



A Randomized Controlled Trial Comparing Telemedical and Standard Outpatient Monitoring of Diabetic Foot Ulcers

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OBJECTIVE

The role of telemedical monitoring in diabetic foot ulcer care is still uncertain. Our aim was to compare telemedical and standard outpatient monitoring in the care of patients with diabetic foot ulcers in a randomized controlled trial.

RESEARCH DESIGN AND METHODS

Of the 736 screened individuals with diabetic foot ulcers, 401 met the eligibility criteria and were randomized between October 2010 and November 2014. The per-protocol telemedical monitoring consisted of two consultations in the patient's own home and one consultation at the outpatient clinic. Standard practice consisted of three outpatient clinic visits. The three-visit cycle was repeated until study end point. The study end points were defined as complete ulcer healing, amputation, or death.

RESULTS

One hundred ninety-three individuals were randomized to telemedical monitoring and 181 to standard care. Demographics were similar in both groups. A cause-specific Cox proportional hazards model showed no difference in individuals monitored through telemedicine regarding wound healing (hazard ratio 1.11 [95% CI 0.87, 1.42], $P = 0.42$) or amputation (0.87 [0.54, 1.42], $P = 0.59$). We found a higher mortality incidence in the telemedical monitoring group compared with the standard outpatient monitoring group (8.68 [6.93, 10.88], $P = 0.0001$).

CONCLUSIONS

The findings of no significant difference regarding amputation and healing between telemedical and standard outpatient monitoring seem promising; however, for telemedical monitoring, a higher mortality throws into question the role of telemedicine in monitoring diabetic foot ulcers. Further studies are needed to investigate effects of telemedicine on mortality and other clinical outcomes and to identify patient subgroups that may have a poorer outcome through telemedical monitoring.

Diabetes currently affects >387 million people worldwide, and this number is expected to rise to >592 million individuals worldwide by 2035 (1). In Denmark, 320,545 people suffer from diabetes, and it is estimated that a further 200,000 individuals are undiagnosed; a further 750,000 have impaired glucose tolerance (2). Approximately 7–15% of the population with diabetes will have one or several foot ulcers during a lifetime, and up to 70% of these ulcers will recur during a 5-year period (3). Diabetic foot ulcers lead to ~500 major amputations every year in

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Denmark, incurring a high financial burden (4). The cost of a major amputation was estimated to be \$59,000–\$87,000 in 1995 (5). Individuals with diabetes are also at an increased risk of developing cardiovascular disease, which is the most common cause of premature death among this population (6). The presence of a foot ulcer is associated with higher all-cause mortality (7), and one study showed a 30-day mortality of 30% after a major amputation and >50% mortality 1 year after amputation (8).

An aging population with comorbidities challenges the health care system (9), and this has led to a growing interest in technical solutions to reduce the number of hospital and outpatient clinic visits. Telemedicine is a growing medical field that has the potential to deliver health care services from a distance (10). It covers a range of technologies for treatment and monitoring, and the creation of innovative health solutions has the potential to improve patient quality of life at a low cost (11). In the present clinical trial, telemedicine was defined and used as a tool for monitoring patients at home to reduce the number of outpatient visits (i.e., telemedical monitoring).

The evidence of telemedical monitoring of ulcers is characterized by heterogeneity in study methods and the interventions applied, making it difficult to assess the safety and efficacy of telemedicine (12,13). A number of randomized controlled trials have investigated the potential and feasibility of telemedicine in ulcer care (14–19), but only two of these present clinical outcomes (15,18). Only one nonrandomized study focused specifically on diabetic foot ulcers and telemedicine (20). The aim of the present study was to compare telemedical and standard outpatient monitoring in the care of patients with diabetic foot ulcers with a focus on ulcer healing and amputation.

