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TERAPIA DE EJERCICIOS PARA ENFERMEDADES CRÓNICAS: DISCAPACIDAD Y RESULTADOS CLÍNICOS A LARGO PLAZO EN UNA COHORTE DE PACIENTES CON ENFERMEDAD ARTERIAL PERIFÉRICA INSCRITOS EN UN PROGRAMA DE REHABILITACIÓN ORIGINAL

EXERCISE THERAPY FOR CHRONIC DISEASES: DISABILITY AND LONG TERM CLINICAL OUTCOMES IN A COHORT OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE ENROLLED IN AN ORIGINAL REHABILITATION PROGRAM

FABIO MANFREDINI, MD

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EXERCISE THERAPY FOR CHRONIC DISEASES:
DISABILITY AND LONG TERM CLINICAL OUTCOMES IN A COHORT OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE ENROLLED IN AN ORIGINAL REHABILITATION PROGRAM

Tesis Doctoral presentada en la Universidad de Córdoba

Directores: Pablo Jesús López Soto
Maria Aurora Rodriguez Borrego

Córdoba, España, 2019

TÍTULO DE LA TESIS: Terapia de ejercicios para enfermedades crónicas: discapacidad y resultados clínicos a largo plazo en una cohorte de pacientes con enfermedad arterial periférica inscritos en un programa de rehabilitación original.

DOCTORANDO/A: Fabio Manfredini

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

En el presente y sin lugar a dudas en el futuro inmediato, el fenómeno del envejecimiento de la población constituye un reto de grandes dimensiones que va a exigir afrontar diferentes vertientes de las personas mayores, entre las que se encuentra el mantenimiento de una calidad de vida aceptable que conlleva entre otros aspectos el mantenimiento de la movilidad.

Aspectos ambos, Calidad de vida y Movilidad, que entroncan a la perfección con el objeto de Estudio de la Enfermería: El Cuidado.

El doctorando, Médico Especialista en Medicina del Deporte, tiene amplia experiencia en la búsqueda de estrategias que faciliten la movilidad. Experiencia que viene sustentada por amplia producción científica. En el *APPENDIX I* (*Table A: Publications*; Table B: *Conference Presentations*) del documento de la tesis, se presenta un extracto referido a los años 2018-2019.

Por todo lo expuesto, los directores de la tesis refrendan que la misma cumple los requisitos formales de calidad y originalidad, mantiene el rigor científico y académico exigible, y viene respaldada por comunicaciones científicas en congresos y publicaciones, por lo que se autoriza la presentación de la tesis doctoral.

Córdoba, 1 de mayo de 2019

Firma del/de los director/es

Fdo.: Pablo Jesús López Soto   Fdo.: María Aurora Rodríguez Borrego

To my family

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Il mio primo ringraziamento va ai Direttori della Tesi, Professori Pablo Jesús López Soto e María Aurora Rodríguez Borrego per il loro supporto prezioso e costante, che mi ha consentito di raggiungere questo ambito traguardo in una prestigiosa Università europea.

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Thank you all because a few are given the opportunity to directly affect the physical and psychological health of patients with their own research. Both in the short and in the long term, as this study tells.

I am one of those lucky researchers.

INDEX

LIST OF ABBREVIATIONS

≤	less or equal than
<	less than
>	higher than
≥	higher or equal than
%	Porcentage
5-HT2	5-hydroxytryptamine receptor 2
6MWT	Six-minute walk test
AAA	Abdominal Aortic Aneurysm
ABI	Ankle-brachial index
ACC	American college of cardiology
ACD	Absolute claudication distance
ACE	Angiotensin-converting-enzyme
AHA	American heart association
Angio-CT	Computed tomography angiography
Angio-MR	Magnetic resonance angiography
ARTEMIS	A Reduction in Time with Electronic Monitoring In Stroke
CAD	Coronary artery disease
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CFA	Common Femoral Artery
CIA	Common Iliac Artery
CLAU-S	Claudication scale
CLEVER	Claudication: Exercise versus Endoluminal Revascularization
CLI	Critical limb ischemia
COD	Claudication onset distance
COT	Claudication onset time
COR I	Class of Recommendation I
COR IIA	Class of Recommentadion IIA
CPT	Current Procedural Terminology
CTA	Computerized Tomography Angiography
DAPT	Dual anti-platelet therapy
EAP	Enfermedad Arterial Periférica
EIA	External Iliac Artery
e.g.	exempli gratia
EPCs	Endothelial progenitor cells
EPC	Endothelial progenitor cell
EQ-5D	European Quality of Life-5 Dimensions
ERASE	Endovascular Revascularization and Supervised Exercise
ESC	European society of Cardiology

ESRD	End-stage renal disease
EuroQOL 5D	European Quality of Life-5 Dimensions
EXCITE	EXercise InTroduction to Enhance performance in Dialysis
GOALS	Group Oriented Arterial Leg Study
GPS	Global positioning system
HB	Home-based
HB-Ex	Home-based exercise
HR	Hazard Ratio
HRQOL	Health Related Quality Of Life
IC	Intermittent claudication
ICD	Initial claudication distance
kmh^{-1}	kilometres per hour
km/h	kilometres per hour
m	metres
LOE A	Level of Evidence A
Log-rank	Longrank test (hypothesis test)
MACE	Major cardiovascular events
mmHg	millimetres of mercury
Mod	Moderate
Mod_{ABI}	Ankle-brachial index in moderate patients
Mod_{Smax}	Maximal (treadmill) speed in moderate patients
MOS SF-36	Medical Outcomes Study Short Form 36 Health Survey
MOS SF-12	Medical Outcomes Study Short Form 12 Health Survey
mph	milles per hour
NHANES	National Health and Nutrition Examination Survey
NIR	Near-Infrared Radiation
MRA	Magnetic Resonance Angiography
MWD	Maximal walking distance
NIRS	Near-infrared spectroscopy
O_2	Oxygen
PAD	Peripheral artery disease
PADQOL	Peripheral Artery Disease on Quality of Life Questionnaire
PAQ	Peripheral Artery Questionnaire
PFWD	Pain-free walking distance
PTS	Pain threshold speed
PWD	Peak walking distance
PWT	Peak walking time
QoL	Quality of life

RCT	Randomized-controlled trial
RCTs	Randomized-controlled trials
REACH	REduction of Atherothrombosis for Continued Health
ROS	Reactive oxygen species
SET	Supervised exercise therapy
Sev	Severe
Sev_{ABI}	Ankle-brachial index in severe patients
Sev_{smax}	Maximal (treadmill) speed in severe patients
SF-12	Short Form 12
SF-36	Short Form 36
SFA	Superficial Femoral Artery
SH-BEx	Structured home-based exercise
Smax	Maximal (treadmill) speed
TASC	Trans-Atlantic Inter-Society Consensus
TBI	Toe-brachial index
TcPO2-NIRS	Transcutaneous Oxygen Pressure - Near Infrared Spectroscopy
Ti-To	Test in-train out
USA	United States of America
VascuQoL	Vascular Quality of Life Questionnaire
Vs	versus
VO_2	Oxygen-uptake
WA	Walking advice
WIQ	Walking impairment questionnaire

INDEX OF FIGURES

INDEX OF TABLES

RESUMEN

INTRODUCCIÓN

La enfermerdad arterial periférica (EAP) en las etapas intermedias es responsable de la incapacidad para caminar y de la reducción de la calidad de vida entre el 3% y 10% de la población y entre el 15% y 20% de los pacientes mayores de 70 años. La cirugía no puede revertir completamente la incapacidad y presenta riesgo de complicaciones y altos costos. El ejercicio es una intervención efectiva, que puede aumentar la capacidad funcional de los pacientes con EAP y claudicación. Desafortunadamente, los programas recomendados realizados en un hospital bajo supervisión están poco desarrollados y limitados por una baja adherencia. Por lo tanto, en base a la evidencia científica, el enfoque del ejercicio en EAP está avanzando progresivamente hacia nuevos modelos de intervención y formas alternativas de ejercicio. Hace quince años, Manfredini F y colaboradores desarrollaron un modelo estructurado original de ejercicio sin supervisión en pacientes con EAP, basado en sesiones de caminata sin síntomas en el hogar a una velocidad prescrita con controles en el hospital. El modelo también fue probado con éxito en pacientes en diálisis y supervivientes de accidente cerebrovascular.

La presente tesis, la cual se centra en el tratamiento de pacientes con EAP con claudicación, en particular en el tratamiento con ejercicios, tiene como objetivo probar la hipótesis de que los resultados de rehabilitación están asociados con mejores resultados clínicos y vasculares a largo plazo. Este problema, descrito en la literatura para la rehabilitación cardíaca, se describe pobremente en la rehabilitación vascular. La confirmación de la hipótesis subraya la importancia de los programas de rehabilitación que también son sostenibles en pacientes ancianos y frágiles, lo que puede tener un impacto positivo en el destino de los pacientes con EAP.

OBJETIVOS

Este estudio evalúa retrospectivamente la asociación de los resultados de rehabilitación después de un programa original estructurado en el hogar y el riesgo de revascularizaciones periféricas y la mortalidad en pacientes ancianos con EAP con claudicación.

SUJETOS Y MÉTODOS

Ochocientos treinta y cinco pacientes se incluyeron en el estudio. Se midió el índice tobillo-braquial (ABI) y la velocidad máxima de caminata (Smax) mediante una prueba incremental en cinta rodante, al inicio y alta de un programa de caminata sin síntomas prescrito en un hospital y ejecutado en casa. Para el análisis, los pacientes se dividieron según el valor ABI de referencia en el grupo Severo (ABI ≤0,5) o Moderado (ABI ≥0,5) y de acuerdo con los resultados de rehabilitación hemodinámicos o funcionales en los que se ajustaban (ABI ≥ 0.10 y / o Smax ≥ 0.5 km / h) o no a la rehabilitación. Se recopilaron datos sobre las revascularizaciones y la mortalidad relacionadas con EAP durante un período de 3 años, según el registro regional de la región de Emilia-Romagna.

RESULTADOS

De acuerdo con los criterios de inclusión, los pacientes de <60 u 80 años, con un valor de ABI ≥0.80 o no medible, o los pacientes que interrumpieron el programa de rehabilitación fueron excluidos. La muestra final incluyó 457 pacientes, específicamente, 146 graves y 311 moderados.

La población total, con valores funcionales y hemodinámicos significativamente mejorados en el momento del alta, durante el período de seguimiento mostró 56 revascularizaciones y 69 muertes, con una tasa de revascularización (12%) fuertemente asociada con el ABI al alta (HR: 0,03; CI 95%: 0,004-0,16).

Los pacientes graves que en el momento del alta mostraron una adherencia, resultados funcionales y hemodinámicos superpuestos con aquellos moderados, en el período de seguimiento mostraron una esperada mayor tasa de revascularización (17% vs. 10%, respectivamente, p <0,001) y muerte (29% vs. 8%, respectivamente; p <0.001). Sin embargo, los pacientes del grupo severo con un ABI mejorado mostraron una tasa de revascularización más baja que aquellos con ABI grave que no respondían (13% vs. 21%, respectivamente; HR: 0.52; 0.201.40) y ninguna diferencia para el grupo Moderado (9%). Se observaron resultados superponibles para los que respondían a la Smax (13% vs. 21%; HR: 0,55; Grupo Moderado: 10%). Entre los que respondían se observaron beneficios similares para la mortalidad.

CONCLUSIONES

Los pacientes ancianos con EAP grave, que al momento del alta hospitalaria lograron mejoras hemodinámicas y de movilidad aceptables, mostraron tasas más bajas de revascularización periférica y muerte a los 3 años de seguimiento, lo cual es comparable a los pacientes con enfermedad moderada. Los programas centrados en el paciente que son reproducibles a bajo costo en un entorno ambulatorio y capaces de mejorar tanto la función como la hemodinámica con bajas dosis de ejercicio, incluso en presencia de una enfermedad grave, pueden representar una opción en la toma de decisiones para pacientes ancianos con poca movilidad. A nuestro conocimiento, los resultados actuales representan un informe novedoso que requiere una evaluación adicional en estudios prospectivos.

Palabras clave: Mortalidad; Ejercicio; Enfermedad de la Arteria Periférica; Rehabilitación; Procedimientos quirúrgicos vasculares.

ABSTRACT

INTRODUCTION

Peripheral artery disease (PAD) at intermediate stages is responsible for walking disability and quality of life reduction among 3-10% of the population and 15-20% of patients over 70 years. Surgery is unable to fully reverse the disability and has a risk of complications and high costs. Exercise is an effective intervention, which can increase the functional capacity of patients with PAD and claudication. Unfortunately, the recommended programs carried out at a hospital under supervision are poorly available and limited by low adherence. Therefore, based on new evidence, the approach to exercise in PAD is progressively moving towards novel models of intervention and alternative forms of exercise. Fifteen years ago, an original structured model of exercise without supervision, based on home-based symptom-free walking sessions at a prescribed speed with check-ups at the hospital, was developed by Manfredini F and coworkers in PAD. The model was also successfully tested in dialysis patients and stroke survivors.

The present thesis, which focuses on the management of PAD patients with claudication, in particular on the exercise therapy, aims to test the hypothesis that rehabilitative outcomes may be associated with better long-term vascular and clinical outcomes. This issue, reported in the literature for cardiac rehabilitation, is poorly described for vascular rehabilitation. Confirmation of the hypothesis would underline the importance of rehabilitative programs that are also sustainable in elderly and frail patients, which may have a positive impact on the fate of patients with PAD.

AIMS/OBJECTIVES

This study retrospectively evaluated the association between rehabilitative outcomes following an original structured home-based program and the risk of peripheral revascularizations and mortality in elderly PAD patients with claudication.

SUBJECTS AND METHODS

Eight-hundred thirty-five patients were enrolled. Ankle-brachial index (ABI) and maximal walking speed (Smax) by an incremental treadmill test were measured at baseline and at discharge from a symptom-free walking program prescribed at a hospital and executed at home. For the analysis, patients were divided according to a baseline ABI value into the Severe (ABI ≤0.5) or Moderate (ABI ≥0.5) group and according to hemodynamic or functional rehabilitative outcomes into responders (ABI ≥ 0.10 and/or Smax ≥ 0.5 km/h) or non-responders to rehabilitation. Data about PAD-related revascularizations and mortality for a 3-year period were collected for the regional registry of the Emilia-Romagna Region.

RESULTS

According to the inclusion criteria, patients aged <60 or >80 years, with ABI value ≥0.80 or unmeasurable, or patients who interrupted the rehabilitation program were excluded. The final sample included 457 patients, specifically, 146 Severe and 311 Moderate.

The whole population, with significantly improved functional and hemodynamic values at discharge, at follow-up showed 56 revascularizations and 69 deaths, with the rate of revascularization (12%) strongly associated with ABI at discharge (hazard ratio, HR:0.03; 95% confidence interval 0.004–0.16).

Severe patients who at discharge showed superimposable adherence, functional and hemodynamic outcomes compared to Moderate, at follow-up showed an expected higher rate of revascularization (17% vs 10%, respectively p<0.001) and death (29% vs 8%, respectively; p<0.001). However, Severe patients with an improved ABI showed a lower rate of revascularization than Severe ABI nonresponders (13% vs 21%, respectively; HR:0.52; 0.20–1.40) and no difference from Moderate (9%). Superimposable outcomes were observed for Smax responders (13% vs. 21%; HR: 0.55; Moderate 10%). Among responders, similar benefits were observed for mortality.

CONCLUSIONS

Elderly patients with severe PAD, who at discharge from rehabilitation attained acceptable hemodynamic and mobility improvements, showed lower rates of peripheral revascularization and death at 3-year follow-up, which is comparable to patients with moderate disease. Patient-centered programs that are reproducible at low cost in an outpatient setting and able to improve both function and hemodynamics with low doses of exercise even in the presence of severe disease may represent an option in the decision-making for elderly patients with low mobility. To the best of our knowledge, the present results represent a novel report that requires further assessment in prospective studies.

Keywords: Mortality; Exercise; Peripheral Artery Disease; Rehabilitation; Vascular surgical procedures.

I. STATE OF ART

1. PERIPHERAL ARTERY DISEASE: THE BURDEN

Peripheral artery disease (PAD) of the lower limbs is a chronic arterial occlusive disease secondary to alterations that cause irreversible damage to the wall of arteries of different caliber. The result is insufficient oxygen delivery in the distal districts to the alteration itself [1]. The disease is often underestimated, notwithstanding the reduction of function and of the quality of life (QoL) at an intermediate stage, and has a high prevalence [2,3].

More than 200 million people worldwide are living with PAD, with the number of people affected continuously rising especially in low- and middle-income countries [2,4]. In these countries, the increase in the prevalence of affected individuals over a 10-year period has more than doubled compared with high-income countries [1,4,5]. In general, the prevalence of PAD increases progressively with age, in particular after 40 years of age, even if it is progressively also involving young adults [1,3]. It ranges from 0.9% between the ages of 40 and 49 to 14.5% after 70 years of age [6] and up to 57% among patients above 85 years of age [7] when evaluated on the basis of a low (< 0.90) ankle-brachial index (ABI) or the ratio of blood pressure in the lower legs to blood pressure in the arms in either leg [1].

In the United States, where the prevalence is estimated to be approximately 5.9% of Americans over 40 years of age, high-risk populations show a prevalence up to 30%, such as African Americans and Hispanics [6,8,9].

The prevalence of PAD tends to be twice as high in males than in women aged 50-70 years, with a tendency towards a balance after age 70 years [6-7, 10-12]. However, the burden of PAD is changing with prevalence, disability and mortality associated with PAD particularly increased in women in the last 20 years [1,13,14]. Few data on the incidence of PAD are available. Mean annual incidence rates of PAD and critical limb ischemia (CLI) were of 2.35% and 0.35%, respectively, among nearly 12 million insured American adults [15].

PAD also indicates a walking disability. Worldwide, it is estimated that approximately 40 million individuals experience disability related to the classic symptoms of intermittent claudication (IC) with a prevalence of approximately 10% in the population according to recent reports from general practitioners [9,16].

The Global Burden of Disease study estimates a more than 30% increase in deaths and disability attributable to PAD between 2005 and 2015, which is largely determined by population aging [17,18]. These numbers illustrate that PAD has become a global health problem [1]. In the next few years, due to the aging of the population, the disease will represent a sanitary and socioeconomic problem, for hypomobility, reduction of quality of life, risk of falls, hospitalizations and related costs [19,20]. Thus, redefining appropriate intervention standards will be necessary.

2. PERIPHERAL ARTERY DISEASE: THE FACES OF THE DISEASE

The spectrum of PAD presentation ranges from asymptomatic disease to IC, to CLI, and limb loss [1]. These different presentations of the disease are outlined in the two recognized clinical classifications, the Leriche-Fontaine and Rutherford classifications [21,22] (Table 1).

Table 1. Leriche-Fontaine and Rutherford classification of peripheral artery disease[21,22]

Leriche-Fontaine				**Rutherford**		
Stage	*Clinical presentation*	*Signs and symptoms*	*Physiopathology*	*Clinical presentation*	*Grade*	*Category*
I	Non-symptomatic	Occasional finding of aorto-iliac calcifications	Atherosclerotic plaque, atherotrombosis	Non-symptomatic	0	0
II A	Mild Claudication	ACD >200m Recovery time < 2 minutes	Discrepancy between muscular request and oxygen delivery	Mild Claudication	I	1
II B	Moderate-Severe Claudication	ACD <200m Recovery time > 2 minutes	Moderate discrepancy between muscular request and oxygen delivery	Moderate Claudication	I	2
		ACD <100-80m Recovery time > 2 minutes	High discrepancy between muscular request and oxygen delivery Metabolic acidosis	Severe Claudication	I	3
III	Rest ischemic pain	Rest pain	Cutaneous hypoxia Tissue acidosis	Rest pain	II	4
IV	Ischemic ulcers, gangrene	Trophic lesions	Cutaneous hypoxia Tissue acidosis Ischemic neuritis	Minor trophic lesion	III	5
		Necrosis or gangrenes	Cutaneous hypoxia Tissue acidosis Necrosis	Major trophic lesion	III	6

Abbreviations: ACD: Absolute Claudication Distance

3. RISK FACTORS, CLINICAL PICTURE AND DIAGNOSIS

Different conditions may be responsible for the arterial insufficiency with IC or peripheral symptoms that occur while walking (Table 2); however, in most cases, PAD is a typical manifestation of atherosclerotic disease.

Table 2. Pathologies potentially responsible of occlusive disease of lower limbs arteries. Adapted from Norgren et al. (2007)[3]

Adventitial cyst of the popliteal artery
Buerger’s disease / Thromboangitis obliterans
Popliteal entrapment
Primary vascular tumors
Pseudoxanthoma elasticum
Remote trauma or irradiation injury
Takayasu’s disease
Thrombosis of a sciatic artery

Therefore, the risk factors responsible for its development are similar to those for coronary artery disease [1,23], which explains the overlap of PAD with the different vascular pathologies (coronary and cerebrovascular) in the same groups of patients [3,24]. In the REduction of Atherothrombosis for Continued Health (REACH) registry, 61% of PAD patients had concomitant coronary artery disease (CAD) and/or cerebrovascular disease [24,25].

Even if unmodifiable risk factors, such as age, gender, race and hereditary factors, may influence the atherosclerotic process, modifiable risk factors play an important role [6,9, 26-28]. Smoking appears to be the most important risk factor for both the development and progression of PAD [29-35], as well as hypertension and high levels of circulating serum cholesterol [36,37]. Hyperhomocysteinemia is another risk factor for the correlations shown between IC progression and plasma homocysteine levels [38]. Diabetes is a condition that is strongly correlated with the development of peripheral arterial disease [39] and associated with worse outcomes, independent of other risk factors [2,40]. A 26% increase in the risk of PAD has been reported for diabetics for every 1% increase in glycated hemoglobin [41], as well a more aggressive manifestation of PAD than in nondiabetic patients. In these patients, an early involvement of large and small vessels has been observed, with a more unfavorable evolution towards advanced stages of disease and negative vascular outcomes [42].

