Long-Term Outcomes of Diabetic Patients With Critical Limb Ischemia Followed in a Tertiary Referral Diabetic Foot Clinic

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OBJECTIVE — We describe the long-term outcomes of 510 diabetic patients with critical limb ischemia (CLI) and an active foot ulcer or gangrene, seen at the University Hospital of Rome Tor Vergata, a tertiary care clinic.

RESEARCH DESIGN AND METHODS — These patients were seen between November 2002 and November 2007 (mean follow-up 20 ± 13 months [range 1–66 months]). The Texas Wound Classification was used to grade these wounds that were either class C (ischemia) and D (ischemia+infection) and grade 2–3 (deep–very deep). This comprehensive treatment protocol includes rapid and extensive initial debridement, aggressive use of peripheral percutaneous angioplasty, empirical intravenous antibiotic therapy, and strict follow-up.

RESULTS — The protocol was totally applied (with percutaneous angioplasty [PA+]) in 456 (89.4%) patients and partially (without percutaneous angioplasty [PA−]) in 54 (10.6%) patients. Outcomes for the whole group and PA+ and PA− patients are, respectively: healing, n = 310 (60.8%), n = 284 (62.3%), and n = 26 (48.1%); major amputation, n = 80 (15.7%), n = 67 (14.7%), and n = 13 (24.1%); death, n = 83 (16.25%), n = 68 (14.9%), and n = 15 (27.8%); and nonhealing, n = 37 (7.25%), n = 37 (8.1%), and n = 0 (0%) (χ^2 <0.0009). Predicting variables at multivariate analysis were the following: for healing, ulcer dimension, infection, and ischemic heart disease; and for major amputation, ulcer dimension, number of minor amputations, and age. Additional predicting variables for PA+ patients were the following: for healing, transcutaneous oxygen tension [$\Delta TcPo_2$]; and for major amputation, basal $TcPo_2$, basal A1C, $\Delta TcPo_2$, and percutaneous angioplasty technical failure.

CONCLUSIONS — Early diagnosis of CLI, aggressive treatment of infection, and extensive use of percutaneous angioplasty in ischemic affected ulcers offers improved outcome for many previously at-risk limbs. Ulcer size >5 cm^2 indicates a reduced chance of healing and increased risk of major amputation. It was thought that all ulcers warrant aggressive treatment including percutaneous angioplasty and that treatment should be considered even for small ischemic ulcers.

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Peripheral vascular disease (PVD) is responsible for the increased risk of lower limb amputation observed in diabetic patients (1). A multidisciplinary approach to diabetic foot problems is mandatory to reduce the frequency of lower limb amputations (2), particularly when PVD is complicated by the presence of infected foot ulcers (3). However, very few reports reveal successful treatments to reduce the frequency of lower limb amputations (4).

Today a significantly better outcome is expected for these patients, based on improved technical options in peripheral revascularization, new options in antibiotic therapy, and aggressive wound debridement and wound care. Increased identification of risk factors and comorbidities has provided improved prognostication for this difficult problem.

One of the most important advances is the increased availability of distal arterial revascularization by distal bypass surgery and by percutaneous angioplasty (5,6). This technique is increasingly important because of it is less invasive than open procedures and it can be used to treat very distal arterial stenosis and/or obstructions. It can be repeated in cases of technical failure. In addition, the risk profile with this procedure is much less than that with more extensive open procedures. Techniques such as subintimal angioplasty, initially used only for femoral and popliteal occlusions, are now applied to long crural artery occlusions (7). Outcomes from percutaneous angioplasty are similar to those for open procedure counterparts, at least when severe limb ischemia is due to infrainguinal disease (8). It is difficult to precisely quantify the clinical improvements offered by this protocol because previous studies were performed using various outcome measures of distal revascularization. These ranged from direct technical success of revascularization, measurement of final wound healing, patency rates of treated vessels, and ultimately limb salvage rates (9). Because of this heterogeneity, statistical comparisons among these studies are not easily performed.