RESEARCH DESIGN AND METHODS

Reporting

This study was reported using the CONSORT (Consolidated Standards of Reporting Trials) guidelines on pragmatic randomized controlled trials (21). The study was a part of the Renewing Health project, a European study aimed at investigating the use of telemedicine in various settings. However, this study was conducted and reported independently (22). The MAST (Model for Assessment of Telemedicine)

was used in this setup, providing a structure for multidisciplinary assessment of the outcomes of telemedical applications, and includes seven major domains. The model guides researchers in evaluating mature technology in health care. The third domain (clinical effectiveness) was used as a framework for the present study (23). The trial protocol in Danish is available on request.

Trial Design

We report on a multicenter pragmatic randomized controlled clinical trial. In a 4-month preliminary phase, patients were assigned by 2:1 randomization in favor of telemedicine to allow us to gain experience with the telemedicine service. Thereafter, a 1:1 randomization between telemedical and standard outpatient monitoring was used. The study was performed according to the Declaration of Helsinki II and was registered with the Danish Data Protection Agency (2008-58-0035) and the U.S. National Institutes of Health. The regional ethics committee noted that ethics approval was not required for this kind of study because it addressed potential differences in monitoring and not treatment.

Study Population

The study took place in the Region of Southern Denmark (RSD), which includes five general hospital units with outpatient clinics specializing in ulcer care. The area included 22 municipalities. These outpatient clinics and municipalities are funded and driven by the government. The population of the RSD is 1.2 million, and the estimated foot ulcer prevalence is 7% among citizens with diabetes. In 2013, 77,040 individuals were living with a diagnosis of diabetes in the RSD (2). Potential study participants were identified at the outpatient clinics of the five general hospital units between October 2010 and November 2014. Inclusion criteria were adults with diabetes aged >18 years residing in the RSD and having a diabetic foot ulcer and referral to an outpatient clinic by a general practitioner or a hospital department. We excluded individuals with conditions that would affect compliance (i.e., psychiatric disease, dementia, alcohol abuse), competing conditions suspected to be the cause of the ulcer (i.e., gout, rheumatoid arthritis, uremia requiring dialysis), past inclusion in the project, and expected ulcer healing within 4 weeks.

Study Intervention

Eligible participants were treated according to standard clinical guidelines (24). The participants were medically and surgically stratified before randomization to telemedical or outpatient monitoring. The per-protocol telemedical monitoring consisted of two consultations in the patient's own home using telemedicine and one consultation at the outpatient clinic. Standard treatment comprised three outpatient clinic visits. The three-visit cycle was repeated as necessary for each patient until study end point. If a patient presented with two or more foot ulcers, one ulcer was selected as the treatment or intervention focus (index ulcer) before randomization. In a few cases, an index ulcer was not defined before randomization; thus, we defined the ulcer meeting one of the end points first as the index ulcer. The ulcers not included as an index ulcer were treated according to recommended guidelines, but these were disregarded in this study.

Patients monitored with telemedicine were treated according to the algorithm shown in Fig. 1. No frequency of telemedicine consultations or clinic visits was predefined by the protocol but was driven by clinical judgment at every consultation be it telemedical or control. Municipal nurses provided standard daily care under supervision of a nurse specialized in ulcer care. The telemedical consultations were conducted by telephone or online written consultations between the specialized municipal nurse and physicians at the outpatient clinic. These consultations were supplemented by an uploaded image of the ulcer and a detailed written assessment through the online database (25). If needed, the treatment strategy was revised, and the next consultation (telemedical or standard) and the indication for further images were agreed on by the nurse and physician. If the treatment or the patient's health condition needed closer supervision by a hospital specialist (i.e., physician, podiatrist, nurse specialist), deviation from the workflow algorithm was allowed.

