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RESEARCH

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A retrospective analysis on optimal medical therapy for patients with symptomatic lower extremity peripheral artery disease: a French observational study

Camille de Kermenguy^{1,3}, Anne Durand^{1,3}, Quentin Tollenaere^{1,3}, Estelle Le Pabic³, François Paillard⁴ and Guillaume Mahé^{1,2,3,5*}

Abstract

Objective Patients with symptomatic lower extremity artery disease (LEAD) should have an optimal management in terms of lipid goal [i.e. controlled LDL-cholesterol (LDLc)] and medical treatment (triple therapy with an antiplatelet agent, a statin and an angiotensin-converting enzyme inhibitor or a angiotensin-receptor antagonist). Prevalence of LEAD patients with a LDLc < 0.55 g/l is unknown. Aims of this study were to: (i) describe the prevalence of patients with a LDLc < 0.55 g/l, (ii) describe the prevalence of patients with an optimal medical treatment; (iii) compare this management between patients with a vascular surgery history and those without a vascular surgery history; and (iv) evaluate the number of patients eligible for new lipid-lowering therapies according to FOURIER and REDUCE-IT criteria.

Methods In this single-center retrospective study, prevalence is expressed as numbers and percentages. Comparison of the number of well managed patients between LEAD patients with a vascular surgery history and those without was performed. Number of patients who would be eligible for FOURIER and REDUCE-IT studies were calculated.

Results Among the LEAD patients included in the analysis ($n = 225$), only 12.4% ($n = 28$) had a LDLc < 0.55 g/L. The prevalence of patients who received the optimal medical treatment was 50.7% ($n = 114$). There was no statistical difference in the prevalence of patients with and without vascular surgery history achieving the LDLc goal ($n = 9$ (10.6%) vs. $n = 19$ (13.6%); $p =$ not significant). Ninety-three patients (46.0%) would be eligible for EVOLOCUMAB treatment according to the Fourier study design whereas 17 patients (8.4%) would be eligible for treatment with ICOSAPENT ETHYL according to the REDUCE-IT study design.

Conclusion A majority of LEAD patients did not reach the LDLc goals. LEAD patients with a vascular surgery history did not experience a better management whereas they had a more consistent follow-up.

Keywords Peripheral artery disease, Treatment, Lipid objectives, Triglycerides

*Correspondence:

Guillaume Mahé
maheguillaume@yahoo.fr

¹Vascular Medicine Unit, CHU Rennes, 2 Rue Henri Le Guilloux, Rennes 35033, France

²Univ Rennes, M2S – EA 7470, F-35000 Rennes, France

³CHU Rennes, Inserm, CIC 1414 (Clinical Investigation Center), Rennes F-35000, France

⁴CHU Rennes, Centre de Prévention Cardiovasculaire, Rennes, France

⁵Univ Rennes, Rennes, France



Introduction

Lower extremity artery disease (LEAD) is a frequent pathology in the world with more than 230 million individuals affected [1, 2]. LEAD, whether symptomatic or asymptomatic, is associated with an increased risk of cardiovascular (CV) mortality and morbidity, including an increased risk of developing major adverse cardiovascular events (MACE) and major adverse limb events (MALE) [3]. Cardiovascular mortality at 5 years in these patients is significantly higher than in the general population (mortality at 5 years of about 30% vs. 10% in patients without LEAD) [4].

An optimal control of CV risk factors is essential and has shown a benefit in terms of morbimortality. This control is achieved primarily through the establishment of a healthy lifestyle, including an appropriate diet, regular physical activity, abstinence from smoking, and optimal medical treatment, including the administration of antihypertensive, lipid-lowering, antidiabetic (if indicated), and antithrombotic medications [5].

Several previous studies in different countries have demonstrated a lack of optimal treatment in LEAD patients [3, 6]. LEAD patients who underwent vascular surgery should normally receive an optimal medical treatment (lipid-lowering (statin), antiplatelet and antihypertensive drugs [ARA (angiotensin-receptor antagonist) or ACE-I (angiotensin-converting enzyme inhibitor)]). The primary hypothesis of this study is that only a few LEAD patients receive an optimal medical treatment and are within therapeutic targets in terms of LDLc (low density lipoproteins cholesterol). The secondary hypothesis is that LEAD patients with a vascular surgery history of the lower limbs receive better medical treatment and are more in LDL ranges compared to LEAD patients without vascular surgery history who have less extensive follow-up.

The primary objective of this study is to describe the prevalence of patients who achieved the recommended target for LDLc level according to latest international guidelines [5, 7]. The secondary objectives are: (i) to describe the prevalence of LEAD patients with an optimal medical treatment; (ii) to compare patients with LEAD who underwent vascular surgery vs. LEAD patients without vascular surgery history in terms of optimal medical treatment and LDLc and triglyceride targets; (iii) to describe the population according to LDLc and triglycerides targets; and (iv) to evaluate the number of patients eligible for new lipid-lowering therapies according to FOURIER and REDUCE-IT criteria [8, 9].

Materials and methods

Study design

Inclusion criteria

Patients were considered to have LEAD if they had at least one of the following conditions: a history of lower extremity vascular surgery, or a resting Ankle Brachial Index (ABI) ≤ 0.90 , or a normal resting ABI associated with a post-exercise ABI decrease of 18.5% (see below), or a resting oxygen pressure delta (DROP) ≤ 15 mmHg (see below) on either lower extremity [5, 10, 11].

Exclusion criteria

All patients with LEAD criteria were included in the analysis provided the data on LDL cholesterol was available.

