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PREVENTION AND PREDICTION OF FOOT ULCER RECURRENCE IN DIABETES

Wouter B. aan de Stegge

PREVENTION AND PREDICTION OF FOOT ULCER RECURRENCE IN DIABETES

Wouter Bernard aan de Stegge

Prevention and prediction of foot ulcer recurrence in diabetes
Doctoral thesis, University of Amsterdam, The Netherlands

Prevention and prediction of foot ulcer recurrence in diabetes

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Chapter 1

General introduction

In 2019, one in every eleven adults, 463 million people worldwide, had been diagnosed with diabetes mellitus (1). By 2045, this number will rise to one in ten adults, or 700 million people, according to estimates from the International Diabetes Federation (1). People with diabetes are at risk of developing numerous complications, including cardiovascular diseases, nephropathy, retinopathy and diabetic foot disease (2). With a life-time prevalence of 19-34%, one of the most common and feared complications is the development of a foot ulcer (3). More than half of these ulcers become infected (4, 5), and they are the main cause of hospitalization and lower-extremity amputation (6-8). The current global prevalence of diabetic foot ulcers is estimated at 18.6 million (4.8% of all people with diabetes), while the estimated annual prevalence of foot ulceration in the Netherlands is close to 60,000 (9). Even following successful healing, recurrent ulcers develop in roughly 40% of the people within one year and 60% within three years (3). Diabetic foot ulcers cause severe morbidity and have a negative impact on a person's mobility and quality of life (4, 10-13). In addition, the treatment of a diabetic foot ulcer costs up to 17.000€ per episode in specialized centers in Europe, placing a large burden on healthcare systems (14, 15). Prevention of foot ulceration is paramount to reduce this burden on people and healthcare systems.

IDENTIFICATION OF ULCER RISK

For ulcer prevention, insights in the pathogenesis of diabetic foot ulceration and its risk factors is important. The most common pathway of a diabetic foot ulcer is through local repetitive tissue stress from being ambulatory, in the presence of peripheral sensory neuropathy (3, 16, 17). Peripheral sensory neuropathy leads to loss of protective sensation of the feet, resulting in the inability to recognize (minor) trauma (e.g. from poor fitting shoes, thermal or mechanical injury), and increased repetitive tissue stress. Besides peripheral sensory neuropathy, the presence of peripheral motor and/or autonomic neuropathy may contribute to the development of a diabetic foot ulcer (3). Peripheral motor neuropathy causes foot deformities that lead to abnormal biomechanical loading on the foot. Decreased sweating and a dry skin caused by peripheral autonomic neuropathy stimulates the formation of (abundant) callus. Furthermore, peripheral artery disease, present in up to 25% of all people with diabetes, is also an important factor contributing to the development of diabetic foot ulceration (3, 4, 17-19).

From its pathogenesis, it is clear that loss of protective sensation, foot deformity, and peripheral artery disease are risk factors for ulceration. Other key risk factors include a previous foot ulcer and a history of amputation (17, 20, 21). Those without any of these risk factors are unlikely to develop a foot ulcer. To target treatment for ulcer prevention, people with diabetes can be stratified according to their risk of ulceration. For this, various classification systems have been developed and reported in (inter)national guidelines based on the above risk factors (22, 23) (Table 1). Both Dutch guidelines and the guidelines from the International Working Group on the Diabetic Foot (IWGDF) stratify people with loss of protective sensation in combination with a history of ulceration to being at high risk (Table 1) (22, 23). However, within this high-risk group, disease severity and ulcer risk may vary substantially (24-26). While people at high risk have a history of

ulceration, they differ in the number and the severity of ulcers developed (24, 25). Some have had only one small ulcer during their life, while others have a recent history of multiple recurrent ulcers or even several amputations. Clearly, the latter person has a higher risk to develop a foot ulcer than the former. Identification of those people who are at highest risk of ulceration within this high-risk group is important to provide appropriate preventative management strategies and to adequately allocate limited recourses.

Table 1: Risk classification systems used in international and Dutch guidelines

Ulcer Risk	IWGDF	Characteristics IWGDF	Dutch guidelines	Characteristics Dutch guidelines
Very low	Grade 0	No LOPS and no PAD	Grade 0	No LOPS and no PAD
Low	Grade 1	LOPS or PAD	Grade 1	LOPS or PAD, without signs of local increased pressure[#]
Moderate	Grade 2	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Grade 2	LOPS + PAD, or LOPS + signs of local increased pressure, or PAD + signs of local increased pressure
High	Grade 3	LOPS or PAD, *and* one or more of the following: - History of a foot ulcer - A lower-extremity amputation - End-stage renal disease	Grade 3	History of foot ulceration or amputation Inactive Charcot neuro-osteoarthropathy End-stage renal disease or dialysis

IWGDF, International Working Group on the Diabetic Foot; LOPS, loss of protective sensation; PAD, peripheral artery disease; [#]Signs of local increased pressures are defined as: abundant callus, and/ or signs of inflammation (swelling, redness or warmth), and/ or subcutaneous haemorrhages, and/ or blisters

To identify those at highest risk of ulceration, various studies have aimed to identify risk factors for ulcer recurrence (Table 2). The strongest independent risk factors reported were: a vibration perception threshold >25V (27), the presence of minor lesions (e.g. abundant callus, blisters or subcutaneous haemorrhage) (28), a previous ulcer on a plantar location of the foot (29, 30), peripheral neuropathy with lost ankle reflexes (31), and peripheral artery disease (29, 31). However, these risk factor studies are inconsistent in description and interpretation of their models, use different starting points for patient follow-up, and have not been validated. Therefore, the best combination of variables to identify the people with diabetes at highest risk of foot ulceration remains unclear.

Table 2: Risk factor studies with their identified independent risk factors for foot ulcer recurrence

Reference	Study design	Study population and characteristics	Outcome	Recurrence rate	Independent risk factors
Peters *et al.* 2007 (29)	Case series	Patients: 81 patients with DM and a foot ulcer Study duration: mean follow-up time (SD): 27.1 (9.2) months	Ulcer healing and ulcer recurrence	49 patients had a recurrent ulcer after initial healing (60.5%)	• Plantar location of the hallux of the previous ulcer (OR 10.1*) • Peripheral artery disease (OR 5.3*)
Monami *et al.* 2008 (27)	Case series	Patients: 80 patients with diabetes and a foot ulcer Study duration: patients who healed within 6 months were included in a 12-month follow-up to assess ulcer recurrence	Ulcer healing and ulcer recurrence	Of the 80 ulcers, 63 (78.8%) healed within 6 months. Of these 63 ulcers, 32 patients had a recurrent ulcer (59.3%)	• Vibration perception threshold >25 Volts# (OR: 12.05; 95% CI 2.10 – 79.90) • A score of ≥10 the Geriatric Depression Scale# (OR: 5.00; 95% CI 3.02 – 13.99)
Dubsky *et al.* 2012 (30)	Case series	Patients: 73 people with a healed foot ulcer Study duration: 3 years	Ulcer recurrence	42 (57.5%) had a recurrent ulcer	• Plantar ulcer location (OR:8.62; 95%CI 2.2 – 33.2)§ • Presence of osteomyelitis (OR: 5.17; 95%CI 1.4 – 18.7)§ • HbA1c (Glycated haemoglobin) >7.5% (OR: 4.07; 95%CI 1.1 – 15.6)§ • C-reactive Protein >5 mg/l (OR: 4.27; 95%CI 1.2 – 15.7)§
Waaijman *et al.* 2014 (28)	Data from a RCT	Patients: 171 patients with a recently healed (<18 months) plantar foot ulcer Study duration: 18 months	1) Plantar foot ulcer recurrence 2) Plantar foot ulcer recurrence suggested to be the result of unrecognized repetitive trauma	71 (41.5%) had a recurrent plantar ulcer 41 (24.0%) had a recurrent plantar ulcer suggested to be the result of unrecognized repetitive stress	Outcome 1: • The presence of minor lesions (OR: 9.06; 95%CI 2.98 – 27.57) • A variation in day-to-day stride count (OR: 0.93; 95%CI 0.89 – 0.99) • Cumulative duration of past foot ulcers (OR: 1.03; 95%CI 1.00 – 1.06) Outcome 2: • The presence of minor lesions (OR: 10.95; 95%CI 5.01 – 23.96) • An in-shoe peak pressure <200 kPa in combination with >80% adherence to this footwear (OR: 0.43; 95%CI 0.20 – 0.94) • Barefoot peak pressure (OR: 1.11; 95%CI 1.00 – 1.22), • A variation in day-to-day stride count (OR: 0.91; 95%CI 0.86 – 0.96)

Study	Type	Patients	Outcome	Results	Risk factors
Khalifa 2018 (31)	Case series	Patients: 93 patients with a healed foot ulcer Study duration: 2 years	Ulcer recurrence	57 patients had a recurrent ulcer (47.1%)	• Smokers (OR: 1.94; 95%CI 0.79 – 2.36) • Poor glycaemic control (OR:2.98; 95%CI 1.58 – 4.48) • Previous ulcer location (plantar) (OR: 1.92; 95%CI 1.07 – 3.44) • Peripheral neuropathy with lost ankle reflex (OR: 5.94; 95%CI 4.67 – 11.50) • Peripheral artery disease (OR: 6.42; 95%CI 3.88 – 18.24)
Hicks et al. 2020 (32)	Case series	Patients: 244 patients with 304 affected limbs with a healed foot ulcer Study duration: 3 years	Ulcer recurrence	Recurrent ulcer occurred in 117 limbs (38.5%)	• Abnormal proprioception (HR: 1.57; 95%CI 1.02 – 4.43) • Younger age (HR: 1.02 per year; 95%CI 1.01 –1.04)
Ogurtsova et al. 2020 (33)	Case series	Patients: 222 patients in Germany (GER) and 99 patients in Czech Republic (CR) with a foot ulcer Study duration: mean 7 years (GER) and 7.7 years (CR)	1) Ulcer recurrence for GER 2) Ulcer recurrence for CR	154 patients (GER) had a recurrent ulcer after initial healing (69%) 69 patients (CR) had a recurrent ulcer after initial healing (70%)	Outcome 1 (GER): • Renal replacement therapy (HR: 3.71; 95%CI 1.26 – 10.87) • Only 1 previous ulcer (HR: 0.62; 95%CI 0.42 – 0.92) Outcome 2 (CR): • Type 2 diabetes (HR: 2.57; 95%CI 1.18 – 5.62) • Previous ulcer healed by minor amputation (HR: 2.11; 95%CI 1.03 – 4.33)

CR, Czech Republic; GER, Germany; HR, Hazzard ratio; OR, Odds ratio, RCT; randomized controlled trial; *Confidence interval was not reported; #After adjusting for age and gender;

$Variables were assessed at the time of the previous foot ulcer

PREVENTION OF FOOT ULCER RECURRENCE

Identification of people with diabetes at the highest risk of ulcer recurrence is important, but is only the start towards prevention of ulcer recurrence, for which treatment is needed. The most recent Dutch guidelines on diabetic foot disease (published in 2017 (22)) recommend that treatment for the prevention of foot ulcers in people at high risk of ulceration consists of an integrated foot care approach that includes:

1. Preventative foot care and screening by a podiatrist and/or diabetes pedicure once every one to three months. In complex cases this can be carried out by a multidisciplinary foot care team.
2. Patient and family education provided by a physician, (diabetes) podiatrist, and/ or diabetes pedicure, addressing ulcer aetiology, risk factors for ulceration and self-care practices.
3. Ensuring routine wearing of appropriate footwear. In the presence of a foot deformity or signs of abnormal loading of the foot (e.g. abundant callus), therapeutic footwear should be considered. Therapeutic footwear includes (semi) custom-made shoes, orthopaedic appliances to footwear or podiatric insoles. Custom-made footwear should be evaluated every three to six months by a medical specialist and/or professional (e.g. orthotist, podiatrist).
4. Prescribe in patients with a history of a plantar ulcer (semi) custom-made shoes with a proven pressure relieving effect and motivate these patients to wear this footwear.
5. Considering to advise patients, as part of a self-management routine, to routinely measure their plantar foot temperature on one or more high-risk locations on the foot to identify inflammation as an early warning sign of impending ulceration.

Despite these recommendations, the risk of ulcer recurrence remains high, as mentioned above (3). There are various possible explanations for these high recurrence rates. First, many factors contributing to the first ulcer, such as the presence of peripheral sensory neuropathy, foot deformities, and, peripheral artery disease, continue to be present after ulcer healing. Second, not all recommended interventions (e.g. at-home temperature monitoring or regular evaluation of the offloading properties of custom-made footwear) are implemented in daily healthcare (24, 34). Third, when interventions are implemented in daily healthcare, patients' adherence to what is recommended is suboptimal, and this affects outcome as well (35, 36). Finally, although most recommended interventions separately are proven to be of some effect in ulcer prevention, it remains unclear if an integrated approach sufficiently reduces the risk of ulceration in high-risk people (3, 24, 37).

Regarding the first explanation, there is currently no treatment that decreases the severity of peripheral sensory neuropathy. Surgical correction of foot deformities for the prevention of ulceration has potential benefit, but has only been investigated in small studies with selected cases; more research is needed to prove both safety and efficacy (3, 37). Also, revascularization of peripheral artery disease is not primarily a preventative strategy for ulcer recurrence in people without an ulcer and critical limb ischemia. With these hard-to-modify risk factors still present after healing, one specific focus to improve preventative treatment outcomes may be patients'

self-management to early identify a foot at risk. With current technological developments, and stimulated by the need of new adjunctive ways to prevent ulcer recurrence, prevention strategies have been developed and existing ones have been improved in the area of self-management (38, 39). For example, a novel foot mat monitoring the patient's foot temperature at home (40) or foot imaging tools (41, 42) both identify signs of pre-ulcerations (i.e. abundant callus) and impending foot ulcers. Once proven (cost-)effective, such telehealth and telemedicine applications might play a pivotal role in the prevention of ulceration in high-risk people with diabetes. These telehealth and telemedicine approaches are the topic of the first part of this thesis.

Telehealth and telemedicine
Telehealth refers broadly to all electronic and telecommunications technologies and services to provide remote care and to improve the healthcare delivery system (43). Telemedicine is more specific and refers only to the practice of medicine using telecommunication to deliver remote care (43).

Several tools and applications have been developed and implemented for diagnostic and self-management purposes in people with diabetes, including the self-monitoring of glucose or screening of diabetic retinopathy (44, 45). Some (e.g. teleophtalmology) have even proved to be cost-effective (46, 47). Self-management in diabetic foot care can be hampered due to physical limitations, such as the loss of protective sensation, limited joint mobility or visual impairment, and sometimes a lack of sufficient knowledge about the disease. Despite these limitations, several telehealth and telemedicine applications have been developed to help in remote assessment, monitoring, prevention, or treatment of diabetic foot disease, including at-home foot temperature monitoring (48), foot imaging tools (49), and mobile phone/video or online technology (50). A clear overview addressing the validity, reliability, effectiveness, and costs of these telehealth and telemedicine applications is currently lacking. Therefore, one of the aims of this thesis is to systematically review the medical-scientific literature on telehealth and telemedicine applications that are used for the assessment, monitoring, prevention, and treatment of diabetic foot disease.

Plantar foot temperature
At-home monitoring of foot skin temperature is a telehealth application that has been the subject of study in the prevention of ulceration in high-risk people with diabetes. As described earlier, most diabetic foot ulcers are caused by repetitive tissue stress over an area under the foot that causes mechanical trauma that goes unnoticed due to the presence of peripheral sensory neuropathy. Repeated tissue stress supposedly leads to inflammation accompanied by local increased skin temperature, necrosis of underlying tissue (autolysis) and finally the breakdown of tissue and ulceration (51, 52); said more popularly: "the skin heats up before it breaks down" (52-54). The evidence for this skin temperature increase caused by repetitive tissue stress originates from histopathological research conducted by Manley and Darby in 1980 (51). They found that after the application of repetitive mechanical stress (10.000 repetitions of 20 pounds per square inch/day for several days) on the footpads of denervated rats, the skin temperature increased before the skin broke down; histology of these footpads also showed many inflammatory cells

and multiple small foci of necrosis before the skin broke down (51). When applying the same mechanical stress to human finger tips, Paul Brand found that several hundred repetitions were experienced by the subject as comfortable, but gradually became more painful with more repetitions (53). When subjects withdrew, the fingertip was hot, red and swollen. Furthermore, the same experiment in rats showed that when mechanical stress was continued for multiple consecutive days, skin temperatures increased more rapidly and lasted longer, supporting that the mechanism might also apply to human tissue (53).

Based on this mechanism, Lavery, Armstrong and colleagues investigated in the early 2000s, in three randomized controlled trials (RCTs), the effect of monitoring foot skin temperatures at home with the goal to help prevent foot ulceration (48, 55, 56). If temperature differences between a specific region of interest on the plantar aspect of the foot exceeded 2.2 ºC (>4ºF) for two consecutive days compared to the same region in the contralateral foot, patients were instructed to reduce ambulatory activity and to call the study nurse. The reasoning was that reducing ambulatory activity with such a 'hotspot' found, decreases the repetitive stress on the tissue, subsequently decreases inflammation, and with that helps prevent a foot ulcer from developing. The study nurse treated, if necessary, the at-risk region of the foot by removing abundant callus or by providing offloading to that specific region. A three- to ten-fold reduction in the incidence of foot ulcers over time was seen in patients who followed this temperature monitoring approach and these instructions. Based on the positive outcomes from these trials, (inter)national guidelines recommend to consider instructing high-risk people with diabetes to monitor their foot skin temperatures at home, in combination with contacting a healthcare provider and reducing ambulatory activity if hotspots are measured, to help prevent ulcer recurrence (22, 23, 37).

DIAbetic foot TEMPerature (DIATEMP) trial
Despite the demonstrated efficacy and the recommendation to consider its use in (inter)national guidelines, at-home monitoring of foot temperatures as a self-management tool is currently not implemented in Dutch healthcare. There may be several reasons for this. First, there may be a lack of generalizability of previous trial results to other settings and geographical regions. All three mentioned trials were conducted by the same research group in one geographical area in the United States. More recently, in 2015, a small pilot study from Norway found no significant reduction in incidence of ulcer recurrence in patients who followed the same study protocol (57). However, with only 41 patients included and a limited follow-up time of one year, these results should be interpreted with caution. Second, ulcer prevention guidelines were non-existent when the above mentioned trials were conducted. The effect of the intervention in current times and practices may be smaller, since the implementation of guidelines may have led to improved general foot care. Third, the burden of daily measuring foot temperature at multiple regions on the foot may be too high for people with diabetes who already monitor many aspects of their disease (e.g. glucose levels, medicine intake, footwear use). Fourth, no data has been published on the cost-effectiveness of this intervention. The extra investment in measurement devices and the costs for intensified monitoring for both the patient and healthcare provider should be evaluated to determine if the intervention is of additional value in preventative foot care. Fifth, information

about diagnostic accuracy of increased foot temperature is limited. In all previous trials on the topic, some important details were missing or only marginally reported, for example, the frequency of above-threshold temperatures (48, 55-57). Also, adherence to reducing ambulatory activity when a so-called 'hotspot' was found was only described in one RCT (56). Finally, the evidence to support the mechanism that ulcers are preceded by an increased skin temperature is meagre at best. Besides previously described histopathological research, no fundamental research on humans has been published to provide further evidence for this mechanism. In only 6 of the 18 patients who developed an ulcer in the four aforementioned RCTs, an above-threshold temperature was measured before ulceration, already showing some inconclusiveness on this matter (48, 55-57). A large case series from Frykberg et al. (40) did show that nearly all 53 ulcers that developed over time (97%) were preceded by an above-threshold skin temperature. But the average lead time from the 'hotspot' to ulceration was 37 days, questioning whether foot ulcers are immediately preceded by a hotspot. To specifically address these last issues, another aim of this thesis is to further investigate whether non-traumatic diabetic foot ulcers are (directly) preceded by above-threshold skin temperature.

To address many of the above issues, the DIAbetic foot TEMPerature (DIATEMP) trial (Netherlands Trial Register NTR5403) was set up. In this trial, people with diabetes, peripheral sensory neuropathy and a history of ulceration or a history of Charcot neuro-osteoarthropathy were randomly assigned to usual care or enhanced therapy that in addition to usual care included the at-home monitoring of foot temperatures in a similar fashion as how previous trials conducted this, with the aim to better understand what mechanisms underlie the development of recurrent foot ulcers in people with diabetes at high risk of ulceration and if their incidence can be reduced through this self-management approach in a cost-effective way.

PREDICTION OF FOOT ULCER RECURRENCE

In addition to assessing (cost-)effectiveness of at-home monitoring foot temperature to prevent diabetic foot ulcer recurrence, the DIATEMP trial will also result in a unique dataset that contains a wide variety of demographic, disease-related, behavioural and biomechanical variables from participants with diabetes, neuropathy and a history of foot ulceration. These data can be used to identify variables that estimate the risk of ulcer recurrence. As mentioned before, risk factor studies summarized in Table 2 have methodological issues. Moreover, all these studies are etiological in nature, aiming to explain whether an outcome (in this case ulcer recurrence) can reliably be attributed to a risk factor, after adjusting for confounders in a multivariate analysis. A different way to identify people who are at highest risk of ulcer recurrence within the high-risk group is by the use of prediction models (58).

Prediction models aim to estimate as accurately as possible the risk of a future outcome (in this case: ulcer recurrence), based on the individuals' clinical and non-clinical characteristics, regardless of causality between the predictor and outcome (58, 59). These models allow us to inform patients

about the future risk of developing a recurrent ulcer. They can also identify factors that might be useful as modifiable targets for intervention to decrease risk of ulcer recurrence. Additionally, prediction models guide doctors and patients in joint decision-making for preventative treatment and can be used to select suitable patients for therapy. This applies, for example, to the frequency at which high-risk people with diabetes should be screened for the purpose of identifying factors to target for foot ulcer prevention. This can determine whether once every three months a foot screening, as is recommended in the (international) guidelines, is sufficient or that a higher or lower frequency is required.

The only prediction model for foot ulceration in people with diabetes that was adequately designed and developed was reported by Crawford et al. (21, 60). Based on individual data from ten cohort studies that included participants from all risk categories, they developed and externally validated a prediction model for foot ulceration. The authors identified as predictors: a history of ulceration, inability to feel a 10-grams monofilament and absence of at least one pedal pulse (21, 60). Unfortunately, no biomechanical factors were considered as potential predictors, likely because the number of included studies with biomechanical measures was low. Furthermore, this model focussed on foot ulceration in all patients included and did not distinguish between people with diabetes stratified to high-risk (IWGDF grade 3) versus those in lower risk strata. To this date, no validated prediction models have been developed for this high-risk group. Therefore, another aim of this thesis is to predict the risk of ulcer recurrence in high-risk people with diabetes based on patient, disease-related, behavioural and biomechanical factors.

AIM OF THIS THESIS

The general aim of this thesis was to expand our knowledge and understanding on the prevention, development and prediction of foot ulcer recurrence in people with diabetes who are at high risk of developing a foot ulcer.

Specific aims:
1. To systematically review the peer-reviewed scientific literature on telehealth and telemedicine applications that are used for the assessment, monitoring, prevention, and treatment of diabetic foot disease.
2. To assess whether at-home monitoring of foot temperatures can reduce the incidence of ulcer recurrence in high-risk people with diabetes.
3. To investigate whether non-traumatic diabetic foot ulcers are (directly) preceded by above-threshold skin temperature.
4. To predict the risk of ulcer recurrence in high-risk people with diabetes based on demographic, disease-related, behavioural and biomechanical factors.

OUTLINE OF THIS THESIS

The first specific aim is addressed in **chapter 2**, presenting a systematic review of the current literature on telehealth and telemedicine applications that can be used for the assessment, monitoring, prevention and treatment of patients with diabetic foot disease. It also provides part of the rationale for the DIATEMP trial. To address the second specific aim, **chapter 3** provides the remainder of the rationale behind the DIATEMP trial and its study protocol, while **chapter 4** presents the results of the DIATEMP trial on the effectiveness of at-home monitoring of foot temperature to prevent foot ulcer recurrence in high-risk people with diabetes. The third aim is the focus of **chapter 5**, analysing temperature values of participants who developed a non-traumatic ulcer during the DIATEMP trial, exploring whether non-traumatic diabetic foot ulcers are preceded by a local increased skin temperature to support or refute the concept that "the skin heats up before it breaks down". To address the fourth and last aim, the prediction of ulcer recurrence, we developed and internally validated prediction models using data from two different RCTs. The first study (**chapter 6**) was based on data from the DIATEMP trial, containing variables that can be easily obtained in every clinical setting. The second study (**chapter 7**) was based on data from a trial on the efficacy of custom-made footwear (DIAFOS) (35) that contained demographic, disease-related, and biomechanical variables that require more advanced equipment. This study focused on the prediction of plantar foot ulcer recurrence in people with diabetes with a recently healed plantar foot ulcer. Finally, in **chapter 8**, the main findings of the studies in this thesis are discussed in the context of the currently available literature and includes a meta-analysis of RCTs on the effectiveness of the at-home monitoring of foot temperature. Furthermore, critical reflections of methodology used, implications for clinical practice and future research are described, and finally a general conclusion is provided.

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Chapter 2

Telehealth and telemedicine applications for the diabetic foot: a systematic review

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ABSTRACT

The aim of this systematic review is to assess the peer-reviewed literature on the psychometric properties, feasibility, effectiveness, costs and current limitations of using telehealth and telemedicine approaches for prevention and management of diabetic foot disease. MEDLINE/PubMed was searched for peer-reviewed studies on telehealth and telemedicine approaches for assessing, monitoring, preventing, or treating diabetic foot disease. Four modalities were formulated: dermal thermography, hyperspectral imaging, digital photographic imaging, and audio/video/online communication. Outcome measures were: validity, reliability, feasibility, effectiveness, and costs. Sixty-one studies were eligible for analysis. Three randomized controlled trials showed that handheld infrared dermal thermography as home-monitoring tool is effective in reducing ulcer recurrence risk, while one small trial showed no effect. Hyperspectral imaging has been tested in clinical settings to assess and monitor foot disease and conflicting results on its diagnostic use show that this method is still in an experimental stage. Digital photography is used to assess and monitor foot ulcers and pre-ulcerative lesions, and was found to be a valid, reliable, and feasible method for telehealth purposes. Audio/video/online communication is mainly used for foot ulcer monitoring. Two randomized controlled trials show similar healing efficacy compared with regular outpatient clinic visits, but no benefit in costs. In conclusion, several technologies with good psychometric properties are available that may be of benefit in helping to assess, monitor, prevent, or treat diabetic foot disease, but in most cases feasibility, effectiveness and cost savings still need to be demonstrated to become accepted and used modalities in diabetic foot care.

INTRODUCTION

Foot complications in patients with diabetes mellitus are worldwide a major medical, social and economic problem, with a lifetime prevalence of foot ulcers of 19-34% (1). The most devastating and costly outcome is lower limb amputation, which is nearly always preceded by a foot ulcer or frequently an infected ulcer (2, 3). Healthcare expenditure on diabetic foot care adds up to one third of total expenditure on diabetes care (4, 5), and the direct costs per episode of a foot ulcer in specialized centers in Europe is €5.000 to €17.000 (6). Prevention of these lower limb complications have major positive impact on morbidity, mortality, and patient well-being, and would lead to large savings on healthcare costs.

International guidelines recommend protective pressure-relieving footwear, patient education, self-management, and integrated foot care at regular intervals to prevent a diabetic foot ulcer (7-9). When a foot ulcer is present, monitoring of the ulcer is important to assess treatment efficacy, predict healing, and respond swiftly in case a complication such as a foot infection develops. Ulcer treatment and monitoring is most often done weekly or bi-weekly at the outpatient foot clinic. Once the foot ulcer is healed, the risk of recurrence is up to 40% in the first year (1, 10). As foot ulcers generally occur outside of the clinic, self-management may help to timely identify pre-signs of ulceration and therewith contribute to a sense of self-efficacy in patients with diabetic foot disease. Self-management, however, may be hampered when patients are physically limited because of loss of protective sensation, limited joint mobility, visual impairment or obesity, or when patients lack sufficient knowledge about the disease (11-13).

Telehealth and telemedicine applications may have value in self-monitoring of foot health status by diabetic patients, mainly for diagnostic, therapeutic, and educational purposes with the goal to improve efficiency and effectiveness of care and patient's well-being and autonomy in a world with rapidly changing socio-economic perspectives in healthcare (14). Several applications have been developed for this purpose, and include dermal thermography, foot imaging tools, and mobile phone/video or online technology. But very few applications have been implemented in diabetic foot care, which may be related to their psychometric properties, feasibility in use, or lack of effectiveness or cost-effectiveness shown. To inform the community on the current state-of-the-art and to guide development and implementation in this field, the purpose was to systematically review the peer reviewed literature on telehealth and telemedicine applications that are used for the assessment, monitoring, prevention and treatment of diabetic foot disease.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15). The population of interest (P), intervention (I) and outcomes (O) were defined, and clinical questions (PICOs) were formulated and reviewed for clinical relevance by all authors. The population of interest for this systematic review was

people with diabetes mellitus who have a foot ulcer or who are at risk of developing one. Risk of ulceration was defined according to the International Working Group on the Diabetic Foot risk stratification as a person with diabetes and with peripheral neuropathy, with or without foot deformities, peripheral artery disease or lower-extremity amputation and/or a history of foot ulceration (16). The modalities considered were any telehealth or telemedicine application, or any medical tool that may potentially serve as telehealth or telemedicine application. We formulated four modalities: dermal thermography, hyperspectral imaging, photographic imaging, and audio/video/online communication. These are defined as:

Dermal thermography
- Infrared thermography: technology detecting radiation in the infrared range of the electromagnetic spectrum (thermal sensors capture the emitted or reflected thermal radiation from objects).
- Liquid-crystal thermography: technology using (layers of) thermochromic liquid crystals, each changing colour within a determined temperature interval which can be read and which provides information concerning the temperature distribution.
- Temperature sensors based on a thermistor, an element with an electrical resistance (resistor) whose resistance changes in response to temperature.

Hyperspectral imaging
Technology that uses the near-infrared range of the electromagnetic spectrum. This can be used to quantify tissue oxygenation by measuring oxygen delivery (oxyhaemoglobin) and oxygen extraction (deoxyhemoglobin) and to generate maps of microcirculatory changes at depths of up to several centimetres.

Photographic imaging
Digital photography, either as stand-alone camera or integrated in a device

Audio/video/online communication
Telephone, video-telephone, videoconference modules, and interactive online communication platforms

The main outcomes in this systematic review were validity, reliability, feasibility, effectiveness and costs in the outcome categories of assessment, monitoring, prevention, or treatment of diabetic foot disease.

Original peer-reviewed research studies written in the English language on the population of interest were included. We included randomized controlled trials, non-randomized controlled trials, case-control studies, cohort studies, cross-sectional studies, case series, case reports and qualitative research; excluded were systematic reviews and meta-analyses. Conference proceedings were only included to search for full-article publications of the same study. We excluded studies on healthy subjects, on persons with other diseases than diabetes, or on

persons with diabetes who were not at risk for foot ulceration. We also excluded studies that had interventions that were not considered to (potentially) be a telehealth or telemedicine approach. The literature search was performed using the MEDLINE/ PubMed database on the 31st of August 2018. The search was not limited by date. The search string used is shown in Supplementary Appendix A. All included studies underwent a reference list cross-check to identify studies that were not found in the initial database search. Two reviewers (CH, WadS) independently assessed all obtained records by title and abstract for eligibility. Three reviewers (CH, WadS and SB) then independently assessed full-article copies of references that were selected based on title/abstract, to determine final eligibility for inclusion. Disagreements between reviewers were discussed and a final decision was made based on consensus.

The Scottish Intercollegiate Grouping Network (SIGN) algorithm for classifying study design was used to classify the studies (http://www.sign.ac.uk/assets/study_design.pdf). SH, WadS and SB independently assessed included studies with a (non) randomized controlled study design for methodological quality (i.e. risk of bias), using scoring sheets developed by the Dutch Cochrane Centre (www.cochrane.nl). Reviewers resolved disagreement regarding risk of bias by discussion until consensus was reached. Risk of bias was scored for each study as ++ (very low risk of bias), + (low risk of bias) or – (high risk of bias). Data were extracted from each included study and summarized in an evidence table (Supplementary Appendix B). This included study design, characteristics of the study population, type and description of intervention/diagnostic test, outcome category (assessment/monitoring, prevention or treatment), results, conclusions and limitations of each study. CH and WadS extracted the data, the other authors checked this for content and presentation. All authors thoroughly discussed the content of the evidence table.

RESULTS

A total of 1311 references were identified in the database search, of which 96 were considered eligible for inclusion based on the assessment of title and abstract. After full-article review, 61 original peer-reviewed research articles were selected for final inclusion. Figure 1 shows the PRISMA flow diagram. Table 1 shows the distribution of included articles across different types of telehealth and telemedicine approaches and different outcome categories. Risk of bias was evaluated for 7 included (non-)randomized controlled trials (Table 2). Detailed results from the 61 included articles are summarized in Supplementary Appendix B.

Figure 1: PRISMA 2009 flow diagram
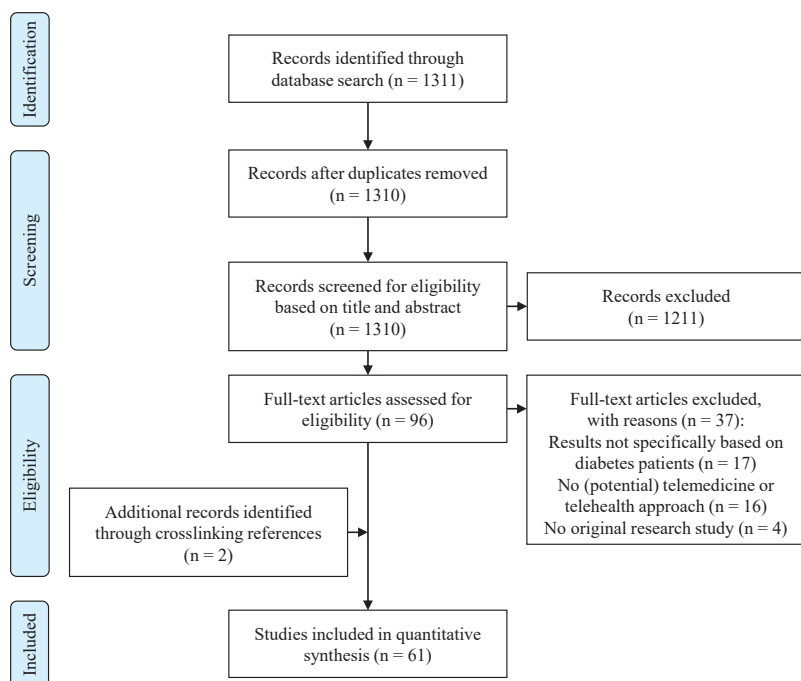
Table 1: Distribution of included studies in the systematic review across type of telehealth and telemedicine approaches and outcome category

	Number of studies	Reference
Type of approach/ technology		
Dermal thermography		
Infrared	19	(17-34, 37)
Thermistor	2	(35, 36)
Liquid-crystal	3	(38-40)
Hyperspectral imaging	11	(41-51)
Photographic imaging	13	(52-61, 63-65)
Dermal thermography + photographic imaging	1	(62)
Audio/video/online communication	12	(66-77)
Outcome		
Ulcer prevention	15	(22-26, 31-37, 39, 48, 65)
Ulcer assessment/ monitoring	27	(17, 20, 27-29, 40-47, 50-61, 63, 64)
Ulcer prevention + assessment	4	(18, 19, 38, 49)
Ulcer treatment	12	(66-77)
Assessment of infection	3	(21, 30, 62)

Table 2: Assessment of risk of bias in the included (non) randomized controlled trials

	Randomization	Independent assignment	Patient / care provider blinded	Outcome assessor blinded	Similarity groups	Withdrawal / drop-out acceptable (<20%)	Intention-to-treat	Patients treated equally except for intervention	Selective reporting ruled out	Free from commercial interest	Score
Thermography											
Lavery *et al.* 2004 (23)	?	?	-	?	+	+	+	+	+	+	6/10
Armstrong *et al.* 2007 (24)	+	+	-	+	+	?	?	+	+	+	7/10
Lavery *et al.* 2007 (25)	+	+	-	?	+	+	+	+	+	+	8/10
Skafjeld *et al.* 2015 (26)	+	?	-	?	-	+	-	+	+	+	5/10
Audio/video/online communication											
Wilbright *et al.* 2004 (69)	-	-	-	?	-	?	?	-	-	+	1/10
Rasmussen *et al.* 2015 (70)	+	+	-	?	+	+	-	+	+	+	7/10
Smith-Strøm *et al.* 2018 (73)	+	+	-	?	+	+	+	+	+	+	8/10

Dermal thermography

In one case series and two cross-sectional studies a significantly higher temperature was measured in the foot with an ulcer or Charcot arthropathy than in the contralateral foot (17-19). These results were confirmed in one other cross-sectional study (20) and case report (21). A small cross-sectional study detected latent inflammation at sites of callus in patients with diabetes using dermal thermography in combination with ultrasonography (22).

In each of four RCTs identified on the use of infrared dermal thermography to prevent ulcer recurrence, patients randomized to the intervention group measured their plantar foot temperatures at home on a daily basis at 6 locations per foot. In case a temperature difference >4°F (2.2°C) between corresponding locations on the left and right foot occurred for two consecutive days, participants were instructed to contact the study nurse and reduce their ambulatory activity until temperatures normalized. The control group in these 4 RCT's had standard follow-up and treatment, which did not include foot temperature monitoring. Lavery et al. reported in 85 patients a 6-month ulceration rate after of 2% in the intervention group versus 20% in the control group

(P=0.01, odds ratio (OR)=10.3) (23). In Armstrong et al. (24), assessing 225 patients, 18-month ulcer recurrence rates were 4.7% and 12.2% for the intervention and control group, respectively (P=0.038, OR=3.0). In Lavery et al. (25), assessing 173 patients, 15-month ulcer recurrence rates were 8.5% for the intervention group and 29.3% for controls (P=0.008, OR=4.48). In the fourth and most recent RCT, Skafjeld et al. found in a small sample of 41 patients that self-monitoring of skin temperature is feasible, but does not result in a significant reduction in 12-month ulcer recurrence rate compared to performing daily inspection of their feet 39% vs 50% (P=0.532) (26).

Van Netten et al. demonstrated in a cross-sectional study that diabetic foot complications can be distinguished using infrared temperature profiles, with feet without complications showing left-to-right temperature differences <1.5°C, those with local complications (e.g. abundant callus or neuropathic ulcer) >2°C, and those with diffuse complications (e.g. Charcot foot, infected ulcer) >3°C (27). A subsequent study by van Netten et al. found the most optimal cut-off temperature difference (2.2°C) to detect diabetes related complications to be 76% sensitive and 40% specific (28). Liu et al. demonstrated a sensitivity of 85% and a specificity of 98.4% for computer-based automated detection of foot complications (e.g. callus, blisters, redness or ulceration) using asymmetric analysis of thermal images in combination with colour imaging (29). Surprisingly, a large cohort study of 362 patients with a foot ulcer and a concomitant infection showed no significant change in left-to-right foot temperature difference (30).

Mori et al. presented in a cross-sectional study more variable thermographic patterns of the foot in patients with diabetes compared to healthy controls (31). This was explained by the individual regularity of blood supply at the angiosome level (due to stenosis of arteries or A-V shunt between angiosomes) (31). Gatt et al. found in two cross-sectional studies that the mean temperatures of the toes and forefoot were significantly higher in patients with foot complications (neuropathy, neuro-ischemia, peripheral artery disease and neuro-ischemic toe ulceration) compared to patients with no foot complications and healthy individuals (32, 33). The counterintuitive results regarding higher foot temperature in ischemic feet are suggested by the authors to be the result of an altered thermoregulation that is affected by both neuropathy and peripheral artery disease (32).

Najafi et al. tested Smart Socks, an optical-fibre-based textile that measures plantar foot temperature, plantar pressure and toe range of motion. They found a moderate agreement (r=0.58) in foot temperature changes between Smart Socks and an infrared thermal camera (34). Frykberg et al. used a wireless thermometric foot mat with temperature sensors based on a thermistor to assess plantar temperature profiles and asymmetries in 132 patients (35). In 34 weeks, a total of 53 non-traumatic diabetic foot ulcers developed in 37 (28.7%) patients, and using a temperature asymmetry threshold of 2.22°C the system correctly identified 97% of these ulcers with an average lead time of 37 days. A false-positive rate of 57% was reported (sensitivity 97%, specificity 43%) (35). A case report also showed that foot ulcers were preceded by thermal asymmetry using this thermometric foot mat (36).

In a small case series of 20 patients who measured their plantar foot temperature at six locations four times a day over 6 days follow-up, Wijlens et al. found single-day temperature differences >2.2 °C in 8.5% of all cases (37). This reduced to 0.3% with confirmation of a temperature difference >2.2°C the subsequent day, and with individually corrected temperature thresholds, this reduced further to 0.2% (37).

Using liquid-crystal thermography, Stess et al. found higher mean foot temperatures in patients with diabetes and a foot ulcer (history) compared to healthy individuals, but no temperature differences between active ulcer locations and the corresponding site on the contralateral foot (38). Benbow et al. found a significantly higher mean plantar foot temperature in neuropathic diabetic patients who went on to develop a plantar foot ulcer, compared to patients who did not develop an ulcer (39). Roback et al. found that 74% of areas classified as clinically large problem areas were identified by measured temperature differences between the feet (40).

Hyperspectral imaging

Studies used hyperspectral imaging to assess tissue oxygenation at or near the ulcer according to measured oxyhaemoglobin and deoxyhemoglobin levels. From these levels, a healing index was calculated to determine the potential for healing. Two case-control studies monitored the healing of 21 and 73 diabetic foot ulcers and reported sensitivity levels of 93% and 80%, specificity levels of 86% and 74%, and positive predictive values of 93% and 90% for ulcer healing in 6 months and 24 weeks, respectively (41, 42). Another case-control study monitored the healing of 24 diabetic foot ulcers and reported a sensitivity of 0.90, specificity of 0.86 and a positive predictive value of 82% for ulcer healing in 4 weeks (43). Four case-control studies observed a significant reduction in oxyhaemoglobin level prior to ulcer closure in those ulcers that healed, compared to unchanged oxyhaemoglobin levels in ulcers that did not heal (44-47). A negative slope in the rate of change of oxyhaemoglobin concentration was indicative for healing in all foot ulcers (44-47).

One case series analysed 21 sites that had ulcerated during follow-up and showed that the occurrence of these ulcers could be predicted using hyperspectral imaging with a sensitivity of 95% and specificity of 80% in a mean of 58 days before skin breakdown became apparent (48). The same research group reported in a case report that an increase in epidermal thickness (callus) was associated with a decrease in oxyhaemoglobin concentration prior to ulceration (49). Liu et al. showed that with hyperspectral imaging callus, ulcers and healthy skin spots could be automatically discriminated with a sensitivity of 97% and a specificity of 96% (50). In contrast with previous studies (41, 42), data from Jeffcoate et al. showed a significantly lower baseline oxygenation level in those 26 of 50 diabetic foot ulcers that healed in 12 weeks compared to the other 24 that did not heal (51).

Photographic imaging

Two cross-sectional studies showed a strong association between ulcer area measurements from photographs and those from live assessments based on ulcer boundary drawings, with correlation coefficients >0.95 (52, 53). Two other cross-sectional studies showed an inter-observer

variation in ulcer area measurements from photographs of 16% and 11.9%, compared to 27% based on live assessments (54, 55); intra-observer variation showed to be 3.3% (55). Wang et al. found a correlation of 0.68 between computer-based wound area determination and to manual annotation (56). Using support vector machines, they could determine the wound boundaries even more accurately (57). Van Netten et al. found that assessment of diabetic foot ulcers using a mobile phone compared to live assessment (as reference), gave strong support for the decision for per-wound debridement, but low interobserver reliability (kappa(k)=0.09-0.49) and a moderate intra-observer reliability (k=0.47-0.64) for assessing the presence of ischemia, infection, granulation, slough, tracking or tunnelling, moist or an exuding wound, cellulitis or erythema (58).

