

**Health-Related Quality of Life predicts major amputation and death, but not time to healing  
in people with diabetes mellitus presenting with foot ulcers – the Eurodiale study.**

Volkert Siersma, PHD<sup>1</sup>, Hanne Thorsen, PHD<sup>1</sup>, Per Ewald Holstein, MD DMSc<sup>2</sup>, Maleen Kars, MD PHD<sup>3</sup>, Jan Apelqvist, MD PHD<sup>4</sup>, Edward B Jude, MD<sup>5</sup>, Alberto Piaggese, MD<sup>6</sup>, Karel Bakker, MD PHD<sup>7</sup>, Michael Edmonds, MD<sup>8</sup>, Alexandra Jirkovská, MD PHD<sup>9</sup>, Didac Mauricio, MD PHD<sup>10</sup>, Gunnel Ragnarson Tennvall, PHD<sup>11</sup>, Heinrich Reike, MD<sup>12</sup>, Maximilian Spraul, MD PHD<sup>13</sup>, Luigi Uccioli, MD<sup>14</sup>, Vilma Urbancic, MD PHD<sup>15</sup>, Kristien van Acker, MD PHD<sup>16</sup>, Jeff van Baal, MD<sup>17</sup>, Nicolaas C Schaper, MD PHD<sup>3</sup>

From the <sup>1</sup>Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; <sup>2</sup>Copenhagen Wound Healing Centre, Bispebjerg University Hospital, Copenhagen, Denmark; the <sup>3</sup>Division of Endocrinology, Department of Internal Medicine and Research School CAPHRI, Maastricht University Medical Centre, Maastricht, the Netherlands; the <sup>4</sup>Department of Endocrinology, University of Malmö, Malmö, Sweden; the <sup>5</sup>Diabetes Centre, Tameside General Hospital, Ashton-under-Lyne, UK; <sup>6</sup>Sezione Dipartimentale Piede Diabetico, Dipartimento di Area Medica, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; the <sup>7</sup>IDF Consultative Section and International Working Group on the Diabetic Foot, Heemstede, the Netherlands; the <sup>8</sup>Diabetic Department, Kings College Hospital, London, UK; the <sup>9</sup>Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; the <sup>10</sup>Department of Endocrinology & Nutrition, Hospital de Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; the <sup>11</sup>Swedish Institute for Health Economics (IHE), Lund, Sweden; <sup>12</sup>Innere Abteilung, Mariannen Hospital, Werl, Germany; <sup>13</sup>Mathias-Spital, Diabetic Department, Rheine, Germany; <sup>14</sup>Policlinico Tor Vergata, Department of Internal Medicine, Rome, Italy; the <sup>15</sup>Department of Endocrinology, University Medical Centre, Ljubljana, Slovenia; <sup>16</sup>H Familie Ziekenhuis & Centre de Santé des Fagnes, Department of Endocrinology, Rumst & Chimay, Belgium; the <sup>17</sup>Department of Surgery, Twenteborg Ziekenhuis, Almelo, the Netherlands. Complete list of participants can be found in the On Line Appendix

Corresponding author: Volkert Siersma, PHD, [siersma@sund.ku.dk](mailto:siersma@sund.ku.dk).

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## Abstract

**Objective:** Low health-related quality of life (HRQoL) has been consistently reported to be associated with poor prognosis for a variety of health outcomes in various settings. We aimed to evaluate whether HRQoL in patients presenting with new diabetic foot ulcers has prognostic significance for ulcer healing, major amputation and death.

**Research design and methods:** We followed 1088 patients with new diabetic foot ulcers presenting for treatment at one of the 14 centers in 10 European countries participating in the Eurodiale study, prospectively until healing (76.9%), major amputation (4.6%) or death (6.4%) up to a maximum of 1 year. At baseline, patient and ulcer characteristics were recorded as well as EQ-5D: a standardised instrument consisting of five domains and a VAS scale for use as a measure of HRQoL. The prognostic influence of the EQ-5D domains was evaluated in multivariable Cox regression analyses on the time-to-event data, adjusting for baseline clinical characteristics of the ulcer and co-morbidities.

**Results:** While predictive effects of HRQoL, adjusted for possible confounders, were absent for time to healing, decreased HRQoL especially in the physical domains were statistically significant for major amputation (Mobility, Self-Care, Usual Activities) and death (Self-care, Usual Activities, Pain/Discomfort).

