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Long-term clinical outcomes in critical limb ischemia – A retrospective study of 181 patients

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Abstract. – OBJECTIVE: Critical limb ischemia (CLI) is the most severe manifestation of the peripheral arterial disease. To date, several prognostic factors have been identified but the data of long-term follow-up in real life setting are scarce. The aim of our study is to describe a large group of CLI patients and identify possible prognostic factors, in a long-term follow-up.

PATIENTS AND METHODS: Case-control, retrospective study. 181 consecutive CLI patients with a minimum follow-up of 5 years were included in the study.

RESULTS: Overall mortality was 15%, 24%, and 43% at 1, 2, and 5 years, respectively. Among known risk factors, only arterial hypertension was significantly correlated with survival rate; no differences were found between diabetics and non-diabetics. Patients treated with intravenous iloprost (46%), compared to untreated patients, showed a better ($p < 0.0001$) long-term outcome in terms of major amputation (6% *vs.* 21%), subsequent vascular surgery (4% *vs.* 32%) and survival rates (69% *vs.* 47%), at 5-year follow-up. Major amputations were significantly correlated with lower median forefoot transcutaneous values of O_2 (0/3 mmHg, $p < 0.001$) and higher median values of CO_2 (83/53 mmHg, $p < 0.0001$) in supine/dependent position, respectively.

CONCLUSIONS: Our results confirm the poor prognosis of CLI patients in a very long-term follow-up and the severe metabolic damage caused by ischemia. A favourable role of iloprost was observed, in agreement with previous evidence in the literature.

Key words:
Critical limb ischemia, Survival rate, Major amputations, Outcome, Transcutaneous gases measurements, Iloprost.

Introduction

Critical limb ischemia (CLI) is a major healthcare issue. Approximately 500-1000 people per million of the population are diagnosed with CLI[1]. Peripheral artery disease (PAD) patients present a number of typical non-modifiable (age, sex, race) and modifiable (e.g. smoke, diabetes, hypertension, dyslipidemia) risk factors, predisposing to atherosclerosis and cardiovascular disease, and have a very high risk of fatal and non-fatal cerebro- and cardio-vascular events. Coronary heart disease, assessed by coronary angiography, is present in about 90% of patients with severe PAD[2].

CLI is a manifestation of both PAD and ischemic disease of lower limbs[3]. In CLI the mismatch between the supply of oxygen and nutrients and the metabolic demand of tissues is critical also at rest, and rest pain and trophic lesions appear. CLI patients also develop microcirculatory defects including endothelial dysfunction, altered hemorheology, white blood cell activation and inflammation, and maldistribution of the cutaneous microcirculation. The term CLI should be used only for patients with chronic ischemic disease, defined as symptoms present for more than 2 weeks (chronic ischemic rest pain, ulcers or gangrene) and attributable to objectively proven arterial occlusive disease, setting off a cascade of pathophysiologic events that ultimately lead to the typical severe symptoms. Thus, the term CLI implies chronicity and is considered the "end stage" of PAD[3-5]. CLI is characterized by a poor long-term prognosis: 1 year after diagnosis major limb amputation is required in 30% of CLI patients, while overall mortality at 1 years is 25%[1], at 5 years is around 50% and at 10 years it raises to 70%. The morbidity and mortality surrounding bypass surgery is also considerable, with up to 3% perioperative mortality and a mortality rate at 1 year approaching 20%[2]. Thus, the prognosis of CLI patients is similar to that of some malignancies.

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The primary goals of the treatment are to relieve ischemic pain, heal (neuro)ischemic ulcers, prevent limb loss, improve patient function and quality of life, and, primarily, prolong their survival. Revascularization could optimally achieve some of these goals, but the severity of comorbidities, along with durability of the reconstruction in patients with CLI, demands a risk-benefit analysis to determine the optimal therapy. Some patients who present to vascular surgeons for surgical or endovascular procedures are poor candidates for such procedures because of medical comorbidities, nonambulatory status, or poor outflow vessels in the limb[4]. Medical management of CLI includes aggressive modification of cardiovascular risk factors, control of pain and infection in the ischemic leg, prevention of progression of the systemic atherosclerosis, and optimization of cardiac and respiratory function[5]. The only pharmacotherapy for CLI recommended by current guidelines in patients unsuitable for revascularization is represented by prostanoids, the only drugs that showed consistent evidence in improving ischemic symptoms[1,6,7]. The synthetic prostacyclin analogue iloprost closely mimics the whole range of endogenous prostacyclin's physiological effects, restoring the altered microcirculation by inducing vasodilation, inhibiting platelet activation, repairing and protecting the endothelium, activating the endogenous fibrinolysis and correcting cytokine imbalances[8]. The effects of iloprost are mediated by its specific binding to PGI_2 receptors (IP receptors) with subsequent increase in intracellular cAMP levels, but also PPARs activation was described, indicating a modulation of the expression of many genes (i.e. VEGF, TGF-beta, CTGF, MCP-1, PAI-1)[9-14], contributing to the explanation of the wide and long lasting effects of the drug[15]. Also, in another study where iloprost has been used for the treatment of patients with CLI, the authors have documented the further potential of the drug to increase significantly the number of circulating endothelial progenitor cells[16].

