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## ORIGINAL ARTICLE

# Incident cardiovascular events and early mortality in patients with revascularized critical limb ischemia

R. Gaisset<sup>a</sup>, F. Lin<sup>b</sup>, O. Borry<sup>c</sup>, C. Quemeneur<sup>d,e</sup>, I. Lazareth<sup>a</sup>,  
 J. Emmerich<sup>a,f</sup>, P. Priollet<sup>a</sup>, A. Yannoutsos<sup>a,f,\*</sup>



<sup>a</sup> Vascular medicine department, Groupe Hospitalier Paris Saint-Joseph, Clinical Investigation Center, Hôpital Européen George-Pompidou, AP–HP, Paris, France

<sup>b</sup> Medical Information department, Groupe Hospitalier Paris Saint-Joseph, Paris, France

<sup>c</sup> Internal medicine department, Hôpital Louis-Mourier, AP–HP, Colombes, France

<sup>d</sup> Department of Anaesthesiology and critical care, GRC 29, DMU DREAM, Sorbonne University, Pitié-Salpêtrière Hospital, AP–HP, Paris, France

<sup>e</sup> Department of Anaesthesiology, Clinique Drouot Sport, 21, rue Rémusat, 75016 Paris, France

<sup>f</sup> Inserm UMR 1153-CRESS, Université Paris, Paris, France

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## KEYWORDS

Critical limb ischemia;  
 Mortality;  
 Cardiovascular events

## Summary

**Objectives.** – Patients with critical limb ischemia (CLI) present a high risk of cardiovascular events and death. This study aimed to investigate the incidence of major adverse cardiovascular events (MACE) and one-year mortality in patients undergoing percutaneous revascularization procedure for CLI.

**Methods.** – This investigation is a retrospective analysis of an ongoing cohort study in patients with CLI undergoing endovascular revascularization, hospitalized in the vascular medicine department from November 2013 to December 2018. Major cardiovascular events were collected during the first year after revascularization procedure and were defined as heart failure, acute coronary syndrome, ischemic stroke and sudden death. Mortality and major limb amputations, defined as above-the-ankle amputation, were determined during the one-year follow-up period. Multivariate logistic regression analyses were performed to identify factors independently associated with the occurrence of MACE and one-year mortality after revascularization procedure. A  $P \leq 0.05$  was considered as statistically significant.

\* Corresponding author.

E-mail address: [ayannoutsos@ghpsj.fr](mailto:ayannoutsos@ghpsj.fr) (A. Yannoutsos).

**Results.** – The study included 285 consecutive patients, 157 men (55%) and 128 women (45%), with a mean age of  $77.8 \pm 12$  years. Treated hypertension was present in 222 (78%) patients; diabetes was present in 137 (48%) patients; 112 (39%) patients had known coronary heart disease and 20 (7%) patients were dialysis dependent. During the one-year follow-up after revascularization procedure, 75 (26.3%) patients presented an incident cardiovascular event, of whom 19 (6.7%) patients in the perioperative period. Cumulative mortality rate was 26.7% (76 patients) mostly from cardiovascular causes. Twenty-five patients (8.8%) experienced major amputation. In multivariate analysis, the occurrence of MACE was associated with an increased mortality risk (HR 6.96 (2.99–16.94),  $P < 0.001$ ). Other variables associated with an increased mortality were living in a nursing home and malnutrition. Decompensated heart failure and coronary heart disease were both associated with incident MACE in multivariate analysis, independently of confounders.

**Conclusion.** – In the present study population, incident MACE were prevalent in the year following endovascular revascularization procedure in patients with CLI and were associated with an increased risk of mortality. Coronary heart disease and decompensated heart failure are important contributors for the occurrence of MACE. In this elderly patient population with CLI, these results should be taken into account during the multidisciplinary team meeting before consideration of revascularization procedure.

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## Introduction

The number of people living with peripheral artery disease (PAD) is increasing, driven mainly by population ageing [1]. Lower limb arterial disease is prevalent in nearly 20% among octogenarian patients [2]. Characteristic symptoms of critical limb ischemia (CLI), the end-stage of PAD, may appear in more than 10% of patients with known PAD or may be diagnosed as primary CLI presentation, in particular in diabetics and in patients with chronic kidney disease [3]. Patients with CLI present a particularly high risk of major limb adverse events (MALE) and overall mortality [4]. Whenever feasible, revascularization is the cornerstone of therapy to relieve ischemic pain and improve amputation-free survival. Limb salvage procedures may include conventional surgery or balloon angioplasty adapted to segmental lesions [5]. The choice for the revascularization procedure is related to many factors: anatomical lesions, distribution of arterial disease, operative risk related to patient's health status, presence of infection and local expertise [6]. Considered as minimally invasive, with lower mortality rate as compared to conventional surgery, endovascular techniques have really taken off during the last decades [7]. Advancement in catheter-based technologies offer the possibility to manage multi-vessel disease and to perform distal revascularization of the plantar arch and the pedal artery [8]. Concomitantly, there has been a decrease in major amputation rate over the past few years [9]. However, early mortality rate remains high in this population with end-stage PAD, reaching 25% through 12 months follow-up after revascularization procedure [10,11]. Adverse cardiovascular events represent a major concern in these patients [12,13]. Furthermore, malnutrition and advanced organ damage, especially heart failure and renal insufficiency, are frequent comorbid conditions associated with poor prognosis in CLI patients [14,15]. Delineating the respective contribution of cardiovascular events and comorbid conditions for mortality is essential to improve clinical outcomes in revascularized CLI patients.