Of additional concern in the patient population with this difficult problem is the clinical heterogeneity of foot wounds studied previously and how this affects final treatment outcomes (10). A more standardized approach to both the objective clinical features of the treated wounds and outcome measures is needed to verify the efficacy of therapeutic approaches aimed to salvage limbs in diabetic patients with critical limb ischemia (CLI). According to the TransAtlantic Inter-Society Consensus (TASC) classification, CLI is defined by the presence of ulceration, gangrene, or pain at rest and ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg or transcutaneous oxygen tension ($TcPo_2$) <30–50 mmHg as reference values (9).

In this study, the clinical outcomes of a large cohort of diabetic patients with

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CLI and either an active ulcer and/or gangrene seen consecutively at the University Hospital of Rome Tor Vergata are described. The outcome measures used were healing, nonhealing, major amputation, and mortality. Nonhealing was defined as patients with persistent ulceration after at least 1 year of follow-up who had functional use of the lower extremities and no evidence of increasing infection.

RESEARCH DESIGN AND METHODS

— All of the diabetic patients seen at the outpatient diabetic foot clinic or at the first-aid station because of a CLI and a foot ulcer and/or gangrene classified as stage C (ischemia) or stage D (ischemia+infection) and grade 2–3 (deep–very deep) according to the Texas Wound Classification (TWC) (11) were considered eligible for our limb salvage protocol.

Management protocol

The management protocol use in this study includes early revascularization of the affected limb with percutaneous angioplasty, early and aggressive surgical debridement of the ulcer and/or gangrene, and initialization of empirical broad-spectrum intravenous antibiotic therapy with at least two different drugs. Additional attention was directed to maintaining patients' electrolyte balance, and patients were hydrated in preparation for contrast angiography. Patients' medical status was also optimized, including intravenous insulin therapy and attention to comorbidities including, in particular, cardiovascular disease. A standard electrocardiogram and echocardiogram were performed. A heart scan was also performed in selected patients. Standard Doppler ultrasound of the carotid arteries was performed in all patients. The procedures used were vascular assessment, revascularization procedure, aggressive surgical debridement, and infection treatment.

Vascular assessment. Magnetic resonance angiography of the lower limbs was performed to detect arterial stenosis and/or obstructions and to determine when interventional treatment was warranted, the "road map" of treatment. The team policy was to treat all patients with CLI whenever possible with percutaneous angioplasty, reserving distal bypass for patients treated unsuccessfully with percutaneous angioplasty. $TcPo_2$ (12) was measured on the dorsum of the foot immediately before percutaneous angioplasty, after the 1st month, and every 6 months thereafter. This parameter was thought to monitor the efficacy of the revascularization procedure. If the $TcPo_2$ value did not increase to >30 mmHg, the threshold value thought to be necessary for spontaneous wound healing, this procedure would be repeated if possible (13).

Revascularization procedure. Percutaneous angioplasty was performed in the presence of significant arterial stenosis (>50% of lumina) and/or obstruction. All arteries were consistent with use of a percutaneous angioplasty procedure in terms of respective site and length of the stenosis/obstruction. In some instances, these were longer than 10 cm, multiple, sequential, or calcified. All procedures were performed under local anesthesia and a bolus of 5,000 IU of sodium heparin was immediately injected in the artery. A 6-Fr vascular introducer was positioned to perform a preliminary angiographic study. An angiographic or percutaneous transluminar coronary angioplasty 0.014- to 0.035-inch guidewire was inserted to pass through the arterial obstruction followed by a 3.0- to 5.0-Fr balloon catheter. This allowed dilatation of 2- to 8-mm diameter arteries. In selected patients, self-expandable stents were inserted in 5- to 8-mm diameter vessels. Stents were not placed below the popliteal arteries as the risk of thrombosis was very high in such low-flow vessels. In selected patients, a subintimal approach was used. In brief, subintimal angioplasty, also known as percutaneous intentional extraluminal recanalization, is a technique of revascularization that creates a new lumen between the intimal and medial layers (7). Patients were treated with aspirin (100 mg/day) and ticlopidine (500 mg/day) before the revascularization procedure and treatment was continued for 6 months thereafter. Long-term aspirin (100 mg) prophylaxis was recommended.

