

Long-Term Prognosis of Diabetic Patients With Critical Limb Ischemia

A population-based cohort study

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OBJECTIVE — To evaluate the long-term prognosis of critical limb ischemia (CLI) in diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 564 consecutive diabetic patients were hospitalized for CLI from January 1999 to December 2003; 554 were followed until December 2007.

RESULTS — The mean follow-up was 5.93 ± 1.28 years. Peripheral angioplasty (PTA) was performed in 420 (74.5%) and bypass graft (BPG) in 117 (20.6%) patients. Neither PTA nor BPG were possible in 27 (4.9%) patients. Major amputations were performed in 74 (13.4%) patients: 34 (8.2%) in PTA, 24 (21.1%) in BPG, and 16 (59.2%) in a group that received no revascularization. Restenosis occurred in 94 patients, bypass failures in 36 patients, and recurrent ulcers in 71 patients. CLI was observed in the contralateral limb of 225 (39.9%) patients; of these, 15 (6.7%) required major amputations (rate in contralateral compared with initial limb, $P = 0.007$). At total of 276 (49.82%) patients died. The Cox model showed significant hazard ratios (HRs) for mortality with age (1.05 for 1 year [95% CI 1.03–1.07]), unfeasible revascularization (3.06 [1.40–6.70]), dialysis (3.00 [1.63–5.53]), cardiac disease history (1.37 [1.05–1.79]), and impaired ejection fraction (1.08 for 1% point [1.05–1.09]).

CONCLUSIONS — Diabetic patients with CLI have high risks of amputation and death. In a dedicated diabetic foot center, the major amputation, ulcer recurrence, and major contralateral limb amputation rates were low. Coronary artery disease (CAD) is the leading cause of death, and in patients with CAD history the impaired ejection fraction is the major independent prognostic factor.

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A variety of consensus statements and reviews (1–3) have assessed the outcomes of diabetic patients with peripheral arterial disease (PAD). However, we are not aware of any prospective studies performed in a diabetic population with critical limb ischemia (CLI). The aim of this prospective study was to evaluate in diabetic patients the prognostic impact of CLI diagnosed accord-

ing to the criteria proposed in 2000 by the Transatlantic Inter-Society Consensus (TASC) (4).

RESEARCH DESIGN AND METHODS

Between 1 January 1999 and 31 December 2003, 564 diabetic patients were hospitalized in our diabetic foot center because of CLI. During the hospital stay, patients and their fami-

lies were trained to manage both an ulcerated and a nonulcerated foot. The importance of prompt immediate referral to our center, irrespective of scheduled visits, was pointed out in cases of insurmountable of ischemic rest pain or ulcerations, even of minimal appearance. All patients who underwent peripheral revascularization were prescribed either 250 mg/day ticlopidine plus 100 mg/day salicylic acid or 500 mg/day ticlopidine.

CLI diagnosis

All diabetic patients referred to our diabetic foot center for ischemic rest pain and/or foot ulcer or gangrene were assessed for the presence of sensory motor neuropathy, infection, and CLI. Sensory motor neuropathy was diagnosed in patients with a biothesiometer vibration perception threshold >25 V, insensitivity to touching with a Semmes-Weinstein 10-g filament in >5 of 9 foot points, and absence of the Achilles tendon reflex. In patients with foot ulcers, the presence of an infection was indicated by local cellulitis, erythema, or purulence with a positive swab culture. CLI was diagnosed in patients with <70 mmHg ankle pressure, when assessable, and <50 mmHg transcutaneous oxygen tension ($TcPO_2$) at the dorsum of the foot.

Vascular procedures

All patients with CLI were referred to an angiographic study. Patients with vessel diameter obstruction $>50\%$ underwent peripheral angioplasty (PTA) during the angiographic study, when possible, as a first-choice revascularization procedure (PTA group) (5). PTA was utilized extensively: no stenosis or occlusion was considered a priori unsuitable for a PTA recanalization. Stenoses or occlusions >10 cm in length and consecutive multiple stenoses (types C and D of the TASC morphological stratification of obstructions) were treated with PTA when possible; PTA was not feasible when calcified vessel occlusions did not permit passage of a balloon catheter. Vessel recanalization was considered successful when direct flow was achieved in at least one

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artery down to the foot and that had no significant residual stenoses along the entire artery.