Bus et al. showed that with using a photographic foot imaging device intended for home use, a good agreement between live and photographic assessment (>74%) and between repeated photographic assessments (>82%) could be obtained for assessing the presence of abundant callus, ulceration and for the absence of signs (59). This was further elaborated on by Hazenberg et al. who showed good agreement between assessment from photographs and live assessment for the presence of ulcers (k=0.87) and for absence of any sign (k=0.83), and moderate agreement for the presence of abundant callus (k=0.61) (60). Outcomes were also reliable between repeated photographic assessments (k=0.70-1.00) (60). Good feasibility of using the photographic foot imaging device in the home environment was also shown: patient adherence was high, referrals based on photographic assessment justified, and perceived usability was good (61). The same authors also showed in a cross-sectional study that diagnosis of foot infection is valid and reliable using photographic imaging in combination with infrared thermography, taking clinical diagnosis as reference (sensitivity >60%, specificity >79%), and better than with using each modality on its own (62). In two case series, Foltynski et al. assessed the feasibility of at-home use of the TeleDiaFoS system for ulcer monitoring, and included: total number of assessed ulcer pictures, the length of the monitoring period, and change in ulcer area after four and 12 weeks follow-up (63, 64). A total 256 images from 10 patients were successfully sent to the Central Clinical Server and observed by the treating physician, who found changes in wound area after 12 weeks or at the end of monitoring ranging from -94.5% to +83.8% (64). Furthermore, patients perceived the usability of the system between moderate and good (63).

Most recently, Yap et al. investigated an application for a tablet to standardize acquisition of digital images for assessing and monitoring the diabetic foot, and they found a high intra- and interobserver reliability for both capturing the image of feet of diabetic patients and control feet (65).

Audio/video/online communication
Two small case series assessed the feasibility of using a mobile phone to connect the physician and home visiting nurse to support ulcer treatment (66, 67). Clemensen and Larsen et al. reported that patients were satisfied with the treatment support because it was timesaving, nurses were capable of handling the technical skills, and physicians found the equipment easy-to-use and

feasible for distance-treatment (66). Furthermore, patients were satisfied and felt safe with this remote treatment support, the visiting nurse felt supported, and physicians felt a good basis for decisions with using the tool (68). In a non-randomized controlled trial, Wilbright et al. reported no significant difference in ulcer healing between weekly telemedicine consultations using video interaction and face-to-face treatment: in 12 weeks, 75% of ulcers healed in the telemedicine group versus 81% (P=0.546) in the face-to-face treatment group (69).

The RCT by Rasmussen et al. compared the effectiveness on ulcer healing of either two telephone or online consultations in addition to one outpatient clinic visit or three outpatient clinic visits, and found no significant difference in hazard ratio for healing or amputation between these two interventions. Remarkably, they found a significantly higher mortality in the telemedicine group (P=0.0001, HR=8.68, 95%CI: 6.93-10.88) (70). In a cost-effectiveness analysis based on this RCT, Fasterholdt et al. reported that the average ulcer treatment cost per patient for the telemedicine group was €12,346 and for the control group €14,395, which was not a statistically significant difference (71). In a qualitative sub-analysis of their RCT, Rasmussen et al. concluded that the involved visiting nurses are empowered by telemedicine and that a key factor for implementing telemedicine was training of these nurses (72). However, concerns were raised regarding lack of multidisciplinary wound care teams, patient responsibility and lack of patient interaction with the physician (72).

Recently, Smith-Strøm et al. found in a cluster randomized controlled noninferiority trial that weekly telemedicine consultations of the community nurse via an interactive Web-based ulcer record and a mobile phone that enabled counselling and communication with the healthcare specialist in addition to outpatient clinic every 6 weeks, was non-inferior to visiting the outpatient clinic every second week for ulcer treatment on time to healing (mean difference -0.43 months (95%CI: -1.50–0.65)) (73). A lower proportion of patients with an amputation was found in the telemedicine group (-8.3%, 95%CI: -16.3%--0.5%) (73). Based on this RCT, four qualitative studies investigated the value of focus groups and individual semi-structured interviews of both patients and healthcare professionals (74-77). Patients from both the telemedicine and the control group mentioned that the best wound care depends on a combination of competence and professional skills in wound management and continuity of care (75). Telemedicine enabled healthcare professionals to approach their patients with more knowledge, better wound assessment skills and heightened confidence (74). Four key factors for success that were identified in using telemedicine were: technology and training must be user-friendly, the presence of someone in the work setting who can facilitate the intervention, the need for support of committed and responsible leaders and effective communication at organizational level (76). In the patient's home setting it is also important for the community nurse to have good access to the ulcer record and adequate equipment with sufficient consultation time for ulcer assessment and treatment (77).

DISCUSSION

This systematic review discusses the peer-reviewed literature on telehealth and telemedicine applications for the diabetic foot. The findings of this review show that there are several technologies available that may be of value in the assessment/monitoring, prevention, and/or treatment of diabetic foot disease. However, they require a larger scientific-base of effectiveness and/or feasibility or are still at an early stage of development and require a technically and economically more efficient approach before they can be widely deployed in the patient's home as telehealth or telemedicine tool.

Dermal thermography

Three RCTs showed that home-monitoring of foot temperatures using infrared thermography is highly effective in reducing diabetic foot ulcer recurrence incidence (23-25). These well-designed RCTs at low risk of bias were from the same research group covering the same geographical region in the US (78). A more recent small RCT from Norway did not confirm the positive findings of the three US trials, but this study was underpowered with a small sample size (26). Two recent systematic reviews suggest that the home-monitoring of foot temperature is an effective way to predict and prevent diabetic foot ulcer recurrence (78, 79). Effect sizes found were large, among the largest of any intervention that aims to prevent foot ulcer recurrence in diabetes (1, 7, 8). It is therefore quite surprising to observe that such home-monitoring is not adopted in clinical practice. This may be because of issues regarding the usability and applicability of such foot temperature monitoring at home, and specifically the use of handheld infrared thermography. Several non-contact infrared skin thermometers have large measurement errors (80). Also the TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) as used in the RCTs may show operational errors in case of presence of abundant callus or dry skin (81). Another issue is the burden on patients of performing these measurements on a daily basis, at multiple, sometimes hard to reach, locations on the foot, and including the recording and calculation of temperatures and differences between the left and right foot. One RCT reported reasons for withdrawal from the study, with 'too much to do' in the home-monitoring group being the main reason (25). This is also the experience in the ongoing DIATEMP trial from the Netherlands (81). Technological advancements in monitoring foot temperature, for example through intelligent handheld infrared thermometers, temperature monitoring through the use of special socks (82), other Smart Sox devices (34) or a thermometric foot mat (35) may reduce this burden. These devices have shown feasibility in measuring plantar foot temperature, and in the case of the foot mat has shown assessments to be predictive of foot ulceration, but the effectiveness and long-term usability of these devices in the prevention of foot ulceration is not known, limiting implementation. An important finding in observational studies investigating the value of thermal asymmetry between the left and right foot is the number of false positives (35, 37). The RCTs on infrared thermography provide limited information on false alarms and protocol compliance. A high false positive rate may demotivate patients to use these tools and may increase health-cost burden due to unnecessary visits to a healthcare professional. Furthermore, specific patient groups at high-risk may not benefit, for example because of presence of amputation, limiting the measurement of left-to-right asymmetry. Finally, apart

from local cost calculations of foot complications (83), no data have been published on the cost-effectiveness of dermal thermography. Well-designed trials are currently underway to investigate cost-effectiveness and usability (81, 84).

Regarding liquid-crystal thermography, only three small clinical studies were found on the prediction of ulceration (38, 39) and diagnosis of foot complications (40). While liquid-crystal thermography is easy-to-use and gives temperature patterns of the entire foot, interpretation of the data can be difficult, and since the year 2000 no studies have been published on the use of liquid-crystal thermography in the diabetic foot, suggesting a limited applicability.

Hyperspectral imaging

Hyperspectral imaging was mostly investigated for assessing and monitoring diabetic foot ulcers in a clinical setting (41-47, 49-51). Most of these studies included a small number of patients (41, 44-47, 49), poorly defined foot ulcers at baseline (42, 45, 48, 49, 51), and report no or limited clinical treatment/follow-up strategies (41-43, 46-48, 50, 51). A healing index based on hyperspectral data was proposed to predict the occurrence of diabetic foot ulcers, however this healing index was retrospectively determined and poorly defined (41, 42). Weingarten et al. described an easier method to predict ulcer healing, but in a small subgroup analysis (43). Additionally, contradicting outcomes from hyperspectral imaging studies have been reported. Previous studies from Nouvong et al. and Khaodhiar et al. showed that oxygenation levels at baseline were higher in ulcers that healed compared to non-healing ulcers, while the most recent study from Jeffcoate et al. showed that healed ulcers had a significantly lower baseline oxygenation level compared to non-healing ulcers (41, 42, 51). Jeffcoate et al. postulate, with limited supporting evidence, that microvascular disease can reduce oxygen delivery to extravascular tissues because of thickening of the basement membrane, so that intravascular haemoglobin rises (51). Secondly, according to the authors, microvascular shunting caused by vasomotor neuropathy might reduce oxygen delivery to extravascular tissue and raise oxyhaemoglobin at microvascular level (51). These conflicting results show that the use of hyperspectral imaging as diagnostic and monitoring tool in diabetic foot disease is still in its infancy and both basic science and clinical effectiveness studies are needed. Furthermore, hyperspectral imaging is currently an experimental and expensive technique, only studied in the clinical setting; effective applications for the home environment are far from being developed.

Photographic imaging

For digitally measuring ulcer area (52-57), photographic imaging is a feasible and applicable tool. Four studies on the measurement of foot ulcer area included a large number of diabetic foot ulcers (20 – 56 cases) to draw relevant conclusions from (52-55).

Two photographic imaging devices, the one used by Hazenberg et al. (61), and the TeleDiaFos system (63, 64), show to be feasible for use in the home environment. The feasibility analysis with the TeleDiaFoS system was done in a small group of relatively young patients and patient characteristics were not reported (63, 64). The feasibility analysis on the photographic foot

imaging device used by Hazenberg et al. included a larger patient sample, but the 4 month follow-up was too short for a sufficient number of foot complications to develop and, therefore, to study feasibility in a robust way (61). A limitation of both systems is that only the plantar foot surface can be assessed.

While two studies suggest that with photographic foot imaging diabetic foot ulcers can be reliably assessed (59, 60), the diagnosis of abundant callus proves to be moderately reliable and the studies were too small to reliably assess other important signs such as blisters, fissures and erythema. The same research group showed that the combination of photographic imaging and infrared thermography improves accuracy over a single modality alone in the diagnosis of diabetic foot infection (62). This is the first time that home-monitoring approaches for the early diagnosis of foot infection have been presented.

More recently, Van Netten et al. concluded that there was a low interobserver and moderate intraobserver reliability in the diagnosis of a variety of diabetic foot problems based on mobile phone images (58). Overall, these findings suggest that digital (mobile phone) images have applicability in some areas of assessment of pre-signs of ulceration, but are limited in use in others. Future research should show the validity and reliability of photographic foot imaging in assessing blisters, fissures and erythema and should investigate the effectiveness of this tool.

Audio/video/online communication
Audio, video and online communication as telemedicine support tool has received quite some recent attention in the scientific literature. Two well-designed RCTs show that this form of telemedicine is feasible and as effective as regular outpatient clinic visits in ulcer management (70, 73). The significant higher mortality rate found by Rasmussen et al. in the telemedicine group could not be explained by the authors (70).

Both above-mentioned research groups study groups investigated qualitative aspects of telemedicine in five studies and identified key factors for successful implementation of audio, video, and/or online communication as telemedicine support tool (72, 74-77). Sufficient training of home-care nurses to increase their competence level, followed by continuity of care is essential for both nurses and patients. This is also shown by a prematurely terminated RCT in France, in which a lack of specialized nurses and a lack of confidence by healthcare providers in the telemedicine system used, resulted in a termination of inclusion of patients (85). Interestingly, the number of outpatient clinic visits did not decrease in the RCT from Rasmussen et al. (72). This was confirmed in the RCT from Smith-Strøm where the total number of outpatient clinical consultations remained equal for the intervention and the control group (73). Subgroup analysis showed that the number of consultations decreased if patients lived further away from the clinic (>25 km) and if there was more experience with telemedicine consultations (73). Taking these key factors into account in future trials and in clinical practice may improve potential for remote ulcer care.

Cost-effectiveness based on the data of the RCT from Rasmussen et al. showed to be similar between the telemedicine and usual care group (71). The trial was, however, not powered to detect differences in costs and cost-analysis was based on only the first 6 months of follow-up. Future studies should further explore the cost-effectiveness of this approach.

Cost aspects
All telehealth and telemedicine approaches discussed in this review require investment in equipment, setup, training, and personnel, and therefore, the benefit for the patient will have to be evaluated in association with the costs involved. Cost-effectiveness is a key aspect that will influence acceptance and implementation in diabetic foot care. Some monitoring tools such as infrared thermometers are low in cost, while other modalities such as hyperspectral imaging are currently still expensive. However, because prevention of a single foot ulcer or an amputation can save the healthcare system between €5.000 and €17.000, telehealth and telemedicine tools have good potential to be cost-effective if they lead to a significant reduction in risk of foot ulceration, expedited healing of ulcers, or less outpatient clinic visits.

Clinical implications and future perspectives
If feasibility, effectiveness and cost-savings are demonstrated, successful implementation of telehealth and telemedicine approaches can improve patient mobility, autonomy, and health-related quality of life, in particular for those patients living alone or in rural areas, who have cognitive, visual or physical impairments, or lack knowledge about the disease. This empowers patients and encourages them to take responsibility in the management of their diabetic foot disease (86).

The development of such a user-friendly, effective approach is not without challenges. Both patients' and healthcare professionals' adherence play an important role in effectiveness and implementation is dependent on whether tools are reimbursed by the healthcare system. The continuous and fast technological development increases the risk that devices of which efficacy has been proven become outdated for practical use. Nevertheless, these technological developments also provide great potential for the design of easy-to-use tools that integrate several of the studied modalities for the prevention and management of diabetic foot disease. A small and easy-to-use, if needed carry-on, device that can measure local foot temperature and takes photographs of the foot and automatically processes data through intelligent algorithms and feedbacks data to the patient when action is needed is probably not far from development. Such tools, when proven feasible and cost-effective can have great impact in the care of patients with diabetic foot disease.

Limitations
We obtained articles from a single database (MEDLINE/Pubmed) and did not include other databases. We do think we covered the important medical-scientific literature on the topic of interest. Additionally, this systematic review includes only studies on people with diabetes and therefore lacks data on the use of telehealth and telemedicine approaches in other patient

populations (with or without foot ulcers) that may be informative. Tchero et al. conducted a systematic review and meta-analysis on telemedicine approaches and also included other than diabetes patients with (risk for) foot ulcers (87). We believe though that diabetic foot disease is a unique entity with its own characteristic aspects, physically and psychologically, that require a specific focus on this topic of interest.

CONCLUSION

This systematic review shows that the application of telehealth and telemedicine approaches for the management of diabetic foot disease is still in its infancy, and technical limitations and implementation issues apply. However, several approaches have shown to be effective or feasible in assessing, monitoring, preventing or treating diabetic foot disease, and additionally require confirmation in studies in order to have more widespread use in diabetic foot care, in particular for patients living in remote areas. Other approaches require further development towards a feasible and effective solution and proof thereof in well-designed studies. Successful implementation of these telehealth and telemedicine approaches can substantially reduce patient and healthcare burden of diabetic foot disease.

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SUPPLEMENTARY APPENDIX A: Search string used for the Medline/PubMed database

("Diabetic Foot"[Mesh] OR "Foot ulcer"[Mesh] OR diabetic foot OR foot ulcer*) AND ("Telemedicine"[Mesh] OR "Home care services" [Mesh] OR "Telenursing"[Mesh] OR "Remote consultation"[Mesh] OR "Community medicine"[Mesh] OR telemed* [tiab] OR tele-med* [tiab] OR telenurs* OR home-environment OR home monitor* OR home-monitor* OR telecommunication* [tiab] OR mobile health OR telerehabilitation [tiab] OR telecare [tiab] OR tele-care [tiab] OR tele-home [tiab] OR telehome [tiab] OR e-health [tiab] OR e health [tiab] OR tele-health [tiab] OR telehealth [tiab] OR remote assessment [tiab] OR remote treatment [tiab] OR remote consultation [tiab] OR telemonitor* [tiab] OR "Cellular phone"[Mesh] OR "Photography"[Mesh] OR photograph* OR "Image processing"[Mesh] OR image processing OR imaging [tiab] OR "Temperature"[Mesh] OR temperature* OR "Thermography"[Mesh] OR thermograph* OR thermometer [tiab] OR "Infrared"[Mesh] OR infrared [tiab] OR video consultation*)

SUPPLEMENTARY APPENDIX B: Summary of data from the included studies in the systematic review

Reference	Study design	Study population and characteristics	Exposure or, Intervention (I) and control (C) conditions	Outcome category	Results	Conclusion (C)/ Limitations (L)
Dermal thermography: infrared						
Armstrong et al. 1996 (17)	Case series	Patients: 25 patients with DM and a neuropathic plantar foot ulcer Study duration: 4 months after return to shoe gear Lost to study: 0	All patients were treated with serial total contact casts until their ulcers healed. Casts were changed in weekly intervals. Dermal thermometry using Exergen Model DT 1001 (Exergen Products, Watertown, MA, USA) recorded at the ulcer location and the corresponding site of the contralateral foot was performed during total contact cast regime and the first 4 months after return to shoe gear.	Ulcer assessment Feasibility	Temperature difference between foot with ulcer and contralateral foot at initial presentation: 6.9°F (P<0.0001, t=8.9, 95%CI: 5.3–8.5) During healing: no significant difference between foot with ulcer and contralateral foot: 83.4°F vs 85.3°F (NS, t=-1.35, 95%CI: -7.5–3.9) Vibration perception >45 Volt: wider temperature gradients (P=0.007) Brachial indices <0.60: wider temperature gradients (P=0.01)	C: There are significant differences in skin temperature in patients with ulcerations compared with the temperature of their contralateral feet at presentation, not during healing, and temperature differences are larger in patients with high degrees of neuropathy or peripheral vascular disease L: Unclear how many neuroischemic ulcers were included (brachial indices <0.60) L: Inefficient method in case of unilateral amputation
Armstrong et al. 1997 (18)	Cross-sectional and case control study	Patients: 143 patients with DM Group 1: 78 patients with asymptomatic peripheral sensory neuropathy Group 2: 44 patients with a new-onset neuropathic ulcer Group 3: 21 patients with Charcot's arthropathy Study duration: mean follow-up time (SD): 22.1 (6.4) months Lost to study: 0	Dermal thermometry using Exergen Model DT 1001 (Exergen Products, Watertown, MA, USA) recorded from 6 sites on the soles of both feet at diagnosis and subsequent clinical visits. Patients from group 2 and 3 were treated with a weekly changed total contact cast.	Ulcer prevention/ assessment Feasibility	Temperature difference between feet at time of diagnosis: Group 1: 0.1°F (P>0.05) Group 2: 5.6°F (P<0.0001) Group 3: 8.3°F (P<0.0001) 3 patients re-ulcerated, after initial healing (mean 12.2 months) with increase of temperature difference in the visit prior to ulceration between feet: 89.6°F vs 82.5°F (P=0.003)	C: Monitoring foot temperature at the corresponding contralateral site may provide clinical information before other clinical signs of injury can be identified L: Underpowered L: No uniform follow-up L: Inefficient method in case of unilateral amputation
Armstrong et al. 1997 (19)	Cross-sectional and case-control study	Patients: 39 patients with DM and Charcot's arthropathy of which 17 had a concomitant foot ulcer Study duration: mean follow-up time of 22.6±7.1 months Lost to study: 0	All patients were treated with a standard protocol involving total contact casting, removable cast walkers, and progression to therapeutic shoes. Cast were checked at regular intervals (with ulceration: weekly; without ulceration: maximum 3 weeks). Dermal thermometry using Exergen Model DT 1001 (Exergen Products, Watertown, MA, USA) recorded from 7 sites on the soles of both feet was performed during treatment and after return to shoe gear.	Ulcer prevention/ assessment Feasibility	Mean skin temperature differences with contralateral foot at initial presentation: 8.8±2.3°F Maximum skin temperature gradient correlated with the site of maximum Charcot's arthropathy (radiographically) in 92% of the cases Three of the 17 patients re-ulcerated during follow-up Skin temperature gradients in the visit prior to ulceration was higher in patients that ulcerated compared non-ulcerated patients at the corresponding clinical visit 4.5±0.9°F vs 0.9±0.9°F (P<0.001)	C: Elevated skin temperatures may be correlated with the location of acute neuropathic osteoathropathy C: Elevated skin temperature gradients may predict ulceration L: Correlation coefficients are lacking L: Underpowered for the last conclusion L: Temperature measurements done with different time intervals

Study	Study type	Patients/Methods	Intervention	Outcome	Results	Comments/Limitations
Lavery et al. 2004 (23)	RCT	Patients: 85 patients with DM with a medium risk (only neuropathy, foot deformity or limited joint mobility) and high risk (history foot ulcer or lower-extremity amputation) for ulceration I: 41 C: 44 Study duration: 6 months Lost to study: I: 3 C: 4	I: Standard therapy with additionally dermal thermometry using TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) recorded form 6 sites on the soles of both feet twice a day; reduce walking activity and contact study nurse in case difference in skin temperature between corresponding location in both feet was >4°F C: Standard therapy: therapeutic footwear, diabetic foot education, regular foot evaluation by a podiatrist	Ulcer prevention Effectiveness	Proportion developing foot complications: I: 1 ulcer C: 7 ulcers, 2 Charcot fractures; OR=10.3 (P=0.01, 95%CI: 1.2-85.3) No statistical differences in Quality of life (SF-36) either between groups or, in the pre- and post-study evaluations, within groups	C: At-home self-monitoring of dermal foot temperature may prevent foot complications L: Method of randomization not reported L: Assignment method not reported L: Blinding outcome assessor not reported L: Compliance/ adherence to protocol not reported L: Short follow-up L: Location of foot ulceration not analysed (dorsal or plantar) L: No reports on primary ulceration or recurrence
Armstrong et al. 2006 (30)	Cohort study	Patients: 362 patients with DM an infected foot ulcer: double blind comparison of intravenous ertapenem or piperacillin /tazobactam (SIDESTEP trial) Study duration: until discontinuation of intravenous antibiotics (mean 11.7±7.5 days) Lost to study: 30 (intervention arm)	Dermal thermometry using TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) recorded from the area of the infection and the corresponding site of the contralateral foot at baseline and at discontinuation of intravenous antibiotic therapy	Assessment of infection Feasibility	Change in mean differences of skin temperature between feet, between baseline and discontinuation of intravenous antibiotic therapy: -0.37°F (P=0.225, 95%CI: -0.98-0.23) Correlation baseline skin temperature differential with: White blood cell count: r=0.058 C-reactive protein: r=0.148 Erythrocyte sedimentation rate: r=0.002 Diabetic foot infection wound score (University of Texas Diabetic Ulcer Classification): r=0.067 Patients with skin temperature differential >10°F had lower clinical response than those with <10°F: 81.4% vs 94.3% (P=0.007)	C: Mean differences in skin temperature between infected and non-infected limbs does not predict the severity of an infection or the outcome of treatment C: No correlation between baseline skin temperature differential with white blood count, C-reactive protein, erythrocyte sedimentation rate, or infection severity score L: Short follow-up L: Clinical response not defined L: Inefficient method in case of unilateral amputation
Armstrong et al. 2007 (24)	RCT	Patients: 225 patients with DM with a medium risk (only neuropathy, foot deformity or limited joint mobility) and a high risk (history foot ulcer or lower-extremity amputation) of ulceration Study duration: 18 months Lost to study: not reported	I: Standard therapy with additionally dermal thermometry using TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) recorded from 6 sites on the soles of both feet twice a day; reduce walking activity and contact study nurse in case temperature differential was >4°F C: Standard therapy: therapeutic footwear, diabetic foot education, regular foot care and performing structured foot inspection daily	Ulcer prevention Effectiveness	Proportion patients developing a foot ulcer: I: 4.7% C: 12.2%; OR=3.0 (P=0.038, 95%CI: 1.0–8.5)	C: High temperature gradients between feet may predict neuropathic ulceration C: Self-monitoring foot temperature may reduce the risk of ulceration L: Number per group (intervention/control) not reported L: Drop-outs not reported L: Compliance/ adherence to protocol not reported L: Veterans only L: Large number of medium risk patients (>80%) L: Location of foot ulceration not analysed (dorsal or plantar) L: No reports on primary ulceration or recurrence

Study	Design	Population	Intervention	Outcome	Results	Conclusions / Limitations
Lavery et al. 2007 (25)	RCT	Patients: 173 DM patients with a history of foot ulceration; I: 59; C1: 58; C2: 56; Study duration: 15 months; Lost to study: I: 10; C1: 6; C2: 6	I: Standard therapy with additionally dermal thermometry using TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) recorded from 6 sites on the soles of both feet daily; reduce walking activity and contact study nurse in case temperature differential was >4°F; C1: Standard therapy: therapeutic footwear, diabetic foot education, regular foot care; C2: Standard therapy with additionally structured foot examination (+ self-assessment twice a day with a mirror)	Ulcer prevention; Effectiveness	Proportion of patients developing a foot ulcer: I: 8.5%; C1: 29.3%, OR=4.48 (P=0.008, 95%CI: 1.53–13.1); C2: 30.4%, OR=4.71 (P=0.0061, 95%CI: 1.60–13.85); Contact study nurse after self-examination: I: 31 (52.5%); C1: 18 (31.0%) (94.4% already had a foot ulceration); C2: 17 (30.4%) (100% already had a foot ulceration); 88% of patients in the intervention group recorded >50% of the time their foot temperature	C: Home-monitoring foot temperature can reduce the risk for foot ulcer recurrence in high risk diabetes patients; L: Location of foot ulceration not analysed (dorsal or plantar); L: Blinding outcome assessor not reported
Nishide et al. 2009 (22)	Cross-sectional study	Patients: 30 patients with DM, neuropathy and with 50 plantar sites of callus, 30 healthy individuals with 65 plantar sites of callus; Study duration: 115 (50 sites of callus in DM patients and 65 sites of callus in healthy individuals) examinations; Lost to study: 0	Dermal thermography of the callus and surrounding tissue using a Thermo Tracer TH5108ME (NEC Avio Infrared Technology Co., Ltd, Tokyo, Japan) and ultrasonography (LOGIQ Book XP, GE Medical Systems, Bedford, UK) for detecting oedematous changes of inflammatory tissue	Ulcer prevention; Feasibility	Five sites of callus in the DM group vs 0 sites of callus in the healthy individuals showed signs of latent inflammation (P=0.014); Temperature differences between callus with signs of latent inflammation and surrounding skin varied between: 1.6–2.3°C	C: Latent inflammation might be detectable with the combination of dermal thermography and ultrasonography; L: Temperature of callus compared with the temperature of the surrounding skin of the same foot; L: No golden standard to define 'latent inflammation'
Oe et al. 2012 (21)	Case report	Patients: 1 patient with DM and a foot ulcer with osteomyelitis; Study duration: 6 months; Lost to study: 0	Dermal thermography of both feet using a Thermo Tracer TH7800N (NEC Avio Infrared Technology Co., Ltd, Tokyo, Japan)	Assessment of infection; Feasibility	Skin temperature was elevated with osteomyelitis and normalized after resolving of osteomyelitis	C: Thermography might be useful for screening osteomyelitis; L: Underpowered; L: Intervals of monitoring were based on the patient's availability
Mori et al. 2013 (31)	Cross-sectional study	Patients: 129 patients with DM, varied from a low to a high risk of ulceration (IWGDF risk classification) and 32 healthy individuals; Study duration: 161 examinations; Lost to study: 0	Dermal thermography: Thermo Tracer TH5108ME (NEC Avio Infrared Technology Co., Ltd, Tokyo, Japan); imaging of temperature distribution of plantar skin using a computer-based, image-partitioning algorithm (segmenting each plantar thermography image into visually coherent image parts	Ulcer prevention; Feasibility	DM patients: 77% of the patterns variously allocated to 6 categories; Healthy individuals: 62% was allocated to 2 typical categories	C: There were wider variations of plantar thermographic patterns in patients with DM, defined by an objective computer-based classification system; L: Subjective method; L: Unclear clinical relevance

Study	Design	Population	Method	Focus	Results	Conclusions / Limitations
Van Netten et al. 2013 (27)	Cross-sectional study	Patients: 15 patients with DM, 5 with no visible signs of foot complication, 5 with local complications (e.g. abundant callus or neuropathic ulcer), 5 with diffuse complications (e.g. Charcot foot, infected ulcer or critical ischemia) Study durations: 15 examinations Lost to study: 0	Experimental setup for high-resolution infrared thermal imaging of the plantar surface of both feet, using an algorithm by combining colour image and thermal image parameters (Colour imaging: Canon EOS 40D (Canon Inc, Tokyo, Japan), infrared imaging: FLIR SC305 (FLIR Systems, Wilsonville, OR, USA)	Ulcer assessment Feasibility	Difference in mean temperature between ipsilateral and contralateral foot: Patients with no complications: no temperature difference >1.5°C Local complications: temperature difference >2°C at the regions of interest Diffuse complications: temperature difference >3°C	C: With this experimental setup it is possible to detect signs of diabetic foot disease and to discriminate between no, local, or diffuse diabetic foot complication L: Underpowered L: Inefficient method in case of unilateral amputation L: Experimental setup limited to the plantar surface of the foot
Van Netten et al. 2014 (28)	Cross-sectional study	Patients: 54 patients with DM Group 1: 9 with complications requiring immediate treatment Group 2: 25 with complications requiring non-immediate treatment Group 3: 20 had no complications Study durations: 54 examinations Lost to study: 0	Experimental setup for high-resolution infrared thermal imaging, using an algorithm by combining colour image and thermal image parameters (Colour imaging: Canon EOS 40D (Canon Inc, Tokyo, Japan), infrared imaging: FLIR SC305 (FLIR Systems, Wilsonville, OR, USA). Calculation of average pixel temperature for 6 predefined spots at the plantar surface of the foot compared with clinical assessment. Observer: 1 wound care consultant trained in the diabetic foot	Ulcer assessment Feasibility	Mean temperature(SD) of the affected foot: group 1 vs 2 vs 3: 31.68(2.4)°C vs 31.61(2.2)°C vs 30.25(3.1)°C (P=0.220) Mean temperature difference (SD) between feet: 2.65(1.4)°C vs 1.36(1.1)°C vs 1.07(0.9)°C (P<0.001) Optimal cut off skin temperature for detecting complications = 2.2°C difference between contralateral region of interest Se=76% Sp=40% Optimal cut off skin temperature for determining urgency of treatment = 1.35°C between feet Se=89% Sp=78%	C: Local temperature assessment isn't an adequate diagnostic method for the detection of diabetes-related foot complications C: Mean temperature differences between feet has more diagnostic values for determining urgency of treatment L: Inefficient method in case of unilateral amputation L: Experimental setup limited to the plantar surface of the foot L: Only 1 observer as reference
Skafjeld et al. 2015 (26)	RCT	Patients: 41 patients with DM, peripheral neuropathy and a history of foot ulceration I: 21 C: 20 Study duration: 12 months Lost to study: I: 3 C: 0	I: Dermal thermometry using TempTouch® (Xilas Medical Inc., San Antonio, TX, USA) recorded form 6 sites on the soles of both feet daily; reduce walking activity and contact study nurse in case temperature differential was >2°C + tailored stage-based counselling via a diabetes study nurse C: Standard therapy: daily inspection and contact study nurse in case of changes in feet	Ulcer prevention Effectiveness	Proportion patients developing a foot ulcer: I: 39% C: 50% (P=0.532) Kaplan Meier survival curves I and C similar (P=0.407) Proportion patients monitoring skin temperature: 67%, ≥80% of the time Proportion patients recording foot inspections: 70%, ≥80% of the time	C: No difference in foot recurrence between interventions C: Self-monitoring of skin temperature is feasible L: Both groups underpowered L: Two interventions in the intervention group/ bias L: Blinding outcome assessor not reported L: No intention-to-treat analysis L: Inefficient method in case of unilateral amputation L: Location of foot ulceration not analysed (dorsal or plantar)

Author	Study type	Population	Method	Outcome	Results	Conclusions / Limitations
Liu et al. 2015 (29)	Cross-sectional study	Patients: 76 high-risk DM patients with diabetic foot complications (e.g. callus, ulceration, or a history of ulceration) Study duration: 76 examinations Lost to study: 0	Experimental setup combining colour imaging and asymmetric analysis of thermal images of the foot complication, compared with manual annotation (Colour imaging: Canon EOS 40D (Canon Inc, Tokyo, Japan), infrared imaging: FLIR SC305 (FLIR Systems, Wilsonville, OR, USA) Observers: wound care specialists	Ulcer assessment Accuracy	Comparing manual association between automated association: Se=85%±1% Sp=98.4%±0.4% With 2.2°C as cut-off point for risk identification 35 of the 37 ulcers were successfully detected	C: Thermal images may automatically detect diabetic foot complications, by combining a asymmetric analysis with foot segmentation from colour images L: Inefficient method in case of unilateral amputation L: No golden standard as reference (manually segmented) L: Unknown number of observers L: Very limited description of the detected foot complications
Najafi et al. 2017 (34)	Cross-sectional study	Patients: 33 high risk DM patients (IWGDF risk classification) Study duration: 33 examinations Lost to study: 0	SmartSox (Novinoor LLC, Wilmette, IL, USA) with embedded highly flexible and thin (<0.3mm) fibre optic sensors based on fibre Bragg gratings. Plantar foot temperature and pressure were measured at 5 regions of interest. Range of motion from the first metatarsophalangeal joint was also measured. Phase 1: laboratory condition Phase 2: in vivo (walking a predefined route of 50-60 steps)	Ulcer prevention Validity	Phase 1: Agreement for temperature and measuring joint angle between SmartSox and the reference system (controllable heater wires and a goniometer): Pearson r>0.98 (P<0.001) Phase 2: Agreement for thermal response test between SmartSox and a thermal camera (Fluke Ti25, Fluke Corporation, Everett, WA, USA): Pearson r=0.55(P<0.050) Agreement for plantar pressure between SmartSox and F-Scan® (Tekscan, Inc, Boston, MA, USA): Pearson r=0.67 (P<0.050)	C: SmartSox can measure thermal stress response, plantar pressure and plantar joint stiffness simultaneously L: SmartSox does not have the sufficient spatial resolution to cover the entire anatomical region of interest L: Only tested in a controlled setting (predefined walking route)
Wijlens et al. 2017 (37)	Case series	Patients: 20 low and medium risk DM patients (IWGDF risk classification) Study duration: 6 days Lost to study: 0	Dermal thermometry using TempTouch® (Xilas Medical Inc, San Antonio, TX, USA) recorded from 6 sites on the plantar surface of both feet 4 times a day	Ulcer prevention Validity	False positive outcomes: Patients >2.2°C difference, after correction (2.2°C - (baseline temperature difference)) for one day = 80% (n=16) Patients >2.2°C difference, without correction, for two consecutive days = 35% (n=7) Patients >2.2°C difference, after correction for two consecutive days = 20% (n=4)	C: Validity of the >2.2°C left to right foot temperature differences improves using two consecutive days of an above-threshold recording and individual correction L: Relatively low risk diabetes patients (IWGDF risk classification: group 1 and 2) L: No ulcers or other foot complications developed during the study L: Limited days of follow-up
Renero-C 2018 (20)	Cross-sectional study	Patients: 186 patients with DM and neuropathy Study duration: 186 examinations Lost to study: 0	Dermal thermography of the feet using FLIR E6 (FLIR Systems, Wilsonville, OR, USA)	Ulcer assessment Feasibility	Temperature differences between two feet are seen in patients with Charcot, ulceration and vascular impairment	C: Thermograms may identify patients that need medical screening L: Poor methodology L: Reporting bias, only data from 5 of the 186 patients is presented

Study	Design	Patients	Intervention	Outcome	Results	Conclusions/Limitations
Gatt et al, 2018 (32)	Cross-sectional study	Patients: Group 1: 15 patients with DM without complications (21 limbs) Group 2: 32 patients with DM and neuropathy (41 limbs) Group 3: 30 patients with DM, neuropathy and PVD (43 limbs) Group 4: 42 patients with DM and PVD (58 limbs) Group 5: 63 healthy controls (126 limbs) Study duration: 289 examinations (1 examination per limb) Lost to study: 0	Dermal thermography of the plantar surface of the feet using FLIR SC7200 (FLIR Systems, Wilsonville, OR, USA) with extraction of temperature for every single toe and the medial, central and lateral region of the forefoot	Ulcer prevention Feasibility	Mean temperature for group 1 and 5 combined was lower in all measured regions compared to the groups 2, 3 and 4 combined (P=0.000)	C: As foot temperature rises, so does the probability of the presence of complications of neuropathy, neuroischemia or PVD L: No possible confounding factors in the logistic regression L: Unclear clinical relevance, since there is no gold standard L: Lack of comparison with contralateral foot
Gatt et al. 2018 (33)	Cross-sectional study	Patients: Group 1: 15 patients with DM without complications (21 limbs) Group 2: 30 patients with DM, neuropathy and PVD (43 limbs) Group 3: 12 patients with DM, neuropathy, PVD and a toe ulcer (12 limbs) Study duration: 76 examinations (1 examination per limb) Lost to study: 0	Dermal thermography of the plantar surface of the feet using FLIR SC7200 (FLIR Systems, Wilsonville, OR, USA) with extraction of temperature for every single toe	Ulcer prevention Feasibility	Mean temperature(SD) per toe: group 1 vs 2 vs 3: 24.9(5.04)°C vs 27.7(2.16)°C vs 28.7(3.23)°C (P=0.001) Post hoc analysis showed: group 1 vs 2 (P=0.001) group 1 vs 3 (P=0.001) group 2 vs 3 (P=0.626)	C: No significant differences between temperatures of ulcerated toes and the non-ulcerated toes of the same foot suggest that all toes of the same foot could potentially be at risk of developing complications L: Underpowered L: Unclear clinical relevance, since there is no gold standard L: Lack of comparison with contralateral foot

Dermal thermography: thermistor

Study	Design	Patients	Intervention	Outcome	Results	Conclusions/Limitations
Frykberg et al. 2017 (35)	Case series	Patients: 132 patients with DM and a history of ulceration Study duration: 34 weeks Lost to study: 44 (33.3%) (14 withdrew consent prior to completion, 3 died, 24 lost to follow-up, 3 unavailable data)	Daily use of a thermometric foot mat (Remote Temperature Monitoring System; Podimetrics, Inc., Somerville, MA, USA) to assess plantar thermal asymmetry	Ulcer prevention Feasibility/validity	37 Patients (28.7%) developed 53 non traumatic diabetic foot ulcers Using a threshold of 2.22°C, 97% of all ulcers could be identified: Se=97%, Sp=43% PPV=16.6%, NPV=99.2% Average lead time to ulcer(SD): 37(18) days	C: Plantar temperature asymmetry is highly predictive for impending foot ulcers L: Relatively many patients lost to study L: Primary outcome is not well defined L: Limited to the plantar surface of the foot L: Thermal asymmetry is assessed at foot level, unclear if this is present at the ulcer location
Killeen et al. 2018 (36)	Case report	Patients: 3 patients with DM, neuropathy and a history of ulceration Study duration: 9 months Lost to study: 0	Daily use of a thermometric foot mat (Remote Temperature Monitoring System; Podimetrics, Inc., Somerville, MA, USA) to assess plantar thermal asymmetry	Ulcer prevention Feasibility	2 of the 3 patients developed an ulcer that was preceded by temperature asymmetry using a threshold of 1.75°C	C: The thermometric foot mat may be useful for early identification of inflammation L: Underpowered L: Limited to the plantar surface of the foot

Dermal thermography: liquid-crystal

Author/year	Study design	Patients	Description	Indication	Results	Conclusions / Limitations
Stess et al. 1986 (38)	Cross-sectional study	Patients: Group 1: 16 healthy individuals; Group 2: 21 Patients with DM without a history of ulceration; Group 3a: 13 Patients with DM and an active ulcer; Group 3b: 15 Patients with DM and a history of ulceration. Study duration: 65 examinations. Lost to study: 0	Liquid-crystal thermography of the plantar surface of the feet using Flexi-Therm sheets (Flexi-Therm Inc., Westbury, NY, USA)	Ulcer prevention/ assessment; Feasibility	Mean temperature readings under each metatarsal head, hallux and heel were increased in group 3a/b compared to group 1 and 2 ($P<0.1$). No significant difference in mean temperature readings under each metatarsal 1, 2, 5, hallux and heel between the affected foot and the contralateral foot in group 3a. The temperature of area around the ulcer (6-8mm) was significantly higher than the center of the ulcer ($P<0.1$) in group 3a	C: Liquid-crystal thermography might be used as a screening tool for determining risk of ulceration. L: Type of ulcers (at inclusion) not reported. L: Only veterans
Benbow et al. 1994 (39)	Case-control study	Patients: 50 patients with DM and neuropathy: 20 with PVD and 30 without PVD. Study duration (range): mean 3.6 years (3.0-4.1). Lost to study: 12 (7 in PVD group)	Liquid-crystal thermography from 8 standard plantar sites of both feet at baseline using Novatherm detectors (Novamedix, Whitchurch, Hampshire, UK)	Ulcer prevention; Feasibility	Number of plantar ulcers: Patients with PVD: 1; Patients without PVD: 7. Mean plantar foot temperature ulceration vs non-ulceration feet in patients without PVD: 30.5°C vs 27.8°C ($P<0.01$)	C: Liquid-crystal thermography may predict neuropathic plantar foot ulceration. L: Underpowered. L: Only thermography at baseline
Roback et al. 2009 (40)	Cross-sectional study	Patients: 65 patients with DM and varies risk factors. Study duration: 69 examinations. Lost to study: 0	Liquid-crystal thermography of the plantar surface of the feet using SpectraSole Pro1000 (SpectraSole AB, Linköping, Sweden). Observers: 2 with experience in diabetic foot care	Ulcer assessment; Feasibility	Proportion foot problems identified by liquid-crystal thermography compared with clinical assessment: 74% of foot problems correctly identified (foot problem clinically defined as several and/or large problem areas, n=27)	C: Liquid-crystal thermography provides valuable diagnostic information in early stages of foot disease. L: Poor definition of categories/groups of foot problems. L: According to the investigators the technique was easy and quick, but no data was reported regarding usability

Hyperspectral imaging

Author/year	Study design	Patients	Description	Indication	Results	Conclusions / Limitations
Rajbhandari et al. 1999 (44)	Case-control study	Patients: 14 patients with DM and neuropathy and 24 foot ulcer sites (17 neuropathic ulcers, 7 neuroischemic ulcers). Study duration: 9 months. Lost to study: 2 (died)	Serial microvascular oxygen saturation (SaO_2) of the foot ulcer, ulcer margin and at identical sites on the contralateral limb was measured using Erlangen micro lightguide spectrophotometer type EMPHO II/BB (Bodenseewerk Geratetechnik, Erlangen, Germany) at baseline and during healing (2-6 weeks interval)	Ulcer assessment; Feasibility	Neuropathic feet vs neuroischemic feet: Mean SaO_2 at baseline: 56% vs 44% ($P\leq0.05$). Healing rate: 15.1% vs -7.9% per week ($P\leq0.001$). Serial SaO_2 in 13 healed ulcer site reduced significant from initially 58±11% to midsize 47±11% and final measurement 45±14% ($P=0.018$). No change in SaO_2 in 8 ulcer sites that not healed due to ischemia or infection ($P=0.2$)	C: Serial SaO_2 measurements may identify ulcers that are unlikely to heal at an early stage. L: EMPHO II is expensive and bulky for clinical use. L: Multiple ulcers at same patients/ bias.