**Conclusions:** Low HRQoL appears to be predictive for major amputation and death, but high HRQoL does not increase healing. Future studies into the influence of HRQoL on ulcer outcome are important in attempts to decrease treatment failure and mortality.

## ***Background***

Diabetic foot ulcers (DFUs) are difficult to treat and heal slowly. In many cases they become chronic in spite of adequate treatment (1;2). To illustrate the extent of the problem, in a European study of DFU patients treated in specialized foot clinics, 12% were still undergoing treatment, 5% had had a major amputation and 6% had died one year after presentation (3). Treatment failure is influenced by a number of pathophysiological factors related to the foot such as infection, ulcer size and localization, related to the leg such as the degree of arterial perfusion and peripheral neuropathy, and related to the patient such as comorbidities, glycaemic control, compliance and demographic factors (3).

Already at the initial presentation in the foot clinic, DFU patients report severely hampered health-related quality of life (HRQoL) (4). Several studies have clearly shown that self-assessed health status is an independent predictor of mortality in a general population, beyond the numerous other risk factors known to be associated with increased mortality (5). Specifically in patients with DFU, a significantly increased risk of amputation has been reported when the patient lacks social connectedness (6), and depression, confrontation coping style and low HRQoL were observed in patients with a non-healing DFU (7;8).

The present analysis of data from a large prospectively followed cohort of people with new DFUs (the Eurodiale study) was undertaken to evaluate whether initial HRQoL had prognostic significance with regard to ulcer healing, amputation and death. Standardized evaluation of HRQoL may in these patients be an additional tool in the assessment of the prognosis, and can be the starting point for the development of supportive initiatives for improving quality of life from a patient perspective.

## **Methods**

Study design and population

The Eurodiale study was an observational, prospective study with the aim of investigating the factors that determine clinical and HRQoL outcomes as well as healthcare consumption in patients with new diabetic foot ulcers. It was a multicentre study in 14 centers with longstanding expertise in the field of diabetic foot disease in 10 European countries. The design and rationale of the study has been described in detail elsewhere (9;10). The ethical committees relevant to the 14 study centers all approved the study protocol.

All diabetic patients presenting for the first time with a new foot ulcer in one of the Eurodiale Study Group centers between 1 September 2003 and 1 October 2004 were included in the study. Patients treated for an ulcer on the ipsilateral foot during the preceding 12 months and patients with a life expectancy shorter than one year were excluded. All patients gave prior written consent.

All patients were treated according to protocols based on the International Consensus on the Diabetic Foot, which include off-loading, regular wound debridement, diagnosis and treatment of infection, critical ischaemia and foot deformities. Furthermore, included patients were monitored on a monthly basis until healing of the foot, major amputation or death (the three primary clinical study outcomes), up to a maximum of one year. An ulcer was considered healed if the skin was intact on the whole of the foot at two consecutive visits. If more than one ulcer was present, the foot was defined as healed once all ulcers were healed. Major amputation was defined as an amputation through the ankle or above.

At presentation, data on demographics, co-morbidities, and foot- and ulcer-related characteristics were recorded on standardized case record forms. Additional HRQoL data were collected on a separate form. All information was recorded by dedicated investigators in each centre who were trained during plenary meetings and on-site visits that took place prior to and during the study. The

methods and definitions used during collection and analysis of the data from the standardized case record forms has been described in detail previously (9).

HRQoL was measured by EQ-5D which is a standardised instrument for use as a measure of health outcome ([www.euroqol.org](http://www.euroqol.org)). EQ-5D consists of five domains – Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression – corresponding to five simple questions, which easily can be used as part of a clinical interview, with three response options: no problems, some problems, and severe problems. The five domains of EQ-5D can be combined into a single aggregated measure scoring 0 (lowest HRQoL) to 100 (highest HRQoL) (11). It additionally includes a visual analogue scale (VAS), also scoring 0 (lowest HRQoL) to 100 (highest HRQoL) for recording an individual's global rating of current HRQoL. Finally, the five domains can also be aggregated into a social tariff index that represents the value society attaches to the EQ-5D responses, scoring -0.594 (lowest tariff) to 1 (highest tariff) (12). EQ-5D is translated into the 10 languages relevant for the present study. Permission to use EQ-5D in the Eurodiale Study was obtained from the EuroQol group.