Patient characteristics

The following data was collected: gender, age, body mass index, presence or absence of diabetes, hypertension, dyslipidemia, smoking status (smoker or former smoker), personal vascular history (peripheral vascular bypass surgery, angioplasty and/or peripheral vascular stenting), personal coronary heart disease history (history of myocardial infarction, coronary bypass surgery or coronary stenting), personal ischemic stroke history (stroke, transient ischemic attack or carotid artery surgery), medications, antihypertensive agents including angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-receptor antagonist (ARA), beta blocker, calcium channel blocker, anticoagulant therapy, platelet aggregation inhibitor, and antidiabetic therapy), lipid-lowering therapies: statins (divided by intensity class defined according to the joint recommendations of the American College of Cardiology (ACC) and the American Heart Association (AHA) [12], ezetimibe, fibrates and anti-diabetic drugs.

Patients were defined as diabetic if they were receiving medication for diabetes or with a glycated hemoglobin (HbA1c) $> 6.5\%$. Patients were defined as hypertensive if they were receiving antihypertensive treatment or if blood pressure exceeded 140/90 mmHg. Smoking status was considered current if patients reported active smoking or smoking cessation for less than 6 months.

The optimal medical treatment is defined by taking antithrombotic drug, antihypertensive drugs (ARA or ACE-I) and a statin without regard to their current LDLc level.

Blood samples

Each patient who performed the walking test in the vascular medicine unit of the University Hospital of Rennes was given, prior to the appointment, a prescription for a biological workup including: complete blood count, platelets, creatinine, glomerular filtration rate (GFR), complete hepatic workup (aspartate aminotransferases,

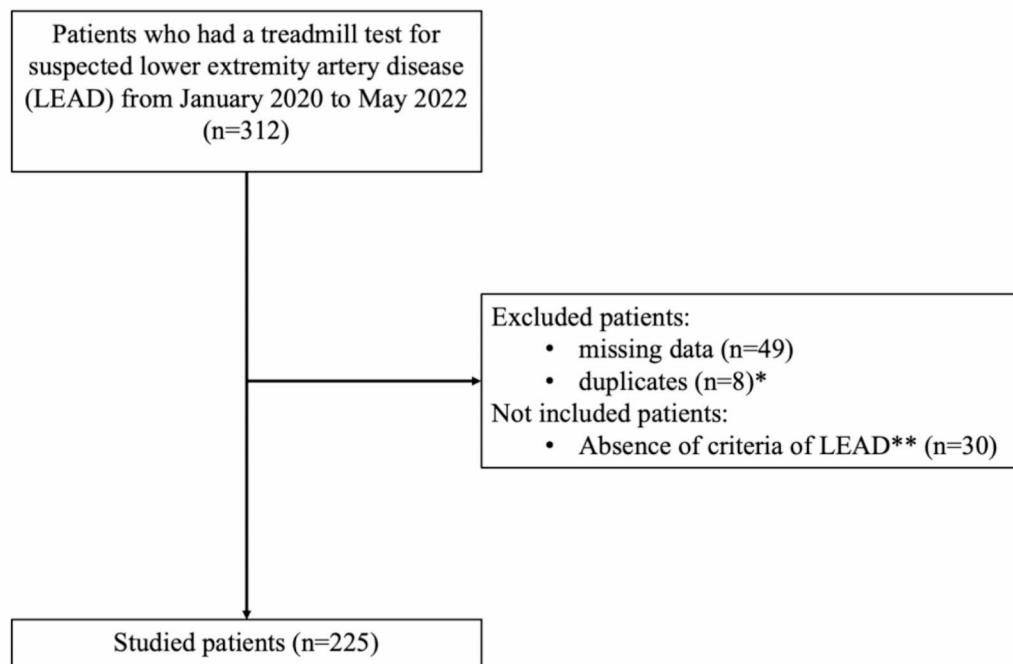


Fig. 1 Diagram flow of the included population. legend: * only the most recent exam was kept; ** history of lower extremity vascular surgery or ankle-brachial index ≤ 0.90 or post-exercise ankle-brachial index $\geq 18.5\%$ or exercise TcPO₂ with Delta from rest oxygen pressure ≤ -15 mmHg

alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, an exploration of lipid abnormalities including total cholesterol, LDLc, High density lipoprotein cholesterol (HDLc), triglycerides, HbA1c.

ABI measurement

Measurement of ABI was performed according to American Heart Association recommendations using a handheld Doppler probe (8 MHz; Basic Atys Medical, Soucieu en Jarrest, France) [13] by a trained vascular medicine physician, except for brachial blood pressure measured with an automated oscillometric blood pressure monitor. Measurements were performed after a 10 min rest period in the supine position, head and heels supported, in a temperature controlled room (21 °C) [14]. The following sequence was used: right brachial artery, right posterior tibial artery, right dorsal pedal artery, left posterior tibial artery, left dorsal pedal artery, left brachial artery, and right brachial artery. The ABI was calculated by dividing the highest limb pressure (dorsal pedicle or posterior tibial pressures) by the highest brachial pressure as recommended [13, 14].

