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Original Article

Prognostic Factors in Patients Treated with Drug-Coated Balloon Angioplasty for Symptomatic Peripheral Artery Disease

Fragiska Sigala[1,2]*, George Galyfos[2]*, Kyriakos Stavridis[1], Konstantinos Tigkiropoulos[1], Ioannis Lazaridis[1], Dimitrios Karamanos[1], Vangelis Mpontinis[1], Nikolaos Melas[1], Ioulia Zournatzi[1], Konstantinos Filis[2], and Nikolaos Saratzis[1]

[1]First Department of Surgery, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Thessaloniki, [2]First Department of Propaedeutic Surgery, Ethnikon and Kapodistriakon University of Athens, Hippocration Hospital, Athens, Greece

Purpose: Aim of this study is to report real-life experience on the treatment of peripheral artery disease (PAD) with a specific drug-coated balloon (DCB), and to evaluate potential prognostic factors for outcomes.

Materials and Methods: This is a retrospective study reporting outcomes in patients with PAD who were treated with the Lutonix DCB during a four-year period. Major outcomes included: all-cause mortality, amputation, clinical improvement, wound healing and target lesion revascularization (TLR). Mean follow-up was 24.2±2.3 months.

Results: Overall, 149 patients (mean age: 68.6±8.3 years; 113 males) were treated, either for intermittent claudication (IC) (n=86) or critical limb ischemia (CLI) (n=63). More than half the target lesions (n=206 in total) were located in the superficial femoral artery and 18.0% were below-the-knee lesions. CLI patients presented more frequently with infrapopliteal (P=0.002) or multilevel disease (P=0.0004). Overall, all-cause mortality during follow-up was 10.7%, amputation-free survival was 81.2% and TLR-free survival was 96.6%. CLI patients showed higher all-cause mortality (P=0.007) and total amputation (P=0.0001) rates as well as lower clinical improvement (P=0.0002), compared to IC patients. Coronary artery disease (CAD), gangrene and infrapopliteal disease were found to be predictors for death whereas CLI and gangrene were found to be predictors for amputation, during follow-up.

Conclusion: PAD treatment with Lutonix DCBs seems to be an efficient and safe endovascular strategy yielding promising results. However, CAD, gangrene, CLI and infrapopliteal lesions were found to be independent predictors for adverse outcomes. Larger series are needed to identify additional prognostic factors.

Key Words: Endovascular procedures, Balloon angioplasty, Peripheral artery disease

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Corresponding author: George Galyfos
First Department of Propaedeutic Surgery, Ethnikon and Kapodistriakon University of Athens, Hippocration Hospital, 6 Melinas Merkouri Street, Neon Irakleion, Attikis, 14122 Athens, Greece
Tel: 30-213-2086243
Fax: 30-210-2086455
E-mail: georgegalyfos@hotmail.com
https://orcid.org/0000-0002-6077-007X
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*These authors contributed equally to this work.

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INTRODUCTION

In the last decade, minimally invasive endovascular techniques have been established as a first-line strategy for the treatment of peripheral artery disease (PAD) [1]. Both femoropopliteal and below-the-knee (BTK) atherosclerotic

lesions are commonly treated with endovascular repair due to the lower 30-day morbidity and mortality reported, compared to bypass surgery [2,3]. Moreover, recent pooled data has shown satisfying limb salvage and overall survival rates using plain angioplasty (PTA) for BTK lesions, even in patients with critical limb ischemia (CLI) [4]. Randomized trials have also found an improved patency when using drug eluting stents in short isolated lesions, although the use of simple PTA or bare metal stents below the knee has shown rather disappointing results [5,6].

Another novel approach for longer and more difficult to treat lesions has been angioplasty with drug-coated balloons (DCBs). Several studies have shown that DCBs could improve patency and reduce target lesion revascularization (TLR) rates for femoropopliteal disease [7,8]. The delivery of paclitaxel directly to the arterial wall aims to inhibit neointimal hyperplasia and restenosis occurrence without the need for deployment of a foreign stent-material. However, early data regarding DCB for BTK lesions angioplasty has been inconsistent [9,10]. Additionally, data reporting on prognostic factors for major outcomes in such patients are limited. Therefore, aim of this study is to report major outcomes of DCB treatment in a series of patients with PAD, and to evaluate potential predictors for adverse events during follow-up.

