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Ulcer-free survival days and ulcer healing in patients with diabetic foot ulcers: A prospective cohort study

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Abstract

Healing rates may not give a complete indication of the effectiveness and management of diabetic foot ulcers because of high recurrence rates. The most important outcome for patients is remaining ulcer-free; however, this has hardly been investigated. The aim of our study was to prospectively investigate ulcer-free survival days and ulcer healing in patients with diabetic foot ulcers. This was a prospective cohort study of all referrals to our diabetic foot expertise centre from December 2014 to April 2017. Outcomes were determined after a minimum follow-up period of 12 months. Primary outcomes were ulcer-free survival days and 12-month healing percentages. Predictors for ulcer-free survival days and healing were investigated in multivariate analyses. A total of 158 patients were included. Median ulcer-free survival days in the healed group were 233 days (interquartile range [IQR] 121-312) and 131 days (IQR 0–298) in the overall population. The healing rate at 12-month follow up was 67% (106/158), and the recurrence rate was 31% (33/106). Independent predictors of ulcer-free survival days were duration of diabetes, peripheral artery disease (PAD), cardiovascular disease, end-stage renal disease (ESRD), and infection. Ulcer-free survival days are related to PAD and cardiovascular disease, and ulcer-free survival days should be the main outcome when comparing the effectiveness of management and prevention of the diabetic foot ulcers.

KEYWORDS

diabetic foot ulcers, ulcer healing, ulcer-free survival days

1 | INTRODUCTION

Diabetes is a growing problem in Europe with a prevalence of around 10% in people aged 20 to 79 years by 2030.[1] With the estimated increasing prevalence comes an increase of direct costs for diabetes care. One of the most costly treatments concerns treating diabetic foot ulcers, with their direct costs exceeding the treatment costs for many cancers.[2,3] In the United States alone, annual costs for diabetic foot care is approximately $58 billion, while in the United Kingdom, annual costs are estimated to be around $770 million.[4,5]

Along with costs and increasing prevalence, diabetic foot ulcers come with high disease burden, morbidity and mortality, and reduced health-related quality of life.[6,7] Approximately 20% of infected ulcers lead to an amputation, with the presence of peripheral artery disease increasing the risk of an amputation.[8-10] In patients with diabetes, the risk of death is twice as high in patients with foot ulcers compared with those without.[11,12] Around 10% of patients die within

30 days of a major amputation, and more than 70% of the patients with diabetes-related amputations will die within 5 years.[11-13]

Not all patients with diabetes are at risk for ulceration.[12] The key factors for developing diabetic foot ulcers are: peripheral neuropathy, foot deformity, peripheral arterial disease, previous foot ulceration, and previous amputation.[14-16] The yearly incidence of diabetic foot ulcers is estimated to be around 2%, with a lifetime prevalence of 19% to 34%.[17]

Because of the various factors involved in the development and progress of an ulcer, treatment is complex and needs to be multidisciplinary. An observational study in European centres of expertise showed that approximately 77% of the ulcers healed within 1 year,[18] while the recent national UK audit showed around two thirds of patients to be alive and ulcer-free after 24 weeks.[19] Yet even when an ulcer heals, recurrence is high, with recurrence rates of around 40% within 1 year after initial healing of the ulcers, almost 60% within 3 years, and 65% within 5 years.[17]

Studies on diabetic foot ulcers almost solely investigate either healing or recurrence rates, both in interventional and observational studies.[20,21] However, it has been argued that a more important outcome from a patient's perspective is their ulcer-free survival days.[22] An ulcer may heal, but from a patient's perspective, it is equally important that it remains healed.[22] Although this statement is already more than a decade old, ulcer-free survival days are hardly reported as an outcome. While the authors of this study stated that "comparative studies are urgently required",[22] only one additional publication on "ulcer-free survival days" is available, from the same research group.[23] None of the larger observational studies in this population have reported this outcome.[24,25] Despite its importance for patients, little is known about the ulcer-free survival days in patients with a diabetic foot ulcer, also because neither of the two studies on ulcer-free survival days investigated associations between this outcome and patient or ulcer characteristics.[22,23]

Investigating both ulcer healing and ulcer-free survival days is necessary in order to adequately inform patients about prognosis and to inform clinicians and researchers about the effectiveness of their treatment. With the limited information on the ulcer-free survival days, the aim of this study was to prospectively investigate ulcer healing and ulcer-free survival days in patients treated in a diabetic foot centre of expertise.