Side effects included retroperitoneal hematomas that occurred in 2.8% of patients and did resolve spontaneously. One patient had a hemorrhage from the injection site that required fast treatment in the operating theater. The occurrence of thrombi was managed by catheter aspiration and/or urokinase infusion. In only three patients was it responsible for a technical failure of the procedure.

Aggressive surgical debridement. The surgical debridement was aimed to drain abscesses, open fistulas, and remove necrotic and all clinically infected tissues (14). Minor amputations, i.e., amputation of toes and/or metatarsal heads, were considered as a part of the extensive debridement. Some patients had initial treatment before percutaneous angioplasty. This was performed immediately after hospital admission to limit the progression of infection. These patients then underwent additional more extensive debridement after percutaneous angioplasty when a significant increase in the $TcPo_2$ value was recorded at the ulcer site (12).

Infection treatment. Broad-spectrum intravenous antibiotic therapy was given immediately with a standard protocol of imipenem plus ciprofloxacin. A routine culture of the ulcer was done before antibiotic therapy was initiated. If necessary, antibiotic treatment would be changed depending on sensitivities of the organisms identified. For osteomyelitis, diagnosed according to Infectious Diseases Society of America guidelines (14), the infected bone was surgically removed.

Outcomes

The primary outcome measures were healing, nonhealing, major amputation, and mortality. The first outcome reached in one of these four categories was the only outcome considered. The time required to reach these outcomes was also recorded. Wound healing was defined as a continuous viable, epithelial covering over all previously seen open wounds. Major amputation was considered to be any amputation above the ankle, and minor amputation was any amputation below the ankle. Nonhealing was defined as unhealed ulceration after at least 1 year of follow-up but no need for major amputation. These patients had a preserved functional limb for ambulation and had no signs of increasing infection.

Secondary outcomes were technical failure of the revascularization procedure, measured as absence of revascularization of any of the three leg vessels and absence of direct arterial flow to the foot. This was considered as an immediate outcome. A $TcPo_2$ value >30 mmHg 1 month after percutaneous angioplasty was considered as an intermediate outcome.

Statistical analysis

Statistical analysis was performed using SAS (release 6.12; SAS Institute, Cary, NC) for personal computers. Data are expressed as means ± SEM. Comparisons between group characteristics were made with a χ^2 test (frequency data) or ANOVA (continuous data). The time to event was evaluated by means of a Kaplan-Meier procedure.

