

New Ulceration, New Major Amputation, and Survival Rates in Diabetic Subjects Hospitalized for Foot Ulceration From 1990 to 1993

A 6.5-year follow-up

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OBJECTIVE — To evaluate 1) the new ulceration, the new major amputation, and the survival rates of 115 diabetic subjects hospitalized for foot ulceration from 1990 to 1993, with an average follow-up of 6.5 years, and 2) the demographic and clinical characteristics associated with these events.

RESEARCH DESIGN AND METHODS — A total of 115 subjects, 31 women and 84 men, were monitored until 31 December 1998. All subjects were provided with therapeutic shoes and received intense education. Data concerning new ulceration, new major amputation, and reamputation events and the date and cause of death were recorded for each patient. The prognostic factors for these events were then evaluated.

RESULTS — The average follow-up was 78.3 ± 15.3 months (range 60–106). During this time, 13 homolateral and 12 contralateral episodes of new ulceration occurred. At univariate analysis, none of the variables considered were significantly associated with the new ulceration. There were three major amputations: two of the limb previously healed and one of the contralateral limb. Of the 115 subjects, 51 (44.3%) died: 24 of the 31 women (77.4%) and 27 of the 84 men (32.1%). Ischemic cardiopathy was the most frequent cause of death (60.8%). Mortality concerned 20 of the 27 subjects (74.1%) undergoing major amputation from 1990 to 1993 and 31 of the 88 healed subjects (35.2%), with a significant difference ($P < 0.0001$). Multivariate analysis showed the independent role of the ankle-brachial index ≤ 0.5 ($P = 0.005$), age ($P = 0.003$), and female sex ($P = 0.027$).

CONCLUSIONS — We believe that the use of therapeutic shoes and intense educational training, including the education of the family, have contributed to the low incidence of new ulceration and major amputation in our study population. The high frequency of ischemic cardiopathy as a cause of death should, perhaps, lead to a more aggressive diagnostic and therapeutic attitude toward this pathology in diabetic subjects admitted to hospitals for foot ulceration.

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Many epidemiological reports have published data regarding foot ulceration, amputation, and relative risk factors (1–5) in diabetic subjects, although data on new ulceration and new amputation in diabetic subjects with foot ulceration is scarce (6,7). There are reports on the survival of diabetic amputees (7–9), but there are few studies on the survival of diabetic subjects hospitalized for foot ulceration (10). The available data vary according to the selection criteria of the population being studied; such criteria may consist of ethnic group (11), age (12), level of amputation (13), or subjects undergoing only vascular procedures (14). The duration of observation varies. Silbert (15) and Whitehouse et al. (16) reported a long follow-up, but these studies are not recent. More recent studies only monitor patients for 2–4 years (9,10,13,17,18).

RESEARCH DESIGN AND METHODS

Between 1990 and 1993, 115 diabetic subjects were hospitalized for foot ulceration at our center (19); they were monitored after discharge until 31 December 1998. The reported data concerned the new ulceration, the new major amputation, and the survival rates of these subjects. We evaluated prognostic factors for these events.

Patient characteristics

The clinical characteristics investigated between 1990 and 1993 were reported in Table 1. During that period, 27 subjects (23.5%) underwent major amputation (above the ankle), and two of these subjects died in the hospital from septic shock. A total of 88 subjects (76.5%) were considered healed, 53 of whom recovered with and 35 without minor amputation. Of the 115 patients, 95 (82.6%) had sensorimotor diabetic neuropathy and 97 (84.3%) had peripheral vascular disease (ankle-brachial index [ABI] < 0.9 , transcutaneous oximetry on the dorsum of the foot ≤ 50 mmHg, and

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Abbreviations: ABI, ankle-brachial index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Clinical characteristics of the study population hospitalized from 1990 to 1993