Patients randomized to standard care followed the usual practice and treatment provided by the outpatient clinic. All visits and consultations took place in the outpatient clinics. Patients stayed in the study until ulcer healing, amputation, or death. If a patient did not meet any of the end points within 1 year (365 days), their condition was considered chronic,

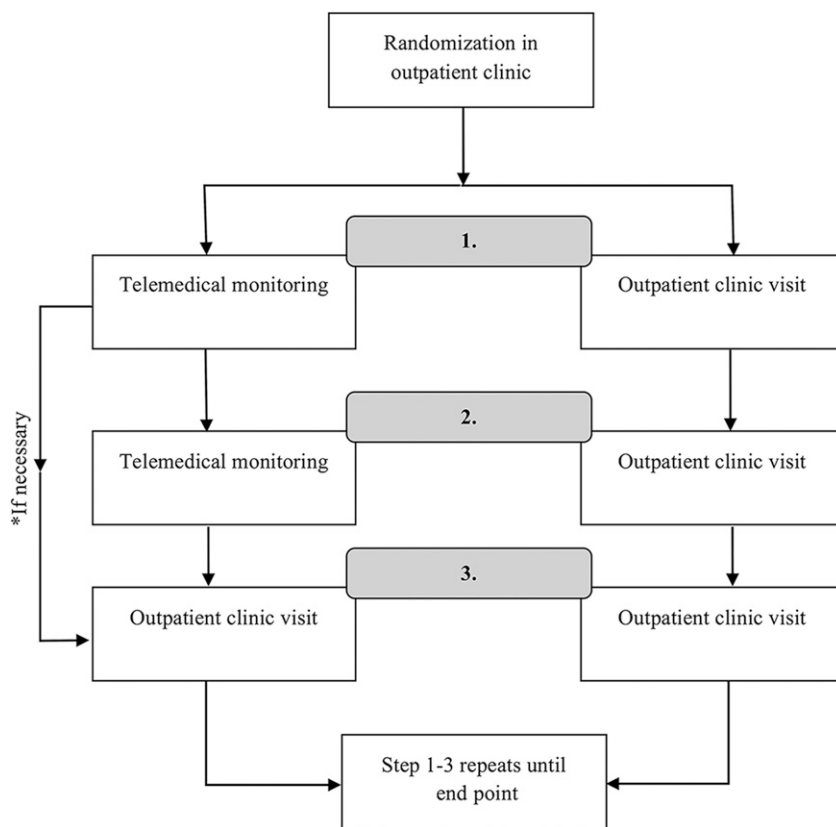


Figure 1—Generic workflow with telemedical monitoring and standard outpatient monitoring.

and they were terminated from the study.

Outcomes

The primary outcome of the overall study was the number of hospital admissions, including the number of inpatient days related to ulcer treatment and surgical procedures. These data will be published elsewhere. We report here the study end points of ulcer healing, amputation, and death. All end points reported in this study were the first to occur for each patient. Amputations below the ankle were classified as minor and those from the ankle and above as major.

Sample Size Calculation

A previous study showed a reduction in the proportion of patients using the emergency department from 73% in the control group to 42% in the telemedical monitoring group (26). Similarly, the average number of emergency department visits was reduced from 2.05 to 0.84 during a 2-year period. The sample size estimate for the present study was 180 patients in each group based on the proportion of patients using the emergency department. We chose to include 400 patients (200 in

each group) to adjust for an estimated 10% dropout rate.

Randomization Procedure

The participants were included and evaluated by the clinical staff at the participating outpatient clinics. Eligible patients were screened for inclusion and exclusion criteria, and the cause of noneligibility was noted. The clinical staffs were supplied with checklists of the procedures required for each patient. When a patient had provided written consent for participation in the trial, manual randomization was carried out using sealed, sequentially numbered envelopes containing a letter assigning the patient to either the telemedical monitoring or the control group. Randomization was performed in blocks of 12 patients (6 to telemedical monitoring and 6 to control). The 12 letters of assignment were placed in separate envelopes, which were sealed and scattered twice in a random order and then assigned a serial number. The 12 envelopes were then grouped in one block (in one large envelope). Grouped letters of assignment were prepared and distributed to the participating clinics from the Department of Quality and Research/Health Technology Assessment

at Odense University Hospital. Staff at the outpatient clinic opened one envelope in sequential order at the time of patient inclusion.

