Dissertation

Relevance of cardiac biomarker in patients with peripheral arterial disease

submitted by

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for the Academic Degree of

Doctor of Medical science (Dr. scient. med.)

at the

Medical University of Graz

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2025

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Evaluation of the utility of cardiac biomarkers for risk stratification in patients with lower extremity artery disease: A retrospective study. Published in PLoS One on the 29th of April 2025.

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3. Acknowledgments

I would like to express my sincere appreciation to my mentors, Marianne Brodmann, Thomas Gary, Reinhard Bernd Raggam, and Gabor Toth-Gayor, whose guidance and support have been pivotal in the completion of my doctoral thesis. I am also grateful to my colleagues and collaborators for their valuable contributions to this work.

I am thankful to my parents for their constant encouragement and belief in my abilities, which have accompanied me throughout my professional and personal development.

My special thanks go to my husband and son for their support, understanding, and encouragement, which have played an important role in enabling me to achieve my goals.

Doctoral student Leyla Schweiger received funding from the Medical University of Graz through the Doctoral School “Sustainable Health Research”.

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5. List of abbreviations

6MWT: Six-Minute walk test
ABI: Ankle-brachial index
ADMA: Asymmetric dimethylarginine
ALI: Acute limb ischemia
ANGPTLs: Angiopoietin-like proteins
Ang-1: Angiopoietin-1
Apo: Apolipoprotein
BMI: Body mass index
CAD: Coronary artery disease
CAMs: Cell adhesion molecules
CKD: Chronic kidney disease
CK-MB: Creatine kinase myocardial band
CLTI: Chronic limb threatening ischemia
CRP: C-reactive protein
CTA: Computed tomography angiography
CVD: Cerebrovascular disease
DAPT: Dual antiplatelet therapy
DSA: Digital subtraction angiography
DUS: Duplex ultrasound
ECM: extracellular matrix
ESC: European Society of Cardiology
FGF: Fibroblast growth factor
GLASS: Global Limb Anatomic Staging System
GLP-1RA: Glucagon-like peptide-1 receptor agonists
HBA1c: Glycated hemoglobin
HDL-C: High-density lipoprotein cholesterol
HGF: Hepatocyte growth factor
hs-TnT: High-sensitivity troponin T
IDDM: Insulin-dependent diabetes mellitus
IL: Interleukin

IQR: Interquartile range

LDL-C: Low-density lipoprotein cholesterol

LEAD: Lower extremity artery disease

Lp(a): Lipoprotein(a)

MACE: Major adverse cardiovascular event

MALE: Major adverse limb event

MDA: Malondialdehyde

MEDOCS: Medical Documentation and Communication network of Styria

MMPs: Matrix metalloproteinases

MRA: Magnetic resonance angiography

NIDDM: Non-insulin-dependent diabetes mellitus

NT-proBNP: N-terminal prohormone of brain natriuretic peptide

OR: Odds ratio

oxLDL: Oxidized low-density lipoprotein

PAD: Peripheral arterial disease

PCSK9: Proprotein convertase subtilisin/kexin type 9

SAPT: Single antiplatelet therapy

SDMA: Symmetric dimethylarginine

SET: Supervised exercise therapy

SGLT2i: Sodium-glucose cotransporter-2 inhibitors

TBI: Toe-brachial index

TC: Total cholesterol

TNF-α: Tumor necrosis factor Alpha

VEGF: Vascular endothelial growth factor

VLDL: Very-low-density lipoprotein

VSMCs: Vascular smooth muscle cells

vWF: Von Willebrand factor

WIfI: Wound, Ischemia, and foot Infection

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8. Zusammenfassung

Hintergrund:

Die periphere arterielle Verschlusserkrankung (pAVK) betrifft über 200 Millionen Menschen weltweit. Das fortgeschrittene Stadium dieser Erkrankung wird als chronisch kritische Extremitätenischämie (CLTI) bezeichnet und ist mit einer erhöhten Morbidität und Mortalität vergesellschaftet. Dies spiegelt sich in einer 1-Jahres-Mortalitätsrate der CLTI von etwa einem Viertel der Betroffenen wider, die Amputationsraten belaufen sich auf etwa 30% innerhalb eines Jahres. Trotz des hohen sozioökonomischen Einflusses der pAVK wird diese im Vergleich zu anderen kardiovaskulären Forschungsfeldern bisher kaum berücksichtigt. Kardiale Biomarker, wie Troponin T und N-terminales pro-Brain natriuretisches Peptid (NT-proBNP) sind im kardiologischen Setting ausreichend erforscht und in der Praxis bereits gut etabliert, jedoch ist ihr Stellenwert bezüglich der pAVK weitgehend unerforscht. Es gibt wenige Studien zu kardialen Biomarker bei pAVK Patient*innen, wobei nachgewiesen werden konnte, dass die pAVK mit erhöhten kardialen Biomarker assoziiert ist. Ziel dieser Studie war es Unterschiede von kardialen Biomarkern zwischen den Stadien der pAVK und den prädiktiven Wert von kardialen Biomarker bei Patient*innen mit pAVK zu untersuchen.

Methoden:

In dieser retrospektiven Querschnittsstudie wurden alle Patient*innen, welche im Zeitraum von 2004-2020 mit einer pAVK in der angiologischen Ambulanz vorgestellt wurden, für einen Studieneinschluss gescreent. Jene Patient*innen, die eine endovaskuläre Rekanalisation erhielten und bei welchen kardiale Biomarker mituntersucht wurden, wurden eingeschlossen. Im Jahr 2022 erfolgte die Datenanalyse wofür demographische und klinische Daten, Komorbiditäten, Laborwerte und Outcome-Daten der Patient*innen erhoben und analysiert wurden. Die Patient*innen wurden dabei in zwei Gruppen aufgeteilt, in solche mit einer CLTI und in diejenigen ohne CLTI. Hauptaugenmerk in der Analyse der Biomarker wurde auf NT-pro-BNP, Troponin T, NT-proBNP/Troponin-Ratio, Kreatinkinase-Myokardtyp (CK-MB) und Myoglobin gelegt.

Ergebnisse:

Von den initial 21712 gescreenten Patient*innen mit pAVK erhielten 367 eine Messung der kardialen Biomarker und eine endovaskuläre Rekanalisation. Die 367 Patient*innen, die in die

Studie eingeschlossen wurden, hatten ein Durchschnittsalter von 71 (IQR: 62-80) Jahren. 226 Männer (61.6%) und 141 Frauen (38.4%) wurden analysiert. Von dieser Kohorte hatten 59 Patient*innen eine CLTI (16.1%). Die Patienten mit einer CLTI hatten höhere Werte für NT-proBNP, NT-pro-BNP/Troponin-Ratio, CK-MB und Myoglobin sowie ein höheres Alter, höhere Werte des C-reaktiven Protein (CRP) und häufiger einen nicht-insulin abhängigen Diabetes mellitus (NIDDM) verglichen mit den Patient*innen ohne CLTI ($p<0.05$ jeweils). In der multivariaten Analyse blieben das Alter, das CRP und NIDDM als signifikante Prädiktoren für die CLTI ($p<0.05$ jeweils) bestehen, während die kardialen Biomarker nicht signifikant mit einer CLTI assoziiert waren. Bezüglich des Todes konnte eine signifikante Assoziation von NT-proBNP, Troponin T und Myoglobin in der univarianten Analyse ($p<0.05$ jeweils) festgestellt werden. In der multivariaten Analyse war ausschließlich Troponin T unabhängig mit dem Tod assoziiert ($p=0.001$).

Konklusion:

Die hier ausgewählten kardialen Biomarker scheinen keine geeigneten Prädiktoren für die Entwicklung einer CLTI bei pAVK-Patient*innen zu sein, wobei ein erhöhtes Troponin T mit einer erhöhten Mortalität einhergeht.

9. Abstract

Background:

Lower extremity artery disease (LEAD) affects over 200 million people worldwide. The advanced stage of this disease is referred to as chronic limb threatening ischemia (CLTI) and is associated with increased morbidity and mortality. This is reflected in a one-year mortality rate of approximately one quarter among CLTI patients, while amputation rates reach about 30% within one year. Despite the significant socioeconomic impact of LEAD, it remains largely underrepresented compared to other cardiovascular research fields. Cardiac biomarkers such as troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) are well-studied and firmly established in the cardiology setting. However, their significance in the context of LEAD is largely unexplored. Only a few studies have investigated cardiac biomarkers in LEAD patients, demonstrating an association between LEAD and elevated cardiac biomarker levels. The aim of this study was to assess differences in cardiac biomarkers between the stages of LEAD and to evaluate the predictive value of cardiac biomarkers in patients with LEAD.

Methods:

In this retrospective cross-sectional study, all patients who had presented with LEAD at the angiologic outpatient clinic between 2004 and 2020 were screened for study inclusion. Patients who underwent endovascular recanalization and had cardiac biomarkers assessed were included in the study. Data analysis was performed in 2022, while demographic and clinical data, comorbidities, laboratory values, and outcome data were collected and analyzed. The patients were divided into two groups: those with CLTI and those without CLTI. The primary focus of the biomarker analysis was on NT-proBNP, troponin T, NT-proBNP/troponin ratio, Creatine Kinase Myocardial Band (CK-MB), and myoglobin.

Results:

From the initially 21712 screened patients with LEAD, 367 patients had received a measurement of cardiac biomarkers and an endovascular recanalization. Those 367 patients, who were enrolled in the study, had an average age of 71 years (IQR: 62-80), with 226 being male (61.6%) and 141 female (38.4%). Of this cohort, 59 patients were diagnosed with CLTI (16.1%). Those patients with CLTI exhibited elevated levels of NT-proBNP, NT-proBNP/troponin ratio, CK-MB, and myoglobin as well as higher rates of age, C-reactive

protein (CRP), and non-insulin-dependent diabetes mellitus (NIDDM) compared to those without CLTI (all $p<0.05$) in univariate analysis. However, in the multivariate analysis, only age, CRP, and NIDDM remained significant predictors of CLI (all $p<0.05$), while cardiac biomarkers did not show a significant association. Regarding mortality, NT-proBNP, troponin T, and myoglobin exhibited a significant association in univariate analysis ($p<0.05$ respectively). In multivariate analysis, only troponin T remained independently associated with death ($p=0.001$).

Conclusion:

Selected cardiac biomarkers do not appear to be robust predictors for differentiating between CLTI patients and non-CLTI patients while only elevated troponin T was a predictor for increased mortality.

10. Introduction

10.1. Definition

According to the 2017 European Society of Cardiology (ESC) Guidelines on the diagnosis and treatment of peripheral arterial disease (PAD), as well as the updated version of 2024, PAD encompasses atherosclerotic disease affecting all extra- coronary arteries including the aorta as well as arteries supplying the head, limbs, and visceral organs [1-2]. The term PAD is, however, often synonymously used for the most common form of it, known as lower extremity artery disease (LEAD) which is also the primary focus of this work.

10.2. Epidemiology

Globally, over 230 million individuals are affected by LEAD, making it the third most common cause of atherosclerotic vascular morbidity after coronary artery disease (CAD) and stroke [3-4]. Between 2000 and 2015, the worldwide prevalence of LEAD increased by approximately 45%, reaching 5.6% in 2015. The prevalence is higher in high-income countries at 7.4% compared to 5.1% in middle- and low-income regions [5].

LEAD prevalence rises with age, with rates around 1% in patients aged 40–49 years, escalating to about 50% in those over 70 years. While overall prevalence does not differ significantly between sexes, men living in high-income countries tend to be more frequently affected than women, whereas in low-income countries, women have higher prevalence rates [4,6-8]. Table 1 illustrates these age-related sex differences in prevalence across different income regions. Additionally, it is well documented that LEAD is more prevalent among Black individuals than White individuals, who are also more likely to receive diagnosis at more advanced stages of the disease [9].

The direct healthcare costs for symptomatic LEAD patients are higher than those for CAD patients. In the United States, LEAD-related treatment incurs about 4,006 USD per patient annually, whereas in Germany, two-year costs average around €2,724 per patient [9-11]. These substantial costs highlight the significant socioeconomic burden associated with LEAD.

	Prevalence women		Prevalence men	
Age (years)	High-income countries (95% CI)	Low-and middle-income countries (95% CI)	High-income countries (95% CI)	Low-and middle-income countries (95% CI)
25-29	2.70% (1.1-6.2)	3.96% (2.3-6.5)	2.76% (1.1-6.4)	1.21% (0.6-2.3)
30-34	3.20% (1.5-6.6)	4.46% (2.8-6.8)	3.27% (1.5-6.8)	1.50% (0.8-2.6)
35-39	3.78% (1.9-7.0)	5.01% (3.4-7.2)	3.88% (2.0-7.3)	1.87% (1.1-3.0)
40-44	4.47% (2.6-7.5)	5.62% (4.1-7.6)	4.58% (2.6-7.8)	2.33% (1.5-3.5)
45-49	5.28% (3.3-8.1)	6.31% (4.8-8.1)	5.41% (3.4-8.4)	2.89% (2.0-4.0)
50-54	6.23% (4.3-8.8)	7.08% (5.7-8.7)	6.38% (4.3-9.2)	3.58% (2.7-4.7)
55-59	7.33% (5.4-9.7)	7.92% (6.6-9.4)	7.51% (5.5-10.0)	4.43% (3.5-5.5)
60-64	8.60% (6.6-11.0)	8.87% (7.5-10.4)	8.82% (6.8-11.2)	5.47% (4.4-6.4)
65-69	10.08% (7.7-12.9)	9.91% (8.3-11.7)	10.33% (8.1-13.0)	6.74% (5.3-8.4)
70-74	11.77% (8.7-15.6)	11.05% (9.0-13.4)	12.07% (9.2-15.5)	8.28% (6.3-10.7)
75-79	13.71% (9.6-19.1)	12.32% (9.6-15.6)	14.05% (10.2-18.9)	10.13% (7.3-13.8)
80-84	15.91% (10.4-23.5)	13.70% (10.2-18.1)	16.30% (11.1-23.1)	12.33% (8.4-17.7)
85-89	18.38% (11.1-28.7)	15.22% (10.8-21.0)	18.83% (12.0-28.2)	14.94% (9.5-22.5)
90-94	21.14% (11.9-34.7)	16.87% (11.3-24.2)	21.65% (12.8-34.0)	17.99% (10.8-28.3)
95-99	24.20% (12.6-41.2)	18.65% (11.9-27.9)	24.77% (13.7-40.4)	21.50% (12.2-34.9)

Ages 25-29 years, 90-94 years, and 95-99 years, the results are estimated predictions and out with the range of the original data. Estimated age-specific prevalence of women and men living with LEAD in high-income countries and in low-income and middle-income countries, by age group

Table 1: Estimated age-specific prevalence of women and men living with LEAD in high-income countries and low- income countries, by age group. Adapted from Eid et al. [8].

10.3. Risk factors

Since LEAD is classified as a cardiovascular disease, its risk factors largely overlap with traditional risks identified for other cardiovascular conditions such as CAD and cerebrovascular disease (CVD). Notably, LEAD often remains clinically silent for extended

periods, and much of the risk factor data comes from cross-sectional analyses capturing patients' profiles only at the point of diagnosis. Accordingly, recent findings on LEAD risk factors should be interpreted carefully [13]. As previously noted, increasing age is a major risk factor, alongside well-established contributors including smoking, hypertension, dyslipidemia, and diabetes mellitus, as summarized in Figure 1.

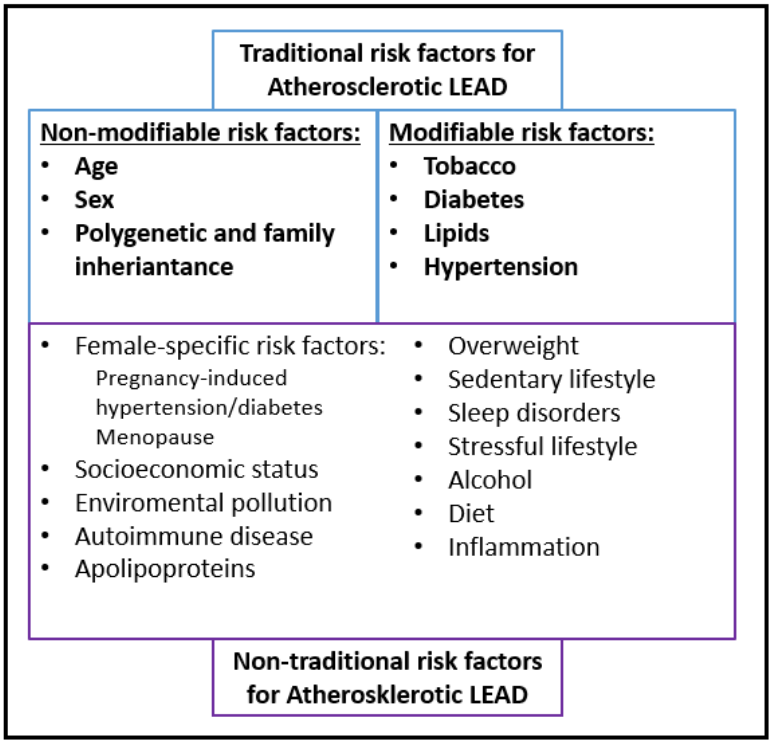

Figure 1: Main risk factors associated with atherosclerosis in LEAD. Adapted from Mazzolai et al. [2].

10.3.1. Smoking

Worldwide, over one billion adults smoke, and smoking is recognized as a leading preventable risk factor for cardiovascular diseases such as CAD and LEAD. Notably, more than 80% of patients diagnosed with LEAD are either current or former smokers. Compared to non-smokers, individuals who smoke or have smoked have at least twice the likelihood of developing LEAD [13-15]. Recent literature suggest that smoking confers a greater risk for LEAD development than for CAD or CVD, indicating a stronger association with LEAD among cardiovascular subtypes [16]. Given smoking's key role in LEAD pathogenesis,

cessation is crucial. However, it may take approximately two decades after quitting for former smokers to reduce their risk to levels similar to those who never smoked [16,17]. Despite intensive cessation efforts, abstinence rates remain low at around 21% after six months [18]. This risk factor seems particularly impactful in the proximal manifestations of LEAD [19].

10.3.2. Arterial hypertension

According to recent European guidelines, arterial hypertension is defined by a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg [20]. It represents a major modifiable risk factor for the development and progression of LEAD. Epidemiological data consistently demonstrate that individuals with arterial hypertension have a higher prevalence of LEAD, and coexistence significantly increases the risk of myocardial infarction, ischemic stroke, critical limb threatening ischemia (CLTI), and cardiovascular mortality [21]. Elevated blood pressure accelerates peripheral atherosclerosis by promoting endothelial dysfunction, arterial remodeling, and plaque formation, which reduces peripheral perfusion and impairs wound healing [22]. Despite the high global burden, patients with both arterial hypertension and LEAD are often undertreated or fail to achieve guideline-recommended blood pressure targets [22]. Current guidelines from major cardiovascular societies, including the American Heart Association/American College of Cardiology and the ESC, recommend blood pressure targets of less than 130/80 mmHg for most LEAD patients due to their heightened cardiovascular risk [21,22]. However, the optimal blood pressure range remains debated, as cohort studies have shown that LEAD patients with systolic blood pressure ≤120 mmHg are at increased risk of major cardiovascular events compared to those with systolic BP in the 121–140 mmHg range. This suggests that intensive blood pressure lowering is not always beneficial, whereas uncontrolled hypertension (≥140 mmHg) is also associated with higher cardiovascular and limb complication rates [23,24].

10.3.3. Dyslipidemia

Dyslipidemia is a well-established risk factor for cardiovascular diseases, including LEAD. Several studies have demonstrated that elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein (a) associate with an increased

risk of LEAD, particularly its proximal form [17]. Conversely, increased concentrations of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) A, the main protein component of HDL particles, appear protective. The majority of studies use TC as a marker. The Framingham Heart Study linked each 40 mg/dl increase in TC with a 20% higher relative risk of claudication [25]. Newman et al. [7] found that a 10 mg/dl increase in TC raised the risk of an ankle-brachial index (ABI) below 0.9 by roughly 10%. Furthermore, low HDL-C levels are associated with increased LEAD risk, and a decrease of 1 mg/dl in HDL-C corresponds to a 1% rise in odds. The ratio of TC to HDL-C is also a significant indicator, with one study reporting a 1.4-unit higher mean ratio in LEAD patients compared to controls [7,26,27]. While some investigations confirm a link between triglyceride levels and LEAD incidence, others show inconsistent results contributing to ongoing debate. Importantly, elevated LDL-C levels have been consistently recognized as a critical factor for LEAD onset and severity [26,28]. Aday et al. [28] demonstrated that higher LDL-C and increased atherogenic lipoproteins strongly relate to declining ABI scores, independent of other cardiovascular risks. Similarly, Ness et al. [29] identified high LDL-C as an independent predictor of symptomatic LEAD in elderly patients, even when adjusting for arterial hypertension, diabetes mellitus, and smoking. These findings highlight the importance of aggressive lipid control in preventing and managing LEAD [28,29]. Additionally, ApoA, the predominant apolipoprotein of HDL, is inversely related to LEAD risk, whereas elevated ApoB, the main apolipoprotein of LDL, correlates with increased risk [26].

10.3.4. Diabetes mellitus

Approximately 90% of patients with abnormal glucose regulation have type 2 diabetes mellitus, with type 1 diabetes mellitus accounting for up to 10% of cases [30]. Over the past two decades, the prevalence of diabetes mellitus has risen by nearly 200%, affecting more than 30 million individuals in the United States alone [31]. The presence of diabetes mellitus confers a 2- to 4-fold increased risk for developing LEAD [32]. Among patients diagnosed with LEAD, up to 30% have coexisting diabetes mellitus [33]. Notably, diabetic patients often present with a distinct pattern of LEAD characterized by more frequent infrapopliteal lesions and severe arterial calcification [34]. Moreover, diabetes mellitus independently predicts poorer clinical outcomes, including higher rates of major limb amputation and hospital

readmission within six months [35].