### Statistical analysis

The predictive values of each of the five EQ-5D domains, the aggregated score, and the VAS were analyzed as hazard ratios (HR) from Cox proportional-hazard regression models for the three primary study outcomes: 1) time from presentation to healing; a  $HR < 1$  indicates a lower rate of healing in the corresponding category as compared to a baseline category. 2) time from presentation to death; a  $HR > 1$  indicates a higher death rate in the corresponding category as compared to a baseline category. 3) time from presentation to major amputation; a  $HR > 1$  indicates a higher rate of amputation in the corresponding category as compared to a baseline category. Note the use here of rate to indicate the hazard, which is the probability of experiencing the event studied at a certain

time in the follow-up. For instance, a HR=2 means that at any time point during follow-up the patients in the corresponding category are twice as likely to experience the outcome as patients in the baseline category. For each of the three outcomes, the outcome was censored at the event time if any of the other two outcomes occurred first, or at 1 year if none of the outcomes occurred in the 1-year follow-up. Each of the analyses were done unadjusted, as well as adjusted for ulcer severity characteristics only and adjusted for ulcer severity characteristics and co-morbidities.

The proportional-hazard assumption was tested by adding the interactions of each of the independent variables in the model with the logarithm of time to healing to the model; a joint test of these interactions tests the assumption. On violation of the proportional-hazard assumption, i.e. one or more of the interactions were significant, the hazard function was estimated separately within strata of the corresponding covariates as to be able to assume proportional hazards for the remaining variables in the model, notably the EQ-5D assessments. The stratified estimation of the hazard function was constructed sequentially, adding to the stratification the covariate with the lowest p-value for the interaction until the joint test of all remaining interactions was insignificant.

## **Results**

Of the 1232 patients initially enrolled, an outcome could not be established for 144 (12%) because of non-compliance, inability to follow the patient, or if care had been taken over by other specialists. At presentation, these patients were slightly older and had higher prevalence of heart failure, deeper ulcers and ulcers of longer duration than those included (10). The remaining 1088 were followed until healing (76.9%), major amputation (4.6%) or death (6.4%) up to a maximum of 1 year. No baseline HRQoL data was collected for 73 (6.7%) of these 1088 patients so that the effective analysis sample consists of data from 1015 patients.

Table 1 shows the distribution at presentation of the patient- and ulcer characteristics and the HRQoL data. At presentation, the prevalence of mobility limitation and pain are high, but also 41.1% of the patients report some degree of anxiety/depression, while only 27.7% report self-care problems.

While the unadjusted analyses show decreased healing for several EQ-5D domains and for the VAS, the aggregated EQ-5D and the social tariff EQ-5D, these are fully explained by confounding by patient and ulcer characteristics (Table 2). Hence, HRQoL does not seem to influence healing. However, especially the physical domains show significantly increased major amputation (Mobility, Self-Care, Usual Activities) and death (Self-Care, Usual Activities, Pain/Discomfort), also after adjustment for DFU characteristics and comorbidities. Also the aggregated EQ-5D and the social tariff EQ-5D are significantly related to major amputation and death, while the VAS shows similar relationships only to a lesser extent.

In the analyses on time to healing, evidence of violations of the proportional-hazard assumption were found for ulcer depth and ulcer size. Hence, except in the unadjusted analyses, the (baseline) hazard function was estimated separately in the (six) strata spanned by ulcer depth and size.

## **Discussion**

Measurements of HRQoL are established predictors of morbidity and mortality as documented in a large number of studies in subjects without diabetes (5). Thus, initial poor HRQoL is a risk factor for chronic pain following cholecystectomy (13), and lumbar surgery (14). HRQoL is a predictor for work ability and disability for patients with low-back or neck problems (15), a measure with predictive value for dialysis patients' survival and hospitalization (16), a predictor of survival for patients before admission to a intensive care unit (17) and even for failure of surgical revascularization for critical lower limb ischaemia with graft occlusion and amputation (18). Since

the present sample of DFU patients has low HRQoL – ratings similar to that of, for example, recurrent breast cancer patients (19) – it therefore gives an adequate opportunity to assess the predictive effects of HRQoL for DFU patients.

The present analysis of people with a new DFU could not confirm HRQoL as independently related to wound healing as suggested previously (7). Discrepancies were expected since Ribu et al. used Short Form 36 (SF-36) as measure for HRQoL and healing was obtained in only 37% after 1 year as compared to 77% in the present study (7). In unadjusted analyses we found decreased healing for several EQ-5D domains. As reported elsewhere, all domains of HRQoL at baseline were affected by both patient characteristics, such as inability to stand or walk without help, and by ulcer-related factors such as ulcer size or limb threatening ischemia (3;4). These factors are also associated with ulcer healing, which may further explain why we did not observe an independent effect of HRQoL on healing after correction for these factors.