n	115
Females	31 (27)
Males	84 (73)
Age (years)	63.4 ± 9.9
Female age (years)	67.2 ± 11.3
Male age (years)	62.0 ± 9.1
Diabetes duration (years)	17.06 ± 8.9
Insulin therapy	80 (60.9)
Oral therapy	45 (39.1)
Wagner wound grade	
II	13 (11.3)
III	32 (27.8)
IV	70 (60.9)
Prior wound	33 (28.7)
Prior major amputation	7 (2.5)
Sensorimotor neuropathy*	95 (82.6)
Vibration perception threshold (n = 92)†	78 (84.4)
Autonomic neuropathy (n = 79)‡	61 (77.2)
Background retinopathy§	47 (40.9)
Proliferative retinopathy§	29 (25.2)
Microalbuminuria	26 (22.6)
Proteinuria¶	22 (19.1)
Renal impairment#	23 (20)
Coronary artery disease	55 (47.8)
Prior stroke	13 (11.3)
Arterial hypertension**	59 (51.3)
Dyslipidemia††	28 (24.6)
Smoking habit	38 (35.5)
BMI >24 for women and >25 for men	36 (31.6)
Arterial calcifications (X-ray of the feet)	55 (48.6)
Claudication	26 (23)
ABI	
≥0.9‡‡	18 (15.7)
>0.5, <0.9	61 (53.0)
≤0.5	36 (31.3)
Transcutaneous oxygen tension	
>50 mmHg§§	18 (15.7)
>30, <50 mmHg	56 (48.7)
≤30 mmHg§§	41 (35.6)
Peripheral angiography	98 (85.2)
Minor amputation (below the knee)	53 (46.1)
Major amputation (above the knee)	27 (23.5)

Data are n (%) or means ± SD. *Electromyography, abnormalities of nerve conduction velocity, and sensory action potential in at least two nerves; †measured on the malleolus with biothesiometer; ‡score >4 at the standard five cardiovascular tests; §fundus oculi by ophthalmologist; ||albumin excretion rate >18, <200 mg/24 h; ¶albumin excretion rate >200 mg/24 h; #creatinine >133 mmol/l; **blood pressure >160/95 mmHg or antihypertensive therapy; ††total cholesterol >6.20 mmol/l and/or HDL cholesterol <0.90 mmol/l for men and <1.16 mmol/l for women and/or triglycerides >2.25 mmol/l or hypolipidemic therapy; ‡‡ABI-to-blood pressure ratio measured with Doppler cw technique; §§measured on the dorsum of the foot.

a peripheral angiography positive for occlusive disease). A total of 18 (15.7%) patients were considered purely neuropathic and 97 (84.3%) were ischemic or neuroischemic. Of these patients, 29 (29.9%) underwent vascular procedures (19 peripheral transluminal angioplasties and 10 bypass grafts).

Follow-up

All 115 subjects were monitored until 31 December 1998. The subjects from our region (57.4%) were examined approximately every 2 months, and patients not living near our center (42.6%) were examined once a year. Patients and families were

Table 2—Causes of death

n	Frequency
Cause of death	
Cardiac event	31 (60.8)
Stroke	9 (17.6)
Uremia	3 (5.9)
Cancer	4 (7.8)
Septic shock (hospitalization between 1990 and 1993)	2 (3.9)
Cachexia	1 (2.0)
Sclerosing cholangitis	1 (2.0)

Data are n (%).

instructed to visit the center if any sign of lesion appeared.

All of the subjects who had undergone a major amputation were given prostheses ~3 months after discharge. Approximately 1 month after discharge, all of the healed subjects were provided with extra-deep rocker shoes with soft thermoformable leather (Buratto, Crocetta del Montello, Italy) and customized insoles, shaped by a cast, in Alkaform (derived from Plastazote) and Alcapy (derived from Professional Protective Technology, Deer Park, NY). In addition, all patients, including amputees, received a therapeutic shoe for the unaffected foot. The insoles were modified or changed every 6 months, and the shoes were modified according to wear.

End points

New ulceration was defined as any ulceration at the same or different site of a previous ulcer or an ulcer in the contralateral foot. Major amputation refers to that performed above the ankle.

We examined 196 limbs: 2 limbs in 81 healed subjects, 1 limb in 7 subjects who had undergone a major amputation before 1990, and the remaining limbs of the 27 subjects who had undergone a major amputation during hospitalization from 1990 to 1993. All of the following were recorded: homolateral and contralateral new ulceration, major amputation of the limb healed during hospitalization, reamputation of the same limb in the subjects undergoing major amputation from 1990 to 1993, major amputation of the contralateral limb, and date and cause of death.

Table 1 shows the association between the incidence of events and the considered variables. However, because we did not consider HbA_{1c} and because procedural meth-

ods for and frequency of the determination of variables differed for subjects living far from the center, the data are not reliable.

Statistical analysis

From the time of hospital discharge (time 0), Kaplan-Meier survival curves were calculated for all causes of death, and the crude percentage of survivors was reported according to the modalities of discrete variables or classes of continuous variables observed at the cutoff points reported in the tables. All patients were exposed to risk of death for at least 5 years.