At intermediate stages, the most common symptom of the presentation is IC, defined as a cramping leg pain that occurs during walking and is relieved after a short period of rest [1]. The symptom derives from the discrepancy between the oxygen demand of the working muscles and the possible oxygen supply, which is limited by the reduced blood flow. This insufficient oxygen delivery anticipates the activation of anaerobic metabolism in active muscles downstream of the lesions with an accumulation of lactic acid [2]. Considering that several arterial segments can be affected (e.g. the aorta and iliac, femoral, popliteal and lower leg arteries), the symptoms may affect the calf but also the foot, thigh and buttocks [1-3].The autonomy of walking free from ischemic pain, the so-called e free interval, may vary. Walking uphill or climbing stairs, conditions that increase the muscular energy cost and oxygen request, may anticipate the appearance of IC, with a further reduction of the free interval or symptom-free distance. The symptoms may also appear very early during walking until they become unsustainable, requiring a forced stop. Cramping pain regresses spontaneously after a certain period of time during which the patient remains standing, but it may require the need to rest in a sitting position. The recovery time usually does not exceed 10 minutes [3].

Already at this intermediate clinical stage, in the presence of IC, PAD significantly diminishes maximal and pain-free walking capacity, affects the work capacity, restricts activity and mobility and considerably reduces health-related quality of life [43,44]. However, the walking disability in PAD is a complex pathophysiological phenomenon. Conflicting data are reported in PAD regarding the relationship between the severity of disease, in terms of ABI and calf blood flow, and functional parameters [45-51]. A mix of factors, including possible maladaptations due to progressive deconditioning discussed elsewhere, have been reported as potential drivers of limb discomfort and claudication [45]. Indeed, only 10% to 30% of PAD patients fall into the group of classic claudication, while 20% to 40% report atypical leg pain [2] or a wide range of nonspecific symptoms in the lower limbs, such as muscle fatigue, weakness and paresthesia. Many patients also report no exertional leg symptoms [52, 53]. Women with PAD may be more frequently asymptomatic or present with atypical symptoms [14].

Patient-reported symptoms may therefore underestimate the presence of PAD. At intermediate stages, when peripheral symptoms are not present at rest, the inactivity of patients may lead them not to perceive claudication [3], leading to a delay in diagnosis. The same may occur in the presence of comorbidities associated with peripheral neuropathy: reduced pain sensitivity, obscuring the symptoms, makes the diagnosis of PAD more complex and delayed.

In addition, the symptoms of IC can be misunderstood and confused with symptoms in the lower limbs derived from other morbid conditions [3] (Table 3).

Table 3. Differential diagnosis for leg pain in peripheral artery disease. Adapted from Norgren et al. (2007)[3] and Writing Committee Members et al. (2017)[23]

Condition	Location	Characteristic Effect of Exercise/Rest	Characteristics and prevalence
Intermittent claudication	Calf, Thigh and Buttock muscles, Foot	Cramping, aching discomfort, severe pain on exercise Reproducible onset Recedes quickly	Atypical limb symptoms on exercise are possible Common prevalence
Symptomatic Baker's cyst	Behind knee, down calf	Swelling, tenderness With exercise Also at rest	Not intermittent Rare prevalence
Venous claudication	Entire leg, worse in calf	Tight, bursting pain after walking Recedes slowly	History of iliac-femoral deep vein thrombosis; edema; signs of venous stasis Possible relief with elevation Rare prevalence
Chronic compartment syndrome	Calf muscles	Tight, bursting pain After much exercise Recedes very slowly	Muscled athletes Possible relief with rest Rare prevalence
Spinal stenosis	Often bilateral Buttocks, posterior leg	Pain and weakness May mimic claudication Variable relief	Possible relief with lumbar spine flexion Worse with standing and extending spine Common prevalence
Nerve root compression	Radiates down leg	Sharp lancinating pain Induced by sitting, standing, or walking Often present at rest	History of back problems; Possible relief with change in position Common prevalence
Hip arthritis	Lateral hip, thigh	Aching discomfort after variable degree of exercise Recedes slowly	History of degenerative arthritis Symptoms variable; Possible relief with not weight bearing Common prevalence
Foot/ankle arthritis	Ankle, Foot arch	Aching pain After variable degree of exercise Recedes slowly	Symptoms variable; may be related to activity or present at rest Possible relief with not weight bearing Common prevalence

In general, the diagnosis of PAD based on the history and physical examination may not be a reliable tool for the identification of disease [2], therefore a more accurate assessment, by means of instrumental evaluations is necessary for the diagnosis [23] (Table 4).

Table 4. Factors useful to recognize the presence of peripheral artery disease. Adapted from Writing Committee Members et al. (2017)[23]

Age **Risk factors**	Age > 65 years Age 50-64 and more risk factors (diabetes, hypertension, hyperlipidemia, history of smoking, family history of peripheral artery disease) Age < 50 diabetes and ≥ 1 risk factor
Atherosclerotic Comorbidities	Other vascular bed(s) with atherosclerotic disease (coronary, carotid, etc.)
Reported function	Impaired Walking function Atypical leg symptoms Claudication Ischemic rest Pain
Objective examination (lower limbs)	Abnormal pulse Vascular (femoral) bruits Non healing wound Gangrene Maneuvers (e.g. foot elevation)

Measurement of the ABI at rest is one of the procedures most frequently used for the diagnosis of PAD for its high sensitivity and specificity [54,55]. ABI measurement, performed in a few minutes with a portable Doppler and a sphygmomanometer [23], is obtained by determining the systolic blood pressures at the arms (brachial arteries) and ankles (dorsalis pedis and posterior tibial arteries) in the supine position. The ABI of each leg is calculated by dividing the higher of the dorsalis pedis pressure or posterior tibial pressure by the higher of the right or left arm blood pressure [56]. ABI values lower than 0.9 depose for the diagnosis of PAD (Table 5).

Table 5. Ankle-brachial index values classification. Adapted from Aboyans et al. (2012)[56]

ABI	***Clinical interpretation***
≥ 1,4	Above-normal; non-compressible vessels
1,4 < ABI < 0,9	Normal
0,9 ≤ ABI < 0,7	Mild peripheral artery disease
0,7 ≤ ABI < 0,5	Mild-moderate peripheral artery disease
≤ 0,5	Severe peripheral artery disease

<u>Abbreviations:</u> ABI: Ankle-brachial index

However, the ABI has some limitations [56]. Some patients could present IC in the presence of ABI values at rest that are considered normal (> 0.9); in this case, measurement of the ABI after the execution of a treadmill walking test can improve the sensitivity of a method: a decrease in ABI exceeding 15-20% measured immediately following the walk test supports the diagnosis of PAD [3]. Furthermore, in certain groups of patients (mostly with diabetes or severe renal impairment), ABI may not be reliable as a diagnostic measure. In these patients, because of the severe calcification of the medium tunica, the vessel can in fact be uncompressible by the sphygmomanometer sleeve, giving incorrect results. Typically, these patients have abnormally high ABI values (> 1.4); therefore, other noninvasive diagnostic techniques are necessary to define the presence or absence of PAD [3]. Furthermore, in some patients, the measurement of ABI may also be incorrect in the presence of obstructive lesions to the subclavian or axillary arteries, or subclavian artery stenosis [57-59], which affect the systolic blood pressure recording. For this reason, it is important to measure the systemic arterial pressure in both upper limbs and use the highest value for an accurate ABI calculation. An interarm blood pressure difference of >15 to 20 mmHg is abnormal, suggestive of subclavian (or innominate) artery stenosis and a marker of increased cardiovascular risk [60,61].

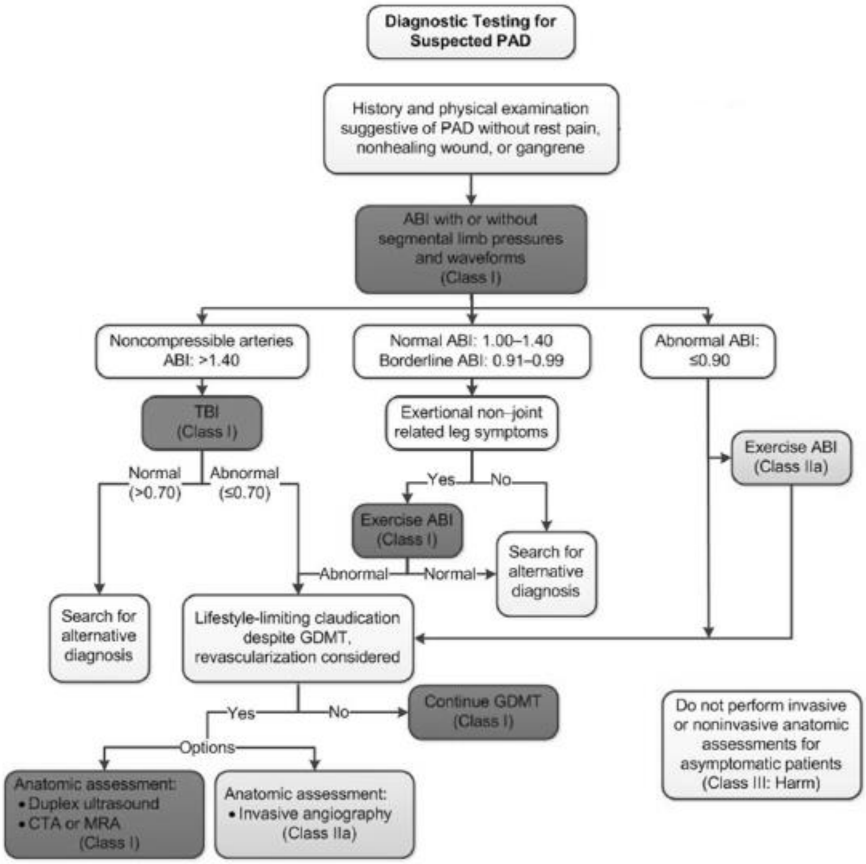
Other measures may support or substitute ABI, when this is considered unreliable. The toe-brachial index (TBI) is used to establish a diagnosis of PAD in the setting of non-compressible arteries (ABI >1.40) and may also be used to assess perfusion in patients with suspected CLI [23]. Segmental lower extremity blood pressures and Doppler or plethysmographic waveforms may offer information in terms of the localization of the anatomic segments affected by PAD. Additional perfusion assessment measures (e.g., transcutaneous oxygen pressure) or skin perfusion pressure can also be performed in selected cases [22, 23, 62-63]. In recent years, muscular near-infrared spectroscopy (NIRS) has also been employed in investigations of PAD. When NIR light propagates through biological tissue, a portion is absorbed and mostly scattered by the tissues, which can be recollected by the detector. The intensity of the recollected light provides information about oxy- and deoxy-hemoglobin concentrations as determined by spectral analysis. This technique allows the noninvasive assessment of muscle metabolism both in static and dynamic conditions for experimental purposes [49-52].

However, the most diffuse and available diagnostic technique, which is useful in the instrumental diagnosis of PAD, is the Echo-Color-Doppler examination, which allows both visualization of the location and extent of the stenotic-obstructive lesions, and the characteristics and directions of blood flow.

More sophisticated and invasive instrumental techniques are mainly used to plan a surgical revascularization procedure, such as digitized image subtraction angiography, which allows one to precisely define the anatomy of the vessel, and Angio-CT and Angio-MR, which allow the most refined analysis of the anatomical relationships between the structures.

The diagnostic pathway of PAD according to the most recent AHA guidelines is reported in Figure 1.

Figure 1. Diagnostic pathway of peripheral artery disease according to the most recent American Heart Association guidelines. Adapted from Olin et al. (2016)[2]



<u>Abbreviations</u>: PAD, peripheral artery disease; ABI, ankle-brachial index; TBI, toe-brachial index

4. PERFORMANCE OF THE PATIENT WITH PERIPHERAL ARTERY DISEASE

Objective determination of functional capacity is an important topic at intermediate stages of disease, when the patient is mainly affected by a walking disability. However, in common clinical practice, walking ability is often simply assessed by asking patients to report the distance covered before they are forced to stop. These data have been considered poorly reliable and inaccurate, both when reported by patients and when estimated by vascular surgeons [64,65], or sufficiently reliable [66]. However, an objective assessment is recommended [3,23]. The functional evaluation can indeed support the diagnostic phase, providing additional elements for patient stratification and the definition of the degree of disability. It may also contribute to determining the most appropriate therapeutic strategy to propose to the patient.

Validated functional assessment protocols include treadmill tests [67], corridor tests [68], and patient-reported symptom measurement questionnaires. The most commons tools are reported in Table 6. The development of new technologies also offers the possibility of in vivo measurements of the functional capacity of patients within their daily activities [69-71].

Table 6. Measurements of functional status and outcome measures of execise therapy in patients with peripheral artery disease. Adapted from Treat-Jacobson et al. (2019)[77]

	Type	Utility	Primary Measure	Detects Treatment Effect
Graded Treadmill test	Exercise test	Objective measure of peak exercise performance	Peak walking time on a treadmill	Exercise training Pharmacotherapy Revascularization Intermittent pneumatic compression
6-MWT 6-minute walk test	Exercise test	Objective measure of maximal walking distance, measured in a corridor	Maximal distance walked in 6 min	Exercise training Supplement Intermittent pneumatic compression Mobility loss
Treadmill test Assisted by technology (TcPO2-NIRS)	Exercise test	Objective measure of dynamic muscle (calf, foot) oxygen discrepancy	Degree of muscle perfusion (Area-under curve) of Oxy-hemoglobin	Exercise training Pharmacotherapy Revascularization Intermittent pneumatic compression, Elastic compression
Accelerometer	Physical activity monitors	Objective measure of activity during daily life	Wearable device	Exercise training
MOS SF-36 **MOS SF-12** Medical Outcomes Study Short-Form	Questionnaire (General)	Health-related quality of life	Physical and mental function	Exercise training Pharmacotherapy Revascularization
EQ-5D EuroQOL 5D	Questionnaire (General)	Functional status and health-related quality of life	State of health and function	Exercise training Revascularization
WIQ Walking Impairment Questionnaire	Questionnaire (specific)	Functional status	Distance, speed, stairs, and claudication severity	Exercise training Pharmacotherapy Revascularization
VascuQoL Vascular Quality of Life Questionnaire	Questionnaire (specific)	Functional status	HRQOL Pain, symptoms, activities, emotional, social	Exercise training Revascularization
PAQ Peripheral Artery Questionnaire	Questionnaire (specific)	Functional status and health satisfaction	Physical function, satisfaction with care	Exercise training Revascularization Medical therapy

PADQOL Impact of PAD on Quality of Life Questionnaire	Questionnaire (specific)	Health-related quality of life	Symptoms/physical limitations, fear/ uncertainty, social interactions, self-sense, feeling states, adaptation	Exercise training

4.1. Treadmill testing

Treadmill tests, used for years in patients with PAD, are still considered the gold standard for the assessment of ambulatory capacity in patients with IC and to measure changes in walking endurance and peak exercise capacity in response to exercise interventions in patients with PAD [72-77]. Treadmill testing has the advantage of being conducted in a standardized setting in which the speed and grade of the treadmill are increased at the same magnitude for each test [75]. These tests, combined with the measurement of ABI before and after exercise, represent a useful diagnostic tool to confirm or exclude the presence of PAD in patients with nonspecific lower limb disorders. Moreover, the American Heart Association (AHA) and the American College of Cardiology (ACC), the American College of Sports Medicine, and the American Association of Cardiovascular and Pulmonary Rehabilitation recommend an exercise treadmill test prior to exercise training to evaluate baseline walking capacity and to assess the degree of exercise limitation (Class I; level of evidence B). [23,78]. The parameters derived from the treadmill tests are the Initial Claudication Distance (ICD) or Pain Free Walking Distance (PFWD) or Claudication onset time (COT) and the Absolute Claudication Distance (ACD) or Maximal Walking Distance (MWD). The first ones correspond to the distance walked to the appearance of the first symptoms of claudication in the lower limbs, while the second one is the maximum distance (or time) that can be walked before the forced stop, when ischemic leg symptoms, fatigue, or other symptoms prevent patients from continuing [77].

There are various protocols used for this purpose in the clinical setting. The so-called constant load tests are performed at fixed speed and slope values generally set between 2 and 4 kmh^{-1} and between 0 and 12% [67], respectively. Incremental protocols, originally adopted by cardiology studies [79], are characterized by the maintenance of a constant walking speed with load variations obtained through progressive slope increases [80]. Most graded protocols in fact have a constant speed and increase the grade every 2 to 3 minutes to a symptom-limited maximal (or peak) walking time [77]. The graded Gardner-Skinner treadmill exercise test is a protocol that is frequently used in randomized trials to assess the functional effects of therapeutic interventions in PAD [80]. In this test, participants walk on the treadmill at 2.0 mph with a grade of zero at the beginning, which is gradually increased by 2% every 2 minutes. A modified version of this test for patients with poorer performance is based on an initial speed of 0.5 mph and a grade of zero, which is increased by 0.5 mph every 2 minutes until 2.0 mph is achieved, and then by 2% every 2 minutes [77,80].

The graded treadmill tests, which allow objective grading of the disability of PAD [80-82] with a better test-retest reliability than constant-load treadmill testing, represent the preferred method of treadmill testing in randomized trials of PAD [67-68,81-83]. Maximal walking capacity assessed by a graded treadmill test is frequently employed as a primary endpoint in randomized-controlled trials (RCTs), and it is sensitive to change with a variety of interventions [1]. The treadmill test also enables the quantification of changes in functional parameters in response to exercise interventions [68]. A mean improvement of peak walking time (PWT) ranging from 3.4 to 4.6 minutes and changes in COT ranging from 1.65 to 2.2 minutes [64,66,69] have been reported after a treadmill-based supervised exercise therapy (SET) program, with respect to a control group [77]. The treadmill-based measures, which were correlated with mortality and the risk of major cardiovascular events [84], also show limitations. Variations in the measured parameters ranging from 17% to 26% [85-87] were observed in the studies also in absence of any therapeutic intervention, for a learning /placebo effect derived from repeating treadmill tests at baseline and follow-up [75].

The treadmill walking during a laboratory measurement is influenced by the speed and slope imposed by an operator, and therefore, the functional capacity may not correspond to the actual disability experienced by patients on the ground and within their daily activities [68,88-89].

From the methodological perspective, different treadmill protocols have been used in the different trials, making it difficult to compare the results obtained in some studies. Other authors have validated protocols with progressive increases in speed in the absence of a slope or combinations of increments between speed and slope [90,91].

In general, individualized ramp protocols, which begin at low work rates and have low work rate increments per stage may be useful among patients with severe claudication symptoms [45]. Purposely, a novel test based on level walking and incremental speed [92] is was based on a starting speed fixed at 1.5 km/h with small increments of 0.1 km/h every 10 meters up to patient exhaustion due to muscle pain or fatigue. The test aims to determine a critical walking speed during a more natural level walking that may be useful to guide the training at home, rather than a generic distance at an increasing slope. The parameters obtained are the speed at the onset of symptoms, the so-called Pain Threshold Speed (PTS), and the Maximal Speed (Smax) [92]. A disadvantage of this protocol in comparison to traditional ones is that the load may not be sufficiently high to evoke pain and therefore to observe and quantify symptoms in case of mild claudication. The test is therefore more useful for patients with moderate-severe disease and very early claudication.

4.2. Corridor tests

Protocols for patient's assessment based on ground walking are also available in the literature. These protocols more closely simulate walking activity during daily life [68,94-100], overcoming some previously reported limitations of the treadmill tests. These tests also enable evaluation of the patient in structures not equipped with ergometers and specialized personnel [74]. These tests have been specifically validated for PAD or simply mediated by tests already used for the assessment of functional capacity in other patient populations as for patients with chronic respiratory diseases [101,102].

The 6-minute walk test (6MWT) [101,103] is carried out in a corridor, where a straight course, possibly of approximately 30 meters, is marked on the ground. The subjects are instructed to walk back and forth with the aim of covering the maximum distance possible in

6 minutes. At the onset of the IC, the patient informs the operator and continues to walk until the symptom becomes unbearable. Participants are allowed to stop and rest - and sit down in a chair while resting - and resume the test as soon as possible. During the rest period, the stopwatch continues to run. At the end of the 6 minutes, the total distance walked in the 6MWT and distance to the appearance of symptoms (PFWD) are recorded. The 6MWT is a validated measure of walking endurance, with a response to therapeutic interventions and not associated with a learning effect when repeated testing is performed. It also predicts rates of mobility loss and mortality [68,74,77,96-99,104-105]. Declines in 6MWT performance have also been linked to clinically meaningful outcomes in people with PAD [100, 106-108] and in elderly people without PAD [109]. A clinically meaningful change in the 6MWT distance has been defined as 20 m (small change) and 50 m (large meaningful change) [77]. An increase from 41 to 53 m were reported following a structured home-based walking exercise program in comparison to a control group not exercising [97,99].

Another corridor test derived from the assessment of other chronic diseases is the Incremental Shuttle Walk test [102]. The patient is instructed to walk from one side to the other of a 10-meter-long space at a progressively increasing speed paced by an acoustic signal with the aim of covering the distance between the two cones before the next audio signal. The test is considered terminated when the patient fails to complete the distance within the pre-established time. A corridor incremental test has also been proposed to determine the pain speed in the patient with PAD during a test at progressively increasing walking speeds [110]. The patient is accompanied during the test by an operator who, with the help of a stopwatch or a metronome, dictates the walking speed by making increments every 10 m up to the maximal speed tolerated. The operator notes the symptoms promptly reported by the patient. As per the previously described treadmill test, the purpose of the test is both to determine the degree of disability and to obtain the individual critical walking speed, specifically assessed for use in home training.

4.3. Physical activity monitoring

More recently, free-living physical activity in daily life [85,86] has become a measure of growing interest to assess the mobility of patients and their lifestyle. The assessment is performed using wearable technology such as activity monitors in the form of wristbands or other types of accelerometers [111]. These tools can help to define the autonomy of the patients and to quantify activity at home before and after therapeutic interventions. Finally, in patients with IC, the aim of each treatment strategy should be the increase in spontaneous activity by a gain of walking autonomy.