Importantly, however, the present analysis documented that HRQoL was independently related to the occurrence of major amputation and death throughout the follow-up period. Adequate action to improve HRQoL may thus be an important part of a future limb salvage strategy, but this hypothesis remains to be tested in future studies. Such a new approach seems very relevant from a patient perspective, as current treatment is focused on biomedical interventions such as wound treatment, infection control and revascularisation. Our data suggest that also strategies that improve mobility, reduce pain and enable the patient to better perform daily activities might also have beneficial effects on the outcome of a DFU. The nature of the relationship between low HRQoL and major amputation needs further exploration; possibly in a qualitative study.

Survival in people with DFU has been studied according to the type of ulceration (20). The 5-year mortality rate was 11% in neuropathic ulcers, 25 % in neuroischaemic ulcers and 29% in ischaemic

ulcers; these differences were explained primarily by age. People with diabetes have increased mortality (21;22) which is further increased in DFU patients (23), and which is of the same order as for patients with breast- or prostate cancer (24). This excess mortality cannot be fully explained by ulcer complications or co-morbidity (25) and our data shows that a low HRQoL can be assessed as a mortality risk factor in accordance with the above studies summarized by Idler et al (5).

Depression is quite common in people with diabetes and it predicts DFU (26). In people with DFU, depression has been found in one third of patients, predicting increased mortality (27), but other studies did not find an effect of depression (28). Our data shows 41% of DFU patients reporting Anxiety/Depression and there was no relation of self-reported Anxiety/Depression with either ulcer healing or treatment failure. Since conflicting results are noted, the value and mode of inquiry into depression and the effect of cognitive and medical therapy should be explored in future research in this important area.

A weakness of the present study is that HRQoL was not measured with a disease specific scale, for example the Diabetic foot ulcer scale (29), which would yield more adequate HRQoL measurement. Studies that investigate HRQoL in patients with DFU mostly use the generic Rand short form 36 (SF-36) (30-32), sometimes in combination with a disease specific scale (29). In contrast, EQ-5D is more used in studies on diabetes in general and its complications (33-35). The present study is performed in 14 centres in 10 countries and the EQ-5D was chosen as a measure of HRQoL because this instrument is easy to use in large scale surveys thereby providing results of consistent quality and with minimum risk for missing data and it is available in many languages. It was felt that a disease specific measure, albeit preferable for scientific purposes, would not be practical for a large multicenter study. The EQ-5D performs well in patients with diabetes (36), and it is

acceptable for DFU patients – typically of high age and with other diabetic complications (37). Finally, the simple wording of the five EQ-5D items makes it particularly suited for use in clinical practice and implementation in a busy diabetic foot clinic. However, the inability of the EQ-5D in the present data to find certain well-documented effects – e.g. an effect of anxiety/depression – challenges the sensitivity and usefulness of this instrument that already has been heavily criticized for its crudeness as measure for health status.

Another weakness is the limitation of patient selection from specialized diabetic foot clinics that may not be representative for the diabetic population in general. Furthermore, we selected only patients with new foot ulcers who did not have a prior ulcer in the previous year, and with an expected survival of at least one year.

The strength of the present study is the large number of patients from different centres all over Europe. This gives adequate statistical power for the various outcomes used in the present paper, even though the proportions of major amputations and deaths were small.

In conclusion, this report is to the best of our knowledge the first study assessing the predictive value of HRQoL, measured with an internationally well-known instrument, with respect to healing, major amputation and mortality in people presenting with DFU. It is in line with several reports documenting the ability of self-reported quality of life data to predict morbidity and mortality. In order to improve assessment of prognosis, it should be considered to routinely inquire into HRQoL with an instrument, that may still has to be developed in future research and that can be administered quickly like EQ-5D but with higher sensitivity for DFU patients, notably in the mental domain. Moreover, patients with a DFU have frequently a very poor HRQoL and knowledge about how inquiry into HRQoL helps to predict treatment success may help to formulate a

multidisciplinary treatment plan that is not only focused on biomedical factors but that also takes patient's experiences and perceptions into account.