When PTA was not feasible, a bypass graft (BPG) was considered (BPG group). BPG was performed using an intraluminal clamping and microsurgical technique. The autogenous saphenous vein was used for grafting when present and in good condition. When it was not available, alloplastic prosthetic material (polytetrafluoroethylene [PTFE]) was utilized and the peripheral anastomosis consisted of a venous cuff. Thus, the absence of an available saphenous vein and an angiographic score run off >7 on the Rutherford scale (6) did not exclude patients from a revascularization with a distal bypass; otherwise, the only recourse for those patients would have been a major amputation. When neither PTA nor BPG were possible, patients received prostanoid therapy (60–120 $\mu\text{g/day}$ alprostadil- α -ciclodextrine) over a period of 5 days after the angiography.

Hemodynamic improvement

TcPO₂ values were reassessed 5–10 days after the PTA, BPG, or prostanoid infusion.

End points

The following end points were recorded: above-the-ankle amputation, ulcer recurrence, clinical restenosis after PTA, BPG failure, CLI, major amputation in the contralateral limb, and survival.

Amputation

Limb salvage was considered successful when the plantar stance was maintained, even when achieved by tarsal-metatarsal amputation (7). Conversely, any above-the-ankle amputation was considered a major amputation, and it was deemed a failure. It was performed when therapies did not relieve patients from resting pain or when gangrene had extended beyond the Chopart joint.

Restenosis after PTA

Restenosis was suspected when ischemic rest pain reappeared or an ulcer worsened or did not heal. In these situations, ankle pressure and TcPO₂ were reassessed and duplex scanning was performed (8). If ankle pressure and TcPO₂ again showed values diagnostic for CLI and had significantly deteriorated ($<15\%$ of the post-PTA value) and Duplex scanning was positive, a further PTA was performed. When a PTA was not possible, a BPG was

considered. Morphological restenoses were not investigated; we did not perform revascularizations in the absence of ischemic resting pain or ulcerations; therefore, we considered morphological restenoses clinically irrelevant (9).

BPG failure

Vascular surgeons assessed graft patency by ultrasonography at 30 days; 3, 6, and 12 months; and every 6 months thereafter (10).

Ulcer recurrence

The reappearance of a foot lesion after the primary ulcer had healed was considered an ulcer recurrence.

Vital status and cause of death

The vital status of all 554 patients was determined at the end of follow-up. Dates and causes of deaths were recorded. All patients in our study population had been referred to our diabetic foot center from other diabetes centers. After admission due to CLI, they were moved to the originating diabetes center for diabetologic and comorbid condition treatments.

Database

The database records included age, sex, diabetes treatment and duration, glycemia (finger-stick glucose) at entry and discharge, A1C (with high-pressure liquid chromatography; normal value 4–6.4%), albumin excretion (mg/24 h; nephelometry; Behring, Scopito, Italy), serum creatinine value (mg/dl, Jaffe; Roche, Milan, Italy), arterial hypertension (antihypertensive treatment), history of cardiac disease, ejection fraction (evaluated with transthoracic echocardiography in patients with a history of cardiac disease), history of stroke, and history of prior major amputation.

Statistical methods

Data were given as average values and SDs for continuous variables or as percentages for discrete variables. We explored the role of continuous variables across the treatment groups with the Student's *t* test and ANOVA. The presence of prognostic factors was assessed with the χ^2 test with Yate's correction. The 95% CI was adopted, and 5% was considered significant for the null hypothesis. The proportion of surviving patients was plotted with a Kaplan-Meier curve, and differences in survival among subgroups were tested by the log-rank test. Cox's proportional hazards model was used to select significant

prognostic factors. Proportionality among the survival rates and attributable factors in the Cox model was assessed by plotting the $\log(-\log[\text{survival function}])$ versus time in each subgroup. The significant role of covariates was measured with the likelihood ratio test, and the role of each covariate entering the model was assessed by the Wald statistic. Statistical analyses were performed with STATA 9.0 for Windows. Analysis of survival was carried out on an intention-to-treat basis.

