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ARTICLE

Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study

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Abstract
Aims/hypothesis Outcome data on individuals with diabetic foot ulcers are scarce, especially in those with peripheral arterial disease (PAD). We therefore examined the clinical characteristics that best predict poor outcome in a large population of diabetic foot ulcer patients and examined whether such predictors differ between patients with and without PAD.
Methods Analyses were conducted within the EURODIALE Study, a prospective cohort study of 1,088 diabetic foot ulcer patients across 14 centres in Europe. Multiple logistic

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regression modelling was used to identify independent predictors of outcome (i.e. non-healing of the foot ulcer).
Results After 1 year of follow-up, 23% of the patients had not healed. Independent baseline predictors of non-healing in the whole study population were older age, male sex, heart failure, the inability to stand or walk without help, end-stage renal disease, larger ulcer size, peripheral neuropathy and PAD. When analyses were performed according to PAD status, infection emerged as a specific predictor of non-healing in PAD patients only.
Conclusions/interpretation Predictors of healing differ between patients with and without PAD, suggesting that diabetic foot ulcers with or without concomitant PAD should be defined as two separate disease states. The observed negative impact of infection on healing that was confined to patients with PAD needs further investigation.

Keywords Co-morbidities · Diabetes · Foot ulcer · Infection · Non-healing · Outcome · Peripheral arterial disease · Predictive model

Abbreviations

ABPI	ankle–brachial pressure index
ESRD	end-stage renal disease
NYHA	New York Heart Association
OR	odds ratio
PAD	peripheral arterial disease
PNP	peripheral neuropathy

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Introduction

Diabetic foot ulcers are a common and much feared complication of diabetes, with recent studies suggesting that the lifetime risk of developing a foot ulcer in diabetic patients may be as high as 25% [1]. Foot ulceration requires long and intensive treatment, has important effects on quality of life of both patients and care-givers [2] and is associated with major healthcare costs [3–5]. Although in recent years much effort has been put into the development of international guidelines in order to stimulate the delivery of uniform and structured care [6], prospective data on outcomes and predictors of outcome in patients with diabetic foot ulcers are limited.

The population of diabetic patients who present with foot ulceration is heterogeneous: although most patients have peripheral polyneuropathy, there are several other characteristics that may vary among patients, such as the presence of peripheral arterial disease (PAD), infection and co-morbidities. PAD is present in approximately one-half of all patients with foot ulcers [7] and is considered an important predictor of outcome [8, 9]. Therefore, outcome data on this important subgroup of patients with diabetic foot disease are needed. Such a requirement is underlined by the fact that although diabetic foot ulcers are usually reported and analysed as one clinical entity, marked differences in patient, foot and ulcer characteristics can exist between patients with and without PAD [7]. These observations raise the question of whether predictors of outcome in patients with and without PAD may differ.

The aim of the present study was therefore: (1) to obtain prospective data on outcome of individuals presenting with a new diabetic foot ulcer, including patients both with and without PAD; (2) to assess clinical characteristics that best predict poor outcome (i.e. non-healing of the foot ulcer) from this large set of patients; and (3) to examine whether such predictors differ between patients with and without PAD.

Methods

Study design and population

The EURODIALE consortium is an international collaborative network that was created to stimulate further research in the field of diabetic foot disease. Its main objective was to assess outcome and the major predictors of clinical outcome in a large sample of European patients with diabetic foot ulcers. The design and rationale of this study have been described in detail elsewhere [10].