MATERIALS AND METHODS

1) Study design

This was a retrospectively designed cohort study conducted in a Vascular Surgery Department at the Aristotle University of Thessaloniki (period of study: April 2013-April 2017). The study included patients with symptomatic PAD (Rutherford stage 1-6) that were treated with endovascular angioplasty using a paclitaxel-coated balloon, namely Lutonix (BARD Peripheral Vascular, Tempe, AZ, USA). All patients were classified according to the severity of chronic ischemia: patients with intermittent claudication (Rutherford stage 1-3) and patients with CLI (Rutherford Stage 4-6). CLI was defined as rest pain, ulcer or other necrotic lesions of the lower limb combined with an absolute arterial pressure of <50 mmHg at the anterior or posterior tibial arteries of the ipsilateral foot [1]. Data on treated vessel segment, the number, diameter and size of DCBs used, the need of additional stenting, predilatation was extracted from medical records.

Major outcomes included the following: overall mortality, overall amputation, major and minor amputation, clinical improvement, restenosis/re-occlusion, wound healing, TLR and hematoma/bleeding. Clinical improvement was defined as improvement of at least one Rutherford stage. Wound healing was defined as total ulcer healing or reduction of its size/depth. TLR was defined as any repeat angioplasty or other type of revascularization during follow-up. TLR was performed when the patient presented a restenosis or re-occlusion plus worsening of symptoms. Major amputation was defined as amputation at the level of the femur or the tibia. Minor amputation was defined as amputation at the level of the foot or the toes.

2) Procedure

The Lutonix DCB is a 0.000889 m (diameter), over-the-wire PTA dilation catheter with a semi-compliant balloon that is coated with paclitaxel at a concentration of 2 μg/mm2 and the excipients polysorbate and sorbitol to facilitate drug release and tissue deposition. The device diameters ranged 3-6 mm and the length 40-150 mm. All endovascular treatment decisions were at the discretion of the operator. When needed, predilatation with an undersized uncoated balloon (diameter >1 mm smaller) was performed before the DCB insertion. Minimum DCB inflation was 3 minutes. If multiple DCBs were needed to cover the entire lesion, an overlap of at least 5 mm had to be ensured. When significant recoil (>30%) occurred after DCB inflation or dissection was observed, stent deployment was performed.

3) Perioperative management

All patients were on a single antiplatelet regimen before the intervention (aspirin 100 mg or clopidogrel 75 mg/day). However, all patients received both agents for at least 3 days before repair or they received a loading dose of 300 mg clopidogrel in urgent cases. Additionally, each patient received a 70 units/kg bolus infusion of heparin during the procedure. Postoperatively, all patients received aspirin (100 mg/day) indefinitely plus clopidogrel (75 mg/day) for at least three months. If a stent was deployed, prolonged dual antiplatelet therapy could be given at the discretion of the physician. In patients with an indication for oral anticoagulation, addition of only 1 antiplatelet drug (either aspirin or clopidogrel) to the anticoagulant regimen was recommended. Before discharge, all patients underwent clinical examination and Doppler ultrasound evaluation. Regarding follow-up, all patients were scheduled for evaluation visits every 6 months after the procedure that included clinical and ultrasound evaluation.

4) Statistical analysis

Statistical analysis was conducted using the StatsDirect

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Statistical ver. 2.8.0 software (StatsDirect Ltd., Cheshire, UK). Comparisons between groups were performed using the t-test for continuous variables and x^2 and Fisher exact tests for categorical variables as appropriate. Continuous data is presented as the means±standard deviation. Statistical significance was defined at a P-value of <0.05. The Kaplan-Meier method was used to estimate rates of overall mortality, freedom from major and minor amputation, restenosis/re-occlusion. Multivariate logistic regression was used to identify independent associations between various risk factors and major outcomes (death, all amputation, TLR).

This study was conducted according to the Helsinki Declaration for human rights. All patients provided a written informed consent.

