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Comparison of a new versus standard removable offloading device in patients with neuropathic diabetic foot ulcers: a French national, multicentre, open-label randomized, controlled trial

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ABSTRACT

Introduction The offloading is crucial to heal neuropathic diabetic foot ulcer (DFU). Removable offloading are the most used devices. *Orthèse diabète* is a new customized removable knee-high offloading device immobilizing foot and ankle joints, with some specific and innovative features that may improve offloading. We aimed to evaluate the efficiency of *this device* in DFU healing.

Research, design and methods The evaluation of Offloading using a new removable ORTHOsis in DIABetic foot study is a French multicenter (13 centers) randomized controlled trial with blinded end points evaluation. Adults with neuropathic DFU were randomly assigned to either *Orthèse Diabète (experimental device*), or any type of conventional (usually used in France) removable offloading devices (control group). The primary outcome was the 3-month proportion of patients with fully healed DFU.

Results Among 112 randomized patients (men 78%, age 62±10 years), the primary outcome occurred in 19 (33%) participants using conventional device vs 19 (35%) *Orthèse Diabète* users (p=0.79). Study groups were also comparable in terms of prespecified secondary end points including occurrence of new DFU (25% vs 27% in conventional and experimental groups), ipsilateral lower-limb amputation (4% vs 10%) or infectious complications (14% vs 13%) (p>0.05 for all). Adverse events were comparable between groups, including 4 deaths unrelated to study allocation (1 sudden death, 2 ventricular arrhythmias and 1 pancreatic cancer). Adverse events believed to be related to the device were higher in the *Orthèse Diabète* group than in the control group (15% vs 4%). *Orthèse Diabète* was less frequently worn than conventional devices (46% vs 66%, p=0.04).

Conclusions *Orthèse Diabète*, a new removable offloading orthosis immobilizing foot and ankle joints did not show superiority compared with conventional removable devices in neuropathic DFU healing and cannot be recommended to heal DFU.

Significance of this study

What is already known about this subject?

- The offloading is crucial to heal neuropathic diabetic foot ulcer (DFU).
- Several removable offloading methods are used but they were rarely compared in randomized controlled trials.

What are the new findings?

- Among 112 randomized patients, a fully healed DFU at 3 months was observed in 19 (33%) participants using conventional device vs 19 (35%) *Orthèse Diabète* users (p=0.79).
- No difference was observed between groups in regard to other outcomes including healing of ulcers, new ulcers or lower-extremity amputations.
- The wearing of devices was significantly lower in the experimental than the conventional group (46% vs 66%, p=0.04).
- There is a higher rate of adverse events in the *Orthèse Diabète* arm compared with conventional arm.

How might these results change the focus of research or clinical practice?

- *Orthèse Diabète* was equally efficient than usual removable devices in DFU healing.

Trial registration number NCT01956162.

INTRODUCTION

Diabetic foot ulcer (DFU) is a severe and common complication in patients with diabetes. It affects between 19% and 34% of people with diabetes at some point over their life.[1] According to the continuous increase of

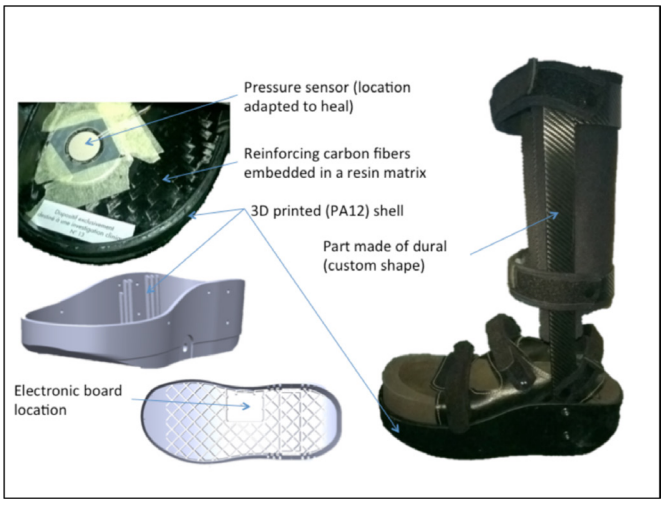

Figure 1 Schematic illustration of '*Orthèse Diabète*' and its different components.

the global prevalence of diabetes worldwide, the management of DFU is an increasing therapeutic challenge. Indeed, DFU is the leading cause of non-traumatic lower-limb amputation (LLA) worldwide.[2–4]

Among the wide range of factors contributing to neuropathic DFU, abnormal rise in foot plantar pressure is likely to be the main causal factor.[5 6] Over the past decades, it has been extensively shown that offloading is a crucial treatment to promote healing of neuropathic DFU.[7] The non-removable knee-high offloading devices allow better offloading, especially because of the 'forced' adherence, and are considered as the gold standard methods to heal neuropathic plantar DFU with no evidence for ischemia or uncontrolled infection.[8] However, non-removable knee-high offloading devices are not widely used in clinical practice because patient preference or potential adverse effects including muscle weakness, falls, new ulcers due to poor fitting and knee or hip complaints.[8–13] On the other hand, a wide range of removable offloading devices are available but only few have been assessed in large enough trials to compare reliably different removable offloading methods.[14] Therefore, it remains some uncertainty whether a specific kind of device may be recommended as a second line if non-removable devices are unavailable, contraindicated or not tolerated.