Briefly, between 1 September 2003 and 1 October 2004, 1,232 patients with a new foot ulcer were included in 14

diabetic foot centres in ten European countries. The mean (range) number of included patients per centre was 88 (40–125). All participating centres have a longstanding expertise in the field of diabetic foot disease. Patients included were those presenting for the first time with a new foot ulcer within a period of 12 months, either at the outpatient or inpatient clinics of participating centres. Excluded patients were those who had been treated at the participating centres for an ulcer on the ipsilateral foot during the previous 12 months and those with a life expectancy of less than 1 year. Participants attended follow-up visits on a monthly basis. At baseline and during all follow-up visits, data were collected and recorded on standardised case record forms. This was done by dedicated investigators in each centre who were trained during plenary meetings and on-site visits. Recorded data included demographics, data on co-morbidities and foot and ulcer characteristics, as well as management. The local ethics committees of the 14 hospitals approved the study protocol and all patients gave written informed consent.

Management of diabetic foot ulcer

All patients were treated according to protocols based on the International Consensus on the Diabetic Foot [11], which include off-loading, diagnosis and treatment of infection, assessment of vascular status, treatment of PAD and regular wound debridement.

Potential predictive factors

Potential determinants of healing were chosen on the basis of (1) current literature; (2) expert opinion after extensive discussions during EURODIALE meetings; and (3) suitability for use in daily clinical practice. In addition to sex, age at baseline and duration of diabetes, several disease-specific characteristics and co-morbidities were investigated [10].

Ulcer characteristics All patients underwent a standardised examination according to the PEDIS system. This was developed by the International Consensus on the Diabetic Foot to enable classification of patients for clinical research purposes [11, 12] and classifies foot ulcers according to five categories: perfusion, extent, depth, infection and sensation.

Perfusion assessment included evaluation of the presence of pedal pulses and measurement of the ankle–brachial pressure index (ABPI) using a handheld Doppler device; PAD was considered to be present if ABPI was <0.9 and/or two foot pulses were absent.

Extent (i.e. size) was determined by multiplying the largest by the second largest diameter perpendicular to the first and divided into three categories: <1 cm^2, 1–5 cm^2 and >5 cm^2.

Depth was described as either deep or superficial if a full thickness lesion of the skin was or was not extending through the subcutis, respectively.

Infection was diagnosed if two or more of the following signs were present: frank purulence, local warmth, erythema, lymphangitis, oedema, pain, fever and foul smell. The term infection covers both soft tissue infection and bone infection.

Evaluation of sensation (peripheral neuropathy [PNP]) included pressure sensation (10 g monofilament on plantar aspect of hallux, metatarsophalangeal joints 1 and 5), tactile sensation (cotton wisp on dorsum of foot), vibration sensation (128 Hz tuning fork on dorsum of the hallux) and blunt/sharp discrimination (dorsum of foot). PNP was diagnosed if the results of two or more of the aforementioned tests were abnormal.

In addition, the location of the ulcer was divided into plantar (on the plantar toes, plantar mid- or forefoot and plantar hind foot) and non-plantar (on the dorsal or interdigital part of the toes, on the dorsal or lateral aspect of the foot and heel ulcers). Ulcer duration was divided into three categories: <1 week, between 1 week and 3 months, and >3 months.

Co-morbidities The following disabling co-morbidities were assessed: presence of severe visual impairment (defined as the inability to read a newspaper after correction), end-stage renal disease (ESRD) (defined as dependency on haemodialysis or peritoneal dialysis or a previous renal transplant procedure), heart failure (New York Heart Association [NYHA] classification III or IV), any neurological disorder (excluding diabetic polyneuropathy) resulting in loss of motor or sensory function (e.g. stroke) and inability to stand or walk without help.

Study main outcome

Main outcome was complete healing (with or without minor amputation) of the foot, within the maximum follow-up period of 1 year. Healing was defined as healing (intact skin) of the whole foot at two consecutive visits. If more than one ulcer was present, the foot was defined as healed once all ulcers were healed. Outcome information was not obtained in 144 patients (11.7% of the patients included) who dropped out of the study and were therefore excluded from the analyses. Reasons for dropout were non-compliance (n=24), inability to follow the patient (lack of transportation, no social support, too sick to attend; n=25) or if care had been taken over by other specialists (n=29); in 66 patients the reason for dropout could not be discovered. At baseline these participants were slightly older and had a higher incidence of heart failure, deeper ulcers and ulcers of longer

duration than those included in the analyses (n=1,088; Table 1).