This study was approved by the ethical committee of the Papageorgiou General Hospital, Thessaloniki (IRB no. 34563245).

RESULTS

Overall, 149 patients (159 limbs) were treated for IC (Group A, n=86) or CLI (Group B, n=63). Mean age of all patients was 68.6±8.3 years and the majority (113/149) were of male sex. Regarding basic demographics, the two groups were similar except for dyslipidemia (P=0.036) and diabetes mellitus (DM) (P=0.004) (Table 1). One fourth of the claudicants were of Stage 1-2, whereas 33 patients with CLI had an ulcer, 6 presented with rest pain and 24 patients presented with gangrene. The majority of atherosclerotic lesions were located in the femoropopliteal segment (81% of all lesions) and almost 40% of patients had a multilevel disease. In almost one third of cases, a stent needed to be deployed, whereas 76% of patients needed a predilatation. Predilatation was not associated with postdissection or stent deployment.

Mean diameter of balloons was 4.78 mm, mean length of balloons was 116.27 mm, and in 27.0% of cases, more than one device was needed. Patients with CLI presented more frequently with stenosis located in the popliteal artery (P=0.004), lesions of the infrapopliteal segment (stenosis: P=0.0001; occlusion: P=0.004), and with multilevel disease (P=0.00004). Moreover, patients with CLI needed predilatation (P=0.002) as well as the deployment of more than 1 DCB (P=0.040) more frequently (Table 2). Perioperative complications were limited. Only five patients presented a hematoma, without requiring further intervention. Additional, one patient presented atrial fibrillation on the 1st postoperative day, one patient presented acute myocardial infarction and one patient presented hematuria. Perioperative mortality was null. No evident embolization was observed.

The mean follow-up in this cohort was 24.2±2.3 months.

Table 1. Characteristics of patients (149 patients/159 limbs)

Variable	Total (n=149)	Claudicants (n=86)	CLI (n=63)	P-value
Age (y)	68.6±8.3	70.5±6.2	66.4±6.4	0.090
Male	113	70	43	0.080
DM	86	41	45	0.004
Hypertension	106	64	42	0.460
Dyslipidemia	71	46	25	0.036
History of Smoking	97	61	36	0.590
CAD	41	24	17	0.990
CKD	7	4	3	0.990
COPD	10	7	3	0.520
Rutherford classification				
1-2	22	22	-	-
3	64	64	-	-
4	6	-	6	-
5-6	57	-	57	-
Ulcer	33	-	33	-
Gangrene	24	-	24	-
Former procedures	38	21	17	0.850

Values are presented as mean±standard deviation or number only.
CLI, critical limb ischemia; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.
Former procedures refer to the target lesion.

Table 2. Type of lesion and procedure characteristics

Variable	Total (n=149)	Claudicants (n=86)	CLI (n=63)	P-value
Type of lesion				
SFA stenosis	93	57	36	0.310
SFA occlusion	38	26	12	0.130
POP stenosis	26	8	18	0.004
POP occlusion	11	5	6	0.530
Infrapopliteal stenosis	26	1	25	0.0001
Infrapopliteal occlusion	12	2	10	0.004
Stent restenosis treated	14	10	4	0.390
Bypass stenosis	2	2	0	0.510
Multilevel disease	60	24	36	0.0004
Procedure				
Only PTA	109	58	51	0.090
Stenting	40	27	13	0.190
Predilatation	114	69	35	0.002
Mean diameter of balloons (mm)	4.78	5.11	4.34	0.140
Mean length of balloons (mm)	116.27	120.63	113.71	0.090
>1 DCB used (patients number)	43	19	24	0.040
Number of devices used (mean number)	1.28	1.23	1.35	0.130
Mean follow-up (mo)	24.2±2.3	25.1±1.8	23.3±2.1	0.080

Values are presented as number only or mean±standard deviation.
CLI, critical limb ischemia; SFA, superficial femoral artery; POP, popliteal artery; PTA, percutaneous transluminal angioplasty; DCB, drug-coated balloon.