The pedometer is the simplest device, capable of measuring the number of steps completed in a day and deriving the distance traveled and energy cost. Pedometers were validated in patients with PAD [69] and used in RCTs as an outcome measure [87,112-114]. Accelerometers measure accelerations on the horizontal and vertical plane and convert the collected movements into an estimate of the energy cost, reflecting the level of activity performed. The validity of these instruments in PAD has been tested [69] and related measures included as secondary outcome measures in clinical trials [115]. Modern devices allow the differentiation between the various positions of the subject and quantification of the time spent in sedentary positions (sitting or lying down), standing and walking, with greater precision in the measurements of daily physical activities in patients with IC [71]. Recently, monitoring of physical activity with the Global Positioning System (GPS) has also been applied in patients with PAD [116], with an exact determination of the spontaneous walking time and distance as well as patterns and walking habits of PAD patients during leisure time [70]. A combination of GPS, which requires adequate satellite coverage, and accelerometers can be more precise in evaluating movements within the entire range of daily activities [116]. Both physical activity monitoring tools and GPS systems are incorporated into the latest generations of smartphones, making these technologies available to a larger group of patients. The use of smartphones for remote supervision of exercise programs was tested in a cardiological rehabilitation setting [117] and recently in PAD home-based walking programs where the activity carried out was monitored by these devices [118]. The limitations derive from the requirement of wearing specific equipment for this measure, resulting in adherence problems. The device might be used by another member of the family with an unreliable assessment of the activity. The measure may represent a possible intrusion into privacy. In addition, the memory of the device is variable, and therefore, strategies for storing data must be established. Finally, further validation and large-scale application of these instruments are needed in patients with PAD for comparison with traditional measurement systems such as treadmill tests.

4.4. Exercise testing assisted by technology

Transcutaneous oximetry assesses the partial pressure of oxygen in mmHg. It is mainly used to determine baseline values of skin perfusion with the patient in the supine position; however, the reproducibility of exercise transcutaneous oximetry has also been reported for the dynamic study of regional blood flow [119].
Near infrared spectrometry is a tool that enables the assessment of deep tissues perfusion [120] under static and dynamic conditions. This technique, which has been previously described, allows the study of the muscle in terms of oxygenation as well as oxygen extraction at rest and during motor tasks (e.g., while walking). This technology, which does not require a special infrastructure and uses relatively low-cost portable instruments, has potential for the dynamic study of oxygen delivery and deconditioning related to the disability and therefore has been utilized for functional and diagnostic tests in PAD patients [122-124].

4.5. Testing patients unable to walk

In the presence of severely limiting or contraindicating pathologies that prevent the execution of dynamic tests, alternative methods of evaluation have been proposed. An evaluation protocol is based on the plantar flexion of the foot, which is correlated with the treadmill test or finger flexion [125]. A further method consists of producing ischemization by inflating a thigh-level cuff to a pressure higher than the systolic value, maintaining this pressure for 3-5 minutes and evoking the related subsequent hyperemia. The reduction of ankle pressure within 30 seconds after the cuff is released corresponds approximately to that observed 1 minute after the onset of claudication [3].

More recently, a toe-flexion test assisted by NIRS has been validated to quickly and dynamically assess the perfusion of the more distal part of the foot [126,127].

4.6. Measurements using questionnaires

Validated and feasible questionnaires measure the functional status and health-related QoL of people with claudication, assessing the subjective perceptions of their ability to function in daily life and their well-being before and after an exercise intervention [77]. Changes in functional capacity assessed by a questionnaire or measured using the treadmill are equally considered [3]. Moreover, the measures derived from questionnaires, when performed in addition to objective measures of walking ability [23], may determine whether a specific therapy able to objectively increase patient's exercise performance is also associated with its perception in daily life [23,77].

The most widely used questionnaire among PAD patients is the Walking Impairment Questionnaire WIQ [128,129]. The WIQ [130] is a disease-specific questionnaire widely used to assess the ability of patients with IC to walk, which collects information on distances, speeds and capacity to climb stairs. It allows an estimation of the ambulatory capacity on the basis of the symptoms reported by the patient in various motor tasks, evaluating claudication severity and the presence of other (e.g., non claudication) symptoms that potentially limit walking [77,130]. Doubts concerning the accuracy and validity of the WIQ questionnaire [131-132] have been dissipated by studies confirming its accurate estimation of the daily walking ability of patients with IC [66, 89] and supporting its capacity to improve mortality risk prediction models [133]. The questionnaire, which has been translated into and validated in more than 50 languages, has been used to evaluate changes in community-based walking ability following an exercise program [134-135], vascular stenting, [136-137] and pharmacological agents [77]. The score ranges from 0 to 100, with higher scores indicating better community-based walking ability.

Quality of life is an important issue to be considered and assessed. The indices commonly used in clinical practice to assess the severity of the disease, such as ABI or some functional assessment tests, may poorly correlate with the overall negative impact of the disease on the patient. Quality of life is reduced in patients with PAD due to lower extremity pain and activity restriction [45, 138], which is not always fully perceived or considered by the physician [139]. Quality of life has been defined as the degree to which people perceive themselves physically, emotionally and socially. In a general sense, QoL is what makes life worth living [140]. The QoL of the patient with PAD is therefore an aspect to be investigated, as it is greatly reduced compared with the healthy population of the same age and sex [43,141-142]. The importance of this aspect means that QoL is indicated as an outcome in clinical trials in cardiovascular diseases [23,143].

The perception of the state of health is linked both to the reduction of autonomy, the continuous perception of pain, or the inability to perform normal work, and it is linked to the patient's lifestyle and social interactions. The concept of QoL is therefore intended as a multidimensional construct that includes different dimensions: physical, psychological and social, which are subjectively evaluated. A reduced QoL has been associated with an increase in the clinical course and a poor prognosis [144] and with the appearance of depression particularly in certain groups of patients such as young women [145]. The evaluation of QoL therefore helps to better understand the basic condition and the clinical evolution of PAD and its treatment. Thus, at intermediate stages of PAD, any procedural treatment should be aimed at reducing the symptoms of the lower limbs to improve the perception of QoL, thus success should not be evaluated only in terms of a good instrumental result (hemodynamic measures, functional capacity, mobility) but also in light of its consequences on patients' daily life [146]. QoL assessment tools [143, 147-148] available to graduate the patient's perception of disability can be filled out directly by the patient himself or administered through interviews.

These questionnaires may cover a wide spectrum of conditions present in various diseases (generic questionnaires) or evaluate the impact on QoL of specific aspects of the disease under study (specific questionnaires).

Specific questionnaires offering PAD-specific measures are available. They assess limitations in walking or QoL as well as patient-reported perceptions after exercise interventions. Validated tools are the Vascular Quality of Life Questionnaire (VascuQoL), [149] the Peripheral Artery Questionnaire (PAQ), [150] and the Impact of PAD on Quality of Life Questionnaire [151]. The VascuQoL, developed in 2001 [149] and translated into several languages, has been appreciated for patients with IC [152-153] and used to assess outcomes of interventions for patients with PAD, including exercise and revascularization [77]. It consists of 25 items, divided into 5 domains: activities performed (8 items), symptoms (4 items), pain (4 items), emotional status (7 items), social role (2 items). Each question has a Likert response scale from 1 to 7, from which a total score is generated for the questionnaire and a score for each domain, with values ranging from 1 (worst quality of life) to 7 (best). The PAQ is a disease-specific health status questionnaire for patients with PAD that assesses both functional status and QoL [150,154]. The PAQ proposed in 2004 [150,155] is composed of 20 questions to determine the physical limitation, the symptoms (frequency, severity and modifications), the social function and the satisfaction of the received therapeutic treatment. The score obtained from the sum of the scores for each single domain is converted into a scale from 0 to 100, where a higher score corresponds to reduced physical limitations, improved QoL and greater satisfaction from the treatment received. The PAQ has been used to assess outcomes in revascularization studies and for a study comparing exercise rehabilitation and endovascular procedures [87]. The Impact of PAD on Quality of Life Questionnaire [151] is a 38-item questionnaire with 5 subscales assessing the impact of the disease on multiple dimensions of life including social relationships and interactions, symptoms and limitations in physical functioning, fear and uncertainty. The scores range from 0 to 100, with higher scores indicating better health-related QoL [77].

The Claudication Scale (CLAU-S), developed in 1985, has been progressively modified, with a number of questions reduced from 89 to 47 and a number of domains from 9 to 5 (daily life, social life, pain, apprehension related to the disease and "state of mind"). The score ranges from 0 to 100, where the highest scores represent a better QoL [156]. The Sickness Impact Profile-Intermittent Claudication is a validated tool [157] adapted from a generic questionnaire Sickness Impact Profile for the evaluation of QoL. Twelve questions have been selectively extracted from the categories of ambulation, mobility, sleep and rest, home management, social interaction, and alarm status. The total score, represented by the sum of the questions, is between 0 (or best QoL) and 12. Other specific tools available for the assessment of Quality of Life are represented by the ARTEMIS Scale [158] and the Peripheral Arterial Occlusive Disease 86 Questionnaire [159].

Generic QoL questionnaires that are applicable to large populations and not dependent on a disease or treatment are also commonly used. They offer the possibility to compare data for patients with different pathologies and with healthy subjects; however, the absence of focus on a specific disease may not be sufficiently sensitive to detect clinically significant changes [160]. The Short-Form (SF)-36 [161] or SF-12 [162] and the Euro-Qol-5D [163] are the most common general health status or health-related QoL questionnaires used to evaluate outcomes of exercise therapy for patients with PAD [77]. The Medical Outcomes Study SF-36 [161] includes 36 items that cover different aspects of quality of life grouped into 8 domains, each with its own score (physical activity, physical role, physical pain, general health, vitality; emotional role; social activities; mental health). The results can then be summarized in two summary scales, for the Physical Sphere and for the Mental Sphere. The scores for each domain can vary between 0 and 100 (best possible perception of QoL). The questionnaire has been widely used in patients with PAD [164-168] in some cases without consistent improvements following some exercise programs [96,169]. More recently, an abbreviated version of his questionnaire, the SF-12 questionnaire, has been produced [161], which consists of only 12 items derived from 6 of the 8 scales of the SF-36 questionnaire. Ten questions are able to explain at least 90% of the variance of the two main scores (physical and mental scale) of the SF-36, and 2 more questions provide a complete description of the 8 scales in the SF-36, with satisfactory results [170].

The general questionnaire EuroQol [163,171] investigates 5 dimensions: mobility, self-care, habitual activities, pain, and anxiety/depression, and it includes a visual-to-analog scale from 0 to 100 where the patient reports the perceived level of their health status. The tool has been used in trials of revascularization and exercise therapy in PAD patients [152,172].

The Nottingham Health Profile [173] measures the patient's disability based on 38 questions divided into 6 domains: mobility, pain, sleep, energy, social isolation and emotional state. A dichotomous response system (yes / no) is used, with a score for each section between 0 (better QoL) and 100. The questionnaire is indicated for surveys in subjects with disability.

Questionnaires represent an important complement to objective measures of improvement after walking exercise interventions, even if they may not congruently change with the functional (treadmill or walking) tests [87,97,168]. Moreover, for research purposes, a combination of generic and specific questionnaires should be useful [174].

5. THE NATURAL HISTORY OF THE PATIENT

Peripheral artery disease does not generally show an aggressive behavior, even if noncessation of the tabagic habit or the presence of diabetes can significantly increase the risk of disease progression to more advanced stages [23,42]. Total limb amputation represents an uncommon outcome as a result of IC, since only 1 to 3.3% of patients with IC require major amputation after a period of 5 years [3]. In a long-term longitudinal study, the cumulative risk of a 10-year aggravation of the condition with the development of rest pain or trophic lesions was 30% and 23% respectively, with a cumulative frequency of major or minor amputations of less than 10% [175]. Conversely, due to the ongoing generalized atherosclerotic process, the risk of appearance of fatal and noncardiovascular events is high [1]. Considering patients at each stage of PAD, the risk of cardiovascular morbidity and mortality is approximately 3 times greater than their peers even in the setting of asymptomatic disease [2,54,176]. At 5 years, 1 out of 5 patients with PAD is affected by a nonfatal cardiovascular event, with a rate of death of 15% to 20%, mostly due to cardiovascular causes

[1-2,8,23,177]. The mortality risk rises at 50% within 10 years, especially for myocardial infarction (60%) or stroke (12%), according to some authors [178-180]. Therefore, only a limited proportion of patients with PAD (20-30%) die from non-cardiovascular causes. Given these data, correction for risk factors such as smoking, dyslipidemia and hypertension, control of diabetes and thrombotic risk, and initiation of physical activity are crucial actions for the patient with IC, in the presence of a widespread pattern of systemic atherosclerosis.

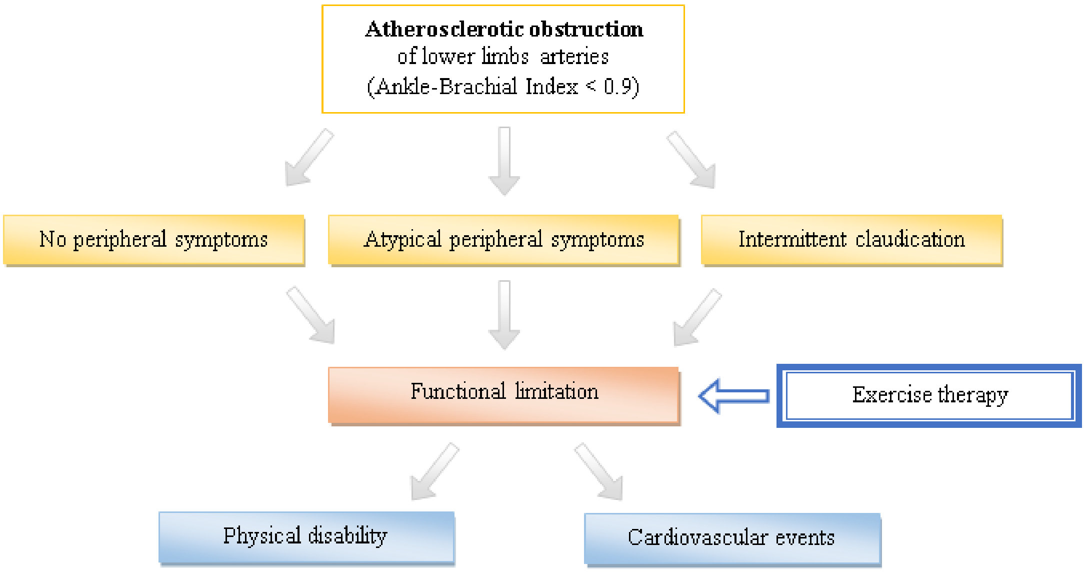
PAD therefore represents an atherosclerotic marker associated with an elevated risk of cardiovascular events in both symptomatic and asymptomatic subjects [45,181]. Systematic reviews and meta-analyses confirm that the presence and severity of PAD, defined by measurement of the ABI [3], are related to a risk of unfavorable events. A low ABI is independently associated with increased CAD and clinical cardiovascular disease risk, after adjusting for Framingham Risk Score factors [182]. A meta-analysis of over 48,000 participants in population-based cohort studies showed a 2-fold risk of death, cardiovascular death, and major coronary events in the presence of a low ABI (defined as < 0.90) at all ranges of the Framingham Risk Score versus those with a normal ABI [45,54,183]. In addition, the severity of disease, defined by lower ABI values, as well as the decrease in ABI values, are associated with increased numbers of cardiovascular events and greater functional decline [2,44,106,108,184-191]. The presence of IC amplifies the cardiovascular risk: the annual incidence of nonfatal myocardial infarction is 2-3%, and the risk of angina pectoris is approximately 2-3 times higher than that of subjects of the same age [3]. Moreover, the progression of IC to CLI increases the rate of negative outcomes to 10% for fatal cardiovascular events at 1 year and 25% for limb amputations [1,2,192]. Therefore, IC, which is responsible or the negative outcomes associated with progressive and significant reductions of mobility, represents a marker of severe generalized cardiovascular disease [24,193-194] and an independent predictor of mortality [195]. In the presence of IC, even in the absence of hemodynamic deterioration, the patient shows a progressive reduction of ambulatory function, physical activity, physical function and calf blood flow [196]. A slower walking speed and a self-restriction of activity are also observed to prevent the occurrence of symptoms and reduce leg pain [45,197-198]. Consequently, reduced physical activity levels during daily life measured with a vertical accelerometer and greater sedentary hours per day, have been associated with higher rates of more rapid functional decline and reduced assessed mobility [199-201]. The reduced health-related QoL in PAD also increases the prevalence of depression, which is largely related to leg symptoms [148, 202]. A progressive mobility loss make patients unable to walk for 6 minutes in comparison to individuals without PAD [44-45,203-204]. This negative transition is well-documented by the Walking and Leg Circulation Study [189]. In comparison to subjects with a normal ABI, PAD patients with an ABI from 0.70 to 0.90 or with an ABI < 0.50 were 2.7 and 11.7 times unable to walk for 6 minutes without stopping, respectively. At the 5-year follow-up, compared with people without PAD, the two PAD groups were 3.2 and 4.2 times more likely to become unable to walk one-quarter of a mile or walk up 1 flight of stairs without assistance, independent of age, comorbidities, and other confounders [189]. The study also showed that also patients with PAD without reported exertional leg symptoms [44,204] were exposed to a functional impairment and functional decline with a higher risk of mobility loss [189,191]. Progressive histological, metabolic and electrophysiological changes in the lower limb muscle induced by the chronic circulatory insufficiency may explain the physical decline observed in PAD patients, as excellently reviewed by Hamburg et al. [45]. These changes include myofiber damage, mitochondrial disfunction and inefficient microcirculation together with an altered fiber composition [45]. A reduced number of type I and IIa fibers and an increased number of type IIb fibers [205] have been reported, as well as the presence of oxidative fibers with reduced muscle oxidative capacity [206]. Signs of oxidative stress produced by reactive oxygen species [207-211], altered mitochondrial metabolism [212] with possible related reductions of angiogenesis and vascular regeneration [213] and peripheral nerve function damages have also been described [214-215]. Moreover, PAD patients with IC also suffer from a loss of muscle mass with sarcopenia [45] favored by deconditioning, which contribute to further reductions of muscle mass and affect the peripheral circulation [216-218]. This general maladaptive condition is associated with metabolic alterations, including muscle insulin resistance [219] and a higher risk of developing clinical diabetes [220-221].

Sarcopenia in PAD is also associated with functional changes, such as alterations of the walking pattern with variations in muscular electrical activity, reduced speed of displacement [222], biomechanical changes in the movements of the hip, knee and ankle joints [223-224], reduced length of the step with greater energy costs and lower walking economy [225].

This combination of early muscular fatigue and reduced walking efficiency contribute to the vicious cycle of illness-disability-deconditioning with a reduction in spontaneous activity. This situation decreases the control of risk factors [226], worsens exercise tolerance and cardiovascular response [227-228], and reduces protective vascular factors (e.g., a reduced nitric oxide bioavailability). A number of studies have previously demonstrated impaired endothelial vasodilator responses in PAD [207-208,212]. This condition, predictive of a higher risk for cardiovascular events [213,229], may generate peripheral arterial vasoconstriction [230-232], reduced augmentation of blood flow during exercise [233,234] and vascular stiffness. These factors have been associated with self-reported and assessed walking disability [48-49,51,235-236]. Again, in this vicious cycle, microcirculatory dysfunction also affects limb function in patients with PAD. Angiogenesis and collateral formation, favored by physical activity [237-238], are inadequate due to inactivity. The endothelial progenitor cells, which are limited in number and function by risk factors and considered to be predictors of cardiovascular events [239-240], are reduced in number in PAD and correlated to the ABI [241] and mobility in ESRD patients [242]. These factors in PAD are associated with higher rates of cardiovascular events and death [76,133,199,243-247], and in a group of PAD patients with a greater decline in ABI over time [248]. In contrast, a lower mortality rate independent of age, ABI, and BMI was observed among PAD patients with claudication who were able to perform any amount of weekly physical activity beyond light intensity in comparison to patients who were sedentary or performed only light-intensity activities [249].

Thus, therapeutic approaches that restore or maintain the functional capacity in patients with PAD may have a wide-ranging health-promoting effect. Unfortunately, this issue is still poorly documented (Figure 2).

Figure 2. Inter-relationships between peripheral symptoms, physical disability, cardiovascular risk and exercise in patients with peripheral artery disease. Adapted from Hamburg & Creager (2017)[45]



6. DISEASE MANAGEMENT

The treatment for PAD is closely related to the clinical stage. Recently, two issues derived from the recent consensus documents [23] merit emphasis:

i) The need for the right procedure for the right patient at the right time, choosing lower-cost strategies, unless there is evidence justifying a more expensive choice. [23]

ii) The need for an interdisciplinary team of professionals representing different disciplines involved in the evaluation and management of the patient with PAD [23].

In the intermediate stage of PAD, of specific interest for the present study, the management of patients is mainly based on optimal medical management, exercise and endovascular therapy [2]. In particular, the main goals of treatment for patients with IC are i) reduction of the risk of major cardiovascular events (MACE; myocardial infarction, stroke, and cardiovascular events related to the atherosclerotic diseases [2], ii) improvement of claudication symptoms, exercise performance, daily functional abilities and QoL [2,3] and iii) prevention of CLI and amputation [2,23].

All patients with IC, because of serious health risks, should therefore receive a multicomponent therapy based on cardiovascular risk modification and including lifestyle coaching and symptomatic treatment [250] (Table 7).