Statistical analyses

All statistical analyses were carried using the STATA software package version 9.2 (STATA, College Station, TX, USA). Comparisons between groups' characteristics were made with χ^2 tests (frequency data) or Student's t test (continuous data).

Multiple imputation of missing values of predictor variables Values for one (n=188), two (n=35) or three (n=13) predictor variables were not available for 236 participants; the number of missing values per predictor ranged from 0 to 6%. In order to decrease bias and increase power of the analyses [13], we used multiple imputation chained equations (procedure 'ICE' in STATA) to impute those missing values (1.7% of all required values) rather than performing complete case analyses [14, 15]. With ICE the imputation model of a single variable uses all the other variables as predictors by appropriate regression models (i.e. linear, logistic or multinomial if imputed variable is continuous, dichotomous or categorical). We generated five imputed datasets that were used to fit the regression models of interest (in each dataset and in the final, i.e. the combined dataset). Parameter estimates and standard errors were combined across the five replicates according to the procedure described by Rubin [16] and Carlin et al. [17] (procedure 'micombine' in STATA).

Development of predictive models First, univariable logistic regression analyses were performed for all potential predictor variables with the outcome of interest (non-healing), with values presented as univariable odds ratios (ORs) along with the respective 95% CI. Second, all potential predictors were entered simultaneously in a multivariable logistic regression model that was reduced to a most parsimonious model using a backward selection method based on Akaike's Information Criterion. These models yielded a set of variables that best predict (and can be regarded as independent predictors of) outcome.

Results

Clinical outcome

Within the 1 year follow-up, 77% of the 1,088 patients healed, 12% were still undergoing treatment, 5% underwent

Table 1 Baseline characteristics of participants included and those excluded (dropouts) from the present study

Variable	Included (n=1,088)	Dropouts (n=144)	p value
Age (years)	64.7±12.5	68.0±11.6	0.003
Male sex, n (%)[a]	703 (64.6)	85 (59.0)	0.189
Duration of diabetes, n (%)[a]			0.418
<5 years	148 (14.1)	19 (13.5)	
5–10 years	169 (16.1)	17 (12.1)	
>10 years	731 (69.8)	105 (74.5)	
Deep ulcer, n (%)[a]	476 (43.8)	80 (55.6)	0.007
Size of ulcer, n (%)[a]			0.843
<1 cm^2	403 (37.2)	50 (35.0)	
1–5 cm^2	563 (52.0)	76 (53.1)	
>5 cm^2	117 (10.8)	17 (11.9)	
Duration of ulcer, n (%)[a]			<0.001
<1 week	184 (17.0)	10 (7.0)	
1 week–3 months	627 (58.1)	68 (47.6)	
>3 months	269 (24.9)	65 (45.5)	
Plantar location, n (%)[a]	493 (48.2)	62 (46.3)	0.675
Pretibial oedema, n (%)[a]	197 (18.2)	29 (20.3)	0.538
Heart failure NYHA III–IV, n (%)[a]	117 (10.9)	23 (16.1)	0.065
Neurological disorder, n (%)[a]	70 (6.5)	9 (6.3)	0.918
Inability to stand or walk without help, n (%)[a]	107 (9.9)	15 (10.4)	0.843
Visual impairment, n (%)[a]	164 (15.3)	19 (13.2)	0.507
ESRD, n (%)[a]	63 (5.8)	7 (4.9)	0.639
Polyneuropathy, n (%)[a]	826 (78.5)	105 (76.1)	0.515
Infection, n (%)[a]	591 (57.2)	82 (61.2)	0.380
PAD, n (%)[a]	505 (47.5)	78 (56.1)	0.056

Unless otherwise stated, data are mean values±SD

[a] Percentages may not sum to 100 due to missing information

a major (i.e. above the ankle level) amputation and 6% died (before healing of the foot ulcer). Among the patients who healed, 17% underwent a minor amputation; this rate was similar to that in those patients who did not heal (20%, $p=0.425$).