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NCS planned the study, collected data and wrote the manuscript, VS researched data and wrote the manuscript, HT wrote the manuscript, PEH planned the study, collected data and wrote the manuscript, MK, JA, EBJ, AP, KB, ME, AJ, DM, GRT, HR, MS, LU, VU, KvA and JvB planned the study and collected the data, reviewed/edited the manuscript and contributed to the discussion.

NCS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data. VS takes responsibility for the accuracy of the data analysis.

Conflicts of interest: none reported.

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**Table 1:** Patient baseline characteristics

	distribution	n
<i>Patient and ulcer characteristics</i>		
Age (years), <i>mean±SD</i>	65.2±12.5	1088
Male sex, <i>n (%)</i>	704 (64.7)	1088
Duration of diabetes, <i>n (%)</i>		1048
<5 years	148 (14.1)	
5-10 years	169 (16.1)	
>10 years	731 (69.8)	
Deep ulcer, <i>n (%)</i>	476 (43.8)	1088
Size of ulcer, <i>n (%)</i>		1083
<1 cm <sup>2</sup>	403 (37.2)	
1-5 cm <sup>2</sup>	563 (52.0)	
>5 cm <sup>2</sup>	117 (10.8)	
Duration of ulcer, <i>n (%)</i>		1080
<1 week	184 (17.0)	
1 week - 3 months	627 (58.1)	
>3 months	269 (24.9)	
Location of ulcer, <i>n (%)</i>		1023
Toes	573 (56.0)	
Midfoot	334 (32.7)	
Heel	116 (11.3)	
Infection, <i>n (%)</i>	591 (57.2)	1033
PAD, <i>n (%)</i>	505 (47.5)	1063
<i>Comorbidities</i>		
Heart failure (NYHA III-IV), <i>n (%)</i>	117 (10.9)	1078
Neurological disorder, <i>n (%)</i>	70 (6.5)	1081
Inability to stand or walk without help, <i>n (%)</i>	107 (9.9)	1082
Visual impairment, <i>n (%)</i>	164 (15.3)	1072
End-stage renal disease, <i>n (%)</i>	63 (5.8)	1081
<i>EQ-5D</i>		
Mobility, <i>n (%)</i>		1004
No problems	330 (32.9)	
Some problems	621 (61.9)	
Severe problems	53 (5.2)	
Self-Care, <i>n (%)</i>		996
No problems	720 (72.3)	
Some problems	224 (22.5)	
Severe problems	52 (5.2)	
Usual activities, <i>n (%)</i>		996
No problems	496 (49.8)	
Some problems	383 (38.5)	
Severe problems	117 (11.7)	

Pain/Discomfort, <i>n</i> (%)		999
None	358 (35.8)	
Moderate	522 (52.3)	
Extreme	119 (11.9)	
Anxiety/Depression, <i>n</i> (%)		1000
None	589 (58.9)	
Moderate	358 (35.8)	
Extreme	53 (5.3)	
Visual Analogue Score, <i>mean</i> ± <i>SD</i>	62.2±19.7	999
Aggregated EQ-5D, <i>mean</i> ± <i>SD</i>	65.3±21.1	981
Social Tariff EQ-5D, <i>mean</i> ± <i>SD</i>	0.59±0.32	981
<i>Treatment</i>		
Treatment outcome after one year, <i>n</i> (%)		1088
Healed	837 (76.9)	
Not healed	131 (12.1)	
Major amputation	50 (4.6)	
Died	70 (6.4)	