10.3.5. Obesity

Obesity, defined as a body mass index (BMI) greater than 30 kg/m², has emerged as a global health crisis currently affecting over 700 million adults worldwide, with prevalence rates continuing to climb annually [36-38]. However, the relationship between obesity and LEAD remains nuanced and sometimes contradictory. For example, Bowlin et al. [39] observed elevated BMI in men with intermittent claudication compared to those without, whereas Heffron et al. [40] reported that a high BMI was linked to increased LEAD risk predominantly in women, suggesting possible sex-specific effects. Additionally, the waist-to-hip ratio, reflecting central fat distribution, has been independently associated with LEAD onset, highlighting the role of adiposity location beyond total body fat [41]. Adding complexity is the obesity paradox, where epidemiological evidence indicates that overweight or mildly obese individuals may sometimes experience better outcomes than those with normal or low BMI [42,43]. This paradox may partly be explained by the fact that low BMI in older adults or patients with multiple comorbidities often signals frailty or severe illness rather than an inherently protective effect of adiposity [13]. Furthermore, obesity often coexists with other major cardiovascular risk factors such as arterial hypertension, dyslipidemia, and diabetes mellitus, all of which contribute to the pathogenesis of LEAD [36]. Taken together, while obesity is a recognized cardiovascular risk factor, its exact role in LEAD risk and prognosis is complex and influenced by sex, fat distribution, and the presence of coexisting conditions.

10.3.6. Alcohol consumption

Alcohol consumption has been long studied for its effects on cardiovascular health and LEAD. While heavy alcohol intake is an established risk factor for cardiovascular disease, emerging evidence suggests that moderate consumption may offer some protection against LEAD development [44]. A number of large cohort studies have documented a U-shaped relationship, where moderate drinking, defined as up to two drinks daily (approximately 50 g ethanol for men, 25 g for women), is associated with a lower incidence of LEAD compared to both nondrinkers and heavy drinkers [44,45]. The biological basis for this protective effect is not

fully understood, but it may involve favorable changes in lipid metabolism, reduced platelet activation, and improved endothelial function. Notably, some data indicate a more pronounced protective association among women. Vliegenthart et al. [46] observed that women consuming over 20 g of ethanol daily had the greatest reduction in LEAD risk. Similarly, the Edinburgh Artery Study found that moderate alcohol intake correlated with lower LEAD prevalence, though this benefit waned at higher consumption levels [47]. Nonetheless, it remains essential to emphasize that excessive alcohol use increases cardiovascular risk, and any potential benefits of moderate drinking should be balanced against the dangers of heavy consumption [44].

10.3.7. Race and ethnicity

Racial and ethnic disparities exist in the prevalence and clinical outcomes of LEAD. Studies have shown that Black individuals in the United States are disproportionately affected by LEAD, with roughly double the risk compared to non-Hispanic White populations after accounting for traditional cardiovascular risk factors and socioeconomic differences [13]. Collins et al. [48] confirmed that Black ethnicity remains an independent risk factor for LEAD, even when controlling for variables such as age, sex, diabetes mellitus, and arterial hypertension. While Hispanic and Asian populations tend to exhibit similar or lower LEAD prevalence relative to White individuals, their data are less comprehensive. Notably, Lefebvre and Chevan et al. [49] found that Black patients with LEAD are at markedly higher risk for major adverse limb events (MALE), including CLTI and amputations, which also occur at younger ages and with greater frequency compared to White patients. These findings underscore the critical need for focused efforts toward prevention, early diagnosis, and equitable management to address these racial and ethnic disparities.

10.3.8. Chronic kidney disease

Chronic kidney disease (CKD) is an established risk factor for the development of atherosclerotic diseases including LEAD. Patients with CKD exhibit a significantly higher prevalence of LEAD and tend to experience worse clinical outcomes, such as increased rates of limb amputation and elevated long-term mortality [50]. The prevalence of LEAD in

individuals with CKD has been reported to be approximately 32.6%, compared to just 9.6% in those without renal impairment, reflecting a more than threefold increased risk. Furthermore, the likelihood of LEAD rises with advancing CKD stages, reaching its peak in patients with end-stage renal disease or those receiving dialysis, where prevalence rates approach 30% [51,52].

10.3.9. Genetic factors

Genetic factors play a substantial role in the predisposition to LEAD, with heritability estimates ranging approximately from 20% to 58% [53]. A positive family history is an acknowledged independent risk factor linked to heightened LEAD susceptibility [53-56]. The National Heart, Lung, and Blood Institute Twin Study explored the influence of inherited and environmental components on ABI variations, a critical diagnostic marker of LEAD, revealing significant genetic contributions [55]. Genome-wide association studies have further elucidated the genetic landscape of LEAD by identifying multiple single-nucleotide polymorphisms associated with disease risk [53]. Notably, Cluett et al. [56] reported a significant association between the 9p21 locus (rs1333049) and both the severity of ABI reduction and LEAD prevalence in elderly populations, suggesting shared genetic architecture with other atherosclerotic disorders like myocardial infarction. Despite these advances, the genetic basis of LEAD remains complex, reflecting the interplay of numerous genetic variants and diverse environmental exposures.

10.4. Pathogenesis

The pathogenesis of LEAD is complex and involves multiple interacting mechanisms, including atherosclerotic plaque buildup, endothelial dysfunction, ongoing inflammation, changes in hemodynamics, and skeletal muscle injury. These interrelated processes together contribute to disease progression and the clinical features seen in LEAD.

10.4.1. Atherosclerosis

Atherosclerosis is the principal pathological mechanism driving LEAD development and

progression. It begins when vascular cells are excessively exposed to LDL-C, particularly in the context of endothelial dysfunction that increases arterial intima permeability to lipoproteins [57-60]. Within the intima, LDL-C accumulates and undergoes oxidative and enzymatic modifications, becoming pro-inflammatory and immunogenic [57,60]. This triggers recruitment of monocytes that differentiate into macrophages, engulf oxidized LDL, and transform into foam cells forming early fatty streaks characteristic of atherosclerotic lesions [57,60]. Concurrently, vascular smooth muscle cells (VSMC) migrate into the intima, proliferate, and produce extracellular matrix (ECM), generating a fibrous cap over plaques [57,58]. Progression involves VSMC apoptosis and foam cell death, destabilizing plaques and predisposing to rupture [58]. Persistent inflammation exacerbates oxidative stress and EM degradation, enhancing plaque instability and thrombosis risk [57-59]. Plaque rupture exposes prothrombotic material leading to acute vessel occlusions [58]. In LEAD, these processes cause progressive arterial narrowing, impaired hemodynamics, and chronic ischemia, inadequately compensated by collateral vessels especially during increased metabolic demand such as exercise. The structural and functional limits of collateral arteries further intensify tissue hypoxia and contribute to clinical symptoms [60].

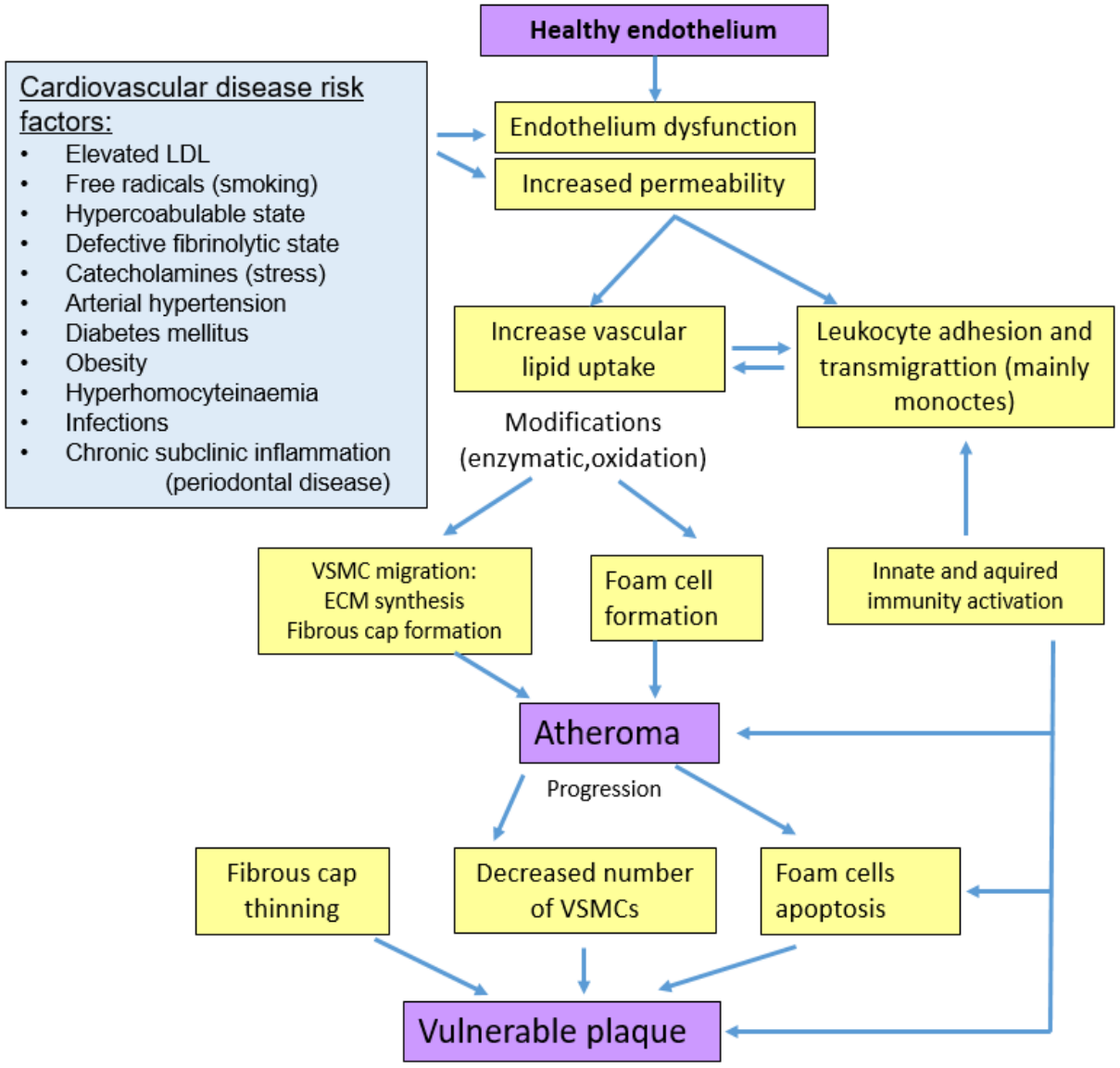

Figure 2: Diagram of the etiopathogenesis of atherosclerosis and vulnerable plaque formation. Adapted from Badimon et al. [58].

10.4.2. Endothelial dysfunction

Endothelial dysfunction is a critical early event in the initiation of atherosclerosis and LEAD. The endothelial lining of blood vessels regulates vascular tone, inhibits platelet aggregation, controls inflammation, and maintains selective permeability. Exposure to risk factors like hypertension, high lipid levels, diabetes, and smoking injures endothelial cells, impairing their function [57,60]. Reduced production of nitric oxide (NO), a key vasodilator and anti-

inflammatory molecule, leads to impaired vasodilation, increased vascular tone, and a prothrombotic state. Dysfunctional endothelial cells upregulate adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, promoting leukocyte adhesion and infiltration that contribute to atherosclerotic plaque formation [57,60]. Increased permeability allows LDL-C penetration and oxidation, sustaining inflammation and vascular damage. Loss of antithrombotic properties favors platelet activation and thrombosis [57,60]. Persistent endothelial impairment accelerates lesion development and impairs adaptive vasodilation during metabolic demands like exercise, thereby causing LEAD symptoms including intermittent claudication and CLTI [59].

10.4.3. Chronic inflammation

Chronic inflammation plays a central role in the development and progression of LEAD, driven by ongoing exposure of vascular tissues to modified lipoproteins, oxidative stress, and immune activation [61]. Early atherosclerosis is characterized by localized low-grade inflammation within the arterial wall due to retention and oxidation of LDL-C, which recruits monocytes and other immune cells. These cells enter the intima, differentiate into macrophages, and release pro-inflammatory cytokines and chemokines, amplifying the inflammatory cascade [62]. As lesions mature, inflammation intensifies to a more destructive state, contributing to plaque instability and potential rupture, which can result in thrombosis and clinical complications [63]. The dynamic interaction between chronic inflammation, disruptions in lipid metabolism, and genetic and environmental risk factors influences both local vascular pathology and systemic metabolic disturbances often seen in advanced LEAD [61-63].

10.4.4. Hemodynamic alterations

Hemodynamic alterations are a significant downstream effect of the arterial changes in LEAD and play a key role in symptom manifestation. As arterial stenoses worsen, the pressure beyond lesions falls, particularly during increased oxygen demand like exercise, causing tissue hypoperfusion and symptoms such as intermittent claudication and in advanced cases, rest pain and ischemic ulcers [13]. Physical inactivity worsens this by limiting the development and

function of collateral vessels. Although compensatory mechanisms like collateral growth and angiogenesis occur, they often remain insufficient and structurally immature, especially in diabetes mellitus and the elderly [64]. Increased arterial stiffness reduces effective blood flow pulsatility to muscles, compounding perfusion deficits [65]. Impaired flow-mediated dilation together with microvascular rarefaction reduces capillary density and oxygen extraction, leading to elevated oxidative stress and mitochondrial dysfunction in ischemic skeletal muscle [65]. These chronic perfusion impairments provoke inflammation, mitochondrial damage, and structural muscle deterioration, driving the progression of LEAD symptoms [65,66].

10.4.5. Muscle damage

Chronic ischemia in LEAD leads to progressive skeletal muscle damage that severely impacts functional capacity and quality of life. Muscles exposed to prolonged hypoperfusion display distinct histopathological and metabolic abnormalities compared to non-ischemic muscle tissue [63]. Mitochondrial dysfunction is a hallmark feature, characterized by impaired oxidative phosphorylation, reduced mitochondrial content, and increased generation of reactive oxygen species. These mitochondrial defects limit adenosine triphosphate production and promote apoptotic pathways and protein oxidation, resulting in permanent muscle cell damage [66]. Daily ischemia-reperfusion cycles during walking cause myofiber degeneration, predominantly affecting the metabolically demanding type II fibers, which undergo atrophy, necrosis, and fibrotic remodeling, accompanied by fat infiltration [66]. Muscle biopsies reveal diminished capillary-to-fiber ratios, indicating impaired oxygen diffusion and confirming microvascular disease. Furthermore, satellite cells essential for muscle repair exhibit reduced proliferation, restricting regenerative potential even after revascularization [66]. Clinically, these changes manifest as reduced walking distance, slower gait, and increased fatigue, reflecting not only the consequences of arterial insufficiency but also intrinsic muscle pathology that contributes independently to disease severity.

10.5. Clinical presentation

Historically, LEAD was categorized using the Rutherford and Fontaine systems. However, recent guidelines, such as those detailed by Gornik et al. [67], classify LEAD into four clinical

subsets: asymptomatic disease, chronic symptomatic LEAD, CLTI, and acute limb ischemia (ALI). This approach provides a clearer framework for clinical assessment and management.

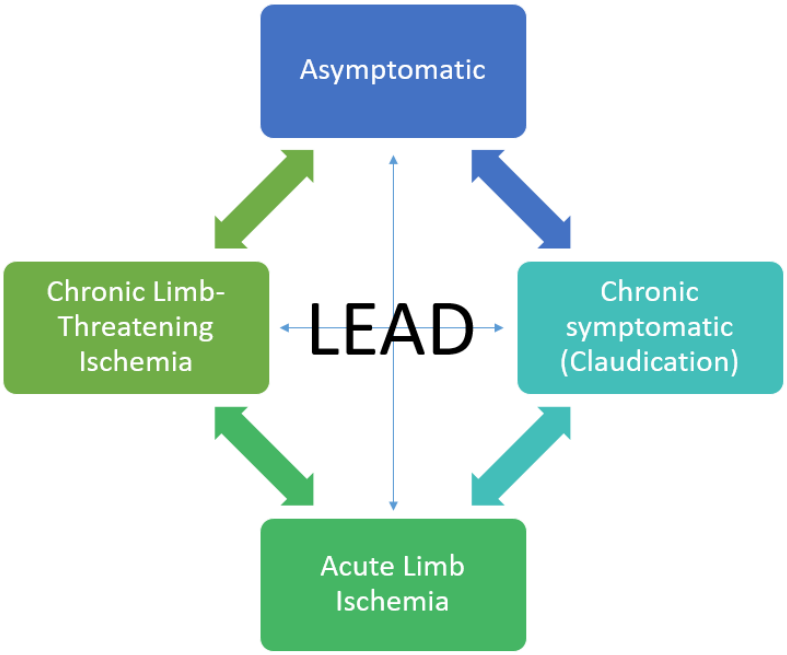

Figure 3: Clinical Subsets of LEAD. Adapted from Gornik et al. [67].

10.5.1. Asymptomatic lower extremity artery disease

Around six million individuals in the United States are estimated to have asymptomatic LEAD, although the true number may be higher due to the absence of routine screening recommendations. Detection typically relies on the ABI, with LEAD defined as an ABI of 0.90 or less, regardless of symptom status. Notably, about 21% of asymptomatic patients progress to develop claudication symptoms within a year of diagnosis [68-71]. Even without clinical symptoms, asymptomatic LEAD independently predicts a two- to threefold increased risk of cardiovascular events such as myocardial infarction, stroke, and cardiovascular mortality compared to individuals with normal ABI values between 1.00 and 1.40 [72,73]. Consequently, the cardiovascular risk associated with asymptomatic LEAD is similar to that observed in symptomatic patients, necessitating equally stringent cardiovascular risk management strategies.

10.5.2. Chronic symptomatic lower extremity artery disease

Chronic symptomatic LEAD is the most prevalent clinical subtype and is characterized primarily by intermittent claudication. Intermittent claudication refers to muscle pain, cramping, or discomfort, most commonly in the calves, which occurs during physical exertion and is relieved by rest. Although traditionally considered the hallmark symptom of LEAD, only about 10% of patients experience classic intermittent claudication. In contrast, up to 47% of patients with established LEAD and as many as 61% of newly diagnosed individuals report atypical symptoms such as generalized leg fatigue, exertional discomfort in various locations, or no symptoms at all [13,74,75]. Beyond causing functional limitations, chronic symptomatic LEAD is linked to significant cardiovascular morbidity and mortality. Numerous cohort studies have demonstrated that individuals with intermittent claudication face elevated risks of non-fatal myocardial infarction, stroke, and cardiovascular death. The 5-year mortality rate ranges between 15% and 30%, largely influenced by comorbidities such as CAD and diabetes mellitus [73]. Cardiovascular causes, including myocardial infarction, stroke, and sudden cardiac death, account for approximately 75% of deaths in symptomatic LEAD patients [72,73]. Progression to CLTI occurs in a notable minority, with about 4–6% of claudicants advancing to CLTI within five years; this proportion increases to 10–15% among high-risk groups like smokers and poorly controlled diabetics [76].

10.5.3. Chronic limb-threatening ischemia

CLTI represents the most advanced and severe stage of LEAD, aligning with Fontaine stages III and IV or Rutherford categories 4-6 (see Table 2 for comparison). It is defined by objectively confirmed atherosclerotic disease of the lower extremities accompanied by ischemic rest pain, non-healing ulcers, or gangrene persisting beyond two weeks [77]. CLTI carries a poor prognosis, characterized by high risks of limb loss, morbidity, and mortality. While precise global prevalence data are scarce, it is estimated that about 10% of LEAD patients present with CLTI at diagnosis [78]. In the United States, insurance data suggest an annual incidence of approximately 3500 new cases per million people, underscoring its significant public health impact [80]. Due to advanced ischemia, patients face a substantial risk of major amputation and death, with both the yearly amputation and mortality rates

reported at 20–25%, indicating that one in four affected individuals may experience limb loss or death within a year without adequate treatment [77]. Among diabetic foot patients, the Eurodiale study highlighted a large proportion presenting with ischemia, infection, and systemic comorbidities, all elevating the risk of MALE [78]. Although CLTI typically marks the terminal stage of LEAD, progression from earlier stages remains uncommon when risk factors are well-controlled and standard care is administered [76]. Management of CLTI is complex, and recent reviews have emphasized the need for standardized, patient-centered outcome measures in interventional research and limb preservation strategies [80].

ACC/AHA/AACVPR/APMA/ABC/ SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease	**Fontaine stage**	**Rutherford category**
Asymptomatic LEAD	I	0
Chronic symptomatic LEAD	II	1 (mild)
	IIa (claudication >200m)	2 (moderate)
	IIb (claudication <200m)	3 (severe)
CLTI	III (ischemic rest pain)	4 (ischemic rest pain)
	IV (ulceration/gangrene)	5 (minor tissue loss)
		6 (major tissue loss)
Acute limb ischemia		

Table 2: Comparison of the different classifications of LEAD. Adapted from Walsworth et al. [81]

10.5.4. Acute limb ischemia

ALI is a limb-threatening emergency caused by a sudden reduction in arterial blood flow to a limb, which can rapidly lead to tissue necrosis if untreated. By definition, symptoms last less than two weeks; otherwise, the condition is classified as CLTI [80]. The incidence of ALI is estimated at approximately 1 to 1.5 cases per 10,000 individuals annually, with embolism, thrombosis, and trauma being the principal etiologies [80-82]. Arterial embolism, often related to atrial fibrillation, is the most frequent cause, followed by arterial thrombosis occurring in the

setting of preexisting LEAD [82,83]. Less common but significant causes include inflammatory arterial occlusions due to vasculitis (e.g. giant cell arteritis or thrombangiits obliterans), paradoxical embolism via cardiac shunts often associated with deep vein thrombosis, and direct arterial injury from trauma or iatrogenic procedures [83-85]. Popliteal artery aneurysms may also present with ALI due to thrombosis or distal embolization, with as many as 50% of these aneurysms initially manifesting as ALI [80,83]. Clinically, ALI presents with acute limb pain distal to the occlusion, and symptom severity depends on occlusion location, collateral circulation, and timing [83,84]. Diagnostic evaluation includes thorough history and the "6 Ps" assessment (pain, pallor, pulselessness, paresthesia, paralysis, poikilothermia) [81]. Immediate diagnosis and urgent revascularization, via endovascular or surgical methods, are critical [80,85]. Despite timely treatment, ALI prognosis remains guarded, with 30-day amputation rates ranging from 10-30% and a five-year survival of about 60% [80,86].

10.6. Diagnostics for lower extremity artery disease

The diagnostic process for LEAD begins with a thorough patient history followed by a physical examination. If LEAD is suspected clinically, further diagnostic testing, both non-invasive and invasive, can be performed to confirm the diagnosis and assess the extent of disease.