Orthèse Diabète is a new customized removable plantar offloading device designed to allow offloading through elimination of the weight bearing on the plantar wound and limitation of the shearing forces (figure 1). It was made with some specific and innovative features to improve offloading including a permanent and integrated pressure measurement system to confirm offloading of the wound. The device was fully described in a prior publication.[15] In a monocentric (Department of Diabetes, Bichat Hospital, Paris France) single-arm pilot study, *Orthèse Diabète* was tested in five patients with neuropathic DFU, with a 3-month healing observed in four (80%) patients (unpublished data). Given the specific features of this new devices and this preliminary finding, we expected the *Orthèse Diabète* to improve healing of DFU. Thus, the aim of our study was to assess the effectiveness of the *Orthèse Diabète* in the healing of neuropathic plantar DFU compared with standard non-removable devices.

METHODS

Study design

The evaluation of Offloading using a new removable ORTHOsis in DIABetic foot (ORTHODIAB) study is a French collaborative multicenter randomized, open-label trial, with a blinded end points evaluation. Details of the trial design and conduct have been published elsewhere.[15] All participants provided informed consent prior to study participation.

Setting and participants

The trial was conducted in 13 secondary or tertiary care French hospitals (the full list of centers and investigators is provided in the online supplementary material). Participants were recruited among patients referred to each center for DFU. The main eligible criteria were (i) age over 18 years; (ii) diagnosis of type 1 or type 2 diabetes based on the American Diabetes Association definition[16]; (iii) sensory peripheral neuropathy (defined as abnormal 10 g monofilament test, ie, not perceived at least 2 times in one of the three areas explored: pulp of the big toe, first and fifth metatarsal heads)[16] and (iv) one or more plantar ulcerations with an area >0.25 cm^2 or LLA wounds (toes or transmetatarsal). We excluded patients with: severe lower-extremity arterial disease (defined as ankle-brachial index <0.7, or transcutaneous oxygen pressure <30 mm Hg, or great toe pressure <30 mm Hg);[17] severe skin or bone infection requiring parenteral antibiotic therapy or surgery; a large non-diabetic leg ulcer in the homolateral leg (>20 cm^2 of area); a contralateral above heel amputation; weight over 130 kg (load limit of the *Orthèse Diabète*); pregnancy or the likelihood of pregnancy; guardianship requirement and loss of functional and/or neuropsychological autonomy. Demographic characteristics, medical history, diabetes complications, comorbidities, ongoing treatments, and wound characteristics were recorded at each visit.

Randomization

Study participants were randomly assigned to one of two parallel groups: *Orthèse Diabète* or conventional device according to a central computer-based 1:1 randomization (block sizes of four) without stratification. Successive sequences of four treatment allocations were assigned to each single center at the site level. The allocation sequence was computer generated by the independent contract research organization (UMANIS Life Science, Paris, France).

Interventions

All included participants were managed according to the standard of care and local guidance of practice. The choice of the wound care frequency and dressing was left

up to the investigator's discretion, but systematic wound debridement and hyperkeratosis removal were recommended. No other specific recommendations in terms of treatments for wound infection, diabetes or other conditions related to the ulcer or not were given during the study.

Orthèse Diabète

A complete description of the removable offloading system '*Orthèse Diabète*' has been published elsewhere.[15] Briefly, *Orthèse Diabète* is a new customized removable plantar knee-high offloading device that allows offloading through limitation of the plantar pressure and that was designed to reduce the shearing forces (figure 1). *Orthèse Diabète* differs from other orthoses in its custom build and a number of essential functions including: 1) a plantar off-loading function through the action of cast sole, increases contact beyond the wound area and eliminates weight-bearing on the wound; 2) a locking function for the joints of the foot with a rigid connection enclosing the leg and the foot in order to limit the shearing forces; 3) a step progress function while walking to avoid seeking the articulations of the foot. The inner sole (foot interface) was designed with its own geometrical and mechanical properties from foot scan. The offloading is achieved by the excavation of the area facing the wound, and a redistribution of the load in the healthy areas. To promote wound healing, the brace system locks all joints of the foot and ankle in a position of 3 degrees of foot dorsiflexion. The device has an outsole with a moderate roll-over shape to counterbalance the loss of mobility of the foot and maintain a comfortable walking. A pressure sensor is integrated in the insole area which has been excavated to confirm the theoretical optimization of the pressure field under the foot. Audible alarm sounds if the wound is not correctly offloaded during walking (threshold: 200 g/cm^2). In the ORTHODIAB trial, this function was activated only during onsite protocol visits to ensure effectiveness of wound offloading. If the wound was not correctly offloaded at a protocol visit the orthotist can modify the foot interface until the absence of alarm. Data from the pressure sensor, available only in the *Orthèse Diabète* group, was not used in the present analysis since it was not planned in the study protocol. In addition to the use of orthosis, technical aids (one or two crutches) are recommended to improve offloading and the stability of walking. Moreover, the patients were asked to avoid prolonged or heavy physical activities, especially on rough, wet or muddy ground.