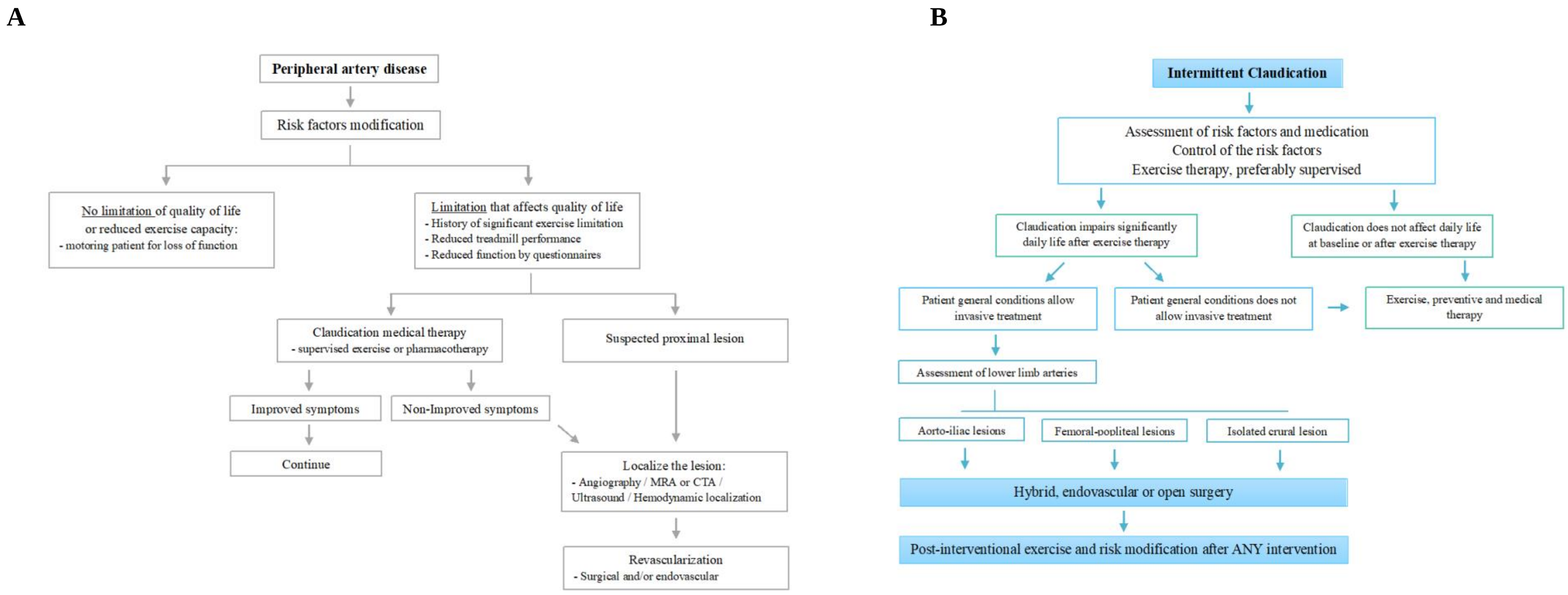
Table 7. Management of prevention of cardiovascular events in patients with peripheral artery disease. Adapted from Writing Committee Members et al. (2017)[23] and McDermott (2018)[52]

Intervention	Objective	Type	Product/dose	Effect
Pharmacological	Prevention of cardiovascular events	Antiplatelet therapy	• Aspirin • Clopidogrel Uncertain utility • Vorapaxar • Rivaroxaban *plus* low-dose aspirin	Reduced platelet activation and platelet aggregation • Lower rates of acute limb ischemia and revascularization but increased bleeding. • Lower cardiovascular event rates compared to aspirin in stable atherosclerosis, including PAD patients
Pharmacological	Prevention of cardiovascular events	Hyperlipidemia therapy	Statins	
Pharmacological	Prevention of cardiovascular events	Hypertension therapy	ACE-inhibitors and angiotensin receptor blockers may have advantages for patients with PAD	No evidence of superiority of a particular class of drugs
Lifestyle **Pharmacological**	Prevention of cardiovascular events	Pharmacotherapy and psychological support for smoking cessation	Advise to quit at every clinical visit. Pharmacotherapy: • varenicline • bupropion, • nicotine replacement therapy	Reduction/abstention from nicotine
Pharmacological	Walking impairment	Vasoactive drugs	Cilostazol Pentoxifylline	• Improvement of treadmill walking performance (25-40%) • No evidence
Lifestyle	Walking impairment	Exercise therapy	Supervised treadmill exercise Home-based walking exercise Upper and lower extremity ergometry Lower extremity resistance training	Improvement of walking performance (supervised more effective than home-based and of the other forms)

Abbreviations: PAD: Pefipheral Artery Disease

In particular, according to the main guidelines (Figure 3), they should receive a comprehensive program of guideline-directed management and therapy, including structured exercise and lifestyle modifications, to reduce cardiovascular ischemic events and improve the functional status [23] (ACC/AHA Class I recommendations). According to the Trans-Atlantic Inter-Society Consensus (TASC), the strategy calls for risk factor modification, antiplatelet therapy and structured exercise [3]. In particular, "supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease" [3,25]. Pharmacotherapy could be prescribed to treat the exercise limitation of claudication in selected patients, and revascularization, as the next level of decision making, could be considered in the case of a negative response to these treatments. When a proximal lesion is suspected, revascularization could be considered before extensive medical therapy. According to European Society of Cardiology (ESC) guidelines [25], the proven efficacy of endovascular therapy and open surgery for improving symptoms, walking ability and QoL in IC is affected by limited durability and risks in terms of mortality and morbidity. Therefore, these interventions should be restricted to patients who do not respond favorably to exercise therapy (e.g., after a 3-month period), or when disabling symptoms substantially alter daily life activities. The proposed management of patients are reported (Figure 3).

Figure 3. Role of exercise therapy for the management of peripheral artery disease at intermediate stages according to the guidelines of vascular surgeons (A; represented by TASC[3]) and of cardiologists (B; represented by ESC[25])



Abbreviations: MRA: Magnetic Resonance Angiography; CTA: Computerized Tomography Angiography

6.1. Modification of risk factors and medical therapy

Smoking is a major risk factor for the development and progression of PAD; therefore, smoking cessation is a vital component of care for patients with PAD who continue to smoke [2,23]. It represents the most important lifestyle modification in preventing CLI, amputation, and MACE in patients with PAD and it is also associated with better long-term outcomes after endovascular intervention [2,251]. Pharmacotherapy group-based programs and/or cognitive behavioral therapy could be offered, and the need to stop smoking should be discussed during every office visit [2,23].

Medical therapy to target cardiovascular risk in patients with PAD and IC, which includes antiplatelet and statin agents as well as drugs to control diabetes mellitus and hypertension [23], reduces cardiovascular morbidity and mortality [8,45]. Unfortunately, medical therapy continues to be underutilized by PAD patients [2,8,45,192] compared with patients with CAD and other forms of cardiovascular disease [252-255]. According to the 1999 to 2004 NHANES (National Health and Nutrition Examination Survey) data, among 7,458 subjects with PAD, the use of statins, angiotensin-converting enzyme inhibitors and aspirin ranged from 25 to 36% [2,8]. Among PAD patients undergoing vascular surgery, only 41% achieved guideline-based medication therapy, while the use of recommended therapies was associated with a reduced 3-year mortality [45].

In relation to antiplatelet therapy, aspirin is recommended in the management of PAD for symptomatic patients [23], reducing the risk of major cardiovascular events [254]. Uncertainty persists regarding its usefulness for reducing cardiovascular events among asymptomatic PAD patients, considering the results of two studies which failed to demonstrate a reduction in fatal and nonfatal cardiovascular events or revascularization with aspirin monotherapy among low-risk patients with borderline ABI [256-257].

Clopidogrel represents a valid alternative for antiplatelet monotherapy among patients with PAD who do not tolerate aspirin [2,258-260]. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study, in the absence of a clear benefit in the whole population compared with aspirin, showed a 23.8% relative risk reduction among the subgroup of patients with symptomatic PAD [2,259]. The superiority of ticagrelor compared with clopidogrel for the reduction of cardiovascular events was not demonstrated among 13,500 patients with PAD [261].

The use of dual-antiplatelet therapy (DAPT) has also been tested in PAD without conclusive benefits. A study examining the combination of low-dose aspirin and clopidogrel showed a

benefit only in subgroup analyses including patients with symptomatic atherothrombosis [262]. Among patients undergoing endovascular intervention, in a population with >50% of patients with CLI [263], a significant reduction in MACE among those with DAPT compared with those taking aspirin monotherapy was observed in a propensity-matched observational study. However, DAPT, usually prescribed for a time period post-intervention, was not superior to aspirin monotherapy in the primary endpoint (death, major amputation, index-graft occlusion, or revascularization) among patients undergoing below-knee surgical bypass for the treatment of CLI [264]. Unsatisfactory results in PAD subgroups were also observed in trials testing the use of gorapaxar [265]. A study testing the combination of rivaroxaban (2.5 mg twice daily) plus aspirin compared with aspirin alone [266] among patients with stable atherosclerotic vascular disease showed better cardiovascular outcomes but more major bleeding events following combined therapy, with a lowered incidence of major adverse limb events and related complications in the subgroup of patients with PAD [267].
The use of oral anticoagulants to reduce the risk of cardiovascular ischemic events or to favor patency after surgical interventions is not recommended [23]. The recent AHA guidelines deal with the use of antiplatelet agents and recommended monotherapy in symptomatic patients [23].

The use of statins is widely recommended in patients with CI and has been shown to reduce long-term cardiovascular events regardless of cholesterol starting levels [268]. An association of statin use with a reduction in adverse limb outcomes (combined endpoint of worsening claudication, new CLI, new revascularization, or amputation) and lower rates of ischemic amputation and of amputations have been reported following lower extremity revascularization [23,269-271]. High-intensity statin medications are therefore recommended by the international guidelines for all patients with PAD on the basis of the ACC/AHA guidelines [23,260]. Interestingly, according to some studies, statins may also improve the ambulatory capacity in these patients [272-274].

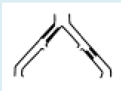
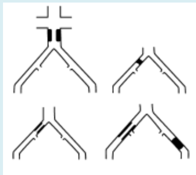
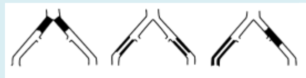
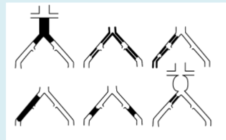
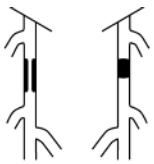
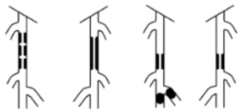
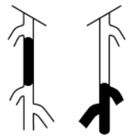
In the presence of high systolic blood pressure, all patients with CI should receive antihypertensive treatment to reduce the risk of major cardiovascular complications [23]. In particular, the use of ACE inhibitors was associated with a significant reduction of MACE among patients with PAD [275], with cardiovascular benefits in patients with both asymptomatic and symptomatic PAD using ramipril and telmisartan [276-278]. The use of ACE inhibitors is therefore considered an appropriate treatment for hypertension in PAD [3], with a possible positive impact on exercise capacity among patients with IC [279].

Diabetes and hyperhomocysteinemia are also considered by the guidelines. In diabetic patients with PAD [3,23], it is recommended that great attention be paid to the control of metabolic compensation to reduce the progression of cardiovascular diseases [280]. Conversely, treatment of hyperhomocysteinemia is not supported by the evidence [23]. Medical therapy to improve claudication is also available. Various drugs have been tested for their possible positive effects on the walking capacity of patients with IC [2,3], particularly cilostazol and naftidrofuryl [281]. Cilostazol, a type III phosphodiesterase inhibitor, improves claudication via unknown mechanisms [282], possibly related both to vasodilatory properties mediated by cyclic adenosine monophosphate and its antiplatelet activity [283]. The effects of cilostazol on claudication symptoms and QoL have been reported in various studies [83,284-287]. In addition, its effects in terms of reduced intimal hyperplasia [288], suggest a possible use after invasive procedures of revascularization [289]. This drug, which is safe for long-term administration has low adherence due to adverse effects (headache, palpitations, and diarrhea) [290], and it is also contraindicated in patients with a history of heart failure [2]. Naftidrofuryl, a 5-HT2 antagonist approved in Europe, improves muscle metabolism and reduces erythrocyte and platelet aggregation [3]. It was found to be effective for claudication [291], with a 26% increase in pain-free walking compared with placebo determined in a pooled analysis [292]. Pentoxifylline, which has been reported to improve red cell and white cell deformability with lower blood viscosity [3], was not effective for the treatment of claudication in various studies and meta-analyses [3,293-295] (Table 7).

6.2. Invasive treatment

Endovascular revascularization plays a key role in the management of patients with PAD [2]. In general, the optimal revascularization procedure varies according to the severity and characteristics (site and diffusion) of PAD disease, which are defined by well-established classification schemes. Besides the previously described functional assessment (Fontaine or Rutherford classification), the anatomic lesion classification (Trans-Atlantic Inter-Society Consensus [3] classifies the aorto-iliac and the femoro-popliteal lesions into four groups (A, B, C, D), associating them with a specific treatment (Figure 4).

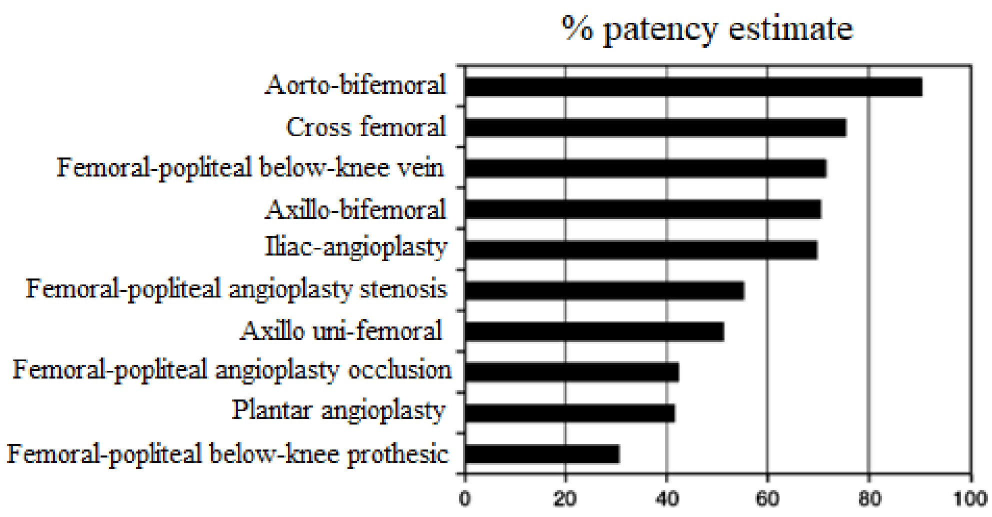
Figure 4. Atherosclerotic lesions classifications according to TASC[3]

	Tasc A	**Tasc B**	**Tasc C**	**Tasc D**
Aorto-iliac	Unilateral or bilateral stenosis of CIA Unilateral or bilateral single short (< 3cm) stenosis of EIA 	Short (< 3cm) stenosis of infrarenal aorta Unilateral CIA occlusion Single or multiple stenoses totaling 3-10cm involving the EIA, not extending into CFA Unilateral EIA occlusion not involving the origins of internal iliac or CFA 	Bilateral CIA occlusions Bilateral EIA stenoses 3-10cm long, not extending into CFA Unilateral EIA stenosis extending into the CFA Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA 	Infrarenal aorto-iliac occlusion Diffuse disease involving the aorta and both iliac arteries Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA Unilateral occlusions of both CIA and EIA Bilateral occlusion of EIA Iliac stenoses in patients with AAA not amenable to endograft placement 
Femoral-popliteal	Single stenosis < 10cm length Single occlusion < 5cm length 	Multiple lesions (stenoses or occlusions) each < 5cm Single stenosis or occlusion < 15cm, not involving infrageniculate popliteal artery Heavily calcified occlusion <5cm Single popliteal stenosis 	Multiple stenoses or occlusions totaling >15cm, with or without heavy calcification Recurrent stenoses or occlusions after failing treatment 	Chronic total occlusion of CFA or SFA (>20cm involving the popliteal artery) Chronic total occlusion of popliteal artery and proximal trifurcation vessels 
Infra-popliteal	Single focal stenosis, < 5cm length, in the target tibial artery, with occlusion or stenosis of similar or worse severity in the other tibial arteries	Multiple stenoses, each < 5cm length, or total length < 10cm, or single occlusion <3cm in length, in the target tibial artery with occlusion or stenosis of similar or worse severity in the other tibial arteries	Multiple stenoses in the target tibial artery and/or single occlusion with total lesion length >10cm with occlusion or stenosis of similar or worse severity in the other tibial arteries	Multiple occlusions involving the target tibial artery with total lesion length > 10cm, or dense lesion calcification or nonvisualization of collaterals; the other tibial arteries occluded or with dense calcification.

Abbreviations: CIA: Common Iliac Artery; EIA: External Iliac Artery; CFA: Common Femoral Artery; AAA: Abdominal Aortic Aneurysm; SFA: Superficial Femoral Artery

Endovascular therapy is an optimal treatment for A type lesions and good treatment for B type lesions; C lesions produce better long-term results after surgical revascularization. However, most PAD patients requiring intervention generally show multiple lesions, at one or more levels, and therefore, these schemes are limited by the need to individually consider the type of lesion. In some cases, the study of the angiosome, an anatomic unit of tissue (consisting of skin, subcutaneous tissue, fascia, muscle, and bone) that is fed by a source artery and drained by specific veins, offers further information about optimal revascularization strategies for limb salvage [2, 296]. However, for the majority of PAD patients requiring revascularization, the "endovascular first" approach is advised by the consensus documents [2,3,23]. In particular, endovascular treatment should be performed for hemodynamically significant lesions targeting selected stenosis with a reasonable likelihood of limiting perfusion to the distal limb [23]. Its role in IC is related to an improvement in claudication symptoms rather than the limb salvage, considering that only a few patients with IC will progress to CLI [23,176,297-299], and it should be considered in the presence of persistent lifestyle-limiting claudication after pharmacological and exercise therapy [2,3,23,87,300-303] defined by the patient [23]. However, the feasibility of the treatment is related to the presence of comorbidities, the favorable risk–benefit ratio, and the preferences of the patients. Clear information about expected risks, benefits and durability of the revascularization procedures (Figure 5) is necessary to support patient decisions [23].

Figure 5. Five-year percentage patency estimates according to TASC[3]



If revascularization in IC is useful, feasible and accepted, it needs to be personalized to improve outcomes on the basis of the available endovascular techniques (angioplasty, stents, and atherectomy and covered stents, drug-eluting stents, cutting balloons, and drug-coated balloons) for the lesions (e.g., anatomic location, lesion length, degree of calcification), as well as the experience of the operator [23].

The surgical option, which is effective for QoL and walking capacity in IC, may offer better functional and patency outcomes compared with endovascular treatments, but with a greater risk of adverse perioperative events [23]. Therefore, in these patients the more invasive option is usually performed in the case of inadequate benefit from nonsurgical therapy, of the arterial anatomy, which offers a durable result, and in the presence of an acceptable risk of perioperative adverse events in relation to the symptom severity and comorbidities. In particular, femoral-popliteal bypass is one of the most common surgical procedures among patients with claudication, as the superficial femoral is a typical anatomic site of stenosis or occlusion. For lesions at the popliteal artery, the site of anastomosis (above versus below the knee) [23] and the type of intervention, e.g., autogenous vein versus prosthetic grafts, positively influence the outcomes of the intervention [304-305].

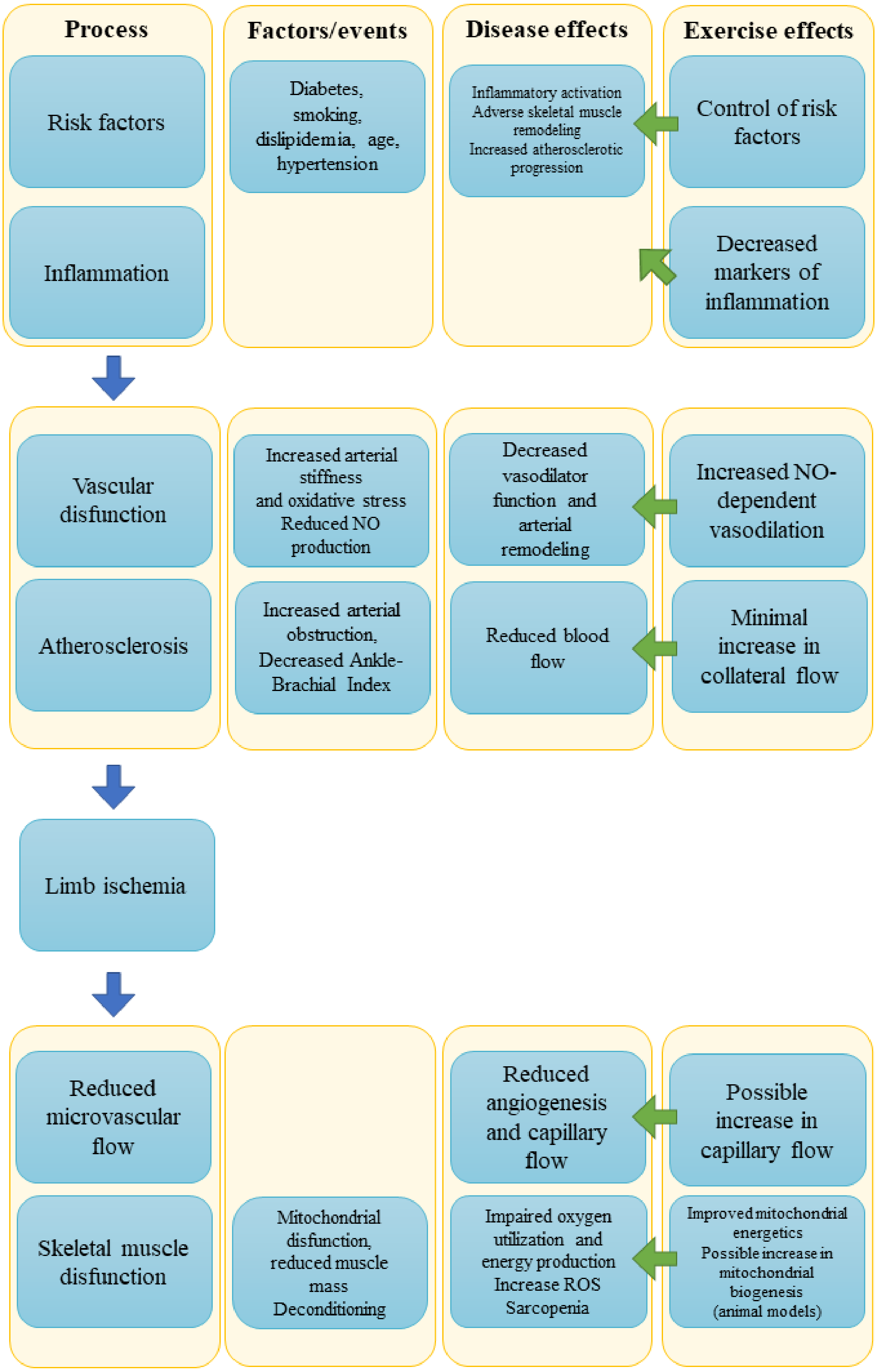
6.3. Exercise therapy

Exercise therapy has a pivotal role in this management of patients with IC, representing the first intervention that is potentially able to improve the status of the patients and to condition future actions [3] with well-demonstrated benefits [1,23,25,250,260]. Since 1898, exercise, particularly walking, has been proposed as a therapy for IC [294]. In 2001, the proven clinical efficacy of exercise in the treatment of claudication resulted in the creation of a Current Procedural Terminology Code (CPT 93668) for PAD rehabilitation [45].