Table 1—*Patients' baseline characteristics according to their outcome*

	Total	Healing	Amputation	Death	Nonhealing	*P* value (χ^2 ANOVA)
n (%)	510	310 (60.8)	80 (15.7)	83 (16.25)	37 (7.25)	
Sex (% male)	63.5	63.2	67.5	62.65	59.5	0.83
Age (years)	70.4 ± 0.8	69 ± 1.6	70.3 ± 1	75 ± 1*†	69 ± 1.6‡	0.0001
Type 2 diabetes (%)	93.3	94.8	90.4	90.7	94.7	0.13
Diabetes duration (years)	20 ± 1.4	20.1 ± 0.7	19.4 ± 1.4	19.3 ± 1.3	21 ± 2	0.07
Blood pressure therapy yes (%)	91	89.8	88.5	97.5	91.9	0.37
Diastolic blood pressure (mmHg)	135 ± 0.9	136.7 ± 0.8	131.4 ± 1.6*	133.7 ± 1.5	139.5 ± 2.4†	0.0057
Systolic blood pressure (mmHg)	79 ± 0.8	80.4 ± 0.5	77.8 ± 1	76.5 ± 1*	80 ± 1.5	0.0012
Dialysis yes (%)	12.8	8.09	23.75	19.28	13.51	0.0008
Ischemic heart disease yes (%)	41.8	38.16	49.37	40.24	59.46	0.041
Carotid stenosis yes (%)	23.2	19.9	31.25	26.51	25	0.16
Current smoker no (%)	78.6	78.2	74.7	81.7	78.6	0.61
Blood glucose (mg/dl)	140 ± 5	143 ± 3	142 ± 7	127 ± 6	136 ± 10	0.17
A1C (%)	7.2 ± 0.1	6.8 ± 0.2	7.1 ± 0.2	7.7 ± 0.11*	7.4 ± 0.3	0.0034
Total cholesterol (mg/dl)	159 ± 3	163.5 ± 2.4	154 ± 5	155 ± 4.7	146.6 ± 7	0.053
HDL (mg/dl)	38 ± 0.8	40 ± 0.9	35.5 ± 1.7	35.2 ± 1.7*	37.3 ± 2.5	0.002
Triglycerides (mg/dl)	137 ± 3	138 ± 4	138 ± 7	138 ± 7	131 ± 10	0.90
LDL (mg/dl)	96.5 ± 2	99 ± 2	93 ± 4	94 ± 4	86 ± 6	0.17
Ulcer dimension >5 cm (%)	46.3	39.9	66.7	45	55.9	0.0003
Infection yes (%)	78.5	76.3	83	78.8	84.8	0.74
TWC D3 (%)	66.7	62.7	76.6	72.1	64.5	0.10
Basal $TcPo_2$	16.1 ± 0.8	16.7 ± 0.9†	10.3 ± 1.7	17.9 ± 1.7†	18.5 ± 2.5†	0.0055
Basal $TcPco_2$	54.8 ± 1.4	53.2 ± 1.5†	63.9 ± 3.1	52 ± 3†	56.4 ± 4.4	0.0145
Emergency yes (%)	41.8	35.8	58.7	45.8	45.9	0.02
Minor amputation	260 (54)	145 (50)	31 (40)	30 (37)	18 (49)	0.12
Peripheral angioplasty yes	456 (89.4)	284 (91.6)	67 (83.7)	68 (81.9)	37 (100)	0.0009
1-month $TcPo_2$	44.6 ± 1.1	46.8 ± 1.4	40 ± 3.1	39 ± 2.6*	41.8 ± 3.2	0.0124
1-month $TcPco_2$	40.7 ± 0.7	39.3 ± 0.8	44.3 ± 2.1	44.6 ± 1.7*	41.5 ± 2.1	0.0127
$\Delta TcPo_2$	27.6 ± 1.4	30.2 ± 1.5	25.6 ± 4.1	18.4 ± 3.5*	22.8 ± 4	0.0096
$\Delta TcPco_2$	−13.9 ± 1.7	−15 ± 1.9	−16.8 ± 5.3	−4.2 ± 4.4	−15.8 ± 5.3	0.14
Steno-obstructions (n)	2.6 ± 0.06	2.6 ± 0.07	2.8 ± 0.14	2.4 ± 0.1	2.8 ± 0.14	0.29
Vessels treated (n)	1.8 ± 0.041	1.8 ± 0.05	1.7 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	0.69
Stent (one) (%)	25.2	25	26	20	24	0.29
Subintimal yes (%)	23	22.8	22.2	18	25.7	0.69
Percutaneous angioplasty technical failure (%)	10.9	5.6	28.6*	16.1	11.1	0.0001

Data are *n* (%) or means ± SEM or %. The variables related to PA+ patients only are shown in italic. *$P < 0.05$ vs. healing. †$P < 0.05$ vs. amputation. ‡$P < 0.05$ vs. death.

Univariable logistic regression analyses were performed for all potential predictor variables with the outcome of interest, with values presented as univariable hazard ratios (HRs) along with the respective 95% CI. All potential predictors were entered simultaneously in a multivariable regression and a set of variables that best predict outcome was identified. $P < 0.05$ was considered statistically significant.

RESULTS — A total of 534 diabetic patients with CLI and lesions in class C (ischemia) and class D (ischemia+infection) and grade 2–3 (deep–very deep) of the TWC were seen during the 5-year recruitment period. Of these, 24 were lost after the first observation. The other 510 were included in our study (mean follow-up 20 ± 13 months [range 1–66 months]).