The aim of the present study was to analyze the incidence of major adverse cardiovascular events (MACE), major limb amputation, overall mortality and associated risk factors through one-year follow-up in patients managed for CLI in the current era of endovascular revascularization procedures.

## Material and methods

### Study design

This investigation was designed as a retrospective cohort study in patients with CLI, managed in the vascular medicine department of Paris Saint-Joseph hospital. Between November 2013 to December 2018, endovascular revascularization procedure for limb salvage was proposed in 297 consecutive patients during a multidisciplinary team meeting consisting of vascular medicine doctors, vascular surgeons and interventional radiologists. Clinical data, with cardiovascular outcomes and one-year follow-up survival, were retrospectively collected in a dedicated report form. Information on survival could not be precised for 12 patients (4%) who were lost to follow-up because of relocation. These patients were excluded from the present analysis and the study population comprised 285 patients. This study is registered according to local reglementary procedures.

### Participants

All patients presented with CLI and underwent endovascular revascularization procedure for limb salvage. Critical limb ischemia was defined as documented atherosclerotic PAD in association with ischemic rest pain or tissue loss of the forefoot evolving for more than 2 weeks. Hemodynamic evaluation consisted of ankle brachial pressure index (ABI) and great toe laser Doppler flowmetry (LDF) measurement. Critical limb ischemia was objectively assessed with hemodynamic measurements: absolute

highest ankle pressure < 50 mmHg, ABI < 0.40 or absolute toe pressure < 30 mmHg [16].

Exclusion criteria were defined as arterial occlusive disease not related to atherosclerosis, acute limb ischemia, presence of active life-threatening condition including life-threatening limb sepsis or contraindication to antithrombotic therapy.

Revascularization procedure was performed under loco-regional anesthesia.

Technical success was defined by the endovascular revascularization patency at the end of the procedure.

### Data collection at baseline

Data were retrospectively collected at baseline during the index hospitalization for revascularization procedure:

- clinical parameters included: gender, age, body mass index (BMI), blood pressure (BP), ABI and great toe LDF, cardiovascular risk factors, history of coronary heart disease (CHD), prior revascularization procedure for PAD, statin and renin-angiotensin-system-inhibitor treatment. Community-living status or institutionalized in a nursing home was also collected;
- admission biological parameters included level of serum albumin and estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) Study equation [17].

Cardiovascular risk factors included smoking status (classified as ever, current or former smoker, or never smoker), hypertension and diabetes mellitus defined by a history of diagnosis or treatment for these conditions. Coronary heart disease was defined by a history of myocardial infarction or coronary revascularization.

### Outcome measures

Patients were followed up as part of their normal care.

Perioperative complications through 30 days were retrospectively recorded:

- complication at the puncture site (groin hematoma or pseudoaneurysm), not requiring invasive treatment procedure;
- major bleeding, defined according to the International Society on Thrombosis and Haemostasis [18] as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of red cells.

Fatal and non-fatal major cardiovascular events (MACE) were retrospectively collected in the one-year follow-up period and were defined as heart failure, acute coronary syndrome, ischemic stroke and sudden death.

Mortality and major limb amputations, defined as above-the-ankle amputation, were determined during the one-year follow-up period.

### Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation; categorical variables were expressed as percentage. For baseline characteristics and mortality events, between group comparisons of continuous variables were made with Student's *t*-test or Mann–Whitney test, and categorical variables were analyzed with Chi<sup>2</sup> test or Fisher's exact test as appropriate.

A  $P \leq 0.05$  was considered as statistically significant. Multivariate logistic regression, including all variables related to mortality at a threshold  $P \leq 0.05$  in the univariate analysis, was performed to identify factors independently associated with one-year mortality and the occurrence of MACE. Kaplan–Meier survival curves were presented, displaying the estimated survival probability one year after revascularization procedure in patients with and without incident cardiovascular event. Statistical analysis was performed using R Statistical Software.