**Table 2:** Cox regression analyses on time to healing, death or major amputation

EQ-5D	Unadjusted			Adjusted for patient and ulcer characteristics <sup>a</sup>			Adjusted for patient and ulcer characteristics and comorbidities <sup>a</sup>		
	HR <sup>b</sup>	95%CI	p-value <sup>c</sup>	HR <sup>b</sup>	95%CI	p-value <sup>c</sup>	HR <sup>b</sup>	95%CI	p-value <sup>c</sup>
<i>Time to healing<sup>d</sup></i>									
Mobility			0.0112			0.8123			0.7851
Some problems vs No problems	0.80	0.69 - 0.93		0.95	0.79 - 1.13		0.98	0.82 - 1.18	
Severe problems vs No problems	0.75	0.52 - 1.07		0.93	0.62 - 1.39		1.13	0.74 - 1.74	
Self-Care			0.0388			0.4938			0.5398
Some problems vs No problems	0.82	0.68 - 0.99		0.88	0.71 - 1.09		0.90	0.72 - 1.13	
Severe problems vs No problems	0.72	0.48 - 1.08		0.91	0.59 - 1.40		1.11	0.71 - 1.74	
Usual Activities			0.0352			0.7928			0.8124
Some problems vs No problems	0.88	0.75 - 1.02		0.95	0.80 - 1.13		0.97	0.81 - 1.16	
Severe problems vs No problems	0.74	0.58 - 0.95		0.92	0.69 - 1.24		1.06	0.78 - 1.46	
Pain/Discomfort			0.4044			0.9975			0.9232
Moderate vs No	0.91	0.78 - 1.06		1.00	0.84 - 1.19		1.03	0.86 - 1.23	
Extreme vs No	0.89	0.67 - 1.14		0.99	0.74 - 1.34		1.05	0.77 - 1.44	
Anxiety/Depression			0.6991			0.6808			0.7055
Moderate vs No	1.05	0.90 - 1.23		1.00	0.83 - 1.20		0.99	0.82 - 1.19	
Extreme vs No	1.11	0.81 - 1.52		1.17	0.82 - 1.66		1.15	0.81 - 1.65	
Visual Analogue Score (Score vs Score+10)	0.96	0.92 - 0.99	0.0169	0.98	0.94 - 1.03	0.4760	0.99	0.95 - 1.04	0.7311
Aggregated EQ-5D (Score vs Score+10)	0.96	0.92 - 0.99	0.0147	0.99	0.95 - 1.03	0.5577	1.00	0.96 - 1.05	0.9447
Social tariff EQ-5D (Index vs Index+0.1)	0.98	0.95 - 0.99	0.0425	0.99	0.97 - 1.02	0.6578	1.01	0.98 - 1.04	0.6792
<i>Time to death</i>									
Mobility			0.0029			0.1767			0.1419
Some problems vs No problems	2.81	1.31 - 6.04		2.05	0.86 - 4.87		2.71	1.00 - 7.34	

Severe problems vs No problems	5.73	2.06 - 15.93		3.04	0.87 - 10.59		2.90	0.69 - 12.29	
Self-Care			0.0000			0.0251			0.0217
Some problems vs No problems	3.60	1.99 - 6.50		1.52	0.77 - 3.02		1.86	0.86 - 4.02	
Severe problems vs No problems	8.69	4.19 - 18.02		3.58	1.43 - 9.00		4.03	1.49 - 10.91	
Usual Activities			0.0000			0.0021			0.0053
Some problems vs No problems	3.16	1.51 - 6.60		1.95	0.86 - 4.46		2.72	1.06 - 7.00	
Severe problems vs No problems	8.91	4.19 - 18.94		4.95	1.96 - 12.53		5.69	1.98 - 16.34	
Pain/Discomfort			0.0055			0.0492			0.0164
Moderate vs No	2.12	1.07 - 4.19		2.47	1.14 - 5.37		2.94	1.23 - 7.02	
Extreme vs No	3.75	1.68 - 8.37		2.92	1.10 - 7.72		4.63	1.56 - 13.77	
Anxiety/Depression			0.2609			0.4603			0.2851
Moderate vs No	1.41	0.82 - 2.44		1.13	0.60 - 2.14		1.28	0.64 - 2.55	
Extreme vs No	1.93	0.74 - 5.03		1.93	0.69 - 5.42		2.36	0.81 - 6.89	
Visual Analogue Score (Score vs Score+10)	1.22	1.09 - 1.38	0.0010	1.16	1.00 - 1.35	0.0574	1.21	1.02 - 1.44	0.0272
Aggregated EQ-5D (Score vs Score+10)	1.42	1.25 - 1.61	0.0000	1.25	1.07 - 1.46	0.0042	1.37	1.14 - 1.64	0.0006
Social tariff EQ-5D (Index vs Index+0.1)	1.19	1.12 - 1.27	0.0000	1.13	1.04 - 1.23	0.0059	1.17	1.06 - 1.28	0.0015
<i>Time to major amputation</i>									
Mobility			0.0016			0.0017			0.0025
Some problems vs No problems	4.71	1.66 - 13.36		2.97	1.01 - 8.71		3.60	1.81 - 10.97	
Severe problems vs No problems	10.15	2.83 - 36.35		13.52	3.20 - 57.23		17.09	3.43 - 85.01	
Self-Care			0.0000			0.0010			0.0012
Some problems vs No problems	3.47	1.85 - 6.50		3.90	1.80 - 8.47		4.28	1.93 - 9.49	
Severe problems vs No problems	5.32	2.12 - 13.35		4.76	1.46 - 15.47		4.41	1.15 - 16.96	
Usual Activities			0.0005			0.0006			0.0008
Some problems vs No problems	4.63	2.11 - 10.16		6.17	2.41 - 15.84		5.80	2.24 - 15.06	
Severe problems vs No problems	4.34	1.63 - 11.55		2.60	0.75 - 8.94		2.14	0.57 - 7.97	
Pain/Discomfort			0.0543			0.1024			0.0571
Moderate vs No	2.23	1.05 - 4.73		2.58	1.06 - 6.29		3.01	1.20 - 7.53	
Extreme vs No	2.95	1.14 - 7.65		2.61	0.80 - 8.47		3.03	0.88 - 10.44	
Anxiety/Depression			0.6748			0.1287			0.1151