Control group

This group included any standard or customized removable offloading devices labeled and available in France. Non-removable offloading was not allowed during the study period. The choice of the conventional device was based on the local practices of each center. As for the *Orthèse Diabète* group, technical aids (one or two crutches) were recommended to improve offloading and the stability of walking in addition to off-loading device. Category of device prescribed was recorded at each visit.

During the period between randomization and device provision, DFU offloading was achieved using some temporary therapeutic shoes appropriately chosen by the investigator according to location of the wound and each center usual care.

Outcomes

The primary outcome was the proportion of patients with complete healing of the index ulcer at the 3-month visit. The index ulcer was defined as a unique ulcer, or as the largest one if the patient has multiple (≥2) ulcerations at baseline. Secondary outcomes included proportion of patients with closure of the index plantar ulcer at the 1-month, 2-month and 6-month visits, ; proportion of patients with closure of all initial plantar ulcers at 1-month, 2-month, 3-month and 6-month visits; relative (%) area reduction of the index plantar ulcer at 1-month, 2-month, 3-month and 6-month visits; time to healing of the index ulcer; appearance of new ulcers (both recurrence of the index DFU after a successful primary healing and new ulcers in different anatomic sites); new cases of non-traumatic LLA; incidence of infectious complications (defined as cutaneous, bone or systemic infections related to foot wound and requiring antibiotic therapy or surgery); self-reported adherence to offloading and patient satisfaction with the prescribed device. The primary and the first four secondary end points were adjudicated by an independent End Point Adjudication Committee according to the Prospective Randomized Open-Blinded End point (PROBE) design, in which site investigators and patients were not blinded but end point adjudicators were blinded.[18] Adjudications were based on analyses of standardized digital photographs of the ulcer taken at each visit. Area of each plantar ulcer were assessed using a Digital Photo Planimetry software (*Tracer.exe.*, University of Glamorgan, UK).[19] Adherence to offloading was evaluated using a semi-quantitative survey suggested to patients at each visit (online supplementary table S1). Patient satisfaction was evaluated at 3-month visit using the Quebec User Evaluation of Satisfaction with Assistive Technology survey.[20]

Reporting of adverse events

All adverse events were recorded and reviewed from randomization to the end of follow-up. An adverse event was defined as an untoward medical occurrence in participant that may or may not have had a causal relationship with the study treatment. A serious adverse event was defined as any untoward medical occurrence that resulted in life-threatening, death, persistent or major disability, incapacity or hospitalization. Adverse events and serious adverse events are monitored independently by the Department of Pharmacovigilance of Dijon University Hospital (Centre Régional de Pharmacovigilance de Bourgogne, Pôle des Pathologies Lourdes et des Vigilances—CHU Le Bocage, Dijon, France).

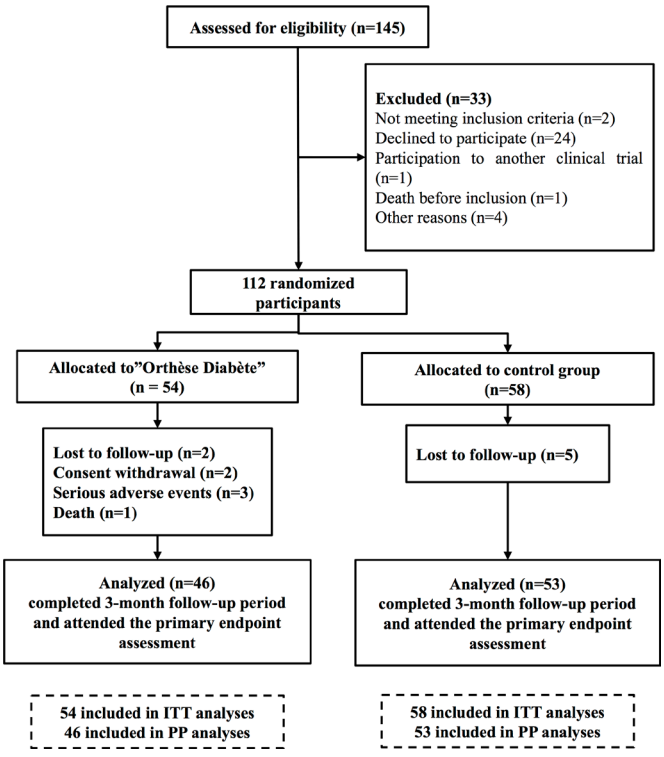

Figure 2 Trial profile. ITT, intention-to-treat; PP, per-protocol.