The clinical characteristics of the patients considered as a whole and divided by outcomes are reported in Table 1. Most of the patients were aged >65 years (75%), were male (63.5%), and had type 2 diabetes (93.3%) with a disease duration of ∼20 years. The majority of the patients had hypertension that was controlled pharmacologically (91%); only a small percentage of patients had end-stage renal disease and were undergoing hemodialysis (12.8%). A history of coronary artery disease or cerebral ischemic attack was present in 41.8 and 23.2% of patients, respectively, and 21.4% were smokers. Mean ± SEM A1C was 7.2 ± 0.1%, and LDL cholesterol was 96.5 ± 2 mg/100 ml. Of the ulcers, 46.3% had an area >5 cm^2, infection was present in 78.5%, and 66.7% of the ulcers were ischemic, infected including extension to the bone (TWC D3). Baseline $TcPo_2$ values were in the range of severe ischemia (<30 mmHg) in 81% of the patients. Percutaneous angioplasty was performed in 89.4% of patients.

Surgical debridement was performed immediately at the first observation, and repeated, as necessary, throughout the follow-up. All of the patients received intravenous antibiotic therapy for 5 ± 1 weeks followed by oral antibiotic therapy driven by results of cultures, repeated serially, until the clinical signs of the infection disappeared.

The patients had the following outcomes: 310 (60.8%) had healed wounds, 80 (15.7%) received a major amputation, and 83 (16.25%) died after 9.4 ± 0.5, 4.9 ± 0.9, and 9 ± 0.9 months, respectively, and 37 (7.25%) had nonhealing wounds after 23.2 ± 1.4 months of observation (log-rank $P < 0.001$).

In comparison with the other groups, patients with healed wounds had smaller ulcers and less coronary artery disease. These patients had lower rates of dialysis treatment and required less emergency room care. The majority of the healed wounds (51%) healed in <6 months. Ulcer area >5 cm^2, infection, TWC D3, and the presence of ischemic heart disease reduced significantly the chance of healing (HR 0.43 [95% CI 0.21–0.58[, $P <$ 0.0001; 0.36 [0.22–0.58], $P < 0.0005$; 0.44 [0.11–0.87], $P < 0.0054$; 0.52 [0.12–0.94], $P < 0.0004$, respectively) at the monovariate analysis.

Patients with amputations underwent dialysis more frequently, and approximately half had ischemic heart disease. They had lower basal $TcPO_2$ and higher transcutaneous carbon dioxide tension ($TcPCO_2$). They had significantly lower systolic blood pressure. More frequently, they were recruited from the emergency department. Ulcer area >5 cm^2, infection, TWC D3, number of minor amputations, ischemic heart disease, dialysis, and age were risk factors for major amputation (HR 2.3 [95% CI 1.2–5.6], $P =$ 0.003; 1.7 [1.1–2.5], $P = 0.019$; 1.6 [1.1–2.2], $P = 0.018$; 2.04 [1.2–3.3], $P =$ 0.003; 1.5 [1.01–2.4], $P = 0.05$; 2.06 [1.2–3.6], $P = 0.004$; and 1.02 [1.01–1.05], $P = 0.02$, respectively) in the monovariate analysis.

Patients who died were older than the patients in other groups and had higher A1C and lower HDL cholesterol and diastolic blood pressure. They were treated with percutaneous angioplasty at a lower percentage. Age was identified as a mortality risk factor (HR 1.022 [95% CI 1.001–1.052], $P = 0.03$).

Patients with nonhealing wounds had a higher percentage of ischemic heart disease; ~56% had an ulcer >5 cm^2. Basal $TcPO_2$ was significantly higher than in the group with amputations. Percutaneous angioplasty was done in all patients.