RESULTS

Of the initial 564 patients, 554 (98.2%) were followed until 31 December 2007 for a mean of 5.93 ± 1.28 years. Of the 554 followed patients, 413 (74.5%) underwent PTA and 114 (20.6%) underwent BPG in the initially affected limb. In the remaining 27 (4.9%) patients, neither PTA nor BPG could be performed (non-revascularized patients).

Demographics and clinical characteristics of the three groups are reported in Table 1. The ankle pressure could not be measured in 297 (53.6%) patients due to the occlusion of both tibial arteries in 105 and due to the presence of arterial calcifications in 192 patients (11). Toe pressure could not be measured in 89 patients due to a previous amputation or gangrene on the big toe. Thus, ankle and toe pressure parameters were not considered in the data analysis.

PTA was performed in 413 (74.5%) patients. In these patients, angiography revealed obstructions $>50\%$ of vessel diameter exclusively located in the iliac-femoral-popliteal axes in 28 patients (6.8%) and exclusively located in the infrapopliteal axis in 137 subjects (32.2%). Obstructions were found in both the iliac-femoral-popliteal and infrapopliteal axes in 248 patients (60.0%). The mean TcPO₂ values were 15.3 ± 11.9 mmHg before and 44.9 ± 12.1 mmHg after PTA ($P < 0.001$). A BPG was performed in 114 (20.6%) patients. The Rutherford grading for runoff was 6.4 ± 2.6 . The BPG was axillo-femoral in one patient, femoral-popliteal (15 PTFE, 44 vein graft) in 58 patients, and femoral-infrapopliteal (16 PTFE, 39 vein graft) in 55 patients. The mean TcPO₂ values were 10.2 ± 10.3 mmHg before and 38.8 ± 11.9 mmHg after BPG ($P < 0.001$).

Neither a PTA nor a BPG was possible in 27 (4.8%) patients due to high surgery risk (7 patients) or lack of outflow (20 patients). These patients received prostanoids treatment for 5 days during the hos-

Table 1—Demographic and clinical characteristics of study population (n = 554) at the study entry in nonrevascularized and revascularized patients with PTA or BPG

