed over time. Therefore, it is currently not clear how often materials should be renewed to maintain offloading over time. Clearly, more research of in-shoe pressure change over time in relation to material characteristics is required to better understand the follow-up pressure change in this study and to determine the required evaluation moments. Finally, selection or development of materials that contain both the required offloading capacity and enough sustainability is required.

In this thesis, it was suggested that the use of a more data-driven and structural approach in footwear prescription could result in better offloaded footwear at delivery, more effective prevention of foot ulcers, and less required time needed for footwear modifications. Whether the use of the offloading effect-matrix in Chapter 5 in footwear prescription results in better offloaded footwear at delivery and whether the risk for ulcer recurrence subsequently can be reduced should be investigated in future trials.

The offloading effect-matrix did not specify which modifications were most effective to offload different foot types or deformities, because not enough patients could be included in the study for such analysis. The current offloading effect-matrix showed the effect of footwear modifications in the target regions based on a measured high pressure, which should ideally be further specified for present foot deformity as the offloading effect of a given modification might be different for different structural deformities.
The pressure parameter ‘peak pressure’ was used as pressure parameter of choice and was leading in the interpretations and recommendations. Next to this parameter, several authors mentioned the importance of shear stress, a component that acts tangential to the plantar surface and that may result in limited blood flow in the foot. As a result, shear stress might be a harmful factor that causes skin breakdown. This biomechanical factor so far received only little attention, mainly because suitable technology for such measurements is currently lacking. Instruments should be developed to quantify the influence of shear stress in the development of foot ulcers. Subsequently, custom-made footwear should be evaluated in its efficacy of reducing both normal peak pressures and shear stress, and the role that these effects have on the risk for ulcer recurrence in diabetic patients.

This thesis showed that, next to assuring adequately offloading footwear, adherence is an important factor in the prevention of diabetic foot ulcers. It was shown that the perceived benefit of wearing customized shoes significantly determined footwear use. Possibly, some patients lack knowledge on the relevance to adhere to footwear and their motivation to wear the footwear is consequently low. Until now, studies concerning the effect of educational interventions in an attempt to improve adherence to diabetic treatment generally reported disappointing results. Because these patients lack adequate protective sensation, improving awareness and motivating neuropathic patients to wear their footwear (more often) may be quite a challenge. Effective interventions that aim to educate patients, to improve the understanding of the actual purpose of their shoes and to motivate them to wear their footwear, are required and should be subject of further research. Finally, it should be confirmed in further trials that recurrent foot ulceration can be effectively prevented in patients with adequately offloaded footwear when high adherence is assured.

GENERAL CONCLUSION

The general aim of this thesis was to expand the knowledge on the effectiveness of custom-made footwear for diabetic patients who are at high risk of foot ulceration, both with respect to offloading the foot and preventing foot ulcer recurrence. Offloading efficacy of custom-made therapeutic footwear was often found insufficient and required improvement. Improvement of offloading could be achieved and maintained by modifying footwear guided by in-shoe plantar pressure assessment. This thesis provided data driven directions for effective footwear modification to reduce plantar pressure. In the DIAFOS trial, it was shown that offloading-improved custom-made footwear did not significantly reduce foot ulcer recurrence rate when compared to usual care, unless adherence to footwear use was assured. It was furthermore shown that adherence to footwear was particularly low in patients who perceived a low benefit of using custom-made footwear. The findings of this thesis suggest that adequate offloading as well as footwear adherence have to be assured to
effectively prevent foot ulcer recurrence in diabetic patients with neuropathy and previous foot ulceration. The described implications for clinical practice and the recommendations for further research may, if implemented correctly, improve outcomes in diabetic patients who are at high risk of ulcer recurrence.
REFERENCES