## Results

### Patients' characteristics

The characteristics of the 285 patients at inclusion are presented in Table 1. The study cohort comprised 128 women (45%) and 157 men (55%) with a mean age of  $77.8 \pm 12$  years. The vast majority of the patients (262 patients (92%)) presented with tissue loss and 23 (8%) patients presented with ischemic rest pain without ulceration. At hospital admission, mean ABI was  $0.59 (\pm 0.44)$ , mean great toe LDF  $25.6 (\pm 14.7)$  mmHg with a mean toe pressure index  $0.20 (\pm 0.11)$ . Treated hypertension was present in 222 (78%) and almost half of the patients were diabetic (48%). History of CHD was present in 112 (39%) patients and 20 (7%) patients were dialysis dependent. Protein malnutrition was highly prevalent, serum albumin level below 35 g/L was present in 176 (62%) patients. Institutionalized status in a nursing home was noted in 57 (20%) patients.

Among the 285 patients, 10 (3.5%) had previously undergone major limb amputation before admission. One hundred and forty-nine patients (52%) had already undergone at least one previous endovascular or surgical revascularization for PAD.

### Clinical outcomes after endovascular revascularization

Immediate revascularization success was achieved in 95.4% of patients; the procedure failed in 13 patients (4.6%) due to massive calcified arteries.

In the post-procedure period, distal hemodynamic parameters improved markedly with a mean ABI of  $0.86 (\pm 0.29)$ , a mean great toe LDF  $49.5 (\pm 18.1)$  mmHg with a mean toe pressure index at  $0.39 (\pm 0.15)$ .

### Peri-procedural adverse events

In the perioperative period (up to 30 days after the procedure), major bleeding, cardiovascular adverse events and

**Table 1** Clinical and biological parameters according to survival status at one year.

	All population; n = 285	Survival; n = 209	Mortality; n = 76	P
<b>Clinical parameters</b>				
Age	77.8 (12.0)	76.4 (12.0)	81.6 (11.1)	0.001
BMI	24.5 (4.88)	24.9 (4.99)	23.4 (4.41)	0.028
Women (%)	128 (44.9%)	86 (41.1%)	42 (55.3%)	0.047
Baseline SBP	132 (18.2)	135 (16.7)	124 (19.8)	< 0.001
Baseline DBP	69.9 (7.79)	71.0 (7.68)	66.9 (7.36)	< 0.001
Baseline PP	62.3 (15.8)	64.1 (15.1)	57.3 (16.7)	0.002
Baseline MBP	90.7 (9.77)	92.3 (9.04)	86.0 (10.3)	< 0.001
Baseline HR	75.1 (11.6)	74.7 (11.4)	76.1 (12.1)	0.362
Diabetes (%)	137 (48.1%)	105 (50.2%)	32 (42.1%)	0.280
Hypertension (%)	222 (77.9%)	167 (79.9%)	55 (72.4%)	0.232
Ever smoker (%)	192 (67.4%)	145 (69.4%)	47 (61.8%)	0.290
Dialysis-dependency (%)	20 (7.19%)	13 (6.37%)	7 (9.46%)	0.537
<b>History (%)</b>				
Ischemic stroke or TIA	48 (16.8%)	31 (14.8%)	17 (22.4%)	0.185
Coronary heart disease	112 (39.3%)	78 (37.3%)	34 (44.7%)	0.319
PAD revascularization <sup>a</sup>	90 (31.6%)	65 (31.1%)	25 (32.9%)	0.885
Left ventricular ejection fraction (%)	59.5 (12.8)	61.6 (11.3)	54.4 (14.7)	0.001
Institutionalized status (%)	57 (20.0%)	32 (15.3%)	25 (32.9%)	0.002
<b>Biological parameters</b>				
Creatinine clearance (mL/mn)	71.0 (28.4)	71.4 (27.4)	70.0 (31.3)	0.737
Hemoglobin (g/dL)	11.2 (1.62)	11.4 (1.66)	10.8 (1.43)	0.009
Albumin (g/L)	32.9 (5.59)	34.1 (5.56)	30.3 (4.76)	< 0.001
C-reactive protein (mg/L)	59.9 (65.8)	55.3 (68.1)	71.2 (58.9)	0.080
Brain natriuretic peptide (pg/mL)	456 (675)	281 (303)	793 (997)	0.001
<b>Hemodynamic parameters pre-procedure</b>				
Ankle-brachial index	0.59 (0.44)	0.58 (0.42)	0.61 (0.50)	0.689
Great toe LDF (mmHg)	25.6 (14.7)	25.6 (15.0)	25.3 (13.8)	0.871
Great toe LDF index	0.20 (0.11)	0.19 (0.11)	0.21 (0.12)	0.398
<b>Hemodynamic parameters post-procedure</b>				
Ankle-brachial index	0.86 (0.29)	0.86 (0.29)	0.87 (0.30)	0.882
Great toe LDF (mmHg)	49.5 (18.1)	49.4 (18.0)	49.6 (18.6)	0.955
Great toe LDF index	0.39 (0.15)	0.39 (0.13)	0.42 (0.18)	0.280
<b>Treatment at discharge</b>				
Statin (%)	251 (88.1%)	187 (89.5%)	64 (84.2%)	0.315
IRAS (%)	182 (63.9%)	141 (67.5%)	41 (53.9%)	0.050
Anticoagulant (%)	93 (32.9%)	62 (30.0%)	31 (40.8%)	0.115