10.6.1. Anamnesis

The initial step in diagnosing suspected LEAD involves a thorough patient history focusing on symptomatology, known risk factors, and family history of vascular diseases. Physicians should pay close attention not only to the typical LEAD symptoms but also to atypical complaints such as leg heaviness, weakness, or paresthesia. Precisely characterizing the pain, its location, onset, relieving factors, and quality, is essential to differentiate LEAD from other conditions [87]. This detailed history also aids in identifying the specific clinical subtype of LEAD. Risk assessment should include lifestyle factors like smoking, alcohol use, physical activity, and coexisting medical conditions [87,88]. Concurrent vascular diseases such as CAD and CVD warrant particular attention, as estimated half of LEAD patients exhibit symptoms of these comorbidities [85]. Family history appears to have a stronger association with LEAD than with other cardiovascular diseases, underscoring its diagnostic significance [89].

Since LEAD has a wide differential diagnosis, clinicians must also consider other vascular conditions like popliteal entrapment syndrome, vasculitides, cystic adventitial disease, fibromuscular dysplasia, and venous claudication due to iliac vein obstruction. Neurological causes include lumbar spinal stenosis leading to neurogenic claudication and peripheral neuropathy, especially in diabetic patients. Musculoskeletal disorders affecting gait can also mimic LEAD symptoms, such as osteoarthritis or muscle injuries causing pseudoclaudication [87]. Table 3 highlights features that help distinguish vascular intermittent claudication from pseudoclaudication.

Differentiating intermittent claudication from pseudoclaudication		
Description of symptom	Intermittent claudication	Pseudoclaudication
Character of discomfort	Pain, tightness, cramping, heaviness, tiredness, and burning	Same plus tingling, weakness, and clumsiness
Location of discomfort	Buttock, hip, thigh, calf, and foot	Same
Exercise-induced	Yes	Yes or no
Distance to claudication	Same each time	Usually variable
Occurs with standing	No	Yes
Relief	Stop walking and stand	Often must sit down or change body position

Table 3: Differentiating intermittent claudication from pseudoclaudication. Adapted from Olin et al. [87]

10.6.2. Physical examination

A systematic physical examination is a crucial part of evaluating patients suspected of LEAD. The examination begins with a careful inspection of both lower extremities for comparison. Signs of chronic ischemia include muscle and skin atrophy, hair loss, brittle nails, and changes in skin color such as pallor, cyanosis, or reactive redness. Ulcers or gangrene may also be present. On palpation, areas of decreased skin temperature and diminished or absent pulses are important findings [4,13,90]. Physicians should palpate the femoral pulse below the inguinal

ligament, the popliteal pulse behind the knee, the posterior tibial pulse behind and below the medial malleolus, and the dorsalis pedis pulse on the top of the foot, assessing both limbs in these specific locations. Absence of pedal pulses has a sensitivity of approximately 63% and specificity of about 99% for LEAD diagnosis [91]. In addition to palpation, auscultation of the aorta, iliac, femoral, and popliteal arteries should be conducted to detect bruits [91]. Another simple yet valuable test is the capillary refill time, which measures the time for color to return to the toe or finger pulp after applying pressure for about five seconds. Normal refill is typically within two seconds, with times exceeding two seconds indicating impaired perfusion [92,93]. If physical findings raise suspicion for LEAD, further diagnostic testing is warranted.

10.6.3. Ankle-brachial index

The ABI is a simple and non-invasive test widely used for the screening and diagnosis of patients suspected to have LEAD. In addition to its role in detecting disease, ABI measurement is valuable for assessing disease severity, monitoring the outcomes of revascularization procedures, and serving as an important prognostic indicator [94]. The concept of ABI measurement in LEAD was first introduced by Winsor in 1950 [95]. ABI is calculated by dividing the higher systolic blood pressure measured at the ankle by the higher systolic blood pressure recorded in the arm [96].

A normal ABI value ranges from 1.00-1.40, which generally excludes significant arterial obstruction and thus the presence of LEAD. Values between 0.90-1.00 may suggest mild LEAD, while values below 0.90 are considered pathological and diagnostic of the disease. Lower ABI values correlate with more advanced disease stages and are associated with an increased risk of cardiovascular events. Individuals with an abnormal ABI have approximately a fourfold greater risk of cardiovascular mortality over a ten-year period compared to those with normal ABI values [69,72]. An ABI exceeding 1.40 typically indicates the presence of non-compressible arteries, often seen in patients with diabetes mellitus or renal impairment due to extensive arterial calcification [97]. In these cases, ABI may not provide reliable diagnostic information, necessitating further assessments such as the toe-brachial index (TBI) to evaluate peripheral circulation more accurately.

10.6.4. Toe-brachial index

The TBI is a valuable noninvasive diagnostic parameter used in the assessment of patients with suspected LEAD. Its utility is particularly evident in clinical circumstances where the ABI cannot be reliably interpreted, most often due to pronounced vascular calcification that leads to falsely elevated ankle pressures. In such cases, the TBI is preferred, as the digital arteries of the toes are less affected by arterial stiffness and thus provide a more accurate representation of true peripheral perfusion [98].

Methodologically, the TBI is obtained in analogy to the ABI by dividing the highest systolic blood pressure measured at the great toe by the highest systolic brachial pressure. A TBI value of ≤0.70 is generally regarded as abnormal. When present together with a pathological ABI in a patient with clinical suspicion of LEAD, this finding substantially strengthens the certainty of the diagnosis and provides a reliable basis for further diagnostic and therapeutic decisions [67].

10.6.5. Treadmill exercise test and six-minute walk test

In addition to resting hemodynamic measurements, several functional tests are available to assess both the severity of LEAD and the associated functional impairment. The most widely applied modalities are the treadmill exercise test and the six-minute walk test (6MWT). These examinations are particularly useful in cases where LEAD cannot be adequately demonstrated under resting conditions.

During the treadmill exercise test, the patient is instructed to walk under standardized settings until exertional leg pain occurs. ABI measurements are performed immediately before and after the exercise protocol, and a significant post-exercise decline in ABI provides diagnostic confirmation of LEAD [69]. The 6MWT represents a straightforward and well-tolerated tool for evaluating walking capacity in patients with LEAD. The patient is asked to walk at the fastest pace possible on level ground for a duration of six minutes, after which the total distance covered is recorded [99].

Despite their practicality and ease of use, these tests have certain limitations. They may not be suitable in advanced disease stages, in patients with reduced mobility, or in individuals with comorbidities that inherently restrict walking performance, such as pulmonary or cardiac conditions. Furthermore, severe arterial calcification may impair the applicability of the

treadmill exercise test, given its dependence on ABI measurements for diagnostic interpretation [100,101].

10.6.6. Duplex ultrasound

Duplex ultrasound (DUS) holds a central position in the diagnostic algorithm LEAD and is most frequently utilized as the initial vascular imaging modality. Owing to its non-invasive nature, broad availability, and favorable cost-effectiveness, DUS represents the preferred first-line tool in routine clinical practice. In addition to its value for initial diagnosis, it is also widely employed for longitudinal follow-up, particularly in patients who have undergone revascularization procedures. From a methodological perspective, DUS integrates various ultrasound modalities into a comprehensive vascular assessment. The combination of high-resolution B-mode imaging with pulsed-wave and continuous-wave Doppler, as well as color and power Doppler techniques, allows for precise detection, anatomical localization, and quantification of arterial lesions. This multimodal approach provides detailed insights into vascular morphology, as well as hemodynamic parameters such as blood flow direction, velocity patterns, and flow intensity. Such detailed hemodynamic and morphologic information enables accurate grading of disease severity and delineation of the extent of LEAD [1]. Importantly, these diagnostic capabilities are achieved entirely without the administration of contrast agents or exposure to ionizing radiation [67]. Despite its numerous advantages, DUS is subject to certain methodological and practical restrictions. The diagnostic reliability is to some degree operator dependent, and the accuracy of the examination may vary with the examiner's level of experience. Furthermore, the visualization of certain anatomical regions remains challenging, particularly in the infrapopliteal arterial segments, where acoustic windows are often limited [102]. In addition, a number of patient-related factors can further diminish image quality and diagnostic accuracy, such as extensive arterial calcification, limb edema, ulcerations, obesity, or severe pain limiting examination tolerance [103].

Nevertheless, the capability of DUS to provide real-time, high-resolution imaging of arterial structures and flow profiles underscores its indispensable role. It remains an essential component of the diagnostic work-up and follow-up surveillance of patients with LEAD, offering a safe, reproducible, and clinically informative method for guiding therapeutic decision-making.

10.6.7. Computed tomography angiography

Computed tomography angiography (CTA) represents a widely used imaging modality in the diagnostic evaluation of LEAD, particularly when revascularization is being considered. Its broad clinical application is attributable to its wide availability, non-invasive character, and high spatial resolution, which render CTA a practical and popular diagnostic option. In comparison to conventional digital subtraction angiography (DSA), CTA is associated with considerably lower radiation exposure while still offering a high level of diagnostic accuracy, with reported sensitivity and specificity values in the range of approximately 90% [104,105]. In clinical practice, CTA is frequently employed alongside magnetic resonance angiography (MRA), as both modalities are well suited for precise localization of arterial lesions and evaluation of the severity of stenotic changes. CTA provides detailed three-dimensional reconstructions of the vascular tree, thereby facilitating treatment planning and enabling careful selection of interventional or surgical strategies. However, CTA is not without limitations. The examination requires the use of iodinated contrast agents, which are associated with potential risks such as nephrotoxicity or allergic reactions. Furthermore, CTA does not provide direct hemodynamic or functional information, restricting its ability to assess the physiological significance of detected lesions. The method also has reduced diagnostic value in cases of heavily calcified arteries or in the evaluation of distal vessels as of the lower leg, where blooming artifacts and limited resolution may significantly impair diagnostic accuracy [1,3].
Despite these constraints, CTA remains an important imaging tool in the work-up of LEAD, particularly for treatment planning, offering a balance between diagnostic precision, non-invasiveness, and procedural feasibility.

10.6.8. Magnetic resonance angiography

MRA, similar to CTA, is a non-invasive imaging modality employed in the diagnostic assessment of LEAD. In clinical use, MRA offers diagnostic accuracy comparable to CTA, with reported sensitivity and specificity values ranging between 90–100% for the detection of stenoses greater than 50% [1,3,106]. Key advantages over CTA are absent ionizing radiation or iodinated contrast agent, thereby reducing risks associated with cumulative radiation exposure

and contrast-induced nephropathy. Moreover, image quality in the presence of heavily calcified arterial lesions is often superior with MRA, since calcification does not generate the same degree of diagnostic artifacts observed with CTA. Nonetheless, MRA is subject to certain limitations. Compared to CTA, it is less widely available, more costly, and requires longer examination times, which can increase motion-related artifacts and thus compromise image quality. Additionally, there are important contraindications to MRA, including the presence of pacemakers or implantable cardioverter-defibrillators, as well as significant patient-related limitations such as claustrophobia or advanced CKD due to risks associated with gadolinium-based contrast agents [1,3,106].

Despite these disadvantages, MRA represents a valuable imaging tool in the diagnostic algorithm of LEAD, particularly in patients for whom exposure to radiation or iodinated contrast agents should be avoided, and in cases where extensive vascular calcification may reduce the diagnostic reliability of CTA.

10.6.9. Digital subtraction angiography

DSA was historically regarded as the gold standard for the diagnosis of LEAD. However, due to its invasive nature, its role as a primary diagnostic modality has largely been replaced by non-invasive imaging techniques such as DUS, CTA, and MRA. At present, DSA is primarily reserved for situations where non-invasive imaging results are inconclusive or when detailed visualization of infrapopliteal arteries is required, vascular segments [107]. The technique of DSA involves the acquisition of a baseline X-ray image of the relevant vessel segment, followed by the intravascular administration of a contrast agent. Subsequent serial radiographic imaging captures the passage of the contrast bolus through the arterial lumen. Subtraction of the baseline image from the contrast-enhanced images allows for optimal delineation of the vascular anatomy [108]. This methodological approach provides high-resolution, dynamic visualization of the arterial tree, enabling both precise morphological assessment and hemodynamic evaluation of stenotic lesions. A further advantage of DSA is its dual diagnostic and therapeutic potential. Once a lesion has been identified, endovascular treatment, such as angioplasty or stenting, can be performed in the same session, thereby streamlining the patient's management pathway. Nonetheless, the invasive nature of the procedure entails certain risks. DSA requires exposure to ionizing radiation and the administration of iodinated contrast agents,

factors that must be taken into careful consideration in patients with contrast media allergy or renal dysfunction.

Thus, although DSA no longer serves as the first-line diagnostic modality for LEAD, it continues to play an indispensable role in specific clinical scenarios where high-resolution imaging and simultaneous therapeutic intervention are required.

10.6.10. Screening in lower extremity artery disease

LEAD is closely associated with an elevated risk of major adverse cardiovascular events (MACE) and MALE. Consequently, early detection and systematic management of cardiovascular risk factors are of central importance to improve long-term outcomes in this patient population. In alignment with this, current international guidelines explicitly recommend targeted screening strategies in populations at elevated risk [2,67].

Systematic assessment for asymptomatic LEAD using the ABI is advised in individuals aged 65 years and older, as well as in adults aged 50 years and above who present with established risk factors such as diabetes mellitus, current or former tobacco use, arterial hypertension, or documented atherosclerotic disease in another vascular bed. Special emphasis is placed on screening women and patients with diabetes mellitus, given that LEAD remains underdiagnosed in these groups while the incidence of adverse cardiovascular and limb outcomes is disproportionately high [2,67]. For patients with diabetes mellitus or those suffering from CKD, the diagnostic accuracy of ABI may be compromised due to medial arterial calcification, which can result in falsely elevated readings. In such cases, the TBI is recommended as a more reliable alternative screening modality. Importantly, guideline recommendations highlight that screening for asymptomatic LEAD not only facilitates timely clinical recognition of PAD but also serves as a critical opportunity to optimize secondary prevention strategies. Integrating intensified control of cardiovascular risk factors into the care of screened patients has been shown to significantly reduce morbidity and mortality in this high-risk population [2,67].

10.6.11. Diagnostic algorithm

According to the 2024 ESC Guidelines, the diagnostic work-up of LEAD follows a structured, stepwise approach that begins with a thorough clinical assessment [2]. This initial evaluation

includes a detailed patient history, careful physical examination, and systematic assessment of cardiovascular risk factors, as these provide the essential context for subsequent diagnostic steps. Non-invasive hemodynamic testing represents the first diagnostic tier. The ABI is established as the standard first-line screening tool and adjunctive diagnostic measurement, including determination of the TBI or the analysis of Doppler waveforms, may be required in selected cases. If LEAD is suspected based on these initial non-invasive assessments, DUS is the preferred imaging modality. It allows for precise anatomical localization of lesions and evaluation of stenosis severity, providing critical information for both diagnostic confirmation and potential treatment planning. In situations where revascularization is under consideration, or when non-invasive imaging is inconclusive, more advanced imaging modalities with CTA or MRA are recommended. DSA is reserved for selected cases where detailed visualization is required and offers the additional advantage of enabling therapeutic intervention in the same session. This systematic, tiered diagnostic strategy, as depicted in the guideline algorithm (Figure 4), ensures a rational and evidence-based approach to the identification and evaluation of LEAD, while minimizing unnecessary risks and optimizing diagnostic yield [2].

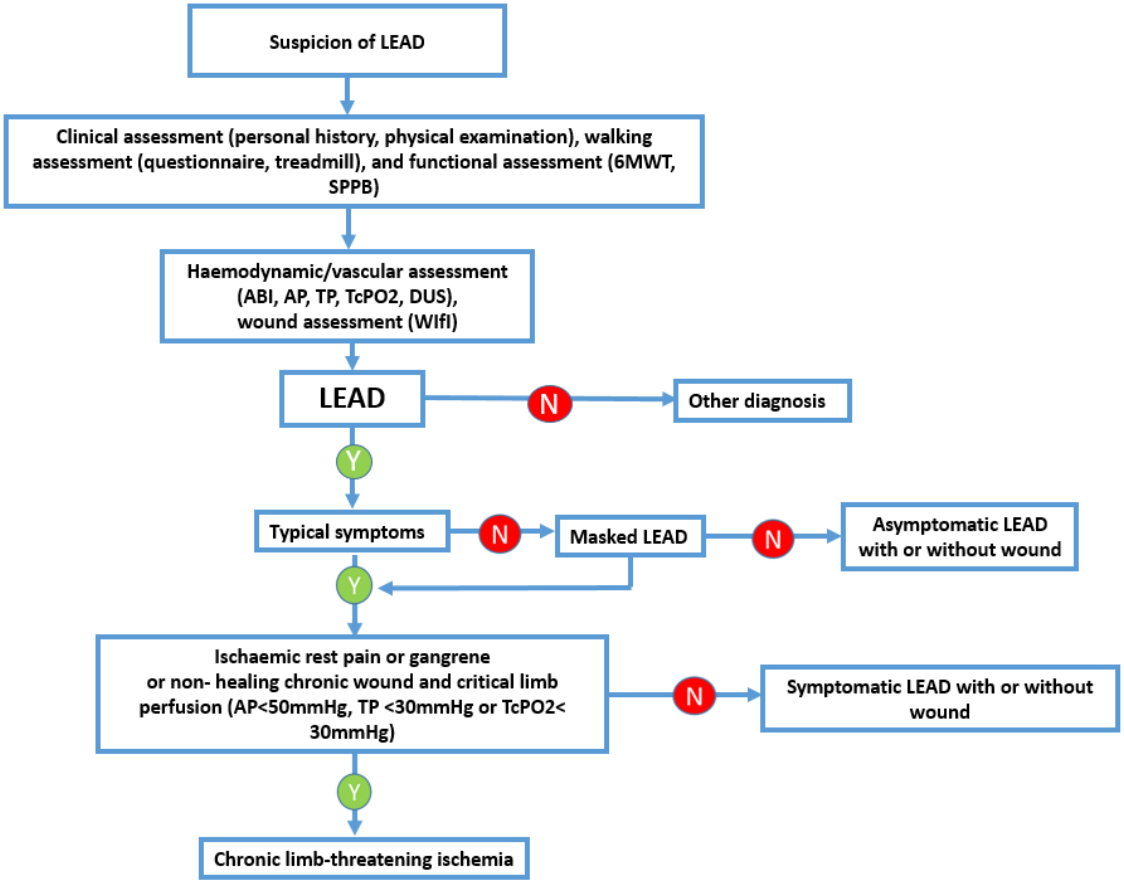

Figure 4: Diagnostic algorithm for LEAD. Adapted from Mazzolai et al. [2].

The differentiation of clinical subtypes of LEAD is of central importance, as LEAD subtypes are directly linked to amputation risk and serve as a critical determinant for therapeutic decision-making [1,2,67]. Precise subclassification ensures appropriate stratification of patients according to their disease severity and anticipated prognosis.

For standardized risk assessement in CLTI, the Wound, Ischemia, and foot Infection (WIfI) classification represents the principal tool currently endorsed by international guidelines. The WIfI classifiaction systematically evaluates wound extent, degree of ischemia, and presence and severity of foot infection. By combining these dimensions, it generates a risk profile that quantifies the threat of limb amputation and provides a framework for individualized, risk-based treatment planning [2,109].

Alongside WIfI, several additional staging and classification systems continue to play an important role in clinical practice and research. The Rutherford classification, one of the earliest and most widely adopted systems, stratifies LEAD severity along a spectrum ranging from asymptomatic disease through intermittent claudication to severe ischemia and impending limb loss, based on clinical signs and symptoms. Similarly, the Fontaine classification offers a symptom-based staging model with a comparable structure. For a more anatomy-focused perspective, the Trans-Atlantic Inter-Society Consensus II (TASC II) classification categorizes arterial lesions according to imaging findings. This anatomical classification is frequently used to guide decision-making regarding revascularization strategies by highlighting lesion complexity and feasibility of specific treatment modalities. In selected contexts, particularly in research settings and specialized vascular centers, more advanced scoring systems have been proposed. The Global Limb Anatomic Staging System (GLASS) integrates angiographic lesion complexity with clinical presentation, thereby allowing a combined anatomical and clinical risk stratification, which can support both procedural planning and risk prediction [2,67].

10.7. Treatment

The therapeutic approach to LEAD is determined primarily by the clinical subtype at presentation, as the overarching treatment goals differ substantially between patient groups. In individuals with asymptomatic LEAD, management is focused on comprehensive cardiovascular risk factor modification and the prevention of disease progression. In contrast,

in patients with chronic symptomatic LEAD, the main therapeutic objective shifts towards improving functional capacity and quality of life, with strategies directed at alleviating claudication symptoms and enhancing walking performance. The clinical priorities change markedly in patients with CLTI, where the risk of major amputation is high. In this setting, preservation of limb viability and prevention of tissue loss constitute the primary treatment goals, making timely and effective revascularization strategies indispensable. A distinct scenario is represented by ALI. ALI constitutes a vascular emergency in which immediate revascularization, executed either surgically or via endovascular techniques, is essential for limb salvage [83]. According to the most recent ESC Guidelines, treatment algorithms are stratified based on whether patients present with chronic LEAD with or without tissue loss. The therapeutic pathway for patients with chronic LEAD without wounds is illustrated in Figure 5, providing a structured, evidence-based guide for clinical decision-making [2].