Variables	PTA group	BPG group	P	Revascularization group	No revascularization group	P
n	413	114		527	27	
Age (years)	69.7 ± 9.5	69.9 ± 9.4	0.910	69.8 ± 9.5	76.7 ± 10.4	0.001
Females	146 (35.4)	35 (30.7)	0.737	181 (34.3)	13 (48.1)	0.152
Insulin therapy	254 (61.5)	73 (64.0)	0.664	327 (62.2)	14 (51.9)	0.314
Diabetes duration (years)	17.7 ± 11.4	14.9 ± 9.9	0.020	17.1 ± 11.1	13.4 ± 10.0	0.013
Glycemia (at entry) (mg/dl)	177.9 ± 72.9	187.6 ± 9.7	0.187	180.7 ± 71.8	177.7 ± 52.3	0.147
Glycemia (at discharge) (mg/dl)	139.6 ± 47.3	134.2 ± 43.7	0.082	138.1 ± 45.5	138.2 ± 63.1	1.126
A1C (%)	7.6 ± 1.7	7.8 ± 1.5	0.625	7.7 ± 1.6	7.5 ± 1.1	0.579
Sensory motor neuropathy	340 (82.3)	92 (80.7)	0.681	441 (82.1)	24 (88.9)	0.599
Albumin excretion (mg/l) (n = 522)	259.8 ± 529.7	283.9 ± 721.3	0.832	264 ± 559.9	251.6 ± 363.6	0.932
Creatinine (mg/dl) (n = 522)	1.29 ± 0.5	1.25 ± 0.4	0.470	1.28 ± 0.5	1.15 ± 0.36	0.208
Dialysis	24 (5.7)	8 (7.0)	0.650	32 (6.0)	—	—
Antihypertensive therapy	298 (72.2)	72 (63.2)	0.065	370 (70.2)	20 (74.1)	0.830
History of cardiac disease	225 (54.8)	64 (59.0)	0.566	289 (53.8)	24 (88.9)	0.003
Ejection fraction (n = 313)	49.1 ± 10.8	49.6 ± 10.1	0.700	49.2 ± 10.5	38.34 ± 8.4	0.001
History of stroke	53 (18.8)	18 (15.8)	0.439	71 (13.8)	9 (33.3)	0.009
Smokers	61 (14.8)	19 (16.7)	—	—	—	—
Total cholesterol (mg/dl)	181.2 ± 43.6	188.0 ± 42.6	0.943	183.0 ± 43.1	186.7 ± 41.8	0.992
HDL cholesterol (mg/dl)	42.1 ± 13.6	43.7 ± 11.2	0.978	42.6 ± 13.1	48.6 ± 19.8	0.070
Triglycerides (mg/dl)	143.6 ± 87.6	137.6 ± 61.9	0.838	142.7 ± 81.1	149.4 ± 175.1	0.762
Wagner grade 0	62 (16.0)	16 (14.0)	0.882	78 (14.8)	3 (11.0)	0.783
Wagner grade 1	63 (15.3)	14 (12.3)	0.549	77 (14.6)	5 (18.5)	0.578
Wagner grade 2	59 (14.3)	14 (12.3)	0.648	73 (13.9)	5 (18.5)	0.567
Wagner grade 3	41 (9.9)	11 (9.6)	1.000	52 (9.9)	3 (11.1)	0.743
Wagner grade 4	188 (45.6)	59 (51.8)	0.245	247 (46.9)	11 (40.7)	0.560
Infected ulcer	268 (64.9)	72 (63.2)	0.741	340 (64.5)	17 (63.0)	0.892
Ischemic rest pain	309 (74.8)	92 (80.7)	0.216	401 (76.1)	25 (92.6)	0.059

Data are means ± SD or n (%).

pital stay after angiography. The average TcPO₂ values were 7.0 ± 8.1 mmHg before and 11.4 ± 8.6 mmHg after prostanoïd treatment (P = 0.055). After revascularization, no significant difference was observed in the TcPO₂ values for the PTA and BPG groups (P = 0.690). In contrast, a significant difference was observed between revascularized and nonrevascularized patients (P < 0.001).

Minor amputation

A total of 440 revascularized patients with foot ulcers showed complete healing of the lesions: 93 patients did not receive any minor amputations (35 patients by means of foot dressings, 12 bone removals, 16 ulcerectomies, and 30 skin grafts). A total of 93 patients had toe or ray amputations, and 254 patients had tarsal-metatarsal amputations. Of 13 nonrevascularized patients who did not receive major amputations, 10 had foot ulcers. Two showed complete healing with a dressing, and eight patients did not

show healing or worsening. All 13 of the nonrevascularized patients experienced reduced pain that did not disappear, and analgesic medication was reduced but not discontinued.

Major amputation

A total of 74 (13.4%) patients received major amputations, 23 in the early period and 51 during follow-up (total incidence per year: 3.72%).

After PTA, six major amputations were required within 30 days and 28 were performed during follow-up, with an incidence per year of 2.3%. After BPG, three major amputations were required within 30 days and 21 were performed during follow-up, with an incidence per year of 5.4%. For patients who received no revascularization, 14 major amputations were required within 30 days and two during follow-up, with an incidence per year of 34.3%.

At 30 days, there was no significant difference in the major amputation rates

of PTA and BPG groups (P = 0.414), but during the follow-up, there was a significant difference (P < 0.001). There were highly significant differences in the major amputation rates of the two groups (revascularized and not revascularized), both in the early period (χ² = 162.6054, P < 0.001) and during follow-up (χ² = 64.3614, P < 0.001).