Several studies have shown that therapy with prostanoids may have a favorable impact on mortality and amputation rates, but usually follow-up was conducted for a maximum period of 1 year[17,18], so that we do not know yet the real effect of this therapy on long-term follow-up.

In the present study, a large number of consecutive CLI patients with long-term follow-up was assessed, with the aim to describe and identify: risk factors, morbidity and complications, predictors, mortality rates, causes of death, and pharmacotherapy response.

Patients and methods

Case-control, retrospective study conducted in accordance with the Declaration of Helsinki ad current ethical standards, which included 181 CLI patients, consecutively admitted to different medical and surgical wards of the University Hospital of Pisa, Italy.

The inclusion criterion was the clinical and instrumental diagnosis of critical ischemia of the lower limbs. The instrumental evaluations included transcutaneous tensiometry of oxygen ($TcpO_2$) and carbon dioxide ($TcpCO_2$). Ultrasound examinations and angiography of the lower extremities were performed in all patients to confirm the diagnosis. In the years after diagnosis, all patients underwent repeated clinical and instrumental examinations.

The data used in this study were obtained from medical records of patients. All patients and/or their families (and possibly family doctors) were contacted by telephone with an invitation for patients undergo a new visit. In case of death, the certificates were collected.

The data collected included demographic and clinical characteristics, concomitant and previous diseases, major and minor amputations, complications of CLI, mortality rates, causes of death, and administered treatments.

Statistical Analysis

The differences between categorical and continuous variables were calculated using ANOVA and the χ-square test, respectively. The statistical associations were calculated using multivariate logistic regression using the status in life as a binary variable (coded as 0 and 1). Descriptive statistics were the mean ± standard deviation (SD) or median for data in non-normal distribution. Statistical significance was considered at p values <0.05.

Results

Characteristics of patients

Table I shows the baseline demographic and clinical characteristics of the study population. The minimum duration of follow-up was 5 years and the maximum period was up to 15 years. Globally, a high average age of the patients, a high prevalence of Fontaine stage IV arteriopathy, and a high positive anamnesis for major known cardio- and cerebro-vascular risk factors and/or events were reported.

Table I. Demographic and clinical characteristics of the total population (n=181).

Male	56 % (n=101)
BMI (kg/m^2) ± SD	25 ± 3
Age (years)	72±10
Fontaine stage III	28 % (n=50)
Fontaine stage IV	72 % (n=131)
Diabetes mellitus	55 % (n=100)
Hypercholesterolemia	75 % (n=136)
Hypertension	68 % (n=123)
Current smokers	45% (n=81)
Ex smokers	14% (n=25)
CAD	37 % (n=67)
AMI	18 % (n=33)
AF	6 % (n=12)
COPD	7 % (n=13)
Stroke	14 % (n=26)
CVD	23 % (n=42)
Cancer	12 % (n=22)
Previous procedures:	
Vascular surgery	31 % (n=57)
Sympathicolysis	7 % (n=12)
SCS	6 % (n=10)
Contralateral amputation	2 % (n=4)
Transcutaneous values	
Symptomatic limb:	
Median $TcpO_2$	
Supine mmHg (range)	0 (0-46)
Dependent mmHg (range)	29 (0-72)
Median $TcpCO_2$	
Supine mmHg (range)	44 (35-175)
Dependent mmHg (range)	39 (34-135)
Contralateral limb	
Median $TcpO_2$	
Supine mmHg (range)	38 (0-73)
Dependent mmHg (range)	51 (0-87)
Median $TcpCO_2$	
Supine mmHg (range)	38 (35-110)
Dependent mmHg (range)	37 (34-100)

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: Partial pressure; CAD: Coronary artery disease; AMI: Acute myocardial infarction; AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease; CVD: Cerebral vascular disease; SCS: Spinal cord stimulation.