As previously reported, patients with PAD present with a complex array of symptoms and limitations in their daily lives [306-307], which accelerates the functional decline leading to physical disability [45,100,202]. The goal, therefore, is to improve the exercise performance of patients with symptomatic PAD to prevent or lessen their physical disability and improve QoL and functional status [2]. A well-established benefit has been reported after a typical 12-week exercise training program [2,208-309]. In addition, considering that in PAD patients reduced physical activity in daily life [310-311] and low exercise capacity are associated with increased mortality and risk of cardiovascular events [138,189,197,199,244], exercise training when included in a comprehensive prevention strategy can reverse this condition and alter the clinical trajectory of these patients, even in the absence of claudication [45,247].

The functional benefits of exercise in PAD are likely attributable to several possible beneficial adaptations (Figure 6), to an opposition to the above-discussed pathophysiologic and maladaptive processes [45] and in general to the atherosclerotic disease.

Figure 6. Physiopathological process, evolution of disease and effect of exercise interventions in patients with peripheral artery disease.



Abbreviations: ROS: Reactive oxygen species; NO: nitric oxyde

The factor that contributes the most remains unclear [1]; however, it is certain that different factors play a role, such as improved vascular angiogenesis, reduced endothelial and mitochondrial dysfunction, reduced inflammation and favorable metabolic adaptations within skeletal muscle [1,250,312-316]. Reduced levels of inflammatory markers [317], improved endothelium-dependent vasodilation [318], increased capillary density of the gastrocnemius muscle [319], and altered skeletal muscle metabolism through an increase in oxidative enzymes have been reported following supervised exercise [320]. Exercise training may also upregulate antioxidant enzymes and enhance nitric oxide release [125,237-238,241,321-323] with induced angiogenesis and vascular regeneration, which are also mediated by endothelial progenitor cells (EPCs) [125,237-238,322-324]. These cells, as predictors of cardiovascular events [235,236], were found to be increased following acute and chronic exercise in healthy subjects and in patients with cardiovascular diseases, end-stage renal disease (ESRD) and PAD [241,325-328]. Exercise training by evoking local tissue hypoxia and changes in shear stress with the local induction of growth factors, cytokines and endothelial nitric oxide synthase may induce vascular structural remodeling [125,237-238,241,321-323]. An augmented peripheral arterial supply [329-332] and gains in collateral blood flow through collateral enlargement have been observed in animal models of arterial insufficiency following exercise training [329,333-335]. Unfortunately, in PAD patients, exercise programs fail to produce clinically relevant gains in peripheral blood flow when a minimal or absent ABI change is reported [45,181]. A meta-analysis of 7 exercise training studies demonstrated no change in the resting ABI, as confirmed by a recent Cochrane report [99,169]. The quality and duration of the training stimulus have been hypothesized to explain the difference in response in terms of an increased blood supply between the animal and human studies [314]. However, few studies based on new training programs aimed at maximizing the induction of aerobic adaptations have shown significant ABI changes [168,336-340] and related angiogenic adaptations [242,340-341]. It is also well-known that exercise therapy, favoring better control or a reduction of cardiovascular risk factors such as diabetes mellitus, hypertension, and dyslipidemia [1-3,342], is an important part of secondary prevention therapies for patients with coronary artery disease [1,343-344].

6.3.1. The exercise programs

To better address the topic, it is useful to refer to the recent definition of the AHA guidelines related to the key terms (Tables 8) and the modalities of vascular rehabilitation in PAD patients (Table 9) [23].

Table 8. Key-terms in peripheral artery disease (intermediate stage). Adapted from Olin et al. (2016)[2] and Writing Committee Members et al. (2016)[23]

Claudication	**Fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10-min).**
Functional status	Patient's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being. Walking ability is a component of functional status.
Structured exercise program	Planned program that provides individualized recommendations for type, frequency, intensity, and duration of exercise. Program provides recommendations for exercise progression to assure that the body is consistently challenged to increase exercise intensity and levels as functional status improves over time. There are 2 types of structured exercise program for patients with PAD: 1. Supervised exercise program 2. Structured community- or home-based exercise program
Supervised exercise program	The program takes place in a hospital or outpatient facility in which intermittent walking exercise is used
Structured community- or home-based exercise program	The program that takes place in the personal setting of the patient rather than in a clinical setting
Interdisciplinary care team	A team of professionals representing different disciplines to assist in the evaluation and management of the patient with PAD. The team members may include: Vascular medical and surgical specialists (i.e., vascular medicine, vascular surgery, interventional radiology, interventional cardiology) Nurses Orthopedic surgeons and podiatrists Endocrinologists Internal medicine specialists Infectious disease specialists Radiology and vascular imaging specialists Physical medicine and rehabilitation clinicians Orthotics and prosthetics specialists Social workers Exercise physiologists Physical and occupational therapists Nutritionists/dieticians
PAD -related events **Limbs**	Worsening claudication, Critical limb ischemia (chronic or ≥2 wk) ischemic rest pain, non-healing wound/ulcers, or gangrene in 1 or both legs attributable to objectively proven arterial occlusive disease Hospitalization: new lower extremity revascularization, or new ischemic amputation
PAD -related events **Cardiovascular system**	Hospitalization: Acute coronary syndrome (acute MI, unstable angina), stroke; cardiovascular death
PAD -related events **Specialists involved**	Individuals who are skilled in endovascular and/or surgical revascularization, wound healing therapies and foot surgery, and medical evaluation and care.

Abbreviations: PAD: peripheral artery disease; MI: myocardial infarction; wk: week

Table 9. Comparison of supervised exercise program and community- or home-based exercise program in peripheral artery disease. Adapted from Olin et al. (2016)[2] and Writing Committee Members et al. (2016)[23]

Type	Supervised exercise program (COR I, LOE A)	Structured community- or home-based exercise program (COR IIa, LOE A)
Setting	Hospital or outpatient facility	Program takes place in the personal setting of the patient rather than in a clinical setting
Organization:	Standalone or within a cardiac rehabilitation program. Directly supervised by qualified healthcare provider(s)	Program is self-directed with guidance of healthcare providers. Patient counseling ensures understanding of how to begin and maintain the program and how to progress the training load (by increasing distance or speed)
Training/Modality	Intermittent walking exercise	Intermittent walking exercise (generally) Program may incorporate behavioral change techniques, such as health coaching or use of activity monitors
Training/Frequency	Sessions performed 3 times/week supervised	
Training/Duration	A minimum of 12 weeks	Healthcare providers prescribe an exercise regimen similar to that of a supervised program
Training/ Session	Performed for a minimum of 30–45 min/session intermittent bouts of supervised walking Warm-up and cool-down periods	Healthcare providers prescribe an exercise regimen similar to that of a supervised program
Exercise prescription		
Intensity	40%–60% maximal workload based on baseline treadmill test or workload that brings on claudication within 3–5 min during a 6-MWT	Healthcare providers prescribe an exercise regimen similar to that of a supervised program.
Claudication Intensity	Moderate to moderate/severe claudication as tolerated	
Work-to-rest ratio	3-2:1 Walking duration should be within 5–10 min to reach moderate to moderately severe claudication followed by rest until pain has dissipated (2–5 min)	
Progression	Every 1–2 wk: increase duration of training session to achieve 50 min As individuals can walk beyond 10 min without reaching prescribed claudication level, manipulate grade or speed of exercise prescription to keep the walking bouts within 5–10 min	
Maintenance	Lifelong, at least 2 times per week	

Abbreviations: COR: Class of Recommendation; LOE: Level of Evidence; 6-MWT: Six-minute walk test

The first main classification is between unstructured and structured exercise programs. Unstructured programs are those in which exercise therapy prescription is based on walking advice [WA], consisting mostly of "go home and walk" advice, from the physician (e.g., general practitioner, vascular surgeon) [1]. This unsupervised approach based on a general recommendation to walk more is usually considered ineffective [23,345]. Alternatively, the physician may provide a comprehensive exercise prescription to offer a home exercise program [2,314,346] that is not based on a one-time recommendation but a continued discussion in an attempt to change the patient's behavior [2].

In contrast, structured exercise programs are planned programs that provide individualized recommendations concerning the type, frequency, intensity, and duration of exercise. The progression of the training load causes adaptations in the body that improve the functional status over time [23]. Two types of structured exercise program are now recognized for patients with PAD: supervised exercise programs and structured community- or home-based exercise programs [23] (table 9).

6.3.1.1. Supervised exercise programs

Supervised exercise programs, carried out in a hospital or outpatient facility, can be autonomous or part of a cardiac rehabilitation program. The treatment modality involves intermittent bouts of treadmill walking to moderate-to-maximum claudication, alternating with periods of rest. Warm-up and cool-down periods precede and follow each session of walking, which are directly supervised by qualified healthcare providers. Training is performed for a minimum of 30 to 45 min per session, in sessions performed at least 3 times/week for a minimum of 12 weeks [23,78,87,134,181,301,308,347-351].

Structured community- or home-based exercise programs, which have been proposed more recently, take place in the personal setting of the patient rather than in a clinical setting [23,349,352-354]. These programs, which may incorporate behavioral change techniques (health coaching and/or the use of activity monitors) are self-directed with the guidance of healthcare providers, who prescribe a structured exercise program comparable to that of a supervised program. The patient receives detailed information on how to begin the program, how to maintain the program or how to increase the training load (e.g., by increasing the walking distance or speed) throughout the program (table 9).

Supervised exercise programs have been recommended as the first-line therapy for the treatment of IC [3,23,181,314], after which RCTs have consistently demonstrated their capacity to significantly improve PFWD and MWD, as assessed by graded treadmill testing in people with PAD [1,52,77,169,349,355-356] both with and without classic symptoms of claudication [96,98]. In 1995, a meta-analysis of 21 studies (3 were RCTs) [355] reported an improved treadmill MWD by 122% and PFWD by 179% following SET based on treadmill walking [52]. The most effective programs included at least 3 supervised sessions per week of exercise performed walking to maximal or near-maximal ischemic pain for at least 30 min per session, for a 6-month duration or longer [52,96,98,355]. A rigorous systematic review including only controlled clinical trials (22 studies with more than 1200 participants) compared SET to usual care in the treatment of claudication [357]. Exercise induced clinically relevant increases in walking time (5 minutes) and walking distance (>100 meters) [357], with a magnitude of functional benefit derived from training exceeding that observed in drug therapy trials with both pentoxifylline and cilostazol [314,358]. A meta-analysis performed by Fakhry et al. in 2012 [73], including the results of 25 RCTs of treadmill-based SET in 1054 patients with PAD and IC, reported an improvement of treadmill MWD between 50% and 99% for 15 studies and >100% for 5 of them [52,359]. In addition, measures of functional status and health-related QoL were improved following treadmill-based SET programs [77,87,134,301,308,317,360-361]. Another meta-analysis by Parmenter and colleagues showed a significant mean improvement in COD and PWD after treadmill-based SET in the studies with 12-week or longer interventions [349].

The Cochrane reviews have progressively compared the effects of SET with nonsupervised exercise therapy [1,361]. A Cochrane review in 2006 [361] including 8 small randomized trials (a total of 319 participants) concluded that SET was superior to nonsupervised exercise with a 150 m greater improvement in walking time [314,361]. Consequently, the ACC-AHA *2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease* provided a Class I recommendation for SET and only a Class IIb recommendation for unsupervised training. In addition to the health benefits of a daily increase in physical activity, limited supporting symptom-based evidence has been provided for programs simply advising patients to walk more independently [314,362] due to lower intensity and poor adherence in comparison to supervised treadmill exercise.

As reported, SET training sessions are based on bouts of treadmill walking to moderate-to-maximum claudication, alternating with periods of rest. Recently, the components of a SET program (intensity, amount of exercise per session, claudication level, progression of volume, work-to-rest ratio, frequency of sessions, and program duration) have been reviewed [77]. In relation to *intensity*, the percentage of the measured maximal workload or peak oxygen consumption (VO_2) attained during a standardized treadmill test was considered. This parameter was related to an improvement in peak Vo2 rather than in walking distance [363]. The *claudication severity* during walking, was mainly considered. Most studies have been performed at a moderate or near-maximal level of claudication [23,73,169,355-356,364]; however, no difference was found when exercising to a mild claudication level in comparison to severe claudication [365].

The optimal *duration of exercise per session* has been poorly studied, with sessions lasting >30 to 60 minutes being more beneficial [355], or 30-45 minutes [73,349,356]. The *progression of increasing volume of exercise***,** which includes both duration and workload of the task, has not also been adequately investigated. A gradual progression of exercise should occur throughout the program to favor continued adaptation to the training stimulus on the basis of each individual patient. Similarly, the optimal *work-to-rest ratio* has not been studied due to the mentioned difficulty in standardizing rest periods, when the time of pain dissipation differs among individuals [366]. The *Frequency* of the SET program, according to meta-analyses, should be at least 3 times per week [23], but the optimal frequency of exercise training to achieve the best outcomes in terms of walking distance has not been specifically studied in RCTs. Finally, the *program duration* of SET should range from 12 weeks to 6 months [23,73,169,355-356,364], with a largest effect size in treadmill walking performance at 3 months [73,169,349,364,367]. A more gradual response to SET has been observed for the 6MWT distance, which peaks after 6 months of exercise training [96].

According to the AHA guidelines [23], SET programs are associated with effectiveness [23,78,134,169,181,308,349-351,353], persistent benefit [87,301,347], favorable risk–benefit ratio and safety [23]. Reported absolute contraindications are related to exercise-limiting cardiovascular disease, amputation or wheelchair confinement, as well as other major comorbidities that would preclude exercise [99,347-348,368-371].

However, a certain variability in the response has been underlined. One of these factors is the magnitude of improvement of the treadmill distance observed in RCTs. The changes of COD following 12-week interventions range from 92 to 243 m among the studies and from 191 to 402 m for PWD [98,112,115,123,165,308-309,348-349,367,368,372-376]. These changes in PWD are greater than 50% in 71% of trials analyzed and higher than 100% improvement in 21% of trials [73,77]. However, a factor of great interest is also the “non-response” to interventions. Among 24 walking-based trials (both treadmill-based and non-treadmill walking) included in a meta-analysis for PWT [73] and 20 trials included in the meta-analysis for COT, 37.5% of them (9 and 7, respectively) showed no benefit of SET compared with the control. Factors such as age, 6MWT performance, ABI value, sex, black race, presence versus absence of diabetes mellitus [354] or presence versus absence of exertional leg symptoms or claudication symptoms [98] were not recognized as useful to identify nonresponders to walking exercise interventions. Interestingly, less improvement after treadmill-based SET has been observed for patients with more severe IC [77]. Controversial results have been reported for gender, with significantly greater PWT for men than women in a randomized trial of SET, with no difference in response in the GOALS (Group Oriented Arterial Leg Study) trial [354], or with lower rates of improvements in COT for women in the presence of diabetes [377]. The wide timespan (more than 20 years) of the studies, the variability of the patients included and the different exercise training protocols used have been considered to explain the differences [73,77]. However greater benefits were observed between 12 to 26 weeks of duration compared with shorter or longer programs [73,77].

6.3.1.2. Home-based programs

Although SET programs have been shown to be more effective in increasing MWD and PFWD or time compared with nonsupervised exercise programs, [1,378] the structural weaknesses of the SET programs have emerged over time, leading to their underutilization [1]. In 2012, an international survey reported that SET programs were poorly available to vascular surgeons and differently implemented [378]. The policy change in the USA regarding coverage for supervised treadmill exercise under determined conditions is expected to increase access to supervised exercise for large numbers of patients with PAD [52]. However, the problem of participation was confirmed by a systematic review analyzing the rate of recruitment of PAD for RCTs for SET programs, which showed that 69% of eligible participants refused participation, partly because of the SET program requirements [379]. In general, issues of reimbursement, awareness, and motivation for these programs and problems related to patient transportation and eligibility affect SET programs, as well long-term adherence to exercise with a limited impact on patient’s lifestyle [181,250,315,379-381].

The proposed structured home-based exercise interventions (SH-BEx) may provide an effective alternative to hospital-based SET programs [382-383]. SH-BEx overcome or reduce some barriers to exercise, such as the availability of facilities [1,378], funding for hospital-based

SET programs [382-383], transportation time and costs for individual patients and families [52]. They also improve overground walking, which is necessary in daily life [68,74]. Since 2011, three RCTs have demonstrated significant benefit from structured SH-BEx in patients with PAD [77]. In the GOALS trial, a group-mediated cognitive behavioral intervention achieved a greater increase in 6MWT performance in PWT and in COT compared with the control group [354]. A study showed that 6MWT improved more significantly in the home-based exercise group compared with the SET group [99]. In contrast, a trial showed no differences in PWT or COT (primary outcome) between a home-based intervention (counseling session at baseline, 1 walking session per week with an instructor at an exercise center and 3 days of walking at home for up to 50 minutes of exercise per session) and the control group [352]. Finally, a recent randomized trial of structured HB-Ex that tested the ability of telephone calls by a coach combined with a wearable activity monitor showed no improvement in the 6MWT at the 9-month follow-up [118].

However, home-based exercise training is considered reasonable for patients with PAD [23] and is recommended with a Class IIa Level of Evidence A by AHA/ACC clinical practice guidelines for PAD. In these programs, patients with PAD have generally been advised to walk for exercise 3 to 5 times per week at a self-selected or to maximal ischemic leg pain, starting with 10 minutes of walking per session and increasing the duration by ≈5 minutes per session each week up to a duration of 45 to 50 minutes per session (excluding rest periods) [97,99,368].

The methodology of these programs has been favored by education and behavioral interventions [2,352] and use of observation components [99,368,378]. Exercise logbooks, pedometers or new technological devices monitor the duration and intensity of home exercise sessions, facilitate self-monitoring [97,99,368], enable periodical coaches or clinicians and favor specific walking advice. The obtained results to date are considered encouraging [2]. Among these programs, an original model of the SH-BEx program based on a specific testing session in the hospital and on a precise exercise prescription to be executed at home has been reported in different studies since 2004 by Manfredini and colleagues and proposed in 2008 [336-337]. A section will be dedicated to the rationale and results of this intervention model.

After the development of home-based (HB) programs, various reviews have evaluated the effects of different conservative treatment options in IC, including a version of the Cochrane comparing SET with HB-Ex and with WA [1,73,169,300,361,364,384-387]. The first systematic review on the effectiveness of H-BEx programs included 12 studies. In three studies, SET was superior to H-BEx in improving functional capacity or equivalent in improving QoL, while H-BEx compared with WA and baseline measurements significantly improved most of the functional capacity and QoL markers [378]. Three randomized trials showed that walking exercise in a home setting significantly improved walking ability and the 6MWT more than a treadmill-based SET program, compared to the control group (by 45 to 54 m vs 15–35 m). [96-99,368]. A recent Cochrane review comparing the treatments [1] included 21 studies involving a total of 1400 participants (SET= 635, H-BEx= 320, WA=445). SET showed an important benefit for treadmill-measured walking distance (MWD and PFWD) compared with H-BEx and WA, respectively. In this case no clear evidence of a difference between H-BEx and WA was observed. However, no clear differences in QoL parameters or in self-reported functional impairment between SET and H-BEx were observed [1].

The effects of SET versus revascularization, another therapeutic option for patients with IC, have also been compared in different studies [77]. Comparison of *SET* versus *Revascularization* versus *SET Plus Revascularization* in patients with above-the-knee occlusive disease and IC showed similar improvements among the three groups alone, with the best results observed for the group combining the treatments [388]. Similar results [389] were obtained in patients with femoro-popliteal disease and IC when comparing the effects of angioplasty, SET, and angioplasty plus SET with improved outcomes (PWD and QoL) [389-390]. The comparison of *SET* versus *Revascularization* showed a significant change at 3 months following angioplasty [391], which remained stable up to 15 months, while improvements of PWD in the SET group were observed up to 15 months. Conversely, better results in terms of functional improvement were reported following open surgical or endovascular procedures at the 1-year follow up compared to the SET or control group [392]. A significantly lower rate of patients with IC was reported in patients undergoing primary endovascular revascularization versus those performing SET, with a loss of this difference at 12 months, at which time functional data and QoL scores improved in both groups [393]. Comparison between *SET* versus *SET Plus Revascularization* in a trial including femoro-popliteal patients showed significantly higher COD and PWD (the primary outcomes) at the 24-month follow-up in the group combining the treatments [394]. Similar, but not statistically significant, the results were acquired in the aortoiliac trial [394]. Again, in the ERASE (Endovascular Revascularization and Supervised Exercise) trial, the primary end point, or the difference in PWD on the treadmill at 12 months, and the secondary outcomes (COD, VascuQoL score, and SF-36 physical functioning score) were significantly greater in the group receiving combination therapy than in the SET alone group [395], which was also highly effective per se in walking ability and QoL [314].

Comparison of *SET* versus *Revascularization* versus *Optimal Medical Therapy* in patients with aortoiliac PAD (CLEVER; Claudication: Exercise versus Endoluminal Revascularization) [87] at the 6-month follow-up showed the largest improvement in PWT (the primary end point) in SET, followed by stenting and finally optimal medical care. Health-related QoL, a secondary end point, was significantly improved in the SET and stenting groups [87].

A Cochrane review [396] of 10 RCTs comparing endovascular revascularization (± conservative therapy consisting of supervised exercise or pharmacotherapy) versus no therapy (except advice to exercise) or versus conservative therapy (i.e., supervised exercise or pharmacotherapy) for IC, confirmed the synergetic effect of endovascular revascularization combined with SET or pharmacotherapy with cilostazol, without significant changes in the functional performance or QoL of endovascular revascularization alone compared with SET alone [396].