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MBP: mean blood pressure; HR: heart rate; TIA: transient ischemic attack; PAD: peripheral arterial disease; LDF: great toe laser Doppler flowmetry; IRAS: inhibitors of the renin-angiotensin system. Data are presented as mean ( $\pm$  standard deviation) or number (%).

<sup>a</sup> Ninety patients underwent more than one endovascular revascularization procedure for critical limb ischemia.

local complication at the puncture site occurred in 37 (13%), 19 (6.7%) and 16 (5.6%) patients, respectively.

Twelve patients died in the perioperative period (within 30 days after procedure) with a perioperative mortality rate of 4%: MACE (6 patients), septic complication related to ulcers (3 patients), limb ischemia (2 patients), hemorrhage (1 patient).

### Overall mortality

A total of 76 patients died during the one-year follow-up (26.7% of the present cohort), with a median death rate at 3 months.

Cardiovascular events were highly prevalent, accounting for 40.8% of overall mortality (31 patients). Sudden

deaths represented one third (10 patients) of cardiovascular deaths.

Ischemic stroke and acute coronary syndrome were the main causes of death in 7 (9.2%) and 5 (6.6%) patients, respectively. Decompensated heart failure was present as either the main or one of the contributing causes of death in 15 patients (19.7% of overall mortality).

Sepsis and lower limb ischemia (acute limb ischemia or extensive gangrene) were reported in 21% (16 patients) and (11.8%, 9 patients) of deaths. Chronic pulmonary insufficiency and end-stage renal disease were the main causes of death in 4 (5.3%) and 2 (2.6%) patients, respectively. Two patients (2.6% of deaths) died from cancer (esophageal cancer and colorectal cancer). One patient faced hemorrhagic

**Table 2** Perioperative complications, incident cardiovascular events and major amputations according to survival status at one year.

	All population; n = 285	Survival; n = 209	Mortality; n = 76	P
Perioperative complications				
Local procedure complication	16 (5.61%)	8 (3.83%)	8 (10.5%)	0.041
Hemorrhages	37 (13.0%)	24 (11.5%)	13 (17.1%)	0.294
MACE	19 (6.67%)	7 (3.35%)	12 (15.8%)	0.001
Incident MACE	75 (26.3%)	27 (12.9%)	48 (63.2%)	< 0.001
Major limb amputation	23 (8.07%)	22 (10.5%)	1 (1.32%)	0.023

MACE: major cardiovascular events.

stroke in the follow-up. The main cause of death could not be precised retrospectively in 10 patients.

**Cardiovascular events**

Overall, 75 patients (26.3%) presented a MACE through the one-year follow-up. Forty-four patients (15.8%) presented a non-fatal MACE: 35 patients (12.3%) presented decompensated heart failure in the peri procedural period, 3 patients (1.0%) presented a cerebrovascular event, and 6 patients (2.1%) presented an acute coronary syndrome.

**Lower limb events**

Twenty-five patients (8.8%) underwent homolateral major amputation surgery within one year after the revascularization procedure. At three months, 44 patients had undergone a minor amputation and 13 patients had undergone a major amputation. Among the 262 patients with CLI and tissue loss, 110 patients (41.9%) had completely healed at one year.