Treadmill test coupled with exercise transcutaneous oxygen pressure measurement (Exercise-TcPO₂):

A treadmill test (3.2 km/h, 10% slope) was used to determine the maximal walking distance (MWD). The patients were asked to inform the physician when the pain appeared [15]. Exercise was stopped according to patient limitation or up to a maximal distance of 525 m (over a period of 10 min) [15]. The exercise-TcPO₂ measurement was performed during the treadmill test as previously described using calibrated TcPO₂ electrodes (TCOM/TcPO₂; PF 6000TcPO₂/CO₂; Perimed; Jarfalla, Suède) [10, 11]. Delta drome Rest Oxygen Pressure (DROP) on each lower extremity was recorded in real time by the validated in-house Oxymonitor as previously described (version 2019.01.05; <https://imagedmed.univ-rennes1.fr/en/oxymonitor/download>) [15, 16]. As defined in previous studies, a DROP ≤ -15 mmHg was used to diagnose LEAD [10, 11, 15].

Post-exercise ABI

Measurements were performed by two vascular physicians: one at the brachial level with the automatic blood pressure device (Carescape Dinamap V100; GE Healthcare) and one at the limb level with the handheld Doppler. Post-Exercise brachial pressure was assessed on the same artery as it was for the ABI measurement at rest. At the time of resting ABI measurement, a black pen was

used to mark the skin area where the highest limb pressure had been recorded with a hand-held Doppler [17, 18] in order to shorten the measurement process post exercise. As defined in a previous study, a Post-exercise ABI decrease $\geq 18.5\%$ was used to diagnose LEAD [15].

Statistical analyses

Quantitative results are expressed as mean \pm standard deviation or median and interquartile range (IQR) and qualitative results are expressed as numbers (%). A patient will be considered to receive an optimal medical treatment if he or she is taking an antiplatelet (or anti-coagulant), an ACE-I or ARA, and a statin [5]. A patient will be considered to receive a sub-optimal medical treatment if he or she is taking an antiplatelet (or anticoagulant) and a statin [7].

The primary objective of this study is to describe the prevalence of patients who achieved the recommended target for LDLc level according to international guidelines. The secondary objectives are: (i) to describe the prevalence of patients with optimal medical treatment, (ii) to compare in terms of optimal medical treatment, LDLc and triglyceride targets patients with LEAD and vascular surgery history vs. LEAD patients without vascular surgery history; (iii) to evaluate the number of patients eligible for new lipid-lowering therapies. For group comparisons, between LEAD patients with vascular surgery history vs. LEAD patients without vascular surgery history, Student t test or Mann-Whitney Wilcoxon test if necessary was used to compare quantitative variables and Chi2 test or Fisher's exact test if necessary was used to compare qualitative variables. The number of patients meeting the criteria of the FOURIER and REDUCE-IT studies are presented in numbers and percentages according to the following criteria: Population eligible for FOURIER or REDUCE-IT: meeting inclusion and exclusion criteria; Population excluded from FOURIER [19] or REDUCE-IT [20]: with at least one exclusion criterion. All statistical tests had a significance level of ≤ 0.05 . Statistical analyses were performed using SAS software, v.9.4[®] (SAS Institute, Cary, NC, USA).

Results

Overall population

From January 2020 to May 2022, 312 patients suspected of LEAD were admitted for a walking test. Forty-nine patients were excluded because of missing data, 8 were excluded because of duplicates (only the most recent test was kept), 30 patients were not included because they did not meet the criteria for LEAD (i.e., history of lower extremity vascular surgery or $ABI \leq 0.90$ or post-exercise ABI decrease $\geq 18.5\%$, or exercise TcPO₂ with DROP ≤ -15 mmHg). A total of 225 patients were included from January 2020 to May 2022 (Fig. 1).

The characteristics of the patients are presented in Table 1. A majority of patients had mild LEAD. Among the included population ($n=225$), 13 (5.7%) patients had no information about the intensity of statins. Sixty-two (27.6%) patients did not receive any statin. Among those who received a statin, 17 (11.3%) received low intensity statins, 55 (36.7%) patients received moderate intensity statins, 78 (52.0%) received high intensity statins. Forty (17.8%) patients received a combination of statins and ezetimibe.

Primary objective

Among the LEAD patients included in the analysis ($n=225$), only 12.4% ($n=28$) had a LDLc < 0.55 g/L.

Secondary objectives

The prevalence of patients who received the optimal medical treatment was 50.7% ($n=114$). Among the 225 included patients, only 19 (8.4%) were well-managed (i.e. receiving an optimal medical treatment [triple therapy with an antiplatelet agent, a statin and an angiotensin-converting enzyme inhibitor or a angiotensin-receptor antagonist] and have a controlled LDL-cholesterol (LDLc)). There was no statistical difference in the prevalence of patients with and without vascular surgery history achieving the LDLc goal ($n=9$ (10.6%) vs. $n=19$ (13.6%); p =not significant). There was no significant difference in terms of percentage of well-managed patients between LEAD patients with and without vascular surgery history (8.2% vs. 8.6%; $p=0.93$). In patients with a vascular surgery history of the lower limbs ($n=85$), 52.9% ($n=45$) benefited from optimal medical treatment compared with 49.3% ($n=69$) in LEAD patients with no vascular surgery history ($n=140$) ($p=0.5949$) (Table 2).

There was no significant difference in the different criteria studied between patients with and without vascular surgery history, except for the use of antithrombotic therapy, which was higher in patients with a vascular surgery (100.0% vs. 93.6%; $p=0.0147$) (Table 2).

Regarding the LDLc < 0.70 g/L, 27.6% ($n=62$) of patients were within the target (recommended by the ESVM and SVS). Regarding triglyceride target, 114 patients (64.4%), out of 177 available assessments, were within the target thresholds < 1.50 g/l (Fig. 2).