Recently, a pilot randomized study compared the SH-BEx Test in-Train out (Ti-To) walking program [336] with hybrid revascularization procedures in elderly patients with PAD at Fontaine's second stage with severe IC over a 4-month period [168]. The study showed a lack of significant between-group differences in the physical component summary score of the SF-36 questionnaire (primary outcome). Both treatments significantly increased this parameter, as well as some secondary outcomes, including treadmill measures (ICD, ACD) and pain-free walking distance in the 6MWT. As expected, ABI and 6MWT were significantly improved in the revascularization group.

6.3.1.3. Alternative modes of exercise

For patients with IC, however, other modes of exercise have been proposed. Some authors have evaluated the efficacy of *lower-extremity cycling* to improve claudication in patients with PAD [370,397-398]. A study in patients with symptomatic PAD performing 6 weeks of treadmill walking, or leg cycling (2 minutes of rest, for a total of 20 minutes of exercise per session), or control showed a reduced improvement of PWD for the leg-cycling group, in which a group of patients showed a positive response to this type of training. In two other studies [370,398], a significant increase was observed in the distance covered in a shuttle test in the leg-cycling group compared with the control participants. The *aerobic arm training* was also studied. Twelve weeks of 3 times per week supervised treadmill training or arm cycling alone or in combination versus usual care in patients with claudication showed an improvement in COD and PWD in the arm-cycling group versus controls, demonstrating that walking ability in people with PAD could be significantly improved by upper-extremity aerobic exercise [348,399].

The effects of *Lower extremity Resistance Training* versus treadmill walking performance in patients with IC in studies with insufficient statistical power showed non-univocal results [52,98,134,400] with lower [309] or comparable effects [98,401]. High-intensity resistance training for seven different muscle groups was superior to low-intensity resistance training in improving walking distance in individuals with PAD [402].

6.3.1.4. Alternative modes of walking

- *Nordic walking:* Nordic walking or Nordic pole walking, a core-focused walking technique assisted by special poles, reduces the load on the legs during walking by involving the muscles of the arms and trunk [403]. A recent systematic review [403] analyzing data from five trials (three comparing supervised Nordic walking programs with supervised standard walking) demonstrated no advantage of Nordic walking programs over control programs.
- *Pain-free treadmill walking:* Supervised pain-free treadmill training was tested in randomized trials, which was based on walking until the onset of claudication [404-407]. Three trials showed a significantly higher functional improvement compared with the controls [404-406] or did not differ from that observed in a group walking to moderate claudication pain [407].

6.3.2. The Test in-train out Pain-Free walking program

An early prototype of the SH-BEx program based on an alternative model of walking for rehabilitation was developed and tested 15 years ago at the Vascular Diseases Center of the University of Ferrara, through the Vascular Rehabilitation Program [408]. The Ti-To model (Table 10) was conceived and proposed when structured home-based exercise programs were not yet available. However, at that time, it was already clear that a third route between the structured programs under continuous supervision and the unsupervised unstructured programs based on simple advice and recommendations was reasonable.

This patient-centered model provides the complete execution of the home exercise and circa-monthly check ups in the structure to determine the degree of disability and to receive the exercise prescription or the update regarding the training program. The program has two original aspects to be considered: the physiological approach to patient training and the organizational issues.

Table 10. Comparison of traditional exercise programs with the Test in-Train out (Ti-To) program in peripheral artery disease.

Type	**Supervised exercise program (COR I, LOE A)**	**Structured community- or home-based exercise program (COR IIa, LOE A)**	**Structured home-based exercise program Ti-To**
Setting	Hospital or outpatient facility	Program takes place in the personal setting of the patient rather than in a clinical setting	Prescription: in a hospital or outpatient facility Execution: home
Organization:	Standalone or within a cardiac rehabilitation program. Directly supervised by qualified healthcare provider(s)	Program is self-directed with guidance of healthcare providers. Patient counseling ensures understanding of how to begin and maintain the program and how to progress the training load (by increasing distance or speed)	Program is prescribed by doctors and exercise physiologists after a battery of hemodynamic and functional tests The exercise is performed at home The patient is periodically re- tested to update the program prescription and to verify the adherence
Training/Modality	Intermittent walking exercise	Intermittent walking exercise (generally) Program may incorporate behavioral change techniques, such as health coaching or use of activity monitors	Intermittent walking exercise at prescribed speed maintained walking in rhythm with a metronome The exercise is performed inside home, in a corridor Log-book for recording exercise
Training/Frequency	Sessions performed 3 times/week supervised		5-6 days/week
Training/Duration	A minimum of 12 weeks	Healthcare providers prescribe an exercise regimen similar to that of a supervised program	16-32 weeks
Training/ Session	Performed for a minimum of 30–45 min/session intermittent bouts of supervised walking Warm-up and cool-down periods	Healthcare providers prescribe an exercise regimen similar to that of a supervised program	Two daily 10-minute walking sessions
Exercise prescription		Healthcare providers prescribe an exercise regimen similar to that of a supervised program.	
Intensity	40%–60% maximal workload based on baseline treadmill test or workload that brings on claudication within 3–5 min during a 6-MWT		From slow speed (60 steps/min) to habitual speed (96-110 steps/min) for 1-minute, followed by 1-min of rest
Claudication Intensity	Moderate to moderate/severe claudication as tolerated		Pain-free
Work-to-rest ratio	3-2:1 Walking duration should be within 5–10 min to reach moderate to moderately severe claudication followed by rest until pain has dissipated (2–5 min)		1:1 (sitting in the rest period) For the first phase (1-min work / 1-min rest) then 2:1 and 3:1
Progression	Every 1–2 wk: increase duration of training session to achieve 50 min As individuals can walk beyond 10 min without reaching prescribed claudication level, manipulate grade or speed of exercise prescription to keep the walking bouts within 5–10 min		Increase of walking speed every 1-2 weeks (individualized) Then increase of work-rest ratio, at fixed working time per session (10-min)
Maintenance	Lifelong, at least 2 times per week		Lifelong, at least 2-3 times per week

Abbreviations: COR: Class of Recommendation; LOE: Level of Evidence; 6-MWT: Six-minute walk test

The physiological bases of the program are as follows:

i) When walking, patients with PAD must provide sufficient energy to satisfy the metabolic demand in the hypoxic area [409], and thus, aerobic support is crucial;

ii) This condition can be evoked by a low to moderate degree of deoxygenation obtained with a low rather than high walking speed, to be progressively increased to create a continuous adaptive aerobic stimulus;

iii) Extremely hypoxic conditions in the muscles may not be optimal to induce a favorable hemodynamic response. High-intensity fatiguing sessions (at moderate to near-maximal pain) that are typically prescribed in SET are associated with anaerobic rather than aerobic conditions [209,410] together with signs of muscular damage [410];

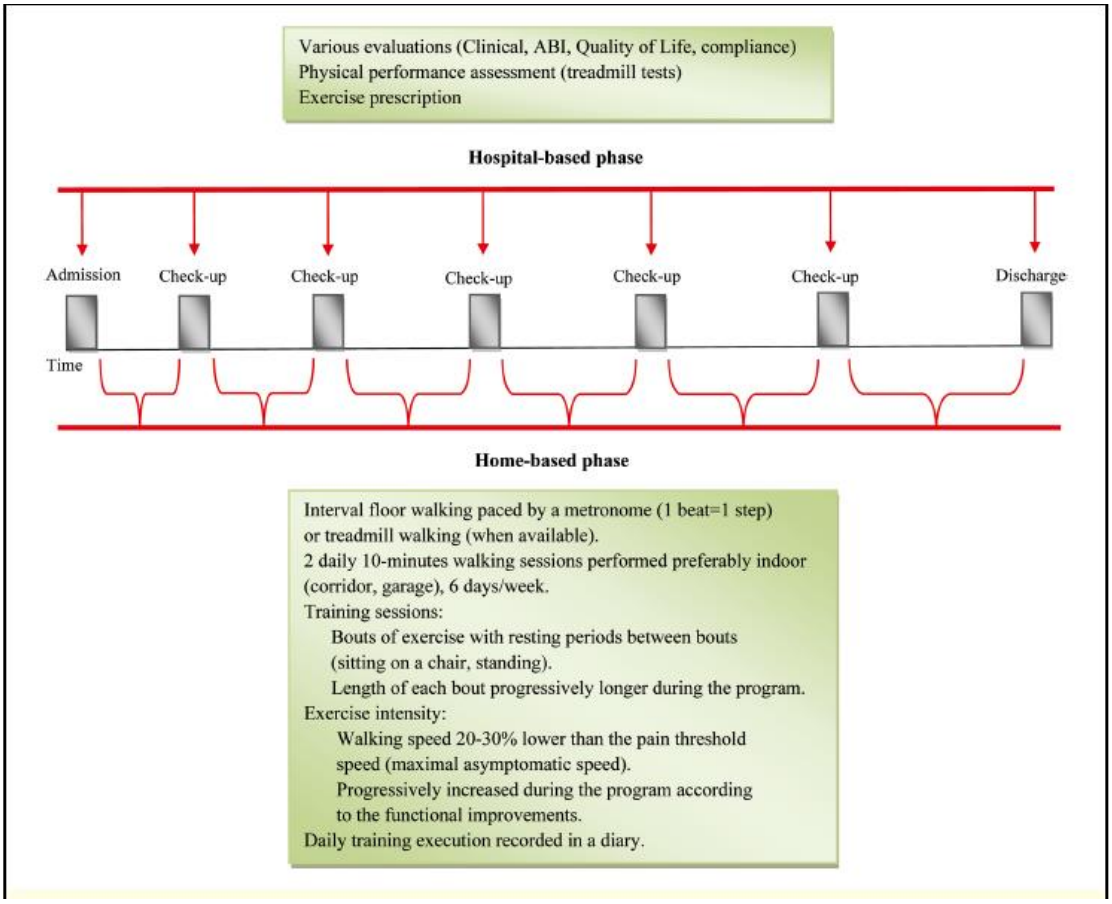
iv) A pain-free walking speed does not increase patients' tolerance to pain, as in SET, but it may favor the patient's adherence to exercise and an increase in spontaneous activity.

It is known that exercise has the potential to stimulate vascular remodeling [411] and to lead to an increase in the number of mitochondria and in the level of oxidative enzymes [412-413]. However, these adaptations are attainable through specific exercises carried out for sufficiently long periods at selected submaximal intensities [412,414-415]. Therefore, training should combine appropriate exercise intensity with an adequate duration. Sports physiologists recognize that at exercise intensities greater than the anaerobic threshold, the total volume of training is limited; conversely, training at the approximate intensity associated with the anaerobic threshold optimizes the intensity-duration relationship [408,416]. Thus, for the first time, an individual critical speed (PTS) determined during level walking, rather than a generic distance covered or time walked uphill, was proposed for assessment of the walking disability. This novel test [92,110] calls for small speed increments to synchronize the hemodynamic supply with the metabolic requirements of the patient, thereby preventing early activation of anaerobic glycolysis in the muscles involved in walking. Moreover, for the first time, a test was used to guide rehabilitation and to calibrate the exercise speed at home in PAD [408] as in sport sciences. Training just below the PTS might induce an "useful" degree of muscle hypoxia, associated with minimal or no pain, at an intensity that is sustainable for longer periods. This approach might favor the induction of the well-known positive effects of aerobic training on vascular adaptations and on the cardiovascular system [123,209,412,415-416].

Therefore, instead of walking at their individual speed or instead to prescribe continuous walking after pain onset [415], as for patients receiving a WA or treadmill-based SET [416], the program was based on walking sessions without pain, performed at home at low, progressively increasing speeds. Low-intensity exercise is carried out for short work units (ranging from 30 seconds to 5 minutes, generally 1-min per unit) to be repeated 3 to 10 times with periods of passive rest (1-2 minutes) after every single repetition. The combination of these factors, which contribute to the prescription in addition to the walking speed, is based on the individual degree of disability. The exercise prescribed at the hospital after a testing session is converted from walking speed into cadence or steps/min and precisely performed at home using a metronome. To test this hypothesis, in a small exploratory study, patients were free to choose one of three options: home-based walking guided by the pain threshold speed, walking at a self-selected speed through the pain, or no additional walking. After 120 days, those patients walking around PTS obtained more evident significant functional and hemodynamic improvements than those who preferred to walk at the self-selected speed, with no changes observed in those who did not add an exercise to the usual habits [408].

In a nonrandomized controlled study [336] of a total of 143 patients with claudication, the effects of the Ti-To program on functional changes was compared with the WA or the traditional HB-free walking exercise. Ti-To was based on two daily 10-min home walking sessions at maximal asymptomatic speed with monthly check-ups at the hospital, while the traditional program was based on 20-30 min of daily walking at self-selected speeds up to pain tolerance (Figure 7).

Figure 7. Schematic description of the test in-train out (Ti-To) exercise program[337]



After 6 months, the Ti-To group showed significantly greater improvements in walking ability as well as hemodynamic changes, which were completely absent in the group that performed the home-based free walking exercise [336].

Confirmatory results to the physiological approach to exercise training in PAD proposed by Manfredini and colleagues were derived in the last 10 years using the NIRS. This technique noninvasively explores tissue microvascular hemodynamics, monitoring the local balance between oxygen delivery and its utilization [417] and allowing an objective study of muscle metabolism at rest and under dynamic and postexercise conditions [418-420]. NIRS, which revealed different patterns in early O_2 desaturation or low muscle O_2 extraction in low-performing populations [421-423], has also been used to study PAD patients, whose performance depends on both oxygen availability and its use [424-427]. However, despite the potential usefulness, its routine use remains limited for PAD assessment [122]. Using this technique for several purposes, Manfredini and colleagues observed and reported the following results:

- An altered pattern of deoxygenation in the calf muscle was determined during an incremental walking test at level walking on a treadmill in PAD patients [123]. This pattern can be useful for diagnosing PAD [123] in the presence of atypical symptoms or in the presence of other conditions, e.g., diabetes, in which the ischemic pain is not reliably perceived and indicated by the patients [487], as well as in the presence of coexisting osteoarticular comorbidities, which are frequent in the elderly [339].

Moreover, early deoxygenation in the muscles of PAD patients at a low walking speed (often approximately 1.5 km/h) has been observed, providing valuable information about the exercise prescription [123]. This finding confirms the rationale based on walking from low to progressively higher speed to induce aerobic adaptations.

- Studied hemodynamic adaptations following different types of exercise programs with NIRS were revealed only in the group performing the low intensity pain-free interval Ti-To program and not in those walking at higher speed through the pain [340], confirming the starting hypothesis.

  Hemodynamic adaptations were also studied following surgery in comparison to walking training (unpublished) in a randomized trial [168], confirming the presence of a hemodynamic response to the Ti-To program that was even markedly lower than in the revascularization group.
- Biomarkers of deconditioning in PAD patients, especially in more severe patients, have been observed using the NIRS technique, such as an abnormally high value of muscle oxygen consumption at rest [124]. This "altered" biomarker has also been observed in patients with multiple sclerosis and ESRD, when it was reversed following Ti-To training [429-430].
- A selective degree of perfusion of the foot in ischemic patients with possible altered microcirculation was determined using a toe-flexion NIRS-based test [126]. This test also allowed the determination of possible hemodynamic tolerability and safety concerning the use of elastic compression in patients with PAD and concomitant chronic venous insufficiency [126-127].

The organizational aspect is another important issue of the Ti-To SH-BEx program. In addition to a general improvement of hemodynamic, functional and QoL parameters [337], the organizational model was found able to favor adherence [337-339], overcoming barriers to exercise. The patient has the possibility to comfortably carry out all the exercises at home, safely and sometimes together with the spouse, who controls the exercise execution (and sometimes also starts the program). The daily low dose of exercise can also be performed by poorly performing patients with comorbidities. Moreover, requiring an acceptable and fixed working time, the exercise is easily inserted into daily life. The program calls for few visits to the hospital, with low costs and a negligible or sustainable commitment on the part of the family [337], while a supervised program requires the need to travel daily or three times a week to facilities for exercise execution [431]. One such original approach is based a rehabilitative program that is actually available for PAD patients at the University Hospital of Ferrara, carried out in an outpatients setting. A rehabilitative team, including a medical doctor, a nurse and an expert in sport sciences, follows the rehabilitation of 200 patients/year. The program, which does not require specific or expensive instruments and is therefore reproducible in any setting [337,432], is offered to patients without cost, which is possible because of the low organizational costs. A study [337] developed in cooperation with the Department of Economy of the University of Ferrara on 250 consecutive patients showed a favorable cost-effectiveness ratio (9 Euros/walking meter gained), which was significantly lower than previously reported costs ranging from 27 to 57.5 Euros or 4,179 Euros for a whole program [433-437]. For both physiological and organizational reasons, the model was successfully implemented in patients with chronic diseases other than PAD. The Ti-To program has been tested in stroke survivors at home and in a community-based version [438-439]. In particular, the model was adapted to dialysis patients, for whom, in a pilot study, it showed an improved quality of life and functional parameters [440], as well as increased mobilization of EPCs [341]. Interestingly, these cells, the baseline level of which is related to the degree of exercise capacity [242], show an increase that is directly and significantly correlated to the patient-reported training load [341]. The program was successfully tested in a national multicenter trial, EXCITE (EXercise InTroduction to Enhance performance in Dialysis [441]), which represents the largest study of home-based exercise in ESRD. The semipersonalized low-intensity exercise program showed a significant improvement of performance as well as a favorable impact on QoL and rate of hospitalizations [442-443], with favorable effects up to 36 months of follow-up. The program among dialysis patients was safe, with no danger reported by patients during 11,325 certified walking sessions and suitable for elderly patients [444]. Analysis of this trial data using multivariate Cox models showed that an increase in mobility (20-meter walked during the 6MWT) was associated with a 6% reduction of risk for the composite endpoint of mortality, cardiovascular events and hospitalizations, and a similar relationship was observed among the 6MWT, mortality and hospitalizations [442,444]. Finally, the program was successfully performed under supervision in severe multiple sclerosis patients with blood flow restriction, with improved gait speed [445].

The differences in terms of training features and rehabilitation outcomes, in the different studies reporting various models of exercise training, are summarized in Table 11.

Table 11. Characteristics and effects of different models of exercise-based interventions in peripheral artery disease proposed by different authors.

Model intervention	Source/ author	Guidelines COR/Loe	Session duration	location	sessions/week	Intensity walking speed	INTERVALS	PAIN	Prescription	recording	duration months	visits	Objective (s)	functional changes	Hemodynamics (ABI)
SUPERVISED	TASC [ref #3]	I A	30-60 minutes including rest periods	**inside** hospital	3	treadmill	pain-limited	near maximal 3 4 out of 5	time and speed increased according to symptoms **patient and operator based**	not necessary	3	12	exercise capacity claudication time	significant superior to unsupervised	no change
HOME BASED STRUCTURED USA	McDermott MM [ref #448] randomized	IIa A	10-50 minutes/session.	outside	??	self-selected pace	pain-limited	severe leg discomfort 12-14/20 Borg	time and speed increased according to symptoms **patient-based**	fit bit web immission	9	4	distance walked 6MWT	no vs control	no change
HOME BASED STRUCTURED USA	Gardner AW [ref #99] randomized	IIa A	20–45 minutes/session	outside	3	self-selected pace	pain-limited based	mild-to moderate claudication pain	time and speed increased according to symptoms **patient-based**	step monitor exercise logs	3	4	exercise capacity claudication time	significant	no change
HOME BASED STRUCTURED FERRARA	Manfredini F [ref #337] controlled non randomized	IIa A alternative	20 minutes (40 min including rest) divided in two daily sessions	inside home	5 6	slow to moderate pace progressively up to self-selected	time-based	pain-free 0-1/10	structured increase of speed and work rest ratio **operator-based** indivualization (perodic tests)	exercise logs	6	4–6	exercise capacity sustainable walking speed hemodynamics	significant superior to unsupervised	ABI changes significant superior to unsupervised
HOME BASED UNSTRUCTURED	literature	0	20-30 minutes	outside	3 5	self-selected pace	pain-limited	3-4 di 5	generic	no	?	?	distance walked		no change

II. RATIONALE OF THE STUDY

Early identification of the PAD patient and start of the appropriate combined therapy may prevent progression of the disease, amputation and MACE, as well reduce walking disability and functional decline.

Evidence supports the effectiveness of exercise in PAD, in particular of the SET programs, also considering the limited availability of medical therapies available to improve their walking performance [52]. However, structured community- or home-based programs for patients with PAD are gaining consideration [97,99,352,354,368,446] for their characteristics as well also for the attainment of greater improvements in ground walking compared with supervised exercise interventions [96-99,368].

Evidence suggests that exercise programs also significantly improve walking endurance in asymptomatic patients with PAD who are at risk of mobility loss [77,106,191,203-204,310].

In addition to the evidence, gray areas are still present in the available literature, and some problematic issues have recently been discussed by the AHA with the creation of a “to-do list” that includes the research priorities [77].

SET shows less benefit for patients who are very limited in their walking ability [77], with a negative response to ischemia-inducing exercise training and decrease in mitochondrial function in patients with greater disease severity [77]. Previous observations have reported an association between repeated episodes of ischemia with negative effects on the limb musculature with altered skeletal muscle structural and metabolic properties [230-231,233]. Alternative exercise strategies for PAD patients should be considered [77], especially for more affected or limited patients, and the variability in responses and nonresponses to different exercise therapies should be evaluated [77]. The fundamentals of the SET and of exercise modalities (intensity, duration, frequency, work-to-rest ratios, etc.) should be studied in greater detail, and alternative forms of exercise walking, which differ from SET and in general from exercise to moderate-severe IC pain, should be considered. Less intense training was found to be effective [410], and a lower degree of increased ischemia-induced inflammation improved mitochondrial function with a positive response to an exercise program [179]. A study published very recently [447] has shown that oxygen-guided exercise training assisted by NIRS improves claudication comparable to pain-based training regimens, with adaptations in mitochondrial function accounting for the functional improvement. The oxygen-guided training intensity was determined by maintaining a 15% reduction in skeletal muscle oxygenation by NIRS rather than relying on symptoms of pain to determine the exercise effort [447]. This level corresponds to training below the pain threshold speed proposed in 2004 by Manfredini et al. and is related to the rationale of the Ti-To program as well as the physiology of aerobic adaptations [408].