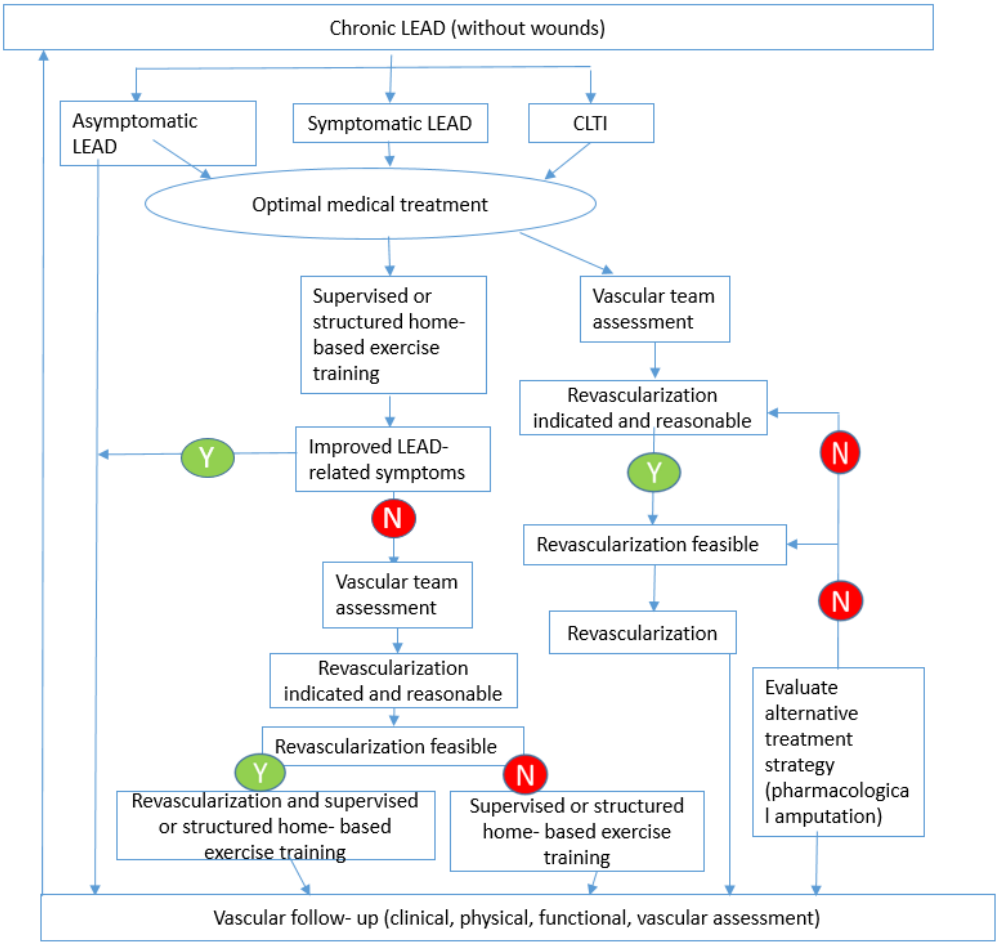

Figure 5: Treatment algorithm in LEAD without wounds. Adapted from Mazzolai et al. [2].

10.7.1. Optimal medical treatment

Optimal medical management of LEAD is multifaceted and encompasses both comprehensive lifestyle modification strategies and pharmacological interventions. In accordance with the 2024 ESC Guidelines, these therapeutic strategies are strongly recommended for all individuals with LEAD, independent of disease stage, as they form the base for preventing disease progression and reducing the incidence of MACE and MALE [2].

Lifestyle modification represents a central cornerstone of therapy. Targeted interventions include complete smoking cessation, adoption of a balanced cardiovascular-protective diet characterized by low intake of saturated fats, reduced salt consumption, and increased intake of fruits, vegetables, and whole grains. In addition, regular physical activity is universally advised, with structured and supervised exercise therapy (SET) occupying a central role. SET has consistently demonstrated significant benefits in increasing pain-free walking distance, improving overall functional capacity, and lowering the risk of secondary cardiovascular events in patients with LEAD.

Beyond lifestyle modifications, pharmacological therapy is an essential component of medical management. Evidence-based therapies include lifelong antiplatelet treatment to reduce atherothrombotic events, statin therapy for intensive lipid lowering, and strict control of arterial hypertension and diabetes mellitus where present. These interventions are universally indicated not only for symptomatic relief but also for their proven effectiveness in reducing the systemic cardiovascular risk burden inherent to LEAD.

Equally important is the integration of comprehensive patient education and multidisciplinary support throughout the treatment process. Educating patients about the chronic systemic nature of LEAD, engaging them in shared decision-making, and providing support through caregivers and healthcare professionals enhance adherence to lifestyle and pharmacological regimens.

Collectively, this integrated treatment approach, uniting pharmacological therapy with intensive lifestyle and exercise interventions, addresses the limb-related symptoms of LEAD and its systemic cardiovascular implications. By positioning overall cardiovascular risk reduction as a central therapeutic goal, optimal medical management contributes substantially to improved survival, reduced morbidity, and better quality of life in patients with LEAD [2].

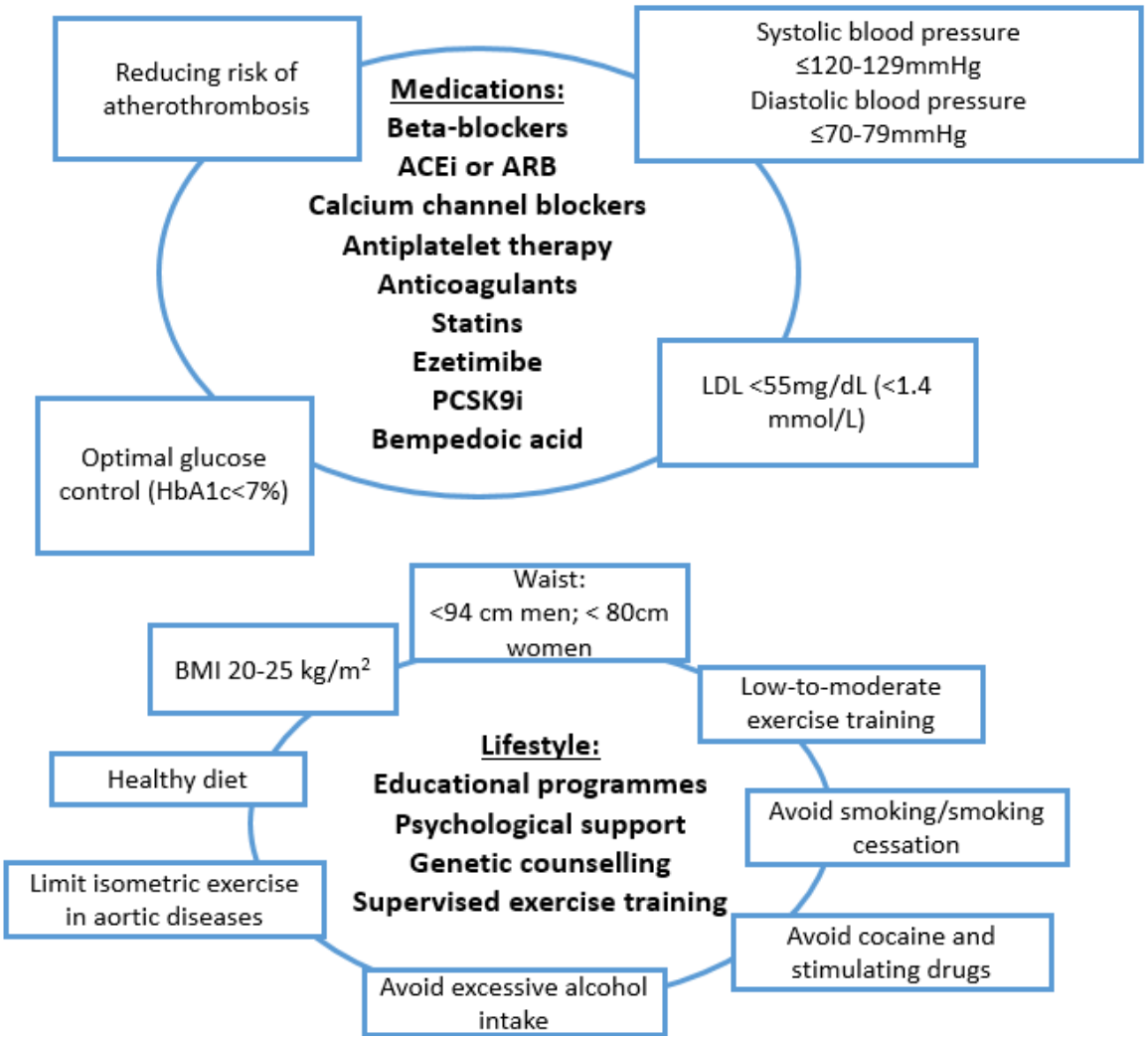

Figure 6: Cardiovascular risk modification and healthy lifestyle interventions and targets in patients with lower extremity artery disease. Adapted from Mazzolai et al. [2].

10.7.1.1. Lifestyle modification

Lifestyle modification constitutes a fundamental cornerstone in the contemporary management of LEAD [2,110]. Beyond its direct benefits on symptom control, comprehensive lifestyle intervention plays a crucial role in reducing the heightened cardiovascular morbidity and mortality associated with LEAD, thereby serving as an essential element of long-term secondary prevention.

Among lifestyle measures, smoking cessation is widely acknowledged as one of the most effective interventions. Complete discontinuation of tobacco use not only mitigates disease progression and recurrence after revascularization but also substantially lowers the risk of

MACE. Dietary modifications are equally emphasized, focusing on the adoption of a cardioprotective dietary pattern that favors reduced consumption of saturated fats and salt, together with increased intake of fruits, vegetables, and whole grains, principles aligned with evidence-based cardiovascular prevention strategies. Regular physical activity forms an additional critical component. Current guidelines specifically recommend structured exercise programs, such as SET, as these have been shown to effectively increase pain-free and maximum walking distance. Thus, overall physical function and positive influence major cardiovascular risk factors including blood pressure, lipid profile, and glycemic control can be achieved [2]. When supervised programs are not feasible, patients should be encouraged to engage in individualized walking regimens or other regular physical activities adapted to their functional capacity. Importantly, implementation of lifestyle interventions should always occur within a patient-centered framework. This requires individualized counseling that addresses barriers to change, tailors recommendations to patient-specific circumstances, and ensures integration of these strategies into a comprehensive management plan. This plan also includes pharmacological and, if indicated, interventional therapies.

In conclusion, lifestyle modification must be regarded as a core component of LEAD management and secondary prevention. Its integration into holistic care not only alleviates claudication-related symptoms but also substantially reduces the overall cardiovascular burden in this high-risk patient population [2,110].

10.7.1.1.0. Smoking cessation

Smoking is firmly recognized as one of the strongest modifiable risk factors for the development and progression of LEAD. Current smokers present with a two- to fourfold higher risk compared to individuals who have never smoked or those who successfully quit [111-114]. Large population-based studies consistently demonstrate a clear dose-response relationship between cumulative smoking exposure, measured in pack-years, and the likelihood of developing LEAD. In other words, the greater the extent of nicotine use, the greater the risk of both disease onset and progression. Creager et al. [111] and Ding et al. [113] emphasized this dose-dependent and cumulative association, underscoring the need for early and complete cessation of smoking. Smoking not only predisposes to incident LEAD but also negatively influences disease outcomes once established. Reitz et al. [112] revealed that active smokers

undergoing revascularization, whether open surgical or endovascular, for intermittent claudication had significantly higher complication rates than nonsmokers. Notably, even after successful cessation, the residual elevated risk of LEAD can persist for up to two decades. This highlights both the long-term vascular damage caused by chronic smoking and the necessity for intervention at the earliest possible stage. Thus, clinical practice guidelines strongly recommend that structured smoking cessation support be offered to all patients with LEAD wishing to stop. [2] This includes pharmacological therapies, such as nicotine replacement products, varenicline or bupropion, in combination with behavioral strategies like individual counseling, group support sessions, and systematic follow-up. Integrated cessation programs have demonstrated promising effectiveness. For example, Hennrikus et al. [18] reported that coordinated interventions could raise quit rates up to 21% among patients with LEAD, substantially higher than outcomes seen with unassisted attempts. Despite robust evidence, the implementation and use of smoking cessation strategies in real-world clinical practice remain insufficient. The international PORTRAIT registry highlighted that smoking cessation advice and counseling are still underutilized in LEAD populations, resulting in missed opportunities for optimized secondary prevention [114]. For this reason, systematic screening for tobacco use should be standard in all patients with LEAD, regardless of disease stage. Proactive, tailored cessation interventions combined with sustained physician engagement and ready access to structured programs are essential to improve both LEAD-related outcomes and overall cardiovascular health.

10.7.1.1.1. Diet

Nutritional strategies constitute a central component in the management of patients with LEAD. They are relevant not only for reducing overall cardiovascular risk but also for potentially influencing disease progression and clinical outcomes. Among the various dietary patterns investigated, the Mediterranean diet remains the most thoroughly studied and consistently recommended for vascular and cardiovascular protection. This dietary model is characterized by abundant consumption of fruits, vegetables, legumes, whole grains, and fish, while utilizing olive oil as the predominant fat source. It further allows for moderate red wine intake, typically with meals, and restricts red as well as processed meats [115]. A large meta-analysis by Sofi et al. [115] demonstrated that adherence to the Mediterranean diet was associated with an 8%

reduction in all-cause mortality and a 10% reduction in the composite outcome of mortality and incident atherosclerotic cardiovascular disease. Subsequent investigations and systematic reviews have corroborated the protective association of this dietary approach with a decreased risk of LEAD development, as well as lower cardiovascular morbidity and mortality among those already diagnosed [115,116]. The beneficial effects of the Mediterranean diet are mostly attributed to its high content of mono- and polyunsaturated fatty acids, antioxidant compounds, and anti-inflammatory nutrients [117]. Some of the studies summarized in the systematic review by Wan et al. [116] further suggest that the Mediterranean diet and similar heart-healthy patterns may actively modulate disease processes, likely by the anti-inflammatory and antioxidant properties inherent to specific food components. Besides the Mediterranean diet, other nutritional frameworks such as the Dietary Approaches to Stop Hypertension diet also demonstrate benefits by improving cardiovascular risk factors. This diet emphasizes high intake of fruits, vegetables, and whole grains, combined with low-fat dairy products and restricted sodium consumption. While direct evidence linking this approach to LEAD-specific outcomes is less extensive compared to the Mediterranean diet, the favorable effects on arterial hypertension, lipid metabolism, and glycemic control support its potential application in LEAD management [116].

In addition, increasing evidence highlights that malnutrition is a clinically relevant and frequently underestimated risk factor in LEAD patients, especially in the setting of CLTI. Malnutrition has been independently linked to worsened outcomes, including prolonged hospitalizations, increased amputation rates, and higher mortality. Systematic nutritional assessments, along with targeted interventions where appropriate, should therefore be regarded as an integral part of comprehensive LEAD care [2,116].

For optimal outcomes, patients with LEAD should receive individualized and culturally sensitive dietary counseling, with the dual objectives of enhancing nutritional status and reducing atherosclerotic risk profiles. Among all available dietary concepts, the Mediterranean diet currently stands out as the best supported by high-quality evidence.

10.7.1.1.2. Weight loss

Obesity, defined as a BMI of ≥30 kg/m², represents a growing global health burden and is widely recognized as a key determinant of morbidity and mortality. In the context of LEAD,

however, the relationship between obesity and clinical outcomes appears to be more nuanced and sometimes contradictory. While excess body weight is a well-established driver of comorbidities such as diabetes mellitus, arterial hypertension, and other cardiovascular conditions, its direct role in LEAD risk and prognosis is less consistently demonstrated [36-38]. An interesting observation within this field is the so-called “obesity paradox.” This term refers to data indicating that patients with mild overweight (BMI 25–29.9 kg/m²) may experience better survival compared to those of normal or low weight. One proposed explanation is that many studies involve predominantly elderly populations, where frailty and sarcopenia, frequently present in underweight individuals, may exert a stronger negative impact on prognosis than moderate excess adiposity [36,38]. Nevertheless, the obesity paradox should not be interpreted as justification against weight management in patients with LEAD. On the contrary, current evidence supports targeted weight reduction as beneficial, especially for functional outcomes. Weight loss interventions that integrate dietary modification, structured physical activity, and behavioral support have been shown to increase walking distance, improve exercise tolerance, enhance overall quality of life, and may even attenuate disease progression. Beyond these direct effects, weight reduction also contributes to better control of associated cardiovascular risk factors such as arterial hypertension, abnormal lipid levels, and impaired glucose regulation, thereby improving long-term vascular health [36-38].

Although the precise prognostic role of obesity within LEAD populations remains the subject of ongoing investigation, particularly across different demographic and clinical settings, the existing evidence justifies recommendations for gradual, sustainable weight control in overweight or obese patients. Such strategies offer not only functional advantages but also a broader cardiovascular risk reduction that extends beyond LEAD alone.

10.7.1.1.3. Supervised exercise therapy

Engaging in regular physical activity is a fundamental element of cardiovascular prevention and has particular relevance in the management of chronic, symptomatic LEAD. SET is clearly identified as the first-line intervention for these patients, as outlined in the 2024 ESC Guidelines [2]. Participation in SET produces significant and sustained improvements in walking distance, functional capacity, and health-related quality of life. Before initiation, every patient should be screened for potential contraindications, such as unstable cardiac or pulmonary conditions,

uncontrolled arterial hypertension or diabetes mellitus, as well as the presence of ALI or CLTI. A careful clinical assessment consisting of a thorough medical history and physical examination is therefore required before therapy begins [118].

SET is a safe and effective therapeutic option. Large-scale clinical trials and systematic reviews have consistently demonstrated its positive effects on walking ability, pain-free and maximum walking distances, and patient-reported outcomes [118]. The most strongly supported modalities are treadmill training and over ground walking, both of which have a solid evidence base. Additional forms of activity, such as cycling and resistance training, can serve as beneficial alternatives, although the majority of data is derived from walking-based regimens [118]. Current recommendations advise that patients should participate in exercise sessions at least three times per week, lasting 30-60 minutes each. Intensity should be sufficient to provoke moderate to severe claudication pain, at which point short rest breaks are taken before resuming walking. This "pain-induced intermittent walking" protocol has been shown to produce the most substantial improvements in walking ability and overall function [118]. Despite clear benefits, implementation of SET in routine clinical practice remains limited. In many European regions, structural and systemic barriers hinder broader uptake. If formal supervised programs are unavailable, structured home-based exercise should be promoted as a substitute. Evidence shows that when home-based exercise is organized and reinforced with monitoring tools, including pedometers, smartphone applications, or remote support from healthcare professionals, it can markedly improve walking performance, though supervised programs remain superior overall [2,118].

SET should not only be regarded as a first-line strategy but also as an important adjunct in patients undergoing endovascular or surgical revascularization. Evidence demonstrates that combining SET with endovascular therapy results in greater gains in walking distance, symptom relief, and quality of life than revascularization alone. Similarly, patients who perform exercise after surgical revascularization achieve added benefits and improved long-term recovery [2,118].

In summary, SET is an indispensable component of comprehensive care in chronic symptomatic LEAD. It should be implemented whenever possible, either as standalone therapy or in conjunction with revascularization, and structured home-based programs should be promoted where formal infrastructure is lacking.

10.7.1.2. **Pharmacological therapy**

The pharmacological management of LEAD aims not only to alleviate symptoms and enhance functional performance, but also, and more importantly, to reduce the elevated risk of cardiovascular morbidity and mortality in this high-risk population. Core elements of treatment include the use of antiplatelet agents, lipid-lowering drugs, antihypertensive therapy, and strict glycemic control in patients with concomitant diabetes mellitus. A comprehensive approach that systematically addresses all major risk factors is essential to improve long-term outcomes and overall prognosis in patients with LEAD.

10.7.1.2.1. Antiplatelet and antithrombotic therapy

The significance of antiplatelet and antithrombotic therapy in LEAD varies considerably depending on the clinical presentation and whether revascularization has been performed. Current evidence emphasizes the need for a differentiated approach that clearly distinguishes between asymptomatic LEAD, symptomatic disease, and the post-interventional setting [2].
For patients with asymptomatic LEAD, even in the presence of severe arterial stenoses or occlusions, the clinical benefit of antithrombotic therapy remains unproven. Several large-scale randomized controlled trials, most notably the Aspirin for Asymptomatic Atherosclerosis Trial, failed to show any significant reduction in MACE, revascularization rates, or prevention of amputations in this population when treated with antiplatelet medication. Instead, therapy with aspirin or other antithrombotic drugs was associated with a considerable increase in bleeding complications. Based on these findings, contemporary ESC guidelines do not recommend the use of antiplatelet or antithrombotic treatment in asymptomatic patients, even when relevant arterial lesions are present. In this context, the harms clearly outweigh the potential but unproven vascular benefits [2,67].
In contrast, patients with symptomatic LEAD, manifesting either as intermittent claudication or CLTI, have a markedly elevated cardiovascular risk. In this setting, antiplatelet therapy forms a key element of secondary prevention strategies. Extensive clinical evidence has demonstrated that single antiplatelet therapy (SAPT) effectively lowers the incidence of MACE. Among available agents, clopidogrel is the preferred choice, as it has been shown to be superior to aspirin in reducing the occurrence of MACE [2]. By contrast, there is no evidence supporting

the routine use of dual antiplatelet therapy (DAPT), intensified combinations of antiplatelet drugs, or therapeutic-dose anticoagulation in patients with stable LEAD who have not undergone revascularization. Such regimens increase bleeding risk without conferring meaningful incremental benefit in preventing ischemic outcomes [2,67].

Therapeutic considerations become more complex after vascular interventions, whether surgical or endovascular. In these cases, the optimal antithrombotic regimen should be determined through individualized risk assessment that accounts for the clinical scenario, comorbidities, bleeding risk, and the likelihood of MACE or MALE. After endovascular procedures, short-term DAPT with aspirin and clopidogrel for one to three months is a widely accepted strategy, largely extrapolated from CAD protocols. Recently, evidence from studies such as the COMPASS trial has contributed to a paradigm shift. In carefully selected patients with low bleeding risk, the combination of aspirin 100 mg once daily with rivaroxaban 2.5 mg twice daily, following an initial period of DAPT, has been shown to significantly reduce both MACE and MALE. Consequently, this regimen is now gaining increasing relevance in clinical practice [2,119,120]. Importantly, extended DAPT beyond three months is not recommended after endovascular therapy, as the excess bleeding risk outweighs any potential ischemic protection [2,67]. In the setting of surgical revascularization, SAPT is generally considered sufficient. However, in patients at higher risk of graft thrombosis, particularly in those who have undergone prosthetic bypass implantation, DAPT may be considered for at least one month. For patients with autologous venous conduits or after isolated surgical endarterectomy, SAPT is usually deemed adequate. Across all surgical scenarios, treatment must be adapted to each patient's clinical status and individualized balance of bleeding versus thrombotic risk [2,118,120].

Special consideration is needed in cases where patients have an independent long-term indication for oral anticoagulation, such as atrial fibrillation, mechanical prosthetic heart valves, or venous thromboembolism. In such circumstances, full-dose anticoagulation remains mandatory. For individuals who have undergone recent revascularization, a temporary addition of SAPT for up to three months may be justified in patients without elevated bleeding risk; however, the necessity of this combination should be re-evaluated regularly [2,67].

Overall, current evidence underscores that the antithrombotic strategy in LEAD requires careful individualization. No therapy is advised for asymptomatic patients, regardless of lesion severity. In symptomatic LEAD, SAPT is essential, with clopidogrel representing the preferred

regimen. After revascularization, treatment strategies differ according to the type of intervention and patient risk profile but generally include short-term DAPT or, following the COMPASS trial findings, the combination of aspirin with very-low-dose rivaroxaban in selected candidates. At all stages, a judicious balance between protection against ischemic events and the potential for bleeding complications must guide clinical decision-making according to recent evidence and international guideline recommendations [2,120]. Table 4 summarizes the recommended antithrombotic therapies for patients with LEAD [2].