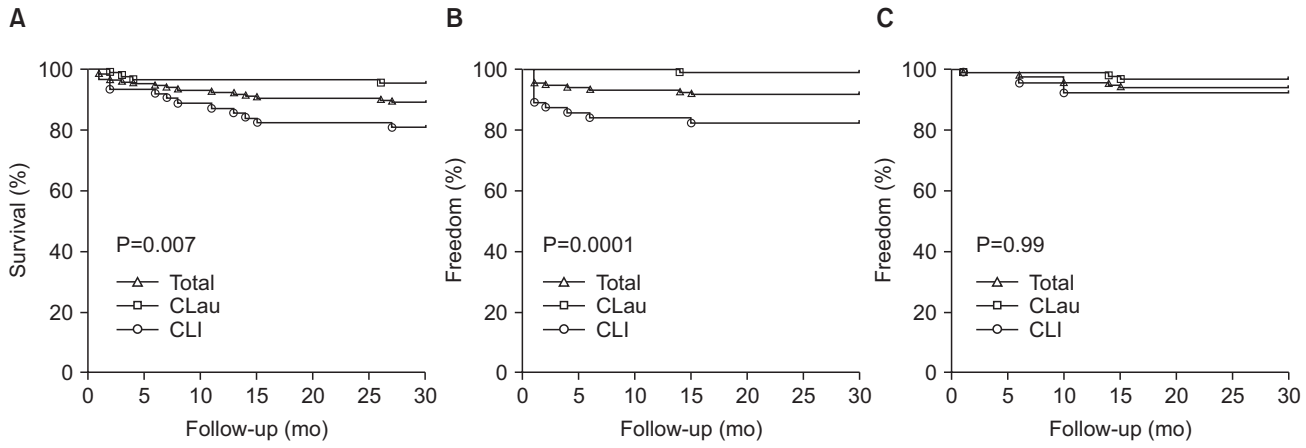

Fig. 1. Kaplan-Meier curves of all patients (Total), claudicants (Clau) and patients with critical limb ischemia referring to: (A) overall survival, (B) freedom from major amputation, and (C) freedom from target lesion revascularization (TLR). CLI, critical limb ischemia.

During follow-up, 10.7% of patients died from various causes: cardiovascular death (n=11), infection (n=3), gastrointestinal bleeding (n=1), craniocerebral injury (n=1). Regarding amputation rate, 12 patients underwent major amputation and 16 patients underwent minor amputation. Overall, 99 patients (66.4%) showed clinical improvement during follow-up, and 27 patients with ulcer (81% of ulcers) showed signs of wound healing. Restenosis or re-occlusion was reported in 12 patients with 9 of them needing a TLR. Kaplan-Meier curves were generated for freedom from death, major amputation and TLR (Fig. 1).

When comparing the two groups during the follow-up period, patients with CLI were associated with a higher mortality rate (19.0% vs. 4.7%; P=0.007) and a higher all

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amputation rate (44.4% vs. 0%; P=0.0001). Moreover, claudicants were associated with a higher rate of clinical improvement (79.1% vs. 49.2%; P=0.0002). However, no difference was found between the two groups as far as restenosis/re-occlusion and TLR rates are concerned (Table 3).

After conducting multi-regression analysis, the following risk factors were independently associated with death during follow-up: CAD (odds ratio [OR], 11.157; 95% confidence interval [CI], 2.054-60.592; P=0.005), gangrene (OR, 3.671; 95% CI, 1.045-14.337; P=0.034) and infrapopliteal disease (OR, 4.795; 95% CI, 1.043-22.051; P=0.044). Additionally, CLI (OR, 19.705; 95% CI, 3.595-108.011; P=0.0006) and gangrene (OR, 3.558; 95% CI, 1.852-7.675; P=0.034) were independently associated with amputation during follow-up. However, none of the potential predictors evaluated did correlate with TLR during follow-up (Table 4).

DISCUSSION

This was a real world, single-center study on the treatment of lower limb occlusive disease using the Lutonix DCB. Outcomes were more favorable in patients with IC compared to CLI, as expected. However, this study also found certain prognostic factors for major outcomes in patients treated with DCBs.