Again, according to the recent AHA statement [77], "further identification of biological mechanisms that underlie improvement in response to exercise training has the potential to advance the field". Ultimately, in vascular disease, the issue of vascular adaptations cannot remain unconsidered. It is generally accepted, and recently confirmed, that a minimal, with moderate to no increase, ankle–brachial index or calf blood flow in humans is associated with SET exercise [87,169,181]. Interestingly, training models at submaximal intensity that avoid ischemia-induced inflammation, such as the Ti-To program, are associated with hemodynamic improvements [168,336-340]. In general, programs that are not only considered to lead to an improvement of walking efficiency and pain tolerance but that attempt to fully exploit the potentialities of aerobic exercise may be of interest to patients with more severe disease and/or disability. The present study aims to support this concept.

In addition, as stated in the recent AHA scientific document [77], "Strategies to translate SET for patients with PAD from the research laboratory to the clinical setting are greatly needed". Trials may exclude patients who represent a population of present and future interest due to the aging of the population, and therefore, different type of studies should be of potential interest (e.g., pragmatic trials), in addition to different primary outcomes (hemodynamics, QoL, etc.) or sex-specific outcomes. In addition, studies designed to increase the participation of patients with PAD in exercise therapy and to favor the transition of patients from supervised, hospital-based settings to community-based settings are necessary to result in a change in lifestyle [77].

However, the *candidate* and group of collaborators who have succeeded since the late 1990s have been considering most of these doubts and have attempted to identify, test and make clinically feasible new training strategies. This approach has allowed the definition of a sustainable model of intervention, especially in frail and more disabled patients.

Waiting for funding to support a trial, the present study aims to retrospectively analyze the results obtained in a large population following a Ti-To program. Interestingly, one of the research priorities of the AHA is solely the evaluation of long-term functional and cardiovascular risk outcomes of participation in exercise programs [77]. The present study aims to understand whether the proposed patient-based intervention may be effective not only at discharge but also over the long-term in relation to the adaptations that occur during the program.

In particular, the primary outcome of the three-year revascularization risk in the elderly with moderate and severe disease is a new piece of information in the literature of possible growing interest.

III. HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

The functional and hemodynamic adaptations evoked by a structured aerobic intervention would favor long-term vascular outcomes, even in severe PAD.

OBJECTIVES

General objective

To determine whether a rehabilitation program altered the rate of PAD-related revascularization and mortality three years post-discharge in a cohort of elderly patient.

Specific objectives

- To know the hemodynamic and functional changes following a rehabilitation program in a population of elderly PAD patients.
- To evaluate the risk of PAD-related revascularization at a three-year follow-up.
-
- To establish the relationship between the outcomes of the rehabilitation program and the risk of PAD-related revascularizations.
-
- To establish the relationship between the outcomes of the rehabilitation program and the risk of all-cause mortality.

IV. MATERIALS AND METHODS

1. DESIGN, POPULATION, SETTING, PERIOD AND ETHICAL CONSIDERATION

This single-center study retrospectively analyzed a prospectively collected database of PAD patients who were referred to the vascular rehabilitation program at the University Hospital of Ferrara between 2005 and 2013. In the prospective approach, 835 consecutive patients with PAD at Fontaine's stage II who were previously diagnosed at the Department of Vascular Surgery were enrolled in the study.

The local ethics committee approved the study and written informed consent was not obtained from patients who were no longer attending the program.

2. STUDY VARIABLES, INCLUSION AND EXCLUSION CRITERIA

The ABI was measured at the beginning of, during, and at discharge from the program according to the established standards [25]. An incremental treadmill test based on level walking [92] was performed to determine the speed at onset of symptoms and the maximal speed (S_{max}) attainable for each patient.

The patients who did not complete the rehabilitation program, had an ABI >0.8 at baseline or was non-measurable, were aged <60 or >80 years, or had missing/incomplete information regarding long-term outcomes, were excluded.

To perform all the analyses, the final PAD population was divided into two groups according to disease severity at entry: severe (Sev), for ABI values ≤0.5 in the more impaired limb and moderate (Mod) for ABI values >0.5.

The improvement obtained at the end of the program compared to the baseline was categorized according to previous prospective studies for further analyses [168,336,340]. The following favorable outcomes were considered: for hemodynamics, an ABI value increase ≥0.10 for the more impaired limb; and for functional capacity, S_{max} variations ≥0.5 km/h.

3. EXERCISE PROGRAM AND INSTRUMENTS

All patients received the "test in–train out" home-based exercise program [336,337]. The structured exercise was prescribed at the hospital during circa-monthly visits, but it was executed at home. The program encompassed two daily 10-minute sessions of intermittent walking (one-minute walk followed by one-minute seated rest) for six days each week at a prescribed speed. The training speed was converted into a walking cadence (steps/minute) and paced at home by using a metronome. It was slower than the individual's walking speed at the beginning and increased weekly. A record of the training sessions was requested and collected at each visit. The patients were discharged from the program when a satisfactory and/or stable improvement in pain-free walking distance was attained. More details on the exercise program are reported elsewhere [336,337].

4. OUTCOMES

PAD-related lower limb revascularization was the primary outcome and all-cause mortality was another outcome of interest. Outcomes were considered after the date of participants' discharge from the program. The clinical data for a 3-year follow-up period after the discharge date were gathered from the Emilia-Romagna health service registry.

5. STATISTICAL ANALYSIS

Differences in baseline characteristics were assessed according to PAD severity. Differences were assessed using chi-squared tests, Student's *t*-test, or the Mann-Whitney U-test as appropriate. Logistic regression with a stepwise selection method was used to identify the factors related to a non-response to rehabilitation.

Kaplan-Meier estimates of the distribution of times from discharge to the clinical events and a log-rank test for trend were used to compare the curves of the four patient subgroups (Sev and Mod, with/without hemodynamic or functional improvement). Data for peripheral revascularization were censored at the time of death.

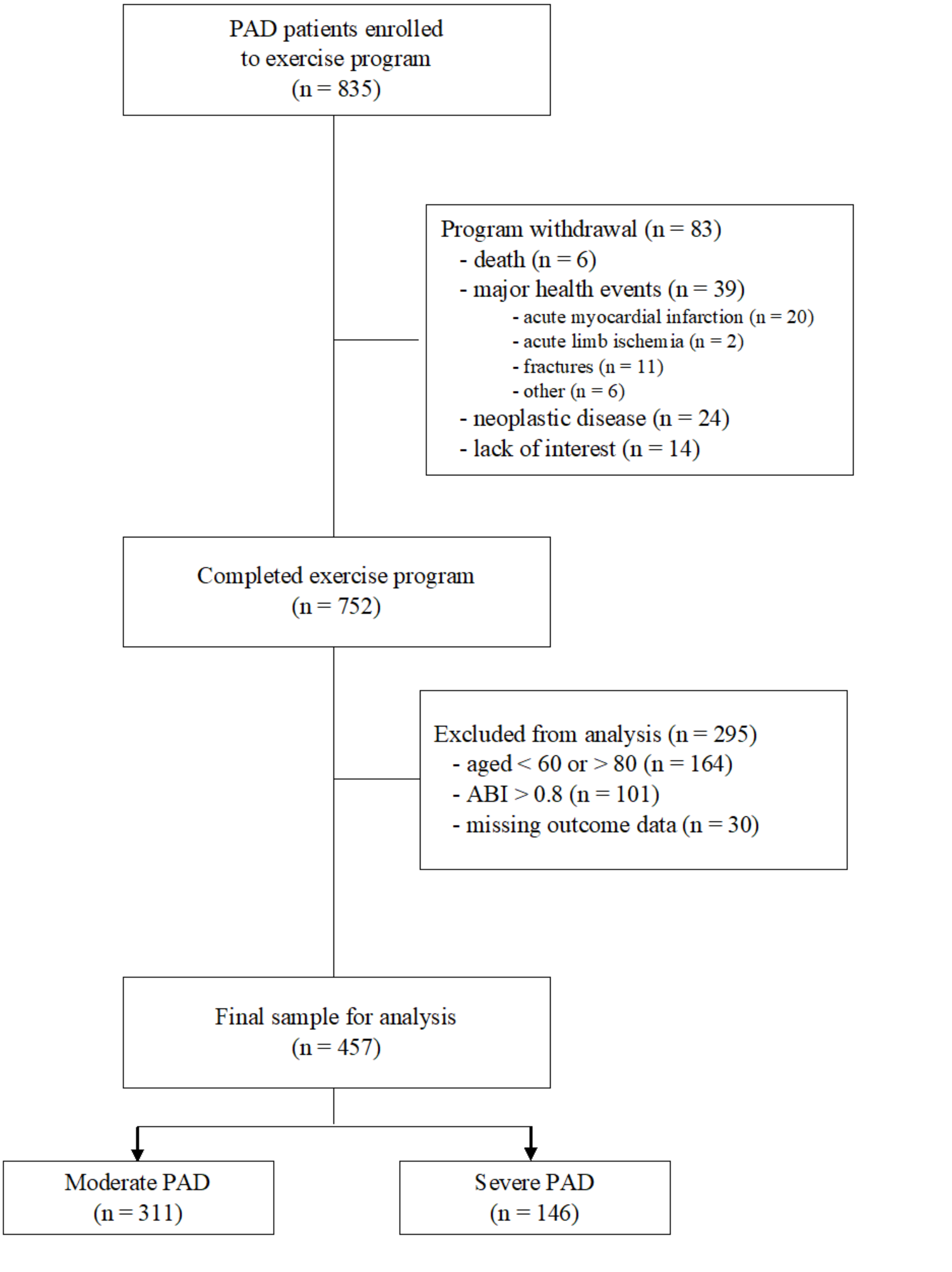
Univariate and multivariate Cox proportional hazards regression analyses were used to analyze the effect of several predictor variables on the primary outcome in the entire population and in each of the two groups. Because of the limited number of events, multivariate hazard ratios (HRs) were calculated using a forward approach, with an entry limit of $p < 0.05$.

A p value of <0.05 was considered statistically significant. All statistical analyses were performed using MedCalc Statistical Software version 18.10 (MedCalc Software bvba, Ostend, Belgium). Research data are available at: http://dx.doi.org/10.17632/4536z7c3nk.1.

V. RESULTS

From January 2005 to January 2013, 835 patients with PAD were enrolled in the rehabilitation program. A flow diagram of the participants and the reasons for exclusion are reported in Figure 8.

Figure 8. Flow diagrams of participants.



Abbreviations: PAD: Peripheral Artery Disease; ABI: Ankle-Brachial index; n: number

The final sample for this study included 457 elderly patients; 146 patients were severe (Sev) and 311 patients were moderate (Mod). The baseline demographics and clinical characteristics of the two subgroups, which differed by more prevalent bilateral disease in Sev, both limbs' ABI and functional capacity, are shown in Table 12.

Table 12. Baseline characteristics of patients included in the analysis.

	Moderate (*n* = 311)	**Severe (*n* = 146)**	***p***
Male sex	223 (72)	110 (75)	0.41
Age, years	71 ± 6	72 ± 5	0.07
Sedentary occupation	209 (67)	89 (61)	0.19
Risk factors; *n* (%)			
Smoking	277 (89)	134 (92)	0.37
Hypertension	247 (79)	121 (83)	0.38
Hyperlipidemia	218 (70)	103 (71)	0.92
Diabetes mellitus	119 (38)	54 (37)	0.79
Chronic Kidney Disease	30 (10)	20 (14)	0.20
Familiarity for CVD	72 (23)	35 (24)	0.85
Comorbidities; *n* (%)			
Chronic Heart Disease	123 (40)	63 (43)	0.47
Stroke	35 (11)	16 (11)	0.93
Osteoarticular disease	78 (25)	35 (24)	0.80
Pulmonary disease	18 (6)	15 (10)	0.08
Neoplastic disease	25 (8)	14 (10)	0.58
Charlson Comorbidity Index	2.6 ± 1.4	2.7 ± 1.5	0.51
Age-adjusted Charlson Index	6.2 ± 1.5	6.4 ± 1.6	0.27
Peripheral artery disease			
Grade I—Category 1	168 (54)	31 (21)	<0.001
Grade I—Category 2	118 (38)	55 (38)	<0.001
Grade I—Category 3	25 (8)	60 (41)	<0.001
Self-reported claudication distance (m)	209 ± 187	114 ± 121	<0.001
Lower limbs revascularization	85 (27)	49 (34)	0.17
Disease duration, years	6 ± 6	7 ± 6	0.09
Bilateral disease	206 (66)	119 (82)	<0.001
ABI more impaired limb	0.64 ± 0.08	0.39 ± 0.10	<0.001
ABI less impaired limb	0.86 ± 0.16	0.66 ± 0.22	<0.001
PTS (km/h)	2.9 ± 1.1	2.5 ± 0.9	<.001
S_{max} (km/h)	3.4 ± 1.1	3.0 ± 1.0	< 0.001

Abbreviations: CVD: cardiovascular disease; ABI: ankle-brachial index; PTS: speed at symptoms; S_{max}: maximal speed. Legend: Disease severity is reported according to Rutherford classification[22].

1. EXERCISE PROGRAM

All patients completed the exercise program, which lasted 394 ± 177 days, but the number of days was significantly greater in the Sev group than the Mod group (433 ± 188 vs. 376 ± 169 days, respectively; $p = 0.001$). Adherence to the program at a controlled speed was high for both groups, with both executing 87% of walking sessions prescribed ($p = 0.77$).

Significant improvements in the ABI of both limbs and S_{max} were observed at the end of the program in the entire population and both groups. Significant between-group differences were found for both ABI values in favor of the Sev group (<0.001). (Table 13, Figure 9).

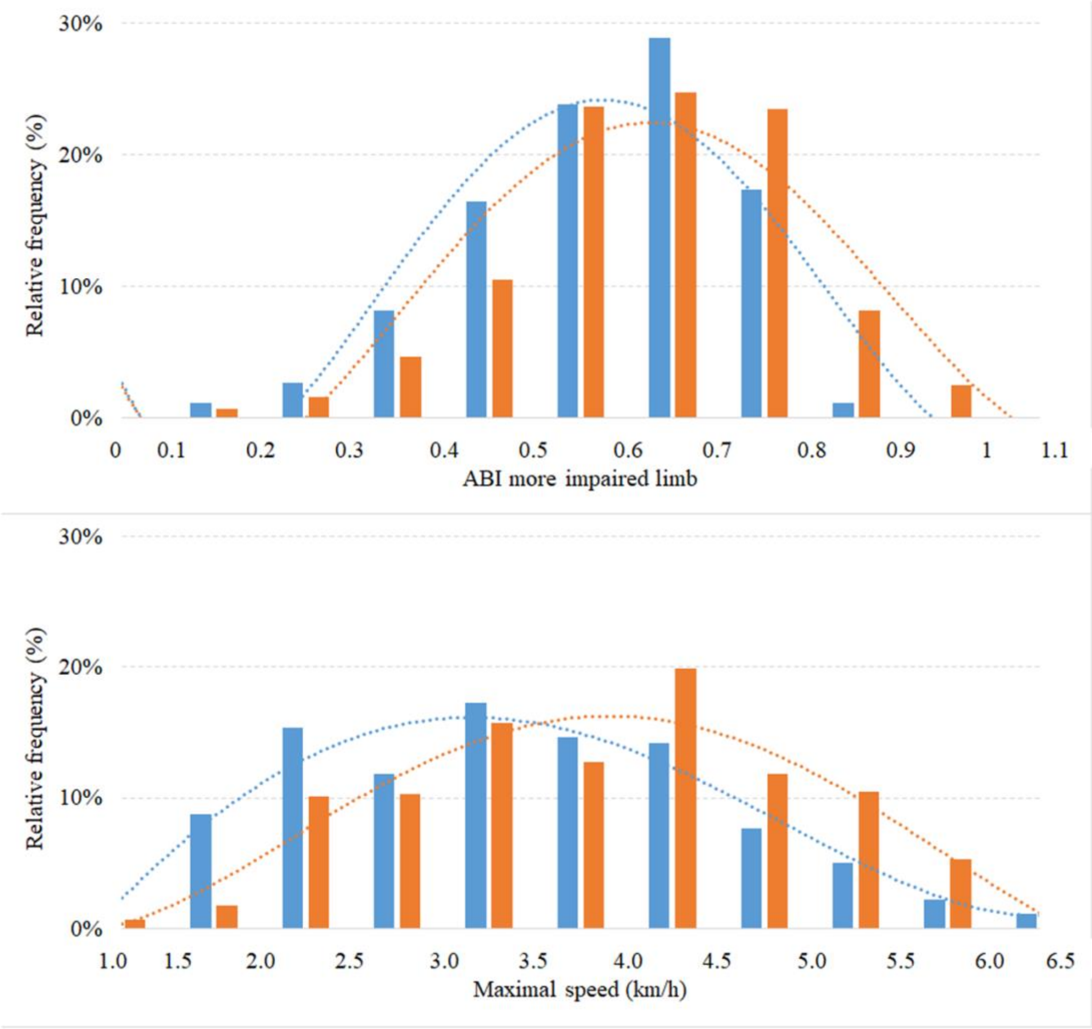
Table 13. Within- and between-group differences in rehabilitation outcomes.

	Moderate (*n* = 311)				**Severe (*n* = 146)**					
	Baseline	End	Δ	*p* Within-group	Baseline	End	Δ	*p* Within-group	Between-group Δ in changes	*p* Between-group
ABI worst leg	0.64 (0.63–0.65)	0.69 (0.67–0.70)	0.04 (0.03–0.05)	<0.001	0.39 (0.38–0.41)	0.50 (0.48–0.52)	0.11 (0.09–0.12)	<0.001	0.06 (0.04–0.08)	<0.001
ABI best leg	0.86 (0.84–0.88)	0.89 (0.88–0.90)	0.03 (0.02–0.04)	<0.001	0.66 (0.63–0.70)	0.72 (0.68–0.76)	0.06 (0.03–0.09)	<0.001	0.03 (0.01–0.05)	<0.001
PTS (km/h)	2.9 (2.8–3.0)	3.7 (3.5–3.8)	0.8 (0.7–0.9)	<0.001	2.4 (2.3–2.6)	3.1 (3.0–3.3)	0.7 (0.6–0.8)	<0.001	0.1 (−0.1–0.2)	0.23
S_{max} (km/h)	3.4 (3.3–3.6)	4.0 (3.8–4.1)	0.5 (0.4–0.6)	<0.001	3.0 (2.9–3.2)	3.4 (3.3–3.6)	0.4 (0.3–0.5)	<0.001	0.1 (−0.2–0.2)	0.10

Abbreviations: ABI: ankle-brachial index; PTS: speed at symptoms; S_{max}: maximal speed.

Legend: Data are expressed as mean and 95% Confidence Interval.

Figure 9. More impaired limb Ankle-Brachial Indexes (upper) and maximal speed (lower) distribution in the whole population at baseline (blue) and at discharge (orange)



For long-term outcome analyses, 71 Sev patients (49%) improved to ABI ≥ 0.10 (Sev_{ABI+}) and 75 (51%) achieved enhanced S_{max} ≥0.5 km/h (Sev_{Smax+}). Eighty-eight (28%) of the Mod patients had improved ABI (Mod_{ABI+}) and 164 (53%) achieved enhanced S_{max} (Mod_{Smax+}). The regression models for the entire population and both groups, including the independent variables related to subjects, risk factors, comorbidities, and PAD characteristics (Table 1), did not identify any factors related to a non-response to rehabilitation when ABI and S_{max} improvements were considered.

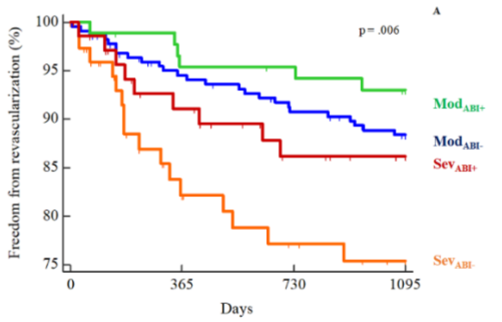
2. PRIMARY OUTCOME: PAD-RELATED REVASCULARIZATION

Fifty-six (12%) patients in the whole population had undergone peripheral revascularization at the 3-year follow-up; 25 from the Sev group (17%) and 31 from the Mod group (10%) (log-rank $p = 0.006$).

Considering the rehabilitative outcomes, analyses of the ABI change showed a 3-year revascularization rate of 21% in Sev_{ABI-}, 13% in Sev_{ABI+}, 11% in Mod_{ABI-} and 7% in Mod_{ABI+} (Figure 10A). Similar rates were observed for functional capacity improvements, particularly 21% in Sev_{Smax-}, 13% in Sev_{Smax+}, and 10% in both Mod subgroups (Figure 10B).

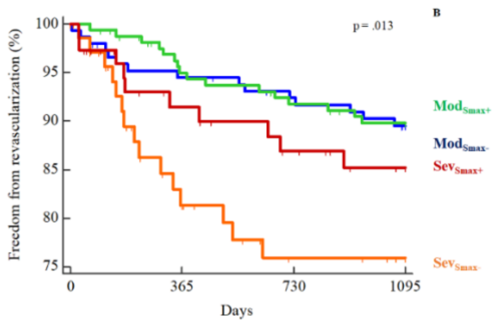
For both analyses within the Sev subgroups, the hemodynamic or functional improvement resulted in a protective, although not statistically significant, HR of 0.52 (0.20–1.40) and of 0.55 (0.20–1.50), respectively, which was enhanced in the case of concomitant improvements of the two outcomes (HR 0.43; 0.13–1.36) (Figure 10C).

Figure 10. Kaplan-Meier curves of revascularizations in the four patients' subgroups according to disease severity and ABI (A), or maximal speed improvements (B), or both (C).