Key Messages

- ulcer-free survival days are associated with peripheral artery disease (PAD) and cardiovascular disease in multivariate analysis, which have not been described before
- in our opinion, ulcer-free survival days should be the main outcome when comparing the effectiveness of management and prevention of the diabetic foot ulcers

2 | MATERIAL AND METHODS

2.1 | Study design and setting

This was an observational, prospective cohort study in a single diabetic foot centre of expertise. At this centre, patients with diabetic foot ulcers are treated by a longstanding multidisciplinary team consisting of vascular surgeons, podiatrists, wound care nurses, casting technicians, specialists in internal medicine, rehabilitation doctors, radiologists, and orthopaedic shoe technicians. All patients were treated according to protocols based on the Dutch Guidelines[26] and the International Working Group on the Diabetic Foot Guidance.[10] This included, among others, off-loading via irremovable or removable knee-high and ankle-high casts, regular wound debridement and wound dressings, treatment of infection, treatment of peripheral artery disease, and education. Intervals between treatments at the outpatient clinic were weekly or once a fortnight. Treatment for ulcer prevention started when patients were close to healing and consisted of regular outpatient clinic control, podiatric treatment, prescription of orthopaedic footwear when required, and education. Once the ulcer was healed, patients were referred for further preventative treatment to their podiatrist and orthopaedic shoe technician.

2.2 | Participants

We prospectively included all patients with diabetes who presented with a new foot ulcer between December 2014 and April 2017. We excluded patients if they were already included with another ulcer during the study period, if they were referred for a second opinion only, or when no follow up was performed in our centre. Prospective inclusion was capped for the current study to ensure 12 months' follow up for all participants. Follow up for all participants in the current study ended at 12 months or when a patient died. Follow up was guaranteed via regular visits at the outpatient clinic. An additional phone call was made to the patient at 12 months to enquire about their status (ulcer-free and alive) if patients did not visit the outpatient clinic anymore between end of ulcer treatment and end of follow up.

2.3 | Variables

We obtained demographic data and data on comorbidities such as coronary artery disease, cerebrovascular disease, end-stage renal disease (ESRD: defined as estimated glomerular filtration rate [eGFR] <15 or dialysis treatment), and peripheral neuropathy (defined as loss of protective sensation[10]) as part of regular history taking at first presentation. Peripheral arterial disease (PAD) was defined as patients with an occlusion or significant stenosis on echo duplex or patients with a toe pressure or Ankle Brachial Index (ABI) lower than 30 mm Hg or 0.9, respectively. The definition of cardiovascular disease was as follows: patients who received a percutaneous coronary intervention (PCI) of one or more of the coronary arteries, a coronary artery bypass grafting (CABG), or patients with a myocardial infarction. HbA1c laboratory tests were performed within 3 months after referral or 3 months prior to referral; 10-g monofilament tests were performed to assess for loss of protective sensation as a result of peripheral neuropathy.

An ulcer was defined as a full-thickness lesion of the skin.[10] Each ulcer was classified according to the University of Texas Ulcer Classification (UT).[27] An ulcer was considered healed if the skin was intact for a minimum of 2 weeks, and for ulcer-free survival days, all ulcers had to be healed. Ulcer-free survival days were all days a patients was alive and ulcer-free during the 12-month follow up. Minor amputation was defined as an amputation below the ankle joint (this included toe, ray, forefoot, and midfoot amputations), and major amputation was defined as amputation through the ankle or above (transtibial, through-knee or trans-femoral; no amputations above the trans-femoral level were performed).[10]

2.4 | Statistical methods

Descriptive statistics were used to analyse the baseline patient and ulcer characteristics. Continuous variables were presented as mean with SD (in case of data that follow a normal distribution) or median with interquartile range (IQR) (in case of non-normal distribution). Categorical data were presented as number with percentage.