Regarding perioperative outcomes, DCB angioplasty has shown promising results with minimal mortality and morbidity in our cohort. This concurs with literature where endovascular treatment in general has been associated with lower morbidity in patients with femoropopliteal disease compared to open surgery [11]. Hence, almost 80% of the lesions treated in our cohort were located in the femoropopliteal segment. However, pooled evidence comparing endovascular to open treatment for infrapopliteal disease or comparing DCB angioplasty to surgery in general are lacking.

Additionally, all-cause mortality and major amputation rates during a mean follow-up of almost 2 years were satisfying in our cohort, reaching 10.7% and 8.1%, respectively. In a recent study by Steiner et al. [12], combined major amputation and mortality rates reached 6.6% and 10.5% after a follow-up period of only 6 and 12 months, respectively. Moreover, the recent randomized trial LEVANT-2 has also found equally low mortality and major amputation rates within 12 months after treatment of femoropopliteal lesions with Lutonix balloon compared to simple angioplasty [13]. However, primary patency with DCB was found to be superior to conventional angioplasty within a 12-month follow-up in the former trial [13]. Finally, in a recent meta-analysis, DCBs were found to have lower TLR rates compared to PTA whereas the death risk was similar between the two methods [14]. Although our TLR rate is almost half of the rate reported in this meta-analysis, this could be justified as they reported 12-month rates and we report a mean 24-month results.

Pooled data have also been published comparing DCB treatment to bare-metal and drug-eluting stents for femoropopliteal disease. Katsanos et al. [15] have shown that vascular restenosis and TLR are significantly lower after DCB angioplasty compared to plain balloon angioplasty or bare-metal stenting, concurring with our results, where TLR was as low as 3.3% during follow-up. Additionally, DCBs showed no difference compared to drug-eluting stenting in the same review, as far as restenosis and TLR are concerned [16].

In the present study, we have evaluated potential predictors both for death and amputation during follow-up. Major predictors for death included CAD as well as the presence of gangrene or infrapopliteal disease, whereas CLI and gangrene were found to be associated with a higher amputation risk. Although large multicentre studies evaluating the Lutonix DCB for femoropopliteal disease have not evaluated potential risk predictors for adverse events, several smaller studies have found certain predictors for future restenosis and TLR [13,16]. Jang et al. [17] have found that major tis-

Table 3. Outcomes for all patients, claudicants and CLI patients during follow-up

Outcome	Total (n=149)	Claudicants (n=86)	CLI (n=63)	P-value
All-cause mortality	16	4	12	0.007
All amputation	28	0	28	0.0001
Major amputation	12	0	12	0.0001
Minor amputation	16	0	16	0.0001
Clinical improvement	99	68	31	0.0002
Wound/ulcer healing	27	0	27	0.0001
TLR	5	3	2	0.990
Hematoma/bleeding	5	2	3	0.990
Restenosis/re-occlusion	12	6	6	0.990

CLI, critical limb ischemia; TLR, target lesion revascularization.

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Table 4. Multiregression analysis

Factor	Death				All amputation				TLR	
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
CLI	5.915 (1.759-19.889)	0.001	3.310 (0.605-18.113)	0.168	Infinity	<0.0001	19.705 (3.595-108.011)	0.0006	0.825 (0.207-3.287)	0.999
DM	0.942 (0.371-2.394)	0.999	-	-	1.132 (0.571-2.247)	0.833	-	-	2.029 (0.428-9.619)	0.373
Hypertension	0.893 (0.329- 2.416)	1.000	-	-	1.014 (0.484-2.124)	0.999	-	-	0.769 (0.194-3.045)	0.709
Dyslipidemia	1.099 (0.435-2.773)	1.000	-	-	0.824 (0.419-1.619)	0.676	-	-	0.796 (0.200-3.172)	0.746
History of smoking	1.072 (0.279-4.113)	1.000	-	-	0.519 (0.233-1.127)	0.096	-	-	0.329 (0.088-1.231)	0.099
CAD	3.095 (1.282-7.473)	0.002	11.157 (2.054-60.592)	0.005	0.722 (0.284-1.834)	0.494	-	-	0.722 (0.153-3.406)	0.681
CKD	1.765 (0.672-4.785)	0.078	-	-	-	-	-	-	-	-
COPD	2.709 (0.459-6.353)	0.067	-	-	-	-	-	-	-	-
Gangrene	5.208 (2.166-12.523)	0.0008	3.671 (1.045-14.337)	0.034	5.208 (2.863-9.474)	<0.0001	3.558 (1.852-7.675)	0.034	3.000 (0.782-11.503)	0.109
Multilevel disease	1.483 (0.589-3.736)	0.429	-	-	1.978 (1.009-3.877)	0.049	0.443 (0.128-1.533)	0.199	1.426 (0.375-5.416)	0.603
Infrapopliteal disease	2.921 (1.178-7.243)	0.030	4.795 (1.043-22.051)	0.044	2.532 (1.328-4.825)	0.008	2.494 (0.708-8.787)	0.155	0.933 (0.199-4.376)	0.930
Stenting	-	-	-	-	0.614 (0.222-1.699)	0.347	-	-	0.366 (0.047-2.858)	0.338