The multivariate analysis includes all of the significant variables found in the monovariate analysis. Predicting variables at multivariate analysis were the following: for healing, ulcer dimension, infection, and ischemic heart disease (HR 0.41 [95% CI 0.18–0.58], $P = 0.0001$; 0.37 [0.11–0.57], $P = 0.0001$; and 0.54 [0.15–0.82], $P = 0.0001$, respectively); and for major amputation, ulcer dimension, number of minor amputations, and age (7.7 [1.2–12.07], $P = 0.0002$; 3.09 [1.7–5.7], $P < 0.0001$; and 1.3 [1.2–1.7], $P = 0.03$, respectively). None of these variables were statistically associated with mortality or nonhealing outcomes.

To better highlight the influence of percutaneous angioplasty on outcomes, a further analysis was performed, dividing the whole patient group according to percutaneous angioplasty treatment: 456 patients were treated with percutaneous angioplasty (PA+), 54 patients were not treated with percutaneous angioplasty (PA−). The two groups had significantly different outcomes for PA+ and PA−, respectively: healing, $n = 284$ (62.3%) and $n = 26$ (48.1%); major amputation, $n =$ 67 (14.7%) and $n = 13$ (24.1%); deceased, $n = 68$ (14.9) and $n = 15$ (27.8%); and nonhealing, $n = 37$ (8.1%) and $n = 0$ (0%) ($\chi^2 < 0.0009$). Differences in time to event were observed only in the time to amputation, which in the PA− group was significantly shorter than that in the PA+ group (1.2 ± 1 vs. 5.2 ± 1 months, $P < 0.01$).

The two groups did not differ for any of the variables listed in Table 1 (data not shown). Additional variables related to PA were described only in PA+ patients and are reported in Table 1.

The number of arterial stenosis that were hemodynamically relevant (>50%) and/or with obstruction detected was 2.6 ± 0.06, and the number of vessels treated by percutaneous angioplasty was 1.8 ± 0.04/patient. The treated arteries were localized below the knee (35%) and above the knee (34%); the remaining were treated at both levels. Stents were used in 25.2% of patients, whereas subintimal recanalization was necessary only in 23% of patients. Technical failure was significantly lower in the patients with healed wounds than in the patients with amputations, which indeed had the highest failure rate ($P < 0.0001$). Major amputation was significantly associated with the technical failure of the procedure ($\chi^2 = 0.0001$), and technical failure was significantly associated with a precocious amputation after percutaneous angioplasty (1.5 ± 1.5 vs. 6.1 ± 1 months, $P = 0.02$) in comparison to the time of amputation observed in the technically successful percutaneous angioplasty procedures. $TcPO_2$ and $TcPCO_2$ values were used to monitor short-term (1 month) efficacy of the revascularization procedure (intermediate outcome).

Patients with healed wounds had a 1-month $TcPO_2$ value that was increased significantly compared with the baseline (46.8 ± 1.4 vs. 15.7 ± 0.8 mmHg, $P <$ 0.001), and 1 month after percutaneous angioplasty the $TcPCO_2$ value significantly decreased compared with the baseline (39.3 ± 0.8 vs. 54.7 ± 1.4 mmHg, $P <$ 0.0001). The revascularization procedure was repeated in 43 patients (9.4%) and in 37 (86%) patients within the 1st month after the initial percutaneous angioplasty. Surgical bypass was performed in 12 patients (2.6% of the total) after failure of a repeated percutaneous angioplasty.

In the multivariate analysis including only PA+ patients (Table 2), in a model containing age, ulcer dimension >5 cm^2, infection, TWC D3, basal blood glucose, basal A1C, presence of ischemic heart disease, number of minor amputations, percutaneous angioplasty technical failure, basal $TcPO_2$, $\Delta TcPO_2$, the predicting variables for healing were ulcer dimension, infection, the presence of ischemic heart disease, and $\Delta TcPO_2$. Predicting variables for major amputation were ulcer dimension, basal A1C, age, percutaneous angioplasty technical failure, basal $TcPO_2$, and $\Delta TcPO_2$. None of these variables were associated to mortality or nonhealing.

CONCLUSIONS — Lower limb amputation is a complication of diabetes mainly due to the presence of PVD (3,9). It is much rarer for PVD by itself to be responsible for lower extremity amputation. In the majority of patients, a small skin lesion, insignificant in appearance, often due to trivial causes, becomes infected and enlarges. All too commonly gangrene follows (13).