Study schedules

Inclusion period started on the October 27, 2013 and ended on the May 27, 2016. Device measurement and casting were scheduled 7 days after randomization, and the offloading system was delivered 7 days later. Each participant was followed for a maximum period of 6.5 months. Follow-up visits were scheduled 1, 2, 3 and 6 months after the device delivery (online supplementary figure S1). The dates of the first patient first visit and the last patient last visit were November 28, 2013 and November 30, 2016, respectively.

Statistical analyses

Based on results of a published randomized controlled trials (RCT) comparing non-removable versus removable off-loading, we assumed that the healing rate will be 52% at 3 months for conventional removable devices,[21] and based on our preliminary data, we assumed that the 3-month healing will be as high as 80% in the *Orthèse Diabète* group. From this assumption to detect such a difference with a statistical power of 80% for an alpha level of 5% and a rate of discontinuation of 5%, we calculated that our study required at least 110 patients (55 for each arm).

The analyses were performed according to the intention-to-treat (ITT) principle, including all randomized participants, whether or not they have used the prescribed device. The per-protocol (PP) population included all subjects from the ITT population, without major deviations from the protocol, who participated in the study from inclusion to the last follow-up visit and who strictly conformed to study protocol.

Continuous variables are expressed as mean (SD), or as median (25th, 75th percentiles) for those with skewed distribution. Categorical variables are expressed as the number of participants with corresponding percentage. Missing data are presented in the characteristics tables, they were not imputed as they were not used for end point analysis.

Proportions of patients with wound closure were compared between study arms at each visit using a χ^2 test. Time to reach wound closure was plotted using Kaplan-Meier cumulative incidence curves according to randomization arms and compared using the log-rank test. Cox proportional hazards regression model was fitted to estimate HRs, with associated 95% CI, for the 3-month likelihood of complete wound closure according to study arms.

Logistic regression models were used to compare the primary end point according to study arms in prespecified subgroups by gender, age, diabetes duration, hemoglobin A1c (HbA1c), history of diabetic kidney disease and cardiovascular disease at baseline.

As sensitivity analyses, primary outcome was evaluated in two adherent populations using two alternative criteria: 1) patients were considered adherent if they replied at least at one visit the modality 'always' or 'most of the time' to the three items of the semi-quantitative survey, 2) adherence score ≥8 (online supplementary table S1). Statistical analyses were performed using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Characteristics of patients at baseline

Among 145 patients assessed for study eligibility, 112 participants were randomized (figure 2). The median (25th, 75th percentiles) number of patients recruited by each center was 4 (3, 6). We did not observe significant difference between centers in term of characteristics of patients at baseline, except for age, infection and lower-limb arterial disease (online supplementary table S2).

In the whole study, participants were mainly men (79%), with type 2 diabetes (89%), aged 62±10 years, had a mean diabetes duration of 19±9 years and a mean HbA1c of 8.1%±1.9%. The rate of renal and retinal complications of diabetes were high in this population. Characteristics of patients at baseline were well balanced between study allocations (table 1).

Characteristics of DFU at baseline by study allocation are displayed in table 2. History of previous DFU, ipsilateral LLA and lower-extremity artery disease were reported at baseline in 66%, 42% and 29% participants, respectively. Hyperkeratosis was the most common peri-wound skin issue. The duration of wound exceeded 2 weeks in 78% participants and 17% patients had more than one DFU at baseline. Type of wound care (wound and peri-wound debridement) and dressings were similar between groups

Table 1 Baseline characteristics of participants in the intention-to-treat population