Clinical Scenario	Therapy	ESC Recommendation
Asymptomatic LEAD	None (no SAPT/DAPT/OAC)	Not recommended, even with significant stenoses/occlusions
Symptomatic LEAD (no intervention)	SAPT (clopidogrel preferred)	Strongly recommended
Post-endovascular revascularization	DAPT (1–3 months) or SAPT + low-dose rivaroxaban	Individualized; longer DAPT not recommended
Post-surgical revascularization	SAPT; consider DAPT 1 month (prosthetic grafts)	Individualized
Other OAC indication	OAC ± SAPT (up to 3 months)	According to indication and bleeding risk

Table 4: Recommended Antithrombotic Therapy for LEAD. Adapted from Mazzolai et al. [2].

10.7.1.2.2. Antihypertensive therapy

Patients with concomitant arterial hypertension and LEAD face a markedly increased risk of cardiovascular complications. Achieving a systolic blood pressure in the range of 120–129 mmHg has been shown to lower cardiovascular risk across all age groups. However, in certain individuals, such as those with orthostatic hypotension, advanced age (≥85 years), frailty, or limited life expectancy, strictly reaching this target may not be feasible. In such patients, the systolic pressure should instead be reduced to the lowest level that can be achieved safely and reasonably [121].

With regard to pharmacological management, any of the established antihypertensive drug classes may be used either as monotherapy or in combination therapy in patients with LEAD. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers remain the preferred first-line agents, since their use is associated with a reduced incidence of cardiovascular events. As alternative treatment strategies, calcium channel blockers, diuretics, and beta-blockers can also be effectively applied. Notably, beta-blockers are considered safe in patients with LEAD and do not adversely influence outcomes [2].

10.7.1.2.3. Lipid-lowering therapy

Dyslipidemia is a major risk factor for the development of atherosclerosis, and patients with LEAD are classified as being at very high cardiovascular risk according to the 2024 ESC Guidelines [2]. Accordingly, strict control of dyslipidemia is essential. The primary therapeutic goal is to achieve at least a 50% reduction in LDL-C levels from baseline and an absolute target of <1.4 mmol/L (<55 mg/dL), in order to lower the risk of cardiovascular death, myocardial infarction, stroke, and MALE, as well as to improve walking capacity [2]. Despite this, patients with LEAD have historically been undertreated in terms of lipid-lowering therapy compared with individuals suffering from other manifestations of cardiovascular disease, with registry studies showing lower rates of statin prescription in the LEAD population compared to patients with CAD [122].

Statins remain the recommended first-line lipid-lowering therapy for all LEAD patients because of their proven efficacy in reducing both MACE and MALE and simultaneously improving walking performance. A recent meta-analysis demonstrated that statin therapy in LEAD was associated with an approximate 30% reduction in MALE, a 35% reduction in amputation risk, and a 39% decrease in all-cause mortality [2,123]. When LDL-C targets cannot be achieved with statins alone, guidelines recommend adding ezetimibe. For patients who fail to reach target levels even on statin–ezetimibe therapy or who are intolerant to statins, bempedoic acid can be considered as an alternative or complementary option. In cases of persistently uncontrolled LDL-C, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as alirocumab or evolocumab are advised. Both agents have been shown in randomized controlled trials to significantly reduce MACE and MALE in LEAD patients compared with placebo [124,125]. Inclisiran, a small interfering RNA agent directed against PCSK9, has demonstrated robust

LDL-C reduction and was also associated with MACE reduction in pooled analyses of patients with atherosclerotic disease on background statin treatment, although large outcome trials specifically in LEAD cohorts are still ongoing. In contrast, icosapent ethyl, an omega-3 fatty acid preparation, is not currently recommended for LEAD-specific event reduction, due to the absence of conclusive evidence for MACE or MALE reduction in this population. Similarly, fibrates have not shown benefits regarding major cardiovascular or limb outcomes in LEAD and are therefore not recommended [2,123,124].

In summary, intensive guideline-based lipid-lowering therapy, with statins for all patients, and escalation to ezetimibe, bempedoic acid, or PCSK9 inhibitors as required, represents a cornerstone of treatment in LEAD, aiming to reduce both cardiovascular and limb-related risks while also potentially improving functional outcomes.

10.7.1.2.4. Diabetes mellitus and pre-diabetes mellitus condition

Diabetes mellitus is a critical risk factor for atherosclerotic cardiovascular disease, substantially increasing vulnerability to LEAD. The likelihood of developing LEAD is estimated to be up to twice as high in patients with diabetes mellitus compared to those without [2,13]. Epidemiological evidence indicates that the prevalence of LEAD among individuals with diabetes mellitus may reach as much as 30%, though less than half of these patients experience or report characteristic symptoms [13]. Importantly, patients affected by both diabetes mellitus and LEAD face particularly unfavorable prognoses, frequently presenting with more advanced disease, higher rates of progression, and significantly increased risks of cardiovascular and limb-related complications [126]. To mitigate this elevated burden, the 2024 ESC Guidelines recommend systematic screening for diabetes mellitus in all patients diagnosed with LEAD and all patients with diabetes mellitus, regardless of the presence of ulcers, should be systematically evaluated for potential LEAD. This bidirectional screening approach supports earlier detection and promotes a comprehensive, interdisciplinary treatment framework [2]. Maintaining optimal glycemic control is fundamental in patients with concurrent diabetes mellitus and LEAD, as stringent glycemic management has been shown to reduce both MACE and MALE. According to the ESC guidelines, the target glycated hemoglobin (HbA1c) should be <53 mmol/mol (<7%), with a minimally acceptable goal of <69 mmol/mol (<8.5%), tailored to individual factors such as comorbidities, age, and duration of diabetes mellitus [2,127]. Supporting

evidence underscores the importance of this recommendation. An observational study revealed that each 1% increment in HbA1c is linked to a 14% increased risk of MACE among patients with symptomatic LEAD and type 2 diabetes mellitus [128].

In terms of pharmacological therapy, metformin remains the preferred first-line treatment for most patients with type 2 diabetes mellitus, including those with LEAD, unless contraindicated due to conditions such as advanced renal impairment [2,127]. If HbA1c goals are not achieved with metformin monotherapy, the addition of newer glucose-lowering agents with proven cardiovascular and limb benefits should be prioritized. Specifically, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) are recommended, given their efficacy in reducing cardiovascular and renal events. Among these, GLP-1RA have demonstrated particular advantages, including enhancements in microvascular function and peripheral perfusion, and have been associated with a reduced risk of lower-limb amputation when compared with SGLT2i. Therefore, in patients at especially high risk for limb loss, GLP-1RA may be the treatment of choice [127]. Both classes additionally provide benefits such as weight reduction and favorable tolerability, thereby constituting a cornerstone of modern diabetes therapy in LEAD. Other antidiabetic drug classes, including dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, glinides, thiazolidinediones, and alpha-glucosidase inhibitors such as acarbose, may be considered when primary and secondary options fail or are not tolerated. However, these agents are generally less preferred due to either limited cardiovascular benefit or higher risk of hypoglycemia or adverse side-effect profiles [127]. Insulin therapy may eventually become necessary in advanced or unstable diabetes but requires careful consideration, as hypoglycemia carries particularly detrimental consequences in patients with LEAD.

Therapeutic goals for glycemic control must always be individualized, taking into account comorbidities, overall functional status, risk of hypoglycemia, and life expectancy [2,126,127]. For patients with LEAD, minimizing hypoglycemic episodes is crucial, given their association with increased cardiovascular morbidity and frailty. Consequently, diabetic management in LEAD should adopt a structured stepwise approach. First-line is commonly metformin, advancing early to GLP-1RA or SGLT2 inhibitors for their solid cardiovascular and limb-protective effects, and integrating additional agents cautiously when required. Such a precision-based, escalation-oriented therapeutic strategy, combined with meticulous risk factor management, forms the foundation for optimizing cardiovascular and limb outcomes in this

particularly vulnerable patient cohort.

10.7.1.2.5. Medication for decreasing the walking impairment

Intermittent claudication, presenting as impaired walking ability, represents one of the hallmark symptoms in patients with LEAD. Over time, various pharmacological strategies have been evaluated to enhance walking distance and mitigate functional limitations in this population.

Cilostazol, a phosphodiesterase III inhibitor, remains the only oral drug with consistent evidence demonstrating clinically relevant improvements in both maximal and pain-free walking distance in patients with intermittent claudication and LEAD. Multiple randomized trials and meta-analyses have reported that cilostazol increases treadmill walking distance by approximately 50% compared with placebo, thereby offering measurable symptomatic relief [2,67]. Beyond its symptomatic effects, cilostazol may also contribute to lowering restenosis rates following femoropopliteal endovascular procedures. Despite this, its overall impact is considered moderate, and its clinical adoption in Europe has been limited due to restricted availability, side effects such as headache, palpitations, or gastrointestinal discomfort, and notable contraindications, particularly in the setting of congestive heart failure. Consequently, ESC guidelines recommend cilostazol only for carefully selected patients with intermittent claudication who remain symptomatic despite exercise therapy and optimal risk factor control, provided no contraindications exist [2]. Recent international guideline updates confirm the selective use [67].

Several other drugs previously explored for walking impairment, including naftidrofuryl oxalate, pentoxifylline, propionyl-L-carnitine, and buflomedil, have yielded only limited or inconsistent efficacy in clinical studies. Due to the lack of convincing benefit, these agents are not endorsed by contemporary international recommendations [2,67].

Prostaglandins such as iloprost and alprostadil, along with other vasodilating compounds, have mainly been tested in patients with CLTI, particularly those with non-healing ulcers who are unsuitable for revascularization. However, systematic evaluations and current guideline analyses consistently conclude that the evidence supporting improvements in ulcer healing or limb salvage is weak, and thus prostaglandins are not advised for the routine management of intermittent claudication or LEAD-related ulcers in the absence of other indications [2,67].

Bosentan, an endothelin receptor antagonist, has been trialed in the context of digital ulcers

secondary to systemic sclerosis as well as in rare peripheral ulcer presentations, though no robust evidence supports its application in ulcer healing or walking impairment related to LEAD [2].

Overall, among pharmacological options, cilostazol remains the only agent currently supported for improving walking capacity in appropriately selected patients with LEAD and intermittent claudication. By contrast, prostaglandins, bosentan, and the historically tested compounds do not have sufficient supportive evidence for therapeutic use in this context. As a result, emphasis continues to be placed on structured exercise programs, aggressive secondary prevention, and timely revascularization when indicated, to improve mobility and overall quality of life in patients with LEAD.

10.7.2. Wound Care

Wound care constitutes a fundamental component in the treatment of patients with CLTI. Effective management of wounds is crucial for promoting tissue repair, preventing infection, lowering the risk of limb loss, and enhancing quality of life [2]. The initial step in wound management involves a thorough evaluation of both the patient and the affected extremity. This includes assessment of vascular status, depth and extent of tissue loss, presence of infection, and relevant comorbidities. International guideline recommendations highlight the necessity of a multidisciplinary approach, typically incorporating vascular specialists, wound care nurses, diabetologists, podiatrists, infectious disease physicians, and when indicated, orthopedic or plastic surgeons. Such integrated care strategies have been shown to increase rates of limb preservation and to optimize clinical outcomes [2,67].

Adequate tissue perfusion is an essential prerequisite for wound healing. Whenever feasible, timely revascularization should be pursued, either via endovascular techniques or open surgical procedures, to restore sufficient blood flow. Local wound treatment alone cannot compensate for severe, ongoing ischemia. Accordingly, revascularization should never be delayed in patients with non-healing wounds or CLTI [2,67]. Once sufficient perfusion is established frequent sharp or mechanical debridement of devitalized tissue is recommended, as this facilitates granulation tissue formation and decreases microbial burden. In contrast, in the setting of dry necrosis without infection and inadequate blood supply, a conservative wound care strategy may be preferred until revascularization is feasible [67].

Local wound care focuses on creating and maintaining a moist wound environment, performing regular and meticulous debridement of necrotic tissue, preventing and managing infection, and protecting the surrounding skin. The use of advanced wound dressings, including hydrogels, hydrocolloids, alginates, and silver-containing materials, should be tailored to the individual wound characteristics. The widely applied “TIME” framework provides a systematic approach: Tissue management, control of Infection/Inflammation, Moisture balance, and advancement of wound Edge [2].

Infection represents a major threat to limb salvage. Therefore, wound infections must be promptly identified and addressed through systemic antimicrobial therapy guided by local microbiological data, combined with proper local management and surgical intervention where necessary. Severe infections warrant immediate multidisciplinary evaluation and urgent intervention [2].

Adjunctive measures such as pressure offloading, ulcer protection, and redistribution of mechanical stress are indispensable, particularly in patients with concomitant diabetes mellitus. This may include specialized footwear, custom orthotic devices, or temporary total contact casting. Additionally, management of systemic comorbidities, including optimization of glycemic control, adequate nutritional intake, and treatment of anemia, is vital to support optimal wound healing [68]. The application of advanced wound therapies, such as negative pressure wound therapy, bioengineered dermal substitutes, or topical growth factor formulations, is generally reserved for selected patients and should always be embedded within a framework of adequate revascularization and multidisciplinary care [2].

10.7.3. Revascularization in lower extremity artery disease

Revascularization is a fundamental therapeutic option in LEAD, particularly when conservative measures are insufficient to preserve limb viability or functional capacity. In recent decades, evidence base and the range of available techniques have expanded significantly. Contemporary management is based on an individualized, risk–benefit–oriented approach that incorporates anatomical features, clinical presentation, symptom severity, comorbidities, and life expectancy. International guideline recommendations consistently highlight the importance of a stage-based, patient-centered strategy. Depending on the clinical context, revascularization may be performed using endovascular, surgical, or hybrid approaches, with the optimal

technique determined by anatomical considerations and overall patient status [2,67]. The therapeutic framework has been shaped by large randomized trials and meta-analyses, which emphasize that best medical therapy, comprising SET, pharmacological risk factor optimization, and patient education, remains the foundation in stable, non-urgent cases. In contrast, timely revascularization is indispensable in situations of critical ischemia. Systematic reviews and network meta-analyses have confirmed that SET can significantly improve symptoms and walking ability, even without intervention [129–132]. Thus, revascularization should not be regarded as a stand-alone measure but integrated as part of a multimodal treatment concept.

For asymptomatic individuals with LEAD, prophylactic revascularization is not recommended. A substantial body of cohort data and guideline-based analyses demonstrate no evidence of reduced cardiovascular events, MALE, or improvements in walking capacity through preventive procedures. Exceptions are rare, limited to cases where improved limb perfusion is required for a necessary surgical intervention or in acute scenarios such as tissue compromise following trauma or infection [2,67]. By contrast, in symptomatic LEAD patients, revascularization is the central treatment option, with procedural preference differing between chronic symptomatic disease, CLTI, and ALI [67]. Today, a wide spectrum of revascularization modalities is available, and the choice of treatment is guided by lesion characteristics, anatomical site, and patient-specific risk factors [2,67].

Endovascular therapy has emerged as the preferred approach in many scenarios, given its minimally invasive nature, lower perioperative risk, and faster recovery. The central technique is percutaneous transluminal angioplasty, employing a balloon catheter to dilate stenosed or occluded arteries. While plain old balloon angioplasty formed the traditional standard, drug-coated balloons (DCB) have demonstrated superiority in reducing restenosis rates for selected lesion types. If angioplasty alone yields insufficient lumen restoration, stenting is performed using bare-metal, drug-eluting, or covered stents. In cases of heavy calcification or large plaque burden, adjunctive techniques such as atherectomy or intravascular lithotripsy, using acoustic shockwaves to fracture calcified plaque, can be employed. For complex or multilevel disease patterns, hybrid procedures combining open surgery with endovascular intervention during a single session are increasingly used in specialized centers [2,67,133–136].

Surgical revascularization continues to play a pivotal role, particularly for long-segment occlusions, involvement of the common femoral artery, and cases unsuitable for endovascular

management or following unsuccessful prior therapy [137]. Surgical approaches include endarterectomy, most commonly employed for the common femoral artery, as well as bypass surgery, in which blood flow is redirected around the diseased vessel using either autologous vein grafts or synthetic prostheses. Conventional bypass configurations comprise aortobifemoral, femoropopliteal, and femorotibial grafts, whereas extra-anatomic bypasses are reserved for special indications. With advancements in both techniques and outcomes, the choice between surgical and endovascular treatment is increasingly personalized and determined within multidisciplinary vascular teams, ensuring patient-tailored therapy [2,67].

10.7.3.2. **Revascularization in chronic symptomatic lower extremity artery disease**

The therapeutic approach to chronic symptomatic LEAD focuses on reducing symptom burden and preserving long-term quality of life. Current evidence strongly supports a conservative-first strategy with best medical therapy and SET [129–131]. Revascularization should only be pursued when symptoms continue to substantially restrict everyday activities despite exhaustive conservative management. This staged approach reflects both international guideline consensus and the principles of patient-centered care, ensuring that the benefits of intervention outweigh procedural risks, particularly in terms of functional recovery and overall well-being [2].

When revascularization becomes necessary, the choice of therapy depends on anatomical pattern, lesion distribution, and individual procedural risk. In the aorto-iliac segment, innovations in endovascular therapies, especially routine primary stenting, have shifted practice toward minimally invasive strategies. For suitable patients, these techniques demonstrate comparable, and in some cases superior, short- and long-term outcomes compared with surgical bypass [134,138]. In femoropopliteal disease, endovascular revascularization, typically employing DCB and stenting when required, has become the preferred option for most lesions. Surgical bypass, particularly with autologous vein grafts, is now largely reserved for extensive or complex cases such as long-segment occlusions, or when endovascular therapy has failed [135,136]. The common femoral artery remains an important exception, where surgical endarterectomy continues to represent the gold standard due to its proven long-term durability. Below-the-knee interventions are most often indicated in advanced cases when improving outflow is essential for limb salvage. These procedures are primarily performed with endovascular techniques, serving as adjuncts to optimize perfusion rather than routine

interventions in less severe disease [2].

In summary, revascularization in chronic symptomatic LEAD is guided by a structured, stepwise strategy in which conservative management is prioritized, and interventions are carefully tailored to anatomical site, lesion complexity, patient risk, and functional needs.

10.7.3.3. **Revascularization in chronic limb-threatening ischemia**

Unlike intermittent claudication, CLTI constitutes a true vascular emergency. Clinical trials and guideline recommendations unanimously stress the necessity for prompt revascularization in order to prevent major amputation and preserve limb function. Optimal outcomes require a fully interdisciplinary approach, involving close collaboration between vascular surgeons, angiologists, diabetologists, podiatrists, wound care specialists, and other relevant disciplines [137].

Both surgical and endovascular strategies are considered valid therapeutic options in CLTI, and the decision between them is informed by patient-related factors such as comorbidities, suitability of autologous vein for bypass, anatomical lesion complexity, and individual patient preference. Recently conducted landmark studies have provided critical insights regarding treatment selection. The BEST-CLI trial showed that patients with an available autologous vein conduit achieved superior outcomes following bypass surgery compared with endovascular therapy, whereas in the absence of such a vein, the results between surgical and endovascular approaches were largely equivalent [137]. The BASIL trial found no overall survival difference between strategies, although longer-term analyses suggest some advantage for surgical revascularization [136]. Despite this, for many patients, modern endovascular therapy offers high initial success rates, robust limb salvage outcomes, and reduced perioperative risk. Hybrid procedures, which integrate surgical and endovascular techniques in a single session, are increasingly applied for patients with extensive or multilevel disease. In the infra-popliteal region, an endovascular-first approach has become predominant, although newer technologies have thus far failed to demonstrate clear superiority over plain balloon angioplasty in improving vessel patency or limb salvage [136]. In highly selected “no-option” scenarios, innovative approaches such as deep vein arterialization may provide a last therapeutic resort [139].

Even with timely and optimal revascularization, complete limb preservation cannot always be achieved. Minor amputations, and in certain cases major amputations, remain relatively

common. Hence, long-term follow-up, comprehensive rehabilitation, and secondary prevention are critical to improve functional prognosis and overall quality of life in this high-risk patient group [2,67].

10.7.3.4. **Revascularization in acute limb ischemia**

ALI represents a true vascular emergency, posing both life- and limb-threatening risks. It is defined by the sudden onset of severely reduced perfusion to a limb, typically occurring within hours to days, and carries the potential for rapid progression to tissue necrosis, systemic complications, and even death if left untreated. Prompt recognition and immediate intervention are therefore essential to optimize outcomes. The initial management of ALI begins with urgent anticoagulation, most often with intravenous unfractionated heparin, to prevent thrombus propagation and stabilize the clinical situation while further treatment is organized. Parallel to this, rapid evaluation of ischemia severity must be performed, commonly employing standardized systems such as the Rutherford or TASC II classification, which stratify the degree of ischemia and inform the urgency and selection of treatment. Early imaging, particularly DUS, CTA or MRA, is critical in defining the anatomical extent of occlusion when it does not unduly delay revascularization [2,67].

Therapeutic strategies include both endovascular and surgical options, with the choice largely dependent on patient hemodynamic stability, comorbidities, time of symptom onset, lesion morphology, and the resources as well as expertise available at the treating center [133,137]. Endovascular therapies encompass catheter-directed thrombolysis, mechanical or aspiration thrombectomy, or a combination of these techniques. These approaches may be preferred in patients with fresh thrombotic occlusions, limited comorbidity burden, or anatomies amenable to minimally invasive access. On the other hand, open surgical procedures such as Fogarty balloon embolectomy, direct thromboendarterectomy, or urgent surgical bypass remain critical options, especially in cases of large-vessel embolic occlusions, advanced ischemia with threatened limb viability, or failure of endovascular measures [67]. In many modern vascular centers, a “tailored” hybrid strategy is increasingly employed, often combining thrombolysis with subsequent endovascular or surgical correction of underlying stenotic or occlusive lesions. This stepwise approach aims at both acute clot removal and secondary prevention of recurrence by addressing contributing anatomical disease [133,137]. Outcomes in ALI are highly time-

sensitive, with delayed treatment strongly associated with poorer limb salvage and higher mortality. Despite best efforts, there are circumstances in which irreversible tissue damage has already occurred at presentation. In such cases, primary amputation may be unavoidable to prevent systemic deterioration, sepsis, or multiorgan failure.