Differences in baseline characteristics between groups were tested using χ^2 tests, Student t test, or Mann-Whitney U test depending on the characteristics of the variables. Spearman correlation analysis was performed to analyse the relationship between continuous variables.

Univariate and multivariate logistic and linear regression analyses with backward elimination were performed to identify independent predictors for ulcer-free survival days (linear regression) and healing (both logistic regression). Variables with a P value <.10 in the univariate analysis were considered potential predictors and were entered into the multivariate analysis.

Statistical significance was set at a P value <.05. Statistical analysis was performed using SPSS Statistics for Windows, version 24.0 (IBM Corp, Armonk, New York).

3 | RESULTS

During the study period, 158 patients presented with a new diabetic foot ulcer. Their mean age was 70.2 years (SD: 12.4), and most were male (65%, n = 103). A summary of the baseline characteristics is given in Table 1. The spectrum of ulcer types is given in Table 2. The majority of the ulcers, 54 (34.2%), were superficial (UT A1); 75 (47.5%) of a total of 158 ulcers were plantar ulcers. The majority of the ulcers were situated at the hallux (n = 40; 25.3%).

3.1 | Ulcer-related outcomes

The healing rate in our population during the 12-month follow up was 67% (106/158). In patients with a healed ulcer, the mean time to healing was 165 days (SD 174.8). A total of

TABLE 1 Baseline characteristics

		Total population (n = 158)
Age	(years)	70.2 ± 12.4
Gender	Male	103 (65.2%)
	Female	55 (34.8%)
Type of diabetes	Type 1	4 (2.5%)
	Type 2	154 (97.5%)
HbA1C mmol/mol		62.0 ± 18.1
	Missing	N = 34
Diabetes duration (years)		14.6 ± 10.3
	Missing	N = 62
Location of ulcer	Forefoot	136 (86.1%)
	Hindfoot	22 (13.9)
Peripheral arterial disease		66 (41.8%)
Ulcer history	First-ever	102 (64.6%)
	Recurrent	56 (35.4%)
Comorbidity	Cerebrovascular disease	27 (17.1%)
	Cardiovascular disease	59 (37.3%)
	End-stage renal disease	12 (7.6%)
	Neuropathy	103 (65.2%)
Infected ulcers		85 (53.8%)

Note: values are n (%) or mean ± SD,. Healed ulcer means the ulcer at presentation healed within 12 months.

TABLE 2 University of Texas ulcer classification of included ulcers

Stage (infection/ischemia)	Grade (depth)			Total
	1: superficial ulcer	2: ulcer to tendon/capsule	3: ulcer to bone or joint	
A: Non-infected non-ischaemic ulcer	54 (34%)	6 (4%)	0 (0%)	60 (38%)
B: Non-ischemic infected ulcer	8 (5%)	11 (7%)	13 (8%)	32 (20%)
C: Ischaemic non-infected ulcer	12 (8%)	19 (12%)	2 (1%)	33 (21%)
D: Ischaemic infected ulcer	3 (2%)	14 (9%)	16 (10%)	33 (21%)
Total	77 (49%)	50 (32%)	31 (19%)	

Note: values are n (%).