Risk factors

Arterial hypertension was the only known risk factor, among those evaluated, significantly and negatively correlated with the survival of patients included in the study ($p<0.01$). Overall, in this study, the diabetic patients had a prognosis similar to that of non-diabetics.

Pharmacological therapy

Following the diagnosis of CLI, all patients underwent the best possible therapy, which, in the first instance, included surgical and/or endovascular revascularization (19%), and, when it was unfeasible in the immediate or ever, patients received pharmacological treatment with i.v. iloprost administered at the rate of 0.5-2 ng/kg/min for 6 hours/day for 2-4 weeks (repeating the administration regimen regularly in time every six months in case of favourable clinical and instrumental responses), or alternative therapy (sympathicolysis in 3%, electrical chronic spinal cord stimulation in 6%).

Overall, iloprost was used in 46% (n = 84) of patients (Table II) and the characteristics of the treated and untreated population at baseline were similar. The medically treated and untreated patients showed statistically significant differences in terms of 5-year survival (69% *vs.* 47%, $p<0.0001$), major amputation (6% *vs.* 21%, $p<0.0001$), subsequent vascular surgery (4% *vs.* 32%, $p<0.0001$) (Figure 1 and Table II). In addition, a reduced number, although not statistically significant, of minor amputations was observed in patients who received iloprost (7% *vs.* 12%).

The other drugs administered to patients included antiplatelet agents (a total of 74% of patients), anti-hypertensives, nitrocompounds, oral anticoagulants, and statins, whose use was homogeneous among the different groups of patients and was not associated with significant differences in survival.

Survival and amputations

Figure 1 shows survival curves of total CLI population and patients treated or not treated with iloprost. The overall curve confirms the poor prognosis of CLI patients: mortality in long-term follow-up reaches 15% after 1 year, 24% after 2 years, and 43% after 5 years.

Figure 2 shows the rates of major and minor amputations, of total deaths and the causes of death, represented by cardio- and/or cerebro-vascular events in the large majority of cases.

In the 25 observed amputees, transcutaneous oximetry, measured in the supine (median 0 mmHg, $p<0.0019$) and dependent positions (median 3 mmHg, $p<0.00001$), and transcutaneous capnometry, assessed in the supine (median 83 mmHg, $p<0.00001$) and dependent positions (median 53 mmHg, $p<0.0011$) were significantly related to the risk of major amputation.

Discussion

Our study confirms the poor prognosis of CLI patients, since the overall mortality rate amounted

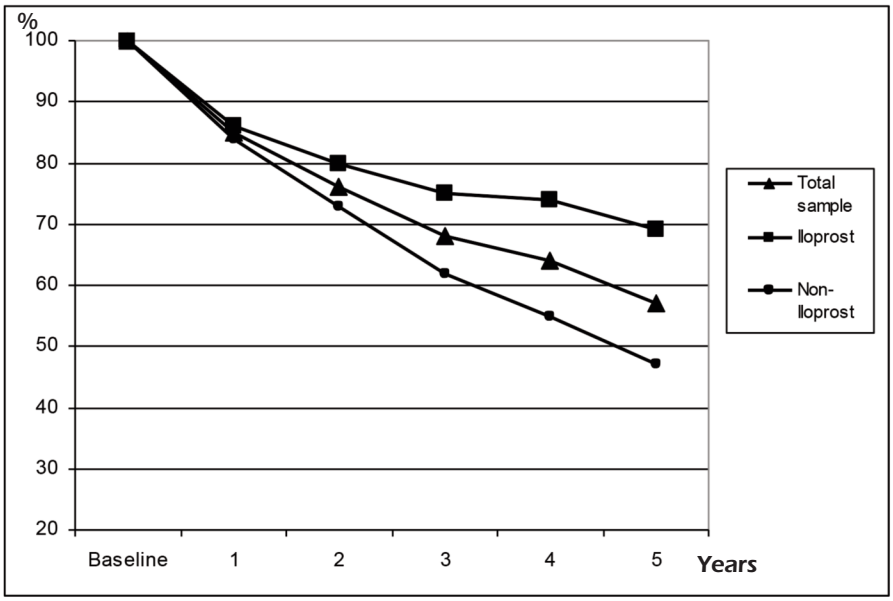

Figure 1. Survival curves of total sample (n=181) and patients treated (n=84) or not treated (n=97) with iloprost.

to 15% after 1 year, 24% after 2 years and 43% after 5 years. However, the mortality rate of 15% at one year is lower than the rate at 1 year according to the natural history of disease (25%[1]), which is reached only on the second year of follow-up, testifying effectiveness of our overall therapeutic approach. As expected for patients suffering from CLI, the main causes of death were due to cardio- and/or cerebro-vascular events.