Ultimately, the management of ALI requires not only rapid initiation of treatment but also integration into a multidisciplinary vascular care framework. Evidence consistently underscores the importance of combining immediate anticoagulation, structured ischemia classification, and appropriately selected revascularization strategies to maximize survival and limb salvage while minimizing complications [2,67,133,137].

10.8. Polyvascular diseases and concomitant cardiac diseases

Polyvascular disease, particularly in the setting of LEAD, is defined by the coexistence of significant obstructive atherosclerotic lesions affecting at least two major arterial territories, most commonly the coronary, cerebral, and peripheral (lower extremity) arteries [140]. Atherosclerosis is a systemic disorder that can manifest across multiple vascular beds, with the extent and severity of disease influenced by local hemodynamic factors and vessel wall characteristics. Although the concept of atherosclerosis as a generalized vascular pathology has long been established, the clinical significance of simultaneous polyvascular involvement has only more recently become widely recognized, largely due to advances in diagnostics and therapeutic options for non-coronary atherosclerosis such as LEAD and CVD [140]. Epidemiological studies indicate that the prevalence of polyvascular disease is around 30% among individuals with subclinical atherosclerosis, but increases dramatically to nearly 70% in patients with established symptomatic disease or LEAD [140]. This high frequency reflects the systemic dimension of atherosclerosis and the interconnection of arterial territories. Evidence consistently shows that polyvascular disease confers a substantially greater risk of adverse outcomes, including both MACE and MALE, with risk rising further as each additional vascular territory becomes involved [140-143].

The prognostic impact is especially pronounced in symptomatic patients. For instance, in individuals presenting with acute coronary syndromes, most notably non-ST-segment elevation myocardial infarction, the coexistence of advanced atherosclerotic disease in three vascular territories is associated with an approximately 50% higher three-year mortality compared with

those having single-territory disease [142]. This highlights the cumulative prognostic burden conferred by polyvascular involvement.

Despite its prevalence and prognostic weight, routine screening for polyvascular disease in asymptomatic populations is not recommended by current clinical guidelines, mainly due to the lack of robust evidence that such detection improves outcomes or lowers event rates [140]. In selected high-risk cohorts, especially patients with symptomatic LEAD, screening for silent CAD or CVD may be considered, not primarily for early detection, but rather to enable optimization of preventive and therapeutic strategies in the context of overall systemic atherosclerotic burden [140–143].

LEAD is particularly linked with coexistent CAD, with prevalence rates up to fourfold higher compared to individuals without LEAD, and the likelihood further increases with advancing severity of peripheral disease. Importantly, a substantial proportion of CAD in this patient group is clinically silent, complicating accurate stratification of risk and potentially delaying secondary prevention [140]. The coexistence of LEAD and CAD significantly elevates overall cardiovascular risk, for example, among patients undergoing percutaneous coronary intervention, the presence of LEAD has been independently associated with increased 30-day mortality [142]. Interestingly, however, in those with both LEAD and CAD, limb-specific outcomes appear not to be significantly worse than in patients with isolated LEAD.

Beyond manifest atherosclerotic disease, additional cardiac comorbidities are commonly encountered in LEAD populations. Up to one-third of these patients exhibit left ventricular dysfunction, and clinical heart failure is linked with a roughly 40% increase in all-cause mortality. Furthermore, atrial fibrillation occurs in about 12% of patients with LEAD, with associated mortality risk exceeding that observed with atrial fibrillation in the absence of peripheral disease [140].

Overall, polyvascular disease should be regarded both as an indicator of advanced systemic atherosclerosis and as a strong predictor of cardiovascular and limb-related events. These insights underscore the value of systematic clinical evaluation for concomitant CAD, CVD, and other cardiac conditions in patients with LEAD or related symptoms. While current guidelines do not endorse routine screening for asymptomatic polyvascular disease, there is increasing support for individualized strategies in high-risk patients. Such an approach, combining rigorous management of risk factors, intensified surveillance, and coordinated multidisciplinary care can potentially improve both cardiovascular prognosis and limb outcomes [2,140–143].

10.9. Biomarker

10.9.1. General aspects

The Biomarker Working Group of the U.S. Food and Drug Administration and the National Institutes of Health defines a biomarker as a specifically identified characteristic that can be objectively measured and evaluated as an indicator of normal biological activity, pathological processes, or pharmacological responses to an exposure or therapeutic intervention [144]. In contemporary medicine, biomarkers play an increasingly central role, extending well beyond mere research applications. They are employed across a wide spectrum of clinical practice, functioning as essential tools for diagnosis, prognosis, disease surveillance, and comprehensive risk stratification [144-147].

10.9.2. Biomarker in lower extremity artery disease

Numerous biomarkers have been investigated for their potential utility in risk stratification, diagnostic evaluation, prognostic assessment, and therapeutic monitoring in individuals with LEAD [146]. Among the wide array of candidates studied, particular attention has been directed toward biomarkers reflecting key pathophysiological pathways relevant to LEAD, including systemic inflammation, endothelial dysfunction, coagulation abnormalities, lipid metabolism, and processes of tissue remodeling and angiogenesis, as well as indicators of concomitant cardiac involvement [147].

10.9.2.2. **Inflammatory biomarkers**

Inflammation plays a pivotal role in the pathogenesis of atherosclerosis and LEAD, and numerous inflammatory biomarkers have been studied for their potential diagnostic and prognostic relevance in this setting. Among these, C-reactive protein (CRP), interleukins (ILs), and tumor necrosis factor Alpha (TNF-α) are the most extensively investigated [148].
CRP represents the most consistently validated inflammatory biomarker in LEAD. Multiple studies have demonstrated that serum CRP is significantly higher in patients with LEAD compared with individuals without the disease. Furthermore, elevated CRP is associated not only with an increased incidence of LEAD in high-risk populations but also with disease

severity, as reflected by greater degrees of arterial obstruction assessed clinically or by imaging [148]. Elevated CRP levels are also predictive of increased cardiovascular morbidity and mortality, thereby underscoring its dual role as a marker of systemic inflammation and a stratifier of cardiovascular risk [149]. In addition, CRP has been linked with adverse procedural outcomes, as higher baseline concentrations have been shown to predict restenosis within six months following peripheral revascularization, highlighting its involvement in pathological vascular remodeling after intervention [150].

The family of IL comprises a broad range of cytokines with diverse pro- and anti-inflammatory activity, many of which exert direct influence on atherogenesis and vascular pathology. Of these, IL-6 is regarded as a central pro-inflammatory, pro-atherogenic mediator [151]. IL-6 promotes endothelial dysfunction, augments local inflammation, and enhances thrombus formation, thereby contributing to arterial occlusion. Elevated IL-6 levels have been documented in patients with LEAD, including asymptomatic individuals, and have been shown to independently predict progressive deterioration in the ABI as well as in-stent restenosis after endovascular treatment. IL-8, a chemokine with strong pro-inflammatory properties, has likewise been implicated in LEAD progression, facilitating recruitment of inflammatory cells to atherosclerotic plaques and fostering neointimal hyperplasia. Beyond IL-6 and IL-8, additional ILs such as IL-1β, IL-12, and IL-17 have been identified as contributors to systemic and local vascular inflammation and to processes driving plaque destabilization, though their precise role and prognostic impact in LEAD remain less well defined [151]. Major ILs in LEAD pathophysiology and their functional contributions are provided in Table 5.

Interleukins	Role in LEAD Pathophysiology
IL-1β	Pro-inflammatory cytokine promoting endothelial activation and plaque formation
IL-6	Pro-atherogenic, induces CRP production, promotes thrombosis and restenosis
IL-8	Chemokine facilitating neutrophil recruitment and vascular inflammation
IL-12	Modulates adaptive immunity, potential role in vascular inflammation
IL-17	Promotes chronic inflammation, linked to plaque instability

Table 5: Interleukins and their role in pathophysiology

TNF-α is recognized as a key regulator of vascular inflammation and injury. Circulating levels of TNF-α are consistently found to be elevated in patients with LEAD when compared with healthy individuals. Mechanistically, TNF-α promotes apoptosis of VSMCs, thereby accelerating vascular calcification, increasing arterial stiffness, and contributing to functional deterioration. In patients with diabetes mellitus and CLTI, higher TNF-α concentrations have been linked to a greater incidence of adverse vascular outcomes following revascularization, indicating its prognostic value as a marker of poor outcome and its potential as a therapeutic target. Given its broad and multifaceted effects on vascular inflammation, TNF-α is considered an important driver in the pathophysiological progression of LEAD [147,152].

10.9.2.3. **Markers of endothelial dysfunction and oxidative stress**

Endothelial dysfunction is considered a key initiating step in the development of atherosclerosis and LEAD. It reflects the breakdown of vascular homeostasis through a complex interplay of inflammation, oxidative stress, and impaired NO bioavailability. The vascular endothelium normally regulates vasomotor tone, leukocyte–endothelium interactions, hemostasis, and vascular permeability. However, in the presence of a chronic state, these functions become dysregulated. As a result, the endothelium transitions into a proinflammatory, prothrombotic, and vasoconstrictive state that accelerates plaque initiation, growth, and destabilization, which ultimately drives the clinical progression of LEAD.

Cell adhesion molecules (CAMs) constitute a central family of mediators of vascular inflammation. These include selectins (P-, E-, and L-selectin), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). They facilitate leukocyte rolling, adhesion, and transmigration across the vascular endothelium, thereby contributing to atherogenesis. Clinical studies in LEAD have repeatedly demonstrated elevated plasma levels of these adhesion molecules compared with healthy individuals. Of particular note, P-selectin and E-selectin are significantly upregulated, corresponding to increased leukocyte recruitment and early endothelial activation. Similarly, higher concentrations of ICAM-1 and VCAM-1 are observed in LEAD, and these elevations correlate not only with the degree of atherosclerotic burden but also with systemic inflammatory status. Importantly, increased VCAM-1 levels have been independently linked to heightened cardiovascular morbidity, which positions CAMs both as biomarkers of endothelial activation and potential mediators in the pathophysiology of

LEAD [147].

Endothelial dysfunction extends beyond CAM expression and encompasses impaired vasodilator capacity and a shift toward a pro-oxidative state. Oxidative stress is central to this process, with ROS driving lipid peroxidation, endothelial apoptosis, and activation of multiple pro-inflammatory pathways. Among molecular markers, asymmetric dimethylarginine (ADMA) is a well-established endogenous inhibitor of nitric oxide synthase (NOS). By limiting NO synthesis, ADMA exacerbates endothelial dysfunction, promotes vasoconstriction, and sustains low-grade systemic inflammation. Elevated circulating ADMA levels show a strong and independent association with vascular dysfunction and incident cardiovascular outcomes in LEAD [153]. Symmetric dimethylarginine (SDMA), a structural analogue of ADMA, indirectly impairs the NO pathway by competing for cellular arginine transport. It has been strongly associated with renal impairment, which synergistically contributes to vascular injury and adverse outcomes in LEAD. Consequently, SDMA is increasingly recognized as an emerging biomarker of endothelial dysfunction and a candidate for risk stratification [154]. Arginine, the precursor substrate for endothelial NOS, plays a central role in regulating vascular NO levels. Alterations in circulating arginine and its methylated derivatives, ADMA and SDMA, disturb endothelial homeostasis, linking impaired substrate availability to heightened oxidative stress and progression of LEAD [155]. Another metabolite of interest is kynurenine, derived from the tryptophan degradation pathway. Elevated kynurenine levels have been consistently reported in atherosclerotic disease, including LEAD. In this context, kynurenine appears to correlate with disease severity and prognosis by introducing oxidative stress and modulating immune–inflammatory signaling [156].

Oxidized phospholipids (OxPLs) represent some of the most widely characterized oxidative stress-related biomarkers in atherosclerosis. Increased levels of OxPLs bound to Apo B-100 particles have been independently associated with LEAD presence and progression, even after adjustment for traditional cardiovascular risk factors. Functionally, OxPLs drive endothelial activation, stimulate foam cell formation, and amplify paracrine inflammatory signaling, thus sustaining and propagating the vascular injury cascade [157]. Additional markers of lipid peroxidation include 8-isoprostane and malondialdehyde (MDA). 8-Isoprostane is a stable by-product of in vivo lipid peroxidation and is considered one of the most specific urinary biomarkers of oxidative stress. Several studies have demonstrated that elevated urinary 8-isoprostane levels are strongly associated with systemic oxidative damage and carry prognostic

implications for cardiovascular morbidity, including in LEAD [157]. High isoprostane levels are also correlated with symptomatic LEAD and reduced walking performance, supporting a link between oxidative stress burden and functional limitation. Similarly, MDA, another lipid peroxidation product, reflects ROS-mediated vascular injury. Elevated MDA levels are associated with greater disease severity, poor clinical outcomes, and impaired prognosis following revascularization, indicating a role for persistent oxidative stress in restenosis and pathological vascular remodeling [147].

Taken together, markers of endothelial dysfunction and oxidative stress capture distinct but interrelated aspects of vascular pathology in LEAD. Beyond simply mirroring disease presence, these biomarkers provide valuable prognostic information, correlating with cardiovascular and limb event risk. Their integration into clinical assessment may allow a more refined stratification of LEAD patients and could pave the way for novel therapeutic approaches that target oxidative and inflammatory pathways [147,153–158].

10.9.2.4. **Markers of coagulation**

Atherothrombosis and thromboembolic processes represent central mechanisms contributing to the elevated incidence of cardiovascular and cerebrovascular complications in patients with LEAD. The prothrombotic state observed in this condition arises from a combination of increased platelet activity, activation of coagulation cascades, and endothelial dysfunction. Together, these mechanisms foster the formation of occlusive thrombi on sites of atherosclerotic plaque disruption. This prothrombotic milieu is mirrored by variations in circulating biomarkers linked to coagulation, vascular activation, and systemic inflammation.

Among the most extensively investigated markers in LEAD are D-dimer and fibrinogen [159,160]. D-dimer, a fibrin degradation fragment released during plasmin-mediated breakdown of fibrin, is well recognized as a diagnostic marker for venous thromboembolism. In the context of LEAD, however, elevated D-dimer levels increasingly serve as an indicator of ongoing coagulation activation and a heightened thrombotic burden. Consistent evidence shows that patients with higher circulating D-dimer concentrations face approximately a twofold increase in the risk of MACE. Furthermore, elevated D-dimer correlates with disease severity and has predictive value for future adverse events, establishing its role as a clinically relevant prognostic biomarker [159,160]. Fibrinogen, a liver-derived soluble glycoprotein and essential

precursor of fibrin, not only plays a fundamental role in blood clot formation but also functions as an acute-phase protein with strong links to vascular inflammation. Elevated fibrinogen promotes platelet aggregation, increases plasma viscosity, and facilitates formation of stable fibrin clots, all of which contribute to thrombus development. In patients with LEAD, higher fibrinogen levels have been repeatedly associated with unfavorable outcomes, including increased cardiovascular and all-cause mortality. Additionally, recent studies indicate that fibrinogen concentrations are positively related to hospital length of stay in patients hospitalized for LEAD, suggesting its utility as a marker of overall disease burden and recovery potential after intervention [156–158]. These findings highlight the broader relevance of fibrinogen as both a mediator of vascular pathology and a tool for clinical risk stratification. Clinically, the measurement of coagulation biomarkers may allow personalized tailoring of antithrombotic therapy in LEAD. Elevated D-dimer or fibrinogen, for instance, can help identify subgroups at disproportionately high thrombotic risk who may benefit from intensified antithrombotic regimens rather than standard single antiplatelet therapy. Furthermore, longitudinal monitoring of these parameters may provide additional information on disease progression or response following revascularization [160,161].

Beyond these well-characterized markers, additional coagulation-associated factors have been identified as relevant in LEAD. Von Willebrand factor (vWF), which mediates platelet adhesion under shear stress, is frequently elevated in LEAD and reflects endothelial activation with concomitant thrombotic risk [159,160]. Thrombomodulin, an endothelial surface glycoprotein with anticoagulant activity, is often diminished on the cell surface or released into circulation, indicating endothelial injury. Moreover, increased circulating microparticles expressing tissue factor have been shown to amplify coagulation activity in LEAD patients. Together, these markers offer greater insight into the intricate procoagulant environment, which is characterized by simultaneous activation of platelets, excessive coagulation, and impaired fibrinolytic pathways [159]. Mechanistically, the progression of LEAD occurs in the setting of chronic oxidative and inflammatory stress, which damages endothelial integrity and exposes prothrombotic surfaces. Activated platelets then release a variety of mediators that promote coagulation, inflammation, and leukocyte recruitment, exacerbating vascular injury. Fibrinogen and vWF contribute to clot stability, while elevated D-dimer serves as a dynamic indicator of the balance between coagulation and fibrinolysis [159,160,162].

Altogether, biomarkers reflecting coagulation provide valuable insight into both

pathophysiological mechanisms and individual thrombotic risk in LEAD. Incorporating these markers into risk prediction strategies holds potential for improving prognostic accuracy and guiding therapeutic decision-making in this high-risk population.

10.9.2.5. **Markers of lipid metabolism**

Alterations in lipid metabolism are central to the initiation and progression of atherosclerosis, and dyslipidemia is recognized as a major determinant of LEAD risk. In addition to conventional lipid parameters, a spectrum of more specific lipid-associated biomarkers has been examined for their relationship with LEAD incidence, severity, and prognosis. These include lipoprotein(a) [Lp(a)], ApoB, ApoA1, oxidized low-density lipoprotein (oxLDL), as well as recently identified markers such as angiopoietin-like proteins (ANGPTLs) [163].

Total cholesterol (TC) has been directly associated with LEAD risk. Hypercholesterolemia is estimated to increase the likelihood of developing intermittent claudication by around 45%, underscoring its importance as a key risk contributor in the pathophysiology of LEAD [25]. The relationship between LDL-C and LEAD, however, is more nuanced. While single baseline LDL-C measurements do not always predict the presence of LEAD, long-term cohort studies demonstrate that cumulative exposure to elevated LDL-C significantly increases disease risk. Accordingly, sustained LDL-C control is crucial to long-term prevention of LEAD [164]. By contrast, HDL-C consistently shows an inverse association with LEAD. For every 5 mg/dL reduction in HDL-C, the risk for LEAD increases by approximately 10%. Elevated HDL-C, on the other hand, exerts protective effects through cholesterol efflux, anti-inflammatory and antioxidant activity, and support of endothelial function [162,165]. Increased concentrations of very-low-density lipoproteins (VLDL) have also been linked to LEAD onset, suggesting a critical role of triglyceride-rich lipoproteins in disease pathogenesis [166].

Among emerging biomarkers, Lp(a) is one of the most clinically relevant in LEAD. Elevated levels of Lp(a) >19.5 mg/dL are independently associated with a nearly 3.7-fold increased risk of developing LEAD in both diabetic and non-diabetic individuals. Beyond disease risk, high Lp(a) concentrations predict adverse limb-related events, including higher incidence of MALE, restenosis after revascularization, and the need for repeat interventions [167–169]. The pathogenicity of Lp(a) is attributed to its LDL-like lipid transport combined with strong prothrombotic and proinflammatory effects.

ApoB, the major Apo of atherogenic lipoproteins such as LDL, VLDL, and Lp(a), is increasingly recognized as a superior measure of atherogenic particle burden compared with LDL-C or non-HDL cholesterol. In patients with LEAD, ApoB levels are consistently elevated relative to controls, pointing to its strong association with systemic atherogenesis and its utility as a reliable biomarker for cardiovascular risk stratification [170,171]. In contrast, ApoA1, the principal protein of HDL particles, exhibits an inverse association with vascular risk. Lower ApoA1 concentrations are linked to greater LEAD prevalence and more unfavorable cardiovascular outcomes. Because of its central role in reverse cholesterol transport and HDL functionality, ApoA1 is a promising marker of vascular health in patients with LEAD [172].

OxLDL reflects oxidative modification of LDL particles and exerts highly atherogenic, proinflammatory, and cytotoxic effects. Elevated oxLDL concentrations are strongly associated with atherosclerosis across multiple vascular territories, including CAD and PAD. In LEAD, oxLDL levels correlate with both disease progression and clinical severity. Mechanistically, oxLDL fosters foam cell formation, promotes plaque instability, and enhances local oxidative stress, making it not only a biomarker but also an active mediator of disease processes [173].

Finally, ANGPTLs are emerging as novel lipid-related biomarkers. These proteins regulate lipoprotein lipase activity, thereby influencing triglyceride metabolism. Although their role in LEAD is still being elucidated, growing evidence suggests they may provide valuable insights into disease pathogenesis and offer potential therapeutic targets [163].

A comprehensive lipid biomarker profile enhances the depth of cardiovascular risk assessment in LEAD. These biomarkers not only improve prediction of disease onset and progression but may also inform treatment decisions, with the ultimate goal of reducing the cardiovascular and limb-related burden associated with LEAD.

10.9.2.6. **Tissue remodeling and angiogenesis markers**

Processes of tissue remodeling and angiogenesis are fundamental in shaping the pathophysiology and clinical trajectory of LEAD. They are governed by a complex interplay of molecular mediators, among which matrix metalloproteinases (MMPs), angiopoietins, and several growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) hold prominent roles.

MMPs, particularly MMP-2 and MMP-9, regulate ECM degradation and the remodeling of

basement membranes, enabling migration and proliferation of endothelial and VSMC in contexts of repair and neovascularization [174]. Under physiological conditions, MMP activity supports normal matrix turnover, angiogenesis, and adaptation to ischemia. However, dysregulation of MMP expression contributes to pathological changes, including excessive ECM degradation and inflammatory infiltration. These changes can destabilize atherosclerotic plaques by weakening the fibrous cap, thus predisposing lesions to rupture and subsequent ischemic events in LEAD [174]. This dual function highlights the ambivalent role of MMPs, simultaneously essential for repair but potentially pathogenic when uncontrolled.

Angiopoietin-1 (Ang-1) exerts key stabilizing influences on the vascular system through activation of the Tie2 receptor. It protects against endothelial apoptosis, suppresses vascular inflammation, and facilitates vessel maturation through reduced permeability and enhanced structural stabilization [175]. Despite these protective capacities, Ang-1 may also contribute to disease progression in certain contexts: recent data suggest that Ang-1 induces recruitment of proinflammatory monocyte subtypes (Gr1+) into atherosclerotic plaques, thereby supporting lesion growth and exacerbating the inflammatory component of LEAD [176]. This dichotomy reflects the delicate balance between adaptive remodeling and maladaptive inflammatory signaling in ischemic vascular beds.