A statin was prescribed in only 72.4% of patients. Among 87.6% of patients with LDLc greater than 0.55 g/L, only 6.1% ($n=12/197$) of patients were treated with a high-intensity statin combined with ezetimibe. Similarly, in the 72.4% of patients with LDLc greater than 0.70 g/L, 4.9% ($n=8/163$) of patients were treated with a high-intensity statin associated with ezetimibe treatment.

In our study, 46.3% ($n=63/136$) received optimal medical therapy in patients with LEAD alone vs. 60% ($n=33/55$) in LEAD patients with a cardiovascular

Table 1 Clinical characteristics of the included population

Clinical characteristics	Patients (n = 225)
Age, mean \pm SD (years)	64.53 \pm 11.17
Body mass index, mean \pm SD (kg/m ²)	28 \pm 5.2
Male, no. (%)	179 (79.5%)
Medical history no. (%)	
Smoker	
Current	79 (35.1%)
Former	119 (52.9%)
Diabetes	58 (25.8%)
Hypertension	182 (80.9%)
Hypercholesterolaemia	173 (76.8%)
Polyvascular patients	89 (39.6%)
Vascular history (bypass, angioplasty/stenting)	85 (37.8%)
Coronary heart disease history (myocardial infarction, angioplasty/stenting, bypass)	66 (29.3%)
Ischemic stroke history(carotid surgery, TIA, stroke)	34 (15.1%)
Atrial fibrillation	17 (7.6%)
Mean right ankle-brachial index	0.90 \pm -0.22
Mean left ankle-brachial index	0.85 \pm -0.23
Severe LEAD (ABI \leq 0.40), no.(%)*	1 (0.0%)
Moderate LEAD (0.40 < ABI \leq 0.70), no.(%)*	23 (10.2%)
Mild LEAD (0.70 < ABI \leq 0.90), no.(%)*	62 (27.6%)
Normal (0.90 < ABI \leq 1.40), no.(%)*	139 (61.8%)
Non-Compressible arteries (ABI > 1.40), no.(%)*	0 (0.0%)
Current medications, no.(%)	
Anti-hypertensives	180 (80.0%)
ACE inhibitor or ARB	144 (64.0%)
Diuretic	8 (3.6%)
CBB	66 (29.3%)
Beta-blocker	82 (36.4%)
Anticoagulants	34 (15.1%)
VKA	5 (2.2%)
OAC	28 (12.4%)
LMWH	1 (0.4%)
Antiplatelets	190 (84.4%)
Aspirin	155 (68.9%)
Clopidogrel	59 (26.2%)
Prasugrel/ticagrelor	3 (1.3%)
Lipid lowering agents	173 (76.9%)
Statins	163 (72.4%)
Statin Intensity (n = 150)	
Low intensity statins	17 (11.3%)
Moderate intensity statins	55 (36.7%)
High intensity statins	78 (52.0%)
Fibrates	7 (3.1%)
Ezetimibe	47 (20.9%)
Biology no. (%)	
Total cholesterol, mean \pm SD (g/l)	1.74 \pm 0.48
LDLc, mean \pm SD (g/l)	0.97 \pm 0.40
HDL, mean \pm SD (g/l)	0.50 \pm 0.15
Triglycerides, mean \pm SD (g/l) (n = 177)	1.53 \pm 1.12
LDLc < 0.55 g/l, no. (%)	28 (12.4%)
LDLc < 0.70 g/l, no. (%)	62(27.6%)
Triglycerides < 1.50 g/l (n = 177)	114 (64.4%)
GFR < 60 ml/min, no. (%)	41 (18.2%)

Table 1 (continued)

Clinical characteristics	Patients (n = 225)
Mean HBA1c ± SD (%)	6.18 ± 1.18
Liver cytolysis, no. (%)	4 (1.8%)
Optimal medical treatment (antiplatelet + statins + ACE Inhibitor or ARB) no. (%)	114 (50.7%)
Antiplatelet therapy or anticoagulation	216 (96.0%)
ACE inhibitor or ARB	144 (64.0%)
Statins	163 (72.4%)
Sub-optimal medical treatment (antiplatelet + statins) no. (%)	161 (71.6%)

Results are presented mean ± standard deviation (SD) or number of observation (%). ACE denotes angiotensin-converting enzyme, ARA: angiotensin-receptor antagonist, CCB: calcium channel blocker, GFR: glomerular filtration rate, LDLc: low-density lipoprotein cholesterol, LMWH: low-molecular-weight heparin, OAC=oral anticoagulant, TIA transient ischaemic attack, VKA vitamin K antagonist. *Note that the classification according to the severity of LEAD was based on the highest Ankle-Brachial Index (ABI) for each patient

history ($p=0.0869$) whereas 63.2% ($n=86/136$) received sub-optimal treatment in patients with LEAD alone vs. 83.6% ($n=46/55$) LEAD patients with a cardiovascular history ($p=0.0057$).

Patients with LDL < 0.55 g/L compared with patients ≥ 0.55 g/L had significantly more polyvascular disease, had more coronary artery disease, took more high intensity statins. (Table 3).

FOURIER eligible population

A total of 93 patients (46.0%) would be eligible for EVO-LOCUMAB treatment according to the Fourier study design (Fig. 3, panel A).

REDUCE IT eligible population

A total of 17 patients (8.4%) would be eligible for treatment with ICOSAPENT ETHYL according to the REDUCE-IT study design (Fig. 3, panel B).

Discussion

This study highlights that (i) only 12.4% ($n=28$) had a LDLc < 0.55 g/L; (ii) 50.7% ($n=114$) received the optimal medical treatment and (iii) LEAD patients with vascular history were not better treated as compared to LEAD patients without vascular history.