We used the log-rank test for comparing groups with respect to survival, and we performed a univariate analysis using Cox's regression model to identify the prognostic role of the considered variables. $P < 0.05$ was sufficient to statistically prove the association with patient survival time. We did the same analysis with a multivariate Cox's regression model and a stepwise selection of variables to identify the prognostic factors independently associated with new ulceration and survival time. The entry criterion was $P \leq 0.10$, and the permanence criterion was $P \leq 0.05$. For dichotomous variables, the constants estimate the mortality hazard ratios and the 95% CIs of the hazard ratios. For age, the hazard ratio and its CI refer to the unitary increment (1 year).

The proportional hazard assumptions were tested graphically for all of the variables with the plot of $-\log \{-\log [\text{survivors proportion } (t)]\}$ versus survival time (t). Elaboration was performed with STATA 5.0 (Stata, College Station, TX) survival analysis routines.

RESULTS—The mean follow-up was 78.3 ± 15.3 months (minimum 60 months and maximum 106 months).

New ulceration

According to the Wagner classification system, there were 25 (12.75%) episodes of new ulceration: 4 grade IV, 3 grade III, 4 grade II, and 14 grade I episodes. All 25 episodes, 13 homolateral and 12 contralateral in terms of the first ulceration, occurred in 23 of the 88 subjects who recovered in the period between 1990 and 1993. No ulceration occurred on the stumps of the amputees. A total of 12 patients were hospitalized, 13 were treated in the outpatients' department, 3 underwent amputation below the knee, 5 under-

went amputation of one or two toes, and 17 recovered without amputation. The average period of time the subjects were free from new ulceration was 32.7 ± 23.8 months. At univariate analysis, no variable in Table 1 was significantly associated with new ulceration.

Major amputation

No reamputation of the same limb was carried out in the 27 patients undergoing major amputation in the 1990–1993 period. In the 88 subjects healed without major amputation, three major amputations were performed: one of the contralateral limb and two of the same limb healed in the 1990–1993 period. The average period of time the subjects were free from amputation was 9.3 ± 3.2 months: 7.5 months for amputation of the same limb and 13 months for amputation of the con-

tralateral limb. Because of the small number of major amputation events, we decided that the possible association with the variables in Table 1 was not significant.

Survival

By 31 December 1998, 64 (55.7%) subjects were alive, and 51 (44.3%) had died (24 of 31 women [77.4%] and 27 of 84 men [32.1%]). Mortality concerned 20 of the 27 (74.1%) subjects who underwent major amputation in the 1990–1993 period and 31 of the 88 (35.2%) healed subjects with a highly significant difference (hazard ratio 3.020, 95% CI 1.71–5.33, $P < 0.0001$). Table 2 shows the causes of death. Figure 1 shows the cumulative survival curve and the survival curve by major amputation carried out during hospitalization from 1990 to 1993.