There is increasing evidence that distal arterial revascularization offers the best chance for limb salvage in diabetic patients with CLI. Outcomes reported in the literature are not always comparable (9,15). Studies detailing outcomes such as healing, major amputation, and mortality are still lacking. Therefore, the impact of peripheral revascularization on the natural history of diabetic patients with CLI followed over a long period is still obscure. Although TASC (9) gives strict criteria about objective mea-

Table 2—*Multivariate model with independent predictors of events for patients undergoing percutaneous angioplasty*

	Healing	*P* value	Amputation	*P* value
Age (years)			1.11 (1.015–1.258)	0.0237
Ulcer dimension (>5 to <5 cm)	0.358 (0.223–0.573)	−0.0001	5.2 (1.2–12.5)	0.0051
Infection (yes–no)	0.431 (0.223–0.851)	−0.0157		
A1C (basal)			4.01 (1.58–13.05)	0.0025
Ischemic heart disease (yes–no)	0.382 (0.242–0.591)	<0.0001		
Percutaneous angioplasty technical failure (yes–no)			0.05 (0.002–0.537)	0.0117
Basal $TcPo_2$ (mmHg)			0.891 (0.804–0.967)	0.0044
$DTcPo_2$ (mmHg)	1.016 (1.004–1.027)	0.0051	0.953 (0.91–0.99)	0.02

Data are HR (95% CI). No predictors for death and nonhealing.

suring (ankle pressure, toe pressure, and $TcPo_2$) to define patients affected by CLI, the criteria fail to separate out patients with ulceration or gangrene.

Several authors have attempted to classify wounds (16,17). Armstrong et al. (10) proposed wound classification related to the presence of ischemia and/or infection and to wound depth. The same authors in a follow-up study described the natural history of patients according to the severity of the wounds. They reported an amputation rate of 28% for patients with a superficial ischemic ulcer (TWC C1) over 6 months, and an amputation rate of 100% (including minor and major) for patients with deep, infected, ischemic lesions (TWC D3) (11). These data suggested that the efficacy of a limb salvage protocol might be highly affected by the clinical characteristics of the wounds included in the study. Therefore, although a distal revascularization may be sufficient alone to deal with ischemic nonhealing superficial ulcers, a much more complex treatment protocol may be needed for deep, infected ischemic wounds and/or gangrene. No studies, even recently, have linked the efficacy of a limb salvage protocol to ulcer dimension. Faglia et al. (18) in their recent report described in detail the outcomes of a group of diabetic patients with CLI but did not describe the type and the extent of the lesions and the presence of infection. Lazaris et al. (19) described a population with only 33 diabetic subjects. In addition, in this report there is no description of the lesions. In the article by DeRubertis et al. (15), only 31.4% had a generic tissue loss and among the total 291 patients only one-half were diabetic subjects. In addition, the limb salvage rate is reported only at 1 year. The recent report of the Eurodiale study focused attention on the characteristics of foot ulceration (size, depth, and infection); however, our data are not comparable with those reported in the Eurodiale study. In that study, only 40 (22%) of the181 patients with nonhealing wounds or amputations underwent revascularization, and only 40 (42.5%) of 94 patients with ankle-brachial index <0.5 underwent revascularization (20).

In this study, our diabetic patients with CLI were characterized by using the TWC. Of the ulcers, 80% had an infection (TWC D]) and in ~70% the infected ulcers were deep to the bone (TWC D3). This finding implies that our patients had worse prognoses according to both TASC and TWC, with the highest risk of lower limb amputation.

This report shows that it is possible to save the limb in ~70% of the patients and to obtain wound healing in > 60% of wounds in a relatively short time. The approach shows improved results in terms of outcomes compared with those of the TASC, which reported a 25% mortality rate, 30% major amputation rate, and only 45% surviving with the two intact lower extremities at 1-year follow-up (9).