Study	Design	Patients	Method	Outcome	Results	Conclusions / Limitations
Khaodhiar et al. 2007 (41)	Case-control study	Patients: 37 patients, 10 patients with DM and 21 neuropathic foot ulcers, 13 patients with DM without ulcers and 14 nondiabetic control subjects Study duration: 6 months Lost to study: 0	Hyperspectral technology; measurement of tissue oxy- and de-oxyhaemoglobin was performed at the plantar aspect of the feet, the palm and the area around the ulcer using CombiVu-R (HyperMed, Waltham, MA, USA) at baseline, 6 weeks, 3 months and 6 months (DM patients) or at baseline and 6 months (nondiabetic control subjects)	Ulcer assessment Feasibility	14 ulcer sites form 9 patients healed 7 ulcer sites from 3 patients did not heal Hyperspectral healing index was determined to separate healing from non-healing ulcers Se=93% (95%CI: 66-100) Sp=86% (95%CI: 42-100) PPV=93% (95%CI: 66-100) NPV=78% (95%CI: 56-93) (P<0.001)	C: Hyperspectral technology can predict ulcer healing and can assist in the management of diabetic foot ulceration L: Hand palm was used as control site L: Multiple ulcers at same patients/ bias L: Treatment strategies not reported L: The exact nature of the healing index was not reported
Nouvong et al. 2009 (42)	Case-control study	Patients: 66 patients with DM with 1 or more foot ulcers Study duration: 24 weeks Lost to study: 12	Hyperspectral imaging from the intact tissue bordering the ulcer using OxyVu™ (HyperMed, Burlington, MA, USA) during 11 visits in 24 weeks	Ulcer assessment Feasibility	54 patients with 73 ulcers were analysed, 54 ulcers healed, 19 ulcers did not heal A healing index to predict healing showed: Se=80%, Sp=74% PPV=90%	C: Hyperspectral imaging may be used to predict diabetic foot ulcer healing L: Treatment strategies not reported L: No control site used L: Type of ulcers (at inclusion) not reported L: The exact nature of the healing index was not reported
Papazoglou et al. 2009 (45)	Case-control study	Patients: 11 patients with DM and a foot ulcer Study duration: 10-61 weeks Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxygenated haemoglobin concentration and total haemoglobin concentration in and around the ulcer and on the contralateral limb on the corresponding sites were conducted prior to debridement on a weekly or biweekly basis	Ulcer assessment Feasibility	Change in concentration oxyhaemoglobin [HbO₂], and total haemoglobin concentration [Tot Hb] in: Healed ulcers (5): reduction and converging to the values at the contralateral site Non-healed ulcers (7): change nearly zero (P<0.05)	C: NIRS can differentiate healing from non-healing ulcers L: Underpowered to determine the predictive capability of rates of change in diffuse photon density wave methodology of NIRS L: Type ulcers (at inclusion) not reported
Neidrauer et al. 2010 (46)	Case-control study	Patients: 16 patients with DM and a neuropathic foot ulcer, without PVD (ABI>0.75) Study duration: maximum of 20 visits (weekly), or healing/amputation Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxygenated haemoglobin concentration and total haemoglobin concentration in and around the ulcer and on the contralateral limb on the corresponding site during weekly measurements	Ulcer assessment Feasibility	Change in [HbO₂] and [Tot Hb] in: Healed ulcers (7): reduction prior to closure converging to the values at the contralateral site Non-healed ulcers (9): remained elevated A negative slope for the rate of change in [HbO₂] and [Tot Hb] was indicative of healing across all wounds	C: Evaluation of diabetic foot ulcers using NIRS may provide an effective measurement of ulcer healing L: Underpowered L: Treatment strategies not reported

Study	Study type	Patients / Study duration	Technology / Method	Assessment / Design	Results	Conclusions (C) / Limitations (L)
Weingarten et al. 2010 (47)	Case-control study	Patients: 16 patients with DM and a neuropathic foot ulcer, without PVD (ABI>0.75). Study duration: maximum of 20 visits (weekly), or healing/amputation. Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxygenated haemoglobin concentration and total haemoglobin concentration in and around the ulcer and on the contralateral limb on the corresponding site during weekly measurements	Ulcer assessment. Feasibility	7 ulcers healed, 6 limbs were amputated, 3 ulcers remained open. Change in [HbO$_2$] and [Tot Hb] in: Healed ulcers: reduction prior to closure and converging to the values at the contralateral site. Non-healed ulcers: remained elevated. The slopes for the rate of change in [HbO$_2$] and [Tot Hb] in healed ulcers are more negative than slopes from non-healed ulcers (P<0.05)	C: Evaluation of diabetic foot ulcers using NIRS may provide an effective measurement of ulcer healing. L: Underpowered. L: Treatment strategies not reported
Yudovsky et al. 2011 (48)	Case series	Patients: 66 patients with DM with 1 or more foot ulcers. Study duration: not reported. Lost to study: 0	Hyperspectral imaging (OxyVu™ (HyperMed, Burlington, MA, USA)) data from 66 DM patients were analysed (42)	Ulcer prevention. Feasibility	21 sites ulcerated. The prediction algorithm of for diabetic foot ulcer formation showed: Se=95%, Sp=80%. 58 days before tissue damage change was apparent to the naked eye	C: Hyperspectral imaging can predict the risk of diabetic foot ulcer development. L: Limited demographic information. L: Study duration not reported. L: Treatment strategies not reported. L: Healing prediction is retrospectively determined
Yudovsky et al. 2011 (49)	Case report	Patients: 2 patients with DM and a foot ulcer. Study duration: 1 months and 11 months. Lost to study: 0	Hyperspectral imaging of the forefoot using OxyVu™ (HyperMed, Burlington, MA, USA)	Ulcer assessment. Feasibility	The estimated average epidermal thickness (L_{epi}) increased at the pre-ulcer site and oxyhaemoglobin concentration decreased compared to the control site. L_{epi} decreased and oxyhaemoglobin concentration increased during ulcer healing	C: Measurements of epidermal thickness may enhance hyperspectral tissue oximetry for early prediction of diabetic foot ulcers. L: L_{epi} is an estimate of the actual epidermal thickness. L: Underpowered. L: Demographic information not reported
Weingarten et al. 2012 (43)	Case-control study	Patients: 46 patients with DM and a neuropathic foot ulcer, without PVD (ABI>0.75). Study duration: maximum of 20 visits (weekly), or healing/amputation. Lost to study: 0	Diffuse photon density wave methodology of near-infrared spectroscopy (NIRS) measurements of subsurface oxygenated haemoglobin concentration and total haemoglobin concentration in and around the ulcer and on the contralateral limb on the corresponding site during weekly or biweekly measurements	Ulcer assessment. Feasibility	17 Ulcers healed, 29 ulcers did not heal. Prediction of ulcer healing: association between NIRS measurements of [HbO$_2$] and [Tot Hb] and ulcer healing in 4 weeks (in 24 patients): - 4μM/week: Se=0.90, Sp=0.86. PPV=82% (P<0.002)	C: It may be possible to predict healing in 4 weeks using NIRS and may provide guidance towards continuation of costly treatment. L: Not all treatment strategies reported. L: Only 24 of the 46 patients were used for the prediction/ selection bias. L: Cost of amputation/ alternative treatment after 4 weeks not calculated
Liu et al. 2013 (50)	Cross-sectional study	Patients: 227 skin spots (95 'healthy', 55 callus, 38 ulcers, 39 'rest' (e.g. necrosis, blister or redness)) of 64 patients with DM. Study duration: 227 examinations. Lost to study: 0	Experimental setup using spectral data of 227 skin spots and live assessment by experienced clinicians	Ulcer assessment. Validity	Automated discrimination between callus, ulcers and healthy skin spots: Se=97%, Sp=96%. Potential savings per patient: US$12,610,80	C: Describing the methodology for designing an intelligent monitoring system by using spectral data for the detection of diabetic foot complications. L: Clinical assessments may vary between observers. L: Unknown number of observers. L: The 'rest' category was not included in the analysis

Study	Study design	Patients	Method	Ulcer assessment	Results	Conclusions/Limitations
Jeffcoate et al. 2015 (51)	Case-control study	Patients: Phase 1: samples of blood taken from normal volunteers Phase 2: 50 patients with DM and a foot ulcer Study duration: 24 weeks Lost to study: 7	Hyperspectral imaging (HSI) of the intact skin adjacent to the ulcer and at the dorsum of the foot using an in-house developed experimental setup: Phase 1: Association with blood gas analysis Phase 2: Association between HSI at baseline and healing at 12 and 24 weeks	Ulcer assessment Validity/Feasibility	Phase 1: Correlation between blood gas analysis and HSI: r=0.994 Phase 2: 26 ulcers healed within 12 weeks. There is a negative correlation between healing by 12 weeks and mean ulcer HSI in arbitrary units (AU) at baseline (P=0.016) with lower oxygenation (median) in healed ulcers at baseline vs unhealed ulcers: 47.9 AU (95%CI: 12.3-75.5) vs 61.9 AU (95%CI 27.2-80.4) There is a no correlation between healing by 24 weeks and mean ulcer AU at baseline (P=0.26)	C: HSI may predict ulcer healing L: Ulcer type at baseline not reported L: Treatment strategies not reported L: Experimental setup not further specified

Photographic imaging

Study	Study design	Patients	Method	Ulcer assessment	Results	Conclusions/Limitations
Rajbhandari et al. 1999 (54)	Cross-sectional study	Patients: 18 patients with DM and with 30 foot ulcers Study duration: unknown number of examinations Lost to study: 0	Foot ulcer area measurements using digital imaging technique, computer software, compared with traditional tracing (1-mm² graph paper) 30 ulcers were studied over 3 months by 5 observers Observers: 3 doctors, 1 diabetes specialist nurse, 1 podiatrist	Ulcer assessment Accuracy	Mean inter-observer coefficient of variation: Digital imaging: 16% Traditional tracing: 27% (P=0.05)	C: Reproducibility of digital method is superior to traditional tracing and usable for monitoring of ulcer healing L: No data reported regarding authors conclusion that digital imaging is also faster and easier to use L: No demographic and type of ulcer information reported L: Unknown number of examinations
Bowling et al. 2009 (52)	Cross-sectional study	Patients: 31 patients with DM and with 36 foot ulcers Study duration: 76 examinations in 12 weeks Lost to study: 0	Foot ulcer area measurements using 3D digital imaging technique, compared with traditional elliptical measurement Observers: clinicians	Ulcer assessment Accuracy	Correlation between digital measurements and traditional hand-measured estimates of the ulcer: Pearson r=0.961 (P<0.001)	C: Accurate digital ulcer area measurement allowing remote in-depth analysis L: Limited demographic information L: Unknown number of observers
Bus et al. 2010 (59)	Cross-sectional study	Patients: Phase 1: 10 patients with DM and a variety of plantar foot problems (e.g. presence of pre-ulceration or ulceration) Phase 2: 10 patients with DM and a variety of plantar foot problems Study duration: multiple examinations in 4 weeks (1 live, 2 photographic) Lost to study: 0	Development of a photographic foot imaging device. A two phase study to improve agreement between live and photographic assessment by optimizing illumination settings. Live assessment was performed directly following imaging and photographic assessment 2 and 4 weeks post imaging. Observers: 2 wound care specialists and 2 surgeons	Ulcer assessment Accuracy	Agreement between live and photographic assessment Phase 1: Abundant callus: 64% Absence of signs: 56% Ulcer: 90% Phase 2: Abundant callus: 82% Absence of signs: 74% Ulcer: 90%	C: Important clinical signs of diabetic foot can be diagnosed from high quality photographs L: Limited to the plantar surface of the foot L: Ulcer and abundant callus only, no inclusion of other pre-signs of ulceration or infection

Study	Study type	Patients / Study duration / Lost to study	Intervention	Assessment	Outcome	Conclusion / Limitations
Hazenberg et al. 2010 (60)	Cross-sectional study	Patients: 32 patients with DM and a plantar foot ulcer or at risk of developing an ulcer. Study duration: multiple examinations in 4 weeks (1 live, 2 photographic). Lost to study: 0	Photographic foot imaging device (PFID) in the home environment, sends photographs automatically of plantar surface to diabetic foot specialist. Live assessment was performed directly following imaging and photographic assessment 2 and 4 weeks post imaging. Observers: 2 wound care specialists and 2 surgeons	Ulcer assessment / Validity	Agreement between live and photographic assessment: Foot ulcer: k=0.97; Absence of signs: k=0.83; Abundant callus: k=0.61. Intra-observer agreement between assessments: k=0.70-1.00. Inter-observer agreement between assessments: Foot ulcer: k=0.72-0.88; Absence of signs: k=0.59-0.75; Abundant callus: k=0.48-0.73	C: Ulcers and pre-ulcerative lesions diagnosed valid and reliable using PFID. L: Limited to the plantar surface of the foot. L: Ulcer and abundant callus only, no inclusion of other pre-signs of ulceration or infection
Bowling et al. 2011 (55)	Cross-sectional study	Patients: Phase 1: 3 patients with DM and a foot ulcer. Phase 2: 20 patients with DM and a foot ulcer. Study duration: Phase 1: 14 images per diabetic foot ulcer (DFU). Phase 2: 20 live assessments by a single observer. Lost to study: 0	3D digital optical imaging. Phase 1: 14 images per DFU, 5 observers. Phase 2: 1 onsite observer for live assessment and answering 11 questions about clinically relevant observations, 3 remote observers (3D imaging) answering the same 11 questions. Observers: 5 clinicians from two centers	Ulcer assessment / Accuracy	Phase 1: agreement (variation) of image wound area measurements: Inter-observer: 11.9%; Intra-observer: 3.3%. Phase 2: agreement remote vs onsite assessment: overall good, but lowest on the subjective clinical assessments, e.g. value of debridement to improve healing	C: 3D digital optical imaging may be reliable in the assessment of DFU. L: One observer for onsite assessments of the ulcers as 'criterion standard' vs three observers for 3D assessments. L: Phase 1 underpowered. L: No demographic and type of ulcer information reported
Foltynski et al. 2011 (63)	Case series	Patients: 10 patients with DM and a neuropathic foot ulcer. Study duration: 3 months. Lost to study: 0	TeleDiaFos: a system that consist a database and a mobile Patient's Module allowing for documentation of foot images and results of blood glucose and blood pressure measurements taken in the home environment	Ulcer assessment / Feasibility	Description imaging process: mean(SD): number of images transmitted: 27.1(17.5), duration of use: 91(21.1) days, average time between image transfer: 4.5(2.5) days. Single case results of area measurements. Usability on 4 domains – mean (range) on VAS: 6.33-8.22 (10 = excellent)	C: TeleDiaFoS is useful as telemonitoring device and is accepted by patients and physicians. L: Underpowered. L: Method wound area measurements not reported. L: Missing data or transfer failures not reported. L: No elderly. L: Limited to the plantar surface of the foot. L: No study protocol was designed for patients
Foltynski et al. 2011 (64)	Case series	Patients: 10 patients with DM and a neuropathic foot ulcer. Study duration: 3 months. Lost to study: 0	TeleDiaFos: a system that consist a database and a mobile Patient's Module allowing for documentation of foot images and results of blood glucose and blood pressure measurements taken in the home environment. Observers: 4	Ulcer assessment / Feasibility	Description imaging process (range): Monitoring period: 54-131 days. Number of assessed wound pictures: 9-53. Change in area after 4 weeks between: -63.2% and 10.4%, after 12 weeks: -98.2% and 83.8%. Coefficient of variation (ranges): Varied between: 3.9% (1.8-10.4) and 64.3% (31.7-80.4)	C: TeleDiaFoS can be used at home and enables assessment of ulcer healing. L: No patient characteristics. L: Large variations in ulcer with not well defined boundaries. L: Observers not further specified. L: Underpowered. L: Limited to the plantar surface of the foot. L: No exact study protocol was designed for the patients

Study	Design	Methods	Outcome	Results	Conclusions / Limitations
Ladyzynski et al. 2011 (53)	Cross-sectional study	Patients: 23 patients with DM and with 33 plantar foot ulcers Study duration: multiple experiments Lost to study: 3 ulcers Observer: 1 nurse with 20 years of experience in wound care	Ulcer assessment Accuracy	Imaging system: TeleDiaFoS/Patient's Module for ulcer area measurements compared with 3 reference methods: (Elliptical method, Visitrak (Smith & Nephew, London, UK) & Silhouette (ARANZ Medical, Christchurch, New Zealand) Correlation for ulcer area measurements between TeleDiaFoS and: Elliptical method: r=0.949 Visitrak system: r=0.985 Silhouette system: r=0.987	C: Ulcer monitoring using TeleDiaFoS is effective L: One observer only L: Limited to the plantar surface of the foot L: Tracing of an ulcer area by the operator using the software only possible after debridement in case ulcer boundaries were not well-defined
Hazenberg et al. 2012 (61)	Case series	Patients: 22 high risk patients with DM Study duration: 4 months Lost to study: 2 (1 patient died, 1 excluded) Observer: 1 diabetic foot specialist (surgeon)	Ulcer assessment Feasibility	Photographic foot imaging device (PFID) in the home environment, sends photographs automatically of plantar to diabetic foot specialist who remotely assessed the images. Patients were asked to image both feet three times a week. Description of imaging process: 12% missing data (122 of 1022 imaging sets) 34/35 referrals were justified Usability on 10 domains; mean (range) on VAS: 7-9 (10 = excellent) Quality of life (EQ-5D) on VAS baseline vs end of follow-up: 7.5 vs 7.9 (P=0.31)	C: PFID is feasible in the home environment L: Small number of events L: Treatment regimens not reported L: Limited to the plantar surface of the foot L: In 1 patient infection was not diagnosed in photographs
Hazenberg et al. 2014 (62)	Cross-sectional study	Patients: 38 patients with DM and with a foot infection or admitted to the hospital with foot-related complications, 36 patients were analysed Study duration: multiple examinations in 4 weeks (1 live, 2 photographic) Lost to study: 2	Assessment of infection Accuracy	Photographic imaging (PFID), combined with infrared thermography (TempTouch®, Xilas Medical Inc., San Antonio, TX, USA), compared with live assessment. Live assessment was performed directly following imaging and photographic assessment 2 and 4 weeks post imaging. Observers: 2 wound care specialists Agreement in diagnosis of infection: Photographic imaging: Se>85%, Sp>60% Thermography: Se>90%, Sp<25% Combination (algorithm) of photo- and thermography: Se>60%, Sp>79%	C: Using the combination of photography and infrared thermography the diagnosis of foot infection seems to be valid and reliable L: Inefficient method in case of unilateral amputation L: Limited to the plantar surface of the foot L: Limited demographic and disease (foot complications) related information
Wang et al. 2016 (56)	Cross-sectional study	Patients: 12 patients with DM and a foot ulcer, a total of 32 images Study duration: 1 to 5 months Lost to study: 0	Ulcer assessment Feasibility/accuracy	Imaging with a smartphone (Nexus 5, LG Electronics, Seoul, South Korea) and an image capture box, compared with clinical assessment. Ulcer image assessment algorithms calculate wound area, colour segmented ulcer areas and a healing score. Observers: 3 experienced wound clinicians	32 foot ulcer images were collected, 28 images were used for clinical validation of the healing score algorithm Accuracy of ulcer area: MCC=0.68 Clinical validity of healing score algorithm: KAC=0.42–0.81	C: Valid assessment with image analysis of ulcer area, and evaluation of ulcer healing status L: Limited to plantar surface L: Limited demographic and ulcer related information L: Healing score is subjective

Study	Study design	Population	Methods	Outcome	Results	Conclusions / Limitations
Van Netten et al. 2017 (58)	Cross-sectional study	Patients: 53 patients with DM and a foot ulcer. Study duration: multiple examinations (1 live assessment, 2 photographic (minimum 2 weeks interval). Lost to study: 3 (healed before live assessments)	5 Observers remotely assessed smartphone images (iPhone 4, Apple Inc., Cupertino, CA, USA) twice for the presence of 9 clinical characteristics and 3 treatment decisions. Live assessment by an independent experienced clinical diabetes podiatrist was used as reference. Observers: 5 registered clinical podiatrists	Ulcer assessment. Validity/ accuracy	Validity of remote mobile phone assessment of DFU calculated between live assessment (reference) and the first assessment by individual remote observers LLR+: 1.3–4.2 LLR-: 0.13–0.88. Inter-observer reliability: MRK=0.09–0.71. Test-retest reliability: MBK=0.45–0.86	C: Mobile phone images should not be used as a standalone diagnostic instrument. L: Live assessment agreement may vary between observers
Wang et al. 2017 (57)	Cross-sectional study	Patients: 15 patients with DM and a foot ulcer, a total of 100 images. Study duration: multiple examinations. Lost to study: 0	Imaging with a smartphone (Nexus 5 LG Electronics, Seoul, South Korea) and an image capture box, using (1) single-stage support vector machines (SVM) based method, (2) single stage artificial neural network based method, (3) two-staged SVM method and (4) two-staged SVM + conditional random field (CRF) technique to determine wound boundaries. Observers: 3 experienced clinicians delineated the wound boundaries	Ulcer assessment. Accuracy	Automatic wound boundary determination: Setup 1: Se 68.3%, Sp 86.9% Setup 2: Se 66.4%, Sp 83.7% Setup 3: Se 71.4%, Sp 92.8% Setup 4: Se 73.3%, Sp 94.6%	C: Two staged SVM + CRF is sufficiently efficient for a smartphone-based image analysis of DFU. L: Limited to plantar surface. L: Limited demographic and ulcer related information
Yap et al. 2018 (65)	Cross-sectional study	Patients: 15 patients with DM, neuropathy and a history of ulceration, 15 patients without DM, a total of 240 images. Study duration: Multiple examinations. Lost to study: 0	Plantar surface of the feet were imaged using FootSnap a mobile application for Ipad (Apple Inc., Cupertino, CA, USA) on two separate occasions by two different operators. Observers: 2	Ulcer prevention. Accuracy	Reproducibility of foot images: Intrarater reliability: Diabetic feet observer 1: mean JSI=0.89 (0.84–0.93) Diabetic feet observer 2: mean JSI=0.91 (0.84–0.95) Control feet observer 1: mean JSI=0.93 (0.87–0.97) Control feet observer 2: mean JSI=0.94 (0.87–0.98). Interrater reliability: Diabetic feet: Mean JSI=0.89 (0.83–0.94) Control feet: Mean JSI=0.93 (0.90–0.98)	C: Footsnap is appropriate for longitudinal follow-up in diabetic feet. L: No assessment of feet problems. L: Observers not further specified

Audio/video/online communication

	Study design	Patients/Participants	Intervention/Comparison	Condition	Outcome	Results	Conclusion/Limitations
Wilbright et al. 2004 (69)	Non-randomized controlled trial	Patients: 140 patients with DM and a neuropathic foot ulcer I: 20 C: 120 Study duration: 12 weeks Lost to study: 3 (intervention arm), 7 (control arm) did not heal or were lost to follow-up	I: Real-time interactive video (Polycom ViewStation video conferencing) and handheld camera to link physician and wound care nurse using management algorithm; weekly telemedicine consultations C: Face-to-face treatment - regional diabetes foot program (DFP)	Ulcer treatment	Effectiveness	I vs C: Healing time: 43.2 vs 29.3 days (P=0.828) Wounds healed in 12 weeks: 75% vs 81% (P=0.546) Healing time ratio: 1.4 vs 1.0 (P=0.104) I : 10 patients required single visit to DFP for offloading device	C: No difference between telemedicine and DFP treatment; telemedicine seems to be feasible L: Telemedicine group underpowered L: Treatment options (regarding offloading) not comparable in both groups, 50% of intervention group visited outpatient clinic once L: Blinding outcome assessor not reported
Clemensen et al. 2005 (66)	Case series	Patients: 5 patients with DM and a foot ulcer Study duration: not reported Lost to study: 0	Teleconsultations via a supporting visiting nurse using a videophone (UMTS) and an internet-based ulcer record 3 consultations per patient	Ulcer treatment	Feasibility	Experience based anecdotes: Experts: had sufficient basis for coordinated treatment Nurses: capable handling technology Patients: satisfied with course of treatment	C: Expert coordinated treatment in the home may be performed successfully L: Underpowered L: Only 4 teleconsultations were performed at time of publication L: Video quality was meagre
Larsen et al. 2006 (67)	Case series	Patients: 5 patients with DM and a foot ulcer Study duration: not reported Lost to study: 0	Teleconsultations via a supporting nurse using a videophone Motorola A920 (Motorola, Chicago, IL, USA) using UMTS and an internet-based ulcer record 3 consultations per patient	Ulcer treatment	Feasibility	Description consulting process: Duration (range): 5–18 min Connection problems: minor 3/15, some 3/15, major 1/15 Audio problems: major 3/15	C: UMTS phones may be feasible for telemedicine L: Underpowered L: No clear definition of connection problems which occurred L: Video quality was meagre
Clemensen et al. 2008 (68)	Qualitative research using field observations, semi-structured interviews and focus group	Participants: 5 Visiting nurses 3 Expert nurses 1 Doctor Study duration: 2-6 weeks Lost to study: 0	Teleconsultations via a supporting nurse using a videophone Motorola A920 (Motorola, Chicago, IL, USA) via UMTS and an internet-based ulcer record 3 consultations per patient Semi structured interviews of the 5 visiting nurses and the doctor individually (90 min) A focus group interview with 3 expert nurses	Ulcer treatment	Feasibility	Experience based anecdotes: Nurse: satisfied decision making and felt secure at a distance Physician: satisfied and felt supported by visiting nurses Patient satisfaction: felt secure, improvement because of autonomy	C: Telemedicine consultations are a viable way of performing treatment in DFU L: Underpowered L: Video quality is meagre L: Limited demographic and ulcer information L: No results regarding healing/ follow-up

Study	Design	Participants	Intervention / Control	Topic	Type	Results	Conclusions / Limitations
Rasmussen et al. 2015 (70)	RCT	Patients: 401 patients with DM and a foot ulcer were randomized, 374 patients were analysed: I: 193 C: 181 Study duration: 1 year Lost to study: 27	I: Two consultations in the patient's own home by a municipal nurse. The telemedicine consultations were conducted by telephone or online written consultations with a physician at the outpatient clinic, supplemented by image of the ulcer and written assessment + one outpatient clinic consultation. C: Three outpatient clinic visits Frequency of telemedicine consultation or clinical visits was driven by clinical judgement	Ulcer treatment	Effectiveness	I vs C: Wound healing: HR=1.11 (P=0.42, 95%CI: 0.87-1.42) Amputation: HR=0.87 (P=0.59, 95%CI: 0.54-1.42) Mortality: HR=8.68 (P<0.001, 95%CI: 6.93-10.88)	C: No differences in healing and amputation rate between both groups C: Higher mortality in telemedicine group L: Treatment variations not reported L: Blinding outcome assessor not reported L: Compliance to protocol not reported L: No intention-to-treat analysis
Rasmussen et al. 2015 (72)	Qualitative research using individual interviews and a focus group Based on RCT from Rasmussen et al. 2015 (70)	Participants: 6 visiting nurses 2 medical doctors 4 nurses from outpatients clinics Study duration: unknown Lost to study: unknown	I: Two consultations in the patient's own home by a municipal nurse. The telemedicine consultations were conducted by telephone or online written consultations with a physician at the outpatient clinic, supplemented by image of the ulcer and written assessment + one outpatient clinic consultation. C: Three outpatient clinic visits A focus group and 8 semi structured individual interviews from approximately 60 minutes	Ulcer treatment	Feasibility	Telemedicine enhanced confidence among collaborators and improved the wound care skills of the visiting nurses. This effect was related to the direct communication between visiting nurses and specialist doctors. Training of the visiting nurses is a key factor in the success to securing implementation. There were concerns regarding lack of multidisciplinary wound care teams, patient responsibility and lack of patient interaction with physicians	C: Telemedicine could provide an additional option to be offered to relevant patients after an individual assessment of their health conditions C: Key factors for the successful implementation of telemedicine were: visiting nurses wound care training, focus on management, economy, periods with absence from work and clinical care L: Selection bias by selecting respondents from email invitation
Kolltveit et el. 2016 (74)	Qualitative research using focus groups Based on RCT from Smith-Strøm et al. 2018 (73)	Participants: 29 Nurses 1 Nurse assistant 2 Podiatrist 2 Physicians Study duration: 2 years Lost to study: unknown	I: At least weekly telemedicine (TM) consultation of the community nurse conducted via an interactive Web-based ulcer record and a mobile phone that enables counselling and communication with the healthcare specialist. Also consultation at the outpatient clinic every 6 weeks. C: Consultations every second week in the outpatient clinic 10 Focus group interviews from 70-90 minutes	Ulcer treatment	Feasibility	TM could increase wound assessments skills of the healthcare professionals TM improved documentation quality TM streamlined the communication between primary healthcare and the healthcare specialist	C: TM intervention enabled the participating healthcare professionals to approach their patients with more knowledge, better wound assessment skills and heightened confidence C: TM streamlined the communication between healthcare levels L: Not all participants were interviewed according to plan (twice)

Study	Design	Sample	Focus	Intervention	Results	Conclusions / Limitations
Fasterholdt et al. 2016 (71)	Based on RCT from Rasmussen et al. 2015 (70)	Patients: 401 patients with DM and a DFU were randomized, 374 patients were analysed: I: 193 C: 181. Study duration: data of 6 months were analysed. Lost to study: 27	Ulcer treatment Cost-effectiveness	I: Two consultations in the patient's own home by a municipal nurse. The telemedicine consultations were conducted by telephone or online written consultations with a physician at the outpatient clinic, supplemented by image of the ulcer and written assessment + one outpatient clinic consultation. C: Three outpatient clinic visits. Frequency of telemedicine consultation or clinical visits was driven by clinical judgement	I vs C: CEA (average treatment costs per patient): 12,356€ (95%CI: 10,402-14,310) vs 14,395€ (95%CI: 11,295-17,495) (P=0.42). Mean ICER as cost per avoided amputation: -67,973€	C: Telemonitoring service in this form has similar costs and effects as standard outpatient monitoring. Cost savings by providing TM care for individuals with diabetic foot ulcers are uncertain. L:Data from SF-36 questionnaires and QALY's was insufficient. L: Study was powered to detect a change in number of emergency department visits, and not differences in the cost of outpatient of inpatients visits. L: Only 6 months of data were analysed
Smith-Strom et al. 2016 (75)	Qualitative research using one-to-one interviews. Based on RCT from Smith-Strom et al. 2018 (73)	Patients: 24 patients with DM and a foot ulcer. I: 13 C: 11. Study duration: 14 months. Lost to study: 0	Ulcer treatment Feasibility	I: At least weekly telemedicine (TM) consultation of the community nurse conducted via an interactive Web-based ulcer record and a mobile phone that enables counselling and communication with the healthcare specialist. Also consultation at the outpatient clinic every 6 weeks. C: Consultations every second week in the outpatient clinic. Individual semi-structured interviews with patients from 35-55 minutes	Competence in wound management of health professional was of great importance for patients' experience of security during wound care. Effective teaching of patients about wound care occurred mainly at the outpatient clinic by specialists and was less frequently done at home by home care nurses. Continuity of care: interpersonal continuity, informational continuity and management continuity are essential to patients	C: Effective wound care pathway for patients with DFUs depends on professionals' competence and professionals' skills in wound management and on continuity of care. C: TM can be an important supplement in that process when it is used as intended. L: Only a sample of the RCT. L: No information on the follow-up of the patients (healing process)
Kolltveit et al. 2017 (76)	Qualitative research using focus groups. Based on RCT from Smith-Strom et al. 2018 (73)	Participants: Group 1: 29 point-of-care professionals working in either primary/home based or in specialist hospital outpatient settings. Groups 2: 5 registered nurses in various clinical leadership roles in primary/home based care or hospital outpatient settings. Study duration: 2 years. Lost to study: 0	Ulcer treatment Feasibility	I: At least weekly telemedicine (TM) consultation of the community nurse conducted via an interactive Web-based ulcer record and a mobile phone that enables counselling and communication with the healthcare specialist. Also consultation at the outpatient clinic every 6 weeks. C: Consultations every second week in the outpatient clinic. 10 Focus group interviews with participants from 70-90 minutes	Healthcare professionals were highly enthusiastic. Four conditions perceived by healthcare professionals are crucial to a successful TM care delivery experience: - User friendly technology and training - A TM champion (someone close who could facilitate the TM intervention) - Committed and responsible leaders - Effective communication channels at the organizational level	C: Successful larger scale implementation of TM must involve consideration of complex contextual and organizational factors associated with different work settings. C: Attention to the distinct needs of each staff group seems an essential condition for effective implementation. L: Only focus group, no observational methods for data gathering. L: Selection bias in group 2

Study design	Study population and characteristics	Intervention and control conditions		Results outcomes	Conclusion/limitations
Kolltveit et al. 2017 (77) — Qualitative research using observations and individual interviews. Based on RCT from Smith-Strom et al. 2018 (73)	Participants: Healthcare professionals recruited form the intervention arm: 3 wound care nurses in home-based care, 4 professionals from the outpatient clinic. Study duration: unknown. Lost to study: 0	I: At least weekly telemedicine (TM) consultation of the community nurse conducted via an interactive Web-based ulcer record and a mobile phone that enables counselling and communication with the specialist healthcare. Also consultation at the outpatient clinic every 6 weeks. C: Consultations every second week in the outpatient clinic. 8 Field observations in the outpatient clinic, 2 in a home-based setting and 7 individual interviews	Ulcer treatment / Feasibility	The use of TM as indented depends on spatial issues, time available to conduct the DFU care, different access to equipment at hand and working in a team versus alone. Using the Web-based record leads to a more comprehensive approach of DFU care and increased the competence of healthcare professionals	C: Application of TM in home-based care is challenging. C: Introducing more updated equipment and minor structural adjustments in consultation time and resources could make the use of TM in home-based care more robust. L: Only a few participants were interviewed and observed. L: Only two observations in the home-based care setting
Smith-Strom et al. 2018 (73) — RCT	Patients: 182 patients with DM and a foot ulcer. I: 94, C: 88. Study duration: 12 months. Lost to study: 0	I: At least weekly telemedicine (TM) consultation of the community nurse conducted via an interactive Web-based ulcer record and a mobile phone that enables counselling and communication with the healthcare specialist. Also consultation at the outpatient clinic every 6 weeks. C: Consultations every second week in the outpatient clinic	Ulcer treatment / Effectiveness	I vs C: Wound healing: SHR=1.16 (95%CI: 0.85-1.59). Amputation rate (mean difference): -8.3% (95%CI: -16.3–-0.5). Mortality rate (mean difference): -0.4% (95%CI: -6.5-5.7). Consultations at outpatient clinic (monthly): 2.0±1.9 vs 2.5±3.0. Consultations by community nurse (monthly): 6.7±3.4 vs 5.9±4.6	C: TM follow-up in patients with DFUs in primary healthcare was noninferior to standard out patients care. C: There were significant fewer amputations in the TM group. L: Only patients with superficial ulcers were included. L: No information on offloading. L: No information on the specific location of the ulcer on the toe (plantar/dorsal/apex)

Abbreviations per column:

Study design: RCT = randomized controlled trial

Study population and characteristics: ABI = ankle-brachial index, DFU = diabetic foot ulcer, DM = diabetes mellitus, IWGDF = International Working Group on the Diabetic Foot, PVD = peripheral vascular disease

Intervention and control conditions: 3D = three dimensional, CRF = conditional random field, DFP = diabetic foot program, HSI = hyperspectral imaging, NIRS = near-infrared spectroscopy, PFID = photographic imaging device, SVM = single-stage support vector machines, TM = telemedicine, UMTS = Universal Mobile Telecommunication System, VAS = visual analogue scale

Results outcomes: AU = arbitrary units, CEA = cost-effectiveness analysis, CI = confidence interval, [HbO2] = concentration of oxygenated haemoglobin, HR = hazard ratio, ICC = interclass correlation coefficient, ICER = incremental cost-effectiveness ratio, JSI = Jaccard similarity index, k = kappa, KAC = Krippendorff's alpha coefficient, Lepi = estimated average epidermal thickness, LLR+ = positive likelihood ratio, LLR- = negative likelihood ratio, MBK = free marginal bi-rater Bennett kappa, MCC = Matthews correlation coefficient, MRK = free marginal multirater Randoph's kappa, NPV = negative predictive value, NS = Non significant, OR = odds ratio, PPV = positive predictive value, r = correlation, RE = relative error, [Tot Hb] = total concentration of haemoglobin, SaO2 = serial microvascular oxygen saturation, SD = standard deviation, Se = sensitivity, SHR = sub hazard ratio, Sp = specificity, t = Student's t-test, [Tot Hb] = total concentration of haemoglobin

Conclusion/limitations: QALY= quality-adjusted life year

Chapter 3

The cost-effectiveness and cost-utility of
at-home infrared temperature monitoring in
reducing the incidence of foot ulcer recurrence
in patients with diabetes (DIATEMP):
study protocol for a randomized controlled trial

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ABSTRACT

Background
Home monitoring of foot temperatures in high-risk diabetes patients proves to be a promising approach for early recognition and treatment of pre-signs of ulceration, and thereby ulcer prevention. Despite previous studies demonstrating its efficacy, it is currently not widely applied in (Dutch) health care.

Methods
In a multicenter, outcome-assessor blinded, randomized controlled trial 304 patients with diabetes mellitus type I or II, loss of protective sensation based on peripheral neuropathy, and a history of foot ulceration in the preceding four years or a diagnosis of Charcot neuro-osteoarthropathy will be included. Enhanced therapy will consist of usual care and additional at-home daily measurement of foot temperatures at 6-8 predefined locations on the foot. If a contralateral foot temperature difference >2.2°C is found on two consecutive days, the participant is instructed to contact their podiatrist for further foot diagnosis or treatment, and to reduce ambulatory activity with 50% until temperatures are normalized. Enhanced therapy will be compared to usual care. The primary outcomes are the cost (savings) per patient without a foot ulcer (i.e. cost-effectiveness) and per quality adjusted life year gained (i.e. cost-utility). The primary clinical outcome in the study is the proportion of patients with foot ulcer recurrence on the plantar foot, apical surfaces of the toes, the interdigital spaces or medial and lateral forefoot surface during 18-months follow-up.

Discussion
Confirmation of the efficacy of at-home foot temperature monitoring in ulcer prevention, together with assessing its usability, cost-effectiveness and cost-utility, could lead to implementation in Dutch health care, and in many settings across the world

Trial registration: Netherlands Trial Registration: NTR5403, date of registration: 8-9-2015.

BACKGROUND

Despite many recent advances in medical therapies, the prevalence of diabetes mellitus and diabetes-related complications continues to increase. With a life-time prevalence of 19-34% (1), foot ulceration is one of the most common complications in people with diabetes. This frequently leads to hospitalization and lower-extremity amputation (2). With an annual incidence rate of 2.2% and 1 million people with diabetes, approximately 22.000 ulcers develop in the Netherlands each year (3, 4). Foot ulcers frequently become infected, cause great morbidity and have a negative impact on health-related quality of life and patient mobility (5-7). Furthermore, mortality risk at 10 years is twice as high in patients who had a foot ulcer compared to those who have not (8). Besides the patient and social burden of diabetic foot disease, foot ulcers cost €5.000 to €17.000 per episode in specialized centers in Europe and place a large burden on the health care systems (9).

Recognizing the potential for severe morbidity and high treatment costs related to foot ulceration, many experts call for widespread establishment of preventative foot care programs for persons with diabetes (10-12). The most common mechanism of foot ulceration involves a cumulative effect of repetitive trauma at pressure points on the foot over the course of several days that goes unrecognized because of the presence of neuropathy (1). Guidelines therefore recommend proper patient education, identification and treatment of the diabetic foot at-risk, integrated foot care and protective pressure-relieving footwear (10, 13, 14). Despite these guidelines, the incidence of foot ulcer recurrence remains very high: 40% in the first year and 60% in the first 3 years after healing of a foot ulcer (1). Therefore, care providers and patients are in need of new adjunctive ways to prevent ulcer recurrence.

Stimulated by the need for innovation in foot ulcer prevention, at the beginning of this millennium, researchers developed the concept of at-home monitoring of foot temperatures as a preventative tool (15-17). Foot ulcers are preceded by increased local skin temperature due to inflammation and enzymatic autolysis of tissue as a result of being ambulatory (16, 18); the foot tends to locally heat up before it breaks down. These increased temperatures can easily be assessed by the patients themselves using some form of thermometry that measures skin temperature at predefined regions of the foot (16). By monitoring these temperatures on a frequent basis (preferably daily), the patient can identify signs of inflammation and impending ulceration. Timely identification of these warning signs allows the patient or care provider to take action to decrease the inflammation before an ulcer develops, for example by reducing ambulatory activity, and/ or providing (further) offloading of the specific regions with footwear, orthoses or felted foam. In three randomized controlled trials (RCTs), such at-home monitoring of the foot temperature was shown to be a highly effective tool in preventing foot ulcer recurrence in patients with diabetes (15-17).

Despite the demonstrated efficacy of at-home monitoring of foot temperature in these studies (15-17), the intervention is currently not widely applied in (Dutch) health care. This may be because

the external validity of the findings of these studies has not been proven to date, as the studies were conducted by the same research group in one geographical location in the US. Recently, another RCT that followed a similar study protocol and used the same infrared temperature device as the previous US studies was conducted in Norway (19). They found no statistical difference in ulcer recurrence rate between patients who monitored their skin temperature at home and patients who did not. However, only 41 patients were included in this study and the follow-up time was only one year, which means that this study was underpowered and caution is needed in interpreting these findings (19). Another reason for the limited implementation in daily foot care may be that the intervention involves the purchase of a thermometer, while it is unclear whether the costs are reimbursed or have to be covered by the patient. Moreover, when 'hot-spots' occur, additional diagnosis and treatment may be needed, of which frequency, costs and reimbursement are all unknown. Furthermore, the daily assessment and recording of foot temperatures may be seen as cumbersome and a heavy load in a situation where patients already have to monitor many aspects of their disease (e.g. glucose monitoring, insulin application, medicine intake, frequent check-ups, footwear use, etc.). Additionally, the knowledge on diagnostic accuracy of foot temperature assessments (e.g. false-positive and false-negative outcomes) is limited. The aforementioned US studies (15-17) did not report false-positive or false-negative outcomes. Eight of the 21 intervention-group patients in the Norwegian RCT measured an increased skin temperature one or more times during that study, but only four of these patients contacted the study nurse, and none developed a foot ulcer (19). Recently, Frykberg and colleagues showed that with the use of a plantar foot temperature-monitoring mat, 97% of all non-traumatic diabetic foot ulcers that developed in a group of 132 patients with a history of foot ulceration could be identified before development of the ulcer through a temperature difference >2.2°C between similar spots on both feet (20). However, a high false-positive rate was also found (57% of temperature differences >2.2°C found were false alarms), and the variation of contralateral temperature differences in the group of patients that did not develop a foot ulcer was substantial: 2.81°C (±1.42°C). Similar high rates of false-positive outcomes were also described by Wijlens and colleagues (21). When such incorrect observations are made, they can result either in over-diagnosis or over-treatment resulting in an additional burden for both the patient and health care system. For these reasons, it is important that more knowledge is gained in different settings on the effectiveness, cost-effectiveness, cost-utility, and diagnostic accuracy of using at-home temperature monitoring in high-risk patients with diabetes.

The International Working Group on the Diabetic Foot (IWGDF) identified ulcer prevention as an area where data on the effectiveness of interventions is scarce and data on their cost-effectiveness is lacking (10-12). A better understanding of how (recurrent) foot ulcers develop and how they can be prevented in a cost-effective way has major relevance for the patient and health care. Therefore, we have designed the DIAbetic foot TEMPerature trial (DIATEMP). DIATEMP aims to assess the effectiveness, cost-effectiveness and cost-utility of at-home infrared foot temperature monitoring to reduce the incidence of foot ulcer recurrence in patients with diabetes mellitus.

METHODS

Primary objective
To evaluate the effectiveness, cost-effectiveness and cost-utility of daily at-home infrared plantar foot temperature monitoring to reduce the incidence of foot ulcer recurrence in patients with diabetes mellitus.

Hypothesis
We hypothesize that enhanced therapy, which includes at-home infrared temperature monitoring of the foot, results in a significantly lower proportion of patients with foot ulcer recurrence, is cost-effective and saves costs per quality-adjusted life years gained when compared to usual care. The hypothesis is based on superiority of enhanced therapy compared to usual care.

Standard protocol items
The DIATEMP trial protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Study design
The study design is a multicenter, outcome assessor blinded parallel group RCT with two study arms:
1. Enhanced therapy, including usual care as provided in the Netherlands and additional at-home daily plantar foot temperature monitoring
2. Usual care as provided in the Netherlands

Patient recruitment takes place from seven university or community-based hospitals with a multidisciplinary diabetic foot clinic in different regions throughout the Netherlands and from professional practices of podiatrists who participate in these multidisciplinary teams. Each diabetic foot clinic will operate as one of the study centers. Within each center, a physician and a podiatrist, both members of the diabetic foot team, will be involved. The participating hospitals are: Academic Medical Center (Amsterdam), VU Medical Center (Amsterdam), Ziekenhuisgroep Twente (Almelo), Maxima Medisch Centrum (Veldhoven), Maastricht University Medical Center (Maastricht), Reinier de Graaf Gasthuis (Delft), and Medisch Spectrum Twente (Enschede). Participants who consent to participate and who meet the inclusion and not the exclusion criteria will be randomized to the usual care or the enhanced therapy group. Each participant will be followed for 18 months or until a foot ulcer develops, after which the participant will be followed for the remainder of 18 months for the cost analysis only. The SPIRIT figure (figure 1) shows an overview of the study design and the main procedures that participants will undergo during the course of the study.