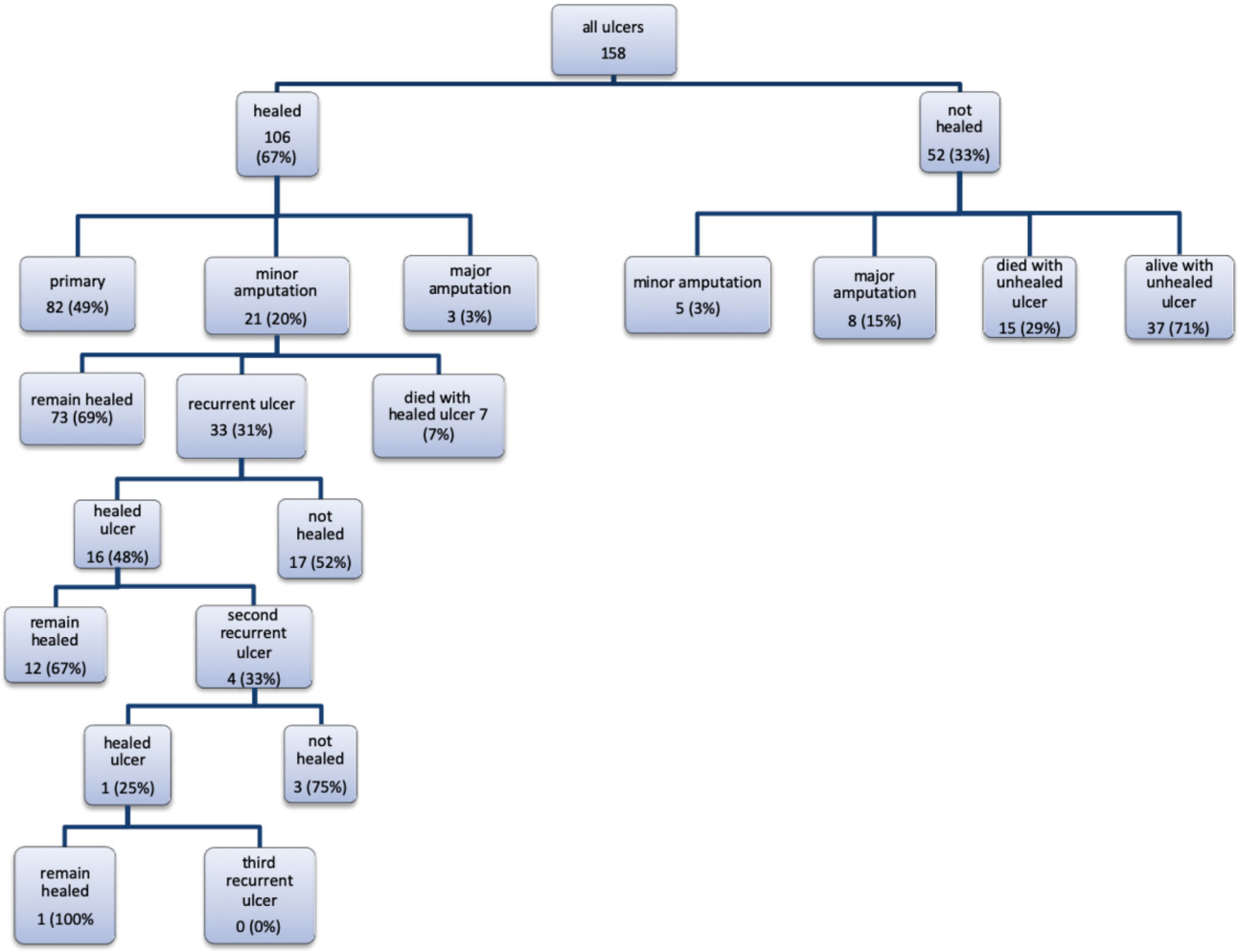

FIGURE 1 Summary of outcome of ulcers

73 (69%) of the 106 patients remained ulcer-free, while 33 (31%) patients had one or more recurrent ulcers within 1 year. Mean ulcer-free survival days in the group whose ulcer had healed was 212 days (SD: 110). In the overall population, including the non-healed ulcers, the average number of ulcer-free survival days was 142 days (SD: 135).

A summary of the results of all patients is presented in Figure 1; 22 patients died (14%), of which 7 (4%) died after their ulcer had healed and 15 (9%) died with an unhealed ulcer. Major amputations were performed in 11 patients (7%), of which 3 (27%) subsequently healed within the follow-up period. Minor amputations were performed in 26 patients (16%), of which 21 (81%) subsequently healed within the follow-up period.