Among angiogenic growth factors, VEGF, FGF, and HGF represent the most intensively studied mediators in LEAD. VEGF-A promotes endothelial cell proliferation, increases vascular permeability, and initiates new capillary networks. Yet, VEGF signaling is isoform-dependent, comprising both pro- and anti-angiogenic subtypes [177]. In patients with LEAD, circulating VEGF-A, is often elevated, presumably as an adaptive response to hypoxia [178]. However, higher concentrations of the VEGF-A165b isoform, which antagonizes angiogenesis, are associated with reduced neovascularization, lower ABI, and more severe ischemia [177]. While theoretically promising, clinical trials administering VEGF have not consistently improved perfusion or clinical outcomes, reflecting the complexity of isoform biology and the need for context-specific therapeutic strategies [177].

FGF, particularly FGF-2, exerts pleiotropic actions by stimulating endothelial and smooth muscle cell proliferation, migration, and ECM production. It also induces VEGF and MMP expression, thereby linking angiogenesis with vascular remodeling [178]. Despite encouraging preclinical evidence, randomized trials of FGF-based therapies in LEAD have failed to achieve durable clinical benefits, with no consistent improvement in walking ability, perfusion, or limb

salvage [179]. The disappointing results are likely attributable to biological redundancy across angiogenic pathways and complex compensatory feedback mechanisms within ischemic tissue. HGF has well-documented antifibrotic, anti-inflammatory, and pro-angiogenic properties. Experimental studies suggest HGF promotes neovascularization and alleviates ischemic injury. However, paradoxically, epidemiological studies have shown that elevated circulating HGF levels predict a higher likelihood of developing LEAD [180]. This implies that HGF may act primarily as a biomarker of vascular stress and compensatory remodeling rather than as a causal driver of pathology, underscoring its role in risk stratification rather than as a straightforward therapeutic target [180].

In summary, molecular markers involved in tissue remodeling and angiogenesis are integral to both physiological adaptation and pathological progression in LEAD. While necessary for vascular repair and neovascularization, their dysregulated activity promotes chronic inflammation, plaque destabilization, and inadequate collateral formation.

10.9.2.7. **Cardiac biomarker**

Cardiac biomarkers have become indispensable tools in cardiovascular medicine, providing critical diagnostic and prognostic information not only in CAD but also in patients with LEAD. In recent years, the clinical and scientific relevance of high-sensitivity troponins (hs-TnT, hs-TnI) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has expanded considerably, as accumulating evidence points to their value in risk assessment, disease progression, and outcome prediction in LEAD [181–183].

Troponins are regulatory proteins of the actin–myosin contractile apparatus that play a central role in cardiomyocyte contraction [181,182]. The troponin complex comprises three subunits, such as C, I, and T, of which troponin I and T have cardiac-specific isoforms. Myocardial damage, whether acute or chronic, triggers their release into circulation. Traditionally, troponins have been used as highly specific markers of acute myocardial infarction, but high-sensitivity assays now enable accurate detection of troponin at very low concentrations, broadening their utility in identifying subclinical myocardial injury [181–184]. Elevated hs-troponin values reflect cardiomyocyte necrosis or stress and have prognostic implications even outside the setting of acute coronary syndromes. The introduction of hs-TnT assays lowered diagnostic thresholds dramatically, permitting identification of values >14 ng/L as indicative of

myocardial injury, albeit with variability depending on assay type and population reference [181,184]. Today, while troponin elevation remains the diagnostic cornerstone for acute coronary syndromes, low-level chronic increases are also frequently observed in conditions such as heart failure, renal dysfunction, advanced age, and systemic atherosclerotic disease, supporting their broader application as markers of global cardiovascular stress.

Natriuretic peptides, particularly BNP and its split product NT-proBNP, are secreted by ventricular cardiomyocytes in response to wall stress from pressure or volume overload [185, 188]. NT-proBNP is favored for clinical use due to its longer half-life and greater stability compared with BNP [185–187]. In heart failure, NT-proBNP reflects both severity and prognosis, with diagnostic cut-off values typically ranging between 150–300 pg/mL, though higher concentrations indicate more advanced dysfunction and worse clinical outcomes [185–189]. Importantly, NT-proBNP serves as a prognostic biomarker not only for heart failure but also across the broader spectrum of cardiovascular diseases, where it can inform treatment strategies, longitudinal monitoring, and decision-making in high-risk groups [189].

Although troponins and natriuretic peptides dominate modern biomarker research and practice, other markers such as creatine kinase myocardial band (CK-MB) and myoglobin remain of historical and, in certain contexts, clinical relevance. CK-MB, an isoenzyme largely localized in the myocardium, has long been used in myocardial infarction diagnostics but shows inferior specificity to troponins [181]. Myoglobin, a cytoplasmic oxygen-binding protein, rises rapidly following cardiac or skeletal muscle injury, making it useful for very early detection of acute infarction. However, its lack of tissue specificity and the eventual superiority of troponins for diagnostic accuracy have substantially limited its current routine use [181,183]. Both CK-MB and myoglobin can still be employed in rare cases where troponin testing is unavailable or confounded by chronic elevations.

Cardiac biomarkers are of particular importance in LEAD research and clinical practice. Numerous studies have demonstrated that patients with LEAD, especially in advanced stages such as CLTI, frequently exhibit elevated hs-troponin and NT-proBNP levels [160,190–192]. These elevations are consistently associated with increased all-cause and cardiovascular mortality, higher incidence of MACE, accelerated disease progression, and adverse long-term outcomes [190–194]. Notably, these associations remain valid even in patients without overt signs of cardiac disease, underscoring their value as prognostic markers in systemic atherosclerotic disease and supporting their integration into vascular risk assessment strategies.

Despite the accumulating evidence, the underlying mechanisms explaining biomarker elevation in LEAD remain debated. The observed rise may reflect concomitant but clinically silent CAD, subclinical cardiac dysfunction resulting from diffuse atherosclerotic burden, or systemic inflammatory and ischemic stress inherent to LEAD itself [190–192]. Interestingly, one study evaluated the ratio of NT-proBNP to troponin as a diagnostic approach to differentiate acute coronary syndromes from other non-ischemic causes of troponin elevation, with promising results in acute care populations. Although this approach has not yet been validated specifically in LEAD cohorts, it may become an emerging tool in refining diagnoses where both cardiac and peripheral ischemic disease coexist [195,196]. By contrast, the prognostic utility of CK-MB and myoglobin in LEAD is limited. While these markers can provide early signals of myocardial injury, they have not demonstrated independent predictive power for vascular events or long-term outcomes in this population, in contrast to the robust prognostic associations reported for troponins and NT-proBNP.

In conclusion, cardiac biomarkers, particularly hs-TnT and NT-proBNP, are of increasing significance in the management of patients with LEAD. They function not only as diagnostic tools for concomitant cardiac conditions but also as independent prognosticators of mortality, MACE, and disease progression in LEAD, even in the absence of overt coronary symptoms. Their integration into risk models represents a promising avenue for improving individualized patient care, early intervention, and outcome prediction in this highly vulnerable patient population [181–196].

11. Study aims

LEAD, and in particular its advanced manifestation as CLTI, poses a considerable clinical burden owing to its close association with heightened cardiovascular risk and increased mortality. While cardiac biomarkers such as TnT, NT-proBNP, CK-MB, and myoglobin have been extensively studied in the context of cardiovascular disorders, evidence regarding their specific diagnostic and prognostic value in LEAD remains scarce. Previous investigations have indicated that elevations in NT-proBNP and troponin correlate with unfavorable outcomes, including higher mortality rates [194,195]. Nevertheless, standardized and clinically validated approaches to harness these biomarkers for risk stratification in LEAD, particularly for distinguishing patients with CLTI from those with less advanced ischemia, are currently lacking.

Therefore, the primary objective of this dissertation is the diagnostic utility of selected cardiac biomarkers, including TnT, NT-proBNP, the NT-proBNP/TnT ratio, CK-MB, and myoglobin, for differentiating patients with CLTI from those presenting with intermittent claudication. Second end point was to evaluate the prognostic relevance of these biomarkers in predicting all-cause mortality among individuals with LEAD.

12. Materials and Methods

12.1. Study design and patient cohort

This study was designed as a retrospective, cross-sectional analysis utilizing a blinded and pseudonymized dataset of patients with a confirmed diagnosis of LEAD. Cohort generation was carried out in April 2022 by the Medical Documentation and Communication network of Styria (MEDOCS), an advanced province-wide electronic health information infrastructure implemented in Austria. MEDOCS aggregates and harmonizes clinical records from all public hospitals across the Styrian region, thereby offering a broad and highly reliable data source for epidemiological and clinical research purposes [197].

The study population included all patients who presented to the outpatient clinic of Angiology at the Medical University of Graz between 2004 and 2020 with a primary diagnosis of LEAD. At baseline presentation, all patients underwent a detailed and standardized clinical evaluation, consisting of a structured medical history, systematic assessment of vascular and systemic symptoms, and a comprehensive physical examination to document comorbidities and objectively determine disease status. As part of routine diagnostic work-up, the ABI was measured as a non-invasive functional assessment of arterial perfusion. In parallel, DUS of the lower extremity arteries was performed to localize and quantify arterial stenosis, occlusion, or flow disturbances. Additionally, routine laboratory analyses were conducted, and standardized blood collection protocols were implemented. Particular emphasis was placed on the measurement of cardiac biomarkers, with the goal of evaluating their potential diagnostic and prognostic significance in LEAD.

The inclusion criteria required a confirmed diagnosis of LEAD with a documented clinical indication for an endovascular intervention. In addition, the availability of laboratory data, including measurements of cardiac biomarkers, was mandatory. These biomarker values had to be obtained within eight days prior to the planned endovascular procedure. This strict temporal requirement ensured that the laboratory parameters accurately reflected the patient's clinical condition at the time of intervention. Patients were excluded if no endovascular procedure was ultimately performed. They were also excluded if laboratory data or cardiac biomarker measurements were missing or if these were obtained more than eight days before the planned intervention. After the selection of eligible patients, individuals were stratified according to disease severity into two predefined cohorts. One cohort included patients with CLTI, and the

other consisted of patients without CLTI. In accordance with current clinical guideline definitions, CLTI was diagnosed when patients presented with ischemic rest pain, with or without tissue loss or infection, corresponding to Fontaine stages III or IV [13]. This classification facilitated subgroup analyses consistent with established clinical practice and guideline-based risk stratification.

12.2. Biomarker measurement

The cardiac biomarkers analyzed in this study comprised troponin T, NT-proBNP, the NT-proBNP/troponin ratio, CK-MB, and myoglobin. All determinations were based on plasma samples collected in lithium heparin tubes according to standardized clinical laboratory procedures. Following blood draw, samples were centrifuged within 60-90 minutes to preserve stability and ensure reliable analytical performance.

Measurements of troponin T and NT-proBNP were carried out using the Cobas 8000 fully automated platform (Roche Diagnostics), in strict adherence to the manufacturer's protocols. Troponin T concentrations were determined with the Elecsys® Troponin T high-sensitivity electrochemiluminescence immunoassay, which has a detection limit of 3 ng/L, a reference interval of 3–14 ng/L, and a quantitative measuring range extending from 3-10,000 ng/L. NT-proBNP levels were assessed using the Elecsys® NT-proBNP II immunoassay, featuring a detection threshold of 5 pg/mL, a reference range from 5-125 pg/mL, and a dynamic range of 5-30,000 pg/mL.

To ensure validity and reproducibility of results, both assays incorporated systematic quality control procedures. Standardized PreciControl Cardiac II controls covering low, intermediate, and high analyte concentrations were applied, with routine quality checks performed at least once daily. These measures guaranteed analytical accuracy throughout the entire study period. It should be noted that over the 16-year timeframe of data collection, minor adjustments in commercially available assay kits and analytical protocols occurred. However, for consistency across the dataset, uniform threshold values for result interpretation were applied throughout. This approach ensured methodological comparability of biomarker data and minimized variability over time.

12.3. Chart review

Patient information, including demographic data, clinical characteristics, comorbidities, and laboratory results, was retrieved from the MEDOCS system in March 2022 and subsequently subjected to analysis. The dataset comprised essential variables such as age, sex, cardiovascular risk factors, concomitant diseases, and prescribed medications. All-cause mortality data was obtained directly from the MEDOCS electronic medical record system covering the entire 16-year observation period. This endpoint provided an objective and uniform outcome measure, ensuring comparability of patient prognosis independent of the specific underlying cause of death.

12.4. Statistical analysis

Continuous variables were summarized using median values together with interquartile ranges (IQRs), a statistical approach chosen to appropriately account for the often-skewed distributions observed in clinical and biomarker data. This method provided a robust measure of central tendency while also illustrating the variability of values within the cohort. Categorical variables were presented as absolute numbers and corresponding proportions, which allowed for clear and transparent depiction of prevalence rates across clinical subgroups.

To explore potential predictors for CLTI as well as all-cause mortality, the analytical process began with a series of univariate logistic regression models. Each clinical parameter, demographic variable, and biomarker candidate was initially evaluated individually with respect to its association with the outcomes of interest. Prior to regression modeling, the distribution of each predictor was thoroughly examined to ensure that the data met statistical assumptions. Specifically, residuals from the regression models were assessed for conformity to the assumption of normality. In cases where predictor variables demonstrated strong skewness or residuals deviated from normality, appropriate mathematical transformations, most commonly logarithmic adjustments, were applied. These transformations improved the performance of the models, minimized the influence of extreme values, and increased the reliability of estimation procedures.

All predictors achieving statistical significance at the univariate level ($p < 0.05$) were subjected to further scrutiny for possible multicollinearity. Because the inclusion of highly intercorrelated

variables can obscure true associations and lead to instability of model estimates, variance inflation factors and correlation matrices were applied to assess redundancy. Variables showing substantial collinearity were removed from further modeling, thereby preserving parsimony and strengthening the interpretability of the resulting multivariate models. A refined set of candidate predictors was then entered into multivariate logistic regression analyses, which were performed using a backward stepwise selection strategy. This sequential approach began with the full model and iteratively removed parameters that did not contribute independent predictive value while retaining only those variables with sustained statistical and clinical significance. Through this process, the analyses identified a final set of independent predictors most closely associated with the presence of CLTI and with long-term mortality. Results from all regression analyses were reported in terms of odds ratio (OR) complemented by their 95% confidence interval (95% CI). For all inferential modeling, a two-tailed p-value threshold of <0.05 was used to indicate statistical significance.

All statistical analyses were conducted with IBM SPSS Statistics software, version 26 (IBM Corporation, Armonk, NY, USA). Throughout the analytical process, measures were taken to comply with international standards for epidemiological research and statistical reporting, ensuring robustness, consistency, and reproducibility of the findings. The combination of systematic pre-modeling variable checks, rigorous quality control in regression modeling, and clearly defined criteria for statistical inference enhances the confidence in the validity of the study outcomes and provides a transparent methodological framework for future investigations in this field.

12.5. Ethical statement

The study protocol received formal approval from the Ethics Committee (Institutional Review Board) of the Medical University of Graz, Austria (EK 34-006 ex 21/22). Given the retrospective study design, the committee determined that obtaining individual informed consent was not required and therefore issued a waiver, considering patient consent unnecessary for the conduct of this analysis.

13. Results

A total of 21,712 patients were screened for study eligibility. Of these, 367 participants with a confirmed diagnosis of LEAD and available cardiac biomarker met all prespecified inclusion criteria and were included in the final analysis. The cohort consisted of 226 male (61.6%) and 141 female (38.4%) patients. The median age was 71 years (IQR, 62–80 years). Disease severity was evaluated according to the Fontaine staging system. 308 patients (83.9%) had stage II, 10 patients (2.7%) stage III, and 49 (13.4%) had stage IV. Thus, 59 patients (16.1%) met the criteria for CLTI, defined as Fontaine stage III and IV.

Arterial hypertension was the most frequent comorbidity, present in 309 patients (84.2%), followed by obesity in 204 patients (55.6%), and a history of smoking in 177 patients (48.2%). Diabetes mellitus was diagnosed in 143 patients (39.0%), including 44 (12.0%) with insulin-dependent diabetes mellitus (IDDM) and 99 (27.0%) with NIDDM. CAD and CVD were present in 78 (21.3%) and 75 (20.4%) patients, respectively. Visceral artery disease and renal artery disease were less frequent with four (1.1%) and six patients (1.6%), respectively. Antiplatelet therapy, including aspirin and other agents, was administered in 353 patients (96.2%) patients. Statin therapy was prescribed to 151 patients (41.1%). Data on other antihypertensive or antidiabetic medications were not systematically collected or available for this analysis. Patients' characteristics are listed in table 1.

Total patients, n	367
Age (years), median (IQR)	71 (62-80)
Sex, n (%)	
Male	226 (61.6)
Female	141 (38.4)
Fontaine Stage, n (%)	
II	308 (83.9)
III	10 (2.7)
IV	49 (13.4)
BMI (kg/m^2), median (IQR)	26.4 (23.8-29.6)

Comorbidity, n (%)	
Obesity	204 (55.6)
Smoking	144 (48.2)
Arterial Hypertension	309 (84.2)
Diabetes mellitus	143 (39.0)
IDDM	44 (12.0)
NIDDM	99 (27.0)
CAD	78 (21.3)
CVD	75 (20.4)
Visceral artery disease	4 (1.1)
Renal artery disease	6 (1.6)
Comedication, n (%)	
Statins	151 (41.1)
Antiplatelet therapy	353 (96.2)

Table 6: Patients' characteristics

Abbreviations: BMI: body mass index; CAD: coronary artery disease; CVD: cerebrovascular artery disease; IDDM: insulin dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus

Troponin T levels above the threshold (>5 pg/mL) were detected in 78 patients (21.3%). The median NT-proBNP concentration was 363 pg/mL (IQR, 131–1,448 pg/mL) and the median NT-proBNP/troponin ratio was 58,600 (IQR, 23,600–146,400). For CK-MB, the median was 14 U/L (IQR, 11–19 U/L), and for myoglobin it was 48.3 ng/mL (IQR, 35.7–75.7 ng/mL).

Total patients, n	367
Cardiac biomarkers, median (IQR)	
Troponin T (pg/mL)	
≤5, n (%)	289 (78.7)
>5, n (%)	78 (21.3)
NT-proBNP (pg/mL)	363 (131-1448)
NT-proBNP/troponin ratio	58600 (23600-146400)
CK-MB (U/L)	14 (11-19)
Myoglobin (ng/mL)	48.3 (35.7-75.7)

Table 7: Cardiac biomarkers

Abbreviations: CK-MB: creatin kinase myocardial band; NT-proBNP: N-terminal prohormone of brain natriuretic peptide

13.1. Differences between patients with and without chronic limb-threatening ischemia

Patients with CLTI were significantly older (median 78 [IQR 68-85] vs. 70 [IQR 61-79] years; $p < 0.001$), had a lower BMI (median 24.9 [IQR 21.6-28.1] vs. 26.9 [IQR 23.9-29.9] kg/m²; $p = 0.002$), and were less likely to be smokers (33.9% vs. 51.0%; $p = 0.018$) or having NIDDM (11.9% vs. 29.9%; $p = 0.006$) than those without CLTI. No statistically significant differences were observed regarding sex, arterial hypertension, obesity, CAD, CVD, statin use, or antiplatelet therapy.

Regarding laboratory parameters, NT-proBNP, NT-proBNP/troponin ratio, CK-MB, and myoglobin were significantly elevated in the CLTI group (all $p < 0.05$), while troponin T levels did not differ significantly. A comparison between CLTI and Non-CLTI patients including uni- and multivariate analysis is listed in table 7. Additionally, odds ratio plot of cardiac biomarkers regarding discrimination between CLTI and non-CLTI is depicted in figure 7.

	CLTI (n=59)	**Non-CLTI (n=308)**	**Univariate**			**Multivariate**		
			OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Age (years), median (IQR)	78 (68-85)	70 (61-79)	1.06	1.03-1.09	**<0.001**	1.06	1.03-1.10	**<0.001**
Male sex, n (%)	37 (62.7)	189 (61.4)	0.94	0.53-1.68	0.845			
Smoking, n (%)	20 (33.9)	157 (51.0)	0.49	0.28-0.88	**0.018**			
BMI (kg/m²), median (IQR)	24.9 (21.6-28.1)	26.9 (23.9-29.9)	0.89	0.83-0.96	**0.002**			
Obesity, n (%)	26 (44.1)	178 (57.8)	0.58	0.33-1.01	0.054			
IDDM, n (%)	8 (13.6)	36 (11.7)	1.19	0.52-2.70	0.686			
NIDDM, n (%)	7 (11.9)	92 (29.9)	0.32	0.14-0.72	**0.006**	0.22	0.09-0.55	**0.001**
CAD, n (%)	12 (20.3)	66 (21.4)	0.94	0.47-1.87	0.851			
CVD, n (%)	11 (18.6)	64 (20.8)	0.87	0.43-1.78	0.710			
Visceral artery disease, n (%)	1 (1.7)	3 (1.0)	-*	-*	-*			
Renal artery disease, n (%)	0 (0.0)	6 (1.9)	-*	-*	-*			
Statins, n (%)	22 (37.3)	129 (41.9)	0.83	0.47-1.47	0.512			

Antiplatelet therapy, n (%)	56 (94.9)	297 (96.4)	0.96	0.53-1.76	0.918			
Troponin T (pg/mL) ≤5, n (%) >5, n (%)	 44 (74.6) 15 (25.4)	 245 (79.5) 63 (20.5)	1.33	0.69-2.54	0.394			
NT-proBNP (pg/mL), median (IQR)	1031 (177-2379)	310 (127-1085)	1.29	1.09-1.54	**0.004**			
NT-proBNP/troponin ratio, median (IQR)	116800 (23800-296800)	53000 (23600-127284)	1.39	1.12-1.72	**0.003**			
CK-MB (U/L), median (IQR)	16 (12-20)	14 (10-19)	1.65	1.04-2.64	**0.034**			
Myoglobin (ng/mL), median (IQR)	55.1 (42.9-108.6)	46.8 (34.6-74.5)	1.77	1.18-2.65	**0.005**			

Table 8: Uni- and multivariate analysis of clinical and laboratory parameters between patients with CLTI and without CLTI.

Abbreviations: BMI: body mass index; CAD: coronary artery disease; CK-MB: creatin kinase myocardial band; CVD: cerebrovascular artery disease; IDDM: insulin dependent diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; NT-proBNP: N-terminal prohormone of brain natriuretic peptide

*: No adequate statistical analysis was made due to a too low number.