Figure 1: Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) figure: study design overview

Time point	Enrolment $-T_2$	Enrolment $-T_1$	Allocation 0	Post-allocation T_3	T_6	T_9	T_{12}	T_{15}	Close-out T_{18}
Enrolment									
Initial eligibility screen*	X								
Study information to participant	X								
Initial willingness to participate		X							
Crosscheck inclusion/ exclusion criteria		X							
Informed consent			X						
Final eligibility screen			X						
Allocation			X						
Interventions									
Usual care			⟶						
Enhanced therapy			⟶						
Assessments									
Demographic and disease-related characteristics			X						
Physical (neuropathy, PAD, foot deformity)			X						
Photographs of the foot			X						
SF-36			X						X
EQ-5D-3L			X	X	X	X	X	X	X
iPCQ & iMCQ				X	X	X	X	X	X
Ulcer outcome			⟶						
Process evaluation				X	X	X	X	X	X

Done by podiatrist, during outpatient clinic visit, or retrospectively, from outpatient visit lists

T_3, T_6, T_9... refer to assessments at 3, 6, 9,... months follow-up

PAD: peripheral artery disease; SF-36: 36-Item Short Form Health Survey; EQ-5D-3L: 3 Level EuroQol Quality of Life Scale; iPCQ: Productivity Cost Questionnaire; iMCQ; Medical Consumption Questionnaire

Participants

The study population consists of patients that are at high-risk of developing a foot ulcer. These are diabetic patients with a loss of protective sensation based on peripheral neuropathy and a history of foot ulceration in the four years prior to inclusion in the study, or a history of Charcot neuro-osteoarthropathy (IWGDF diabetic foot risk classification category 3 (22)).

Inclusion and exclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following inclusion criteria:

1. Diabetes mellitus type 1 or 2;
2. Aged 18 years or above;
3. Loss of protective sensation based on the presence of peripheral neuropathy (22);
4. Recent history of a foot ulcer or foot amputation, i.e. an ulcer, defined as cutaneous erosion through the dermis without reference to time present (22, 23), has been present for at least 2 weeks and has healed within four years before randomization; or a confirmed diagnosis of midfoot or forefoot Charcot neuro-osteoarthropathy;
5. Ability to provide informed consent;
6. Ambulatory status (i.e. not permanently wheel-chair bound);
7. The participant has foot care from a podiatrist or is willing to undergo foot care by a podiatrist.

And not have any of the following exclusion criteria:

1. Active foot ulceration or open amputation sites;
2. Active Charcot neuro-osteoarthropathy;
3. Active foot infection, based on criteria of the PEDIS classification (23);
4. Amputation proximal to the Chopart joint in both feet;
5. Critical limb ischemia, based on criteria of the PEDIS classification (23);
6. Severe illness that would make 18-months survival unlikely, based on the clinical judgment by the physician;
7. Concomitant severe physical or mental condition(s) that limit the ability to follow instructions for the study, based on the clinical judgment by the physician. This includes the inability to perform temperature measurements, without having a caretaker who can perform the temperature measurements;
8. Current use of at-home foot temperature monitoring.

Sample size calculation

Based on the results of a footwear efficacy trial that was largely conducted in the same centers as this trial and also assessed patients with a history of foot ulceration (24), we anticipate for the usual-care group that 44% of participants will develop a recurrent foot ulcer during 18 months follow-up. Using a conservative estimate from three previous trials on the effectiveness of at-home foot temperature monitoring (15-17), we anticipate that 28.6% of participants in the enhanced therapy group will develop a recurrent foot ulcer in 18 months; this represents a 35% effect size. With α 0.05 (two-sided), power 80%, and based on an intention-to-treat analysis in which clinical outcome data from all included patients will be assessed, 304 eligible participants are required and will be randomly assigned.

Randomization and blinding

After the baseline assessment, participants will be randomly assigned to either usual care or enhanced therapy using an online-accessible computer-generated allocation sequence (TENALEA Clinical Trial Data Management System; National Cancer Institute, Amsterdam, the Netherlands) that uses the nondeterministic minimization method. The allocation sequence will be prepared and managed by a non-involved investigator from the Clinical Research Unit of the Academic Medical Center in Amsterdam. Randomization will be stratified according to participating center and gender.

The persons responsible for assessing the primary clinical outcome (i.e. foot ulcer) will be blinded to the group allocation. Participants are asked not to disclose their allocation in the study to their treating physician. The involved podiatrists and investigators are not blinded to group allocation.

Usual care

Usual care as provided in the Netherlands generally follows universal guidelines (10, 13, 25), and consists of, but is not limited to:

1.   Therapeutic (custom-made) footwear that is evaluated every 3 to 6 months by a medical specialist and/ or professional (e.g. orthotist, podiatrist). Footwear can include custom-made shoes, semi-custom-made shoes, and orthopaedic appliances to footwear or podiatric insoles.

2.   Patient education that is provided by verbal and/ or written information by physician, podiatrist or the investigator during the baseline visit. Information addresses ulcer aetiology, risk factors for ulceration, and self-care practices.

3.   Once every 3-6 months multidisciplinary foot care and screening and/ or once every 1-3 months preventative foot care and screening by a podiatrist and/ or diabetes pedicure.

Participants are advised to contact their podiatrist if they identify an area of concern.

Enhanced therapy

Enhanced therapy consists of:

- Usual care (see above), *and*
- At-home daily measurement of foot temperatures with an infrared thermometer on six predefined plantar regions on each foot, plus an additional one or two locations based on participants' ulcer history or pre-ulcer status, if indicated and if different from the predefined locations.

Using an infrared thermometer (TempTouch®, Diabetica Solutions, San Antonio, TX, USA) (15-17), skin temperature is measured at six predefined locations on the plantar surface of each foot: hallux, second and third toe, first, third and fifth metatarsal heads. In addition, based on the participants' ulcer history or pre-ulcer status, a maximum of two plantar foot regions can be added to the six predefined locations. For example, a midfoot region could be added for a person with Charcot deformity.

The foot temperature will be measured once per day at both feet, per instruction in the morning directly after waking up. To standardize measurements, a video for the correct use of the thermometer has been developed and is shown to the participants in the enhanced therapy group during the baseline visit. To facilitate measurements and to facilitate adherence to measuring foot temperatures, the participant is advised to place the thermometer, logbook and a pen on their bedside table. The participant will record each temperature value in a logbook. The participant will be asked to return completed logbooks to the coordinating study center (Academic Medical Center) every 4 weeks. Participants will receive once in two weeks a text reminder on their mobile phone to stimulate adherence in temperature monitoring and to remind them to decrease their ambulatory status if skin temperature in a region is >2.2°C compared to the corresponding region on the contralateral foot for two consecutive days.

If skin temperature measured in a region is >2.2°C compared to the corresponding region on the contralateral foot for two consecutive days, the participant is instructed to contact their podiatrist. The podiatrist will ask them about any swelling, change in colour, change in structure, or drainage present at the high-temperature location. Based on these outcomes, further diagnosis at the podiatrist's office may take place. In any case, the participant will be asked to decrease ambulatory activity with approximately 50% until the temperatures normalize (≤2.2°C temperature difference) (15-17). If the temperature difference exceeds 4°C, or if temperatures do not normalize and are abnormal for four consecutive days, the participant is advised to arrange to be seen immediately by their podiatrist. If pre-signs of a foot ulcer are identified by the podiatrist, necessary precautions will be taken. This may include further offloading with therapeutic footwear or insoles, orthoses, felted foam or debridement. If needed, direct referral for treatment to specialized multidisciplinary care will take place. This may involve, among other things, immobilization of the foot.

During the first two weeks after randomization, patients are instructed to contact their local study investigator in case of abnormal (>2.2°C) temperature differences at the predefined regions on two or more consecutive days. These measurements may reveal structural temperature differences (>2.2°C) between the regions of interest of both feet without any symptoms or signs of inflammation or ulceration present (e.g. due to mild to moderate unilateral peripheral artery disease). In these cases an individually calculated threshold temperature will be used based on the mean temperature difference between the left and right foot measured in the first two weeks after randomization.

Participants who are unable to measure skin temperature at the standard predefined regions due to amputation will measure at an alternative region to replace the amputated site according to a specifically-designed amputation protocol (Table 1).

Table 1: Amputation protocol

Amputation site	**Alternative region for measurement on the ipsilateral foot**	**Region(s) for comparison on the contralateral foot**
Hallux	MTH I or second toe*	Hallux
Second Toe	Third toe	Second toe
Third Toe	Second or fourth toe*	Third toe
Hallux and (trans)metatarsal I	Most distal plantar part of the amputation site or second toe*	Hallux
	Most distal plantar part of the amputation site	MTH I
Second toe and (trans)metatarsal II	Third toe	Second toe
Third toe and (trans)metatarsal III	Fourth toe	Third toe
	Most distal plantar part of the amputation site	MTH III
Fifth toe and (trans)metatarsal V	Most distal plantar part of the amputation site	MTH V
Transmetatarsal amputation of the forefoot	Most distal plantar part of the amputation site at the base of the first, third and fifth metatarsal bone	MTH I, III and V[#]
Amputation of the forefoot trough the Lisfranc joint	The plantar site of the first cuneiform bone, third cuneiform bone and the cuboid bone	MTH I, III and V[#]
Amputation of the forefoot trough the Chopart joint	Most distal plantar part of the amputation site: medial, mid and lateral	MTH I, III and V[#]

*Based on temperature values in the first two weeks, the investigator chooses the alternative region

[#] In case of a transmetatarsal amputation of the forefoot, or a more proximal amputation, no alternative region to measure for the hallux, second and third toe can be identified. In these cases, the measured temperatures of these regions in the intact foot are compared with the mean temperature of these regions measured in the first two weeks of temperature monitoring, using the same foot as reference. This is comparable to the protocol used for participants with a unilateral transtibial amputation. For further explanation, see the text.

If participants have a transtibial or a more proximal amputation, plantar foot temperatures at the predefined regions of the intact foot will be compared to a calculated mean temperature of the same regions as obtained during the first two weeks of measurement after randomization. The investigator calculates the mean temperature for each region over the first two weeks, enters these as reference in the logbooks of the participant and sends the logbooks to the participant. Starting in the third week, participants compare their daily temperatures with these new reference temperatures. The same threshold temperature (>2.2°C) applies.

Outcomes

The primary outcomes in this study are the cost (savings) per patient without a foot ulcer (i.e. cost-effectiveness) and per quality-adjusted life year (QALY) gained (i.e. cost-utility). The primary clinical outcome is the proportion of participants with a recurrent foot ulcer on the plantar foot, apical surfaces of the toes, interdigital spaces or medial and lateral forefoot surface during 18-months follow-up. A foot ulcer is defined as a cutaneous erosion through the dermis without reference to time present (22, 23). Endpoints in the study are either a foot ulcer, or 18 months of follow-up.

Secondary outcomes are the costs of therapy and of ulcer treatment, adherence to at-home foot temperature monitoring, and a multivariate risk score for ulcer recurrence.

Study procedures

The study investigators will obtain informed consent and will perform all study measurements, during baseline and the 3-month semi-structured interviews with participants by phone.

Baseline assessment

After providing informed consent, participants will undergo a baseline assessment at their study center to confirm definitive eligibility for inclusion in the study. The following characteristics will be obtained during the baseline visit:

1. Demographic information and disease-related characteristics (e.g. diabetes duration and control, presence of complications, ulcer history, footwear use, etc.);
2. Peripheral neuropathy assessment:
    a. Presence of neuropathy will be assessed by measuring the loss of protective sensation by using the 10-grams (5.07) Semmes-Weinstein monofilament at the plantar surface of the hallux and the first and fifth metatarsal heads of both feet (10). Neuropathy is defined when the monofilament is not felt on 2 or more locations (22).
    b. 128-Hz Tuning fork held on the apex of the great toe (10). Neuropathy is defined when the participant indicate not to feel the vibration (22).
3. Peripheral vascular assessment by palpation of the dorsalis pedis and posterior tibial pulses of both feet, according to the PEDIS classification system (23). If pulses are not palpable, additional assessment of peripheral vascular status will be done by measuring toe pressures or the participant's medical record is checked for their vascular status.

4.   Presence of foot deformity will be assessed clinically. These include hammer/ claw toes, prominent metatarsal heads, hallux valgus, pes planus, pes cavus, Charcot deformity, and any amputation. Participant's feet will be classified into one of four categories according to the severity of deformity present: no deformity, mild deformity, moderate deformity, and severe deformity (24).

If definitive eligibility has been confirmed, photographs of the plantar and dorsal surface of both feet will be taken according to a standardized protocol (24), and health-related quality of life will be assessed by using the 36-Item Short Form Health Survey (SF-36) and the 3 level EuroQol Quality of Life Scale (EQ-5D-3L) questionnaires.

Ulceration

If the participant, treating physician, podiatrist or pedicure identifies an ulcer in-between regular study visits, they are instructed to inform the diabetic foot team or podiatrist immediately, and have photographs taken of the foot. The podiatrist will take photographs of the wound, debride the wound if required to assess outcome, classify the ulcer using the University of Texas system and the PEDIS classification system, and again take photographs of the lesion after debridement using a standardized protocol and enter all data in an outcome case report form (CRF) (23, 26). This information will be sent to the investigator, who will upload all information anonymously to a web-based environment for ulcer outcome assessment by a panel of minimally three blinded and independently operating foot care specialists that will determine the definitive outcome (24).

Health-related quality of life and costs

For the cost-effectiveness and cost-utility analyses, the following data will be collected at 3-monthly intervals:

1.   Health-related quality of life will be assessed by asking participants to complete the EQ-5D-3L questionnaire. These questionnaires will be sent to the participant's home and returned after completion in an enclosed return-envelope.
2.   At the same time-interval of three months, or in case a foot ulcer develops at monthly intervals, the participant is asked to complete the study specified versions of the institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire (iPCQ) and iMTA Medical Consumption Questionnaire (iMCQ) (27) to gather volume data on productivity loss, out-of-hospital use of health care resources (e.g. podiatrist, pedicure), and out-of-pocket expenses.
3.   Use of intramural health care resources during the study will be obtained from the participants' medical status.

Process evaluation

At 3-monthly intervals, the investigator will contact the participant by phone to conduct a process evaluation of the intervention. Intervention group participants will be asked in a semi-structured interview about their experiences with at-home temperature monitoring. All participants will also be asked about contacts with health care professionals and any foot problems encountered in

the previous 3-months period, to crosscheck for the completed iPCQ and iMCQ questionnaires and for any lesion that may have developed.

Data management

The participants will be coded by the number of the participating center (two digits) followed by the number of the participant (three digits). All information referring to the patients will be saved in a locked record-office or on a computer with password security. Only the investigators have access to this study information. Name and date of birth of the participants will only be recorded on the informed consent form, which will be kept in a locked cupboard with the lead investigator per center, separate from the digital data and without a possibility to trace the data. All study data will be entered anonymized in an electronic database OpenClinica®. All study information will be saved for at least 15 years after the study has ended.

Monitoring

Given the pragmatic nature of the intervention and the very low, negligible, risk for the participants in the study, an independent Data Safety and Monitoring Board is not established. The investigators are responsible for procedures of data monitoring. To facilitate compliance with good clinical practice guidelines, the investigator will permit study-related monitoring, audits, and inspections by authorized organizations. Aspects that will be monitored may include: inclusion rate; trial master file; informed consent progress; in- and exclusion criteria; source data verification; safety reporting; investigational product; trial procedures; and closing and reporting. Currently, the DIATEMP trial is monitored internally by the Academic Medical Center Amsterdam, VU Medical Center and the Maastricht University Medical Center. The role of the data monitor is to review study documentation, CRFs and informed consents.

Withdrawal of participants

Participants can withdraw from participation in the study at any time for any reason if they wish to do so, and without any consequences for their normal care. The physician can decide to withdraw a participant from the study in case of urgent medical reasons. After withdrawal from the study, information on ulcer outcome at 18 months will be obtained from the participant's medical record if the participant consents to this procedure. Ulcer outcome data from participants who die during the study will be based on outcome at the moment of death (last observation carried forward).

Serious adverse events (SAEs)

Any SAE that occurs during the study will be reported by the principal investigator to the accredited medical research ethics committee (METC) that approved the protocol, within 15 days of when the principal investigator has been informed about the serious adverse event (within 7 days if death is the SAE).

Statistical analysis

Statistical analysis will be performed after the last follow-up visit of the last participant in the study, and will be conducted using SPSS statistical software (IBM Corporation, Armonk, NY). All tests will assess group effects, will be two-sided, and use $P<0.05$ as significance level. All comparisons between groups are based on both an intention-to-treat and a per-protocol analysis.

Effectiveness of the intervention will be assessed using Chi-square analysis. A competing risk analysis will be done to assess the difference by time to ulcer recurrence, with unrelated death as the competing risk and absence of ulcer at 18 months as censored observation.

Economic evaluation

The economic evaluation will be performed as a cost-effectiveness analysis with the costs per prevented foot ulcer as the primary outcome. A cost-utility analysis will be performed with the costs per quality-adjusted life-year (QALY) as outcome. Both will be performed from a societal perspective. Considering the time horizon of 18 months, we will discount the effects and costs during the second year of follow-up. The Dutch government recommends a discount rate of 4% for costs and 1.5% for effects (28).

Given the societal perspective, data will be collected on direct medical and non-medical costs as well as indirect non-medical costs. Direct medical costs include for example the costs of foot care, the thermometer and care provided by other health care professionals (general practitioner, medical specialist). Direct non-medical costs include for example out-of-pocket expenses by patients for travel to and from health care providers, private household assistance and over-the-counter medication. Indirect non-medical costs reflect the costs of productivity loss due to sick leave from work or lower productivity while at work. Costs will be calculated as the product sum of resource volume data and their respective unit costs, as described in the Dutch manual for costing in health care research (29). Costs associated with productivity loss will be based on the friction cost method, applying the actual mean friction period in the base year of the study. After price-indexing with general yearly consumer price indices, all costs will be expressed in Euros for the base year 2015.

Incremental cost-effectiveness ratios will be calculated as the extra costs per additional patient without foot ulcer and the extra costs per QALY gained. To account for sampling variability, group differences will be assessed by calculating the 95% confidence intervals after correction for bias and using accelerated non-parametric bootstrapping. If enhanced therapy does not dominate usual care, results will be displayed graphically with cost-effectiveness acceptability curves for willingness to pay values up to €100.000.

Health utilities associated with the scoring profiles on the EQ-5D-3L are available through the cross-walk value sets from the www.euroqol.org website and will be used to derive a QALY estimate for each patient. This QALY will be calculated as the product sum of health utilities and the lengths of the periods in-between successive measurements. In case of missing assessments, the last observation will be carried forward. Sensitivity analyses will be performed for different (Dutch and UK population based) health utility scoring algorithms used to derive QALYs as well as for different discounting rates to reflect time preference.

A subgroup analysis of cost-effectiveness and cost-utility will be performed by level of adherence to temperature monitoring.

The cost consequences of monitoring foot temperature at home, such as by the use of the measurements device and intensified monitoring costs, may affect health care budgets. A budget impact analysis (BIA) will be carried out from governmental, health care provider and insurer perspectives. The governmental perspective is chosen to help setting priorities in health care optimization while simultaneously considering the wider implications of stimulating enhanced therapy for diabetic patients at a high risk of ulcers beyond the health care sector. The provider perspective is chosen to support local decisions on economies of scale and affordability. The insurer perspective is chosen to assess the net financial consequences of offering intensified monitoring to high-risk patients who have a history of ulceration, which may help to shift health care use from the second to the first echelon. For this study, the BIA will be conducted using a decision-tree model developed in Microsoft® Excel. The BIA will be performed according to the ISPOR Task Force principles (30).

Finally, a scenario analysis will be carried out, simulating three implementation scenarios against the base scenario (usual care): I) immediate use of the device, II) gradual use (an absolute 25% yearly increase of patients in the target group using the device), and III) partial use (up to 70% of the whole target population). Sensitivity analyses will be applied for the level of adherence to temperature monitoring and for a potential shift from podiatric to pedicure foot care. The BIA will have a time horizon of 4 years. Results will be reported for successive calendar years.

Ethical approval and consent to participate
Ethical approval for the trial has been obtained by the METC of the Academic Medical Center in Amsterdam (NL 52735.018.115). Important protocol modifications are communicated to the accredited METC and only effective after a favourable opinion by the METC. Informed consent to participate in the trial is obtained from all participants. The trial is conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act.

DISCUSSION

The DIATEMP trial is a multicenter randomized controlled trial with the aim to determine cost-effectiveness and cost-utility of at-home monitoring of plantar foot temperature for preventing foot ulcer recurrence in high-risk diabetes patients. Following three successful RCTs demonstrating the efficacy of at-home foot temperature for preventing diabetic foot ulcer recurrence in one geographical region (Texas) in the United States of America (15-17), this is the first adequately designed and powered RCT to investigate this intervention in another geographical location (the Netherlands). In addition to the previous RCTs, we include assessment of cost-effectiveness and cost-utility. After the start of participant inclusion in the study, we modified and improved our protocol to a limited extent based on new insights and necessities; the most important changes are described and clarified below.

Crucial in any trial is sufficient patient recruitment. We anticipated, based on calculations of recruitment rate from a previous trial (24), that the required period for including the 304 participants would take 15 months in the participating five centers. Unfortunately, the response rate of potentially eligible participants was below 25%, while we hypothesized a response rate of approximately 50%. To increase participant inclusion, we intensified the collaboration with the study centers and the involved podiatrists, and we added two more study centers (VU Medical Center, Amsterdam, and Medisch Spectrum Twente, Enschede). We additionally adjusted one of the inclusion criteria. We initially included only participants with a healed foot ulcer in the 2 years prior to study randomization. This had the advantage of selecting only the highest risk patients, with re-ulceration rates being approximately 60% in the first three years after healing (1). To increase the potential for inclusion we prolonged the ulcer-free period before study randomization to a maximum of 4 years. These changes in the protocol resulted in increased recruitment rates for the trial.

Due to the high risk of ulceration and frequent occurrence, diabetic patients with a history of amputation are important to include in a prevention trial (2). In the trial of Lavery and colleagues, patients with a minor amputation such as a great toe were instructed to measure their foot temperature at the basis of the amputated region, while patients with an amputation proximal of the forefoot were excluded (17). Other trials on at-home monitoring of skin temperature describe no specific protocol for patients with an amputation (15, 16, 19). Since at-home foot temperature monitoring is based on the principle of comparing bilateral foot temperatures at the same anatomical region, a specific protocol is needed for participants with an amputation. Initially, we used the protocol of Lavery and colleagues as described above; however, this often resulted in participants finding temperature differences that were consistently above 1.5°C in the first two weeks of monitoring, increasing the potential for false positive outcomes. These high temperature differences occur due to the changed anatomy and biomechanics following amputation, with tissue stress and temperature being structurally higher at the stump location.

We modified our measurement protocol to take such systematic differences into account, as described in the methodology. Consequently, only participants with a bilateral amputation proximal to the Chopart joint had to be excluded from participation in the trial.

The measurement protocol in our trial was largely based on previous trials of Lavery and Armstrong and colleagues, in which six predefined regions of interest were measured: hallux, first, third and fifth metatarsal heads, midfoot and hindfoot (15-17). Since many foot ulcers occur at the toes, and re-ulceration occurs mostly at the previous ulcer location (31), we added the option of measuring a maximum of two regions of interest in addition to the standard six, to provide a solution for previous foot ulcers or signs of pre-ulceration (e.g. abundant callus, subcutaneous haemorrhage or blister) being present at toes 2 to 5. During the trial, we noticed (blinded to group allocation) that ulcers did not develop at the midfoot or hindfoot. Therefore, in October 2017, we modified the six standard regions of interest to include the plantar surface of the second and third toe instead of the midfoot and hindfoot (20, 24). For participants with a high risk of developing a foot ulcer at the midfoot or hindfoot, such as in midfoot Charcot deformity, this region would still be selected for temperature measurement, as an additional region of interest.

A strength of this trial is that, in addition to assessing effectiveness in preventing foot ulcer recurrence, we assess cost-effectiveness and cost-utility of the procedure. These outcomes are important given the extra investment in measurement equipment and time of the health care professional and the patient in monitoring the foot. Another strength is that not just any foot ulcer, but only plantar foot ulcers and ulcers that develop at the apex of the toes, the interdigital spaces, and the lateral and medial forefoot are the primary clinical outcome. These locations are often subject to foot ulceration as a result of repetitive mechanical stress due to deformity present and rubbing of the toes. If inflammation occurs at these areas before foot ulceration develops, we anticipate that the temperature increase due to the inflammation is being measured at one of the measurement locations on the foot.

In conclusion, the DIATEMP trial aims to provide level one evidence for the effectiveness, cost-effectiveness and cost-utility of at-home monitoring of foot skin temperature to prevent foot ulcer recurrence in high-risk diabetes patients. The outcomes of this RCT, together with analyses on the usability and implement ability of the intervention, is expected to have impact on the use of foot temperature monitoring and the design of foot temperature monitoring systems as method for self-management to prevent diabetic foot complications in high-risk patients with diabetes.

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The effectiveness of at-home skin temperature monitoring in reducing the incidence of foot ulcer recurrence in people with diabetes: a multicenter randomized controlled trial (DIATEMP)

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ABSTRACT

Introduction
The skin of people with diabetic foot disease is thought to heat up from ambulatory activity before it breaks down into ulceration. This allows for early recognition of imminent ulcers. We assessed whether at-home monitoring of plantar foot skin temperature can help prevent ulcer recurrence in diabetes.

Research design and methods
In this parallel-group outcome-assessor-blinded multicenter randomized controlled trial (7 hospitals, 4 podiatry practices), we randomly assigned people with diabetes, neuropathy, foot ulcer history (<4 years, n=295) or Charcot's neuro-arthropathy (n=9) to usual care (i.e. podiatric treatment, education, and therapeutic footwear) or usual care plus measuring skin temperatures at 6-8 plantar sites per foot each day (enhanced therapy). If $\Delta T>2.2°C$ between corresponding sites on the left and right foot for two consecutive days, participants were instructed to reduce ambulatory activity until this hotspot disappeared, and contact their podiatrist. Primary outcome was ulcer recurrence in 18 months on the plantar foot, interdigital, or medial/lateral/anterior forefoot surfaces; secondary, ulcer recurrence at any foot site.

Results
On the basis of intention-to-treat, 44 of 151 (29.1%) participants in enhanced therapy and 57 of 153 (37.3%) in usual care had ulcer recurrence at a primary outcome site (RR: 0.782 [95%CI: 0.566 – 1.080], P = 0.133). Of the 83 participants in enhanced therapy who measured a hotspot, the 24 subsequently reducing their ambulatory activity had significantly fewer ulcer recurrences (n = 3) than those in usual care (RR: 0.336 [95%CI: 0.114 – 0.986], P = 0.017). Enhanced therapy was effective over usual care for ulcer recurrence at any foot site (RR: 0.760 [95%CI: 0.579 – 0.997], P = 0.046).

Conclusions
At-home foot temperature monitoring does not significantly reduce incidence of diabetic foot ulcer recurrence at or adjacent to measurement sites over usual care, unless participants reduce ambulatory activity when hotspots are found, or when aiming to prevent ulcers at any foot site.

INTRODUCTION

With a lifetime incidence up to 34%, foot ulceration is a common complication in people with diabetes that poses a large burden on the patient and healthcare system (1-3). The risk for ulceration is particularly high in people with a foot ulcer history: 40% within one year after healing (1). Therefore, prevention of foot ulcers and their recurrence is important, but it is underexposed in research and clinical practice (4). The need for more randomized controlled trials (RCTs) on this topic has been emphasized, together with widespread adoption of evidence-based ulcer prevention programs (5, 6).

The most common mechanism of ulceration, particularly on the plantar foot, involves the cumulative effect of repetitive stress during ambulation that goes unrecognized because of peripheral neuropathy (1). International guidelines therefore recommend pressure-relieving footwear for people at high risk of plantar ulceration (6). But the alarmingly high ulcer recurrence rates necessitate adjunctive modalities for prevention (1). It has been suggested that foot ulceration is preceded by increased local skin temperature due to inflammation (enzymatic autolysis) of the tissue caused by accumulating mechanical stress from being ambulatory (7, 8). These increased local skin temperatures can be assessed by patients in their own homes using thermometry, thus providing a method for early recognition of this sign of impending ulceration (9). This method allows people at-risk and care providers to act timely by reducing ambulatory activity or providing (further) pressure relief to reduce the local inflammation. Three RCTs investigated such at-home foot temperature monitoring and showed large effects in reducing incidence of foot ulcer recurrence in people with diabetes (10-12). Therefore, this approach has been recommended in international guidelines (6).

Notwithstanding these findings and recommendations, skin temperature monitoring is currently rarely used in preventative foot care. This may be because of generalizability issues with the three RCTs being conducted by the same research group in one geographical location in the USA in the early 2000's. A more recent pilot RCT from Norway using the same intervention found no beneficial effect on ulcer recurrence, but was underpowered (13). An important scientific argument relates to the fact that all four previous RCTs had as their primary outcome an ulcer at any foot site, while temperatures were only measured at six predefined local sites on the plantar foot. If measuring local skin temperature is the key to this intervention, one would expect a reduction in ulcer incidence at or adjacent to measurement sites, but not necessarily elsewhere on the foot. Ulcer sites are not reported in these four trials, which limits interpretation of results. More practical reasons for a lack of implementation may be the minimal attention for this intervention in ulcer prevention guidelines until 2015, the scarcity of proper measurement equipment, and the burden of long-term daily measurement and false-positive readings on a population already monitoring many aspects of their disease (6, 14, 15).

In addition to these arguments, recent meta-analyses have reported uncertainty over the effect of this intervention, deserving further evaluation in larger studies (16-18). For these reasons, we assessed the effectiveness of at-home infrared foot temperature monitoring on the incidence of foot ulcer recurrence in people with diabetes and hypothesized to find significantly less ulcers at or adjacent to measurement sites when compared to usual care.

RESEARCH DESIGN AND METHODS

Study design
This study was an investigator-initiated, multicenter, outcome-assessor-blinded, two study-arm parallel-group RCT with a 1:1 allocation ratio. The medical ethics committee of Amsterdam UMC as coordinating center approved the protocol for this RCT (ID 2015_105), which has been published in detail elsewhere (19), and is summarized below. All participants gave informed consent before taking part.

Setting and recruitment
We enrolled participants from the multidisciplinary diabetic foot clinics of three university medical centers (UMCs) and four community hospitals, and from four affiliated podiatry practices, spread across the Netherlands (i.e. in six of the 12 provinces).

Participants
The inclusion criteria were: diagnosis of diabetes mellitus type 1 or 2; age ≥18 years; loss of protective sensation (LOPS) as a result of peripheral neuropathy; history of a foot ulcer or an amputation in the four years preceding randomization, or diagnosis of Charcot neuro-osteoarthropathy in chronic state (i.e. IWGDF risk grade 3) (6); ambulatory status (i.e. not wheel-chair bound); regular foot care provided by a podiatrist or willingness to undergo such care; and ability to follow study instructions. Exclusion criteria were: foot ulcer or open amputation site; active Charcot neuro-osteoarthropathy; foot infection; chronic limb-threatening ischemia, as defined by previously published criteria (20); bilateral amputation proximal to the tarsometatarsal joint; severe illness that would make 18-months survival unlikely; or current use of at-home foot temperature monitoring.

Interventions
Usual care, as provided in the Netherlands according to evidence-based guidelines (6), consisted of: a) professional foot care and foot screening once every 1-3 months by a podiatrist; b) therapeutic (custom-made) footwear, if indicated based on ulcer risk and foot condition; and c) education about self-care practices, ulcer risk factors and ulcer aetiology. Education was provided via verbal and written information by a clinician or an investigator at baseline and ad libitum by clinicians during follow-up clinic visits. All participants were advised to contact their podiatrist if they identified any area of concern on their foot.

Enhanced therapy consisted of usual care plus at-home measurement of plantar foot skin temperature, per instruction once per day in the morning directly after waking up. Participants used an infrared thermometer (TempTouch®, Diabetica Solutions, San Antonio, TX, USA) (11), to measure skin temperature at six predefined sites on the plantar surface of both feet where foot ulcers most commonly occur: hallux, second and third toe, first, third and fifth metatarsal heads (21). A maximum of two additional plantar foot sites were measured if a previous ulcer or pre-ulcerative lesion (i.e. abundant callus, haemorrhage or blister) had been or was present at another than a predefined site. This selection of measurement sites was different than in previous trials, where only six predefined sites (four at the forefoot, one midfoot and one heel) were used (10-13). Participants with a minor or unilateral major amputation that prevented measurement at a predefined site, measured at an adjacent site or used average temperatures during run-in for comparison, as described in our protocol (19). Participants recorded each temperature value and the difference between corresponding sites on both feet in a customized form. These forms were returned to the investigator after two weeks at the start and on a four-weekly basis thereafter.

If the temperature difference at corresponding sites was >2.2°C for two consecutive days, it was defined as a "hotspot". Participants were instructed verbally and in writing on their form to then substantially reduce their ambulatory activity, i.e. by at least 50% as judged subjectively, until the temperature difference normalized to <2.2°C, and to contact their podiatrist for further instruction and, if needed, treatment (11). Participants recorded these actions in their forms. When foot temperature difference exceeded 4°C or did not normalize in two days, participants were instructed to immediately contact and see their podiatrist. Participants received mobile-phone text reminders twice every week for the first six weeks and once every 2 weeks for the remainder of follow-up, to encourage them in measuring their foot temperatures and in reducing ambulatory activity and contacting their podiatrist if a hotspot was found.

Procedures
After providing informed consent, participants underwent assessment at their study center by an investigator. Demographic and disease-related characteristics were obtained. LOPS was assessed and confirmed present when the pressure of a 10-grams (5.07) Semmes-Weinstein monofilament was not felt at ≥2 sites of plantar hallux, first and fifth metatarsal heads on both feet or when the vibration of a 128-Hz Tuning fork placed on the apex of the hallux was not felt (22). Peripheral artery disease was assessed and classified according to previously published procedures (20), first by palpation of the dorsalis pedis and posterior tibial pulses of both feet. If non-palpable, the participant's medical file was checked for vascular status and, if status was not clear, toe pressures were assessed. Foot deformity was assessed clinically for presence of hammer/claw toes, prominent metatarsal heads, hallux valgus, pes planus, pes cavus, and Charcot deformity and classified into one of four categories according to the severity of deformity present (23).

If after assessment study eligibility was confirmed, participants were randomly assigned to usual care or enhanced therapy using an independent online-accessible computer-generated allocation sequence that used the nondeterministic minimization method (19). Randomization was stratified according to participating center and sex.

Participants allocated to enhanced therapy watched a video with instructions for at-home measuring and recording of foot temperatures, and for activity reduction and podiatrist contact when a hotspot was found. These participants did a first complete measurement of foot temperature to demonstrate ability in doing so, and to identify if any further instruction was needed. Participants were then handed all necessary equipment and materials to take home.

All participants were followed for 18 months for study outcomes. An investigator contacted participants every 3 months by phone, or more frequently if needed, to ask about study execution, foot ulcer development, and any contact with a foot care provider. If participants identified or suspected an ulcer in-between regular podiatry visits, they were instructed to immediately see their podiatrist or multidisciplinary foot team for diagnosis and foot care. The foot care provider debrided the specific area if required to assess outcome, and in case of a (suspected) ulcer classified the ulcer according to the University of Texas system, took photographs of the lesion, and completed an outcome case report form (19, 24). The investigator then sent these materials anonymized to a panel of three to five foot care specialists for blinded assessment of ulcer outcome, as described in our protocol (19).

Outcomes
The primary outcome for this study was the proportion of participants with a recurrent foot ulcer in 18 months at a primary site (i.e. the plantar foot, interdigital space or medial, lateral, or anterior forefoot). These are primary sites because they are at or adjacent to a temperature measurement site where any increased temperature is most likely picked-up, increasing validity for group comparisons on effectiveness of this intervention. A foot ulcer was defined as a full-thickness lesion through the dermis without reference to time present (25). Study endpoints were ulceration at a primary site, death, or 18-month follow-up. Secondary outcomes analysed using intention-to-treat were for ulcer recurrence at a primary site i) complicated by ischemia or infection; ii) per center category (i.e. UMC, community hospital, or podiatry practice); and iii) per center; and analysed per-protocol in participants who: iv) measured foot temperature >70% of days until endpoint, and v) reported to have reduced ambulatory activity when a hotspot was found. Other secondary outcomes analysed using intention-to-treat were for: ulcer recurrence at i) the previous ulcer site; ii) an exact measurement site; and iii) any foot site (which was the primary outcome in previous trials (10-13)). Any serious adverse event was promptly reported to the accredited medical research ethics committee for assessment.

Sample size calculation

Based on data from a previous trial including the same study centers (23), we anticipated a 44% ulcer recurrence incidence in 18 months for usual care. Using a more conservative estimate for relative reduction of incidence of 35% compared to the 61–85% found in three previous trials (10-12), we anticipated a 28.6% ulcer recurrence incidence for enhanced therapy. With α 0.05 (two-sided), power 80%, X^2 analysis, and intention to treat analysis for which primary outcome data from all participants could be obtained, 304 eligible participants were required.
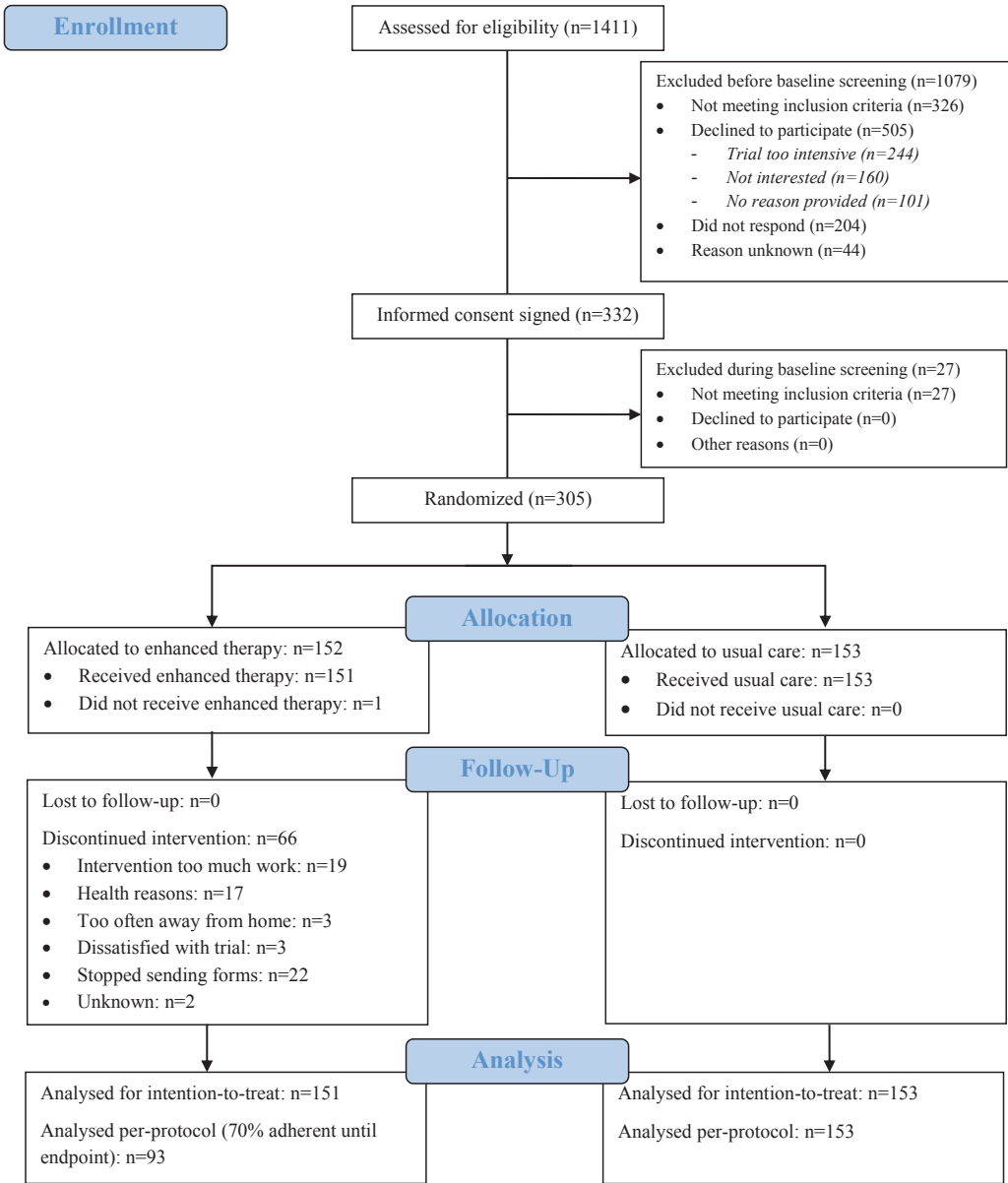
Statistical analysis

Identification of group allocation and statistical analysis were performed after the last follow-up visit of the last participant and was conducted using SPSS statistical software (version 26.0, SPSS Inc, Chicago, IL, USA). All tests assessed group effects, were two-sided, and used P<0.05 as significance level. Baseline participant characteristics were assessed with independent sample t-tests when data were normally distributed or Mann-Whitney U tests when data were not normally distributed. Effectiveness of the intervention was assessed using Pearson's X^2 analysis. Ulcer outcome data from patients who died during study follow-up was based on outcome at moment of death (last observation carried forward). From participants who discontinued their study participation, information on outcome at 18 months for the purpose of the intention-to-treat analysis was obtained from their medical file after informed consent from the participant was obtained. Outcome of ulcer recurrence over time was assessed using log-rank testing and presented as Kaplan-Meier plots that were censored for death.

RESULTS

Baseline characteristics

A study flow diagram is shown in Figure 1. Participants were recruited between November 5, 2015 and June 12, 2018, and the last participant follow-up was on December 12, 2019. A total 295 participants were included based on a foot ulcer history and nine on having a Charcot foot. Baseline participant characteristics are shown in Table 1.