3.2 | Predictors for ulcer-free survival days

Differences in ulcer-free survival days were not related to age, gender, type of diabetes, HbA1C, location of ulcer,

ulcer history, cerebrovascular disease, and neuropathy. The number of ulcer-free survival days was positively correlated with duration of diabetes (correlation coefficient 0.21, $P = .043$). Patients with PAD, cardiovascular disease, ESRD, and infected ulcers all had a significant lower number of ulcer-free survival days compared with patients without, with a median of ulcer-free survival days of, respectively, 13.0 vs 195.0 ($P < .001$), 14.0 vs 183.0 ($P = .001$), 0.0 vs 146.5 ($P = .005$), and 30.0 vs 194.0 ($P = .005$). Multivariate regression analysis showed PAD and cardiovascular disease as independent predictors of ulcer-free survival days with coefficients of, respectively, −64.3 (95% CI −107.7 to −20.9), $P = .004$) and − 55.7 (95% CI −100.0 to −11.5), $P = .014$). All findings are summarised in Tables 3 and 4.

3.3 | Predictors for ulcer healing

Differences in healing versus non-healing were not related to age, gender, type of diabetes, HbA1C, diabetes duration, ulcer history, cerebrovascular disease, ESRD, neuropathy, and infection. In the healed group (n = 106), only 36 patients with PAD healed (54.5%) compared with 70 patients without PAD (76.1%) ($P = .002$). Cardiovascular disease was also associated with lower healing rates as 73 (73.9%) patients without cardiovascular disease healed versus 33 patients (55.9%) with cardiovascular disease ($P = .021$). These findings are shown in Table 3. Multivariate regression analysis showed only PAD as an independent predictor for ulcer healing with an odds ratio (OR) of 0.4 (95%CI 0.2-0.8, $P = .005$) as is shown in Table 4.

4 | DISCUSSION

Diabetic foot ulcers are a major complication of diabetes, and timely healing of these ulcers is important.[9] However, measures of healing rate may not provide a complete indication of the effectiveness of overall management of diabetic foot ulcers because of high recurrence rates. The most important outcome for patients is to remain ulcer-free, yet these ulcer-free survival days have hardly been investigated

TABLE 3 Univariate variables associated with ulcer-free survival days and ulcer healing

		Ulcer-free survival days		Ulcer healing	
		Correlation coefficient or median (interquartile range)	***P*-value**	**Healed ulcers**	***P*-value**
Age (years)		Correlation coefficient − 0.01	.904	70.0 vs 70.3	.908
Gender	Male	123.0 (0.0-264.0)	.567	70 (66.0%)	.749
	Female	146.0 (0.0-326.0)		36 (65.4%)	
Type diabetes	Type 1	73.5 (0.0-285.0)	.660	2 (50.0%)	.599
	Type 2	131.0 (0.0-279.5)		104 (67.5%)	
HbA1C mmol/mol		Correlation coefficient 0.02	.861	63.6 vs 61.1	.475
Diabetes duration (years)		Correlation coefficient 0.21	*.043*	15.2 vs 13.6	.483
Peripheral arterial disease	No	195.0 (2.0-319.8)	*<.001*	70 (76.1%)	*.004*
	Yes	13.0 (0.0-184.3)		36 (54.5%)	
Ulcer history	First-ever	153.5 (0.0-291.3)	.231	70 (68.6%)	.579
	Recurrent	39.5 (0.0-260.8)		36 (64.3%)	
Cerebrovascular disease	No	123.0 (0.0-288.0)	.575	90 (68.7%)	.342
	Yes	166.0 (0.0-273.0)		16 (59.3%)	
Cardiovascular disease	No	183.0 (0.0-296.0)	*.001*	73 (73.9%)	*.021*
	Yes	14.0 (0.0-189.0)		33 (55.9%)	
End-stage renal disease	No	146.5 (0.0-290.0)	*.005*	100 (68.5%)	.211
	Yes	0.0 (0.0-11.0)		6 (50.0%)	
Peripheral neuropathy	No	64.0 (0.0-272.0)	.335	36 (65.5%)	.749
	Yes	157.0 (0.0-288.0)		70 (68.0%)	
Infected ulcers	No	194.0 (0.0-322.5)	*.005*	53 (72.6%)	.172
	Yes	30.0 (0.0-216.5)		53 (62.4%)	