In the 181 CLI patients included in this study, the transcutaneous measurements in symptomatic forefoot provided a markedly image of the severe metabolic damage caused by ischemia.

Overall, 14% of patients underwent major amputation, despite the administered therapies, confirming the poor prognosis described in the literature[1].

The importance of an immediate approach to a vascular specialist who can address the early CLI patient to the best possible treatment was emphasized by the studies of Dormandy et al[19,20] which reported that in about 30% of the cases the major

Table II. Characteristics and outcomes of patients treated or not treated with iloprost.

	Iloprost (n=84)	Non-Iloprost (n=97)	*p*-value
Age (years) ± SD	74 ± 6	71 ± 7	NS
Diabetes mellitus	52% (n=44)	39% (n=38)	NS
Hypertension	64% (n=54)	69% (n=67)	NS
Fontaine stage III	30% (n=25)	26% (n=25)	NS
Fontaine stage IV	70% (n=59)	74% (n=72)	NS
Previous procedures			
Vascular surgery	30% (n=25)	33% (n=32)	NS
Sympathicolysis	1% (n=1)	11% (n=11)	NS
SCS	12% (n=10)	0% (n=0)	<0.05
Contralateral amputation	1% (n=1)	3% (n=3)	NS
Subsequent procedures			
Major amputations	6% (n=5)	21% (n=20)	<0.00001
Minor amputations	7% (n=6)	12% (n=12)	NS
Vascular surgery	4% (n=3)	32% (n=31)	<0.00001
Sympathicolysis	0% (n=0)	5% (n=5)	NS
SCS	1% (n=1)	7% (n=7)	<0.05
Survival:			
1 year	86% (n=72)	84% (n=81)	NS
2 years	80% (n=67)	73% (n=71)	NS
5 years	69% (n=58)	47% (n=46)	<0.0001

SCS: Spinal cord stimulation

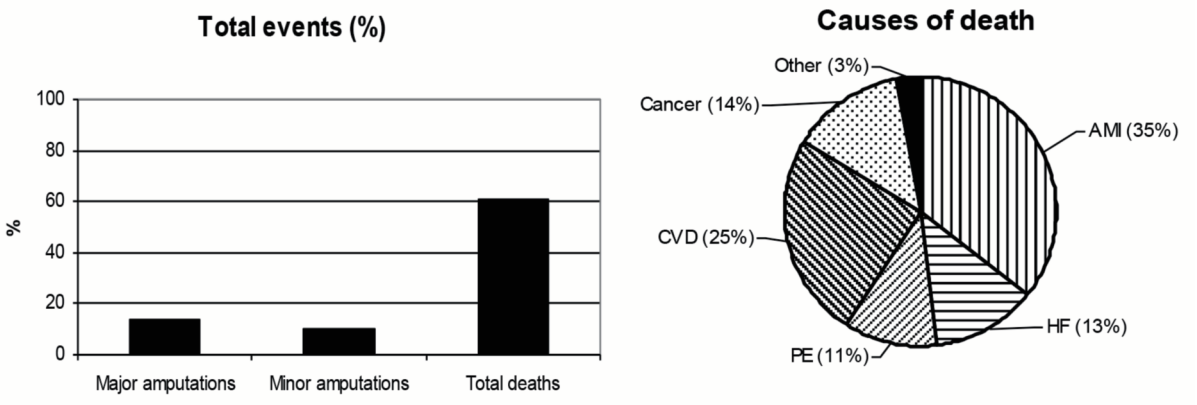

Figure 2. Rates of major and minor amputations, of total deaths and causes of death of the study population (n=181). Key: AMI: Acute myocardial infarction; HF: Heart failure; PE: Pulmonary embolism; CVD: Cerebrovascular disease.

amputation of the symptomatic limb is performed without the evaluation of a vascular surgeon. Similar considerations have been formulated by Abou-Zamzam et al[21] who point out that a quarter of CLI patients arrive at the vascular surgeon, in the presence of an extended limb gangrene or infection, symptoms that prevent limb salvage.