Figure 1: Flow diagram for the DIATEMP trial (CONSORT)

Enrollment

Assessed for eligibility (n=1411)

Excluded before baseline screening (n=1079)
- Not meeting inclusion criteria (n=326)
- Declined to participate (n=505)
  - *Trial too intensive (n=244)*
  - *Not interested (n=160)*
  - *No reason provided (n=101)*
- Did not respond (n=204)
- Reason unknown (n=44)

Informed consent signed (n=332)

Excluded during baseline screening (n=27)
- Not meeting inclusion criteria (n=27)
- Declined to participate (n=0)
- Other reasons (n=0)

Randomized (n=305)

Allocation

Allocated to enhanced therapy: n=152
- Received enhanced therapy: n=151
- Did not receive enhanced therapy: n=1

Allocated to usual care: n=153
- Received usual care: n=153
- Did not receive usual care: n=0

Follow-Up

Lost to follow-up: n=0

Discontinued intervention: n=66
- Intervention too much work: n=19
- Health reasons: n=17
- Too often away from home: n=3
- Dissatisfied with trial: n=3
- Stopped sending forms: n=22
- Unknown: n=2

Lost to follow-up: n=0

Discontinued intervention: n=0

Analysis

Analysed for intention-to-treat: n=151

Analysed per-protocol (70% adherent until endpoint): n=93

Analysed for intention-to-treat: n=153

Analysed per-protocol: n=153

Table 1: Baseline characteristics of the intention-to-treat population

Characteristic	All	Enhanced therapy	Usual care	Missing values
Number of participants	304	151	153	
Age (years)	64.6 ± 10.5	65.0 ± 10.6	64.2 ± 10.5	
Male sex	220 (72.4%)	109 (72.2%)	111 (72.5%)	
Ethnic origin: Caucasian	283 (93.1%)	140 (92.7%)	143 (93.5%)	
Type of diabetes				4 (1.3%)
Type 1	66 (21.7%)	30 (19.9%)	36 (23.5%)	
Type 2	234 (77.0%)	119 (79.9%)	115 (75.3%)	
Years diagnosed with diabetes	20 ± 14	20 ± 14	21 ± 15	3 (1.0%)
HbA1c (mmol/mol)	60.7 ± 16.0	60.5 ± 16.5	60.9 ± 15.5	65 (21.4%)
Body mass index (kg/m^2)	29.8 ± 5.3	29.6 ± 5.4	30 ± 5.3	1 (0.3%)
Retinopathy	151 (49.7%)	83 (55.0%)	68 (44.4%)	2 (0.7%)
Nephropathy	60 (19.7%)	31 (20.5%)	29 (19.0%)	1 (0.3%)
Dialysis	4 (1.3%)	0 (0.0%)	4 (2.6%)	
Smoking or history of smoking	169 (55.6%)	88 (58.3%)	81 (52.9%)	
Consumption of alcohol	199 (65.5%)	102 (67.5%)	97 (63.4%)	
Living alone	105 (34.5%)	52 (34.4%)	53 (34.6%)	
Using a walking aid	89 (29.3%)	49 (32.5%)	40 (26.1%)	
Education				2 (0.7%)
Low	117 (38.5%)	61 (40.4%)	56 (36.6%)	
Medium	96 (31.6%)	45 (29.8%)	51 (33.3%)	
High	89 (29.3%)	44 (29.1%)	45 (29.4%)	
Employed	75 (24.7%)	38 (25.2%)	37 (24.2%)	
Footwear				2 (0.7%)
Conventional	97 (31.9%)	52 (34.4%)	45 (29.4%)	
Semi custom-made	37 (12.2%)	19 (12.6%)	19 (12.4%)	
Full custom-made	168 (55.3%)	80 (53.0%)	89 (58.2%)	
Walking barefoot at home	113 (37.2%)	54 (35.8%)	59 (38.6%)	
Participating center category				
University medical center	88 (28.9%)	42 (27.8%)	46 (30.1%)	
Community hospital	134 (44.1%)	68 (45.0%)	66 (43.1%)	
Podiatry practice	82 (27.0%)	41 (27.2%)	41 (26.8%)	
Participating center				
Amsterdam UMC, location AMC	95 (31.3%)	47 (31.1%)	48 (31.4%)	
Amsterdam UMC, location VUmc	18 (5.9%)	9 (6.0%)	9 (5.9%)	
Maastricht UMC+	25 (8.2%)	12 (7.9%)	13 (8.5%)	
Ziekenhuisgroep Twente	49 (16.1%)	23 (15.2%)	26 (17.0%)	
Reinier de Graaf Gasthuis	41 (13.5%)	21 (13.9%)	20 (13.1%)	
Maxima Medisch Centrum	64 (21.1%)	32 (21.2%)	32 (20.9%)	
Medisch Spectrum Twente	12 (3.9%)	7 (4.6%)	5 (3.3%)	
Frequency of professional foot care, every:				
1-4 weeks	82 (27.0%)	41 (27.2%)	41 (26.8%)	
5-8 weeks	199 (65.5%)	102 (67.5%)	97 (63.4%)	
>8 weeks	23 (7.6%)	8 (5.3%)	15 (9.8%)	
LOPS based on inability to sense				
10-g monofilament	276 (90.8%)	138 (91.4%)	138 (90.2%)	
128 Hz tuning fork only	28 (9.2%)	13 (8.6%)	15 (9.8%)	
Peripheral artery disease				
Grade 1	230 (75.7%)	114 (75.5%)	116 (75.8%)	
Grade 2	74 (24.3%)	37 (24.5%)	37 (24.2%)	

Foot deformity				
Absent	17 (5.6%)	10 (6.6%)	7 (4.6%)	
Mild	58 (19.1%)	32 (21.2%)	26 (17.0%)	
Moderate	202 (66.4%)	99 (65.6%)	103 (67.3%)	
Severe	27 (8.9%)	10 (6.6%)	17 (11.1%)	
Minor lesions at entry[a]	121 (39.8%)	54 (35.8%)	67 (43.8%)	31 (10.2%)
Amputation[b]				
No amputation	223 (73.4%)	110 (72.8%)	113 (73.9%)	
Lesser toe(s)	29 (9.5%)	14 (9.3%)	15 (9.8%)	
Hallux or ray	39 (12.8%)	19 (12.6%)	20 (13.1%)	
Forefoot	6 (2.0%)	5 (3.3%)	1 (0.7%)	
Major	7 (2.3%)	3 (2.0%)	4 (2.6%)	
Previous ulcer site				1 (0.3%)
Plantar forefoot	95 (31.3%)	50 (33.1%)	45 (29.4%)	
Medial/ lateral/ interdigital/ apex forefoot	104 (34.2%)	52 (34.4%)	52 (34.0%)	
Plantar mid-/ hindfoot	23 (7.6%)	11 (7.3%)	12 (7.8%)	
Dorsal side of the foot	72 (23.7%)	34 (22.5%)	38 (24.8%)	
No previous ulcer (i.e. Charcot foot)[c]	9 (3.0%)	4 (2.6%)	5 (3.3%)	
Months between healing of most recent ulcer and study entry	7 [2 – 14]	8 [2 – 15]	6 [2 – 12]	10 (3.3%)#
Months duration of last 2 previous ulcers	4 [2 – 9]	4 [2 – 8]	4 [2 – 9]	1 (0.3%)

Data are n (%), mean ± SD or median [IQR], AMC: Academic Medical Center; VUmc: Vrije Universiteit medical center.

[a]Minor lesion defined as a haemorrhage, blister, abundant callus, or erythema, identified at entry and confirmed present from photographic assessment. [b]In case of bilateral amputation, the highest level was chosen. [c]Including 9 participants that were included based on having a history of Charcot neuro-osteoarthropathy and having no history of ulceration.

Ulcer recurrence at a primary site

Ulcer outcome data is provided in Table 2. A total 101 participants (33.2% of the total group) had a recurrent foot ulcer at a primary site in 18 months. All ulcers were in participants with a foot ulcer history. Of participants included in the UMCs, significantly more ulcerated (45.5%) compared to those included in the community hospitals (32.1%) or podiatry practices (22.0%, P = 0.005). There was no significant effect of sex or ethnicity on the primary outcome.

Table 2: Study outcomes

Outcome parameter	Enhanced therapy	Usual care	Relative risk [95%CI]	P value
Number of participants	151	153		
Ulcer recurrence at primary site				
Participants with ulcer	44 (29.1%)	57 (37.3%)	0.782 [0.566 – 1.080]	0.133
Ulcer site				0.316
Hallux plantar/apex	9 (20.5%)	10 (17.5%)		
Toes plantar/apex	7 (15.9%)	4 (7.0%)		
Interdigital spaces	3 (6.8%)	3 (5.3%)		
Plantar metatarsal heads	15 (34.1%)	19 (33.3%)		
Medial border 1st ray	3 (6.8%)	9 (15.8%)		
Lateral border 5th ray	4 (9.1%)	6 (10.5%)		
Midfoot plantar	2 (4.5%)	4 (7.0%)		
Heel plantar	1 (2.3%)	2 (3.5%)		
Reported cause of ulcer				0.994
Mechanical stress	34 (77.3%)	45 (78.9%)		
Direct trauma	3 (6.8%)	4 (7.0%)		
Ischemia	1 (2.3%)	1 (1.8%)		
Unknown	6 (13.6%)	7 (12.3%)		
Ulcer per center category				0.005
University medical center	21 (50.0%)	19 (41.3%)	1.211 [0.765 – 1.195]	0.413
Community hospital	13 (19.1%)	30 (45.5%)	0.421 [0.241 – 0.733]	0.001
Podiatry practice	10 (24.4%)	8 (19.5%)	1.250 [0.549 – 2.846]	0.594
Ulcer per participating center				
Amsterdam UMC, location AMC	15 (31.9%)	14 (29.2%)	1.094 [0.596 – 2.008]	0.771
Amsterdam UMC, location VUmc	5 (55.6%)	3 (33.3%)	1.667 [0.559 – 4.973]	0.343
Maastricht UMC+	8 (66.7%)	8 (61.5%)	1.083 [0.602 – 1.949]	0.790
Ziekenhuisgroep Twente	6 (26.1%)	11 (42.3%)	0.617 [0.271 – 1.402]	0.234
Reinier de Graaf Gasthuis	6 (28.6%)	8 (40.0%)	0.714 [0.301 – 1.694]	0.440
Maxima Medisch Centrum	2 (6.3%)	13 (40.6%)	0.154 [0.038 – 0.627]	0.001
Medisch Spectrum Twente	2 (28.6%)	0 (0.0%)	0.714 [0.447 – 1.141]	0.190
Complicated ulcer[a]	11 (25.0%)	19 (33.3%)	0.750 [0.400 – 1.408]	0.363
Ulcer in participants >70% adherent[b]	32 (34.0%)	57 (37.3%)	0.914 [0.645 – 1.295]	0.610
Ulcer in participants with reported activity reduction[c]	3 (12.5%)	57 (37.3%)	0.336 [0.114 – 0.986]	0.017
Ulcer recurrence at alternative sites				
@previous ulcer site	10 (6.6%)	22 (14.4%)	0.461 [0.226 – 0.939]	0.028
@measurement site	23 (15.2%)	36 (23.5%)	0.647 [0.404 – 1.038]	0.067
@any foot site	54 (35.8%)	72 (47.1%)	0.760 [0.579 – 0.997]	0.046
Serious adverse events				0.154
Deaths	5 (3.3%)	3 (2.0%)		0.462
Hospital admissions	37 (24.5%)	28 (18.3%)		0.187

Data are n (%). Effects are shown as relative risk ratiowith 95% confidence intervals for enhanced therapy relative to usual care. [a]Complicated foot ulcer defined as a University of Texas depth 3 (i.e. bone contact) or grade B, C or D (i.e. infection and/or ischemia present); analysis on proportion of complicated ulcers of all ulcers at a primary site. [b]Per-protocol analysis in which for the enhanced therapy group 93 participants who measured their foot temperature on 70% or more of all follow-up days were included. [c]Per-protocol analysis in which for the enhanced therapy group 24 participants who reported to have reduced their ambulatory activity when finding a hotspot were included.

Intention-to-treat analysis

In the enhanced therapy group, 44 of 151 (29.1%) participants had a recurrent ulcer at a primary site, which was not significantly different from the 57 of 153 (37.3%) participants in the usual care group (RR 0.782 [95%CI: 0.566 – 1.080], P = 0.133). Kaplan-Meier curves were also not significantly different between groups (log-rank: 1.907, P = 0.167) (Figure 2).

Figure 2: Kaplan-Meier plots on cumulative survival of foot ulcer recurrence over 18 months of follow-up with censored data for participants who died. Numbers at-risk are given per 3-month interval. Top: intention-to-treat on ulcer recurrence at primary site (primary); Bottom: intention-to-treat on ulcer recurrence at any site (secondary).
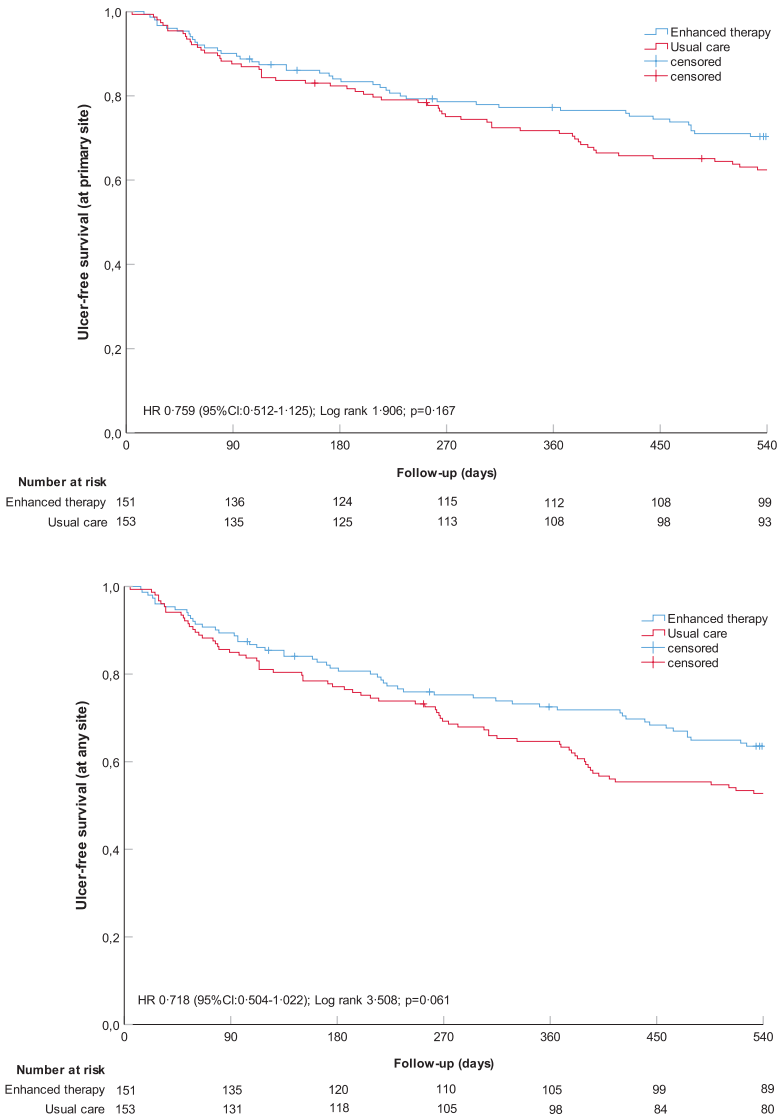
Of the 134 participants (44.0%) enrolled in a community hospital, 13 (of 68, 19.1%) in enhanced therapy had a recurrent foot ulcer at a primary site, significantly lower than the 30 (of 66, 45.5%) in usual care (RR: 0.421 [95%CI: 0.241 – 0.733], P = 0.001) (Table 2).

Adherence and hotspots
Ninety-four participants in enhanced therapy (62.3% of total) measured foot temperature at least 70% of days until a study endpoint. Seventeen participants (11.2%) never measured foot temperature and 51 (33.8%) did not have a hotspot during follow-up, as analysed from returned weekly logs. A total 83 participants (55.0%) had at least one hotspot during follow-up. Of these 83, 24 (28.9%) reported reducing their ambulatory activity level with at least 50% and 14 (16.9%) reported contacting their podiatrist with at least one hotspot, of which 12 did both. With 32.5% of the hotspots found, the participant either reduced ambulatory activity or contacted the podiatrist. In 506 of the total 5862 weeks (i.e. 112.7 person-years) of registered temperature measurements, a hotspot was found; this equates to 4.5 hotspots/person-year.

Per-protocol analysis
Thirty-two of the 94 (34.0%) participants who were adherent to temperature monitoring had a recurrent foot ulcer at a primary site (Table 2). This was not significantly different from the 57 of 153 in the usual care group (RR: 0.914 [95%CI: 0.645 – 1.295], P = 0.610). Of the 24 of 83 participants who reported to have reduced ambulatory activity when finding a hotspot, three (12.5%) had a recurrent foot ulcer at a primary site. This was significantly lower than the 21 of 59 participants (35.6%) who found a hotspot but did not reduce ambulatory activity (RR: 0.351 [95%CI: 0.115 – 1.069], P = 0.035), and significantly lower than the 37.3% in usual care (RR: 0.336 [95%CI: 0.114 – 0.986], P = 0.017).

Secondary analyses of ulcer recurrence at alternative sites
Thirty-two ulcers (31.7% of all ulcers) recurred at a previous ulcer site and 59 (58.4% of all ulcers) at a measurement site, with a significant group effect found for the former (Table 2). A total 126 participants (41.4%) had a recurrent ulcer at any foot site, of which 54 in enhanced therapy and 72 in usual care (RR: 0.760 [95%CI: 0.579 – 0.997], P = 0.046). Kaplan-Meier curves were not significantly different between groups (log-rank: 3.514, P = 0.061) (Figure 2).

Adverse events
Ninety-five serious adverse events occurred in 70 participants during follow-up, of which 8 deaths and 87 hospital admissions (32 because of diabetic foot disease). Incidence of serious adverse events was not significantly different between study groups (P = 0.154) and none were reported to be related to the intervention.

DISCUSSION

In the largest RCT on the topic to date, with enhanced therapy, we showed a non-significant relative 21.8% lower incidence of ulcer recurrence at a primary foot site compared to usual care alone. While not significant and potentially underpowered due to lower than expected ulcer incidence in the usual care group, the effect may still be attributable to the intervention, and is a clinically important one given the burden of diabetic foot disease (2). Our per-protocol analysis showed that adherence to monitoring foot temperatures had no effect on ulcer recurrence (relative 8.6% lower incidence), however, adherence to reducing ambulatory activity after identifying a hotspot did, with a relative 64.9% lower incidence found. Secondary analyses also showed that when ulcer recurrence at only the previous ulcer site (relative 53.9% lower incidence) or at any site on the foot (relative 24.0% lower incidence) was considered as outcome, enhanced therapy was effective over usual care. These results show a variable pattern of at-home foot temperature monitoring in prevention of foot ulcer recurrence.

We found a much smaller effect of enhanced therapy than the three American RCTs that used the same handheld thermometer and tested a similar population in a similar study design: relative 24% versus a 61-85% lower incidence of ulcers an any foot site compared to usual care (10-12). Our results are in line with the relative 22% lower incidence found in a more recent pilot RCT from Norway (13), and the relative 31% lower incidence per patient-year found in a very recent retrospective pre-post temperature measurement cohort analysis (26). Some study aspects were different, with the American trials being ~15 years older, performed by the same research group in one geographical region, having fewer participants with PAD, renal disease or long-standing diabetes as risk factors and more with a diverse ethnic background than the European trials, and measuring at other predefined plantar foot sites. Furthermore, one American trial reported an absolute 35% higher adherence (64% vs. 29%) to reducing ambulatory activity when hotspots occurred compared to our study (11). As reducing the cumulative stress on the foot is the primary suggested mechanism in ulcer risk reduction and temperature monitoring itself is only conditional to identify a hotspot and come into action (7, 8), a higher adherence is expected to result in better outcomes. Our per-protocol analysis supports this. It is unclear to what extent the variation in effect sizes between trials might be explained by above differences. Another RCT on this topic is ongoing (27), and more are needed, to further clarify the preventive effect of at-home foot temperature monitoring (16, 17). More specifically, given the benefit of reducing ambulatory activity with a hotspot identified, studies should focus on the specific offloading actions required (including the continuous use of prescribed footwear) and on how to improve adherence to achieve a best possible effect from this intervention (28-30).

In secondary analyses, enhanced therapy showed to be effective over usual care when the previous ulcer site was considered, and showed a relative 35% reduction in ulcer incidence (albeit statistically not-significant) when the exact measurement sites were considered. This demonstrates that the smaller effect found for the primary outcome sites is mainly because of inclusion of adjacent sites. However, one should realize that only 32% of ulcers developed at a previous ulcer

site, other studies find even lower percentages (21, 31), and only 58% at a measurement site, limiting thermometry when only these sites are targeted. With a more liberal choice of ulcer at any foot site, the intervention was also effective over usual care. This may suggest a surrogate function of foot thermometry, increasing the participant's attention to the foot and the chance of picking up an early ulcer sign anywhere on the foot and acting upon that. While previously a twice-per-day structured self-examination of the foot using a mirror to increase awareness did not show any benefit (11), our effect found may be from being guided by quantitative measurements rather than just looking. Enhanced therapy was also effective over usual care for those participants enrolled in the community hospitals, but not for those enrolled in the UMCs or podiatry practices. Generally in the Netherlands, the most complex patients at highest risk are seen in UMCs and the least complex at lowest risk in the podiatry practices and we speculate that a single intervention may not differentiate adequately between study groups in these two settings; the optimum effect may be for those 'medium' high-risk patients enrolled in community hospitals (4). Overall, these secondary analyses suggest that a benefit of the intervention may be dependent on outcome sites chosen, restricted to selected participants, and through a surrogate means of improving self-care. In support of this, a third of our study participants never identified a hotspot and would therefore not benefit from this intervention. Future studies should carefully consider participants and outcome sites and investigate above hypotheses, so to make targeted provision of this intervention possible (4), and limit over-treatment and unnecessary patient burden. Furthermore, studies should assess the cost-effectiveness of this intervention (ongoing analysis of the current trial data) and the intervention as part of a multimodal treatment plan to move towards more personalized preventative care in diabetic foot disease (a new project we are starting) (4).

Adherence to monitoring foot temperatures was comparable to that found with other self-management strategies in diabetes (32), but disappointingly low for acting when hotspots occurred, while the working mechanism of the intervention is in this action. In explaining this, first, it may be that our instructions for reducing activity level were insufficiently clear, not clearly enough presented in the log or not memorized by the participant by the time a hotspot occurred, which could be months after study entry. Second, the complexity and burden of daily measuring and logging foot temperature in order for an event not to occur (i.e. the "prevention paradox" (4)), may require too much effort of the participant to continue monitoring (4, 33). Third, people with foot disease may develop the sense that they have little influence whatsoever on the outcome of foot ulceration, creating an otiose effort to control this (34). Finally, participants may have judged that a hotspot found was not serious enough to require any action, which also relates to the problem of false-positive outcomes for this intervention (14). These aspects should be considered in the development of more user-friendly and effective technologies and methods for this purpose, that alarms users or their health care provider when a hotspot is found (26) and can provide specific instructions and encouragement for subsequent action to offload the foot, increasing patient engagement and benefit.

Several limitations apply. First, while ulcer recurrence incidence for enhanced therapy was as estimated, for usual care it was lower than estimated in the sample size calculation. This reduces the effect size and the statistical power in finding a potentially present effect of the intervention. Secondly, with handheld thermometry, participants may not have measured exactly at the predefined sites. Third, many different options for outcome sites could be considered for analysis, which affected the interpretation of results, as our analyses showed. While we lacked evidence to support choosing sites adjacent to the measurement site as the primary outcome sites, we considered that choosing only the measurement site would limit validity, as many ulcers may occur elsewhere, as would, for the same reason, choosing any foot site. Handheld devices with automated/semi-automated measurement reporting increase efficiency and would allow assessing more locations (35). Platform systems also increase usability and foot coverage, and can automatically report measurement data, but are limited to measuring only the surface that is in contact with the platform (i.e. mostly only part of the plantar foot surface) (14, 26). Temperature sensors in socks can overcome this limitation, but are also confined to a limited number of measurement sites (36). Any choice made regarding outcome site and measurement method is to a certain extent flawed, and therefore reporting for different options for outcome sites is important. Fourth, we subjectively obtained adherence to activity reduction when a hotspot was found, based on self-report. Finally, given the effect on the study findings of this adherence, our instruction to participants at baseline and repetition thereof in text messages twice a week during follow-up, may have been too complex, infrequent or ineffective (33). Data from a recent trial confirms that text and voice reminders in using thermometry do not affect adherence and outcome (37). This may be inherent to this treatment approach and addresses an important barrier to implementation.

CONCLUSION

At-home daily foot temperature monitoring in addition to usual care does not significantly reduce incidence of foot ulcer recurrence at or adjacent to measurement sites compared to usual care alone in people with diabetes, peripheral neuropathy, and a foot ulcer history or Charcot foot. Being adherent to monitoring foot temperature does not mitigate this effect, but when participants reduce their activity when a hotspot is identified, the intervention is effective over usual care. Also, when only ulcers at the previous ulcer site or ulcers at any foot site (including non-measurement sites) are considered, the intervention is effective over usual care. Thus, the effect of at-home foot temperature monitoring in preventing ulcer recurrence is not as straightforward as previously found, and may be limited to those adherent to change in behaviour when guided by temperature measurement, to specific foot sites that should be targeted, or as method to increase awareness for the foot. And although the intervention has potential, the findings highlight that it is not a solution on its own and a multimodal treatment approach is required to substantially and continuously reduce risk of ulcer recurrence in people with diabetes.

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Chapter 5

Does the skin heat up before it breaks down in diabetic foot ulceration?

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ABSTRACT

Aim
To investigate whether non-traumatic diabetic foot ulceration is preceded by increased skin temperature, a suggested mechanism for which only little evidence exists.

Methods
Participants with diabetes, peripheral sensory neuropathy, and a healed foot ulcer or Charcot neuro-osteoathropathy measured temperature at 6-8 plantar locations on each foot each day, for 18 months or until ulceration. A hotspot was a temperature difference >2.2 °C between corresponding locations on both feet for two consecutive days. Participants with non-traumatic ulcers were classified by having in the two months prior to ulceration: 1) a true hotspot, at or adjacent to the ulcer; 2) a false hotspot, at another location; 3) no hotspot. First and last lead time were the number of days between occurrence of the first and last hotspot, respectively, and ulceration.

Results
Of 151 participants, 29 developed a non-traumatic ulcer while being adherent to measuring foot temperatures. Eight participants (28%) had a true hotspot (mean (SD) first lead time: 37 (14) days, last lead time: 9 (9) days), seven (24%) a false hotspot (first lead time: 29 (17) days, last lead time: 18 (16) days), and 14 (48%) did not have a hotspot.

Conclusions
The skin of the majority of non-traumatic diabetic foot ulcers did not heat up before it broke down, or, when it did, not directly before breakdown. This questions the mechanism of foot temperature increase before ulceration and with that the potential of at-home foot temperature monitoring in preventing ulcers in the majority of high-risk patients.

INTRODUCTION

Foot ulcers are a common and feared complication in people with diabetes, with a 19-34% lifetime incidence (1). Most ulcers are caused by plantar tissue stress from being ambulatory in people with diabetes without protective sensation, and are suggested to be preceded by a local increase of skin temperature due to inflammation of underlying tissue: "the skin heats up before it breaks down" (1-3).

The notion of skin temperature increase before breakdown originates from histological research showing that repeated application of mechanical stress to denervated rats' footpads leads to inflammation and skin temperature increase, necrosis of underlying tissue (autolysis) and, finally, tissue breakdown (2, 3). Applying mechanical stress to human fingertips showed skin temperature increasing more rapidly and lasting longer each successive application day, supporting that this mechanism might apply to human tissue (3).

In people with diabetes, such hotspots occurring before skin breakdown was first described in five cases where temperature asymmetry between left and right foot (4.5±0.9 °F) was present before re-ulceration (4). Based on this, three trials showed that at-home monitoring of foot skin temperatures helps prevent (re-)ulceration when patients offload hotspots when they occur (5-7). This intervention is recommended in international guidelines for diabetic foot ulcer prevention in high-risk patients (8). However, some inconclusiveness on the 'hotspot-ulceration' relationship originated from these trials and one other trial (9): of the aggregated 231 participants that monitored foot temperature,18 ulcerated; while hotspots were reported for six in the weeks before ulceration, no data were reported for the other 12.

If the mechanism exists, one expects a hotspot to: 1) be at or adjacent to the ulcer location; and 2) immediately precede ulceration. A recent observational study of 129 participants using a thermometric foot mat, showed that nearly all (97%) of 53 non-traumatic plantar foot ulcers in 37 patients were preceded by a hotspot; however, they did not report whether this hotspot was at the ulcer location (10). This study further reported a mean first lead time of the hotspot of 37 days, but not whether the hotspot immediately preceded ulceration, apart from some selected cases reported in this and subsequent papers (10-12).

With additional support coming only from case reports (13), the evidence for increased skin temperature occurring at the ulcer location and immediately preceding ulceration seems meagre at best. We therefore aimed to investigate whether non-traumatic diabetic foot ulceration is immediately preceded by increased local skin temperature.

METHODS

We included 151 participants with diabetes, peripheral sensory neuropathy, and a healed foot ulcer in the last 48 months or Charcot neuro-osteoathropathy, being the intervention arm of our multicentre randomised controlled trial on effectiveness of at-home foot temperature monitoring to prevent ulcer recurrence (Netherlands Trial Registration NTR5403) (14) Participants received usual care plus instructions to measure each day at home their skin temperatures at 6-8 predefined plantar locations (hallux, second and third toe, first, third and fifth metatarsal heads and maximum two additional high-risk locations (e.g., previous ulcer or pre-ulcerative lesion present) on each foot using a handheld infrared thermometer (TempTouch®). Participants logged their temperature values and calculated left-to-right foot temperature difference. A hotspot was a temperature difference >2.2 °C between corresponding locations on both feet for two consecutive days. If present, participants were instructed to reduce ambulatory activity with 50%, as judged subjectively, until temperatures normalized. Participants logged these actions. Follow-up was 18 months or until ulceration at the plantar foot, apical toe surface, interdigital spaces or medial or lateral forefoot. The trial protocol was approved by the medical ethics committee; each participant provided written informed consent.

We analysed temperature profiles up to two months prior to ulceration, in all participants who developed a non-traumatic ulcer while adherent to measuring foot temperatures. Participants were classified as having: 1) a true hotspot, one at or adjacent to the ulcer; 2) a false hotspot, one at another location; or 3) no hotspot. We defined first and last lead time as the number of days between the day the first and last hotspot, respectively, occurred, and day of ulceration. We calculated the percentage of days hotspots were present between the day of first hotspot and ulceration. We compared demographic, disease- and ulcer-related characteristics between the three groups using one-way ANOVA, X^2-tests, and Kruskal-Wallis tests, and hotspot-related outcomes between those with a true or false hotspot using independent samples t-tests or Mann-Whitney U tests (SPSS v26, Chicago, IL, USA).

RESULTS

Of the 151 participants, 83 measured ≥1 hotspot during follow-up, of which 24 reported reducing their ambulatory activity and 24 developed an ulcer (including 3 among those who reduced their activity). In total, 44 participants ulcerated during 18 months follow-up: 11 did not measure foot temperature in the two months prior to ulceration, resulting in 33 participants with temperature profiles until a non-traumatic ulcer developed. Four were excluded as valid hotspot assessment was impossible because of following a different amputation protocol or bilateral hallux ulcers. Of the 29 participants included, seven had less than two months of temperature data, by ulcerating soon after study commencement (range: 15 – 43 days).

Eight participants (28%) had a true hotspot (Table 1, Figure 1). Mean (SD) first and last lead times were 37 (14) and 9 (9) days, respectively; a hotspot was present 26% of days between first hotspot and ulceration. Seven participants (24%) had a false hotspot. Mean (SD) first and last lead times were 29 (18) and 18 (16) days, respectively; a hotspot was present 11% of days between first hotspot and ulceration. Only one of eight participants with a true hotspot and none of the seven with a false hotspot reported to have reduced ambulatory activity. Fourteen participants (48%) did not develop a hotspot. No significant group differences were found for demographic, disease- and ulcer-related characteristics (Table 1).

Table 1: Demographic, disease- and ulcer-related characteristics and outcomes for participants with a non-traumatic diabetic foot ulcer stratified by having a hotspot

	True hotspot	False hotspot	No hotspot	*P* value
Characteristics				
Number of participants	8 (27.6%)	7 (24.1%)	14 (48.3%)	
Age (years)	57 (10)	70 (8)	63 (11)	0.073
Gender (male)	5 (62.5%)	5 (71.4%)	12 (85.7%)	0.450
Body mass index (kg/m^2)	28.8 (2.7)	27.8 (6.4)	28.0 (5.0)	0.914
Years diagnosed with diabetes	5 [3 – 25]	27 [18 – 37]	19 [10 – 32]	0.125
Peripheral artery disease	3 (37.5%)	3 (42.9%)	4 (28.6%)	0.792
Foot deformity[a]				0.542
Absent	1 (12.5%)	0 (0.0%)	2 (14.3%)	
Mild	0 (0.0%)	1 (14.3%)	0 (0.0%)	
Moderate	6 (75.0%)	6 (85.7%)	11 (78.6%)	
Severe	1 (12.5%)	0 (0.0%)	1 (7.1%)	
Months previous ulcer healed to entry	10 (7)	12 (10)	15 (9)	0.531
Ulcer location				0.234
Hallux plantar/apex	3 (37.5%)	1 (14.3%)	2 (14.3%)	
Lesser toes plantar/apex	2 (25.0%)	2 (28.6%)	3 (21.4%)	
Metatarsal heads	2 (25.0%)	2 (28.6%)	5 (35.7%)	
Forefoot medial or lateral	1 (12.5%)	0 (0.0%)	4 (28.6%)	
Midfoot plantar	0 (0.0%)	2 (28.6%)	0 (0.0%)	
Ulceration at previous ulcer location	3 (37.5%)	1 (14.3%)	1 (7.1%)	0.188
University of Texas Wound Classification[b]				0.549
1A	6 (75.0%)	5 (71.4%)	11 (78.6%)	
1B	1 (12.5%)	1 (14.3%)	2 (14.3%)	
Other	1 (12.5%)	1 (14.3%)	1 (7.1%)	
Outcomes				
First lead time (days) {range}	37 (14) {21 – 57}	29 (17) {9 – 59}	NA	0.334
Last lead time (days) {range}	9 (9) {1 – 24}	18 (16) {2 – 41}	NA	0.194
Percentage of days with hotspot(s)[c]	26 [11 – 55]	11 [5 – 40]	NA	0.487

Note: values are Median [Inter Quartile Range], Mean (Standard Deviation) or n (%); NA: not applicable; [a]mild: hammer/claw toes, hallux limitus, pes planus, moderate: prominent metatarsal heads, hallux rigidus, severe: Charcot deformity; [b]assessed by the treating clinician at ulcer presentation; [c]Percentage of days with hotspot(s) between first hotspot and ulceration.

Figure 1: A: Visualization of ulcers that developed at a measurement location (green) or an adjacent location (yellow) and the number of those ulcers that were preceded by a true hotspot (e.g. 6/3 at the hallux means that 3 of the 6 ulcers that developed at the hallux were preceded by a true hotspot). Locations drawn outside the foot represent the medial and lateral side of the forefoot. B and C: 60-day (2-months) temperature profiles leading up to an ulcer of participants with a true hotspot (B) and no hotspot (C). Photographs of the ulcer are also included. MTH, metatarsal head; B: multiple hotspots at the right plantar hallux starting 21 days prior to ulceration at that location (University of Texas (UT) grade 1A); B: hotspot C: no hotspots found at the left hallux or first MTH prior to ulceration just distal to the first MTH (UT 1A).
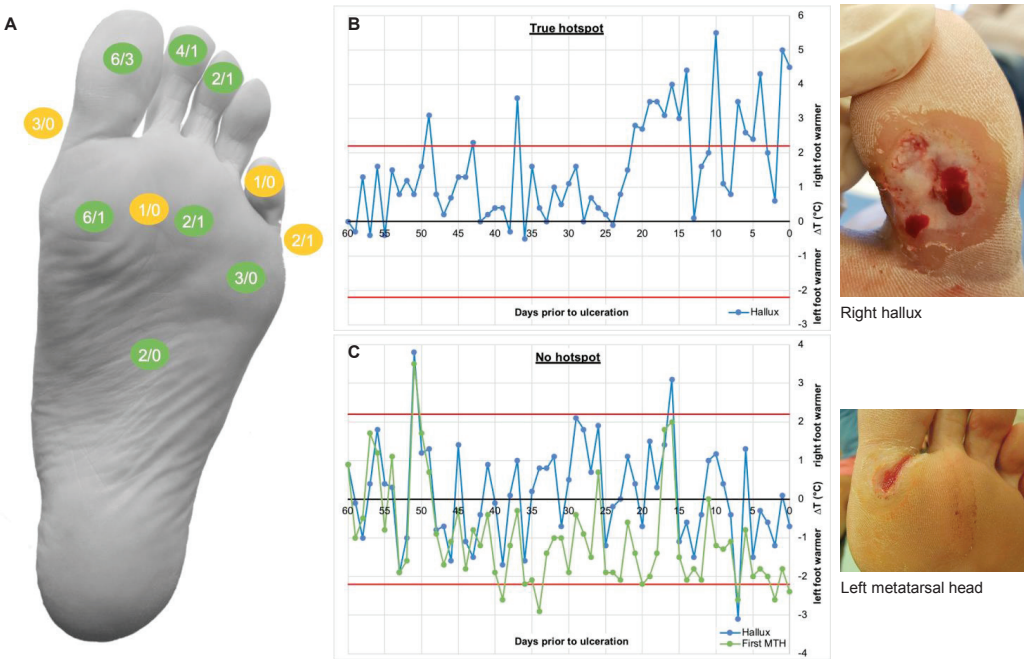
DISCUSSION

Investigating foot temperature profiles in high-risk people with diabetes, only 28% of participants had a hotspot at or adjacent to their ulcer location before ulcerating, while 24% had a hotspot at another location and 48% did not have a hotspot at all. These outcomes contradict suggestions that the skin heats up before it breaks down in diabetic foot ulceration (2-7, 9, 10).

In those with a true hotspot, mean first lead time was 37 days; however, the hotspot remained (or re-appeared) in only 26% of the days until ulceration. More strikingly, these hotspots were no longer present in the nine days before ulceration. While a previous study also showed a first lead

time of 37 days, it did not report percentage days present or last lead time (10). The current first-ever published results on hotspot profiles show that most hotspots do not immediately precede ulceration and are not continuously present. This is contrary to what was expected.

Plantar foot temperature seems a more complex variable than we think, that may not only be determined by inflammation following accumulating mechanical stress, but also by factors such as core temperature, blood flow, neuropathy, and others, that in their interaction determine foot skin temperature in the days and weeks before skin breakdown. Unfortunately, we gained no insights from demographic, disease- and ulcer-related differences between groups, limiting interpretation on why hotspots are false or absent in most participants. While no study to date has shown a valid association between accumulating mechanical stress, increased skin temperature and ulcer development in high-risk people with diabetes (15), this association seems less straightforward than believed (2-7, 9, 10). While more comprehensive and fundamental analyses are needed, investigating this relationship is not easy as it requires long-term follow-up of foot biomechanics, ambulatory activity, and temperature measurements in a large cohort of which only a minority ulcerates, and measurement of shear stress that is currently unavailable.

A limitation of our study, similar to others (10), was possible overestimation of lead times, as the exact day of ulcer occurrence is difficult to determine in people who lack sensation to an ulcer event. Secondly, 25% of participants did not measure foot temperature prior to ulceration and were therefore excluded from the analysis. Finally, with instructing participants to reduce ambulatory activity when finding a hotspot, the number of true (and false) hotspots could have been lower. However, only one participant reported having reduced ambulatory activity following a hotspot.

Despite hotspots being false or absent in the majority of participants, positive results from foot temperature monitoring trials cannot be ignored (5-7, 14). Perhaps at-home thermometry works as an effective proxy to stimulate self-management, in addition to being beneficial in selected yet unidentified patients with true hotspots.

In conclusion, the skin of nearly three-quarters of people with non-traumatic diabetic foot ulcers did not heat up before it broke down. In ulcers where this did occur, most hotspots did not persist in the days up to ulceration. This questions the suggested mechanism of foot temperature increase from repetitive mechanical stress and inflammation before ulcer development in high-risk people with diabetes. This implicates that more careful selection of people with diabetes who might benefit from at-home foot temperature monitoring as preventative treatment is needed.

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Chapter 6

Development of a prediction model for foot ulcer recurrence in people with diabetes using easy-to-obtain clinical variables

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ABSTRACT

Introduction
We aimed to develop a prediction model for foot ulcer recurrence in people with diabetes using easy-to-obtain clinical variables and to validate its predictive performance in order to help risk assessment in this high-risk group.

Research design and methods
We used data from a prospective analysis of 304 people with foot ulcer history who had 18-month follow-up for ulcer outcome. Demographic, disease-related and organisation-of-care variables were included as potential predictors. Two logistic regression prediction models were created: model 1 for all recurrent foot ulcers (n = 126 events) and model 2 for recurrent plantar foot ulcers (n = 70 events). We used ten-fold cross validation, each including five multiple imputation sets for internal validation. Performance was assessed in terms of discrimination using area under the receiver operator characteristic curve (AUC) (0 – 1, 1 = perfect discrimination), and calibration with the Brier score (0 – 1, 0 = complete concordance predicted versus observed values) and calibration graphs.

Results
Predictors in model 1 were: a younger age, more severe peripheral sensory neuropathy, fewer months since healing of the previous ulcer, presence of a minor lesion, use of a walking aid and not monitoring foot temperatures at home. Mean AUC for model 1 was 0.69 (2SD: 0.040) and mean Brier score was 0.22 (2SD: 0.011). Predictors in model 2 were: a younger age, plantar location of previous ulcer, fewer months since healing of the previous ulcer, presence of a minor lesion, consumption of alcohol, use of a walking aid, and foot care received in a university medical center. Mean AUC for model 2 was 0.66 (2SD: 0.023) and mean Brier score was 0.16 (2SD: 0.0048).

Conclusions
These internally validated prediction models predict with reasonable to good calibration and fair discrimination who is at highest risk of ulcer recurrence. The people at highest risk should be monitored more carefully and treated more intensively than others.

Netherlands Trial Register (ID: NTR5403)

INTRODUCTION

A foot ulcer is a feared and common complication in people with diabetes mellitus. The presence of a foot ulcer has a major impact on an individual's quality of life and places a large burden on both healthcare systems and society (1-3). The annual incidence of a foot ulcer in people with diabetes is approximately 2% (4), while recently the global prevalence was estimated at 18.6 million (4.8% of all people with diabetes) (5). Approximately 40% of the patients who heal from an ulcer develop another one within the first 12 months, and 60% within three years (6). Because of the high incidence of recurrence and subsequent risk of infection, hospital admission and amputation prevention of ulcer recurrence is paramount (7).

In (inter)national guidelines and in current clinical practice, treatment to help prevent a foot ulcer starts with the determination of someone's risk of developing one (8-10). Various systems have been developed and validated to stratify people with diabetes according to their risk for ulceration (11-13). Guidelines, such as those from the American Diabetes Association (9), or the International Working Group on the Diabetic Foot (IWGDF) (10), recommend that people should be screened more frequently when their risk for ulceration increases. In all systems, people with neuropathy and a foot ulcer history are stratified as those at highest risk. However, within this risk group, disease severity and ulcer risk vary substantially (14-19). To provide appropriate preventative treatment strategies and to adequately allocate limited recourses, it is important to further differentiate for foot ulcer risk within those people in the highest risk stratum.

Risk factor models can be used for this purpose. Armstrong and colleagues reviewed studies reporting risk factor models for ulcer recurrence (6), and found a vibration perception threshold >25 Volt (20), a minor lesion (15), a previous ulcer at the plantar foot surface (14, 21), and peripheral artery disease (14) to be the most important independent risk factors. However, the risk models used in these studies are incomplete and inconsistent in description and interpretation and often lack validation. Also, these studies aimed to explain whether foot ulcer recurrence can reliably be attributed to a risk factor, after adjusting for confounders, in a multivariate analysis, i.e. a search for causality. In contrast, prediction models use multiple variables to predict, as accurately as possible, the risk of a future outcome, regardless of causality (22). All causal factors are predictors, but not every predictor is a cause. Therefore, more and often easier-to-obtain variables can be considered in a prediction model than an aetiological (causal) model, making prediction models more suitable in daily practice to timely identify people at high risk of ulcer recurrence.

Crawford and colleagues were the first to develop and externally validated a prediction model for people with diabetes at low to high risk of ulceration, and identified as predictors a history of ulceration, inability to feel a 10-grams monofilament and absence of at least one pedal pulse (23). These are easy-to-obtain variables in every clinical setting, which facilitates implementation. However, this model does not distinguish between the ulcer risk of people who are stratified as high risk (IWGDF grade 3). The only prediction model developed for high-risk people is our own, on data from 171 people with a recently healed plantar foot ulcer who participated in a

trial on efficacy of custom-made footwear (24). This model included quantitative biomechanical parameters that are not available in every clinical setting. Furthermore, this model focused on plantar foot ulcer recurrence only, while at least half of all foot ulcers develop at other anatomical locations (7). It also used a selected group of high-risk people that all wore custom-made footwear and had their previous foot ulcer healed within 18 months of study entry, limiting its generalisability and implementation. We therefore aimed to develop a prediction model for foot ulcer recurrence using a variety of more easy-to-obtain clinical variables in a diverse group of high-risk people with diabetes (all IWGDF risk 3), and to validate its predictive performance, so to help risk assessment and preventative treatment in this high-risk group.