These results suggest that significant gaps remain in the treatment of hypercholesterolemia in LEAD patients. These results are consistent with the studies on LDLc levels in patients with symptomatic LEAD [3, 21, 22]. A single-center observational Swiss study conducted on 1109 patients between 2010 and 2017 found that only 27% of patients reached the target threshold of 0.70 g/l consistent with the 27.6% in our cohort [23]. Similar results are found in coronary patients. The EUROASPIRE IV study (2015) conducted in coronary patients, show that in the 93% of patients treated with statins, only 20% achieve a target LDLc level below 0.70 g/L [24]. This result is all the more alarming as studies show that treatments, provided that they are well adhered to, make it possible to reach the targets and limit cardiovascular events and adverse limb outcomes [25, 26].

Nevertheless, some points can explain these unsatisfactory results: (i) the tolerance of the drugs is limited (muscular adverse events, a major limitation of the use of statins) [27, 28]; (ii) non-adherence of patients, often in poly-treated patients; (iii) refusal of statin treatment often supported by misinformation concerning these treatments, i.e. a lack of knowledge on the part of practitioners concerning the target thresholds to be reached as well as the new therapies available [29], and (iv) a more restrictive LDLc target level often difficult to achieve with current therapies.

The imputability of LDLc in the development of atherosclerosis being no longer to be demonstrated [30] and given the prevalence of LEAD we can imagine that obtaining adapted and tolerable treatments allowing a respect of the target thresholds of LDLc would have a major effect on public health as well as for the people with LEAD (as well in term of MACE as MALE) [19, 25].

New therapeutic perspectives have emerged for several years, with a significant effect in terms of reducing LDLc and improving morbidity and mortality, the use of PCSK9 inhibitors, a monoclonal antibody that inhibits PCSK9 and reduces LDLc levels by about 60% [8, 31]. Several trials such as the FOURIER, ODYSSEY, or MENDEL-2 trials have demonstrated the efficacy of PCSK9 inhibitors in combination or not with statins in terms of reducing LDLc [8, 31, 32].

The FOURIER trial [8] showed a reduction in terms of cardiovascular events, particularly in LEAD patients. LEAD patients seem to have a significantly greater benefit in terms of cardiovascular morbidity and mortality compared with other patients at very high risk of CV or with other arterial diseases.

Several cardiovascular societies agree in recommending that a PCSK9 inhibitor be combined, if necessary, with statin and ezetimibe treatment in patients who are insufficiently stabilized, or be introduced alone if intolerance is observed and the therapeutic objective is not achieved [5]. According to the inclusion criteria of the FOURIER study in relation to our main population,

Table 2 Comparisons between LEAD patients with vascular surgery history and LEAD patients with no vascular surgery history

Clinical characteristics	Patients with lower limb surgery <i>n</i> = 85	Patients without lower limb surgery <i>n</i> = 140	<i>p</i> -value
Age, mean ± SD (years)	66.33 ± 9.59	63.44 ± 11.93	0.0594
Body mass index, mean ± SD, Kg/m ²	28.35 ± 5.05	27.80 ± 5.25	0.4368
Male, no. (%)	69 (81.2%)	110 (78.6%)	0.6385
Medical history no. (%)			
Smoker	24 (28.2%)	55 (39.3%)	0.0922
Diabetes	16 (18.8%)	42 (30.0%)	0.0631
Hypertension	75 (88.2%)	107 (76.4%)	0.0289
Hypercholesterolaemia	71 (83.5%)	107 (76.4%)	0.2040
Polyvascular patients	27 (31.8%)	62 (44.3%)	0.0626
Coronary heart disease history (MI, angioplasty/stenting, bypass)	22 (25.9%)	44 (31.4%)	0.3757
Ischemic Stroke history (carotid surgery, TIA, stroke)	8 (9.4%)	26 (18.6%)	0.0629
Current medication no. (%)			
Anti-hypertensives	73 (85.9%)	107 (76.4%)	0.0856
ACE inhibitor or ARB	58 (68.2%)	86 (61.4%)	0.3024
Diuretic	3 (3.5%)	5 (3.6%)	1.0000
CBB	28 (32.9%)	38 (27.1%)	0.3544
Beta-blocker	31 (36.5%)	51 (36.4%)	0.9949
Anticoagulants	16 (18.8%)	18 (12.9%)	0.2257
VKA	1 (1.2%)	4 (2.9%)	0.6523
OAC	15 (17.6%)	13 (9.3%)	0.0655
LMWH	0 (0.0%)	1 (0.7%)	1.0000
Antiplatelets	77 (90.6%)	113 (80.7%)	0.0476
Aspirin	62 (72.9%)	93 (66.4%)	0.3063
Clopidogrel	30 (35.3%)	29 (20.7%)	0.0159
Prasugrel/ticagrelor	0 (0.0%)	3 (2.1%)	0.2917
Lipid lowering agents	67 (78.8%)	106 (75.7%)	0.5917
Statins	65 (76.5%)	98 (70.0%)	0.2922
Fibrates	0 (0.0%)	7 (5.0%)	0.0466
Ezetimibe	19 (22.4%)	28 (20.0%)	0.6738
Biology no. (%)			
Total cholesterol, mean ± SD (g/l)	1.74 ± 0.45	1.75 ± 0.50	0.9638
LDLc, mean ± SD (g/l)	0.95 ± 0.36	0.98 ± 0.41	0.6596
HDLc, mean ± SD (g/l)	0.51 ± 0.15	0.50 ± 0.15	0.5534
Triglycerides, mean ± SD (g/l) (<i>n</i> = 66 operated, <i>n</i> = 111 non operated)	1.49 ± 0.93	1.56 ± 1.23	0.6821
LDLc < 0.55 g/l	9 (10.6%)	19 (13.6%)	0.5110
LDLc < 0.70 g/l	18 (21.2%)	44 (31.4%)	0.0952
Triglycerides < 1.50 g/l (<i>n</i> = 66 operated, <i>n</i> = 111 non operated)	41 (62.1%)	73 (65.8%)	0.6243
GFR < 60 ml/min	13 (15.3%)	28 (20.0%)	0.3753
Mean HBA1c ± SD (%)	6.02 ± 0.74	6.27 ± 1.39	0.9380
Optimal medical treatment (antiplatelet + statins + ACE Inhibitor or ARB), no. (%)	45 (52.9%)	69 (49.3%)	0.5949
Antiplatelet therapy or anticoagulation	85 (100.0%)	131 (93.6%)	0.0147
ACE inhibitor or ARB	58 (68.2%)	86 (61.4%)	0.3024
Statins	65 (76.5%)	98 (70.0%)	0.2922
Sub-optimal medical treatment (antiplatelet + statins) no. (%)	65 (76.4%)	96 (70.0%)	0.2029