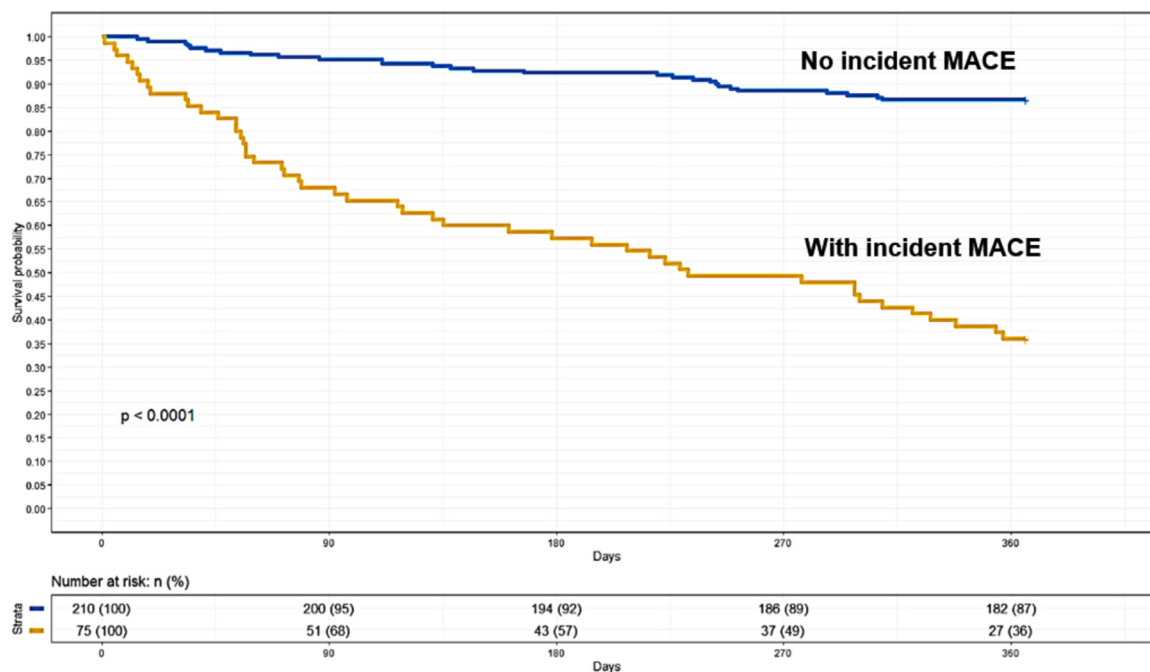
**Table 3** Multivariate regression model for 1-year mortality.

	HR (95% CI)	P
Age	1.02 (0.99–1.07)	0.22
Gender (men)	0.81 (0.35–1.85)	0.61
Body mass index	0.97 (0.89–1.06)	0.49
Non-institutionalized status	0.34 (0.12–0.92)	0.03
Mean blood pressure	0.94 (0.89–0.99)	0.01
LVEF < 60%	0.71 (0.25–1.91)	0.51
Hemoglobin	1.07 (0.81–1.43)	0.65
BNP ≥ 500 pg/mL	1.52 (0.40–6.03)	0.54
Albumin < 33 g/L	3.14 (1.15–9.02)	0.03
Local procedure complication	2.87 (0.60–14.58)	0.19
Major cardiovascular events	6.96 (2.99–16.94)	< 0.001
Major limb amputation	0.06 (0.003–0.50)	0.03

Area under the curve: 0.87.

**Predictors of mortality and cardiovascular events**

In univariate analysis for mortality, age ( $P=0.001$ ), body mass index ( $P=0.028$ ), gender ( $P=0.047$ ), mean BP