Moderate vs No	1.31	0.71 - 2.41		1.75	0.88 - 3.49		1.77	0.88 - 3.59	
Extreme vs No	0.95	0.23 - 4.01		0.31	0.03 - 2.88		0.25	0.03 - 2.60	
Visual Analogue Score (Score vs Score+10)	1.21	1.06 - 1.38	0.0052	1.16	0.97 - 1.39	0.1005	1.10	0.92 - 1.33	0.3005
Aggregated EQ-5D (Score vs Score+10)	1.32	1.15 - 1.52	0.0000	1.30	1.08 - 1.56	0.0056	1.31	1.09 - 1.58	0.0041
Social tariff EQ-5D (Index vs Index+0.1)	1.16	1.08 - 1.25	0.0001	1.19	1.06 - 1.33	0.0028	1.19	1.06 - 1.33	0.0033

<sup>a</sup>Patient and ulcer characteristics: age, sex, duration of diabetes, ulcer depth, ulcer size, duration of ulcer, ulcer location, infection, PAD. Comorbidities: heart failure, neurological disorder, inability to stand and walk without help, visual impairment, end-stage renal disease. See Table 1.

<sup>b</sup>A hazard ratio (HR) < 1 indicates a lower rate of healing, a lower mortality rate, or a lower rate of amputation, respectively, in the corresponding category as compared to the baseline category.

<sup>c</sup>p-value of a Wald chi-squared test.

<sup>d</sup>in the analyses on time to healing, the (baseline) hazard function is estimated separately in the (six) strata spanned by the categories of ulcer depth and ulcer size.

## Participating Centers

Copenhagen Wound Healing Centre, Bispebjerg University Hospital, Copenhagen, Denmark  
(P.E. Holstein)

Division of Endocrinology, Department of Internal Medicine and Research School CAPHRI,  
Maastricht University Medical Centre, Maastricht, the Netherlands (N.C. Schaper, M. Kars)

Department of Endocrinology, University of Malmö, Malmö, Sweden (J. Apelqvist)

Diabetes Centre, Tameside General Hospital, Ashton-under-Lyne, UK (E.B. Jude)

Sezione Dipartimentale Piede Diabetico, Dipartimento di Area Medica, Azienda Ospedaliero-  
Universitaria Pisana, Pisa, Italy (A. Piaggese)

Diabetic Department, Kings College Hospital, London, UK (M. Edmonds)

Diabetes Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (A.  
Jirkovska)

Department of Endocrinology & Nutrition, Hospital de Sant Pau, Autonomous University of  
Barcelona, Barcelona, Spain (D. Mauricio)

Innere Abteilung, Mariannen Hospital, Werl, Germany (H. Reike)

Mathias-Spital, Diabetic Department, Rheine, Germany (M. Spraul)

Policlinico Tor Vergata, Department of Internal Medicine, Rome, Italy (L. Uccioli)

Department of Endocrinology, University Medical Centre, Ljubljana, Slovenia (V. Urbancic)

St Joseph Clinic, Bornen, Belgium (K. van Acker)

Department of Surgery, Twenteborg Ziekenhuis, Almelo, the Netherlands (J. van Baal)

**Participating institutions**

IDF Consultative Section and International Working Group on the Diabetic Foot, Heemstede, the Netherlands (K. Bakker)

Swedish Institute for Health Economics (IHE), Lund, Sweden (G. Ragnarson Tennvall)

The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark (V. Siersma, H. Thorsen)