ACE denotes angiotensin-converting enzyme, ARA: angiotensin-receptor antagonist, CCB: calcium channel blocker, GFR: glomerular filtration rate, LDLc: low-density lipoprotein cholesterol, LMWH: low-molecular-weight heparin, OAC: oral anticoagulant, MI: myocardial infarction, TIA: transient ischaemic attack, VKA: vitamin K antagonist

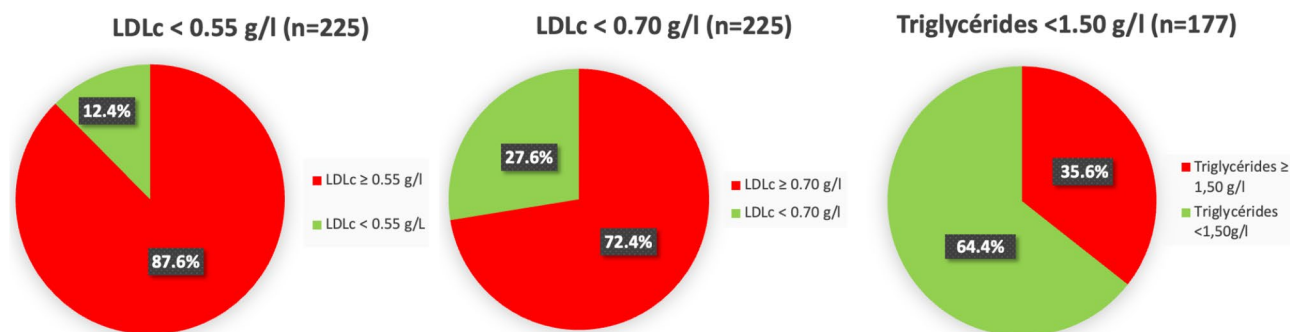


Fig. 2 Percentage of patients with LDLc level < 0.55 g/l and LDLc < 0.70 g/l and triglycerides < 1.50 g/l in the whole population. LDLc means Low Density Lipoprotein cholesterol

46.0% ($n=93$) of patients would be eligible for treatment with EVOLOCUMAB.

Our study included patients from January 2020 onwards, i.e. after the publication of the new ESC recommendations for lipid targets [7]. However, we note that only 27.6% of LEAD patients meet the target of 0.70 g/l of LDLc in use before 2020 according to the ESC society. This reinforces the finding of therapeutic and/or professional gaps in respect recommendations.

Triglycerides are considered to be an independent risk factor for CV events. Fibrates which benefit of drug approval in France have not yet proven their effectiveness in reducing morbidity and mortality [33, 34]. The REDUCE-IT trial demonstrated the benefit of a high dose of icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, in reducing morbidity and mortality in patients with hypertriglyceridemia [9]. Its effect on patients with hypertriglyceridemia and LEAD was studied in the REDUCE IT PAD trial [20]. According to the study's inclusion criteria, 17 patients would be eligible for this new treatment.

Regarding the use of optimal medical treatment, 50.4% (114/225) of patients received the recommended optimal tri-therapy. Several studies have shown that the use of therapy to prevent CV events is lower in LEAD patients than in coronary patients [3, 21]. A Canadian study found that only 60% of post-vascular surgery patients received a combination of statin, ARA/ACEI and antiplatelet therapy at discharge, and that this proportion was higher in patients with concomitant coronary artery disease than in those with isolated LEAD (78% and 46%, respectively) [22]. We found a similar trend in LEAD patients with a cardiovascular history vs. LEAD patients alone (60.0% vs. 46.3%, $p=0.0869$, respectively). Thus, there is a need to

increase awareness and improve pharmacological management of this largely neglected patient group.

We hypothesized that LEAD patients with a vascular surgery history were better treated than LEAD patients with no vascular surgery history [35]. Our results shows that it was not the case. These data are consistent with a 2018 French study in which medical treatment was prescribed in only 54% of patients at discharge [35]. These treatment regimens for patients with LEAD are similar to those in the United States as well [36]. According to Thiney et al., the rate of new vascular surgery in patients with LEAD who received the best medical treatment tended to be lower than in those who did not (incidence rate ratio=0.58; 95% confidence interval, 0.31–1.06; $p=0.08$) [35]. The implementation of appropriate treatment at discharge of hospital would be of major importance in terms of reducing MALE [35, 36]. New RNA-based hypolipidemic agents are developed which can facilitate the achievement of the LDL targets [37].