**Figure 1** Kaplan–Meier survival curves according to the occurrence of major cardiovascular events (MACE).



**Table 4** Clinical and biological parameters in patients according to incident cardiovascular events.

	Total population; <i>n</i> = 285	No cardiovascular events; <i>n</i> = 210	Cardiovascular events; <i>n</i> = 75	<i>P</i>
<b>Clinical parameters</b>				
Age	77.8 (12.0)	77.0 (12.3)	80.0 (10.9)	0.047
BMI	24.5 (4.9)	24.8 (4.7)	23.6 (5.3)	0.117
Women (%)	128 (45%)	89 (42%)	39 (52%)	0.193
Baseline SBP	132 (18)	134 (18)	128 (19)	0.031
Baseline DBP	70 (8)	71 (8)	68 (8)	0.009
Baseline PP	62 (16)	63 (15)	60 (17)	0.242
Baseline MBP	91 (10)	92 (10)	88 (10)	0.005
Baseline HR	75 (12)	76 (11)	74 (13)	0.341
Diabetes (%)	137 (48.1%)	95 (45.2%)	42 (56.0%)	0.142
Hypertension (%)	222 (77.9%)	162 (77.1%)	60 (80.0%)	0.727
Ever smoker (%)	192 (67.4%)	144 (68.6%)	48 (64.0%)	0.561
Dialysis-dependency (%)	20 (7.2%)	14 (6.9%)	6 (8%)	0.956
<b>History (%)</b>				
Ischemic stroke or TIA	48 (16.8%)	30 (14.3%)	18 (24.0%)	0.080
Coronary heart disease	112 (39.3%)	69 (32.9%)	43 (57.3%)	<0.001
PAD revascularization <sup>a</sup>	90 (31.6%)	69 (32.9%)	21 (28.0%)	0.527
Left ventricular ejection fraction (%)	59.5 (12.8)	62.0 (10.9)	54.0 (15.0)	<0.001
Institutionalized status (%)	57 (20.0%)	36 (17.1%)	21 (28.0%)	0.064
<b>Biological parameters</b>				
Creatinine clearance (mL/mn)	71.0 (28.4)	73.3 (29.2)	64.8 (25.2)	0.022
Hemoglobin (g/dL)	11.2 (1.6)	11.3 (1.7)	10.9 (1.5)	0.042
Albumin (g/L)	32.9 (5.6)	33.4 (5.4)	31.6 (5.8)	0.062
C-reactive protein (mg/L)	59.9 (65.8)	55.8 (64.9)	70.1 (67.5)	0.144
Brain natriuretic peptide (pg/ml)	456 (675)	269 (336)	807 (958)	<0.001
<b>Hemodynamic parameters pre-procedure</b>				
Ankle-brachial index	0.59 (0.44)	0.59 (0.42)	0.59 (0.49)	0.984
Great toe LDF (mmHg)	25.6 (14.7)	25.2 (14.9)	26.6 (13.9)	0.500
Great toe LDF index	0.20 (0.11)	0.19 (0.11)	0.21 (0.11)	0.350
<b>Hemodynamic parameters post-procedure</b>				
Ankle-brachial index	0.86 (0.29)	0.85 (0.29)	0.92 (0.30)	0.218
Great toe LDF (mmHg)	49.5 (18.1)	48.6 (17.5)	51.7 (19.5)	0.344
Great toe LDF index	0.39 (0.15)	0.38 (0.15)	0.42 (0.14)	0.201
<b>Treatment at discharge</b>				
Statin (%)	251 (88.1%)	187 (89.0%)	64 (85.3%)	0.519
IRAS (%)	182 (63.9%)	137 (65.2%)	45 (60.0%)	0.503
Anticoagulant (%)	93 (32.9%)	61 (29.3%)	32 (42.7%)	0.049

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MBP: mean blood pressure; HR: heart rate; TIA: transient ischemic attack; PAD: peripheral arterial disease; LDF: great toe laser Doppler flowmetry; IRAS: inhibitors of the renin-angiotensin system. Data are presented as mean ( $\pm$  standard deviation) or number (%).

<sup>a</sup> Ninety patients underwent more than one endovascular revascularization procedure for critical limb ischemia.

( $P=0.001$ ), left ventricular ejection fraction ( $P=0.001$ ), institutionalized status ( $P=0.002$ ), hemoglobin level ( $P=0.009$ ), serum albumin level ( $P<0.001$ ), brain natriuretic peptide ( $P=0.001$ ) and MACE ( $P<0.001$ ) were correlated with mortality at one year (Tables 1 and 2). In multivariate analysis, MACE ( $P<0.001$ ), malnutrition ( $P=0.03$ ) and institutionalized status ( $P=0.03$ ) were positively associated with one-year mortality, whereas mean BP ( $P=0.01$ ) and major limb amputation ( $P=0.03$ ) were inversely correlated with mortality (Table 3). Fig. 1 illustrates the survival curves according to the occurrence of MACE during the one-year follow-up.

In univariate analysis for the incidence of fatal and non-fatal MACE, age ( $P=0.047$ ), mean BP ( $P=0.005$ ), history of coronary heart disease ( $p<0.001$ ), left ventricular ejection fraction ( $P<0.001$ ), creatinine clearance ( $P=0.022$ ), hemoglobin level ( $P=0.042$ ), brain natriuretic peptide ( $P<0.001$ ) and anticoagulant treatment ( $P=0.049$ ) were correlated with the incidence of MACE through the one-year following revascularization (Table 4). In multivariate analysis, decompensated heart failure ( $P=0.009$ ), history of coronary heart disease ( $P=0.004$ ) and local procedure complication ( $P=0.04$ ) were positively associated with MACE occurrence (Table 5).

**Table 5** Multivariate regression model for 1-year major cardiovascular events.

	HR (95% CI)	P
Age	1.02 (0.99–1.06)	0.12
Mean blood pressure	0.99 (0.95–1.03)	0.54
LVEF < 60%	1.05 (0.47–2.30)	0.90
eGFR	1.002 (0.99–1.02)	0.71
BNP ≥ 500 pg/mL	3.89 (1.43–11.11)	0.009
Hemoglobin	0.87 (0.70–1.08)	0.21
Coronary heart disease	2.83 (1.41–5.78)	0.004
Local procedure complication	3.50 (1.05–12.32)	0.04
Anticoagulant treatment	1.78 (0.88–3.58)	0.11

Area under the curve: 0.78.