METHODS

Population
We used data from a multicenter randomized controlled trial (RCT) on the effectiveness of at-home monitoring of foot temperatures to prevent foot ulcer recurrence in diabetes (25). In this trial we recruited participants between 2015 and 2018 from multidisciplinary outpatient diabetic foot clinics of three university medical centers and four community hospitals, and several affiliated professional podiatry practices, all from various regions across the Netherlands. The participants received their primary foot care in the centers where they were recruited. From a total 1411 people screened for eligibility, 304 participants with diabetes, loss of protective sensation and a history of foot ulceration (<48 months prior to enrolment) or a history of Charcot neuro-osteoarthropathy were included in this study. Loss of protective sensation was assessed using a 10-grams Semmes-Weinstein monofilament and a 128Hz tuning fork (10). We defined a Charcot neuro-osteoarthropathy as a non-infectious destruction of bone and joint(s) associated with neuropathy, in the acute (active) phase associated with signs of inflammation such as oedema, erythema and skin temperature changes (26, 27). After consolidation and in the absence of clinical signs the episode of active Charcot neuro-osteoarthropathy was considered to be resolved (26, 27). We excluded individuals if they had a foot ulcer, a foot infection, an active Charcot neuro-osteoarthropathy, chronic limb threatening ischemia (i.e. grade 3 PEDIS classification) (28), bilateral amputation proximal to the tarso-metatarsal (Lisfranc) joint, an estimated survival less than 18 months, or if they already used at-home foot temperature monitoring. Participants were randomly assigned to usual care or enhanced care that in addition to usual care included at-home daily measurement of foot temperature at six to eight predefined locations on the foot using infrared thermometry (25). Follow-up time was 18 months. This study was registered in the Netherlands Trial Registration (ID: NTR5403), approved by the research ethics committee of all seven participating centers, and we obtained written informed consent prior to inclusion from all participants.

Primary outcome

The primary outcome was foot ulcer recurrence during the 18 months follow-up. A foot ulcer was defined as a full-thickness lesion of the skin of the foot, irrespective of duration (27). If the participant or treating healthcare professional identified an ulcer during follow-up, the professional was instructed to complete a foot ulcer form, take photographs of the ulcer, and send all materials to the study team. During 3-monthly follow-up calls, participants were asked about any lesion that had occurred, and we checked electronic patient files for any unreported ulcer. Three independent diabetic foot experts assessed ulcer forms and photographs to determine ulcer outcome. If not unanimous, two other experts were consulted and a majority vote determined outcome.

Potential predictors

We included demographic, disease-related, and organisation-of-care variables as potential predictors of foot ulcer recurrence. These potential predictors were collected at baseline through anamnesis, physical examination or questionnaires, and are listed in Table 1.

We classified the consumption of alcohol as none versus ≥1 unit per week and employment as none versus any (retirement was considered as unemployed). If participants were treated by a nephrologist or ophthalmologist, they were considered to have diabetic nephropathy or diabetic retinopathy, respectively. Peripheral neuropathy was assessed by measuring the loss of protective sensation (LOPS) by using the 10-grams (5.07) Semmes-Weinstein monofilament at the plantar surface of the hallux and the first and fifth metatarsal heads of both feet (10). LOPS was present when the monofilament was not felt on two or more locations. If the monofilament was felt on two or more locations, a 128-Hz tuning fork was used to assess loss of vibratory sensation. The tuning fork was held on the apex of the great toe and loss of vibratory sensation was present when the participant indicated not to feel the vibration (10). We defined severity of peripheral neuropathy as mild when participants were able to sense the 10-grams monofilament, but not the 128Hz tuning fork, and as severe when they were unable to sense both. Peripheral artery disease was defined as grade 1 or 2 (28). We classified foot deformity as absent, mild, moderate or severe (15, 29). A minor lesion was defined as a non-ulcerative lesion of the skin on the foot, i.e. abundant callus, haemorrhage, or blister (15).

We asked participants seven questions regarding their self-care behaviour in ulcer prevention (e.g. "do you walk barefoot at home?", see Supplementary Table 1), and scored their adherence to self-care from 0 (worst) to 7 (best). We obtained health-related quality of life on eight domains of the RAND® 36-Item Short Form Health Survey (SF-36) (Version 1.0) (30) and the EuroQol visual analogue scale (EQ VAS) (31). SF-36 scores were recoded and combined and ranged from 0 (worst) to 100 (best). The EQ VAS score also ranged from 0 (worst imaginable health) to 100 (best imaginable health). We assessed the socioeconomic status (SES) per participant as per postal code, provided by the Netherlands Institute for Social Research (outcome ranges from -5 for lowest possible SES to +5 for highest possible SES).

There were no potential predictors that showed to be strongly correlated with each other (i.e. correlation coefficient >0.5) and therefore we considered all the above-mentioned potential predictors as variables in the model.

No variable had more than 25% of missing data (Table 1). We used five multivariate imputations for all variables with missing values by applying the chained equations approach (32). This provided multiple imputations for multivariate missing data for any variable type, where each incomplete variable was imputed by a separate model (fully conditional specification method).

Model development

We developed two logistic regression models to predict foot ulcer recurrence: one for any ulcer recurrence (model 1), and one for plantar foot ulcer recurrence (model 2). We adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement (33).

We considered all potential predictors as variables for the models based on clinical reasoning, knowledge from peer-reviewed literature, and availability in everyday clinical practice.

Model fitting and validation

Model development was conform previous strategies (24), and went through four stages: 1) the creation of five datasets without missing values using multiple imputation; 2) selection of potential predictors selected in the majority of the imputed datasets; 3) fitting a logistic regression model on each of the five imputed datasets to predict ulcer outcome based on these variables; and 4) pooling the coefficients of the separate five models to obtain the final prediction model. The final logistic regression model was represented by its linear predictor. Predicted probabilities were calculated using the linear predictor in the formula: $1/(1+e^{-\text{linear predictor}})$.

In each imputation dataset we used backward variable selection based on the Akaike Information Criterion (AIC) to find the optimal set of predictors (34). By giving a penalty for model complexity (in terms of the number of included variables), the AIC strikes a good balance between the likelihood of the model (which always increases with the number of included variables) and its complexity (the more complex the model, the more likely it overfits the data).

We used 10-fold cross validation to internally validate our prediction model. This means that the entire model development strategy (including the five multiple imputation datasets and the variable selection process) was repeated in each of the 10 folds on the training set (90% of the data) and tested on the 10% held-out dataset of that fold.

Because our RCT may show that at-home foot temperature monitoring reduces risk of ulcer recurrence, this intervention may predict outcome in one or both models. We therefore developed the model both including and excluding this intervention, as foot temperature monitoring is not yet standard of practice, and other predictors may enter the model if the intervention is not considered.

Model performance

We assessed model performance in terms of discrimination and calibration (35). Discrimination refers to the ability of a model to give a higher probability of the event (i.e. ulcer recurrence) to those participants with the event than those without. We measured discrimination for the final prediction model by the area under the receiver operator characteristic curve (AUC) using the mean and two times the standard deviation (2SD) (36). The AUC ranges from 0 to 1, with 1 representing perfect discrimination. Furthermore, we presented the AUC plots of the final models. Calibration refers to the closeness of the predicted values to the observed ones. We assessed the calibration using calibration graphs. The Brier score, that combines both discrimination and calibration, was also assessed for all five pooled models and the final prediction model (mean, 2SD). The Brier score is the mean squared error of a prediction and ranges from 0 to 1, with 0 representing perfect concordance between predicted and observed values (37).

We performed descriptive statistics using SPSS Version 26.0 (SPSS Inc, Chicago, IL, USA) and all model analyses in the R statistical environment (R Foundation for Statistical Computing V4.0.2 for Windows (http://www.R-project.org)) (38), with the mice V3.11.0 and bootStepAIC V1.2-0 packages (both available on https://cran.r-project.org/ at the time of publication).

RESULTS

Baseline participant characteristics are presented in Table 1. Of a total 304 participants, 220 were male and the mean age was 64.6 years. Demographic data corresponded with previous studies (7, 29). Foot ulcer recurrence in 18 months occurred in 126 participants (41.4%), with a mean time to ulceration of 212 days (SD:154, range 5–532). Plantar foot ulcer recurrence occurred in 70 participants (23.0%), with a mean time to plantar ulceration of 206 days (SD:159, range 15–532). During 18 months follow-up there were no participants lost to follow-up, while eight participants died during follow-up. Table 2 provides the univariate analyses of all potential predictors with both outcomes.

Table 1: Characteristics of the 304 study participants

Potential predictor	Outcome	Missing values n (%)
Age (years)	64.6 ± 10.5	
Males	220 (72.4)	
Body mass index (kg/m^2)	29.8 ± 5.3	
Caucasian	283 (93.1)	
Type of diabetes		4 (1.3)
Type 1	66 (21.7)	
Type 2	234 (77.0)	
Years of diabetes	20 ± 14	3 (1.0)
HbA1c (%)	7.7 ± 3.6	65 (21.4)
Retinopathy	151 (49.7)	2 (0.7)
Nephropathy	60 (19.7)	1 (0.3)
Dialysis	4 (1.3)	
Smoking or history of smoking	169 (55.6)	
Consumption of alcohol	199 (65.5)	
Walking aid	89 (29.3)	
Living alone	105 (34.5)	
Level of education		2 (0.7)
Low	117 (38.5)	
Medium	96 (31.6)	
High	89 (29.3)	
Employed	75 (24.7)	
Custom-made footwear	205 (67.4)	2 (0.7)
Walking barefoot at home	113 (37.2)	
Adherence to self-care	4.7 ± 1.4	
At-home foot temperature monitoring	151 (49.7)	
Care center		
University medical center	88 (28.9)	
Community hospital	134 (44.1)	
Podiatry practice	82 (27.0)	
Peripheral neuropathy		
Mild	28 (9.2)	
Severe	276 (90.8)	
Peripheral artery disease		
Grade 1	197 (64.8)	
Grade 2	107 (35.2)	
Foot deformity		
Absent	17 (5.6)	
Mild	58 (19.1)	
Moderate	202 (66.4)	
Severe	27 (8.9)	
History of amputation		
Absent	223 (73.4)	
Lesser toe(s)	29 (9.5)	
Hallux or more proximal[a]	52 (17.1)	
Minor lesions at entry	121 (39.8)	31 (10.2)
Plantar location previously healed ulcer		1 (0.3)
Non-plantar[b]	185 (60.9)	
Plantar	118 (38.8)	
Months since healing previous ulcer[c]	7 [2 – 15]	1 (0.3)
Months duration previous two ulcers	4 [2 – 9]	1 (0.3)

36-Item Short Form Health Survey		13 (4.3)
Physical functioning	59 ± 22	
Role functioning/physical	50 [0 – 100]	
Role functioning/emotional	100 [33 – 100]	
Energy/fatigue	60 ± 22	
Emotional well-being	78 ± 18	
Social functioning	75 [63 – 100]	
Pain	67 ± 27	
General health	49 ± 20	
EuroQol visual analogue scale	69 ± 15	23 (7.6)
Social economic score	-0.24 ± 1.17	3 (1.0)

Data are expressed as number (%), mean ± SD or median [IQR]; [a]Seven participants had a unilateral transtibial or transfemoral amputation; [b]Including nine participants that were included based on having a history of Charcot neuro-osteoarthropathy, [c]For participants included based only on having a history of Charcot neuro-osteoarthropathy, 48 months was used.

Table 2: Univariate analyses for potential predictors associated with outcome 1 (all recurrent foot ulcers) and outcome 2 (all recurrent plantar foot ulcers)

Potential predictor	Ulcer recurrence at any foot site Odds ratio (95% CI)	P-value	Plantar foot ulcer recurrence Odds ratio (95% CI)	P-value
Age (years)	0.977 (0.956 – 0.999)	0.042	0.974 (0.950 – 0.998)	0.038
Males	1.299 (0.775 – 2.180)	0.321	1.032 (0.567 – 1.880)	0.917
Body mass index (kg/m^2)	0.982 (0.941 – 1.026)	0.418	0.997 (0.948 – 1.049)	0.920
Caucasian	1.064 (0.434 – 2.607)	0.892	0.774 (0.252 – 2.379)	0.654
Type of diabetes				
Type 1	Reference		Reference	
Type 2	0.938 (0.544 – 1.620)	0.820	0.869 (0.464 – 1.629)	0.661
Years of diabetes	1.001 (0.985 – 1.017)	0.923	0.999 (0.980 – 1.017)	0.881
HbA$_{1c}$ (%)	1.003 (0.989 – 1.017)	0.690	1.008 (0.992 – 1.025)	0.329
Retinopathy	1.242 (0.787 – 1.962)	0.352	1.250 (0.732 – 2.136)	0.414
Nephropathy	1.024 (0.579 – 1.812)	0.934	1.244 (0.652 – 2.374)	0.507
Dialysis	1.419 (0.197 – 10.212)	0.728	1.116 (0.114 – 10.900)	0.925
Smoking or history of smoking	0.997 (0.630 – 1.579)	0.991	1.365 (0.791 – 2.356)	0.264
Consumption of alcohol	1.315 (0.809 – 2.135)	0.269	1.879 (1.024 – 3.448)	0.042
Walking aid	1.487 (0.903 – 2.447)	0.119	1.604 (0.912 – 2.820)	0.101
Living alone	1.231 (0.763 – 1.986)	0.394	0.907 (0.515 – 1.598)	0.736
Level of education				
Low	Reference	0.163	Reference	0.516
Medium	1.367 (0.787 – 2.374)	0.268	1.177 (0.612 – 2.262)	0.625
High	1.714 (0.978 – 3.002)	0.060	1.462 (0.765 – 2.794)	0.251
Employed	0.994 (0.585 – 1.687)	0.982	0.709 (0.369 – 1.364)	0.303
Custom-made footwear	1.582 (0.958 – 2.612)	0.073	1.472 (0.808 – 2.684)	0.207
Walking barefoot at home	1.134 (0.708 – 1.816)	0.602	0.922 (0.529 – 1.607)	0.774
Adherence to self-care	1.089 (0.924 – 1.282)	0.309	1.141 (0.939 – 1.388)	0.185
At-home foot temperature monitoring	0.626 (0.395 – 0.992)	0.046	0.814 (0.476 – 1.390)	0.451
Care center				
University medical center	Reference	0.152	Reference	0.045
Community hospital	0.729 (0.424 – 1.252)	0.252	0.592 (0.322 – 1.088)	0.091
Podiatry practice	0.543 (0.292 – 1.008)	0.053	0.404 (0.192 – 0.849)	0.017

Peripheral neuropathy				
Mild	Reference		Reference	
Severe	6.699 (1.976 – 22.711)	0.002	4.250 (0.983 – 18.375)	0.053
Peripheral artery disease				
Grade 1	Reference		Reference	
Grade 2	1.103 (0.685 – 1.777)	0.687	0.803 (0.454 – 1.422)	0.452
Foot deformity				
Absent	Reference	0.060	Reference	0.113
Mild	0.698 (0.221 – 2.204)	0.540	0.747 (0.175 – 3.193)	0.694
Moderate	1.444 (0.514 – 4.056)	0.486	1.495 (0.412 – 5.417)	0.541
Severe	2.292 (0.656 – 8.009)	0.194	2.745 (0.630 – 11.956)	0.179
History of amputation				
Absent	Reference	0.005	Reference	0.044
Lesser toe(s)	1.424 (0.652 – 3.111)	0.375	1.032 (0.397 – 2.685)	0.949
Hallux or more proximal	2.805 (1.506 – 5.223)	0.001	2.277 (1.186 – 4.373)	0.013
Minor lesions at entry	3.066 (1.908 – 4.925)	0.001	2.659 (1.532 – 4.616)	0.001
Plantar location previously healed ulcer				
Non-plantar	Reference		Reference	
Plantar	1.497 (0.938 – 2.389)	0.091	2.667 (1.545 – 4.603)	0.001
Months since healing previous ulcer	0.949 (0.926 – 0.973)	0.001	0.951 (0.921 – 0.983)	0.003
Months duration previous two ulcers	1.025 (0.999 – 1.051)	0.059	1.024 (0.998 – 1.052)	0.072
36-Item Short Form Health Survey				
Physical functioning	0.997 (0.989 – 1.005)	0.464	0.997 (0.988 – 1.007)	0.595
Role functioning/physical	1.000 (0.995 – 1.005)	0.982	1.001 (0.995 – 1.007)	0.720
Role functioning/emotional	0.998 (0.992 – 1.003)	0.406	1.003 (0.996 – 1.010)	0.415
Energy/fatigue	0.997 (0.986 – 1.007)	0.549	0.998 (0.986 – 1.011)	0.806
Emotional well-being	0.993 (0.980 – 1.006)	0.284	1.001 (0.986 – 1.016)	0.874
Social functioning	0.995 (0.985 – 1.004)	0.270	1.000 (0.989 – 1.011)	0.958
Pain	1.000 (0.991 – 1.008)	0.991	0.998 (0.989 – 1.008)	0.766
General health	0.994 (0.983 – 1.005)	0.294	1.004 (0.991 – 1.018)	0.531
EuroQol visual analogue scale	0.999 (0.984 – 1.014)	0.898	1.007 (0.990 – 1.025)	0.417
Social economic score	1.044 (0.857 – 1.272)	0.670	0.986 (0.784 – 1.241)	0.903

Model 1: ulcer recurrence at any foot site

This model contained six predictors (Table 3): a younger age, more severe peripheral sensory neuropathy, fewer months since healing of the previous ulcer, presence of a minor lesion, and the use of a walking aid were positive predictors for ulcer recurrence and at-home foot temperature monitoring was a negative predictor for ulcer recurrence. The linear predictor was: 0.284 – 0.0299 * age in years + 1.57 * more severe peripheral sensory neuropathy – 0.0486 * months since healing of the previous ulcer + 0.704 * minor lesion present + 0.800 * use of walking aid – 0.503 * use of at-home foot temperature monitoring. When model 1 was re-run excluding foot temperature monitoring as intervention, the model contained the same predictors (results not shown).
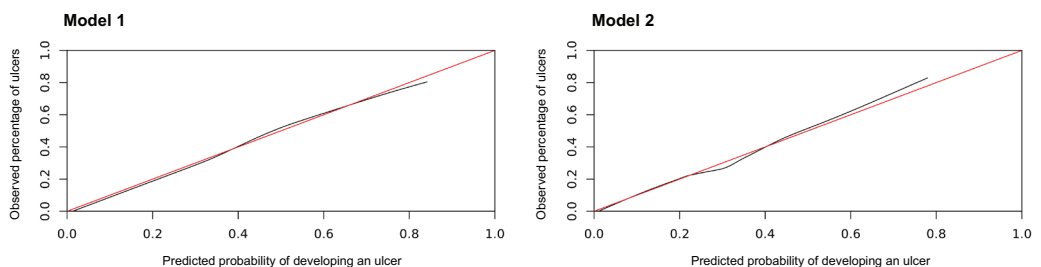
Table 3: Predictors for model 1 (all recurrent foot ulcers) and model 2 (all recurrent plantar foot ulcers)

Predictor	Coefficient	95% CI
Model 1: All recurrent foot ulcers		
Intercept	0.284	–0.163 to 2.20
Age	–0.0299	–0.0541 to –0.00570
Severity of peripheral sensory neuropathy	1.57	0.327 to 2.82
Months since healing previous ulcer	–0.0486	–0.0757 to –0.0215
Minor lesions	0.704	0.170 to 1.24
Walking aid	0.800	0.225 to 1.37
At-home foot temperature monitoring	–0.503	–1.01 to 0.000222
Model 2: All recurrent plantar foot ulcers		
Intercept	–0.129	–2.07 to 1.81
Age	–0.0313	–0.0608 to –0.00191
Plantar location of previous ulcer	0.921	0.313 to 1.53
Months since healing previous ulcer	–0.0379	–0.0721 to –0.00370
Minor lesions	0.777	0.140 to 1.41
Walking aid	0.828	0.179 to 1.48
Consumption of alcohol	0.966	0.274 to 1.66
Care center		
University medical center	Reference	
Community hospital	–0.564	–1.23 to 0.104
Podiatry practice	–0.917	–1.74 to –0.0941

Based on the average predictions per participant of the final model in the five imputed datasets, the predicted probability of foot ulcer recurrence and the observed number of recurrent foot ulcers agreed over almost the whole range of probabilities (Figure 1). When the predicted probability was >0.70 the model slightly underestimated the proportion of observed ulcers. The mean AUC of the model was 0.69 (2SD: 0.040) (Figure 2). The mean Brier score was 0.22 (2SD: 0.011).

Figure 1: Calibration graphs for model 1 (all recurrent foot ulcers) and model 2 (all recurrent plantar foot ulcers). In each graph the black lines show the observed proportion of the event versus the probability of the event as predicted by the model. Ideally all the points fall on the diagonal red line.

Figure 2: AUC for model 1 (all recurrent foot ulcers) and model 2 (all recurrent plantar foot ulcers)
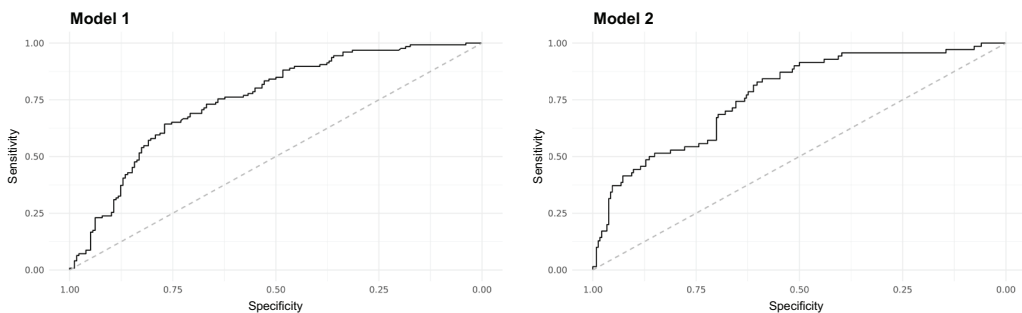
Model 2: plantar foot ulcer recurrence

This model contained seven predictors (Table 3): a younger age, plantar location of the previous ulcer, fewer months since healing of the previous ulcer, presence of a minor lesion, use of a walking aid, consumption of alcohol and foot care received in a university medical center. The linear predictor was: −0.129 − 0.0313 * age in years + 0.921 * plantar location of the previous ulcer − 0.0379 * months since healing of the previous ulcer + 0.777 * minor lesion present + 0.828 * use of walking aid + 0.966 * consumption of alcohol − (0.564 * foot care received in a community hospital| − 0.917 * foot care received in a podiatry practice). For this equation, foot care received in a university medical center was the reference category.

Based on the average predictions per participant of the final model in the five imputed datasets, the predicted probability of foot ulcer recurrence and the observed number of recurrent foot ulcers agreed over almost the whole range of probabilities (Figure 1). The predicted probability underestimated the observed ulcer recurrences when around 0.30 and slightly overestimated when >0.50 (Figure 1). The mean AUC of the model was 0.66 (2SD: 0.023) (Figure 2). The mean Brier score was 0.16 (2SD: 0.0048).

Table 4 provides the predicted probabilities including the 95% confidence intervals for two characteristic persons with diabetes using synthesized data.

Table 4: The predicted probability of ulcer recurrence within 18 months using model 1 (all recurrent foot ulcers) and model 2 (all recurrent plantar foot ulcers) for two characteristic persons with diabetes using synthesized data.

	Person A	Person B
Model 1: All recurrent foot ulcers		
Age	50	80
Severity of peripheral sensory neuropathy	Severe	Mild
Months since healing previous ulcer	3	24
Minor lesion present	Yes	No
Use of a walking aid	No	Yes
At-home foot temperature monitoring	Yes	No
Probability of ulcer recurrence (95% CI)	0.60 (0.54 – 0.66)	0.08 (0.04 – 0.13)
Model 2: All recurrent plantar foot ulcers		
Age	50	80
Plantar location of previous ulcer	Yes	No
Months since healing previous ulcer	3	24
Minor lesion present	Yes	No
Use of a walking aid	No	Yes
Consumption of alcohol	No	Yes
Care center		
University medical center	University	
Community hospital		
Podiatry practice		Podiatry
Probability of ulcer recurrence (95% CI)	0.47 (0.38 – 0.56)	0.06 (0.04 – 0.10)

DISCUSSION

We used data from the largest 2-arm trial on foot ulcer recurrence in diabetes to date, including a representative and demographically and disease-related diverse group of people all at high risk of diabetic foot ulceration (IWGDF risk 3) (10). In this group we found six predictors of foot ulcer recurrence. These predictors are all easy-to-obtain in clinical practice, and together capable of predicting ulcer recurrence with good calibration and fair discrimination. We found seven predictors of plantar foot ulcer recurrence, also all easy-to-obtain variables, together predicting with reasonable calibration and fair discrimination. These prediction models can help in risk assessment and in re-allocating resources for ulcer prevention treatment in this high-risk group of people with diabetes.

Four predictors were identified in both models: younger age, use of a walking aid, presence of a minor lesion, and fewer months since healing of the previous ulcer. A younger age has previously also been associated with a higher risk of ulcer development (2, 39-41). Use of a walking aid was not previously considered as potential predictor in studies and subsequently never associated with ulcer recurrence. Use of a walking aid may represent more disease severity (e.g. neuropathy, peripheral artery disease, foot deformity) or more frailty, affecting one's ability to walk without additional support, and thus increasing risk of trauma and recurrence. Both of these variables are easy to obtain in clinical practice.

A minor lesion is a well-known risk factor of plantar foot ulcer recurrence, as previous studies have shown (15, 24). Our findings confirm these results and extend them to any foot ulcer recurrence. The presence of a minor lesion should therefore warn healthcare professionals that immediate treatment is needed, such as through callus removal or offloading the minor lesion, and that patients should be seen more frequently until the minor lesion has been resolved (13, 42). Fewer months since healing of the previous ulcer is likely a predictor because skin and underlying tissue are still regaining strength and remain vulnerable for breakdown in the first months after epithelisation. Our models confirm earlier reports of a higher risk when time since the previous ulcer healed is shorter (6). This suggests that extra attention to offloading and more frequent foot care should be given in the first months after healing.

Peripheral sensory neuropathy and at-home monitoring foot temperature were specific predictors for ulcer recurrence at any foot site. Peripheral sensory neuropathy has been studied extensively in ulcer risk estimation in populations with and without ulcer history (23, 43, 44). Few studies found it to be associated with ulcer recurrence (20, 40), presumably because most high-risk people have neuropathy, limiting its differential effect in risk analyses. However, peripheral sensory neuropathy advances progressively (45, 46), where inability to perceive vibration from a tuning fork is a sign of an earlier stage of neuropathy, while inability to perceive pressure of a monofilament is a later stage sign (45, 46). This may explain our finding that more severe peripheral sensory neuropathy (i.e. lack of perception of both the vibration from the tuning fork and pressure from the monofilament) predicted ulcer recurrence (in comparison to only not sensing the vibration from the tuning fork).

These prediction models were based on data from an RCT explaining that the intervention of at-home monitoring of foot temperature was one of the potential predictors and turned out to be a predictor of ulcer recurrence in the study. Despite evidence from two meta-analyses (47, 48) and recommendations for its use included in international guidelines (13), at-home monitoring of foot temperatures is not standard in clinical practice. We therefore ran the prediction model with and without this intervention and found the same predictors of ulcer recurrence regardless of its inclusion, indicating that these predictors are important, independent from this intervention, in foot ulcer recurrence.

Specific predictors for ulcer recurrence on the plantar foot were a plantar location of the previous ulcer, consumption of alcohol and foot care received in a university medical center. The first may be understandable from the more biomechanical aetiology of plantar versus non-plantar foot ulcers, with plantar ulcers more likely to recur at the same site (6, 15). Increased attention to offloading these high-risk plantar areas is needed (29, 42). Only one previous study associated more alcohol consumption with ulcer recurrence (19). While moderate use of alcohol is acceptable in people with diabetes, a potential explanation could be the effect of alcohol on a person's health in general and specifically on blood glucose regulation, which may in turn increase ulcer risk (49). Unfortunately, detailed information on the use of alcohol was not available in our study, and more research on this association is needed.

Foot care in a university medical center represents tertiary foot care as proposed in the IWGDF guidelines, and is therefore probably a marker for more disease severity (10). Furthermore, since it is only a predictor for plantar foot ulcer recurrence, it most likely reflects the more advanced biomechanical burden in these people treated in tertiary care. This larger burden might be explained by the wider availability of biomechanical assessment tools in university medical centers and subsequent referral from secondary to tertiary care of patients requiring such assessment.

Because data were obtained from a large multicenter trial in diabetic foot disease, our prediction models are limited to high-risk people with diabetes that match the inclusion criteria for the trial. While external validation is needed to determine generalisability of the models, the only trial-specific criteria concerned excluding participants with bilateral amputation proximal to the Lisfranc joint and expected survival <18 months. Future external validation may show differences in the performance due to potential selection bias in our trial compared to the situation were a prospective observational cohort analysis would have been conducted. Furthermore, with 126 and 70 ulcer events in the first and second model, respectively, we were limited by the number of predictors to select for the final model to avoid overfitting. Despite considering multiple potential predictors, our models had only fair discriminating performance. To increase performance, one likely needs to include more complex behavioural (e.g. therapy adherence (29), stride count measures (15, 24, 50)), social-economic (51), or biomechanical (e.g. barefoot or in-shoe plantar pressures (15, 24)) variables. However, that would jeopardize clinical utility as these variables are hard to obtain in everyday clinical practice. Another limitation is the inter-observer variability in assessing some foot-related parameters by different investigators, such as foot deformity, peripheral sensory neuropathy, peripheral artery disease and minor lesions. To improve on the latter, two independent observers assessed photographs of the feet for presence of foot deformity and minor lesions and they reached consensus on outcome.

All predictors found can be easily obtained by healthcare professionals when screening people at high risk, and thus the prediction models can be readily applied in everyday clinical practice. Using the linear predictor from both models, a healthcare provider can determine someone's risk of ulcer recurrence. When doing so, it is important to know that predictors should not be interpreted individually, but only as a combination of variables that together may determine the

risk of ulceration. To illustrate the potential use of the prediction models in clinical practice, we used synthesized data of two characteristic persons with diabetes and estimated the probability for ulcer recurrence (Table 4). Person A has a high probability of developing a recurrent ulcer within 18 months, while person B has a low probability of developing a recurrent ulcer within 18 months. The combination of non-modifiable and modifiable predictors may help healthcare providers to better determine the frequency of foot screening and care, while the modifiable predictors (i.e. minor lesions, use of at-home foot temperature monitoring, alcohol use) may suggest potential preventative treatment that aims to mitigate the risk for recurrence. Because of the high risk of ulcer recurrence, person A might, for example, be monitored carefully and treated for minor lesions. However, we emphasize that to understand the effect on ulcer recurrence risk of interventions targeting these modifiable predictors, adequately powered trials or aetiological analyses are needed. On a more macroscopic level, our prediction models may help national health authorities and healthcare insurance companies in health policy so to better allocate the limited resources for foot care for people with diabetes who are at risk of foot ulceration.

CONCLUSION

These internally validated prediction models contain easy-to-obtain modifiable and non-modifiable variables and are built from a representative and diverse group of people with diabetes, neuropathy and foot ulcer history. These models better stratify people at high-risk of foot ulceration and help determine who should be monitored more carefully and treated more intensively with the aim to improve on the prevention of foot ulcer recurrence in people with diabetes.

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SUPPLEMENTARY TABLE 1: Questions that address self-prevention, as used in daily practice in the Netherlands and provided by the Dutch Society for Podiatrists (NVvP)

Questions	Yes / No
Do you inspect your feet for abnormalities daily?	
Do you inspect the inside of your shoes for abnormalities daily?	
Do you sometimes walk on bare feet, socks or flip flops	
Do you salve the dry skin of your feet with emollient ointment?	
Do you, or someone else, cut your toe nails straight?	
Do you wash your feet daily?	
In case of any (suspected) foot problems, do you call your health care provider immediately?	

Every 'Yes' is scored as one point (with the exception of question 3, where no is scored as 1 point). The accumulated score indicates someone's self-prevention.

Chapter 7

The development of a multivariable prediction model for plantar foot ulcer recurrence in high-risk people with diabetes

WB aan de Stegge
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SA Bus

ABSTRACT

Introduction
Forty percent of people with diabetes who heal from a foot ulcer recur within one year. The aim was to develop a prediction model for plantar foot ulcer recurrence and to validate its predictive performance.

Research design and methods
Data were retrieved from a prospective analysis of 171 high-risk patients with 18 months follow-up. Demographic, disease-related, biomechanical, and behavioural factors were included as potential predictors. Two logistic regression models were created. Model 1 for all recurrent plantar foot ulcers (71 cases) and model 2 for those ulcers indicated to be the result of unrecognized repetitive stress (41 cases). Ten-fold cross validation, each including five multiple imputation sets, was used to internally validate the prediction strategy; model performance was assessed in terms of discrimination and calibration.

Results
The presence of a minor lesion, living alone, increased barefoot peak plantar pressure, longer duration of having a previous foot ulcer and less variation in daily stride count were predictors of the first model. The area under the receiver operating curve was 0.68 (IQR: 0.61 - 0.80) and the Brier score was 0.24 (IQR: 0.20 - 0.28). The predictors of the second model were presence of a minor lesion, longer duration of having a previous foot ulcer, and location of the previous foot ulcer. The area under the receiver operating curve was 0.76 (IQR: 0.66 - 0.87) and the Brier score was 0.17 (IQR: 0.15 - 0.18).

Conclusions
These validated prediction models help identify those patients that are at increased risk of plantar foot ulcer recurrence and for that reason should be monitored more carefully and treated more intensively.

INTRODUCTION

Foot ulceration is a common and feared complication in people with diabetes mellitus; its presence has a great impact on the individuals' quality of life, healthcare and society (1, 2). The annual incidence of a foot ulcer in people with diabetes is approximately 2% (3). The risk of developing an ulcer increases if peripheral neuropathy, a history of ulceration, a foot deformity and/or peripheral vascular disease is present (4-6). Approximately 40% of patients who heal from an ulcer have a recurrence in the first 12 months and 60% within 3 years (7). This high recurrence rate is due to the many contributing factors that are still present after healing of the first ulcer, such as, neuropathy, foot deformity, increased plantar stress and peripheral vascular disease. Because of the high incidence of recurrence and subsequent risk of infection, hospital admission and amputation, a strong focus in diabetic foot disease is currently on the 'patient in remission' and prevention of foot ulcer recurrence (7). To develop adequate strategies for prevention, it is important to identify predictors of foot ulcer recurrence in diabetes.

The risk factors for diabetic foot ulcer recurrence have recently been reviewed by Armstrong et al. (7). The strongest independent risk factors reported were: a vibration perception threshold greater than 25V (8), the presence of minor lesions (e.g. abundant callus, blister formation or haemorrhage) (9), the plantar location of the previous ulcer (10, 11) and the presence of peripheral artery disease (10). Many risk factor models have been developed with various clinical outcomes in mind, such as ulcer recurrence (2, 8-12). However these studies are inconsistent in description and interpretation of these models, use different starting points for patient follow-up, identify only individual etiological risk factors, and are often not validated. A validated prediction model uses multiple variables to more accurately predict the risk of a future outcome, regardless of causality between the predictor and outcome (13).

Well-designed prediction models can be of additional value in the prevention of ulcer recurrence. A prediction model allows the clinician or practitioner to timely identify patients that are at risk of developing a recurrent foot ulcer and to communicate this risk with the patient. Additionally, it can be used to select suitable patients for therapy and guides the clinician and patients in joint decision-making for preventative treatment. This applies, for example, to the frequency at which high risk patients are screened to help identity risk and to prevent foot ulceration (once every one to three months is currently the recommendation for high-risk patients in international guidelines) (14). Therefore, the aim of this study was to develop a prediction model for plantar foot ulcer recurrence in high-risk people with diabetes and to validate its predictive performance.

METHODS

Population

Data were retrieved from a multicenter randomized controlled trial on effectiveness of custom-made footwear to prevent plantar foot ulcer recurrence (15). Patients were recruited between 2007 and 2010 from the multidisciplinary outpatient diabetic foot clinics of two academic and eight large general public hospitals across the Netherlands. From a total 267 possibly eligible participants, 171 people with diabetes with loss of protective sensation, a recent history of plantar foot ulceration (<18 months prior to inclusion) and newly prescribed custom-made footwear were included in this study. Loss of protective sensation was assessed using 10-g Semmes-Weinstein monofilament and biothesiometer (Biomedical Instruments, Newbury, OH) testing (16). Patients were excluded if they had a plantar ulcer, bilateral amputation proximal to the tarso-metatarsal (Lisfranc) joint, an estimated survival of less than 18 months, or the inability to walk unaided. Participants were randomly assigned to pressure-improved custom-made footwear (~20% peak pressure relief by modifying the footwear) or non-improved custom-made footwear. Follow-up time was 18 months or until plantar foot ulceration. The research ethics committee of all 10 participating centers in the trial approved this study. Written informed consent was obtained prior to inclusion from all patients.

Potential predictors

As potential predictors of plantar foot ulcer recurrence (9, 15), demographic, disease-related, biomechanical, and behavioural factors were included. The demographic and disease-related factors were collected at baseline through anamnesis or physical examination and included: age, gender, body mass index, diabetes type and duration, HbA1c, smoking (history), consumption of alcohol, living alone, employment status, highest education level, vibration perception threshold, presence of peripheral artery disease (grade I or II (17)), duration of previous ulcer(s), time between healing of the previous ulcer and study entry, location of the previous ulcer (i.e. hallux, 2nd to 5th toe, metatarsal heads, or midfoot), history of amputation, severity of foot deformity and the presence of minor lesions. Foot deformity was defined as absent, mild, moderate, severe and major amputations (9, 15). Minor lesions were defined as non-ulcerative lesions of the skin on the plantar foot, including abundant callus, haemorrhage, or a blister.

The biomechanical variables assessed at study entry were barefoot plantar foot pressure (measured using an Emed-X pressure platform, Novel, Munich, Germany) and in-shoe plantar foot pressures (measured using a Pedar-X system, Novel) during comfortable level walking. Regional peak barefoot and in-shoe plantar pressure were calculated as well as two parameters that represented the cumulative load on the foot: weighted pressure (WP) and cumulative plantar tissue stress (CPTS), as described elsewhere (9, 15).

The behavioural factors assessed during the study were footwear adherence and walking activity. Adherence to wearing prescribed footwear was measured over a 7-day period using the @ monitor (Academic Medical Centre, Amsterdam, the Netherlands (18)). Next to overall adherence,

adherence was assessed for when patients were at home and when away from home, using self-report forms. Walking activity was measured as stride count over the same 7-day period, using a StepWatch activity monitor (Orthocare Innovations, LLC, Oklahoma City, OK) (9, 15). The outcome parameters were average daily stride count and day-to-day variation in stride count (i.e., standard deviation (SD) in daily stride count over a 7-day period).

For the parameters footwear adherence at home and away from home more than 25% of the data was missing across subjects (namely 39.2%), and these parameters were therefore excluded as potential predictor. We used multivariate imputations for parameters with up to 25% of missing data by applying the chained equations (mice) approach as implemented by the mice package in R (19). This provided multiple imputations for multivariate missing data regardless of variable type, where each incomplete variable is imputed by a separate model (this is the fully conditional specification method). We used 5 imputation sets with a maximum of two iterations and the quick selection of predictor option, which is useful when there are many variables. Little's missing completely at random test (20) failed to show potential patterns in missing data ($\chi^2 = 58.57$, DF $= 49$, $p = 0.16$).

Primary outcome

The primary outcome was plantar foot ulcer recurrence in 18 months. Foot ulcer was defined as a full-thickness lesion of the skin, irrespective of duration (14, 17). Recurrence was defined as an ulcer at the same location as the previous one, or at any other plantar location on the ipsi- or contralateral foot. If a patient, treating physician, or other healthcare provider (e.g. podiatrist) identified an ulcer during follow-up, they were instructed to report the lesion, complete a foot ulcer form, and have photographs of the lesion taken. During 3-montly follow-up visits, patients were asked about any lesion that had occurred and electronic patients files were checked for any unreported ulcer. Outcome assessment was done blinded by three independent diabetic foot experts who assessed photographs of the plantar foot if an ulcer was suspected. Two additional foot experts were consulted when unanimity was not reached.

Model development

Two logistic regression prediction models of plantar foot ulcer recurrence were developed. The first model was on prediction of all recurrent plantar foot ulcers in the study. The second model was on prediction of those recurrent plantar foot ulcers that were suggested to be the result of unrecognized repetitive stress. This was defined as an ulcer occurring at the same location as the previous ulcer and not being the result of a traumatic event, as reported by the patient. This division in models was analogous to Waaijman et al. (9). Dependent on the prediction model, the foot with the worst outcome for a given parameter with bilateral outcomes was chosen (first model), or the foot where the previous ulcer was located (second model). Reporting on the development of these models was done according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (21).

Based on clinical reasoning, knowledge from the literature and clinical feasibility in assessment, we considered all the above-mentioned potential predictors as variables in the model. Potential predictors that showed to be strongly correlated with each other (i.e. correlation coefficient >0.5) contribute little independent information to the model. Using clinical reasoning regarding which potential factor to exclude, we excluded the following variables based on high inter-variable correlation: age, HbA1c, and type of diabetes (all correlated with duration of diabetes), education (correlated with living alone), and average daily stride count (correlated with day-to-day variation in stride count). Both WP and CPTS were excluded from the model, because they strongly correlated with each underlying factor in these composite variables.

Model fitting and validation
The model development strategy went through 4 stages: (a) creating 5 imputed datasets with no missing values, (b) further variable selection in each imputed dataset, (c) fitting a logistic regression model on each of the five imputed datasets to predict ulcer outcome based on these variables, and (d) pooling these five models into a final prediction model. The final logistic regression model for plantar foot ulcer recurrence will be represented by its linear predictor (LP). The predicted probability can be calculated from this LP with the following formula: $1/(1+e^{-LP})$.

Further variable selection (stage "b" above) was deemed important because after initial expert selection of variables many potential predictors remained and the dataset of 171 patients is relatively small. Definitive variables for the model were selected in two steps. First, we selected variables that had a univariable association with the primary outcome with a p-value <0.2. Secondly, we developed a multivariable model with those selected variables and used backward variable selection based on the Akaike Information Criterion (AIC) (22, 23) aiming at finding the optimal set of predictors. By giving a penalty for model complexity (in terms of the number of included variables), the AIC strikes a good balance between the likelihood of the model (which always increases with the number of included variables) and its complexity (the more complex the model, the more likely it would overfit the data).

We used 10-fold cross validation to internally validate the prediction strategy. This means that the whole model development strategy (including the 5 multiple imputation datasets and the variable selection process) is repeated in each of the 10 folds on the training set (90% of the data) and tested on the 10% held-out dataset of that fold.

Model performance
Model performance was assessed in terms of discrimination and calibration (24). Discrimination was measured for all 5 pooled models and the final prediction model by the area under the receiver operating curve (AUC) using the median, interquartile range (IQR), and minimum and maximum over 10 folds (25). The AUC curves of the final models are also presented. It refers to the ability of the model to provide a higher probability of the event (i.e. ulcer recurrence) to those patients with the event than those without the event. The higher the value of the AUC the better the discrimination ability. Calibration refers to the closeness of the predicted probabilities to the

true ones as estimated by appropriate patient groups, and was assessed using calibration graphs. The Brier score (26), which is the mean squared error of a prediction, combines both elements of discrimination and calibration and was also assessed for all 5 models on the imputed datasets and the final pooled prediction model (median, IQR, and minimum and maximum over 10 folds). A Brier score ranges from 0 to 1. and if the predicted values by the model and the observed values are completely concordant then the Brier score is 0. Finally, the positive predictive value (PPV), the proportion of positive results that are truly positive, was calculated in each fold when the threshold was set at the 75th percentile of predictions.

We used the average predictive comparison to assess the change on the probability of the outcome due to the change in each predictor in the model, hence indicating the influence of each of the individual predictors on the probability of ulcer recurrence when all other predictors remain constant (27). Descriptive statistics were performed using SPSS version 22.0 software (IBM Corporation, Armonk, NY). All model analyses were performed in the R statistical environment (R Foundation for Statistical Computing for Windows version 2.9.0 (http://www.R-project.org) (28).

RESULTS

Table 1 describes the characteristics of the study sample. Of the total 171 patients, 141 were male and the mean age was 63.3 years. Seventy-one patients (=42%) had a recurrent ulcer with a mean time to ulceration of 197 days. Forty-one of those 71 patients (=24% of the total group) had a recurrent ulcer due to unrecognized repetitive stress, with a mean time to ulceration of 173 days.