Note: Italics are statistical significant. ulcer-free survival days were all the days a patients was alive and ulcer free during the 12-month follow up; ulcer healing was the percentage of ulcer healed at 12-month follow up.

TABLE 4 Summary of variables associated with ulcer-free survival days and ulcer healing in univariate and multivariate logistic regression

	Ulcer-free survival days				Ulcer healing			
	Univariate		Multivariate		Univariate		Multivariate	
	Unstandardized coefficient (95% CI)	*P*-value	Unstandardized coefficient (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Peripheral arterial disease	−83.7 (−125.0 to − 42.5)	*<.001*	−64.3 (−107.7 to −20.9)	*.004*	0.4 (0.2-0.8)	*.005*	0.4 (0.2-0.8)	*.005*
Cardiovascular disease	−79.0 (−121.3 to − 36.6)	*<.001*	−55.7 (−100.0 to −11.5)	*.014*	0.5 (0.2-0.9)	*.022*		
End-stage renal disease	−110.1 (−188.8 to −31.3)	*.006*						
Infected ulcers	−65.3 (−106.9 to −23.8)	*0.002*						

Note: Italics are statistical significant. Ulcer-free survival days were all the days a patients was alive and ulcer free during the 12-month follow up; ulcer healing was the percentage of ulcer healed at 12-month follow up.

since they were first introduced.[22,23] We prospectively followed a cohort of patients presenting with a new diabetic foot ulcer and found an average of ulcer-free survival days of 142 in the total cohort, with an average of ulcer-free survival days of 212 in those whose ulcers had healed.

Our findings can only be compared with the two studies on ulcer-free survival days. However, the inclusion criteria differed, which limits comparison. Jeffcoate et al performed a study in 2006 and reported median number of 272 ulcer-free days for ulcers that healed without amputation and 196 if they had an amputation in the 12 months after referral.[23] Ulcer outcomes were defined at 6 and 12 months, and they recruited patients during a 4-year period in which 449 patients were included.[23] These numbers are approximately the same as in our study. Average ulcer-free survival days in the healed population in the study performed by Pound and colleagues were 474 days and in the healed population with a recurrent ulcer were 126 days.[22] They included 370 patients in their total cohort after referral to their centre, with a study period of 31 months. We must note that this study had a median follow-up time of 715 days, with a minimum follow-up period of 6 months, compared with the 12-month follow-up in all of our patients.[22] Furthermore, Pound and colleagues stopped counting ulcer-free survival days as soon as there was a recurrent ulcer, while we continued counting when a recurrent ulcer healed within the 1-year follow-up period.

Based on outcome data in specialised tertiary care hospitals in Europe, approximately 77% of diabetic foot ulcers heal within 1 year.[18] These numbers are of the Eurodiale study, and they also noted the factors associated with wound healing, such as congestive heart failure, PAD, and ESRD requiring renal-replacement therapy.[18] The healing outcomes in our cohort (67% at 12 months) are lower than those reported in Eurodiale. This may be caused by the degree of the wound grades with a higher percentage of deeper wounds (43.8% in Eurodiale vs 51% in our cohort) but also by the overall condition of the patient, with more patients experiencing cardiovascular and cerebrovascular disease.[18] As mentioned before, a more recent UK audit showed approximately 66% to be alive and ulcer free at 24 weeks; this, however, is shorter than our follow up.[19] Jeffcoate et al reported a 65% healing rate at 12-month follow up in their study on ulcer-free survival days, which is comparable with ourcohort.[23]