## Discussion

The present study cohort included elderly patients with CLI, with a subsequent high mortality rate of 26.7% during the one-year follow-up following endovascular revascularization procedure. Incident cardiovascular event, malnutrition and institutionalized status were the major predictors of overall mortality.

This high mortality rate (26.6%) is in line with national and international literature data and confirms the poor short-term prognosis of patients managed for CLI [10,12–15]. As previously underlined, major cardiovascular events frequently occurred in patients with CLI following endovascular procedure [13]. Patients who experienced a MACE during the follow-up had a significantly higher mortality rate than patients without incident MACE (HR 6.96, 95% CI 2.99–16.94), indicating that the mortality risk of an individual patient increases almost 7 times from the moment the adverse cardiovascular event occurs.

It is now well established that symptoms, severity, and acuteness of PAD are major determinants of subsequent risk of MACE and mortality. Independent of symptoms, patients diagnosed with PAD are at an increased risk of subsequent myocardial infarction and stroke, and are 6 times more likely to die within 10 years than those without PAD [19,20]. In the multinational, prospective Reduction of Atherothrombosis for Continued Health (REACH) registry, among symptomatic individuals with established coronary artery disease, cerebral vascular disease, or PAD, stable patients with PAD had a numerically higher risk of vascular death, myocardial infarction, or stroke compared with stable patients with coronary artery disease at 1 year and at 3 years [12,21]. Patients with severe PAD requiring amputations are at even higher risk of mortality [22]. Similarly, PAD patients requiring revascularization procedures are at increased risk of cardiovascular complications, especially in the first year following the procedure. Even among the less invasive endovascular procedures and despite preoperative cardiac evaluation, short-term cardiovascular complications and mortality remain high in patients with CLI [13], as underlined in the present results. These patients present a significant underlying cardiac comorbidity (history of CHD was present in 39% of the present patient population), and decompensated heart failure was prevalent in the

peri-procedural period, in line with previously published data [13].

With the advent of improved technology and widespread accessibility, endovascular therapy is fast becoming the first-line treatment. Catheter-based technologies have made it possible to perform distal revascularizations to achieve tissue perfusion in a multidisciplinary team approach. In the same time, amputation's rate appears to have drastically reduced in the last decades [23]. However, major amputation rates are still considerable in revascularized patients with CLI, of up to 12% during the first 6 months following procedure [24]. In the present study, major amputation was performed in 25 patients (8.8%) and was associated with improved one-year survival. However, these data should be interpreted with caution. Indeed, major amputation is a severely debilitating procedure that is discussed only as a last therapeutic option in the absence of feasible revascularization and in patients with preserved general condition, to ultimately relieve ischemic pain and prevent sepsis. Amputated patient's profile is therefore very different from patients who do not undergo this procedure [11].

Furthermore, the multivariate analysis brings out malnutrition as a risk marker for one-year mortality in our cohort of patients with CLI following revascularization. It is currently established that malnutrition is associated with morbidity and mortality risk after cardiovascular surgeries [25–27] and more specifically in CLI patients following endovascular procedures [14,28]. Our results support the clinical usefulness of serum albumin determination, as a marker of malnutrition during patient's hospital stay, as it may help to improve overall survival.

In conclusion, despite technological and therapeutic advances in revascularization procedures, CLI remains a condition associated with a poor overall survival. Major cardiovascular events frequently occurred in the year following revascularization and are associated with an increased mortality risk. Decompensated heart failure and coronary heart disease are important contributors for the occurrence of MACE. Furthermore, in elderly patients with CLI, these results should be taken into account during the multidisciplinary team meeting before consideration of revascularization procedure. In addition, malnutrition appears as an important determinant for overall mortality and it remains to demonstrate if perioperative nutritional supplementation has the potential to ultimately improve outcomes.

## Disclosure of interest

The authors declare that they have no competing interest.

## References

- [1] Cardoso CRL, Melo JV, Santos TRM, Leite NC, Salles GF. Traditional and non-traditional risk factors for peripheral artery disease development/progression in patients with type 2 diabetes: the Rio de Janeiro type 2 diabetes cohort study. *Cardiovasc Diabetol* 2021;20:54.
- [2] Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in