When stratifying patients according to the presence or absence of PAD, significantly ($p<0.001$) worse healing rates were observed in patients with than in those without PAD (69% vs 84%, respectively). Major amputation and mortality rates were also higher in patients with (8% and 9%, respectively) than in patients without PAD (2% and 3% respectively; $p<0.001$). Baseline characteristics of patients with PAD compared with those without PAD are provided in Table 2.

Predictors of healing

Table 3 shows the univariable associations of the potential predictors of non-healing in the overall population and Table 4 presents the variables retained in the predictive models after backward selection in the combined imputed datasets. The estimates were similar to those obtained in the complete cases dataset ($n=854$) indicating that missing values were non-selective (data not shown). These include the following eight characteristics, all of which predict lower probabilities of healing: older age, male sex, larger ulcer size, heart failure, inability to stand or walk without help, ESRD, PNP and PAD. These variables were consistently identified in all five imputed datasets.

Since we hypothesised that, from an aetiological point of view, predictors of non-healing would differ between patients with and those without PAD, predictive models were also fitted for these two groups separately (Table 4). In patients with PAD almost all of the predictors identified in the whole study population, with the exception of PNP, were again found to be independent predictors of healing. In addition, the presence of infection emerged as an additional independent predictor of non-healing. In patients without PAD, older age, larger ulcer size, inability to stand or walk without help, ESRD, PNP and, in addition, longer ulcer duration were independent predictors of poorer healing.

The observed interaction between infection and PAD status partly supports the classification of foot ulcer disease into four stages as suggested by Armstrong et al. (University of Texas classification system) [9]. Accordingly, upon analysis of the odds of non-healing per PAD × infection status, it was only in those patients with both PAD and infection that the odds of non-healing were markedly

Table 2 Patients' baseline characteristics according to their PAD status

Variable	Patients with PAD ($n=505$)	Patients without PAD ($n=558$)	p value
Age (years)	69.1±11.2	60.5±12.3	<0.001
Male sex, n (%)[a]	321 (65.6)	366 (63.6)	0.490
Duration of diabetes, n (%)[a]			0.265
<5 years	63 (12.9)	80 (14.9)	
5–10 years	72 (14.7)	93 (17.4)	
>10 years	354 (72.4)	363 (67.7)	
Deep ulcer, n (%)[a]	266 (52.7)	200 (35.8)	<0.001
Size of ulcer, n (%)[a]			0.002
<1 cm^2	173 (34.4)	219 (39.5)	
1–5 cm^2	259 (51.5)	294 (53.0)	
>5 cm^2	71 (14.2)	42 (7.5)	
Duration of ulcer, n (%)[a]			<0.001
<1 week	58 (11.5)	120 (21.7)	
1 week–3 months	296 (58.0)	318 (57.5)	
>3 months	148 (29.5)	115 (20.8)	
Plantar location, n (%)[a]	197 (40.9)	284 (55.0)	<0.001
Pretibial oedema, n (%)[a]	111 (22.0)	83 (14.9)	0.002
Heart failure NYHA III–IV, n (%)[a]	64 (12.7)	47 (8.5)	0.027
Neurological disorder, n (%)[a]	40 (8.0)	27 (4.9)	0.039
Inability to stand or walk without help, n (%)[a]	65 (12.9)	36 (6.5)	<0.001
Visual impairment, n (%)[a]	89 (17.9)	66 (12.0)	0.007
ESRD, n (%)[a]	35 (7.0)	25 (4.5)	0.082
Polyneuropathy, n (%)[a]	383 (77.2)	424 (79.3)	0.429
Infection, n (%)[a]	293 (60.9)	282 (53.4)	0.016