Multivariate analysis of the variables that were found to be associated in the univariate analysis confirmed the independent roles of no revascularization (odds ratio 35.9 [95% CI 12.9–99.7], P < 0.001), occlusion of each of the crural arteries (8.20 [1.35–49.6], P = 0.022), dialysis (4.7 [1.9–11.7], P = 0.001), and wound infection (2.1 [1.3–3.6], P = 0.004). The analysis shows that a high TcPO₂ value after the treatment has a protective effect (0.8 [0.74–0.87], P < 0.001).

PTA restenosis

After the PTA, a total of 127 clinical restenoses occurred in 94 patients (incidence

per year: 6.4%). The restenosis diagnosis was made in 100 case subjects based on the lack of wound healing, with or without pain, and in 27 case subjects based on the reappearance of resting pain without a foot lesion. The resulting ischemic limb was further revascularized in 81 patients; 72 patients underwent a further PTA and 9 patients underwent a BPG. These procedures were not practicable in the remaining 13 patients; thus, a major amputation was required. After the further PTA, 29 patients required further surgical intervention due to diastasis of the surgical wound.

BPG failure

A total of 36 BPG failures were observed (incidence per year: 8.8%). Fifteen of these received a PTA or further BPG. Twenty-one patients who could not sustain further revascularization either by PTA or BPG required major amputations. In all 21 patients, the major amputation was performed due to the reappearance of ischemic rest pain with or without ulcers. After recanalization of the graft, two patients also required a further surgical intervention due to diastasis of the surgical wound.

Ulcer recurrence

A total of 71 patients were readmitted to our hospital due to ulcer recurrence without evidence of CLI (incidence per year: 4.3%). The Wagner grades of these ulcers were 1 for 57 patients, 2 for 11 patients, and 4 for 3 patients. All the lesions healed without the need for a major amputation; 7 patients required toe amputations and 64 patients required no minor amputations. No ulcer recurrences were observed in patients who had PTA restenoses or BPG failures during follow-up.

CLI incidence and amputation in the contralateral limb

CLI in the contralateral limb was observed in 225 (40.6%) patients (incidence per year: 14.76%). A major contralateral limb amputation was performed in 15 (6.7%) patients. The amputation rate was significantly lower in the contralateral limb compared with that in the limb that had the initial CLI ($\chi^2 = 7.3$, $P = 0.007$).

Survival

A total of 276 (49.8%) patients died, 4 at 30 days and 272 during follow-up, with an incidence per year of 12.53%. Table 2 reports the causes of death.

Table 2—Causes of death in the followed population (n = 554)

Cause of death	n
Cardiac disease	179 (64.9)
Stroke	35 (12.7)
Cancer	28 (10.1)
Pulmonary embolism	4 (1.4)
Aneurysm	2 (0.7)
Renal insufficiency	6 (2.2)
Gastroenteric disease	4 (1.4)
Cirrhosis	5 (1.8)
Pneumonia	4 (1.4)
Geromarmasmus	7 (2.5)
Septic shock	1 (0.4)
Suicide	1 (0.4)

Data are n (%).

The annual death incidence was not different between patients who received PTA ($n = 202$; 48.9%) and those who received BPG ($n = 51$, 44.7%; $\chi^2 0.74$, $P = 0.391$). The annual death incidence in patients who received peripheral revascularization (11.9%) was different from that in patients who did not receive revascularization (52.9%; $\chi^2 53.6$, $P < 0.001$). Figure 1 shows the Kaplan-Meier major amputation and survival estimates for patients who received PTA, BPG, or no revascularization. Cardiac disease was the leading cause of death, with an annual incidence rate of 8.1%. Cardiac disease was due to acute myocardial infarction in 89 (49.7%), pump failure in 72 (40.0%), and sudden death in 18 (10.1%) patients.

Multivariate analysis of the variables that were found to be associated in the univariate analysis confirmed the independent roles of age (hazard ratio 1.05 for 1 year, $P < 0.001$, 95% CI 1.03–1.07), unfeasible peripheral revascularization (3.06, $P < 0.005$, 1.40–6.70), dialysis (3.00, $P < 0.001$, 1.63–5.53), and history of cardiac disease (1.37, 1.05–1.79). In patients with history of cardiac disease, impaired ejection fraction was independently associated with death (1.08 for 1% point, $P < 0.001$, 1.05–1.09).