An alternative therapy combining antiplatelet, ACE inhibitor or ARA and statin in a single dose has been studied in patients with coronary artery disease and would reduce the risk of major cardiovascular events compared to usual treatments taken separately (9.5% vs. 12.7%, HR 0.76, $p=0.02$) [38]. It would be interesting to evaluate this therapy in the context of LEAD.

Our study has several limitations. The first relate to the fact that, for our study is monocentric and thus our results cannot be extrapolated to the whole country. Second, the reasons to explain the low number of patients treated with statins could not be studied in this study, but the objective of this study was to assess the current state of management and not to seek the reasons for these prescriptions.

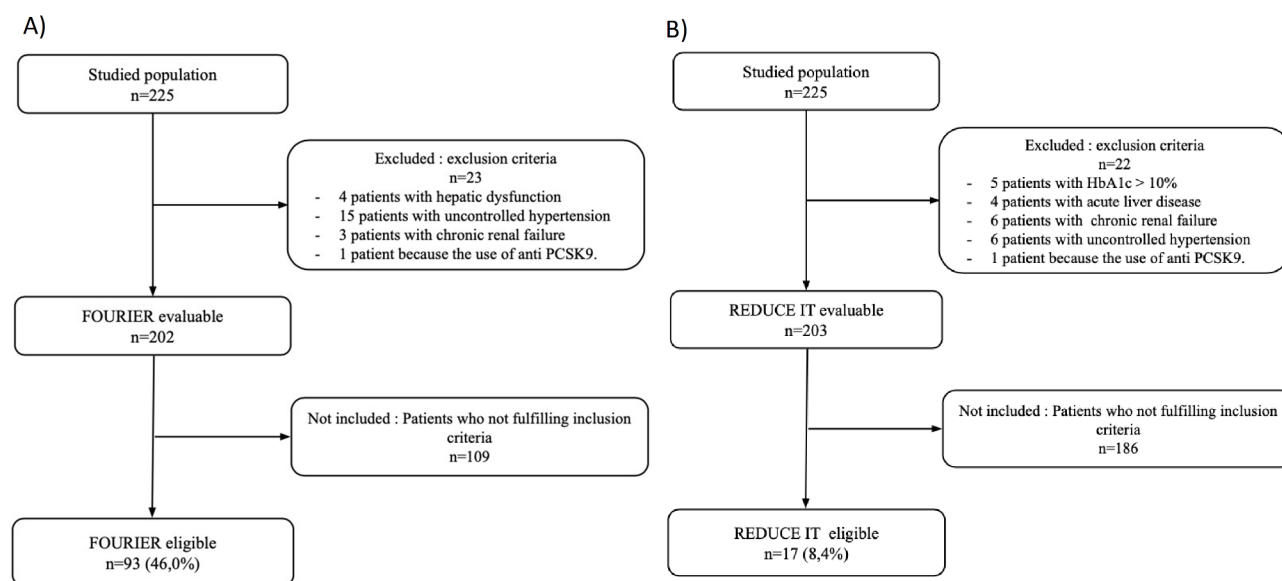
Table 3 Comparisons of patients with controlled (<0.55 g/L) and uncontrolled (LDL ≥0.55 g/L) LDLc