Statistical Method

Continuous variables are expressed as mean ± SD and median and interquartile range, and categorical variables are presented as percentages. Data from participants who discontinued (chose not to participate or left the study area) during the study period or still had an unhealed ulcer after 1-year follow-up were censored. Patients lost to follow-up were censored on the date of last known follow-up. Data were analyzed through a competing-risks multistate model among death, amputation, and healing (27). Cumulative incidence functions for amputation and healing were calculated for the telemedical and control groups separately using the Aalen-Johansen estimator. Cause-specific Cox proportional hazards models were adjusted for age at entry, sex, and municipality as a cluster effect. Hazard ratios (HRs) and 95% CIs are based on these models. The HRs reported in this article compare the intervention to the control group.

The proportional hazards assumption was assessed and retained in the analysis. *P* < 0.05 was considered statistically significant. All analyses were carried out using the development environment R (28) and R packages survival (29) and etm (empirical transition matrix) (30).

RESULTS

Study Population

Of 736 individuals with diabetic foot ulcers identified in the 4-year screening period, 401 were randomized as eligible participants, and 374 were included in the final analysis (193 [52%] in the telemedical monitoring group and 181 [48%] in the control group) (Fig. 2). Median time in the study was 74 and 91 days in the telemedical monitoring and control groups, respectively. The mean number of teleconsultations was 3.0 (95% CI 2.55, 3.47) in the telemedical monitoring group. The baseline demographics showed equal distribution of selected variables in the two groups (Table 1).

Complete Healing

Of 374 participants, 271 (73%) experienced complete healing within the study period. Of these, 138 (72%) were from the telemedical monitoring group (*n* = 193) and 133 (73%) from the control