	Overall	Conventional	*Orthèse Diabète*	Missing data (n)
Number	112	58	54	
Female	24 (21)	9 (16)	15 (28)	0
Age (years)	62±10	61±10	63±11	0
BMI (kg/m²)	31±6	30±6	31±5	4
Heart rate (bpm)	77±11	76±12	78±10	12
SBP (mm Hg)	136±18	135±18	137±19	7
DBP (mm Hg)	75±11	75±10	75±12	7
Diagnosed diabetes duration (years)	19±9	20±10	19±8	0
Type of diabetes				0
1	12 (11)	8 (14)	4 (7)	
2	100 (89)	50 (86)	50 (93)	
HbA1c				19
(%)	8.1±1.9	8.2±2.1	8.0±1.6	
(mmol/mol)	65±20	66±17	64±13	
eGFR (mL/min/1.73 m²)	71±31	70±31	72±31	0
History of diabetic nephropathy				10
Microalbuminuria	34 (30)	20 (34)	14 (26)	
Macroalbuminuria	22 (20)	12 (21)	10 (19)	
End-stage renal disease	11 (10)	6 (10)	5 (9)	
History of diabetic retinopathy				6
Non-proliferative	29 (26)	15 (26)	14 (26)	
Proliferative	38 (34)	22 (38)	16 (30)	
Current smokers	20 (18)	13 (23)	7 (13)	3
History of coronary heart disease	25 (21)	17 (29)	8 (15)	3
History of stroke	2 (2)	1 (2%)	1 (2%)	4
Current treatments				
Insulin therapy	54 (48)	27 (47)	27 (50)	0
Diuretics	17 (15)	10 (17)	7 (13)	0
Beta-blocking agents	17 (15)	9 (16)	8 (15)	0
Calcium channel blockers	21 (19)	11 (19)	10 (19)	0
Renin-angiotensin system blockers	30 (27)	11 (19)	19 (35)	0
Oral antibacterial	23 (21)	15 (26)	8 (15)	0
Lipid-modifying agents	38 (34)	18 (31)	20 (37)	0
Antithrombotic agents	35 (31)	16 (28)	19 (35)	0

Data expressed as number (percentage) of participants and mean±SD.
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SBP, systolic blood pressure.

and alginate dressing was the most prescribed dressing in each group. The wound debridement, the frequency and type of dressing used were similar between groups.

Before screening, 28% participants in the conventional group and 43% in the *Orthèse Diabète* group had prescribed offloading device. The types of offloading provided by investigators in the conventional group during the trial are described in table 3. The most prescribed offloading devices were removable offloading devices that did not immobilize the ankle joint (67%).

Outcomes

The median duration of the treatment period was 189 (105, 201) days for the *Orthèse Diabète* group and 186 (175, 201) days for the conventional group. The mean number of visits per patient was 5.5±1.1 and 5.5±1.0 in the *Orthèse Diabète* and conventional groups, respectively. The study allocation and the primary end point were not significantly different between the study centers (online supplementary table S2).

Table 2 Baseline characteristics of wound

	Overall	Conventional	*Orthèse Diabète*	Missing data (n)
Number	112	58	54	
Previous foot ulcer	74 (66)	39 (67)	35 (65)	1
Wound location				21
Right foot	44 (39)	23 (40)	21 (39)	
Toe	29 (32)	16 (35)	13 (29)	
Forefoot	39 (43)	16 (35)	23 (51)	
Midfoot	16 (17)	10 (22)	6 (13)	
Hindfoot	7 (8)	4 (8)	3 (7)	
Wound duration				21
<1 week	3 (3)	1 (2)	2 (4)	
1–2 weeks	17 (19)	8 (18)	9 (20)	
>2 weeks	71 (78)	37 (80)	34 (76)	
Wound depth (mm)	5 (2 to 10)	5 (2 to 10)	6.5 (3 to 10)	21
Multiple ulcers (>1)	21 (17)	12 (21)	9 (17)	0
Infection	26 (23)	14 (24)	12 (22)	21
Soft tissue infection	21 (19)	10 (17)	11 (20)	
Osteomyelitis	10 (9)	4 (7)	6 (11)	
Ipsilateral ankle brachial index	1.14±0.19	1.10±0.21	1.19±0.17	20
≤0.9 range	12 (13)	9 (19)	3 (7)	
≥1.40 range	11 (12)	5 (10)	6 (14)	
Lower-extremity artery disease	33 (29)	19 (33)	14 (26)	2
History of lower-limb amputation				0
Ipsilateral	47 (42)	26 (45)	21(39)	
Toe	37 (79)	21 (81)	16 (76)	
Transmetatarsal	10 (21)	5 (19)	5 (24)	
Controlateral	16 (14)	4 (7)	12 (22)	
Toe	14 (77)	4 (100)	10 (83)	
Transmetatarsal	2 (13)	0 (0)	2 (17)	
Classification of index ulcer according PEDIS score*				
Perfusion				
Grade 1	83 (90)	42 (88)	41 (93)	
Grade 2	9 (10)	6 (12)	3 (7)	20
Extent/Size (cm^2)	1.4 (0.6 to 3.7)	1.2 (0.5 to 3.6)	1.6 (0.8 to 4.2)	0
Depth/Tissue loss				12
Grade 1	69 (69)	32 (65)	37 (72)	
Grade 2	22 (22)	12 (25)	10 (20)	
Grade 3	9 (9)	5 (10)	4 (8)	
Infection				21
Grade 1	65 (71)	32 (70)	33 (74)	
Grade 2	16 (18)	10 (21)	6 (13)	
Grade 3	10 (11)	4 (9)	6 (13)	
Sensation				0
Grade 1	0	0	0	
Grade 2	112 (100)	58 (100)	54 (100)	
Clinical status of the wound bed tissue				1