TLR, target lesion revascularization; OR, odds ratio; CI, confidence interval; CLI, critical limb ischemia; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

sue loss (Rutherford class 6) and long length of lesion are associated with future restenosis although no association was found with TLR. Additionally, Schmidt et al. [18] have found that heavy calcification of lesion and obesity are both predictors for primary patency and TLR. However, no major predictors for TLR were observed in our cohort.

Regarding BTK disease, 25.5% of our patients were treated for infrapopliteal lesions, with infrapopliteal disease being independently associated with mortality. However, in other cohort studies, BTK disease was strongly associated with limb loss after endovascular-first approach for patients with CLI [19]. Moreover, Vierthaler et al. [20] have tried to evaluate in a large study of 1,244 patients to identify potential predictors of amputation after endovascular treatment for CLI and they did not find any association with the level of occlusive disease, concurring with our results. Furthermore, randomized trials have compared DCBs with plain balloon angioplasty for infrapopliteal lesions, as far as early and midterm outcomes are concerned. Concerning 30-day safety outcomes (cardiovascular events, amputations and TLR) as well as 6-month outcomes (patency loss and major amputations), DCB treatment did not show any difference with PTA in these trials [21]. Moreover, pooled data on infrapopliteal disease indicates that DCB treatment shows a similar one-year benefit with PTA as well [22]. Finally, pooled data also reveals similar clinical outcomes and angiographic efficacy during one-year follow-up after DCB treatment compared to drug-eluting stenting [23].

Moreover, CLI patients showed higher mortality and amputation rates as well as a lower clinical improvement rate during follow-up, as expected. This concurs with literature data showing that patients with CLI is associated with up to a 40% amputation rate at 6 months and 20%-25% mortality rate at one year after presentation [24,25]. This could be justified as CLI seems to be a systemic inflammatory condition associated with increased levels of circulating cytokines that may explain the worse prognosis [26]. Additionally, other authors have compared outcomes between these two patient groups and have reported controversial results. Todoran et al. [27] have found a higher mortality rate in CLI patients with femoropopliteal lesions compared to claudicants, although patency rates were similar between the two groups during follow-up. Conversely, Trocciola et al. [28] have found significantly lower patency rates in CLI patients compared to claudicants within one year of follow-up. However, most of comparative studies refer to patients treated with plain angioplasty, and comparative data on patients treated with DCBs are limited.

Limitations of this study include the small number of patients, and especially the low number of cases with infrapopliteal lesions. However, statistically significant associations were established. Second, the retrospective design of the study and the reliance on patient records are also major limitations. Third, the follow-up period is longer than one year but shorter than in some randomized trials. Additionally, single-institution series are often biased towards particular patient demographics and practice patterns, but these data represent the real-world application of DCBs. Finally, angiography was not routinely performed during follow-up, but only when a re-operation was necessary.

In conclusion, treatment with Lutonix DCB shows promising early and midterm results in patients with symptomatic PAD. Patients with CLI have clearly worse outcomes compared to patients with IC during follow-up, as expected. CAD, gangrene, CLI and infrapopliteal lesions seem to be independently associated with adverse outcomes, and therefore a closer observation is needed for such patients.

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