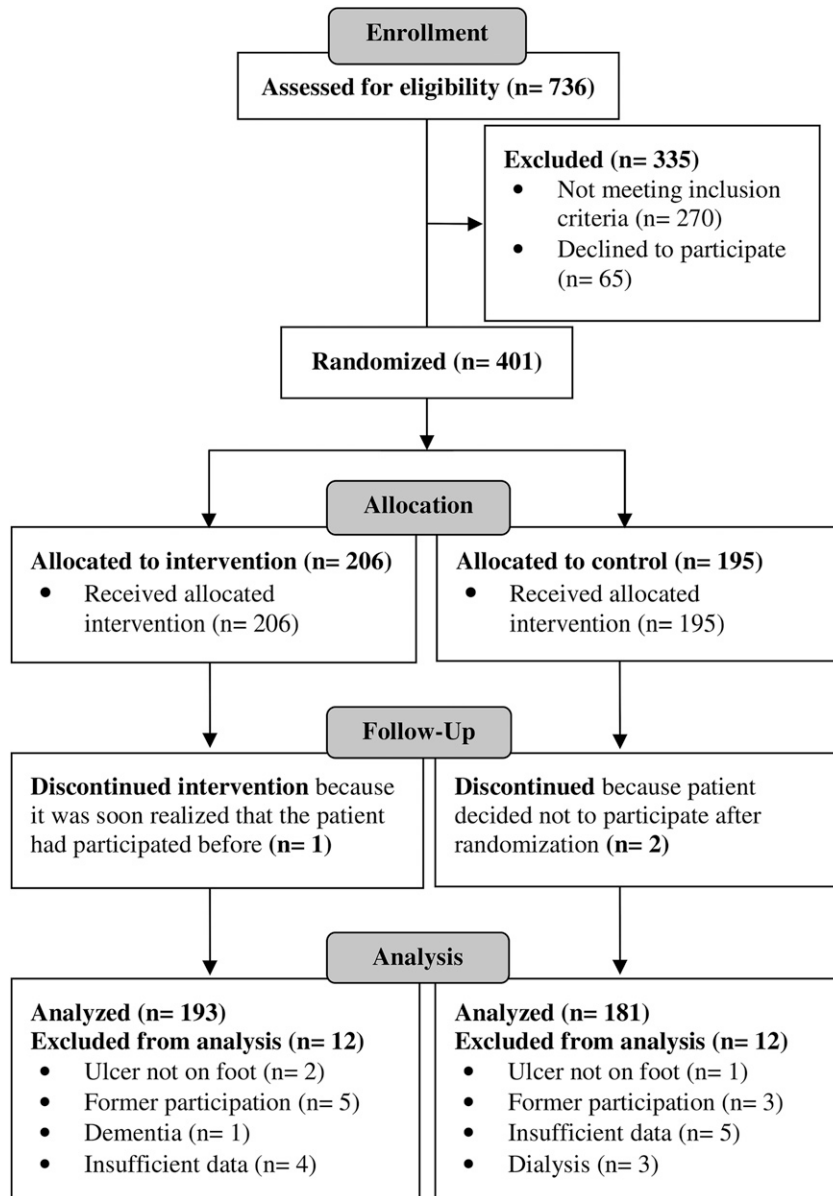


Figure 2—Patient flow in the randomized controlled study of telemedical monitoring (intervention) vs. standard outpatient monitoring (control).

group ($n = 181$). We found no difference between the two groups with respect to incidence of healing (Fig. 3, left panel). After adjustment for age, sex, and municipality, a cause-specific Cox proportional hazards model showed no difference in completed healings (HR 1.11 [95% CI 0.87, 1.42], $P = 0.42$).

Amputation

Of 374 participants, 47 (13%) underwent amputation. Of these, 21 (11%) were from the telemedical monitoring group ($n = 193$) and 26 (14%) from the control group ($n = 181$). We found no difference between the two groups with respect to incidence of amputation (Fig. 3, right

panel). After adjustment for age, sex, and municipality, a cause-specific Cox proportional hazards model showed no difference (HR 0.87 [95% CI 0.54, 1.42], $P = 0.59$). In the telemedical monitoring group, 12 amputations were major and 9 minor. In the control group, 15 amputations were major and 11 minor. No difference was found in numbers between the groups.

Mortality

Of 374 participants, 9 (2.4%) died. Of these, eight (4%) deaths occurred in the telemedical group ($n = 193$) and one (0.5%) in the control group ($n = 181$). After adjustment for age, sex, and municipality, a cause-specific Cox proportional hazards

model showed a significant difference between the two groups (HR 8.68 [95% CI 6.93, 10.88], $P = 0.0001$). This difference could not be explained by considering additional covariates, including smoking or comorbidity. Of the nine patients who died, two died at home, four in a regular hospital department, and three in the intensive care unit. All had chronic heart disease, four had chronic kidney disease, and one had prostatic cancer. The average age was 72 ± 8 years, and male:female ratio was 8:1. Six patients had sepsis, five pneumonia, and one gangrene.

CONCLUSIONS

In this randomized controlled clinical trial of telemedical monitoring versus standard outpatient monitoring of diabetic foot ulcers, we found no between-group differences in healing or amputation. However, significantly higher mortality was found among those monitored by telemedicine.

Few other studies have looked into the clinical effects of telemedical monitoring of diabetic foot ulcers. A non-randomized study by Wilbright et al. (20) showed no significant difference between the telemedical group and the control group in time to complete healing of diabetic ulcers. The present results also demonstrate no difference with respect to healing and amputation and thus suggest that telemedicine is at least as good as standard clinic visits. In addition, we found no difference regarding the level of amputations. These results indicate that the clinical information (i.e., general health, wound condition) gained through telemedical monitoring was sufficient. Of note, all patients were medically and surgically stratified before randomization to ensure the proper care for each patient during the trial despite monitoring method. Other studies have documented reduced time to healing with telemedicine (31,32) but typically included ulcers of mixed etiology and different approaches to telemedicine, thus making validating comparisons between studies difficult (13). These results seem promising for the further use of telemedicine in wound care.