Unless otherwise stated, data are mean values±SD

[a] Percentages may not sum to 100 due to missing information

Table 3 Association of each potential predictor with non-healing in the overall population (n=1,088)

Predictor variables	Outcome: healing		
	OR	95% CI	p value
Age, per 10 year increase	1.32	1.17–1.49	<0.001
Sex, men vs women	1.50	1.07–1.97	0.018
Duration of diabetes			0.712
5–10 vs <5 years[a]	0.96	0.56–1.65	
>10 vs <5 years[a]	1.05	0.69–1.60	
Depth of ulcer, deep vs superficial	1.66	1.25–2.20	<0.001
Size of ulcer			<0.001
1–5 vs <1 cm^{2}[a]	2.25	1.60–3.17	
>5 vs <1 cm^{2}[a]	4.22	2.64–6.72	
Duration of ulcer			<0.001
1 week to 3 months vs <1 week[a]	1.81	1.15–2.85	
>3 months vs <1 week[a]	2.61	1.60–4.27	
Location, plantar vs non-plantar	0.73	0.55–0.98	0.035
Pretibial oedema, yes vs no	1.79	1.27–2.51	0.001
Heart failure (NYHA III–IV), yes vs no	2.03	1.35–3.05	0.001
Neurological disorder, yes vs no	1.44	0.85–2.46	0.176
Inability to stand or walk without help, yes vs no	2.50	1.62–3.79	<0.001
Visual impairment, yes vs no	1.36	0.94–1.98	0.105
ESRD, yes vs no	2.20	1.30–3.73	0.004
Polyneuropathy, yes vs no	1.41	0.98–2.04	0.065
Infection, yes vs no	1.47	1.09–2.00	0.012
PAD, yes vs no	2.31	1.72–3.10	<0.001

[a]Reference category

increased compared with those without PAD or infection: OR 2.82, CI 1.88–4.22, p<0.001 in unadjusted analyses (Fig. 1) vs OR 1.87, CI 1.20–2.91, p<0.001 after adjustments for the other variables included in the predictive model.

Discussion

The EURODIALE study is one of the few large prospective, international studies on outcome and determinants of outcome in diabetic foot disease. Despite the severity of

Table 4 Multivariable models with independent predictors of non-healing in the whole study population and in patients with and without PAD

Variable	All patients			Patients with PAD			Patients without PAD		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Age, per 10 year increase	1.28	1.11–1.47	0.001	1.42	0.17–1.73	<0.001	1.55	0.91–2.63	0.105
Sex, men vs women	1.72	1.23–2.40	0.002	1.97	1.25–3.11	0.003	–	–	–
Size of ulcer			<0.001			<0.001			0.008
1–5 vs <1 cm^{2}[a]	2.26	1.58–3.22		3.22	1.95–5.32		1.25	0.74–2.12	
>5 vs <1 cm^{2}[a]	3.88	2.37–6.34		3.84	1.97–7.48		3.48	1.62–7.46	
Duration of ulcer			–			–			0.086
1 week to 3 months vs <1 week[a]	–	–		–	–		2.14	1.05–4.36	
>3 months vs <1 week[a]	–	–		–	–		2.18	0.98–4.84	
Heart failure (NYHA III–IV), yes vs no	1.55	0.99–2.43	0.054	1.54	0.87–2.74	0.141	–	–	–
Inability to stand or walk without help, yes vs no	2.00	1.27–3.14	0.003	2.36	1.34–4.17	0.003	1.91	0.86–4.24	0.112
ESRD, yes vs no	2.51	1.41–4.48	0.002	3.04	1.38–6.70	0.006	2.00	0.76–5.25	0.161
Polyneuropathy, yes vs no	1.42	0.96–2.08	0.078	–	–	–	1.70	0.89–3.25	0.108
Infection, yes vs no	–	–	–	1.63	1.03–2.58	0.036	–	–	–
PAD, yes vs no	1.71	1.23–2.37	0.001	N/A			N/A		