Continued

Table 2 Continued				
Granulation tissue	43 (38)	18 (31)	25 (46)	
Sloughy	44 (39)	18 (31)	26 (48)	
Heterogenous	4 (4)	3 (5)	1 (2)	
Necrotic	2 (2)	0 (0)	2 (4)	
Hemorrhagic	12 (11)	7 (12)	5 (9)	
Infected	6 (5)	4 (7)	2 (4)	
Hyperkeratosis	56 (50)	30 (52)	26 (48)	1
Type of dressing				1
Fat	23 (21)	10 (17)	13 (24)	
Hydrocolloid	10 (9)	7 (12)	3 (6)	
Hydrogel	0 (0)	0 (0)	0 (0)	
Alginate	56 (50)	33 (57)	23 (43)	
Hydrofibre	7 (6)	2 (3)	5 (9)	
Antimicrobial	2 (2)	0 (0)	2 (4)	
Others	18 (16)	8 (14)	10 (19)	
Offloading before inclusion	39 (35)	16 (28)	23 (43)	21

Data expressed as number (percentage) of participants and mean±SD or median (25th, 75th percentiles) for continuous variables with skewed distribution (wound depth). Missing data are presented as number of participants.
*From Schaper.[33]

The primary outcome, the full healing of the index ulcer at the 3-month visit, was achieved in 19 (33%) patients in the conventional group and 19 (35%) in the *Orthèse Diabète* group (p=0.79) according to ITT analysis (table 4).

This result was similar in different subgroups (online supplementary figure S2) and adherent population (online supplementary table S3). No significant difference was observed in terms of prespecified secondary outcomes including the median time to reach wound closure (81 (61, 102) vs 85 (66, 103) days in conventional and experimental groups, respectively, p=0.80), and the occurrence of new plantar DFU (25% vs 27%, p=0.82), ipsilateral LLA (4% vs 10%, p=0.20) or infectious complications (14% vs 13%, p=0.68) (table 4 and online supplementary figure S3). There was a non-significant trend for a higher rate of wound closure at 1 month in the *Orthèse Diabète* than the conventional group (17% vs 7%, p=0.11).

Table 3 Type of offloading devices prescribed in the conventional group during the study

Offloading devices	Conventional group (n=58)
Removable knee-high offloading	9 (16%)
Removable offloading devices that did not immobilize the ankle joint	39 (67%)
Footwear or padded slipper with customized insole	6 (10%)
Footwear or padded slipper without customized insole	2 (3%)
Wheelchair or confined to bed	1 (2%)
Unknown	1 (2%)

Offloading observance and satisfaction

The self-reported overall adherence to offloading was significantly lower in the experimental than the conventional group (46% vs 66%, p=0.04) (online supplementary table S4). Global satisfaction at 3-month visit was also similar between groups (online supplementary table S5). No item of the satisfaction survey was statistically significantly different between study arms. Although, participants reported a much easier use of the offloading device in the conventional group (34% vs 13% in the *Orthèse Diabète* group) and a better follow-up quality in the *Orthèse Diabète* group (28% vs 11% in the conventional group).

Safety outcomes

The incidence of adverse events (including non-serious and serious adverse events) were not different between groups (54% vs 46% in *Orthèse Diabète* and conventional groups, respectively, p=0.24), except for those believed to be related to the offloading device, which were significantly higher in *Orthèse Diabète* than the control group (15% vs 4%) (table 4). Four deaths occurred during the study period (one in the conventional group and three in *Orthèse Diabète* group) with no significant difference between study arms. Deaths were judged as not related to device or DFU worsening but to other causes (one sudden death, two ventricular arrhythmias with cardiac arrest and one pancreatic cancer). A detailed list of the other adverse events occurring during the follow-up