CONCLUSIONS— PAD is an underrecognized complication of diabetes (12). CLI is an even more underrecognized complication (13,14). For diabetic patients, the onset of CLI is a dramatic event; the risk of major amputation and death is considerable. The proper management of CLI could improve the amputation outcome. Compared with the data reported

in the literature, our series of revascularized patients required decidedly fewer major amputations in both the early and follow-up periods (15). This is most likely due to the ability of our diabetic foot center to perform both endoluminal and surgical revascularization techniques, thus providing >95% of the patients with vessel revascularization. The rate of amputation was consistently lower in patients that received revascularization compared with patients that could not undergo revascularization (16). Moreover, the amputation rate would certainly have been higher if the latter group of patients had not had such a high mortality rate. Nevertheless, the center's optimal capacity for revascularization is not enough to reduce the rate of major amputations. An excellent diagnostic ability and an adequate ulcer management program postrevascularization are also required (17).

Recent reports in the literature, and in particular the recent Cochrane review, have reported that surgical and endoluminal revascularizations had similar outcomes in terms of mortality and major amputation rates (18,19). We also observed similar amputation rates for the two procedures in the early period, but during the follow-up, the BPG group had a higher amputation rate than the PTA group. The difference appeared in the Kaplan-Meier curves at the late follow-up. The only significantly different parameter between the two groups at admission was the TcPO₂. However, in our protocol, the BPG was performed only when PTA was impossible; this may have selected patients with more severe arteriopathy. Nevertheless, the most important message that emerged from this study regarding the treatment of diabetic patients with CLI was the enormous difference in the amputation rate between patients that received and those that did not receive revascularization; this difference was evident in both the early and the late follow-up periods. This showed that a successful revascularization was more important than the type of revascularization used.

Readmission to the hospital occurred frequently due to late failure of revascularization (because of restenosis after PTA or because of failure of BPG). We found that antiplatelet therapy played an important role in both PTA restenosis and BPG failure (i.e., we frequently found that patients had been prescribed insufficient doses of ticlopidine). However, many patients, particularly those who developed