Current knowledge on the effects of telemedicine has been established through low-powered studies (33), and clinical telemedical trials of ulcers have mainly focused on healing as the primary outcome without consideration of other clinical outcomes,

Table 1—Baseline characteristics of patients with diabetic ulcers randomized to either telemedical or standard outpatient monitoring

	Telemedical monitoring (n = 193)	Standard outpatient monitoring (n = 181)
Age at inclusion (years)	66.8 ± 13.0	66.7 ± 12.8
Men	151 (78)	129 (71)
BMI (kg/m ²)	28.9 ± 6.2	28.9 ± 6.0
Smokers	42 (26)	30 (20)
Nonsmokers	119 (74)	119 (80)
Type 1 diabetes	24 (15)	25 (16)
Type 2 diabetes	131 (85)	127 (84)
Years of diabetes at inclusion	14 (7–20)	14 (7–21)
Ulcer duration before inclusion*	1 (1–2)	1 (1–3)
Comorbidities		
Heart disease	64 (34)	59 (33)
Hypertension	135 (70)	133 (74)
Cerebrovascular disease	21 (11)	17 (9)
Chronic pulmonary disease	11 (6)	20 (11)
Connective tissue or rheumatic disease	10 (6)	9 (5)
Liver disease	1 (1)	3 (2)
Diabetes	193 (100)	181 (100)
Hemiplegia	1 (1)	3 (2)
Renal disease	17 (9)	11 (6)
Cancer	6 (3)	1 (1)
Other	36 (19)	42 (23)

Data are mean ± SD, n (%), or median (interquartile range). *For ulcer duration of less than 14 days, 0 months was chosen as duration.

such as amputation and mortality. Because diabetic foot ulcers are associated with a high risk of amputation and 85% of patients with amputation initially present with a diabetic foot ulcer (34,35), data on this and other risks associated with diabetic ulcers should be collected when evaluating new interventions.

The significant difference in mortality between the telemedical and standard outpatient monitoring groups could not be explained by the selected variables. Further investigation of comorbidities and other possible reasons has been undertaken. A possible explanation could relate to the physicians' clinical assessment through telemedicine depending on secondhand information from a nurse and an uploaded image of the ulcer; thus, some vital information could be missed. This would seem unlikely, however, given the insignificant differences in healing and amputation between the two groups. Furthermore, the municipal nurses were experienced in ulcer care. The findings contrast with those of the Whole System Demonstrator telemedical study that showed a lower mortality in the intervention group (odds ratio 0.54 [95% CI 0.39, 0.75]) (36). The authors of this study did not include individuals with diabetic foot

ulcers per se in the highly fragile group (comprising both high comorbidities and high mortality) (7), which might explain the differences. The rather low mortality reported in our study should

be seen in relation to the statistical method used.

Strengths and Limitations

One of the study limitations is that clinicians could deviate from the telemedical