In the present study, all patients after diagnosis of CLI, have been subjected to the best possible treatment, represented, first, by revascularization surgery and/or endovascular treatment, when appropriate. Only 19% of patients has been subjected to such treatment, that is a lower value compared to that of patients theoretically operable as assumed in the literature (about 50%). However, considering that 31% of patients had undergone vascular surgery prior to entry into the study, the proportion of the total population surgically treated rises to 50%. This number would be even higher if other interventions such as sympaticolysis or SCS were considered.

When the vascular intervention was not feasible, at the time of diagnosis (for concomitant serious comorbidity) or in general (for anatomical reasons), as suggested by main current guidelines, our patients were treated with i.v. iloprost administered for several weeks, or with alternative therapies.

The use of iloprost as prostanoid of choice results from our favorable experience and the well documented efficacy reported in the literature[1,15,22,23]. In particular, in the meta-analysis of Loosemore et al[22] of 6 RCTs that included 705 Fontaine stage III and IV patients unsuitable for revascularization, therapy with iloprost for two to four consecutive weeks showed significant beneficial effects on ulcer healing, pain relief, and with regards to the probability of being alive with both legs at six months of follow-up. Moreover, in another RCT that evaluated the effects of iloprost and alprostadil, in a group of 267 Fontaine stage IV patients, iloprost showed a higher responder rate (52.7% *vs.* 43.1%), a reduced number of deaths (7.5% *vs.* 14.6%), and similar effects in diabetics and non-diabetics (53.3% and 51.4% response rates, respectively), while the diabetics treated with alprostadil had a considerably poorer outcome (36.6% *vs.* 53.3%)[23].

In addition, in 2010 the meta-analysis of Ruffolo et al[24] has documented the efficacy of prostanoids in the treatment of CLI and, in particular, the favourable use of iloprost in rest pain relief, in ulcer healing and reduction of major amputations.

More recently a consensus of the Italian Societes of Diabetes, Radiology and Vascular Endovascular Surgery has proposed in diabetic CLI patients the use of iloprost not as alternative to peripheral revascularization, but in reduction of rest pain before revascularization or as its pharmacological use after revascularization, to improve tissue perfusion and quality of life of patients[25].

Overall, in our series, the patients treated with iloprost, compared with untreated patients, showed a significant reduction in mortality at 5 years (31% *vs.* 53%) and major (6% *vs.* 21%) and minor (7% *vs.* 12%) amputations, which represent the most important endpoints for patients with CLI. It is noteworthy to emphasize that the difference in survival rates between the patients treated and not treated with iloprost is at the fifth

year of follow-up, that is, at very long-term. So, if we state the response to iloprost therapy only immediately or one-six month after treatment, we cannot fully understand its real clinical effect.

In addition, in CLI patients treated with iloprost, the subsequent vascular surgery procedures were also reduced (4% *vs.* 32%), indicating a stabilization of the clinical picture, with a lower need of performing further procedures. These are hard and clinically relevant outcomes. Our data show, therefore, that iloprost resulted in a significant clinical benefit both locally, as expected, and primarily systemically in terms of reduction of cardiovascular mortality and morbidity in very long-term follow-up. Prostanoids mainly act on adaptive metabolic capacities to ischemia and, so far, iloprost is the only pharmacological agent that has been convincingly shown to have a positive influence on the prognosis of CLI patients.

Thus, without being an alternative to revascularization, iloprost should be used: in every patient unsuitable for revascularization, in every patient suitable for revascularizations as adjuvant therapy (both pre-and post-operatively, using different infusion schemes), preferentially in the early stages of critical ischemia, when the damage is limited and not irreversible and in CLI patients who cannot be revascularized immediately, because of the limited prospects of success[3,26-28].

Althoug it is a retrospective design and the analysis of data are extracted from medical records, the authors believe that these results can be considered reliable, as complete informations were recovered for each patient. In addition, our findings are consistent with previous randomized trials and observational data in the literature, indicating the poor prognosis of CLI patients, and the role of risk factors and drug treatment, particularly with iloprost. In the future, it will be necessary to confirm our results through the collection of information in prospective multicenter registries.

Conclusions

Our study confirms the poor prognosis of CLI patients and shows the correlation between important clinical endpoints, such as amputation rates and overall mortality, and cardiovascular risk factors and pharmacological treatment in a very long-term follow-up. In particular, iloprost administration is associated with an overall better clinical outcome in a real life setting, confirming previous evidence in the literature.

Conflict of Interest

Alberto Farina is an employee of Italfarmaco S.p.A. The other authors report no conflict of interest in the preparation of the present article.

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