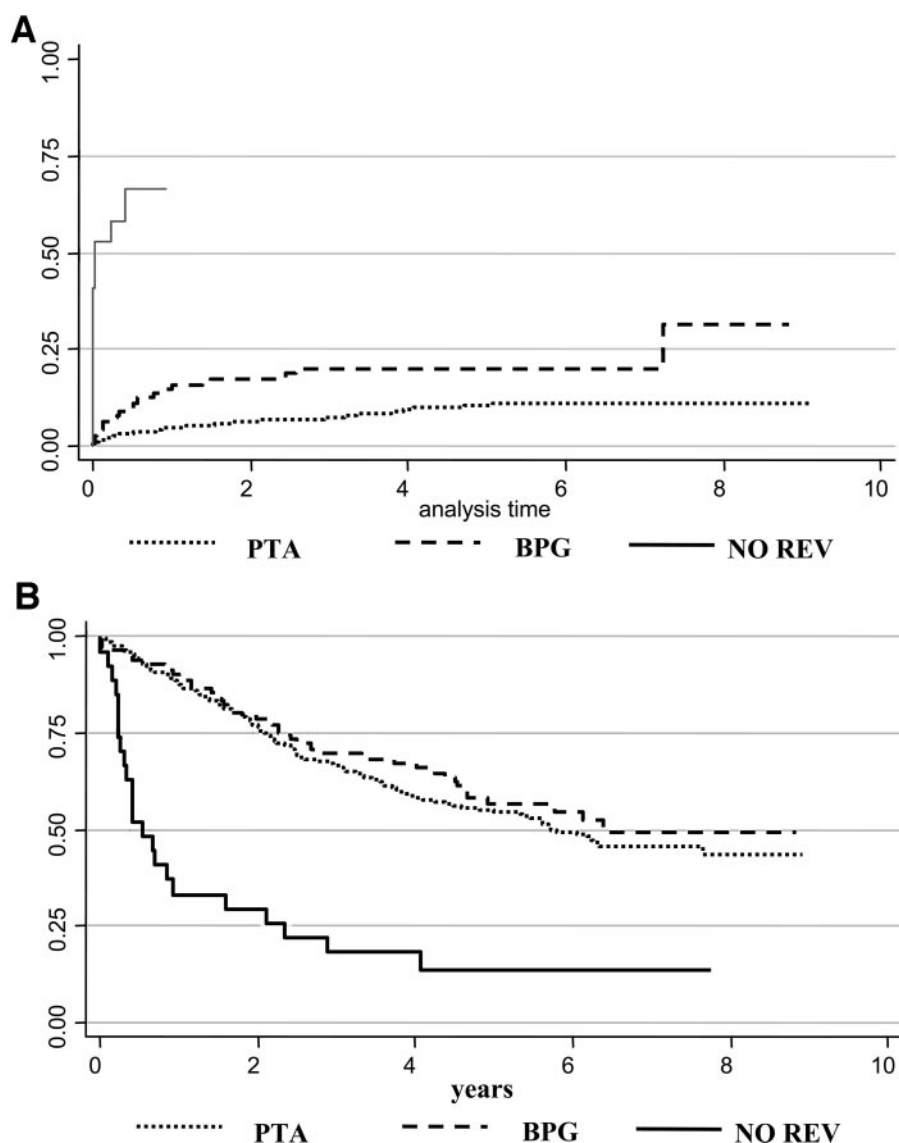


Figure 1—Kaplan-Meier major amputation (A) and survival (B) estimates in nonrevascularized (NO REV) or revascularized with PTA or BPG patients.

restenosis after PTA, received a further revascularization that enabled them to avoid amputation. These events contributed to the high number of hospitalizations required to minimize the rate of major amputation. Our data fully agree with other authors who also found that this population required multiple procedures and admissions (20).

Incidence of ulcer recurrence was low (~13% over 6 years) in this study compared with that reported in the literature (estimated at 50% over 2–5 years) (21). We believe that this low recurrence was achieved due to the instructions given to the patients, the relationships established between the caregivers and the patient, and the protection of therapeutic shoes (22).

Almost half of our study population developed CLI in the contralateral limb over an ~6-year period. Data from the literature are rather scarce regarding the fate of the contralateral limb in a diabetic population with prior CLI in one limb. A few studies published in the early 2000s reported surveys on the fate of contralateral limbs in patients selected for major amputations of the initially affected limb, patients with mixed ulcers, or patients with either neuropathy or ischemia (23). Apart from the epidemiological value of our data on the incidence of CLI, our finding that there was significantly lower frequency of above-the-ankle amputations in contralateral limbs compared with that of initially affected limbs is predicted to have a high impact on the management of

CLI in diabetic patients. This result shows that early recognition of the pathology and prompt referral of patients to the diabetic foot center allowed commencement of treatment under conditions more favorable for combating CLI. Thus, the prognosis for the contralateral limb was more promising than that for the initially affected limb.

It is well-known that death associated with cardiac disease occurs considerably more frequently than amputation in diabetic and nondiabetic patients affected by PAD. It also is well known that life expectancy is negatively correlated to the severity of the arteriopathy (24). Thus, considering the late onset of CLI, it is not surprising that age had an independent prognostic value on life expectancy in this study (25). It may have been possible to increase the survival rate in these patients if, during the hospitalization for CLI, we had considered improving existing coronary artery disease (CAD) treatment or evaluating the possibility of silent ischemia in patients without a history of cardiac disease. In the future, ad hoc studies will be necessary to investigate this question.

Data of this series suggest that aggressive treatment of CLI in diabetic patients, as practiced in our diabetic foot center, made it possible to achieve a low rate of major amputation in the initially affected limb and an even lower rate in the contralateral limb. CAD was the main cause of death, and in patients with history of CAD, the impaired ejection fraction was the major independent prognostic factor.

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