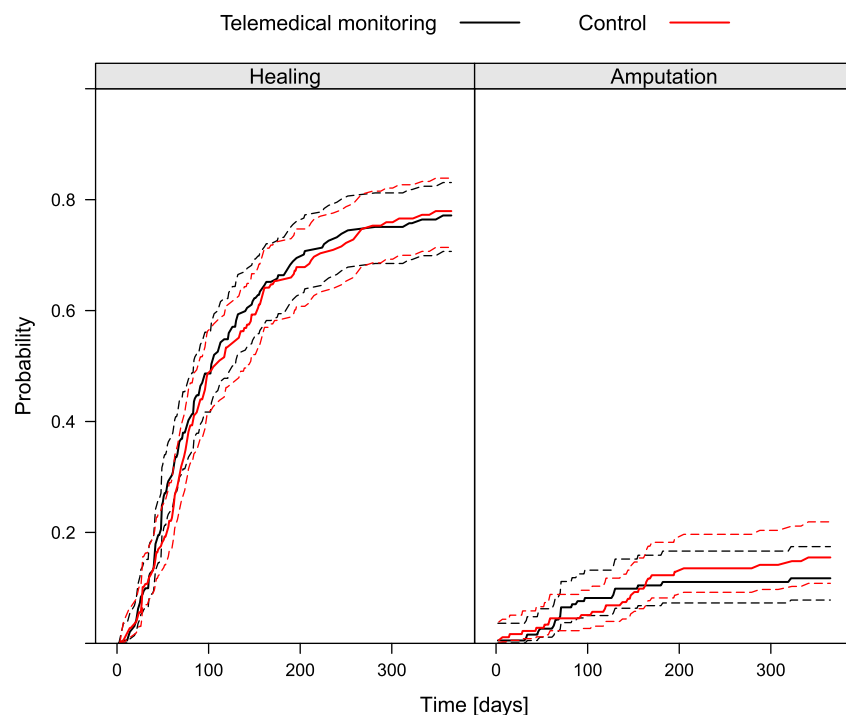


Figure 3—Cumulative probability of healing and amputation as a function of time. Dashed lines represent 95% CIs.

workflow if required by the clinical condition. This ethical and clinical choice was driven by the local clinicians to ensure the best care for the individual patient. Furthermore, the telemedical monitoring was provided by several outpatient clinics with small variations in clinical approach. These differences were anticipated because of the overall study design and pragmatic trial approach investigating telemedical monitoring of diabetic ulcers in a real-life setting. We did try, however, to minimize the differences by ensuring overall guidelines and the per-protocol algorithm. This approach may have affected the internal validity of the trial but ensured a high external validity (37).

We used manual randomization at an individual level to minimize selection bias (38) and found that the overall block randomization worked well. An intention-to-treat approach was applied in the data analysis, but several participants had to be excluded mainly due to former participation or insufficient data as shown in Fig. 2. Additionally, some patients allocated to the telemedical monitoring group did not receive monitoring according to the suggested algorithm. This was done with respect to ethical considerations. Steventon et al. (36) noted some of the same limitations in the Whole System Demonstrator study, one of the largest studies to date investigating a telemedical approach to health care.

The clinical data were retrieved from the electronic patient records and the online database used for the telemedical monitoring. This minimized double registration but may have affected the data quality as reflected in the number of missing answers in the baseline data. A full set of baseline data can be found in the Supplementary Data.

Evaluation of a complex intervention such as telemedical monitoring requires assessment of clinical, organizational, economical, and patient-related aspects (23,39). The MAST was used as a multidisciplinary approach to the evaluation of telemedical monitoring, and the clinical data reported here represent only one part of the assessment. Results on organizational, economical, and patient-related aspects will be published separately.

Clinical and Research Implications

Notwithstanding the limitations of this study, the findings suggest that patients with diabetic foot ulcers monitored with

telemedicine are at higher risk of death than patients attending standard outpatient visits. No obvious reason was found that could explain these results. On the basis of the promising results regarding healing and amputation, we recommend a cautious approach to the use of telemedicine in the monitoring of diabetic foot ulcers. Furthermore, a no-tolerance approach to noncompliant ulcers is recommended until more evidence is presented. The identification of particularly vulnerable patients is essential, and future studies should investigate the possible influence of ulcer size and severity.

To the best of our knowledge, this study is the largest clinical trial involving telemedical monitoring of diabetic foot ulcers. Furthermore, it is the first to evaluate telemedical monitoring of patients with diabetic foot ulcers in a randomized clinical controlled setting. The findings of no significant difference regarding amputation and healing seem promising; however, for telemedical monitoring, a higher mortality throws into question the role of telemedicine in monitoring diabetic foot ulcers. Further studies are needed to investigate the effects of telemedicine on mortality and other clinical outcomes and to identify patient subgroups that may have poorer outcome from telemedical monitoring.

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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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