- 2000 and 2010: a systematic review and analysis. *Lancet* 2013;382:1329–40.
- [3] Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg* 2014;60:686e2–95e2.
- [4] Conte MS, Bradbury AW, Kolh P, White JV, Dick F, et al., GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg* 2019;58:S1e33–O9e33.
- [5] Wübbelke LF, Naves CCLM, Daemen JW, Jacobs MJ, Mees BME. Mortality and major amputation after revascularisation in octogenarians versus non-octogenarians with chronic limb threatening ischaemia: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2020;60:231–41.
- [6] Zghouzi M, Moussa Pacha H, Ullah W, Sattar Y, Ahmad B, Osman H, et al. In-hospital outcomes of endovascular versus surgical revascularization for chronic total occlusion in peripheral artery disease. *Catheter Cardiovasc Interv* 2021;98:E586–93.
- [7] Blevins Jr WA, Schneider PA. Endovascular management of critical limb ischemia. *Eur J Vasc Endovasc Surg* 2010;39:756–61.
- [8] Lin JH, Brunson A, Romano PS, Mell MW, Humphries MD. Endovascular-first treatment is associated with improved amputation-free survival in patients with critical limb ischemia. *Circ Cardiovasc Qual Outcomes* 2019;12:e005273.
- [9] Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg* 2009;50:54–60.
- [10] Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: the COPART Registry. *Eur J Vasc Endovasc Surg* 2010;39:577–85.
- [11] Yannoutsos A, Lin F, Billuart O, Buronfosse A, Sacco E, Beaussier H, et al. Low admission blood pressure as a marker of poor 1-year survival in patients with revascularized critical limb ischemia. *J Hypertens* 2021;39:1611–20.
- [12] Steg PG, Bhatt DL, Wilson PW, D'Agostino Sr R, Ohman EM, Röther J, et al., REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;297:1197–206.
- [13] Roijers JJP, Rakké BYS, Hopmans NCJ, Buimer TMG, Ho GGH, de Groot HHGW, et al. Adverse cardiac events and mortality in patients with critical limb ischemia. *Ann Vasc Surg* 2020;66:486–92.
- [14] Shiraki T, Iida O, Takahara M, Masuda M, Okamoto S, Ishihara T, et al. The Geriatric Nutritional Risk Index is independently associated with prognosis in patients with critical limb ischemia following endovascular therapy. *Eur J Vasc Endovasc Surg* 2016;52:218–24.
- [15] Engelhardt M, Boos J, Bruijnen H, Wohlgemuth W, Willy C, Tannheimer M, et al. Critical limb ischaemia: initial treatment and predictors of amputation-free survival. *Eur J Vasc Endovasc Surg* 2012;43:55–61.
- [16] Constans J, Bura-Rivière A, Visona A, Brodmann M, Abraham P, Olinic D-M, et al. Urgent need to clarify the definition of chronic critical limb ischemia – a position paper from the European Society for Vascular Medicine. *Vasa* 2019;48:223–7.
- [17] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al., Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–54.
- [18] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of anti-thrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
- [19] Morris DR, Rodriguez AJ, Moxon JV, Cunningham MA, McDermott MM, Myers J, et al. Association of lower extremity performance with cardiovascular and all-cause mortality in patients with peripheral artery disease: a systematic review and meta-analysis. *J Am Heart Assoc* 2014;3:e001105.
- [20] Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992;326:381–6.
- [21] Abola MT, Bhatt DL, Duval S, Cacoub PP, Baumgartner I, Keo H, et al., REACH Investigators. Fate of individuals with ischemic amputations in the REACH Registry: three-year cardiovascular and limb-related outcomes. *Atherosclerosis* 2012;221:527–35.
- [22] Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *Am Heart J* 2013;165:809–15.
- [23] Egorova NN, Guillerme S, Gelijns A, Morrissey N, Dayal R, McKinsey JF, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. *J Vasc Surg* 2010;51:878–85 [885.e1].
- [24] Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, et al. Amputation rates, mortality, and preoperative comorbidities in patients revascularised for intermittent claudication or critical limb ischaemia: a population based study. *Eur J Vasc Endovasc Surg* 2017;54:480–6.
- [25] Peacock MR, Farber A, Eslami MH, Kalish JA, Rybin D, Doros G, et al. Hypoalbuminemia predicts perioperative morbidity and mortality after infrainguinal lower extremity bypass for critical limb ischemia. *Ann Vasc Surg* 2017;41:169e4–75e4.
- [26] Boitano LT, Wang EC, Kibbe MR. Differential effect of nutritional status on vascular surgery outcomes in a veterans affairs versus private hospital setting. *Am J Surg* 2012;204:e27–37.
- [27] Bhamidipati CM, LaPar DJ, Mehta GS, Kern JA, Upchurch GR, Kron IL, et al. Albumin is a better predictor of outcomes than body mass index following coronary artery bypass grafting. *Surgery* 2011;150:626–34.
- [28] Yannoutsos A, Lin F, Gaisset R, Jaillette C, Lazareth I, Emmerich J, et al. Characteristics and outcomes of octogenarians with revascularized critical limb ischemia: Impact of altered cardiac function for early mortality. *J Med Vasc* 2021;46:224–31.