Table 4 Primary, secondary and safety study outcomes

	Cohort	Conventional group	*Orthèse Diabète*	P value
Primary outcome				
Blinded assessment of wound closure of the index plantar ulcer at the 3-month visit*	ITT	19 (33)	19 (35)	0.79
Blinded assessment of wound closure of the index plantar ulcer at the 3-month visit	PP	18 (34)	17 (37)	0.76
Secondary outcomes				
Closure of the index plantar ulcer				
1-month visit	ITT	4 (7)	9 (17)	0.11
2-month visit	ITT	15 (26)	17 (31)	0.51
6-month visit	ITT	28 (48)	31 (57)	0.33
Closure of all initial plantar ulcers				
1-month visit	ITT	4 (7)	8 (15)	0.19
2-month visit	ITT	12 (21)	13 (24)	0.82
3-month visit	ITT	17 (30)	18 (33)	0.84
6-month visit	ITT	24 (42)	23 (43)	0.96
Relative area reduction of the index plantar ulcer (%)				
1-month visit	ITT	63 (52 to 74)	58 (47 to 70)	0.56
2-month visit	ITT	76 (67 to 85)	77 (68 to 87)	0.88
3-month visit	ITT	85 (76 to 94)	85 (76 to 94)	0.96
6-month visit	ITT	87 (79 to 94)	92 (85 to 99)	0.33
Estimated time to reach closure of the index plantar ulcer (days)	ITT	81 (61 to 102)	85 (66 to 103)	0.80
New plantar ulcer	ITT	14 (25)	14 (27)	0.82
Ipsilateral limb-amputation	ITT	2 (4)	5 (10)	0.20
Infectious complication	ITT	8 (14)	7 (13)	0.68
Safety				
Any adverse events	Safety	16 (28)	19 (28)	0.97
Any serious adverse events	Safety	41 (72)	48 (72)	0.97
Any adverse events related to offloading device	Safety	2 (4)	10 (15)	0.03
Adverse events leading to discontinuation	Safety	0	3 (4)	0.11
All-cause hospitalization	Safety	23 (40)	18 (27)	0.11
Death	Safety	1 (2)	3 (4)	0.39

Data presented as number (percentage) of participants and compared using χ^2 test, except relative area reduction and estimated time to reach closure of the index plantar ulcer, which are presented as median (25th, 75th percentiles) and compared by using Wilcoxon test. P<0.05 was considered as significant.
*End points were assessed at 2-month visit in 13 participants for whom no data were available at 3-month visit in the ITT cohort analysis (see figure 2).
ITT, intention to treat; PP, per protocol.

period according to study allocation are reported in online supplementary table S6.

CONCLUSIONS

This multicenter randomized, open-label trial, did not show any superiority of a new customized removable knee-high offloading system compared with conventional removable devices in terms of healing of neuropathic plantar DFU. This result was reliable in different study populations and subgroups. Study groups were also comparable in terms of prespecified secondary end points including reduction of ulcer area, time to reach ulcer closure and occurrence of new ulcers, LLA, or infectious complications.

As far as we know, our study is one of the first RCTs evaluating blinded end points in patients with DFU. Bus *et al*, conducted the first single-blinded multicenter RCT to compare three removable offloading devices for neuropathic DFU healing.[14] They did not observe significant differences in healing efficacy between the three devices.

Our study also showed that *Orthèse Diabète*, a removable knee-high offloading device immobilizing all joints of the foot and ankle, did not improve DFU healing compared with standard removable devices. Similar result was observed after exclusion of participants (n=9) from whom removable knee-high offloading devices were prescribed (post hoc analysis, not shown).

The rate of 3-month healing was lower than expected and compared with previous RCTs investigating neuropathic DFU.[9 14 21–23] This is a clear limitation of the present study; our statistical considerations regarding power calculation were too optimistic and did not fit with the observed rate of healing. Another explanation could be related to the blinded and independent adjudication process based on consensual decision between the three experts using remote photographic tools. In a post hoc analysis, the unblinded rate of the 3-month complete healing reported by the local investigators was higher than those established by the blinded adjudicators: 49% (*Orthèse Diabète*) vs 36% (conventional), p=0.18. Furthermore, local investigators judged the wound healed or highly improved at 3 months in 83% (*Orthèse Diabète*) vs 66% (conventional) participants (p=0.05), which is much more consistent with previous RCTs without adjudication process.

We also observed a high rate of adverse events and serious adverse events, which may be explained by inclusion of participants with severe disease and associated conditions. Of note, the number of participants experiencing any offloading device-related adverse events was higher in the *Orthèse Diabète* group compared with the conventional one. This may be explained by the physical composition of *Orthèse Diabète*, heavier and greater than usual devices, which could be responsible for conflicting wounds, trauma or falls. However, the rates of any adverse events, any serious adverse events, adverse events leading to discontinuation, all-cause hospitalization, LEA and infectious complications were comparable between study groups. We also reported a high occurrence of new plantar ulcers. A very high rate of DFU recurrence is well established and previously reported.[1 24 25] Apelqvist *et al* reported that 34% of patients with DFU developed a new foot ulcer after 1 year of follow-up, and this may reach 70% after 5 years. In our study, the 6-month rate of new plantar ulcers seems to be high (25% and 27% of participants in control and experimental group, respectively), but it included the recurrence of the index DFU (after a successful primary healing) and new ulcers in different anatomic sites.