In particular, aggressive early surgical debridement appears to be crucial in the management of these patients. This explains the relatively high number of minor amputations that have been done to limit gangrene progression. It is noteworthy that the number of minor amputations is a risk factor for a major amputation in the univariate analysis. Delayed debridement allows infection to destroy significant portions of the foot. Even successful revascularization failed with deep infection because of the foot anatomy characterized by closed compartments predisposed to progression (21). Aggressive surgical management is critical when infection spreads from an ulcer into these compartments. There is a rapid progression of infection through empty space. In this situation a large surgical approach to open the foot compartments is required to avoid further spread of the infection and worsening of the gangrene.

Antibiotic therapy is also important in our experience; combined antibiotic therapy has efficacy, including early clinical improvement. In only a few patients was it necessary to change the antibiotic therapy due to antibiotic resistance.

Over the last few years percutaneous angioplasty has earned increased respect in the treatment of PVD in diabetic patients (6,22). This is our method of choice to treat peripheral ischemia.

In our experience, percutaneous angioplasty has been tried in almost all patients (~90%). A small group of patients was not treated with percutaneous angioplasty. The indication to skip percutaneous angioplasty was related to their general conditions or to the extension and evolution of the foot lesion. In 15 patients, percutaneous angioplasty was not performed because of the presence of severe comorbidities (almost all of those patients died within 6–12 months); in 13 patients, the extension of the foot lesion was incompatible with limb salvage, and they were treated by primary major amputation. In 26 patients, percutaneous angioplasty was not performed because the lesions were small and showed a relatively fast evolution to spontaneous healing.

Percutaneous angioplasty was tried in all of the other patients. Patients in whom percutaneous angioplasty failed, either as an index treatment or revision, also had an unsuccessful surgical approach with open bypass. Percutaneous angioplasty has been shown to be safe overall with a very low complication rate. In addition, percutaneous angioplasty is still technically feasible in the presence of infected wounds of the lower limb, whereas the open surgical approach may be contraindicated. It has been effective with femoral, tibial, and peroneal arteries, both with standard techniques and with a subintimal approach (7,19).

From a technical point of view, percutaneous angioplasty has been performed in almost all stenoses and/or obstructions independent of length, in the presence of arterial calcifications, and also in the presence of multiple stenoses. Technical success has been extremely high and supports the aggressive approach of peripheral revascularization with the aim to revascularize as much as possible wherever and whenever a suitable lesion is found. Multivariate analysis of the technical success of percutaneous angioplasty does show a significant reduction for the risk of major amputation; 1-month $\Delta TcPO_2$ is also significantly associated with healing and with a reduced risk of major amputation.

These patients often have coexistent coronary artery disease and percutaneous angioplasty offers the potential advantage that, where performed, the veins that could be necessary for cardiac bypass are spared. However, failed percutaneous angioplasty also does not exclude a surgical approach with open bypass, which, in our experience, offered no additional clinical benefit after failed percutaneous angioplasty bypass.

Another important topic concerns how the dimensions of the ulcer and the presence of infection influence the outcomes of these patients with CLI. Ulcer size >5 cm^2 alone is a large risk factor for amputation. Our data support the logic that larger-sized ulcers have a larger amputation rate. Obviously no lesion caused by PVD starts this large, justifying the more aggressive approach of our protocol to smaller lesions, which our study has shown to have improved outcomes.

Multivariate analysis of our study echoes findings that basal A1C levels are a risk factor for amputation, and in similar studies hyperglycemia in perioperative patients has been identified as a separate risk factor for morbidity and mortality (23). Our data suggest that the treatment of the ischemic ulcers with aggressive revascularization reduces the risk of major amputation. This is also further supported by the Eurodiale study (20). Analysis of the data allows outcome comparison among centers. Centers with the best outcomes used vascular imaging, revascularization, surgery, and other imaging modalities more aggressively (20).

In summary, our comprehensive approach allows the salvage of limbs that otherwise may be amputated. Crucial lesion procedures early and aggressive debridement, revascularization by percutaneous angioplasty, multiagent intravenous antibiotic therapy, and controlled follow-up. It is our conviction that this approach can save many legs that previously would have been amputated.

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