Table 1: Characteristics of the study

Potential predictor	Outcome*	Missing values n (%)
Age (years)	63.3 ± 10.1	
Male	141 (82.5)	
Body mass index (kg/m^2)	30.7 ± 5.7	
Smoking or history of smoking	114 (66.7)	2 (1.2)
>2 units alcohol intake per day	20 (11.7)	1 (0.6)
Living alone	46 (26.9)	
Education		
Low	98 (56.1)	
Medium	31 (18.1)	
High	44 (25.7)	
Employed	37 (21.6)	
Type of diabetes		
Type 1	49 (28.7)	
Type 2	122 (71.3)	
Years of diabetes	17.3 ± 13.5	2 (1.2)
HbA1c (%)	7.58 ± 1.44	9 (5.3)

Months duration of previous ulcer	8.7 ± 13.3	7 (4.1)
Daily stride count	3,359 ± 1,749	15 (8.8)
Variation in daily stride count	1,194 ± 713	15 (8.8)
Adherence (%)	72.8 ± 24.3	20 (11.7)
Adherence (%) at home	62,4 ± 32.4	67 (60.8)
Adherence (%) away from home	87,8 ± 26.5	67 (60.8)
Previous ulcer location		
Hallux	41 (24.0)	
2nd to 5th toe	34 (19.9)	
Metatarsal heads	91 (53.2)	
Midfoot	5 (2.9)	
History of amputation	65 (38)	
Foot deformity		
Absent	6 (3.5)	
Mild	55 (32.2)	
Moderate	77 (45.0)	
Severe	27 (15.8)	
Major amputation	6 (3.5)	
Minor lesions at entry	60 (35.1)	
Peripheral artery disease		4 (2.3)
Grade 1	93 (54.4)	
Grade 2	74 (43.3)	
Vibration perception threshold (Volt)	47.5 ± 8.2	
Months between healing of previous ulcer and study entry	5.0 ± 5.5	8 (4.7)
Improved custom-made footwear	85 (49.7)	
Barefoot peak plantar pressure forefoot (kPa)	1029 ± 257	4 (2.3)
Barefoot peak pressure at previous ulcer location (kPa)	726 ± 396	24 (14.0)
In-shoe peak pressure forefoot (kPa)	275 ± 78	1 (0.6)
In-shoe peak pressure at previous ulcer location (kPa)	186 ± 94	21 (12.3)
In-shoe peak pressure forefoot < 200 kPa and adherence > 80%	6 (3.5)	22 (12.9)

Data are expressed as number (%) or mean ± standard deviation

Model 1: All recurrent plantar foot ulcers

The model for this outcome contained five positive predictors for ulcer recurrence (Table 2): increased barefoot peak plantar pressure at the forefoot (in kPa), presence of a minor lesion, duration of the previous ulcer in months, and living alone; and one negative predictor: a higher variation in day-to-day stride count (in SDs). The linear predictor (LP) of the logistic regression model for recurrent plantar foot ulcer was: -2.1 + 0.76 * living alone + 1.4 * minor lesion present + 0.034 * duration of previous ulcer in months + 0.0013 * barefoot peak plantar pressure at the forefoot in kPa – 0.047 * variation in daily stride count in SDs.

Table 2: Predictors for Model 1 (all recurrent plantar foot ulcers) and Model 2 (plantar foot ulcer recurrence from unrecognized repetitive stress)

Predictor	Coefficient	95% Confidence Interval	Change in variable	Change in ulcer probability
Model 1: All recurrent plantar foot ulcers				
Intercept	-2.1	-3.8 – -0.37		
Living alone	0.76	0.015 – 1.5	No to Yes	0.16
Minor lesions	1.4	0.69 – 2.1	No to Yes	0.25
Duration of the previous ulcer	0.034	0.0026 – 0.065	12 months	0.085
Barefoot peak plantar pressure	0.0013	-0.00013 – 0.0027	255 kPa	0.07
Variation in daily stride count	-0.047	-0.10 – 0.0098	700 steps	-0.065
Model 2: Plantar foot ulcer recurrence from unrecognized repetitive stress				
Intercept	-1.8	-2.5 – -1.1		
Minor lesions	2.2	1.3 – 3.1	No to yes	0.37
Duration of the previous ulcer	0.038	0.0047 – 0.071	12 months	0.064
Previous ulcer location:				
MTH	Reference		In comparison to	
Hallux	-1.6	-2.8 – -0.40	patients with an	-0.028
Toes	-2.0	-3.6 – -0.41	ulcer at the	-0.21
Midfoot	0.024	-2.3 – 2.4	metatarsal heads	0.21

Table 2 also shows the average predictive comparison for model 1. If a patient has a minor lesion present or lives alone there is a 0.25 or 0.16 higher probability, respectively, for ulcer recurrence. If a patient has a duration of past ulceration of 12 months or an increase in barefoot peak plantar pressure of 255 kPa there is a higher probability of 0.085 or 0.07, respectively, for ulcer recurrence. An increase of variation in day-to-day stride count of 700 steps decreases the probability for ulcer recurrence with -0.065.

Figure 1 shows the calibration graph based on the average predictions per patient of the final model on the 5 imputation datasets. The graph shows that the predicted probability of a recurrent ulcer and the observed number of recurrent ulcers agreed over almost the whole range of probabilities. Only when the predicted probability is lower than 0.35, the prediction slightly underestimates the proportion of observed recurrent ulcers. Figure 2 shows the AUC of the final model. The median AUC of this final model was 0.68 (IQR: 0.61 - 0.80). The minimum AUC was 0.53 and the maximum AUC was 0.89 over the 10 folds with a standard deviation of 0.159. The median Brier score was 0.24 (IQR: 0.20 - 0.28). The median PPV was 65% (IQR: 50% - 79%).

Figure 1: Calibration graphs for model 1 (all recurrent plantar foot ulcers) and model 2 (plantar foot ulcer recurrence from unrecognized repetitive stress). In each graph the black line shows the observed proportion of the event versus the probability of the event as predicted by the model. Ideally the black line falls on the diagonal red line.
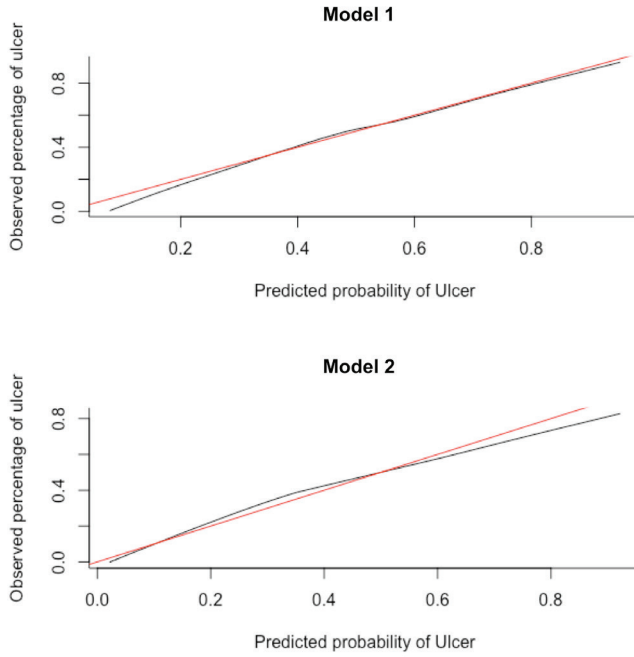
Figure 2: Area under the receiver operating curve for model 1 (all recurrent plantar foot ulcers) and model 2 (plantar foot ulcer recurrence from unrecognized repetitive stress).
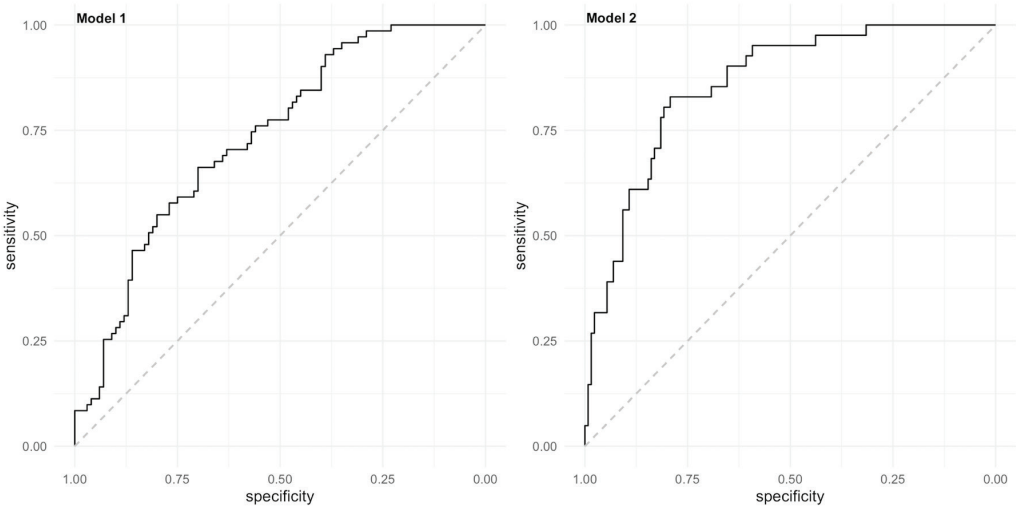
Model 2: Plantar foot ulcer recurrence from unrecognized repetitive stress

The model for this outcome contained three predictors (Table 2): presence of a minor lesion, duration of the previous ulcer in months and the location of the previous ulcer. Based on these results, the linear predictor of the logistic regression model was: -1.8 + 2.2 * minor lesion present + 0.038 * duration of previous ulcer in months + -1.6 * ulcer location " hallux"; -2.0 * ulcer location "lesser toes"; 0.024 * ulcer location "midfoot". For this formula ulcer location under the metatarsal heads was the reference category.

The average predictive comparison is shown in Table 2. If a patient has a minor lesion or a duration of past ulceration of 12 months there is a 0.37 or 0.064 higher probability, respectively, for ulcer recurrence. If the previous ulcer was located on the plantar hallux or toes, the probability for ulcer recurrence decreased with -0.028 or -0.21, respectively compared to patients who had the previous ulcer under the metatarsal heads. However, if the previous ulcer was located under the midfoot, the probability increased with 0.21 compared to patients with a previous ulcer under the metatarsal heads.

Figure 1 shows the calibration graph based on the average predictions per patient for the model on the 5 imputation datasets. The graph shows that the predicted probability of ulcer recurrence from unrecognized repetitive stress slightly overestimates the observed proportion of recurrent ulcers from unrecognized repetitive stress when the predicted probability is between 0.10 and 0.50 and slightly underestimates the observed proportion of recurrent ulcers from unrecognized repetitive stress when the predicted probability is higher than 0.50. Figure 2 shows the AUC of the final model. The median AUC of this final model was 0.76 (IQR: 0.66 - 0.87). The minimum AUC was 0.50 and the maximum AUC was 0.88 over 10 folds with a standard deviation of 0.175. The median Brier score was 0.17 (IQR: 0.15 - 0.18). The median PPV was 65% (IQR: 50% - 79%).

DISCUSSION

This study showed that presence of a minor lesion, living alone, increased barefoot peak plantar pressure, longer duration of having a previous foot ulcer and less variation in daily stride count are predictors of plantar foot ulcer recurrence in high-risk people with diabetes. This prediction model showed relatively poor discrimination but had good calibration. Presence of a minor lesion and longer duration of having a previous foot ulcer were also predictors of plantar foot ulcer recurrence attributed to unrecognized repetitive stress, in addition to location of the previous foot ulcer. This model showed fair discrimination and reasonable calibration.

The first prediction model contains a combination of biomechanical, behavioural, patient-related, and disease-related factors; the second model only includes biomechanical and disease-related factors. The fact that both models include biomechanically-related factors is because we focus on foot ulcers on the plantar surface, which have a stronger biomechanical ethology than non-plantar foot ulcers (7). The presence of a minor lesion was in both models a predictor, showing

the largest observed change in ulcer recurrence probability of all predictors. This is in accordance with Waaijman et al. who showed on the same data set that presence of a minor lesion was the strongest associated factor with plantar ulcer recurrence (9). Minor lesions such as abundant callus and blisters are the result of mechanical stress and are therefore amendable through pressure-relieving footwear. Furthermore, they allow early identification of impending ulceration that helps to inform the patient about risk and helps to reduce ulcer recurrence risk if treated appropriately (15, 29).

Living alone predicted plantar foot ulcer recurrence in our first model. This suggest that partners or relatives are important in helping to preserve the patient's foot health. Social status and its association with ulcer recurrence was previously investigated, but has not before shown to be a significant one (9, 30). Variation in stride count negatively predicted ulcer recurrence in the first model, suggesting that less variation in daily stride count predicts recurrence. This is contrary to Armstrong et al. who found in medium-to-high risk patients that a higher variability in daily stride count increases risk of ulceration (31). They postulate that high-risk patients are less able to withstand repetitive stress and that modulating the 'peaks and valleys' of their daily stride activity might reduce ulcer recurrence risk (31). These authors also showed that daily stride count in patients who ulcerated was significantly lower than in those who did not, an outcome that was not found in our data (9). This sounds counterintuitive given the lower cumulative stress exerted on the foot in these non-ulcerated cases, but suggestions that biomechanical loading of the foot leads to tissue adaptation and improved load tolerance (32, 33), supports these findings. More research is needed to untangle the apparent complex interaction between amount of daily activity and risk of plantar foot ulcer recurrence.

The location of the previous foot ulcer predicted recurrence in our second model. The probability of developing an ulcer at the same location was lower for a previous ulcer at the hallux compared to one at the metatarsal heads, and even lower for a previous ulcer at the lesser toes. The probability of ulcer recurrence at the midfoot was high, likely because all patients with a midfoot ulcer had Charcot midfoot deformity. In general, a plantar location of a previous ulcer increases risk of ulcer recurrence (9, 11). Peters et al. found that plantar hallux ulcers are more prone to recurrence than any other ulcer (plantar or dorsum) (10). The distribution of plantar pressures over the foot likely explains our results, where highest pressures are generally found at the metatarsal heads, followed by the hallux and then the lesser toes (34). Offloading these high-risk areas can help in reducing ulcer recurrence risk (15, 35).

Most predictors identified in both models are variables that can be easily and readily obtained by healthcare professionals through anamnesis, physical examination and measurement. Only barefoot plantar pressure analysis is not easily obtained in every setting, although its use is increasing, and the need for such measurements is indicated in this and other studies. For the purpose of clinical practice it is possible to integrate these models in an electronic health care system that can provide predictive risk when data input based on anamnesis and physical

examination is completed. When using both models, the treating physician should be aware that the first model slightly underestimates the risk in patients at a low risk of ulcer recurrence, while the second model slightly overestimates the patients at low risk of ulcer recurrence and slightly underestimates the patients at high risk of ulcer recurrence. Based on the second model it might therefore be possible that patients with a high predicted probability of ulcer recurrence may be treated or seen less frequently than they supposed to be based on the actual probability of ulcer recurrence.

However, while accurate predictions give valuable insight into which patients are at a high risk of developing plantar foot ulcer recurrence and need more frequent follow up, the coefficients in our prediction models are mainly useful for implementing these models by others (for example for external validation). They should not be interpreted causally, and due to possible correlations between them odds ratios might not be meaningful. Nevertheless, some predictors are modifiable factors that can be targeted for intervention using current literature and clinical knowledge. Minor lesions for example can be treated on sight and peak plantar pressures can be reduced by limiting barefoot walking (35). Advice regarding an appropriate and safe level of daily activity is also possible (35). It is important, however, to stress that it is unclear what effect these interventions will have on the predicted risk of plantar foot ulcer recurrence.

Several strengths and limitations apply to this study. We used the same dataset as Waaijman et al, however, their models are etiological in nature and aim to explain whether an ulcer recurrence can reliably be attributed to a risk factor. Missing data was not accounted for by these authors, which may lead to bias. In our models, missing data was multiply imputed. Additionally, their study lacked internal validation; the reported sensitivity of 81% and specificity of 50% are likely overestimated. Another strength of our study is that we used AIC and cross validation for the selection of potential predictors while other studies used a multivariate regression analysis with significant factors (P<0.10) from a univariate analysis (2, 8-11). Also, most studies do not or only partly report the performance of their models in terms of discrimination and calibration (2, 8-11).

A first and important limitation is the limited number of patients included in our database. With only 71 and 41 events for model 1 and 2, respectively, only a small number of predictors is warranted in the model in order to avoid overfitting. Because we have many candidate predictors, the choice of predictor set is not very stable and other predictors could be selected when having other samples of the same size. However, we relied on clinical knowledge for the initial selection of variables, then we used a liberal p-value of 0.2 for the second stage and then used the AIC to select the remaining variables. Secondly, the outcome of the second model was partly based on the patient's self-report that an ulcer was not a result of an acute trauma, which might introduce a recall bias. Thirdly, some variables had too much missing data that prevented us from including them in the model. Finally, external validation of our model on another database to evaluate model performance in other high-risk patients with diabetes was not performed.

CONCLUSION

We provided well-designed and internally validated prediction models for risk of plantar foot ulcer recurrence in high-risk people with diabetes. The model predicted recurrence based on presence of a minor lesion, living alone, increased barefoot peak plantar pressure, longer duration of having a previous foot ulcer, and less variation in daily stride count, with good calibration but relatively poor discrimination. The model for repetitive stress ulcers predicted recurrence based on presence of a minor lesion, longer duration of having a previous foot ulcer and the location of the previous ulcer, with fair discrimination and a reasonable calibration. These models help identify those patients that are at increased risk of plantar foot ulcer recurrence and for that reason should be monitored more carefully and frequently and treated more intensively.

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Chapter 8

General discussion

The general aim of this thesis was to expand the knowledge and understanding on the prevention, development and prediction of foot ulcer recurrence in people with diabetes who are at high risk of developing a foot ulcer. The following four specific aims were addressed: 1) to systematically review the peer-reviewed scientific literature on telehealth and telemedicine applications that are used for the assessment, monitoring, prevention, and treatment of diabetic foot disease; 2) to assess whether at-home monitoring of foot temperatures can reduce the incidence of ulcer recurrence in high-risk people with diabetes; 3) to investigate whether non-traumatic diabetic foot ulcers are (directly) preceded by above-threshold skin temperature; and 4) to predict the risk of ulcer recurrence in high-risk people with diabetes based on demographic, disease-related, behavioural and biomechanical factors.

In this final chapter, the main findings of the studies in this thesis are discussed in the context of the currently available literature and includes a meta-analysis of randomized controlled trials (RCTs) on the effectiveness of the at-home monitoring of foot temperature. Furthermore, critical reflections of methodology used, implications for clinical practice and future research are described, and finally a general conclusion is provided.

TELEHEALTH AND TELEMEDICINE IN DIABETIC FOOT DISEASE

As illustrated in **chapter 1**, preventing foot ulcers in people with diabetes is a challenging task. One promising way to improve ulcer prevention strategies is through self-management that is assisted by telehealth and telemedicine applications, as these have shown to be technological advancements in foot care in the past decades. In **chapter 2** the scientific literature on telehealth and telemedicine applications for the management of diabetic foot disease was systematically reviewed. Based on 15 studies, including four randomized controlled trials (RCTs) (not including the DIATEMP trial), we concluded that at-home monitoring of foot temperature is a feasible and an effective approach for the prevention of foot ulcers in people with a medium to a high risk of developing a foot ulcer. However, very recently, authors of two meta-analyses on the topic addressed some uncertainties in the reported evidence (1, 2). All included RCTs that were assessed had relatively small sample sizes and consequently showed large confidence intervals around the effect of the intervention and had a high risk of bias (1, 2). Furthermore, a leave-one-out sensitivity analyses showed that the effectiveness of the intervention was largely based on the very positive results from one trial (2). Therefore, the authors of both meta-analyses advocated that larger well-conducted trials are needed to help in interpreting the effect of at-home monitoring of foot temperature as a self-management tool to help prevent diabetic foot ulceration.

DIABETIC FOOT TEMPERATURE TRIAL (DIATEMP)

Guided by our own considerations regarding the previous RCTs as elaborated in **chapter 1** and in retrospect also supported by the above-mentioned meta-analyses, we aimed to conduct a multicenter trial on the effectiveness of at-home foot temperature monitoring on the prevention of ulcer recurrence. The study protocol was described in **chapter 3**: the DIAbetic foot TEMPerature trial (DIATEMP). The trial design, including the use of the thermometry device (TempTouch®), largely corresponded with the designs of previous RCTs (3-6), but differed in the primary outcome chosen. All four previous trials had a first-ever or recurrent ulcer at any site on the foot as primary outcome, whereas we only considered ulcers located at or near the measurement site (i.e. plantar surface, interdigital space or medial, lateral, or anterior surface of the forefoot) as primary outcomes. If identifying and managing increases in local foot temperature is the key to this intervention, a reduction in incidence of ulcers at or adjacent to measurement sites would be expected and not necessarily elsewhere on the foot.

From November 2015 to June 2018, we included 304 participants in the DIATEMP trial and followed each participant for 18 months. In **chapter 4** we reported the results on the effectiveness of at-home monitoring foot temperature (i.e. enhanced therapy) to reduce the incidence of ulcer recurrence when compared to usual care. Based on an intention-to-treat analysis, a 22% reduction in incidence of ulcer recurrence at a primary outcome site was found in the enhanced therapy group compared to usual care; however, this risk reduction was not statistically significant (P=0.133) (7). Using foot ulcer recurrence at any foot site as secondary outcome, we found a 24% reduction in incidence of ulcer recurrence through enhanced therapy, which was statistically significantly different compared to usual care (P=0.039) (7). A per-protocol analysis showed that in the group of participants who were adherent to monitoring their foot temperatures at least 70% of the days, a non-significant 9% reduction of ulcer recurrence incidence at a primary outcome site was found (7). However, if on top of measuring their foot temperatures participants found a hotspot and reported to have reduced ambulatory activity, a significant reduction in ulcer recurrence incidence at a primary site of 65% was found compared to participants who had not reduced their ambulatory activity upon finding a hotspot (P=0.035), and of 66% when compared to usual care (P=0.017) (7).

The effect of enhanced therapy found in the DIATEMP trial was much smaller than found in previous American RCTs: 24% versus a 61-85% lower incidence of foot ulcers at any site of the foot compared to usual care (3-5). The effect found in the DIATEMP trial is more in line with the 22% lower incidence found in the pilot RCT from Norway (6). This difference in effect size between trials is driven by the incidence of ulceration found in the enhanced therapy group: this was remarkably low in all three American RCTs (2.4%, 4.5% and 8.5% in a follow-up of 6 to 18 months), both in comparison to usual care in these trials (15.9%, 12.3% and 29.3%, respectively) and in comparison with the incidence of ulceration in the enhanced therapy groups in the European RCTs (29.1% and 33.3%). These differences can partly be explained by differences in included study participants. In two American RCTs, only 17.5% and 41.2% of the participants were classified

as high risk (IWGDF risk 3) (3, 4) and all American RCTs had fewer participants with peripheral artery disease, renal disease or long-standing diabetes compared to the European RCTs (3-7). Furthermore, in contrast to a follow-up of at least 12 months in other RCTs, one American RCT had only 6 months follow-up (3).

Another argument for the higher incidence of foot ulcers in the enhanced therapy group in the DIATEMP trial compared to at least one American RCT (5) is the lower reported adherence to reducing ambulatory activity (29% vs 64%). Since reducing the cumulative effect of repetitive stress on the foot is the assumed working mechanism in ulcer prevention, a higher adherence is expected to reduce the incidence of foot ulcers. In the other RCTs, data on adherence to reducing weight bearing activities was lacking (3, 4, 6). In the following sections, the importance of adherence to the intervention is highlighted and several suggestions to improve adherence are provided.

At-home foot temperature monitoring: a meta-analysis
To determine the overall effect of at-home monitoring of foot temperature based on the results of the previous four RCTs and the DIATEMP trial, we conducted a meta-analysis and pooled the evidence from all five RCTs (Figure 1A/B). Analyses were performed based on an intention-to-treat principle using Mantel-Haenszel's statistical method and random effect models anticipating heterogeneity (8). Statistical heterogeneity was assessed using the I2 statistic and interpreted as low (9). All analyses were conducted using RevMan 5, version 5.4 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). From the pooled evidence, a 49% risk reduction in ulcer recurrence for people monitoring their foot temperatures at home compared to usual care was found. While this effect is substantial, it is largely based on the positive effects of the three RCTs from Lavery and Armstrong in the early 2000s (3-5). When analysing the data specific to geographical region and time period of trial execution, separate meta-analyses show a 70% reduction in ulcer incidence at any foot site in the three older American RCTs and a 25% reduction in the two more recent European RCTs (Figure 1C/D). Given the aforementioned differences in participants and length of follow-up between these two groups of RCTs and the fact that the preventative foot care described in the more recent European trials is in line with current international guidelines, an effect size of 20% to 30% in ulcer recurrence seems more realistic. Another RCT that is currently being conducted will add more evidence to the estimation of the preventative effect of at-home monitoring of foot temperature (10). Future studies should focus on the use of new temperature-monitoring devices, specific offloading actions that are required when a hotspot occurs and how to improve adherence to temperature monitoring and offloading the foot in order to achieve the best possible effect of at-home monitoring foot temperature.

Figure 1: The effect of at-home monitoring foot temperature on the prevention of diabetic foot ulceration, including: **A** all RCTs and for Bus *et al.* (DIATEMP trial) primary outcome ulcers, **B** all RCTs and for Bus *et al.* ulcers at any foot site, **C** American RCTs, **D** European RCTs and for Bus *et al.* ulcers at any foot site.
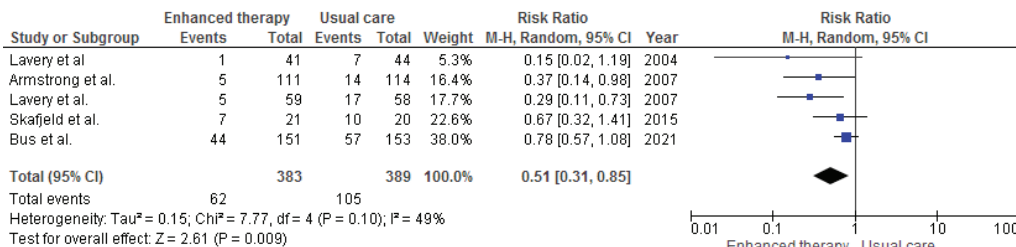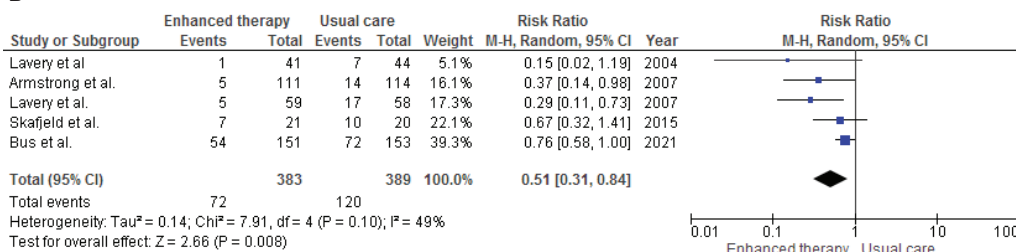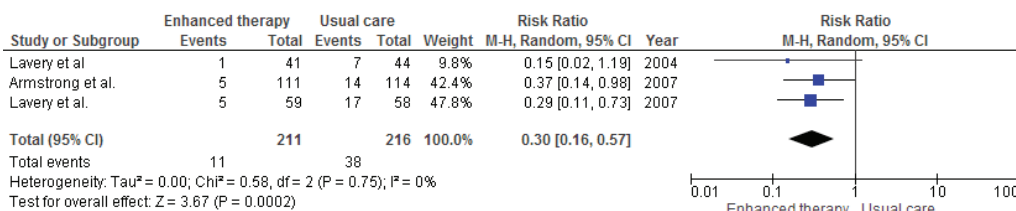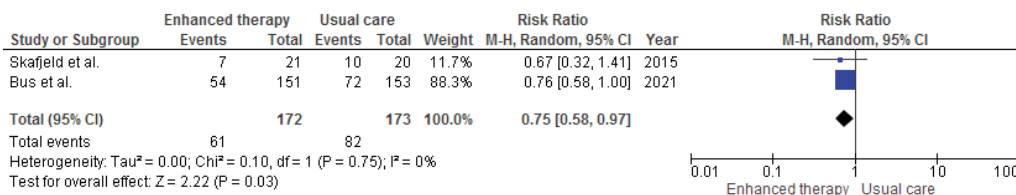
The skin does not always heat up before it breaks down

At-home monitoring of foot temperatures is supposed to identify early warning signs for impending ulceration. Ulceration is commonly caused by the cumulative effect of repetitive tissue stress under an insensate foot (11, 12). Increased repetitive stress supposedly leads to inflammation (accompanied by locally increased skin temperature, a 'hotspot'), necrosis of underlying tissue

(autolysis), the breakdown of the skin and finally ulceration (13, 14). Unfortunately, evidence supporting that these ulcers are preceded by increased skin temperature is meagre at best. Therefore, we investigated this in more detail in **chapter 5**. Of the 151 participants in the DIATEMP trial who were in the enhanced therapy group, 29 were adherent to at-home monitoring of foot temperature and developed a non-traumatic ulcer. Surprisingly, we found that only a quarter of these 29 participants had a hotspot prior to ulcer development. When viewing photographs taken from the ulcers for study outcome analysis, often no or only minor signs of callus were present at the ulcer site. This was remarkable, as callus is an effect of repetitive stress on the foot, and is expected with stress-related foot ulcers. This outcome indicates that the proposed mechanism of increased temperature from inflammation due to repetitive mechanical stress prior to ulceration may be inaccurate or is not the causative mechanism in all or the majority of plantar foot ulcers. This last suggestion is supported by finding that more than a quarter of the primary outcome ulcers in the DIATEMP trial were considered to result from poorly fitted shoes, orthoses or compression stockings, or direct trauma. These ulcers are less likely to be preceded by a hotspot. Based on these findings, the pathophysiology of foot ulceration is probably variable and less dominated by the repetitive-stress mechanism as commonly presented. As a consequence, not all (plantar) foot ulcers are likely to be prevented by the use of at-home monitoring of foot temperature.

PATHOPHYSIOLOGY OF ULCER DEVELOPMENT

The pathophysiological mechanism of a 'typical' foot ulcer in diabetes has been described in the guidelines of the International Working Group on the Diabetic Foot (15), and also displayed by Armstrong et al. (Figure 2) (12). However, as discussed above and in **chapter 5**, many ulcers in the DIATEMP trial likely did not develop according to this typical mechanism of ulceration. Others also identified different pathways to ulceration. For example, Brand suggested that a foot may be damaged in one or more of three ways: 1) from a constant low pressure causing necrosis, 2) from a very high pressure causing direct mechanical damage and 3) from repetitive moderately-high stress from being ambulatory causing inflammatory enzymatic autolysis (11). Macfarlane and Jeffcoate found that approximately 35% and 20% of 393 diabetic foot ulcers studied were caused by poorly fitted footwear and direct trauma, respectively (16). Furthermore, Reiber et al. identified 32 unique pathways to diabetic foot ulcers in 92 people with diabetes (17). In their study, the combination of neuropathy, minor trauma and foot deformity was present in more than 60% of the causal pathways to ulceration. Abundant callus was present in 30% of the pathways. This means that, in addition to the typical pathway of the cumulative effect of (moderate) repetitive stress resulting in the formation of callus or haemorrhage, roughly two more mechanical pathways to ulceration can be distinguished: constant low level stress (e.g. a tight shoe) causing local ischemic necrosis and direct trauma from very high stress causing direct mechanical damage (e.g. stepping on a nail with a bare foot or a burning wound caused by a hot water bottle in bed). In addition to these three mechanical pathways, a vascular pathway can be distinguished in diabetic foot ulceration in which critical limb ischemia causes necrosis.

These four pathways can individually or in combination cause foot ulceration in people with diabetes, and are depicted in a pathophysiological model (Figure 3). However, classifying ulcers according to one of these four pathways remains a challenge and speculative at best, since the documentation of the cause of ulceration in the DIATEMP trial, as in other studies, is difficult; determining the cause is mainly based on the ulcer as presented and the (limited) information that the patient may provide. Judging the cause may furthermore vary between healthcare providers. Unfortunately, up to this date, no studies are available that developed and/or validated more comprehensive models for the pathophysiology of diabetic foot ulceration. Future large prospective population-based studies on ulcer development are necessary to explore existing pathways in more detail, and perhaps identify new pathways.

Instead of just one strategy that focusses on the prevention of ulcers developed via one pathway, a combination of different preventative strategies that target different pathways to ulceration may be more successful in reducing ulcer incidence. This may include proper education for people with diabetes and peripheral sensory neuropathy emphasizing the importance of daily shoe inspection and not walking barefoot to reduce the risk of ulcers caused by direct trauma (18, 19). Secondly, wearing appropriately fitting and pressure-relieving footwear in combination with regular evaluation of this footwear by a medical specialist and/or professional (e.g. pedorthist, orthotist, podiatrist) helps to prevent ulcers caused by both the cumulative effect of repetitive stress and the effect of constant pressure (20). Thirdly, adequate and timely revascularisation can help prevent (neuro)ischemic ulcers, and corrective surgery can help reduce the risk of repetitive-stress based ulcers (12, 21). Ultimately, an integrated approach encompassing multiple preventative strategies that aim to prevent the various types of ulcers may result in a larger reduction of ulcer incidence compared to a single intervention strategy. Future research should focus on assessing the effect of multiple preventative strategies on the incidence of diabetic foot ulceration.

Figure 2: Common pathway of a typical diabetic foot ulcer. Diabetic foot ulcers are caused by a number of factors that ultimately lead to skin breakdown. These factors include sequelae related to sensory, autonomic, and motor neuropathies. *Reproduced with permission from Armstrong DG, Boulton AJ, and Bus SA, Diabetic foot ulcers and their recurrence. N Engl J Med, 2017. Copyright Massachusetts Medical Society.*

Figure 3: An extended model for the pathophysiology of diabetic foot ulcer development. Precipitating factors caused by diabetes increase the risk of developing a foot ulcer (green). The four main pathways to ulceration depicted here are stratified for mechanical pathways (yellow) and a vascular pathway (red). These four pathways to ulceration can individually or in combination cause the development of a diabetic foot ulcer.
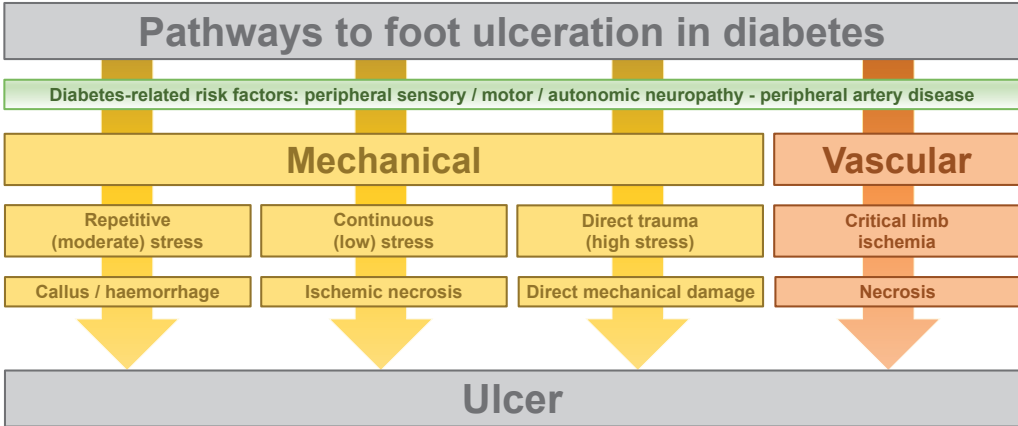
ADHERENCE

Although not all ulcers could be prevented with at-home foot temperature monitoring, a sub-analysis from the DIATEMP trial presented in **chapter 4** showed that significantly less ulcers developed if participants reduced their ambulatory activity after a hotspot was identified, compared to participants who did not report reducing their activity and participants in the usual care group. Such an effect requires adherence to both measuring foot temperature and reducing activity when a hotspot is found. As reported in **chapter 4**, 62.3% of the participants measured their foot temperature at least 70% of the days of follow-up (up to 18 months). Given the complexity of the intervention, the adherence of 62.3% is reasonable and comparable with the 67% adherence to at-home monitoring of foot temperature (≥ 80% of the time) in another RCT (6). A lower adherence in people with a chronic disease has been reported in far less complex interventions such as taking medicine for asthma (adherence of approximately 40%) (22, 23). The second part of the adherence, reducing ambulatory activity, was low as only 28.9% of all participants reduced their ambulatory activity after identifying a hotspot. This should be interpreted with caution, since reducing ambulatory activity was solely based on self-report and not objectively assessed. However, it is clear that adherence to both measuring foot temperature and reducing activity is crucial for this intervention to be effective, and a higher adherence to both seemed to result in better outcomes. In **chapter 4** several reasons for the reported adherence to the intervention in the DIATEMP trial were discussed. Here, the findings on adherence will be placed in a broader perspective using the theory of planned behaviour (TPB).

The theory of planned behaviour

The TPB is designed to explain and predict social behaviour including health-related behaviour (24, 25). It states that an individual's intention to perform particular behaviour is the most important determinant for actual behaviour. This intention depends on the attitude, subjective norm and perceived behavioural control towards this intended behaviour (Figure 4) (24-26).

Figure 4: Theory of planned behaviour diagram by Icek Azjen (26). Actual behaviour is predicted by the intention to perform behaviour in combination with the perceived behavioural control over this behaviour. Behaviour is immediately preceded by intention which is the function of attitude toward the behaviour, subjective norm and perceived behavioural control; these determinants follow, respectively, from beliefs about the behaviour's likely consequences, about normative expectations of important others, and about the presence of factors that control behavioural performance (24, 25).
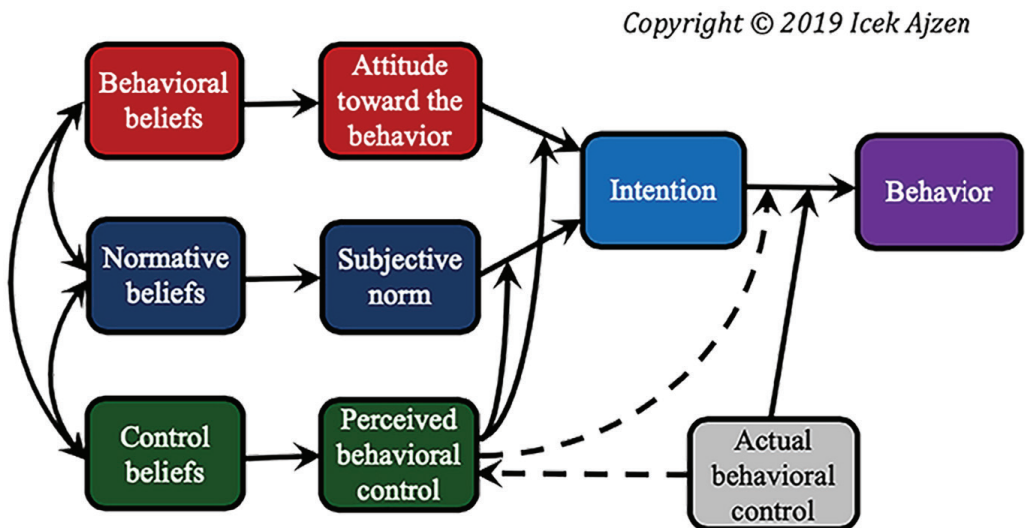
A participant's attitude is guided by behavioural beliefs, the subjective probability of the outcome (in this case: ulcer recurrence) and the importance attached to this outcome (24-26). For example, if a participant believes that both at-home monitoring of foot temperature and reducing ambulatory activity are important to prevent ulcer recurrence, there is a strong attitude towards being adherent to the intervention. However, if participants do not understand why at-home monitoring in combination with reducing activity is important, simply because they do not understand the mechanism, this might result in a weak attitude towards adherence to the intervention. During follow-up it became clear that some participants did not understand why they measured foot temperature despite repeated explanation. This suggests that both communication and education need to be improved. It is also possible that participants do not believe that the intervention can prevent ulcer recurrence at all. This is not unlikely, as it was

reported that people at high risk of ulceration felt limited control in preventing these ulcers at all (27), which obviously results in a weak attitude towards adherence to the intervention.

Subjective norm is guided by the normative beliefs of participants (24-26). These are the perceived expectations of opinions of important others, in our case frequently their healthcare provider or their life partner, and the motivation to conform to these opinions (24-26). We observed that quite a lot of the participants decided to participate and continued to be adherent to monitoring of foot temperature because their healthcare provider (strongly) advised them to do so. These participants had a strong subjective norm. We also observed that some healthcare providers did not stimulate participants to be adherent which resulted in a weaker subjective norm. In some participants, the life partner had an important role, because the partner performed the measurements and, in some cases, even instructed the participant to reduce their ambulatory activity.

Finally, perceived behavioural control is guided by control beliefs (24-26). Control beliefs are the beliefs of a participant about the presence of factors that may facilitate or hinder being adherent to the intervention (24-26). An example of a frequently observed weak control belief that resulted in a weak perceived behavioural control was that participants found that daily measuring foot temperature was too time consuming, which resulted in terminating the monitoring of foot temperatures. An observed weak control belief in reducing ambulatory activity was the inability to do so, for example in participants who were caregiver for their life partner or who reported that they were hardly ambulatory already.

Based on this discussion of adherence according to the TPB, several elements appear that can be targeted to improve adherence to the intervention in future trials. First, better education and/or instructions for both participants, their life partners and their healthcare providers might result in a better understanding of the working mechanism, extra motivation and a higher adherence to both parts of the intervention. Such education should go beyond simply repeating instructions, and should incorporate checking for understanding (28, 29). Furthermore, motivational interviewing may be used to improve knowledge on self-care and may provide insights in a persons' willingness to change and thereby commitment to the intervention (30, 31). Second, individuals should be screened before initiating the intervention to assess whether an individual is suitable for and willing to commit to the intervention. For this, individuals could be given a familiarization period of four weeks in which they can experience if the intervention is feasible for them. Third, a less cumbersome measurement tool might result in higher adherence. To this end, platform systems that automatically measure foot temperature may be helpful and are currently becoming available, but these are limited to the plantar foot surface (32). Temperature monitoring socks are another tool, but they lack both accuracy and resolution and have not been studied for clinical effect (33-35). Handheld or smartphone-based thermal imagers have a higher accuracy and resolution and seem feasible for clinical practice (36). Unfortunately, none of these new technological devices have been investigated in proper trials, as was discussed in **chapter 2**, and none were available at the start of the DIATEMP trial.

PREDICTION OF FOOT ULCER RECURRENCE IN HIGH-RISK PEOPLE WITH DIABETES

To address the fourth and last aim of this thesis, we developed two prediction models (**chapter 6** and **chapter 7**) to estimate the risk of ulcer recurrence in high-risk people with diabetes. As stated in **chapter 1**, prognostic research in diabetic foot disease is scarce and even absent for the prediction of ulcer recurrence. For successful implementation of prediction models in clinical practice, three consecutive phases should be followed (37). In the first phase, a multivariable prediction model is developed to identify important predictors (38). Relative weights are assigned to each predictor and the model's predictive performance and its internal validity is assessed. In the next phase, the predictive performance of the developed model is validated in a newly collected patient population (39). Finally, in the last phase it is assessed whether the new model truly improves decision making in clinical practice and ultimately patient outcomes (40). The two studies on prediction models in this thesis (described in **chapter 6** and **chapter 7**) both cover the first phase. The initial plan was to also validate the predictive performance of the models from each dataset on the other dataset, to also perform phase 2 studies. Unfortunately, this was impossible because the study populations of both datasets were too different and not all identified predictors were collected in both datasets. Despite only covering phase 1, the development of our prediction models is promising for further validation studies and identified clinically relevant predictors, and contain implications for daily practice.

Identification of clinically relevant predictors
In the models described in **chapter 6**, a younger age, fewer months since healing of the previous ulcer, the presence of a minor lesion, the use of a walking aid, more severe peripheral sensory neuropathy and not monitoring foot temperatures at home predicted with a good calibration and a fair discrimination ulcer recurrence at any site on the foot. The same first four predictors, and in addition the consumption of alcohol, plantar location of the previous ulcer and foot care received in a university medical centre, predicted with a reasonable calibration and a fair discrimination ulcer recurrence on the plantar surface. These models were based on the diverse group of high-risk people (IWGDF risk 3) that were included in the DIATEMP trial. Therefore, these models may be, after external validation, useful in clinical practice when screening any person classified as IWGDF risk 3, to identify - within this high risk population - those at highest risk of ulceration, and to allocate limited available resources in diabetic foot care to those who need it most. Moreover, these easy-to-obtain variables ensure that the models can be used by every healthcare provider in diabetic foot disease.