[a] Reference category
N/A, not applicable

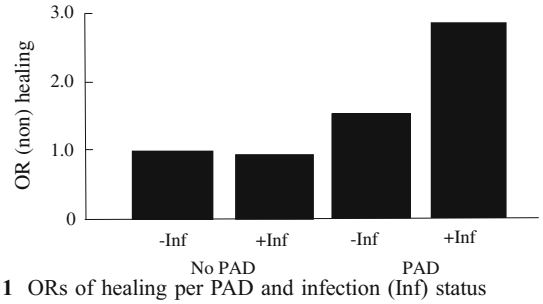

Fig. 1 ORs of healing per PAD and infection (Inf) status

the underlying disease and the important co-morbidity [7], clinical outcome of this population within a 1 year follow-up can be considered favourable. In our cohort, 77% of the patients healed (with or without a minor amputation), 5% underwent a major amputation and 6% died. However, healing rates in patients with PAD were considerably worse. In addition, predictors of healing also differed between the groups with and without PAD. The presence of infection, which is generally regarded as an important predictor of healing, was only predictive in individuals with PAD.

With regard to the overall outcome in our cohort, two recent studies found relatively comparable outcomes. Jeffcoate et al. [18] reported healing (excluding minor amputations) rates of 66% and an amputation rate of 5% with a similar prevalence of PAD. In a German cohort, Beckert et al. [19] found healing rates between 57% and 93% and major amputation rates of 3%, although the data as presented in that report cannot be easily compared because of their unique classification system. Oyibo et al. [20] also found similar rates of major amputation in their cohort (5%).

Our study shows that the combination of PAD and infection has a major impact on healing rates (Fig. 1); this significant interaction between PAD and infection is, in our opinion, one of the major findings of this study. In the patients without PAD we did not observe an association between infection and non-healing, which suggests that in these patients current antibiotic regimens and surgical techniques seem adequate to save a limb with adequate perfusion. However, within the total population of individuals with diabetic foot disease in developed countries, the group of infected and ischaemic ulcers accounted for almost one-third of all patients in our earlier report [7]. In a recent study, a significant relation between PAD, infection and poor outcome was also observed: in that study's large cohort of outpatients with type 2 diabetes, PAD was an independent predictor of infection-related mortality [21]. Unfortunately, there is very little insight into the pathophysiology and treatment of infection in individuals with PAD. Currently it is not clear why infection is more prevalent and more difficult to treat in individuals with PAD. Remarkably, very few patients with PAD were included in most of the randomised trials on antibiotic therapy in diabetic foot infections [22, 23]. It has previously been demonstrated that lower limb tissue levels of antibiotics can be markedly decreased as a result of impaired perfusion in PAD [24]. It is open to speculation whether aggressive revascularisation will improve control of infection in these patients.

Although some earlier studies have examined the impact of co-morbidities on ulcer healing [25], no studies, to our knowledge, have systematically assessed in a multivariable analysis the effects on ulcer healing of patient characteristics including co-morbidities, as well as foot and ulcer characteristics at baseline. In our study, older age, ulcer size and several co-morbidities were independent predictors of non-healing in patients with and without PAD. Recently a number of larger studies reported data on determinants of outcome in diabetic foot disease such as the single-centre study by Beckert in Germany and the UK multi-centre study initiated by Jeffcoate [19, 26]. The former focused on wound-based characteristics and also found that the presence of PAD (defined as absence of pedal pulses) was an independent predictor of outcome (healing), while infection was not. In the recent UK multi-centre study, ulcer area was a strong predictor of outcome, as was the presence of PAD; co-morbidities were not taken into account in the regression analyses. Surprisingly, depth of the ulcer was not associated with outcome in our multivariable model, a finding also shown by Ince et al. [26]. In a retrospective study, Miyajima et al. [27] reported on patient characteristics that determined major lower extremity amputation and found that haemodialysis was an independent predictor of major amputation; in this study wound characteristics were not part of the regression analyses. The poor prognosis of foot ulcers for individuals in our study with ESRD is in line with earlier reports, in which amputation rates of 57% in individuals on haemodialysis were observed [25]. Although in our study ESRD was a predictor of non-healing in patients with and without PAD, it seemed to have a particularly negative effect in the latter patient group. PAD is frequently diagnosed and associated with adverse outcomes in haemodialysis patients [28]. PAD in ESRD patients is more severe and is accompanied by diffuse vascular calcifications, involvement of both distal infrapopliteal and foot arteries, and by impaired microcirculatory perfusion [29–31]. The severity of PAD in ESRD may explain the importance of ESRD in our healing models; additional mechanisms are probably impaired host defences in chronic renal failure and uraemia, or the presence of more resistant micro-organisms [32, 33].