A recent review reported recurrence rates of approximately 40% within 1 year.[17] Our population had a recurrence rate of 31%; however, we had a follow-up period of 1 year from the moment patients presented with a new ulcer, which is shorter than 1-year follow up after healing of the ulcer. The high recurrence rate is probably because of biological factors, behavioural factors, or both. Most of the underlying disease, such as PAD, neuropathy, and increased plantar stress, are still present after an ulcer has healed, which means that the risk of a recurrent ulcer remains.[20,21,28] No univariate or multivariate analysis on ulcer recurrence could be performed in our study cohort as patients had different follow-up times after healing.

A limitation of our study was that we only used medical variables to predict outcomes. However, as recently reported, biological and behavioural factors are also related with outcomes, especially ulcer recurrence, such as vibration perception threshold, geriatric depression scale, or footwear adherence.[17] We could not take these factors into consideration. In future cohort studies, these will need to be included. Another limitation was the missing ulcer size measurements for many patients, which means we could not investigate its association with outcomes, even though this is known to be associated with ulcer healing.[18,29] It is also questionable whether missing data could have influenced the data of our study. Not all patients in our cohort had an ABI or a toe pressure at baseline (23 of 158). All these patients had either pulsations of the arteries or had healed within 2 weeks with low suspicion of PAD. In future studies, it is preferable to classify ulcers according to SINBAD instead of the UT classification as recommended in the new IWGDF Guidelines.[30] Furthermore, when all cohort studies use the same internationally recommended classification system, this provides

the opportunity to compare ulcer characteristics from different settings, regions, and countries. That will allow us to compare these differences and to follow potential changes to these differences over time. Furthermore, although we use ESRD as a predictor for our primary outcomes, we must note that previous studies also reported chronic kidney disease as an independent risk factor in the development of diabetic foot ulcers.[31] We did not include other stages of kidney disease because eGFR was missing for several patients. Another limitation was that the study was not adequately powered to detect all potential correlations, but those were secondary aims. A final limitation was that not all patients received physical follow up at the outpatient clinic but were contacted by telephone in order to investigate whether they did remain alive and ulcer free. However, we considered the self-report of a lack of new ulcers reliable in our case, first, because we expected patients with an ulcer history treated at a centre of expertise to know their current status and, second, because these patients receive frequent (once every 6 weeks) podiatric care from qualified professionals. If an ulcer was present, these professionals would have told patients. Third, these professionals would have referred patients to our centre in case of an ulcer. From a clinical perspective, this study reopens the debate on the most important outcome for patients, which is to remain ulcer free. While healing, recurrence, and mortality are indeed important outcomes for separate studies as described, we would like to argue that the more holistic composite outcome of ulcer-free survival days needs to be collected to better reflect the burden on a patient. From a patient perspective, we have to work towards as many ulcer-free survival days as possible. To achieve that, two things are needed: fast healing and no recurrence. At the moment, the first is in the hands of a multidisciplinary team: supercomprehensive care, expensive, and effective in preventing amputations.[2,6,18,20,21] However, as soon as an ulcer is (almost) healed, patients are referred to primary care for preventative treatment. With 40% recurrence in the first year after healing,[17] this might be the area with the biggest room for improvement. To improve outcomes, there may be a need to combine healing and prevention in multidisciplinary centres for this complex group of patients, especially in the first phase after healing. Integrated preventative care, as recommended in international guidelines,[32] can best take place in multidisciplinary centres that already have expertise in treating this population rather than in primary care.

5 | CONCLUSION

Ulcer-free survival days are related to variables that explain poor healing outcomes and, presumably, recurrence. We therefore consider ulcer-free survival days the most important outcome for patients. In our opinion, this should be the main outcome to compare the effectiveness of management and prevention of diabetic foot ulcers. More research is needed to place our finding of an average 142 ulcer-free days in the 12 months since presentation in the perspective of other centres and systems.

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