



# Health-Related Quality of Life Predicts Major Amputation and Death, but Not Healing, in People With Diabetes Presenting With Foot Ulcers: The Eurodiale Study

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## 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 (DFUs) has prognostic significance for ulcer healing, major amputation, and death.

## RESEARCH DESIGN AND METHODS

We followed 1,088 patients with new DFUs presenting for treatment at one of the 14 centers in 10 European countries participating in the Eurodiale (European Study Group on Diabetes and the Lower Extremity) 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 standardized instrument consisting of five domains and a visual analog 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 comorbidities.

## RESULTS

While predictive effects of HRQoL, adjusted for possible confounders, were absent for healing, decreased HRQoL, especially in the physical domains, was 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.

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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 1 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, glycemic 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 nonhealing DFU (7,8).

The present analysis of data from a large prospectively followed cohort of people with new DFUs (the Eurodiale [European Study Group on Diabetes and the Lower Extremity] 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.

## RESEARCH DESIGN AND 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 health care consumption in patients with new DFUs. It was a multicenter 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 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 1 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 included offloading, regular wound debridement, diagnosis and treatment of infection, critical ischemia, 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 1 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, comorbidities, 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 center 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 have been described in detail previously (9).

HRQoL was measured by EQ-5D, which is a standardized instrument for use as a measure of health outcome

(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 analog 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 current 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 (HRs) from Cox proportional-hazard regression models for the three primary study outcomes: 1) time from presentation to healing, where an HR  $<1$  indicates a lower rate of healing in the corresponding category as compared with a baseline category; 2) time from presentation to death, where an HR  $>1$  indicates a higher death rate in the corresponding category as compared with a baseline category; and 3) time from presentation to major amputation, where an HR  $>1$  indicates a higher rate of amputation in the corresponding category as compared with 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, an HR of 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 comorbidities.

The proportional-hazard assumption was tested by adding the interactions of each of the independent variables in the model with the logarithm of event time 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 was 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 1,232 patients initially enrolled, an outcome could not be established for 144 (12%) due to noncompliance, due to an inability to follow the patient, or because 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 1,088 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 were collected for 73 (6.7%) of these 1,088 patients, so the effective analysis sample consisted of data from 1,015 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.

## CONCLUSIONS

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 a predictor for failure of surgical revascularization for critical lower limb ischemia 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 SF-36 (short-form 36) as measure for HRQoL and healing was obtained in only 37% after 1 year as compared with 77% in the current 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 revascularization. Our data also suggest that 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 neuroischemic ulcers, and 29% in ischemic 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 comorbidity (25), and our data show that a low HRQoL can be assessed as a mortality risk factor in

**Table 1—Patient baseline characteristics**

	Distribution	<i>n</i>
<b>Patient and ulcer characteristics</b>		
Age (years), mean $\pm$ SD	65.2 $\pm$ 12.5	1,088
Male sex, <i>n</i> (%)	704 (64.7)	1,088
Duration of diabetes, <i>n</i> (%)		1,048
<5 years	148 (14.1)	
5–10 years	169 (16.1)	
>10 years	731 (69.8)	
Deep ulcer, <i>n</i> (%)	476 (43.8)	1,088
Size of ulcer, <i>n</i> (%)		1,083
<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> (%)		1,080
<1 week	184 (17.0)	
1 week–3 months	627 (58.1)	
>3 months	269 (24.9)	
Location of ulcer, <i>n</i> (%)		1,023
Toes	573 (56.0)	
Midfoot	334 (32.7)	
Heel	116 (11.3)	
Infection, <i>n</i> (%)	591 (57.2)	1,033
Peripheral arterial disease, <i>n</i> (%)	505 (47.5)	1,063
<b>Comorbidities</b>		
Heart failure (NYHA III–IV), <i>n</i> (%)	117 (10.9)	1,078
Neurological disorder, <i>n</i> (%)	70 (6.5)	1,081
Inability to stand or walk without help, <i>n</i> (%)	107 (9.9)	1,082
Visual impairment, <i>n</i> (%)	164 (15.3)	1,072
End-stage renal disease, <i>n</i> (%)	63 (5.8)	1,081
<b>EQ-5D</b>		
Mobility, <i>n</i> (%)		1,004
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> (%)		1,000
None	589 (58.9)	
Moderate	358 (35.8)	
Extreme	53 (5.3)	
VAS, mean $\pm$ SD	62.2 $\pm$ 19.7	999
Aggregated EQ-5D, mean $\pm$ SD	65.3 $\pm$ 21.1	981
Social tariff EQ-5D, mean $\pm$ SD	0.59 $\pm$ 0.32	981
<b>Treatment</b>		
Treatment outcome after 1 year, <i>n</i> (%)		1,088
Healed	837 (76.9)	
Not healed	131 (12.1)	
Major amputation	50 (4.6)	
Died	70 (6.4)	

NYHA refers to the New York Heart Association functional classification.

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 show 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 current study is that HRQoL was not measured with a disease-specific scale, for example, the DFU scale (29), which would yield more adequate HRQoL measurement. Studies that investigate HRQoL in patients with DFU mostly use the generic Rand 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 current study is performed in 14 centers 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 diabetes 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.



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>
<b>Time to healing<sup>d</sup></b>									
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	
VAS (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
<b>Time to death</b>									
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	
VAS (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
<b>Time to major amputation</b>									
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	
VAS (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 are age, sex, duration of diabetes, ulcer depth, ulcer size, duration of ulcer, ulcer location, infection, and peripheral arterial disease. Comorbidities are heart failure, neurological disorder, inability to stand and walk without help, visual impairment, and end-stage renal disease. See Table 1. <sup>b</sup>An 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 with the baseline category. <sup>c</sup>P value of a Wald  $\chi^2$  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.

Another weakness is the limitation of patient selection from specialized diabetic foot clinics who 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 1 year.

The strength of the current study is the large number of patients from different centers 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 have 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 not only is focused on biomedical factors, but also takes patient's experiences and perceptions into account.

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M.S., L.U., V.U., K.v.A., and J.v.B. planned the study, collected the data, reviewed and edited the manuscript, and contributed to the discussion. V.S. and N.C.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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