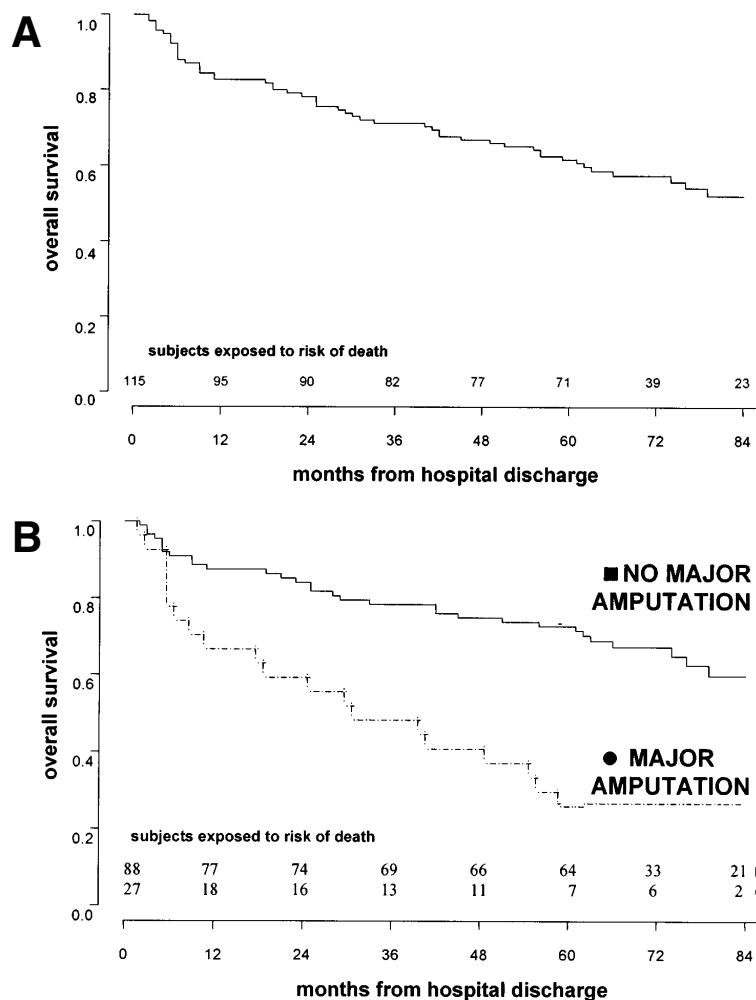


Figure 1—A: Kaplan-Meier overall survival estimates of diabetic subjects hospitalized for foot ulceration from 1990 to 1993. B: Kaplan-Meier survival estimates from 1990 to 1993 of subjects who underwent a major amputation and those who did not undergo major amputation.

Table 3—Univariate analysis of association between variables and death

Variable	P	Hazard ratio	95% CI
Age (by increase of 1 year)	0.000	1.063	1.031–1.096
ABI $\leq 0.5^*$	0.000	2.758	1.578–4.819
Major amputation (above the ankle)	0.000	3.020	1.711–5.33
Sex	0.004	0.433	0.244–0.766
Smoking habit	0.008	0.472	0.272–0.820
Renal impairment†	0.013	2.569	1.219–5.411
Coronary artery disease	0.026	1.892	1.077–3.324
Autonomic neuropathy‡	0.053	0.804	0.644–1.003
Transcutaneous oxygen tension ≤ 30 mmHg§	0.143	1.675	0.840–3.337
Microalbuminuria	0.188	1.684	0.775–3.660
Background retinopathy¶	0.194	0.570	0.244–1.333
Proteinuria#	0.199	1.679	0.762–3.703
Diabetes duration (years)	0.205	1.018	0.990–1.047
Wagner wound grade	0.228	1.307	0.845–2.019
BMI >24 for women and >25 for men	0.239	1.413	0.795–2.512
Dyslipidemia**	0.258	1.418	0.775–2.594
Arterial calcification (feet X-ray)	0.313	0.750	0.429–1.311
Minor amputation (below the knee)	0.333	1.616	0.612–4.270
Prior ulcer	0.515	0.811	0.432–1.523
Peripheral vascular procedures	0.589	0.979	0.906–1.057
Claudication	0.732	1.120	0.585–2.141
Vibration perception threshold >25 V††	0.743	1.077	0.689–1.685
Proliferative retinopathy‡‡	0.786	1.125	0.481–2.629
Prior major amputation	0.839	0.388	0.562–1.250
Arterial hypertension‡‡	0.911	1.032	0.595–1.787
Sensorimotor neuropathy§§	0.936	0.695	0.672–1.303
Prior stroke	0.972	1.015	0.433–2.381
Diabetes therapy (oral, insulin)	0.976	0.987	0.444–2.196

*ABI-to-blood pressure ratio measured with Doppler cw technique; †creatinine >133 mmol/l; ‡score >4 at the standard five cardiovascular tests; §measured on the dorsum of the foot; ||albumin excretion rate >18 , <200 mg/24 h; ¶fundus oculi by ophthalmologist; #albumin excretion rate >200 mg/24 h; **total cholesterol >6.20 mmol/l and/or HDL cholesterol <0.90 mmol/l for men and <1.16 mmol/l for women and/or triglycerides >2.25 mmol/l or hypolipidemic therapy; ††measured on the malleolus with biothesiometer; ‡‡blood pressure $>160/95$ mmHg or antihypertensive therapy; §§electromyography, abnormalities of nerve conduction velocity, and sensory action potential in at least two nerves.

The results of univariate analysis are shown in Table 3. The multivariate analysis of the variables that were found to be associated with death during univariate analysis confirmed the independent role of ABI ≤ 0.5 (hazard ratio 2.29, 95% CI 1.29–4.08, $P = 0.005$), age (hazard ratio by increase of 1 year 1.05, 95% CI 1.02–1.08, $P = 0.003$), and the female sex (hazard ratio 1.96, 95% CI 1.08–3.56, $P = 0.027$). In Fig. 2, the relative survival curves are illustrated. The association with major amputation carried out during hospitalization from 1990 to 1993 is alternative to ABI ≤ 0.5 .