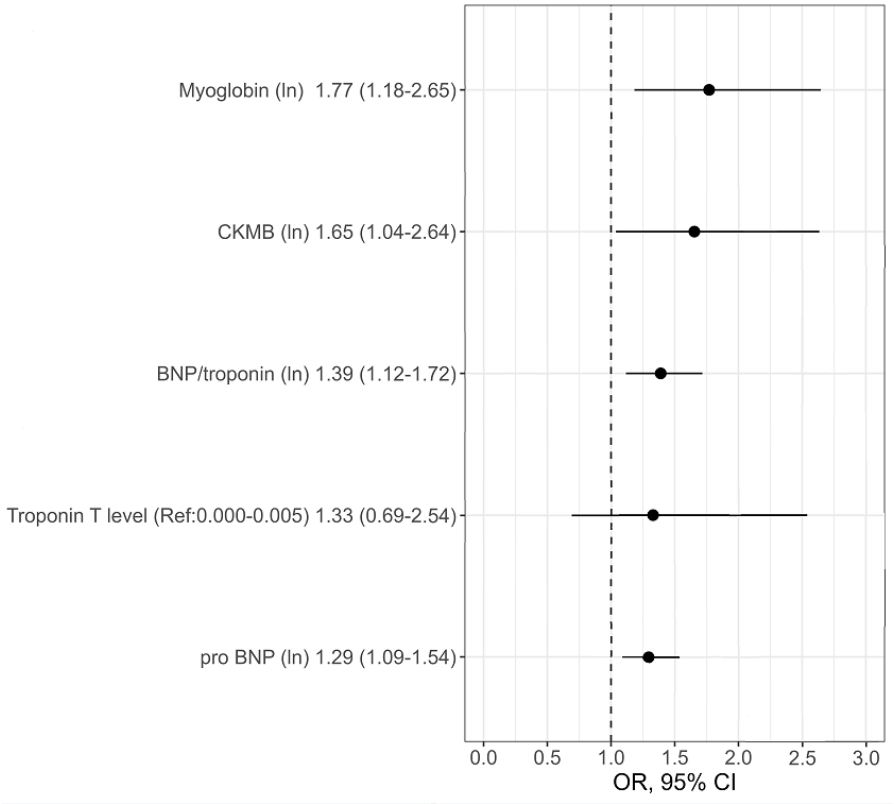

Figure 7: Odds ratio plot of cardiac biomarkers regarding discrimination between CLTI and non-CLTI.

Abbreviations: CK-MB: creatin kinase myocardial band; proBNP: prohormone of brain natriuretic peptide

13.2. Association of cardiac biomarkers with mortality

During the observation period of 16 years, 53 patients (14.4%) died. In univariate analysis, elevated levels of troponin T (OR 2.96, 95% CI 1.59-5.50; p = 0.001), NT-proBNP (OR 1.26, 95% CI 1.05-1.50; p = 0.012), and myoglobin (OR 1.87, 95% CI 1.23-2.83; p = 0.003) were significantly associated with increased mortality, whereas in multivariate analysis only troponin T remained an independent predictor with a nearly threefold higher mortality risk (OR 2.96, 95% CI: 1.59–5.5, p = 0.001) (Table 8).

	Univariate			**Multivariate**		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Troponin T	2.96	1.59-5.50	0.001	2.96	1.59-5.50	0.001
NTproBNP	1.26	1.05-1.50	0.012			
NT-proBNP/troponin ratio	1.02	0.82-1.27	0.842			
CK-MB	0.89	0.56-1.40	0.613			
Myoglobin	1.87	1.23-2.83	0.003			

Table 9: Uni- and multivariate analysis of cardiac biomarkers regarding mortality.

Abbreviations: CK-MB: creatin kinase myocardial band; NT-proBNP: N-terminal prohormone of brain natriuretic peptide

14. Discussion

This dissertation examined the diagnostic and prognostic significance of cardiac biomarkers in patients with LEAD focusing on individuals with CLTI who underwent endovascular revascularization. The principal finding was that the investigated biomarkers, including troponin T, NT-proBNP, the NT-proBNP/troponin ratio, CK-MB, and myoglobin, did not consistently distinguish between patients with and without CLTI and, aside from troponin T, did not emerge as independent predictors of mortality. These observations are in contrast with a substantial body of previous literature that has demonstrated marked prognostic associations between cardiac biomarker levels and outcomes in LEAD [190]. The divergence underscores the complexity of LEAD and reflects its multifactorial pathophysiology, whereby systemic vascular involvement, the presence of multiple comorbidities, and methodological variability across clinical studies can heavily impact the relationship between biomarkers and patient prognosis.

From a demographic perspective, the median age of 71 years in this cohort is consistent with previous epidemiological evidence, supporting the characterization of LEAD as predominantly affecting an older population. The reported prevalence of approximately 20% among individuals over the age of 70 in earlier studies further reflects the age-dependent burden of LEAD and its pronounced rise in frequency with advancing age [198,199]. Collectively, these findings underscore the critical need for targeted prevention strategies, early recognition, and proactive management of LEAD in elderly populations, where the cumulative effects of comorbidities, functional deterioration, and frailty present ongoing challenges for optimal therapeutic outcomes.

Regarding secondary prevention, it is noteworthy that antiplatelet therapy was prescribed to the vast majority of patients (96.2%), indicating a high rate of adherence to guideline-recommended cardiovascular protective measures in this real-world cohort. In contrast, statin therapy was initiated in only 41.1% of patients, a surprisingly low percentage given the well-established benefits of statins in lowering cardiovascular events and mortality among individuals with LEAD. This observed underutilization may be attributable to persistent obstacles in the widespread use of lipid-lowering agents, such as reluctance to initiate therapy, clinical inertia, concerns about polypharmacy in older adults, and adherence issues. The data highlight a pressing need to strengthen the implementation of evidence-based guidelines, patient education,

and systematic follow-up to optimize cardiovascular outcomes in those affected by LEAD [2,3,198,199].

Comparison with previous studies revealed significant variation in comorbidity patterns. Notably, CAD was detected in just 21% of patients within the recent analysis, which is considerably lower than rates reported in earlier literature, where CAD prevalence reached approximately 30% among those undergoing peripheral vascular interventions and up to 52% in symptomatic LEAD cohorts [200,201]. This discrepancy is most plausibly explained by the retrospective nature of the study, which relies solely on chart-confirmed diagnoses and may therefore be susceptible to underdiagnosis. In contrast, prospective investigations incorporating systematic cardiac screening protocols are likely to capture a greater number of subclinical or asymptomatic CAD cases. As such, the observed lower prevalence of CAD in the recent cohort likely arises from differences in methodological approaches to case identification rather than representing a true difference in disease burden. Conversely, the prevalence of diabetes mellitus in this cohort was notably higher than anticipated. With 39% of patients diagnosed with diabetes mellitus, this surpasses the 20–30% prevalence commonly documented in earlier studies [33]. This observation aligns with global epidemiological patterns showing a persistent rise in diabetes mellitus incidence. For instance, a population-based study in western Iran estimated an incidence of 4.45 per 1,000 person-years [202], while registry data from Australia revealed an increase in type 2 diabetes mellitus prevalence from 1.985 per 100,000 in 1990 to 3.429 per 100,000 in 2019 [203]. Multiple factors may explain the elevated rates observed here, including demographic transitions, lifestyle changes, enhanced diagnostic capabilities, and potential selection bias inherent in tertiary care settings that typically treat patients with more advanced disease and multiple comorbidities. Considering the well-established bidirectional relationship whereby diabetes mellitus amplifies the risk of LEAD two- to threefold, these findings emphasize diabetes mellitus as a pivotal and modifiable risk factor. This underscores the necessity for stringent screening, comprehensive risk factor management, and integrated therapeutic approaches to reduce the substantial vascular burden in this high-risk population [200,201]. In this study cohort, approximately half of the patients were active smokers, a prevalence consistent with previously reported data in populations affected by LEAD [17]. This high rate of tobacco consumption highlights the well-recognized role of smoking as a critical and modifiable risk factor in both the onset and progression of LEAD, indicating that despite enhanced public health campaigns, smoking remains a significant contributor to

vascular disease within this group. Although some differences in the prevalence of comorbid conditions compared to prior studies were noted, the overall patient characteristics closely align with those documented in the existing literature. Variations observed, particularly regarding CAD and diabetes mellitus prevalence, may reflect evolving patterns in disease epidemiology, improvements in early diagnosis and management of cardiovascular risk factors, or differences in study design and methodology.

In this study cohort, approximately 16% of patients with LEAD were diagnosed with CLTI, a prevalence closely mirroring the 11% reported in recent literature. This aligns with other research estimating that at least one in ten LEAD patients progress to CLTI [204]. Similarly, Danish registry data reported 14,941 CLTI cases among 92,845 LEAD patients, corresponding to a prevalence of 16.1% [205]. Such consistencies across populations suggest that recent findings reflect broader European trends in LEAD. Nonetheless, significant variability in reported CLTI prevalence remains across studies, likely driven by differences in patient populations, diagnostic criteria, and study methodologies. For instance, some studies may have utilized more rigorous diagnostic protocols or included patients at earlier disease stages, impacting prevalence estimates. Furthermore, the documented increase in CLTI prevalence over recent years, such as a 6.7% rise in CLTI-related hospitalizations in the United States from 2016 to 2019, signals a growing public health challenge that demands enhanced preventive and therapeutic strategies [206]. The recent cohort exhibited a marginally higher proportion of men in both CLTI and non-CLTI groups, though this difference was not statistically significant. This contrasts with some prior findings suggesting a higher CLTI prevalence among women. The anticipated higher female prevalence stems from evidence that women tend to present later and with more advanced LEAD. For example, Makowski et al. [207] found that, while men comprised 57% of CLTI hospitalizations, women were significantly older (median age 81.4 vs. 73.8 years), indicating potential gender disparities in disease progression and access to care. Delayed presentation in women may be influenced by differences in symptom interpretation, healthcare-seeking behavior, and possibly distinct pathophysiological trajectories. Women often experience atypical symptoms such as generalized weakness or fatigue, which can hinder timely diagnosis and intervention [208]. Societal and cultural factors may further contribute to delays in healthcare utilization among women. Importantly, women with CLTI frequently experience worse clinical outcomes than men, including lower rates of revascularization and receipt of guideline-based therapies like

statins [207,208]. These treatment disparities may reflect clinical presentation differences or biases in clinical decision-making. Additionally, women commonly have more severe, diffuse atherosclerotic disease, especially in the femoropopliteal region, complicating therapeutic options and outcomes [207]. These findings underscore the critical need to recognize and address gender-specific differences in LEAD presentation and management through earlier diagnosis, equitable healthcare access, and tailored therapeutic approaches, which could substantially improve outcomes for women with advanced disease. The variability in CLTI prevalence across studies also highlights the importance of standardized diagnostic definitions and reporting standards. The Global Vascular Guidelines advocate for early identification and aggressive management of CLTI, particularly in high-risk groups such as those with type 2 diabetes mellitus [204]. Enhanced standardization and guideline adherence will improve epidemiological accuracy and optimize clinical care to mitigate the rising burden of CLTI.

Another observed difference in the study's CLTI subgroup was a significantly higher average age compared to non-CLTI patients, with age confirmed as a potential independent risk factor for CLTI in multivariate analysis. This finding highlights the critical influence of age on disease severity and progression. The recent results align with prior research indicating patients over 80 years old have a two- to threefold increased likelihood of developing CLTI compared to younger individuals [34]. Supporting this, one study showed that after adjustment for age and comorbidities, female sex was actually associated with significantly better overall survival (HR 0.95; 95% CI 0.94–0.96) and amputation-free survival (HR 0.84; 95% CI 0.83–0.85) [34,205]. The prognostic value of age is further emphasized by research validating the GLASS score in CLTI patients, where multivariate analysis found age, nutritional status, and GLASS stage as significant predictors of 2-year overall survival [209]. Interestingly, a study on younger CLTI patients revealed that 39.6% of commercially insured CLTI cases were under 65 years old. Notably, these younger patients exhibited worse limb-related outcomes, with a 24% higher amputation risk and a 10% increase in MALE compared to older patients [210]. These results illustrate the complexity of age as a risk factor and underscore the need for targeted interventions across all age groups. The findings, supported by wider literature, emphasize the importance of age in predicting disease severity and advocate for tailored management approaches that consider differing risk profiles and outcomes based on age and gender.

The lower BMI observed in the CLTI group compared to the non-CLTI group in this study

cohort may be attributable to the so-called "obesity paradox." However, recent evidence has questioned the validity of this phenomenon, especially in the context of LEAD and CLTI. A large community-based investigation identified a J-shaped relationship between BMI and prevalent LEAD, which was more prominent among women [40]. Notably, some studies suggest that abdominal obesity, rather than overall obesity, may serve as a stronger predictor of adverse outcomes in LEAD patients, including worsening intermittent claudication and reduced quality of life [36]. Specifically in CLTI, the association between BMI and clinical outcomes is complex. While patients with CLTI are at high risk for amputation and mortality, certain research has indicated that elevated BMI correlates with lower mortality rates in individuals with lower extremity ulcers [36]. Nevertheless, recent data have raised doubts about the obesity paradox hypothesis. For example, one study found that if more precise body fat measurments were utilized, like waist-to-height ratio, the survival benefit observed in overweight heart failure patients disappeared [211]. These contradictory results underscore the need for additional studies to clarify the role of body composition in CLTI and related cardiovascular conditions. It is increasingly clear that BMI alone is an insufficient predictor of outcomes, highlighting the necessity for future research to adopt more comprehensive assessments of body fat distribution and composition.

The results of the recent study concerning the prevalence of smoking and NIDDM among patients with CLTI reveal an interesting divergence from established knowledge. Smoking has traditionally been identified as a major risk factor for LEAD, with active tobacco use linked to a two- to threefold increased risk [212]. However, the recent findings revealed a statistically significant lower rate of active smokers within the CLTI group, which challenges this conventional association. Similarly, the reduced prevalence of NIDDM observed in the CLTI subgroup differs from prior studies demonstrating that diabetes mellitus generally exacerbates LEAD outcomes and is associated with higher rates of amputation [213,214]. A potential reason for the observed lower smoking prevalence may lie in the retrospective nature of the recent study, which did not include full information on former smokers. Since the inclusion criteria targeted patients with available cardiac biomarker data, it is plausible that a substantial proportion of subjects had cardiovascular histories and may have ceased smoking prior to enrollment. Consistent with current guidelines, all patients in the cohort were recommended to participate in preventive programs, including smoking cessation, before undergoing revascularization procedures [1-3]. Nonetheless, while some reports have documented

relatively high success rates for smoking cessation interventions in the general population, patients with LEAD face unique challenges in quitting smoking [3,18]. A comprehensive study showed that combination therapies employing both pharmacologic and behavioral approaches achieve success rates of approximately 24% at one year [215]. However, such rates are less consistently observed in LEAD populations. For instance, a study focusing on uninsured patients with symptomatic LEAD reported significantly lower cessation success, with only 17.7% quitting compared to 35.1% among insured counterparts [216]. Furthermore, Patel et al. [114] observed that although 21% of smokers with LEAD stopped smoking within three months of diagnosis, relapse was common. These data highlight the need for more intensive, individualized smoking cessation interventions tailored to the specific barriers faced by LEAD patients. Interestingly, Schillinger et al. [217] described a paradoxical finding whereby individuals smoking ten or more cigarettes daily exhibited reduced restenosis rates following lower limb endovascular revascularization. The recent study did not differentiate patients based on prior endovascular recanalization or treatment history, which may have influenced the observed smoking prevalence and disease severity. It is conceivable that patients presenting initially with advanced LEAD and active smoking habits may have altered or temporarily ceased smoking following revascularization, leading to symptom improvement and potential downstaging of disease severity at study inclusion. Thus, the relationship between smoking status, earlier interventional therapies, and LEAD severity is complex and warrants further prospective investigation. Regarding NIDDM, the lower prevalence observed in the CLTI group could stem from several factors. It is possible that patients presenting with CLTI were unaware of a concurrent NIDDM diagnosis due to neglecting self-health monitoring. Therefore, the recent findings may not fully capture the true burden of NIDDM but perhaps reflect differences in severity between IDDM and non-diabetic states. Supporting this view, Darling et al. [218] found fewer NIDDM patients within their CLTI cohort compared to IDDM or non-diabetic groups, alongside lower long-term mortality and adverse event rates in the NIDDM subgroup, paralleling the observations in the recent study. It is also important to acknowledge that in the retrospective design, diabetes mellitus status was determined based on existing medical records rather than direct measurement of HbA1c levels. A limitation that may have contributed to underdiagnosis, similar to the potential underreporting of smoking status.

NT-proBNP and troponin are well-recognized cardiac biomarkers with established prognostic relevance in LEAD. Elevated levels of these biomarkers have been correlated with unfavorable

outcomes, including limb events and increased mortality [161,196,219]. However, the recent study identified differing patterns between cardiac biomarker levels and clinical outcomes in LEAD compared to previous reports. Although NT-proBNP levels were significantly elevated in the CLTI group in univariate analysis, they did not emerge as an independent predictor of CLTI in multivariate analysis. This contradicts findings by Kumakura et al. [220], who reported an independent association between elevated NT-proBNP and CLTI in a larger cohort. Interestingly, troponin T levels did not differ significantly between groups, which again diverges from prior studies [192,221,222]. Other assessed cardiac markers demonstrated significance also only in univariate analysis, suggesting only a limited role in predicting CLTI risk. Troponin T may predict adverse outcomes in LEAD, as demonstrated by Vrsalovic et al. [191] in a meta-analysis linking elevated troponin T on admission with increased all-cause mortality and MACE. Moreover, Linnemann et al. [223] reported that symptomatic LEAD patients with detectable pre-procedural troponin T undergoing endovascular therapy exhibited an over eightfold elevated one-year mortality risk. However, while univariate analysis for mortality prediction revealed that troponin T, NT-proBNP, and myoglobin were significant predictors, only troponin T retains its significance in multivariate models. Despite established literature describing strong links between troponin T and NT-proBNP with higher mortality and amputation rates in LEAD patients, most of the measured cardiac biomarkers failed to demonstrate robust predictive power [223,224]. Discrepancies between recent study's findings and previous research may reflect differences in cohort size, study design, and methods of data acquisition. Additionally, the recent stratification of patients into CLTI and non-CLTI groups, along with inclusion limited to those patients who underwent endovascular recanalization could contribute to divergent results. Furthermore, confounding factors such as arterial hypertension and renal insufficiency, which may impact these associations, were not incorporated into the multivariate model, warranting cautious interpretation of troponin T’s prognostic significance. The relatively small sample size increases the risk of overfitting and limited adjustment for confounders.

The underlying pathophysiology of troponin T elevation in LEAD is multifactorial. It likely reflects systemic atherosclerotic burden affecting the coronary arteries or chronic myocardial ischemia secondary to microvascular dysfunction, inflammation, and increased cardiac workload induced by LEAD [225]. Whether troponin elevations predominantly signify concomitant CAD or direct myocardial injury from systemic atherosclerosis remains debated.

Emerging evidence suggests persistent subclinical myocardial damage in LEAD patients driven by metabolic and hemodynamic stress resulting from chronic ischemia and the systemic nature of atherosclerotic disease. Chronic peripheral ischemia elevates cardiac workload and promotes microvascular impairment, leading to ongoing low-grade myocardial injury even absent overt coronary events. This highlights the systemic pathogenesis of atherosclerosis affecting both peripheral vessels and myocardium. Supporting this, Smith et al. [147] demonstrated subtle myocardial injury in LEAD patients without known cardiac disease, indicating persistent myocardial stress within this population.

Other cardiac biomarkers, including CK-MB and myoglobin, have been less extensively studied within the LEAD context and have produced variable findings. For example, Scrivner et al. [219] observed elevated serum myoglobin levels in symptomatic LEAD patients, which correlated with increased mortality and likely reflect underlying muscle injury and vascular impairment. Nevertheless, these markers lack the specificity and sensitivity of NT-proBNP and troponin T for detecting chronic myocardial injury. In more advanced disease states such as CLTI, CK-MB and myoglobin concentrations may be markedly increased, offering potential utility in risk stratification or in identifying cardiac involvement. However, their prognostic relevance requires validation through larger, prospective studies. An emerging but not yet fully validated biomarker in LEAD research is the NT-proBNP/troponin ratio. In broader cardiology contexts, such as Takotsubo syndrome, this ratio has proven effective in differentiating myocardial strain from necrosis, thereby enhancing understanding of myocardial injury mechanisms [162,226]. However, current evidence in LEAD patients indicates that this ratio does not significantly differ between individuals with and without CLTI, nor does it reliably predict adverse clinical outcomes. This limited utility likely arises from the heterogeneous pathophysiology of LEAD, the presence of diverse cardiac comorbidities, assay variability, and confounding factors such as renal dysfunction and advanced age that influence NT-proBNP levels, all of which diminish the discriminatory capacity of the ratio. Comprehensive prospective studies with larger cohorts and detailed cardiac phenotyping are necessary to elucidate the clinical value of this ratio and other combined biomarker strategies.

The present study has several important limitations affecting the generalizability and validity of its findings. These include the retrospective design, methods of data collection, and patient selection criteria. The retrospective approach inherently introduces biases and restricts data quality, with reliance on medical records potentially omitting key confounders and leading to

incomplete or inaccurate information on patient characteristics and treatments. Additionally, selection bias arises as only patients undergoing endovascular interventions were included, excluding those treated surgically or with immediate amputation, thereby narrowing the study population and limiting applicability to the entire LEAD spectrum. The small sample size and inconsistent measurement of cardiac biomarkers further reduce statistical power and result robustness, especially in subgroup or rare outcome analyses. The cohort may also be skewed toward patients with more severe cardiovascular comorbidities, possibly overestimating biomarker prevalence and impact in LEAD.

In conclusion, the findings of this thesis indicate that cardiac biomarkers generally lack sufficient discriminatory power to differentiate between patients with CLTI and those without, and, except for troponin T, do not serve as reliable predictors of mortality in individuals with LEAD. These results emphasize the inherent complexity of LEAD as a clinical entity and highlight the substantial influence that study design and patient selection criteria exert on observed outcomes. Addressing these methodological limitations in future research, particularly by larger, prospective, and multicenter studies, will be critical to obtain more robust and generalizable evidence. Such advancements are essential for improving the clinical relevance and translational applicability of findings, ultimately contributing to enhanced patient care and optimized therapeutic strategies for LEAD.

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