The main strength of our study was its robust methodology and design—a randomized, open-label trial, with a blinded end point evaluation by an adjudication committee according to the PROBE method in a large national setting of 13 secondary and tertiary centers in France. A double-blind design was obviously not feasible due to ostensible aspect of the offloading devices. We chose a PROBE method, using a strict randomization procedure for allocation and blinded assessment of the primary and some secondary outcomes, to reduce methodological bias.[18] Moreover, wound healing outcomes were analyzed in ITT population to avoid non-compliance, protocol deviations or withdrawal which could be high in offloading trials.[26–28] Our study fulfills the most recent recommendations for the planning and reporting of intervention studies on the management of DFU.[29 30] Furthermore, ORTHODIAB is also the largest randomized trial assessing an offloading system in DFU population with comprehensive clinical data at baseline and prespecified end points as well as observance, satisfaction, safety and tolerability assessments during 6-month follow-up.

The main limitation of our trial could be the use of different removable devices in the control group instead of a single comparator. We did not choose a single comparator because of the lack of a gold standard tool among the removable devices, the wide range of different practices between centers and the offloading methods may vary according to the wound size and anatomic locations. Otherwise, our selection criteria yield the inclusion of a broad types of wound, from superficial neuropathic ulcer to non-severe lower-extremity arterial disease, skin and soft skin infections and osteomyelitis, except those needing parenteral antibiotics or surgery. This selection criteria could introduce bias as the healing of an infected or ischemic wound depend on other aspects of care further than offloading, which are not assessed in our study. We also included LLA wounds, although these wounds likely have different healing trajectories than chronic plantar ulcerations. However, our selection criteria may allow the generalisability of our results to a larger DFU population.

Of note, *Orthèse Diabète* was equally efficacious than the conventional removable devices despite its significantly lower rate of overall adherence (46% vs 66%). However, even it is tempting to speculate that *Orthèse Diabète* might be more efficient if it was more frequently worn, we are aware of the obvious limitations of the self-reported adherence assessment methods used here. Indeed, self-reported adherence survey have been shown to be unreliable.[31 32] Furthermore, we did not assess the plantar pressure reductions and weight-bearing activity, which along with adherence heavily influence healing outcomes in DFU.[14 29]

Taken together, our findings suggest that the outcomes associated with the use of *Orthèse Diabète* (similar DFU healing and patient satisfaction with lower adherence rate and some higher adverse events) outweigh any of the potential benefits of using this new tool over usual removable offloading devices for clinical practice. So, this new device cannot be recommended in DFU management. Also, the lack of standardization in the control group limits the conclusions that can be made in comparing the control group with *Orthèse Diabète*.

Overall, in this multicenter study, we showed that *Orthèse Diabète*, a new customized removable knee-high offloading orthosis, did not significantly improve wound

healing in participants with neuropathic DFU, with no severe infection or lower-extremity arterial disease, compared with conventional non-removable devices. *Orthèse Diabète* was also less regularly worn emphasizing the need to develop specific process to enhance removable offloading adherence and encourage patients to consistently wear removable devices and then improve DFU healing.

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Contributors KM, J-CD, DM and MM designed the study and wrote the protocol. LP and KM wrote the manuscript. MFr, DD, MFe, NB, EN-D, MD, LB, RD, AC, D-FE, TCA, AS, LB-B, VR, EG, P-JS, GV, RR, QP, J-CD, DM and MM contributed to discussion and made critical revision of the manuscript. All authors approved the current version of the manuscript. KM and LP take the full responsibility for the content of the manuscript.

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Competing interests LP reports receiving personal fees from Novo Nordisk, Lilly, Sanofi and Servier and grants from Sanofi, outside the submitted work; RR is an advisory panel member for AstraZeneca, Sanofi, MSD, Eli Lilly, Novo Nordisk, Vaiomer and Physiogenex; is a speaker for Bayer and Servier and has received research funding and provided research support to Danone Research, Diabnext, Boehringer-Ingelheim, Amgen, Sanofi and Novo Nordisk. MM reports receiving personal fees from Novo Nordisk, Sanofi, Eli Lilly, Servier, Merck, Sharp and Dohme, Abbott, Novartis and AstraZeneca and grant support from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme and Novartis, outside the submitted work; KM reports receiving personal fees from Novo Nordisk, Sanofi, Eli Lilly, Proteor and AstraZeneca, and travel support from Novo Nordisk, Sanofi, Boehringer Ingelheim and Takeda outside the submitted work.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the ANSM agency (Agence nationale de sécurité du médicament et des produits de santé; The French National Agency for Medicines and Health Products Safety) and by the ethics committee of Saint-Louis University Hospital, Paris (Institutional Review Board; Agreement of US Department of Health and Human Services N° IRB 00003835). Comprehensive information on the study including a Patient Information Sheet has been provided to each patient who must give written informed consent before enrollment. Four amendments were approved by the Institutional Review Board regarding the extension of inclusion period (from 18 to 24 months), integration of further centers and investigators and inclusion of six additional participants because of more loss of follow-up than expected.

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