CONCLUSIONS — Published data concerning new ulceration are scarce. One study (20) during the 1960s showed a 23% increase in rate of ulceration of the opposite extremity within a year in diabetic subjects

amputated for gangrene. Only 6% had an intact contralateral limb after 5 years. Recurrence rates for ulcers in neuropathic subjects were estimated at 32% (21), and the incidence of ulcers at the same or different sites in a foot with prior ulceration was estimated at 50% over a period of 2–5 years (22).

In two recent studies (23,24), the use of special shoes significantly decreased the incidence of new ulcerations. The population considered in these studies was, however, an outpatient population of neuropathic subjects, whereas our population mostly comprised neuroischemic subjects hospitalized for severe foot ulcer.

All of our subjects had therapeutic shoes and received education on foot care; their families also received education on foot care. Our patients also received slippers with a rigid sole and thermoformable

lining. The percent of new ulcerations in our population was very low, and the period of time the subjects were free from new ulceration was reasonably long.

The lack of significant association between new ulceration and the investigated variables surprised us. We believe that some variables that we did not record, such as social status, limited joint mobility, degree of patient compliance regarding the continual use of the orthosis, and educational learning (25–28), may play a role in episodes of new ulceration. We excluded alcoholism (29), because none of our patients consumed much alcohol. The lack of association with minor amputation seems particularly interesting; we believe that this indicates the effectiveness of orthosis, even in a deformed foot.

Available published data on ipsilateral and contralateral amputation is discouraging. Reiber (7,30) reported that 13% of amputees in California and 9% in New Jersey would undergo reamputation within a year of initial amputation, and he estimated that 30–50% of the amputees would undergo contralateral limb amputation within 1–3 years of initial amputation. In the 1980s, two studies (8,9) reported an incidence rate of contralateral amputation of 44.3% and ipsilateral amputation of 23.1% after a 4-year follow-up and an incidence rate of contralateral amputation of 26.4% after a 5-year follow-up.

Considering these data, we believe that the number of new ulcerations and new major amputations in our follow-up was very low. We reached this goal by providing instructions and education regarding orthosis to our patients (31) and their families. It seems that the use of therapeutic shoes is recommended (32), but, to date, they are not used much among diabetic patients (33,34). It should be emphasized that there is no difference in new ulceration between patients monitored directly at our center and patients monitored infrequently at distant locations. Therefore, undergoing an intense informational program on admission to a hospital for ulceration and the fitting of therapeutic shoes may reduce the number of new ulcerations, an independent risk factor for amputation (35). Thus, we feel that the American Diabetes Association (36) should provide more specific information on and a more assertive recommendation for the use of therapeutic shoes for subjects with previous diabetic foot ulceration.