Clinical characteristics	Patients with LDL < 0.55 g/L (n = 28)	Patients with LDL ≥ 0.55 g/L (n = 197)	P value
Age, mean ± SD (years)	64.79 ± 9.44	64.49 ± 11.42	p = 0.8969
Body mass index, mean ± SD (kg/m ²)	27.68 ± 5.49	28.05 ± 5.14	p = 0.7221
Male, no. (%)	22 (78.6%)	157 (79.7%)	p = 0.8902
Medical history no. (%)			
Smoker			
Current	10 (35.7%)	69 (35.0%)	p = 0.9430
Former	16 (57.1%)	103 (52.3%)	p = 0.6299
Diabetes	6 (21.4%)	52 (26.4%)	p = 0.5739
Hypertension	25 (89.3%)	157 (79.7%)	p = 0.2270
Hypercholesterolaemia	23 (82.1%)	155 (78.7%)	p = 0.6732
Polyvascular patients	18 (64.3%)	71 (36.0%)	p = 0.0042
Vascular history (bypass, angioplasty/stenting)	9 (32.1%)	76 (38.6%)	p = 0.5110
Coronary heart disease history (myocardial infarction, angioplasty/stenting, bypass)	13 (46.4%)	53 (26.9%)	p = 0.0337
Ischemic stroke history(carotid surgery, TIA, stroke)	7 (25.0%)	27 (13.7%)	p = 0.1540
Mean right ankle-brachial index	0.84 ± 0.20	0.91 ± 0.23	p = 0.1558
Mean left ankle-brachial index	0.85 ± 0.23	0.85 ± 0.24	p = 0.2709
Distribution of ABI			
Severe LEAD (ABI ≤ 0.40), no.(%)*	0 (0.0%)	1 (0.5%)	
Moderate LEAD (0.40 < ABI ≤ 0.70), no.(%)*	5 (17.9%)	18 (9.1%)	
Mild LEAD (0.70 < ABI ≤ 0.90), no.(%)*	11 (39.3%)	51 (25.9%)	
Normal (0.90 < ABI ≤ 1.40), no.(%)*	12 (42.9%)	127 (64.5%)	
Non-Compressible arteries (ABI > 1.40), no.(%)*	0 (0.0%)	0 (0.0%)	
Current medications, no.(%)			
Anti-hypertensives			
ACE inhibitor or ARB	25 (89.3%)	155 (78.7%)	p = 0.1893
Diuretic	20 (71.4%)	124 (62.9%)	p = 0.3815
CBB	5 (17.9%)	3 (1.5%)	p = 0.0009
Beta-blocker	7 (25.0%)	59 (29.9%)	p = 0.5904
Anticoagulants	12 (42.9%)	70 (35.5%)	p = 0.4511
VKA	6 (21.4%)	28 (14.2%)	p = 0.3945
OAC	0 (0.0%)	5 (2.5%)	p = 1.0000
LMWH	6 (21.4%)	22 (11.2%)	p = 0.1309
Antiplatelets	0 (0.0%)	1 (0.5%)	p = 1.0000
Aspirin	25 (89.3%)	165 (83.8%)	p = 0.5843
Clopidogrel	20 (71.4%)	135 (68.5%)	p = 0.7564
Prasugrel/ticagrelor	11 (39.3%)	48 (24.4%)	p = 0.0930
Lipid lowering agents	0 (0.0%)	3 (1.5%)	p = 1.0000
Statins	27 (96.4%)	146 (74.1%)	p = 0.0088
Statin Intensity	27 (96.4%)	138 (70.1%)	p = 0.0031
Low intensity statins	0 (0.0%)	17 (13.7%)	p = 0.0101
Moderate intensity statins	6 (23.1%)	49 (39.5%)	
High intensity statins	20 (76.9%)	58 (46.8%)	
Fibrates	0 (0.0%)	190 (96.4%)	p = 0.6007
Ezetimibe	8 (28.6%)	39 (19.8%)	p = 0.2852
Biology no. (%)			
Total cholesterol, mean ± SD (g/l)	1.16 ± 0.16	1.83 ± 0.45	p < 0.0001
LDLc, mean ± SD (g/l)	0.46 ± 0.07	1.04 ± 0.37	p < 0.0001
HDL, mean ± SD (g/l)	0.48 ± 0.13	0.51 ± 0.16	p = 0.4734
Triglycerides, mean ± SD (g/l) (n = 177)	1.06 ± 0.50	1.60 ± 1.17	p = 0.0150
LDLc < 0.70 g/l, no. (%)	28 (100.0%)	34 (17.3%)	p < 0.0001
Triglycerides < 1.50 g/l (n = 177)	17 (77.0%)	97 (62.6%)	p = 0.1780
GFR < 60 ml/min, no. (%)	7 (25.0%)	34 (17.3%)	p = 0.3208

Table 3 (continued)

Clinical characteristics	Patients with LDL < 0.55 g/L (n = 28)	Patients with LDL ≥ 0.55 g/L (n = 197)	P value
Mean HbA1c ± SD (%)	6.20 ± 1.13	6.17 ± 1.19	p = 0.7869
Liver cytolysis, no. (%)	0 (0.0%)	4 (2.0%)	p = 1.0000
Optimal medical treatment (antiplatelet + statins + ACE Inhibitor or ARB) no. (%)	19 (67.9%)	95 (48.2%)	p = 0.0518
Antiplatelet therapy or anticoagulation	28 (100.0%)	188 (95.4%)	p = 0.6061
ACE inhibitor or ARB	20 (71.4%)	124 (62.9%)	p = 0.3815
Statins	27 (96.4%)	138 (70.1%)	p = 0.0031
Sub-optimal medical treatment (antiplatelet + statins) no. (%)	27 (96.4%)	134 (68.0%)	p = 0.0018

Results are presented mean ± standard deviation (SD) or number of observation (%). ACE denotes angiotensin-converting enzyme, ARA: angiotensin-receptor antagonist, CCB: calcium channel blocker, GFR: glomerular filtration rate, LDLc: low-density lipoprotein cholesterol, LMWH: low-molecular-weight heparin, OAC=oral anticoagulant, TIA transient ischaemic attack, VKA vitamin K antagonist. *Note that the classification according to the severity of LEAD was based on the highest Ankle-Brachial Index (ABI) for each patient

**Fig. 3** Diagram flow of the FOURIER eligible population and REDUCE-IT eligible population. Panel **A**: FOURIER results; Panel **B**: REDUCE-IT results

Conclusion

This study highlights that LEAD patients did not reach LDLc goals, even in LEAD patients with a vascular surgery history. Increased awareness in terms of achieving lipid targets and prescribing optimal medical treatment for patients with symptomatic LEAD is needed by all health professionals. The optimal strategy to increase the number of LEAD patients receiving best medical treatment and achieving LDLc targets remains debated and may require further clinical studies.

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None.

Author contributions

Study design: CdK and GM; Data collection: CdK, AD, QT and GM; Data Analysis: ELP and GM; Writing original draft: CdK, FP, and GM; review: CdK, AD, QT, ELP, FP and GM. All authors approved the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was reviewed and approved by the Ethics Committee of the University Hospital of Rennes, in accordance with French law and the Declaration of Helsinki (N°2018/07). The patients who performed the walking test between January 2020 and May 2022 provided an informed consent allowing the collection of data.

Consent for publication

Not Applicable.

Competing interests

GM received personal fees for consulting, boards from Amgen, Sanofi, Amarin, Novartis, Bayer Healthare, Bristol Myers Squibb, Pfizer. FP received personal fees for consulting, boards from Amgen, Sanofi, Amarin, Novartis.

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