The outcome of patients without PAD in our study was relatively favourable: 84% of the patients healed with or without minor amputation, 2% underwent a major amputation and 3% died. In our multivariate models, loss of sensation was associated with a poorer outcome in these patients, suggesting that loss of protective sensation is not

only a key factor in the development of an ulcer, but also affects its outcome. This may be related to the preserved mechanism of off-loading the ulcer in individuals with intact protective sensation. However, neuropathy may also have direct effects on wound healing. Although data on the effect of neuropathy on wound healing in humans are scarce, some animal studies suggest that denervation may contribute to impaired wound healing in diabetes [34, 35]. A large dataset on individuals with neuropathic ulcers comes from retrospective database analyses in which healing rates of 47% were observed [36]. Although this study reported on healing at 20 weeks (whereas the current one examined healing rates at 1 year), the different results compared with our study are striking and may be related to an increased awareness of the importance of adequate off-loading, as a result of publication of international guidelines and reports on casting techniques [37–39].

There are several limitations to our study. Individuals who were lost to follow-up were excluded from the analyses as healing status could not be obtained; these individuals were slightly older and had a greater incidence of heart failure, deep ulcers or ulcers with a longer duration and PAD at baseline. In addition, we excluded patients who had had a previous ulcer within 12 months prior to presentation (i.e. we probably excluded patients with recurrent ulcers). Also we excluded patients with a life expectancy shorter than 1 year because of anticipated problems with follow-up. The estimates obtained in our models may therefore have underestimated the probability of non-healing in patients with a recurrent foot ulcer, although in one earlier study healing rate of neuropathic foot ulcers did not decrease in patients with multiple recurrences [40]. Since our study was embedded in daily clinical practice, limitations had to be set with regard to the number and type of data collected. It was therefore not possible to record more characteristics of these patients such as medication and extensive documentation of all complications. Moreover, to facilitate data collection, some continuous data (e.g. ulcer size) had to be transformed into a limited set of categories. Nevertheless, the set of potential predictors used in the present study do cover relevant patient and disease-specific aspects that can be easily assessed and used for patient risk estimation in clinical practice. Finally, our predictive model is based on outcomes that can be obtained in developed countries with access to the necessary resources such as antibiotic treatment and revascularisation; our results, therefore, are most relevant for diabetic foot ulcer patients in developed countries.

In conclusion, the results of this study have several implications. Both ulcer characteristics and several patient-related characteristics affected the outcome of diabetic foot ulcers. Therefore, a holistic approach by healthcare professionals who are familiar with the treatment of complicated diabetic patients is essential in order to identify the high-risk patient and start appropriate treatment. We found that patients with and without PAD differ in clinical characteristics, outcome and predictors of outcome. Taking into account these findings and the different pathophysiology and treatment of PAD and non-PAD ulcers, we feel that that diabetic foot ulcer with and without PAD should be defined as two separate disease states. The prevalent combination of PAD and infection is a unique entity; an important challenge lies in the development of evidence-based strategies to improve the poor outcome of these patients. Both studies comparing different antibiotic regimens in PAD, and studies evaluating the effects of early revascularisation on control of infection are urgently needed.

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