Because of the small number of new major amputations, we did not feel that it

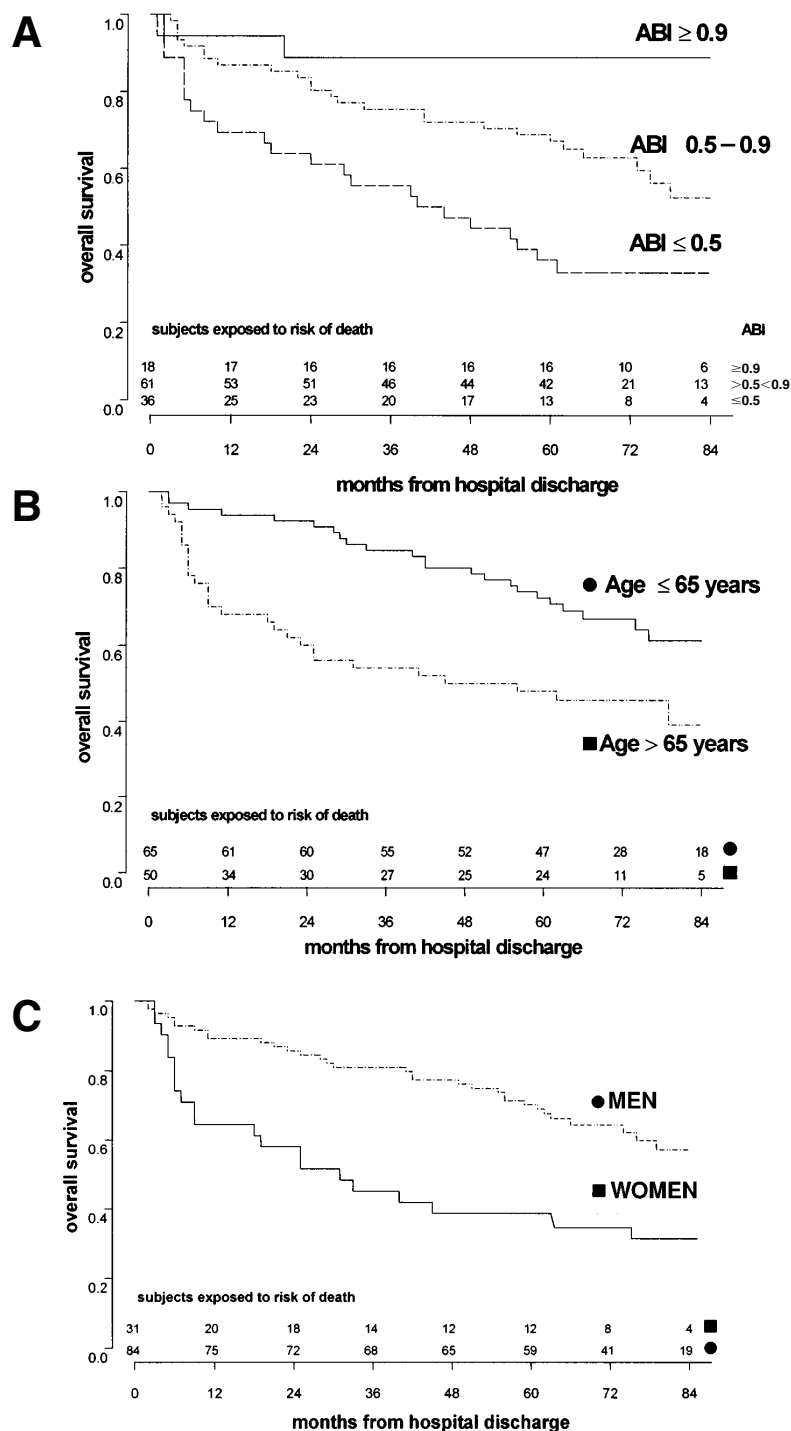


Figure 2—Kaplan-Meier survival estimates of diabetic subjects hospitalized for foot ulceration from 1990 to 1993 characterized by ABI (A), age (B), and sex (C).

was necessary to evaluate an eventual association with the variables in question. However, we must specify that all three patients amputated in the follow-up had an ABI < 0.5 and could not be revascularized.

Our data lead us to conclude that the current epidemiological data on new ulcer-

ation, new major amputation, and reamputation in diabetic subjects who have undergone major amputation or who have recovered from a severe foot ulcer are much more accurate than those previously reported. In these subjects, major amputation only occurred in those with severe

occlusive disease, when revascularization was impossible.

The rate of survival in our amputees was similar to that found in other published studies. Reiber (30) reported a 39–68% mortality rate over a 5-year period. In the study by Deerochanawong et al. (17), the mortality rate was similar to ours, but the follow-up period was shorter. In addition, Frykberg et al. (12) reported a higher mortality rate, but their subjects were much older. The data reported by Roseblum et al. (14) presented a better outcome than previously reported data, but Roseblum et al. chose a population who had undergone vascular procedures under general anesthetic, presumably with a low recurrence of ischemic cardiopathy. Survival rates of our nonamputated subjects present a worse outcome than those reported in a recent study by Ramsey et al. (10), who analyzed the survival of diabetic patients after ulcerative episodes, but during a very short observation period. Furthermore, the presence of ischemic cardiopathy in the Ramsey population (7%) was much lower than that in our study (47%), in which it was the most frequent cause of death.

In addition, the protective value of smoking in our population was particularly surprising. These results were contingent on the fact that the women, who were older and had a higher mortality rate, were nonsmokers. However, when sex and age were not considered, smoking lost its significant association.

In conclusion, ischemic cardiopathy is the most frequent cause of death among diabetic subjects with foot ulceration. These data are well documented in nondiabetic and diabetic subjects with peripheral vascular disease (37,38), but little is known about diabetic subjects with foot ulceration who present with ischemic cardiopathy. Therefore, we modified our protocol to adopt a more aggressive diagnostic and therapeutic approach of ischemic cardiopathy in diabetic subjects who were admitted to our hospital for foot ulceration.

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