The models described in **chapter 7**, however, were based on the more select group of high-risk people that were included in the DIAFOS trial compared to those included in the DIATEMP trial. These people had a recent history of plantar foot ulceration (<18 months) and received newly prescribed custom-made footwear at inclusion. Furthermore, the models predicted only plantar ulcer recurrence and contained, besides three easy-to-obtain variables (presence of a minor lesion, living alone and a longer duration of having a previous ulcer), some more complex variables: increased barefoot plantar pressure and less variation in daily stride count. Therefore,

these models can only be applied by healthcare providers who can obtain these predictors in their daily practice.

For prognostic models to be clinically useful, they should be simple and contain reliable measurements (37). More complex models tend to be too optimistic in their predictions and are hard to validate (37). Our models contain reliable measurements, but are rather complex with some advanced measurements and up to seven predictors in a single model. This complexity is also illustrated by the moderate performance of all our models. This can partly be explained by our study design. Ideally, prediction models are based on a large observational cohort of participants with a substantial amount of events occurring to identify predictors, while we used data from RCTs. Inevitably we did not capture all variables that may predict ulcer recurrence, such as the amount of shear stress and the exact degree of both peripheral neuropathy and peripheral artery disease. Future studies should aim to further validate the presented prediction models for ulcer recurrence and if possible improve these models based on large observational cohorts that contain a wide variety of easy-to-obtain clinical variables.

CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

Refining international guidelines
International guidelines recommend to consider at-home foot temperature monitoring in people with diabetes that are at a medium to a high risk of ulceration to identify early warning signs of foot inflammation, to help prevent the first or recurrent foot ulcer (15). The Dutch guidelines recommend to consider at-home foot temperature monitoring only in people that are at high risk of ulceration (41). Since both recommendations are based on previous RCTs that have a high risk of bias and limitations in reporting, as addressed in this thesis, the evidence is considered moderate and the subsequent recommendations weak in both guidelines. Based on the results of the DIATEMP trial and the above performed meta-analyses, the recommendations in both guidelines may be refined. At-home foot temperature monitoring should only be advised to people that can be expected to remain adherent to monitoring foot temperature and to reducing their ambulatory activity when they find a 'hotspot'. Suggestions to improve adherence are described above and in the paragraph personalized medicine below. In addition, future research should identify better ways to improve treatment adherence and determine how targeted provision of this intervention can be facilitated. Future research should also focus on identifying those people who are adherent to both aspects of the intervention (at-home monitoring of foot temperature and reducing ambulatory activity when finding a hotspot) and should explore the value of more easy-to-use technology for monitoring foot temperature, in order to avoid overtreatment and unnecessary individual burden. Redefining the national and international guidelines may result in better implementation of at-home foot temperature monitoring in current practice to prevent diabetic foot ulcer recurrence.

Personalized medicine

The finding that only a select group of people with diabetes benefits from at-home foot temperature monitoring strengthens the current believe that a shift in paradigm from stratified healthcare to personalized healthcare is needed (42). Personalized treatment given through an integrated approach of specific forms of treatment may result in better preventative diabetic foot care. As already suggested in the international guidelines and throughout this thesis, an integrated approach of multiple preventative interventions may be more effective than one single intervention. The key in personalized medicine is to deliver the right treatment to the right person at the right time, where different treatment strategies for ulcer prevention are available for different persons. Personalized treatment plans may reduce the self-care burden for people with diabetes, which in turn may result in higher adherence and regaining the feeling of control in preventing ulcers (27, 42). Therefore, three suggestions for personalized temperature monitoring are provided. First, people can be advised to monitor foot temperature at just one or two high-risk locations based on their temperature profiles and previous ulcer location(s), rather than at 6-8 locations as was done in all temperature monitoring trials. Second, one can reduce the frequency of measurements when people do not measure hotspots and remain (pre-)ulcer-free for a certain time period. Especially since one third of the participants from the DIATEMP trial never developed a hotspot. In these cases, daily temperature measurements may be reduced to, for example, three times per week. However, as suggested in **chapter 4**, measuring foot temperature might also be a surrogate for increasing the participant's attention to the foot, suggesting that daily assessment may have an additional function in that case. At last, as suggested in **chapter 4**, only the 'medium' high-risk people may benefit from at-home monitoring of foot temperature since enhanced therapy was only effective over usual care in participants enrolled in community hospitals, but not in university medical centres or podiatry practices. The latter are suggested to be the most and least complex participants, respectively. However, future research is necessary to prove the true value of personalized temperature monitoring healthcare for the prevention of diabetic foot ulceration.

Towards dynamic *very-high-risk* categories

As discussed in **chapter 1**, disease severity and ulcer risk vary substantially within the highest risk group in all current risk classification systems (42-44). The models presented in **chapter 6** and **chapter 7** confirm this. Based on the presented models and other studies, suggestions for variables that may help to differentiate within the high risk group are: duration of previous ulcer (45), severity of peripheral sensory neuropathy (46, 47), plantar location of the previous ulcer (48-50), the time since healing of the last ulcer (12) and the presence of minor lesions (15, 45). Some of these risk factors are modifiable and can be targeted for preventive treatment, others are time-dependent, and some are not modifiable. Using (some of) these variables it may be possible to identify people who are (at least temporary) at *very high risk* of ulceration. These people should be monitored more carefully and more often, and should be treated more intensively. Once people at *very high risk* of ulceration remain ulcer-free for a certain period of time, the risk of ulceration decreases, and they may be considered at *high risk* again. Further research, using large (population-based) observational cohort studies or large RCTs, is needed to better stratify people

with diabetes at *high risk* of ulceration. Ideally, this future research will be combined with research on exploring and identifying pathways for ulcer development as suggested above.

METHODOLOGICAL CONSIDERATIONS

Throughout this thesis several methodological considerations have been discussed already. In this last section some important overarching methodological issues are highlighted.

First of all, the DIATEMP trial consisted of a single intervention for the prevention of recurrent ulcers located at the plantar surface of the foot, interdigital spaces and medial/lateral/anterior site of the forefoot. An alternative approach is to embed the intervention in a larger integrated (personalized) preventative treatment strategy, better mimicking normal clinical practice, where multiple interventions are applied simultaneously. This strategy may, for example, include pressure-optimized custom-made shoes, structured education about diabetic foot disease and foot care every 1-3 months in a multidisciplinary setting. Future studies should focus on such an integrated approach consisting of several preventative measurements together, instead of assessing the effectiveness of one single intervention.

Second, when the DIATEMP trial was designed, no handheld device other than the TempTouch® (Diabetica Solutions, San Antonio, TX, USA) was available and validated in clinical studies. The TempTouch® had some operational flaws, mainly when measuring temperature in the presence of abundant callus, and measuring temperature at the correct location on the foot was sometimes difficult for participants with physical impairments. Recently, technological advancements in at-home monitoring of foot temperature led to the development of special socks, smartphone-based thermal cameras, and a thermometric foot mat (32-34, 36). Although, the foot mat is feasible for temperature monitoring at the plantar surface of the foot, its effectiveness in the prevention of foot ulcers has not been investigated yet. If this foot mat would have been used during our study, adherence to monitoring of foot temperature would probably have been higher, since the measurement itself and the calculation of temperature differences would be automated and therefore less cumbersome for participants. However, the suggestion, discussed in **chapter 4**, that monitoring of foot temperature with the TempTouch® increased the participant's attention on the foot and helped prevent (dorsal) ulcers, may not apply when participants only need to stand on a foot mat for a brief moment. This suggests that each technique has its advantages and disadvantages, and should be tested in properly designed trials. More user-friendly and effective technologies should be developed that alarm both users and healthcare providers if a hotspot is found. Furthermore, technologies should provide specific instructions for reducing ambulatory activity and contacting healthcare providers in case of a hotspot. Possible technologies may be a smartphone application with a (direct) connection to a healthcare provider that requires input from a foot mat, sock or thermal camera and the answers to a few short questions (e.g. is your foot swollen or red?). Ideally, this application has the possibility to upload photographs or videos and may store important additional information, for example, reminders for appointments with a foot care specialist, glucose levels, dietary logs, etc. (51).

Third, in the DIATEMP trial a foot ulcer was defined as a full-thickness lesion through the dermis without reference to time present (52). Some ulcers were only present for one or two weeks and needed only one single visit to the healthcare provider for wound care. Others were present for several months and needed multidisciplinary treatment including surgical debridement and prolonged total contact casting. In both cases an endpoint was reached. By choosing a binary outcome (i.e. ulcer vs. no ulcer), a potential additional effect of our intervention, the early identification of ulceration and thus less severe ulcers, may have been underestimated. To assess ulcer severity we documented the University of Texas classification system (53) at presentation, but this is only a single clinical observation, most of the time prior to imaging or laboratory assessment and has only a fair inter-observer reliability (54). Changing the outcome in ulcers that were present for more than one month did not result in a higher reduction in ulcer recurrence in enhanced therapy over usual care (data not reported). As an alternative for severity, the costs associated with treating ulcers might be considered. A future, and ongoing, cost-effectiveness analysis of the DIATEMP trial may determine if at-home monitoring of foot temperature is cost-effective over usual care (55).

Finally, in both our prediction models we chose to perform a binary logistic regression analysis. Other forms of analysis with different outcomes may also provide valuable insights. For example, a Cox regression analysis can be performed, which investigates the effect of variables on time to an event (i.e. time to ulceration or ulcer-free survival days). Ulcer-free survival days have hardly been reported in the literature (56-58), but are clinically important since an important goal is to stay ulcer-free for as long as possible. The useful simplifying aspects of the Cox model require, however, the proportional hazards assumption (hazard ratio between two groups is assumed to be constant over time), lack of high leverage points and censoring should be independent to time to event. We opted for logistic regression because it requires less assumptions and is easier to interpret. Future research can focus on Cox regression analysis for predicting ulcer-free survival days.

GENERAL CONCLUSION

With this thesis the knowledge and understanding on the prevention, development and prediction of foot ulcer recurrence in people with diabetes who are at high risk of developing a foot ulcer is expanded. For the prevention of ulcer recurrence several telehealth and telemedicine approaches are feasible and can help to improve efficiency and effectiveness of foot care. The DIATEMP trial showed that at-home monitoring of foot temperature in addition to usual care is a telehealth approach that did not significantly reduce the incidence of ulcer recurrence at or adjacent to measurement locations. A beneficial effect of the intervention on ulcer recurrence may be specific to those who have a medium high-risk for ulceration, and to those who are adherent to monitoring foot temperature and changing their behaviour when measuring a hotspot. In order to identify people at high-risk of ulceration, the first-ever prediction models for ulcer recurrence have been reported in this thesis. Several important predictors were identified,

some of which can be targeted for preventative treatment. However, the prediction of ulcer recurrence remains difficult and external validation is necessary before these models can be implemented in daily foot care. Ultimately, a personalized treatment approach, preferably given as an integrated care solution containing multiple forms of preventative treatment, is likely required to significantly reduce the risk of ulcer recurrence in high-risk people with diabetes. Hopefully, the findings in this thesis inspire researchers and clinicians to intensify their quest to improve outcomes in preventing foot ulcer recurrence in high-risk people with diabetes.

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Chapter 9

Summary

Prevention and prediction of foot ulcer recurrence in diabetes

People with diabetes are at risk of various complications. A common complication is the development of a foot ulcer. These ulcers cause severe morbidity and have a negative impact on a person's mobility and quality of life. Moreover, the treatment of a diabetic foot ulcer is costly. Even after successful healing, a recurrent foot ulcer develops in roughly 40% of the people within one year. Prevention of these ulcers is paramount to reduce the large burden on people and healthcare systems. Stimulated by the need for innovation in foot ulcer prevention, at-home monitoring of foot temperatures is developed as a telehealth application. Foot ulcers are suggested to be preceded by local increased skin temperature caused by accumulating repetitive stress from being ambulatory. Early recognition of imminent ulcers by monitoring foot temperature allows people at-risk to act timely by reducing their ambulatory activity to reduce local inflammation. Despite that three randomized controlled trials (RCTs) showed large effects in reducing first-ever and recurrent ulcers, at-home monitoring foot temperature is rarely used in preventative foot care. Moreover, recent meta-analyses have reported uncertainty over the effect of at-home monitoring foot temperature. Therefore more RCTs on this topic are needed. Furthermore, to improve the treatment for prevention, insights in the pathogenesis of diabetic foot ulceration and its risk factors are important. Finally, it is important to identify those people who are at highest risk of ulceration in order to provide appropriate preventative treatment and to adequately allocate limited recourses. Therefore, the general aim of this thesis was to expand the knowledge and understanding on the prevention, development and prediction of foot ulcer recurrence in people with diabetes who are at high risk of developing a foot ulcer.

Chapter 1 provided the introduction for this thesis and described in more detail the problem of diabetic foot ulcer recurrence and its burden on people with diabetes and healthcare systems. It provided insights in the pathogenesis of foot ulceration and described risk factors associated with ulcer recurrence. Furthermore, this chapter summarized the current guidelines for the prevention of ulcer recurrence and introduced the DIAbetic foot TEMPerature (DIATEMP) trial: an RCT on effectiveness of at-home monitoring foot skin temperature as a telehealth application for the prevention of ulcer recurrence in high-risk people with diabetes. Finally, the use of prediction models was introduced as a method to estimate the risk of ulcer recurrence in high-risk people with diabetes.

In **chapter 2** the current peer-reviewed literature on telehealth and telemedicine applications was discussed. The findings of this systematic review showed that there were several technologies available that may be of value in the assessment/monitoring, prevention, and/or treatment of diabetic foot disease. At-home monitoring of foot temperature was the most investigated telehealth application for diabetic foot disease and was found to be a feasible and effective approach for the prevention of foot ulcers in people with a medium to a high risk of developing a foot ulcer. Other telehealth and telemedicine approaches required a larger scientific base of effectiveness and feasibility, or were still in an early stage of development and required technically and economically more efficient approaches before they can be widely deployed in people's home as telehealth or telemedicine application.

In **chapter 3** the study protocol of the DIATEMP trial was presented. This multicenter, outcome-assessor blinded, randomized controlled trial aimed to assess the effectiveness, cost-effectiveness and cost-utility of daily at-home monitoring foot temperature monitoring to reduce the incidence of foot ulcer recurrence in high-risk people with diabetes. In total 304 participants with diabetes, peripheral sensory neuropathy, a history of foot ulceration (<4 years) or a Charcot neuro-osteoarthropathy were randomly assigned to usual care or usual care plus the daily measurement of skin temperatures at 6-8 plantar sites per foot (enhanced therapy). The primary outcome of the study was ulcer recurrence within 18 months follow-up on the plantar foot, interdigital, or medial/lateral/anterior forefoot surfaces.

In **chapter 4** the results of the DIATEMP trial on the effectiveness of at-home monitoring of foot temperature in reducing the incidence of foot ulcer recurrence in high-risk people with diabetes were presented. Based on an intention-to-treat analysis the DIATEMP trial showed that, with enhanced therapy, there was a statistically non-significant 21.8% lower incidence of ulcer recurrence at a primary foot site compared to usual care alone. A per-protocol analysis showed that adherence to monitoring foot temperatures had no significant effect on ulcer recurrence (8.6% lower incidence), however, adherence to reducing ambulatory activity after identifying a hotspot did, with a 64.9% lower incidence found. Secondary analyses also showed when ulcer recurrence at only the previous ulcer site (53.9% lower incidence) or at any site on the foot (24.0% lower incidence) was considered as outcome, that enhanced therapy was effective over usual care. Taken together, it is concluded that at-home foot temperature monitoring does not significantly reduce incidence of diabetic foot ulcer recurrence at or adjacent to measurement sites over usual care, unless participants reduce ambulatory activity when hotspots are found, or when aiming to prevent ulcers at any foot site.

Chapter 5 focused on the underlying mechanism of ulcer development of participants in the DIATEMP trial. Of the 151 participants in the enhanced therapy group, 29 participants developed a non-traumatic ulcer while being adherent to monitoring their foot temperatures. Only eight of these participants (28%) had a hotspot at or adjacent to the ulcer within the two months prior to ulceration. This is in contrast to the general thought that most plantar foot ulcers are caused by elevated plantar tissue stress form being ambulatory and are suggested to be preceded by a local skin temperature increase. The last hotspot before ulceration was seen a mean 9 days before the ulcer developed. These results question to some extent the validity of this suggested mechanism of foot temperature increase before ulceration in people with diabetes at high risk.

Chapter 6 described the development, internal validation and performance assessment of two logistic regression prediction models for foot ulcer recurrence. These models were based on data from the DIATEMP trial and contained a variety of easy-to-obtain clinical variables. Predictors for ulcer recurrence at any site of the foot were: a younger age, more severe peripheral sensory neuropathy, fewer months since healing of previous ulcer, presence of a minor lesion, use of a walking aid and not monitoring foot temperatures at home. Predictors for ulcer recurrence on the plantar foot surface were: a younger age, plantar location of previous ulcer, fewer months since

healing of previous ulcer, presence of a minor lesion, consumption of alcohol, use of a walking aid, and foot care received in a university medical centre. These prediction models can help in risk assessment, defining treatment options and in re-allocating resources for ulcer prevention treatment in this high-risk group of people with diabetes.

Chapter 7 described the development, internal validation and performance assessment of two logistic regression prediction models for plantar foot ulcer recurrence. These models were based on data from the DIAFOS trial, an RCT on the effectiveness of custom-made footwear to prevent plantar foot ulcer recurrence. Predictors for plantar foot ulcer recurrence were: presence of a minor lesion, living alone, increased barefoot peak plantar pressure, longer duration of having a previous foot ulcer and less variation in daily stride count. Predictors for recurrent plantar ulcers that were identified to be the result of unrecognized repetitive stress were: presence of a minor lesion, longer duration of having a previous foot ulcer, and location of the previous foot ulcer. These prediction models may help to identify those people with diabetes who are at risk of developing a recurrent plantar foot ulcer and for that reason should be monitored more carefully and frequently and treated more intensively.

In **chapter 8** the main findings of the studies in this thesis were discussed in the context of the currently available literature. This general discussion included a meta-analysis of RCTs on the effectiveness of the at-home monitoring of foot temperature. The pooled evidence showed a 49% risk reduction for ulcer recurrence for people who monitored their foot temperatures at home compared to usual care. Also in this chapter, the findings on adherence in the DIATEMP trial are placed in a broader perspective, given the importance of adherence for the intervention to be effective. This is done by using the theory of planned behaviour. The development of the first-ever prediction models for ulcer recurrence are discussed together with their limitations. Furthermore, critical reflections of methodology used, implications for clinical practice and future research are described, and finally a general conclusion was provided.

Samenvatting

*Het voorkomen en voorspellen van een recidief voetulcus
bij diabetes*

Mensen met diabetes hebben risico op diverse complicaties. Een veel voorkomende complicatie is het krijgen van een voetulcus (voetwond). Een voetulcus veroorzaakt ernstige morbiditeit en heeft een negatieve impact op de mobiliteit en kwaliteit van leven. Daarnaast is de behandeling van een diabetisch voetulcus duur. Bovendien zal na succesvolle genezing ongeveer 40% van de mensen een recidief ulcus ontwikkelen binnen een jaar. Het voorkomen van deze ulcera is derhalve uitermate belangrijk om de hoge lasten voor zowel de mensen als de gezondheidszorg te verminderen. Binnen de preventieve zorg van diabetische voetulcera is het thuis monitoren van voettemperatuur ontwikkeld als 'telehealth' toepassing. Er wordt namelijk verondersteld dat een voetulcus wordt voorafgegaan door een verhoogde huidtemperatuur. Dit als gevolg van de cumulatieve mechanische stress onder de voet die ontstaat tijdens het staan en lopen. Een vroege herkenning van een dreigend ulcus door het monitoren van deze voettemperatuur stelt mensen die risico lopen op een voetulcus in de gelegenheid tijdig hun ambulante activiteit te beperken en daarmee lokale inflammatie onder de voet te verminderen. Ondanks dat drie gerandomiseerde gecontroleerde onderzoeken (RCT's) grote effecten lieten zien in het verminderen van zowel het eerste als het recidief ulcus, wordt thuismonitoring van de voettemperatuur zelden gebruikt in de preventieve zorg. Recent hebben meta-analyses ook enkele de beperkingen van deze RCT's aangekaart en geconcludeerd dat er meer RCT's over dit onderwerp nodig zijn. Daarnaast is het voor het verbeteren van de preventieve zorg belangrijk om meer inzicht te krijgen in de pathogenese en de risicofactoren van een diabetisch voetulcus. Als laatste is het belangrijk om juist die mensen te identificeren die het hoogste risico hierop lopen, zodat gepaste preventieve zorg geleverd kan worden en dat de beperkt beschikbare middelen ingezet kunnen worden voor de juiste mensen. Daarom is het algemene doel van dit proefschrift het uitbreiden van de kennis en begrip omtrent het voorkomen, ontwikkeling en het voorspellen van een recidief voetulcus in mensen met diabetes die een hoog risico hebben op het ontwikkelen van een dergelijk voetulcus.

Hoofdstuk 1 was de introductie van dit proefschrift en hierin wordt in meer detail het probleem van een recidief voetulcus beschreven en de last hiervan op zowel de mensen met diabetes als op de gezondheidszorg. Het gaf inzicht in de pathogenese van een voetulcus en de risicofactoren die geassocieerd waren met een recidief worden beschreven. Verder werd in dit hoofdstuk een samenvatting gegeven van de huidige richtlijnen voor de preventie van een recidief voetulcus en werd de 'DIAbetic foot TEMPerature' (DIATEMP) studie geïntroduceerd: een RCT over de effectiviteit van thuismonitoring van de voettemperatuur als telehealth toepassing voor het voorkomen van een recidief voetulcus bij mensen met diabetes en een hoog risico op een dergelijk voetulcus. Als laatste werd ook het gebruik van predictiemodellen geïntroduceerd als een methode om het risico op een recidief voetulcus in te schatten in hoog risico mensen met diabetes.

In **hoofdstuk 2** werd de huidige wetenschappelijke literatuur omtrent telehealth en telemedicine toepassingen bediscussieerd. Deze systematische review toonde aan dat er diverse technologieën beschikbaar waren die van waarde kunnen zijn bij de beoordeling, monitoring, preventie dan wel behandeling van de diabetische voet. Thuismonitoring van de voettemperatuur was de meest onderzochte telehealth toepassing voor de diabetische voet en werd gezien als een haalbare en effectieve toepassing voor de preventie van een voetulcus in mensen met diabetes met een gemiddeld tot een hoog risico hierop. Andere telehealth en telemedicine toepassingen

hadden een grotere wetenschappelijke basis nodig die de effectiviteit en haalbaarheid van deze toepassingen kunnen aantonen of waren nog in een vroege fase van ontwikkeling en hebben daarom nog technische en economische efficiëntie nodig voordat ze in de thuissituatie kunnen worden toegepast.

In **hoofdstuk 3** werd het onderzoeksprotocol van de DIATEMP studie gepresenteerd. Dit multicenter, uitkomst-geblindeerd, gerandomiseerd en gecontroleerd onderzoek had als doel het bepalen van de effectiviteit, kosteneffectiviteit en kostenutiliteit van het dagelijks monitoren van de voettemperatuur om zo het aantal voetulcus recidieven te verminderen bij mensen met diabetes met een hoog risico op een voetulcus. In totaal werden 304 deelnemers met diabetes, perifere sensorische neuropathie, en een voetulcus in de voorgeschiedenis (<4 jaren) of een Charcot neuro-osteoathropathie gerandomiseerd naar reguliere zorg of naar reguliere zorg inclusief het dagelijks meten van de huidtemperatuur op 6 tot 8 locaties onder beide voeten. De primaire uitkomst van het onderzoek was een recidief ulcus binnen 18 maanden follow-up op de plantaire zijde van de voet, interdigitaal of mediale/laterale/anterieure zijde van de voorvoet.

In **hoofdstuk 4** werden de resultaten gepresenteerd van de DIATEMP studie naar de effectiviteit van thuismonitoring van de voettemperatuur om het aantal voetulcus recidiveren te verminderen bij mensen met diabetes met een hoog risico op een voetulcus. Gebaseerd op de intention-to-treat analyse liet de DIATEMP studie zien dat er in de interventiegroep een niet-statistisch significant lagere incidentie van 21.8% aan ulcus recidieven was op de primaire uitkomstlocatie in vergelijking met de controlegroep. Per-protocol-analyses toonden dat therapietrouw aan het meten van de voettemperatuur geen significant effect had op het percentage recidieven (8.6% lagere incidentie), echter therapietrouw aan het verlagen van ambulante activiteiten na het identificeren van een hotspot had wel een significant effect. Dit zorgde voor een 64.9% lagere incidentie van recidiverende ulcera in de interventiegroep. Ook toonde secundaire analyses aan wanneer het recidief ulcus op de vorige ulcuslocatie (53.9% lagere incidentie) of op elke locatie van de voet (24.0% lagere incidentie) werden beschouwd als uitkomstmaat, dat de interventie effectiever was in vergelijking tot reguliere zorg. Samenvattend kan geconcludeerd worden dat thuismonitoring van de voettemperatuur niet leidde tot een significante vermindering van het aantal recidiverende diabetische voetulcera ter plaatse of in de buurt van de meetlocaties, tenzij deelnemers hun ambulante activiteit verminderden wanneer ze een hotspot hadden gevonden of wanneer het doel is om ulcera op alle locaties van de voet te voorkomen.

Hoofdstuk 5 richtte zich op het onderliggende mechanisme van de ontwikkeling van een ulcus bij deelnemers van de DIATEMP studie. Van de 151 deelnemers in de interventiegroep, ontwikkelde 29 deelnemers een niet-traumatisch ulcus terwijl ze ook hun voettemperatuur monitorden. Slechts acht van deze deelnemers (28%) had een hotspot ter plaatse of in de buurt van het ulcus in de twee maanden voorafgaand aan dit ulcus. Dit is in tegenstelling tot de algemene gedachte dat de meeste plantaire ulcera worden veroorzaakt door verhoogde plantaire stress als gevolg van het ambulant zijn en daarmee worden voorafgegaan door een lokaal verhoogde temperatuur van de huid. De laatste hotspots werden gemiddeld 9 dagen voor het ontstaan van het ulcus gemeten. Deze resultaten zorgen voor twijfel over de validiteit van het gesuggereerde

mechanisme van verhoogde huidtemperatuur voorafgaand aan het ontstaan van een voetulcus in hoog risico mensen met diabetes.

Hoofdstuk 6 beschreef de ontwikkeling, interne validatie en prestatiebeoordeling van twee logistische modellen voor het voorspellen van een recidief voetulcus. Deze predictiemodellen waren gebaseerd op data van de DIATEMP studie en bevatten eenvoudig te verkrijgen klinische variabelen. Voorspellers voor een recidief ulcus op elke locatie van de voet waren: een jonge leeftijd, meer ernstige perifere sensorische neuropathie, minder tijd (maanden) sinds genezing van het vorige ulcus, de aanwezigheid van kleine laesies, gebruik van een loophulpmiddel en het niet thuis monitoren van de voettemperatuur. Voorspellers voor een recidief plantair ulcus waren: een jongere leeftijd, een plantaire locatie van het vorige ulcus, de aanwezigheid van kleine laesies, de consumptie van alcohol, het gebruik van een loophulpmiddel en het krijgen van voetzorg vanuit een universitair medisch centrum. Deze predictiemodellen zouden kunnen helpen bij het inschatten van het risico op een recidief ulcus, het bepalen van behandelstrategieën en het juist inzetten van beperkte middelen voor ulcuspreventie bij mensen met diabetes en een hoog risico op een voetulcus.

Hoofdstuk 7 beschreef de ontwikkeling, interne validatie en prestatiebeoordeling van twee logistische modellen voor het voorspellen van een recidief plantair voetulcus. Deze predictiemodellen waren gebaseerd op data van de DIAFOS studie: een RCT over de effectiviteit van orthopedisch maatschoeisel ter preventie van een recidief plantair voetulcus. Voorspellers voor een recidief plantair ulcus waren: de aanwezigheid van kleine laesies, alleen wonen, verhoogde blootvoetse piekdrukken, langere duur van het vorige ulcus en minder dagelijkse variaties in het aantal gezette stappen. Voorspellers voor een recidief plantair voetulcus welke verondersteld werd te zijn veroorzaakt door onopgemerkte herhaaldelijke stress waren: de aanwezigheid van kleine laesies, langere duur van het vorige ulcus en de locatie van het vorige ulcus. Deze predictiemodellen zouden kunnen helpen bij het identificeren van mensen met diabetes die een hoog risico hebben op een recidief plantair ulcus en vanwege dit hoge risico zouden deze mensen zorgvuldiger en frequenter moeten worden gemonitord en intensiever moeten worden behandeld.

In **hoofdstuk 8** werden de belangrijkste bevindingen van de studies in dit proefschrift ter discussie gesteld in de context van de huidige beschikbare literatuur. De algemene discussie bevatte een meta- analyse van RCT's over de effectiviteit van thuismonitoring van de voettemperatuur. Het samengevoegde bewijs toonde een 49% risicovermindering op een recidief voetulcus in mensen die thuis hun voettemperatuur hadden gemeten in vergelijking tot reguliere zorg. Ook werden de bevindingen van de DIATEMP studie in een breder perspectief geplaatst, gezien het belang van therapietrouw voor de effectiviteit van deze interventie. Dit werd gedaan aan de hand van de theorie van gepland gedrag. De ontwikkeling van de allereerste predictiemodellen voor het voorspellen van een recidief voetulcus werd bediscussieerd, samen met de beperkingen van deze modellen. Daarnaast werd er kritisch gereflecteerd op de gebruikte methoden, werden implicaties voor de klinische praktijk en toekomstig onderzoek beschreven en werd een algemene conclusie gegeven.

Appendices

CONTRIBUTIONS OF THE AUTHORS

Chapter 2
CEVB Hazenberg, WB aan de Stegge, JG van Baal, FL Moll and SA Bus. Telehealth and Telemedicine applications for the diabetic foot: a systematic review. *Diabetes Metab Res Rev 2019; 36: e3247*.

CH, JvB, FM, SB conceived and designed the study. CH and SB designed the search string. CH, WadS and SB performed the literature search, assessed the literature, extracted data and drew conclusions. CH and WadS wrote the manuscript. JvB, FM and SB critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Chapter 3
WB aan de Stegge, N Mejaiti, JJ van Netten, MGW Dijkgraaf, JG van Baal, TE Busch-Westbroek and SA Bus. The cost-effectiveness and cost-utility of at-home infrared temperature monitoring in reducing the incidence of foot ulcer recurrence in patients with diabetes (DIATEMP): study protocol for a randomized controlled trial. *Trials 2018; 19: 520*.

SB conceived and designed the DIATEMP trial. SB, WadS, NM, JvN drafted or edited the trial protocols. SB and NM obtained ethical approval. TB and JvB advised and contributed to the trial design. MD developed the statistical analysis plan for the cost-effectiveness and cost-utility analysis. WadS and SB drafted the article and all other authors read and commented on the article, and approved the final version of the manuscript.

Chapter 4
SA Bus, WB aan de Stegge, JG van Baal, TE Busch-Westbroek, F Nollet and JJ van Netten. The effectiveness of at-home skin temperature monitoring in reducing the incidence of foot ulcer recurrence in people with diabetes: a multicenter randomized controlled trial (DIATEMP). *BMJ Open Diabetes Res Care 2021; 9: e002392*.

SB conceived and designed the DIATEMP trial, obtained ethical approval, and registered the trial. FN contributed to trial design. SB, WadS, and JvN drafted or edited the trial protocols. SB, WadS, JvN, and TB collected data for the trial. TB and JvB provided clinical advice and had clinical responsibility for patient-related matters. WadS performed the statistical analyses, SB and JvN verified the underlying data. SB wrote the manuscript and all other authors read, commented and edited the manuscript for intellectual content. All authors approved the final version of the manuscript.

Chapter 5
WB aan de Stegge, JJ van Netten and SA Bus. Does the skin heat up before it breaks down in diabetic foot ulceration?

WadS, JvN and SB conceived and designed the analysis for this study. WadS performed the statistical analysis and wrote the manuscript. JvN and SB critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Chapter 6
WB aan de Stegge, MC Schut, A Abu-Hanna, JG van Baal, JJ van Netten and SA Bus. Development of a prediction model for foot ulcer recurrence in people with diabetes using easy-to-obtain clinical variables. *BMJ Open Diabetes Res Care 2021; 9: e002257.*

SB conceived and designed the original trial from which the data were used. WadS, AA-H and SB conceived the plan for this study. WadS, JvN and SB collected data. MS, AA-H and WadS ran the prediction models and performed statistical analysis. WadS wrote the manuscript. MS, AA-H, JvN, JvB and SB critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Chapter 7
WB aan de Stegge, A Abu-Hanna and SA Bus. Development of a multivariable prediction model for plantar foot ulcer recurrence in high-risk people with diabetes. *BMJ Open Diabetes Res Care 2020; 8: e001207.*

WadS, AA-H, SB conceived and designed the analysis for this study, using existing data. AAH performed the statistical analysis. WadS wrote the manuscript. AA-H and SB critically reviewed and edited the manuscript. All authors have read and approved the final manuscript.

CURRICULUM VITAE

Wouter aan de Stegge was born 1 September 1988 to Theo and Yvonne aan de Stegge in Zwolle, the Netherlands. He grew up together with Milou, his younger sister, in Raalte, a village located in Overijssel. In 2006 he completed high school at Carmel College Salland and began his BSc in Human Movement Sciences at the University of Groningen. After obtaining his bachelor's degree, he remained at the University of Groningen to study Medicine. During his last years of medical school, he became increasingly interested in surgery. To further his studies, he followed an orthopaedic surgery internship abroad at Pelonomi Hospital, Bloemfontein in South Africa. Upon his return to the Netherlands he completed his final surgical internship at Isala in Zwolle.

In December 2014, Wouter joined Ziekenhuisgroep Twente (ZGT) in Almelo/Hengelo as a medical doctor in the surgical department. Under the supervision of dr. J.G. Van Baal, he became interested in vascular surgery, and especially the diabetic foot. In June 2015 he began his PhD, researching prevention and prediction of foot ulcer recurrence in diabetes at the Department of Rehabilitation Medicine at the University of Amsterdam under the supervision of dr. S.A. Bus and prof. dr. F. Nollet. His surgical training at ZGT, under the supervision of dr. M.F. Lutke Holzik, started in January 2017.

Currently Wouter works at University Medical Center Groningen in Groningen as a fifth-year surgical resident, focusing on vascular surgery under the supervision of dr. R.J. van Ginkel and dr. M.J. van der Laan.

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KH Hutting, **WB aan de Stegge**, JJ van Netten, WA ten Cate, L Smeets, GMJM Welten, DM Scharn, JPPM de Vries and JG van Baal. Surgical treatment of diabetic foot ulcers complicated by osteomyelitis with gentamicin-loaded calcium sulphate-hydroxyapatite biocomposite. *J Clin Med 2021; 10: 371.*

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FJ Rovers, JJ van Netten, TE Busch-Westbroek, **WB aan de Stegge** and SA Bus. Adherence to at-home monitoring of foot temperatures in high-risk people with diabetes. *Submitted.*

BM Perrin, JJ van Netten, **WB aan de Stegge**, TE Busch-Westbroek and SA Bus. Health-related quality of life and associated factors in people with diabetes at high risk of foot ulceration. *Submitted.*

PORTFOLIO

Name PhD Student	Wouter Bernard aan de Stegge
Department	Rehabilitation medicine
PhD period	Part-time (20%) from June 2015 until December 2019 and full-time from January 2020 until June 2020
Promotores	dr. S.A. Bus, prof. dr. F. Nollet
Copromotores	dr. J.J. van Netten, dr. J.G. van Baal
Total ECT	26.2

	Year	Workload (Hours/ECTS)
1. PhD training		
Courses		
• Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers (BROK)	2015	28 / 1.0
• OpenClinica Training	2015	14 / 0.5
• Herregistratie Regelgeving en Organisatie voor Klinische onderzoekers (BROK)	2020	7 / 0.25
Oral presentations		
• XVe Diabetische voet symposium Almelo, Almelo, The Netherlands. *Prediction of recurrent ulcers in high-risk diabetes patients.*	2016	14 / 0.5
• Research Meeting, department of Rehabilitation, Amsterdam UMC, location AMC, Amsterdam, The Netherlands. *Predictie van re-ulceratie in hoog risico diabetes patiënten.*	2016	14 / 0.5
• 13th Scientific meeting Diabetic Foot Study Group, Stuttgart, Germany. *Prediction of recurrent ulcers in high-risk diabetes patients.*	2016	14 / 0.5
• 6de ZGT Wetenschapsdag, Almelo, The Nederlands. *Voorspellen van recidief voetulcera bij hoog-risico diabetes patiënten.*	2016	14 / 0.5
• Annual Dutch Diabetes Research Meeting 2016, Oosterbeek, The Netherlands. *Prediction model for plantar foot ulcer recurrence in high-risk diabetes patients.*	2016	14 / 0.5
• XVIe Diabetische voet symposium Almelo, Almelo, The Netherlands. *Prediction of ulcer recurrence and time to ulcer recurrence in high-risk diabetes patients.*	2017	14 / 0.5
• Research Meeting, department of Rehabilitation, Amsterdam UMC, location AMC, Amsterdam, The Netherlands. *DIATEMP - Het bepalen van de kosteneffectiviteit en kostenutiliteit van het thuis monitoren van de voettemperatuur ter preventie van recidief voetulcera bij mensen met diabetes.*	2017	14 / 0.5
• 52nd International Meeting of the European Society for Surgical Research, Amsterdam, The Netherlands. *The relation between (day-to-day changes) in left-to-right differences in cumulative plantar tissue stress and plantar foot temperature at high-risk locations in diabetes patients.*	2017	14 / 0.5

	Year	
• Annual Dutch Diabetes Research Meeting 2017, Oosterbeek, The Netherlands. *The association between cumulative stress and plantar foot temperature at high-risk locations in diabetes patients.*	2017	14 / 0.5
• XVIIe Diabetische voet symposium Almelo, Almelo, The Netherlands. *The association between cumulative stress and plantar foot temperature at high-risk locations in diabetes patients.*	2018	14 / 0.5
• Vascular Course 2018, Valencia, Spain. *Telemedicine bij de diabetische voet, de feiten.*	2018	14 / 0.5
• 7de ZGT Wetenschapsdag, Almelo, The Nederlands. *Telemedicine bij de diabetische voet, de feiten.*	2018	14 / 0.5
• Research Meeting, department of Rehabilitation, Amsterdam UMC, location AMC, Amsterdam, The Netherlands. *Telemedicine bij de diabetische voet, de feiten.*	2019	14 / 0.5
• XVIIIe Diabetische voet symposium Almelo, Almelo, The Netherlands. *Factors associated with recurrent ulceration in high-risk patients with diabetes.*	2020	14 / 0.5
• 16th Scientific meeting Diabetic Foot Study Group, virtual. *Prediction models for recurrent ulcers in people with diabetes using easy-to-obtain clinical variables.*	2020	14 / 0.5

Poster presentations

• 14th Scientific meeting Diabetic Foot Study Group, Porto, Portugal. *The relation between (day-to-day changes) in left-to-right differences in cumulative plantar tissue stress and plantar foot temperature at high-risk locations in diabetes patients.*	2017	14 / 0.5
• 15th Scientific meeting Diabetic Foot Study Group, Berlin, Germany. *Telemedicine and home-monitoring applications for the diabetic foot: a systematic review.*	2018	14 / 0.5
• 9th International Symposium on the Diabetic Foot, Den Haag, The Netherlands. *Telemedicine and home-monitoring applications for the diabetic foot: a systematic review.*	2019	14 / 0.5

Workshop presentations

• XVIIIe Diabetische voet symposium Almelo, Almelo, The Netherlands. *Non-invasieve diagnostische methoden voor de diabetische voet.*	2020	14 / 0.5

Attending conferences

• 8th International Symposium on the Diabetic Foot, Den Haag, The Netherlands: May 20 – May 23.	2015	28 / 1.0
• XVe Diabetische voet symposium Almelo, Almelo, The Netherlands: January 19 – January 20.	2016	14 / 0.5
• 13th Scientific meeting Diabetic Foot Study Group, Stuttgart, Germany: September 9 – September 11.	2016	14 / 0.5
• 6de ZGT Wetenschapsdag, Almelo, The Nederlands: October 12.	2016	7 / 0.25
• Annual Dutch Diabetes Research Meeting 2016, Oosterbeek, The Netherlands: December 1.	2016	7 / 0.25

•	XVIe Diabetische voet symposium Almelo, Almelo, The Netherlands: January 17 – January 18.	2017	14 / 0.5
•	52nd International Meeting of the European Society for Surgical Research, Amsterdam, The Netherlands: June 17.	2017	7 / 0.25
•	14th Scientific meeting Diabetic Foot Study Group, Porto, Portugal: September 8 – September 10.	2017	14 / 0.5
•	Annual Dutch Diabetes Research Meeting 2017, Oosterbeek, The Netherlands: November 30.	2017	7 / 0.25
•	XVIIe Diabetische voet symposium Almelo, Almelo, The Netherlands: January 23 – January 24.	2018	14 / 0.5
•	Vascular Course 2018, Valencia, Spain: September 23 – September 25.	2018	14 / 0.5
•	15th Scientific meeting Diabetic Foot Study Group, Berlin, Germany: September 28 – September 30.	2018	14 / 0.5
•	7de ZGT Wetenschapsdag, Almelo, The Nederlands: October 10.	2018	7 / 0.25
•	9th International Symposium on the Diabetic Foot, Den Haag, The Netherlands: May 22 – May 25.	2019	28 / 1.0
•	XVIIIe Diabetische voet symposium Almelo, Almelo, The Netherlands: February 4 – February 5.	2020	14 / 0.5
•	16th Scientific meeting Diabetic Foot Study Group, virtual: September 18 – September 19.	2020	14 / 0.5

Committees

•	Organizing committee XVIe Diabetische voet symposium Almelo, Almelo, The Netherlands.	2017	14 / 0.5
•	Plenary session DIATEMP study group, Amsterdam, The Netherlands.	2017	2.8 / 0.1
•	Organizing committee XVIIe Diabetische voet symposium Almelo, Almelo, The Netherlands.	2018	14 / 0.5
•	Plenary session DIATEMP study group, Amsterdam, The Netherlands.	2019	2.8 / 0.1
•	Organizing committee XVIIIe Diabetische voet symposium Almelo, Almelo, The Netherlands.	2020	14 / 0.5

1. Teaching

Supervision master's thesis

L.K. Schrijver, Movement Sciences, University of Groningen, Groningen, The Netherlands. *The relation between in-shoe plantar pressure and local skin temperature in patients with a diabetic foot who are at high-risk for developing a foot ulcer.*	2016	28 / 1.0
C.M. Schrijver, Movement Sciences, University of Groningen, Groningen, The Netherlands. *The relation between barefoot plantar pressure and foot temperature in high-risk diabetes patients.*	2016	28 / 1.0

S. Dieltjes, Biomedical Sciences, Radboud University Nijmegen, Nijmegen, The Netherlands. *Plantar foot temperature increases in diabetic foot patients may be induced by prolonged periods of cumulative stress.*	2018	28 / 1.0
D. Schouten, Health Science, VU University Amsterdam, Amsterdam, The Netherlands. *Cost-effectiveness of offloading-improved custom-made footwear compared to usual care for people with diabetes.*	2019	7 / 0.25
V.A.L. Bosch, Health Science, VU University Amsterdam, Amsterdam, The Netherlands. *Predicting treatment costs in high-risk diabetes patients who monitor their foot temperature at-home to prevent diabetic foot ulcers.*	2019	7 / 0.25

Supervision research projects

K.H. Hutting, department of Surgery, ZGT Almelo/Hengelo, The Netherlands. *Infrared thermography for monitoring severity and treatment of diabetic foot infections.*	2020	28 / 1.0
F.J. Rovers, department of Rehabilitation medicine, Amsterdam UMC, location AMC, Amsterdam, the Netherlands. *Adherence to at-home monitoring of foot temperature in high-risk people with diabetes.*	2021	28 / 1.0

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