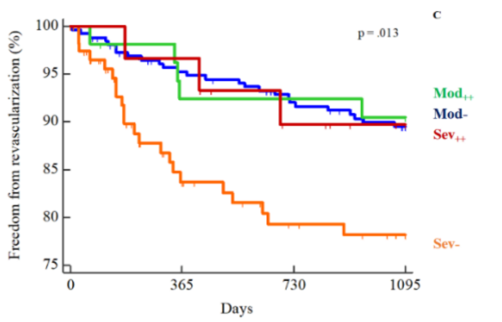
Number at risk (%)

Mod_{ABI+}	88 (100)	82 (93)	81 (92)	78 (89)
Mod_{ABI-}	223 (100)	203 (91)	191 (86)	181 (81)
Sev_{ABI+}	71 (100)	59 (83)	50 (70)	44 (62)
Sev_{ABI-}	75 (100)	50 (67)	45 (60)	41 (55)



Number at risk (%)

Mod_{Smax+}	164 (100)	149 (91)	142 (87)	136 (83)
Mod_{Smax-}	147 (100)	136 (93)	130 (88)	123 (84)
Sev_{Smax+}	75 (100)	61 (81)	55 (73)	48 (64)
Sev_{Smax-}	71 (100)	48 (68)	40 (56)	37 (52)



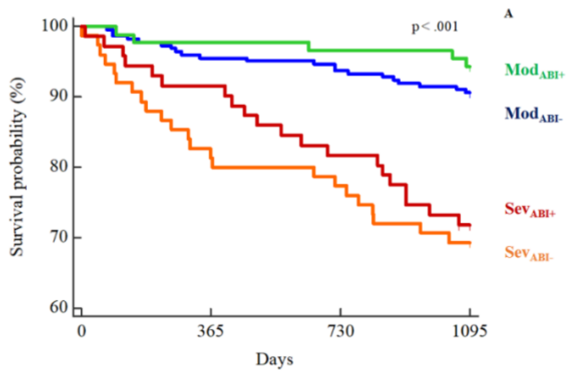
Number at risk (%)

Mod_{++}	54 (100)	48 (89)	48 (89)	47 (87)
Mod-	257 (100)	237 (92)	224 (87)	212 (82)
Sev_{Smax++}	30 (100)	29 (97)	24 (80)	19 (63)
Sev-	116 (100)	80 (69)	71 (61)	66 (57)

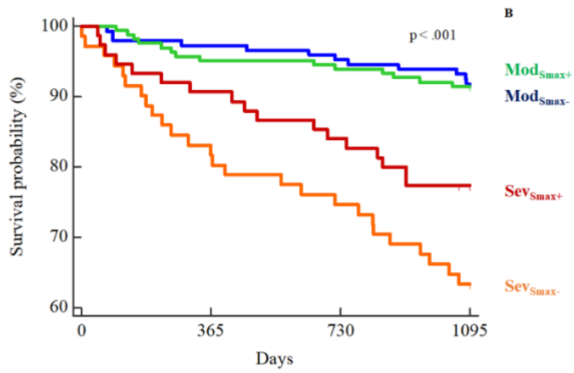
3. SECONDARY OUTCOME

There were 69 deaths (15%) during the study period; 43 in the Sev and 26 in the Mod group (29% vs. 8%, respectively, log-rank $p < 0.001$). Higher mortality rates were observed for Sev_{ABI-} (31%) compared to the other subgroups, including Sev_{ABI+} (28%), Mod_{ABI-} (9%), and Mod_{ABI+} (6%) (Figure 11A). Similarly, the subgroup Sev_{Smax-} showed a higher mortality at 37% compared to Sev_{Smax+} (23%), Mod_{Smax-} (8%), and Mod_{Smax+} (9%) (Figure 11B). No statistically significant differences were observed between the Sev subgroups.

Figure 11. Kaplan-Meier curves of survival in the four patients' subgroups according to disease severity and ABI (A), or maximal speed improvements (B).



Number at risk (%)				
Mod_{ABI+}	88 (100)	86 (98)	85 (97)	83 (94)
Mod_{ABI-}	223 (100)	213 (96)	209 (94)	202 (91)
Sev_{ABI+}	71 (100)	65 (92)	58 (82)	50 (70)
Sev_{ABI-}	75 (100)	61 (81)	58 (77)	52 (69)

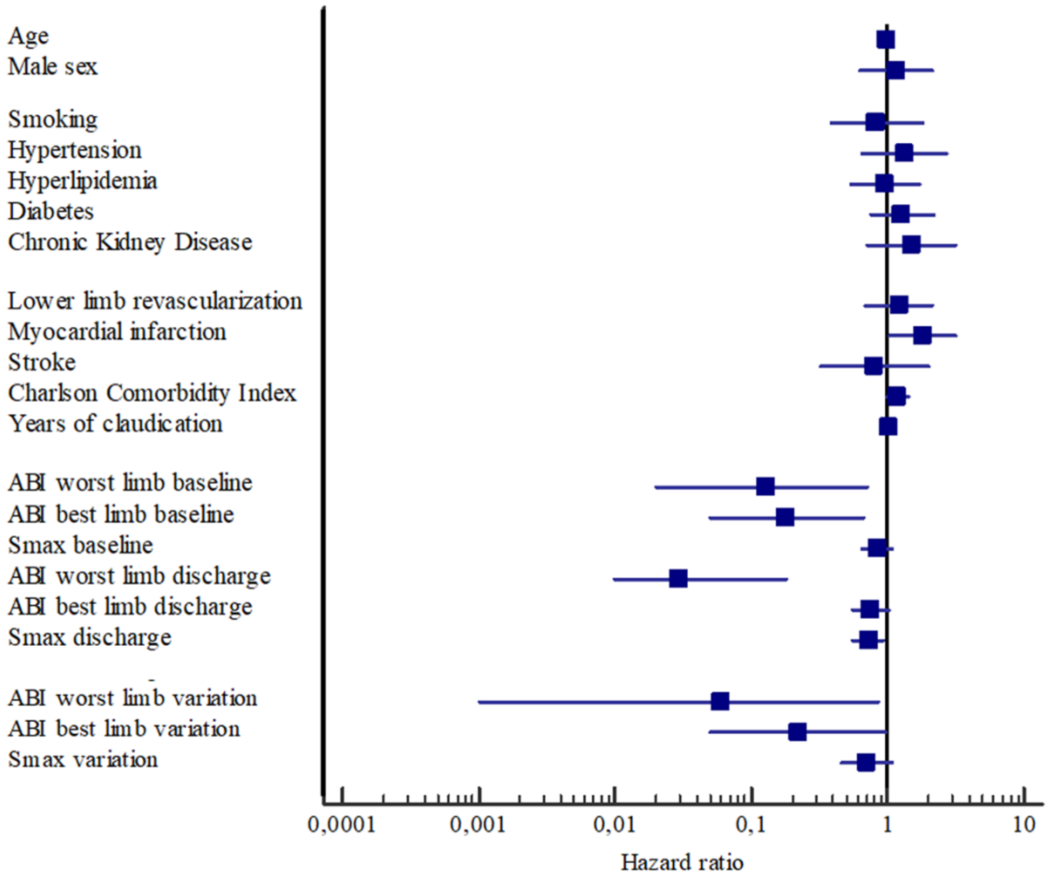


Number at risk (%)				
Mod_{Smax+}	164 (100)	156 (95)	154 (94)	150 (91)
Mod_{Smax-}	147 (100)	143 (97)	140 (95)	135 (92)
Sev_{Smax+}	75 (100)	68 (91)	63 (84)	57 (76)
Sev_{Smax-}	71 (100)	58 (82)	53 (75)	45 (63)

4. PREDICTORS OF REVASCULARIZATION

History of myocardial infarction (HR: 1.90; 1.07–3.36) and the ABI value of the more impaired limb at discharge (HR: 0.03; 0.004–0.16) were the only predictors of peripheral revascularizations in the entire population according to multivariate Cox regression. The univariate analyses highlighted the impact of baseline ABI values and their changes following rehabilitation (Figure 12, Table 14).

Figure 12. Forest plot showing association between PAD-related revascularizations and study variables in the whole population.



<u>Abbreviations:</u> ABI: Ankle-braquial index; Smax: maximal speed

Table 14. Results of Cox proportional hazards regression analyzing the capability of the study variables for the prediction of 3-year revascularization in the whole population and in the two patient groups.

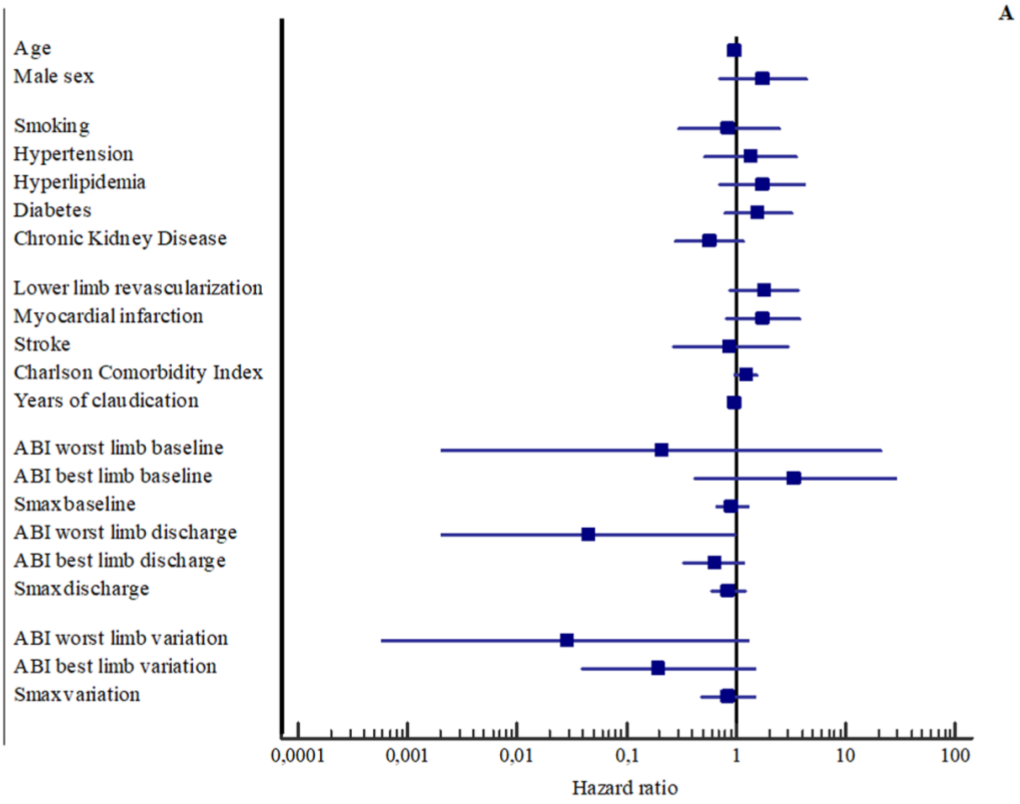
	Whole population (*n* = 457)		**Moderate (*n* = 311)**		**Severe (*n* = 146)**	
	Univariate HR (95% CI)	*Multivariate HR (95% CI)*	*Univariate HR (95% CI)*	*Multivariate HR (95% CI)*	*Univariate HR (95% CI)*	*Multivariate HR (95% CI)*
Age	0.99 (0.94–1.04)		0.97 (0.91–1.03)		1.01 (0.93–1.08)	
Male sex	1.15 (0.63–2.12)		1.76 (0.72–4.30)		0.64 (0.28–1.50)	
Smoking	0.83 (0.38–1.83)		0.86 (0.30–2.46)		0.72 (0.21–2.39)	
Hypertension	1.31 (0.64–2.69)		1.36 (0.52–3.56)		1.16 (0.40–3.39)	
Hyperlipidemia	0.96 (0.54–1.69)		1.75 (0.71–4.26)		0.52 (0.24–1.15)	0.24 (0.10–0.60)
Diabetes mellitus	1.27 (0.74–2.15)		1.57 (0.78–3.19)		0.95 (0.42–2.14)	
Chronic Kidney Disease	1.50 (0.71–3.18)		2.50 (1.03–6.12)	2.99 (1.20–7.45)	0.60 (0.14–2.54)	
Lower limbs revascularization	1.21 (0.69–2.12)		1.81 (0.88–3.72)		0.62 (0.25–1.57)	
Myocardial infarction	1.80 (1.02–3.19)	1.90 (1.07–3.36)	1.75 (0.82–3.73)		2.20 (0.92–5.27)	3.63 (1.44–9.14)
Stroke	0.79 (0.31–1.99)		0.89 (0.27–2.93)		0.66 (0.16–2.79)	
Charlson Comorbidity Index	1.19 (1.00–1.42)		1.22 (0.97–1.54)		1.12 (0.88–1.45)	
Disease duration	1.02 (0.98–1.06)		0.99 (0.93–1.06)		1.04 (0.99–1.10)	
ABI worst limb baseline	0.13 (0.02–0.70)		0.21 (0.002–20.62)		1.52 (0.02–82.29)	
ABI best limb baseline	0.18 (0.05–0.66)		3.46 (0.42–28.60)		0.06 (0.01–0.44)	0.02 (0.001–0.22)
S_{max} baseline	0.84 (0.65–1.07)		0.92 (0.67–1.27)		0.81 (0.54–1.21)	
ABI worst limb discharge	0.03 (0.006–0.18)	0.03 (0.004–0.16)	0.05 (0.002–0.98)	0.02 (0.001–0.42)	0.04 (0.002–0.93)	
ABI best limb discharge	0.76 (0.55–1.02)		0.64 (0.33–1.16)		0.82 (0.24–2.92)	
S_{max} discharge	0.72 (0.56–0.93)		0.85 (0.59–1.21)		0.69 (0.47–1.01)	0.57 (0.37–0.89)
Δ ABI worst limb	0.06 (0.004–0.84)		0.03 (0.001–1.29)		0.01 (0.0002–0.45)	0.003 (0.0001–0.09)
Δ ABI best limb	0.22 (0.05–0.97)		0.20 (0.04–1.47)		0.23 (0.03–1.66)	
Δ S_{max}	0.70 (0.45–1.08)		0.85 (0.49–1.49)		0.57 (0.29–1.14)	

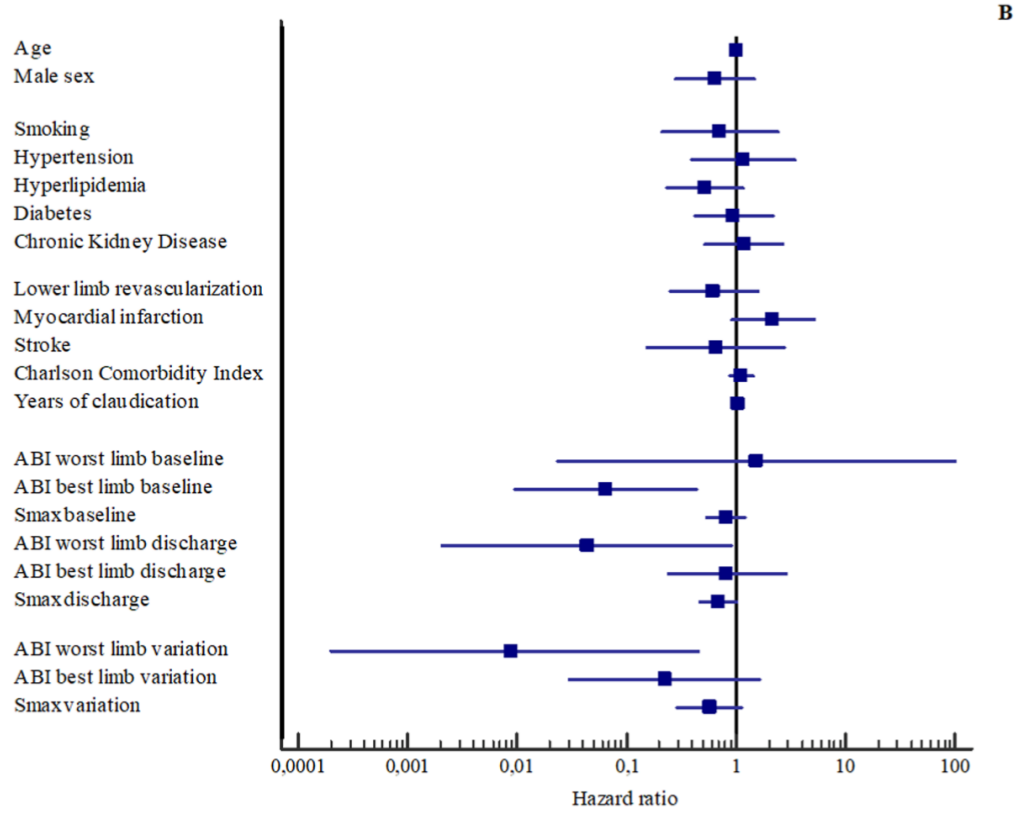
Abbreviations: HR: Hazard Ratio; ABI: Ankle-brachial index; S_{max}: maximal speed

Several independent predictors were identified in the Sev group, but the ABI improvement in the more impaired limb was the most protective factor against peripheral revascularization (HR: 0.003; 0.0001–0.09), which reduced the risk by greater than 300%.

Only chronic kidney disease and the ABI of the more impaired limb at discharge were included in the analysis in the Mod group (Table 14, Figure 13).

Figure 13. Forest plots showing association between PAD-related revascularizations and study variables in the Moderate (A) and Severe (B) groups.





Abbreviations: ABI: Ankle-brachial index; S_{max}: maximal speed

VI. DISCUSSION

This retrospective study shows for the first time that hemodynamic and functional changes following a rehabilitation program in a population of elderly PAD patients are associated with a significant reduction in the risk of PAD-related revascularization at a three-year follow-up. Notably, the severe PAD patients who attained some degree of hemodynamic and functional changes showed a lower risk of limb revascularizations that was comparable to patients with moderate disease. As a starting point, the present study confirmed the effectiveness of a structured, home-based program [168,336,337] on exercise capacity in the entire population and both PAD subgroups. Patients with severe disease and significantly lower functional values at baseline achieved the same improvements as patients with moderate disease. A significant ABI increase was also observed in the entire population and both PAD subgroups, which has been observed in previous studies [168,326,336-337,340,449] and poorly reported following supervised programs [169]. Notably, hemodynamic changes were more evident in the severe PAD patients. However, the most significant aspect of the study reveals an important, yet poorly reported, effect of rehabilitation on long-term outcomes and particularly the vascular interventions in PAD.

The clinical outcomes of the entire PAD population under study after three years were comparable or even better than previous reports in the literature [76,450-451]. A rate of 12% of vascular intervention (2.6% for acute limb ischemia) was observed, with 0.8% amputations and 15% deaths. As expected and previously reported [185,187-188], worse vascular and clinical outcomes at three years were observed in PAD patients with severe disease, with a 2–3-fold higher rate of events compared to patients with moderate disease (17% vs. 10% for interventions and 8% vs. 29% of deaths, respectively).

Previous studies reported negative outcomes (deaths, functional decline, re-interventions) associated with low exercise capacity [76,100], negative changes of ABI over time [186,190], and rehabilitation poorly attended [452] or not combined to revascularization [453].

Notably, the present study showed that it was not the functional and hemodynamic values at baseline, but the variations in these factors following rehabilitation that were primarily associated with the fate of elderly patients. Namely, the improvements observed at discharge from the program reduced the relative risk of lower limb revascularizations at a three-year follow-up, especially in the population with severe disease. The ABI improvement of the more impaired limb in this group of patients represented the most protective factor against peripheral revascularization, with a reduction in risk of over 300%. In particular, an ABI improvement ≥0.10 was a relevant outcome that was associated with a lower risk of future interventions. This hemodynamic change, associated with personalized aerobic training, may have favored a significant gain in mobility in a subgroup of severe patients. Those who attained hemodynamic and functional improvements showed vascular outcomes that were almost comparable to the moderate group and a lower mortality rate. The data collected highlight the role of rehabilitation, considering that interventional procedures may be not effective or satisfactory for mobility [453-454] in patients with intermittent claudication.

The present study demonstrated the sustainability of the program, which bypasses most barriers of the supervised programs [431,455]. The program is without gender differences [338] or limitations from pre-existing osteoarticular pathologies [339] and enables the enrolment of frail patients with restricted mobility. This exercise is based on over-ground personalized walking sessions inside the home and it is safe and painless [337]. The duration of the program, which was deliberately made longer in the severe group, allows for a protective monitoring of lifestyle and therapy adherence [456]. The program calls for few hospital visits, which maintains a low cost for the National Health Service [168,337].

This study has several limitations. First, its retrospective design may have influenced data recording. However, the same team prospectively collected the data from patients enrolled consecutively, and the data were secondarily elaborated and analyzed by personnel who were not involved in the study. A control group not exposed to rehabilitation is absent, but the objective was to explore the long-term response to the measured hemodynamic and functional effects of rehabilitation. The cut-off values for the analyses of the rehabilitative outcomes were arbitrary but in accordance with previous studies [168,337,340]. Patients with non-measurable ABI were excluded because it was not possible to classify them according to hemodynamic severity. Patients aged over 80 years were also excluded on the basis of the life expectancy in our province (average of 82.2 years).

Finally, a treadmill test was used instead of an over-ground walking test to favor standardization.

VII. CONCLUSIONS

A structured home-based rehabilitation program evoking functional and hemodynamic improvements reduced the long-term risk of vascular outcomes and deaths in elderly patients with claudication and in the presence of severe PAD.

The hemodynamic and functional changes are associated with a significant reduction in the risk of PAD in a population that follow a rehabilitation program.

Patients with severe disease and significantly lower functional values at baseline achieved the same improvements as patients with moderate disease

The rehabilitation program shows effectiveness on long-term outcomes and particularly on the vascular interventions in PAD patients.

A lower risk of mortality was also associated to the hemodynamic and functional improvements at the end of rehabilitation.

As implications of clinical practice, patient-centered programs may represent an option in the decision-making for elderly patients with low mobility and severe disease, but a prospective study is warranted to confirm the data presented in this study.

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IX. APPENDEXES

APPENDIX 1: TABLES A AND B

Doctoral student: Fabio Manfredini

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (1/2)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2017**
1	Gasparello J, Lamberti N, Lampronti I; Cosenza LC; Fabbri E; Bianchi N; Zambon C; Dalla Corte F; Govoni M; Reverberi R, **Manfredini F;** Gambari R, Finotti A.	Altered erythroid-related miRNA levels as a possible novel biomarker for detection of autologous blood transfusion misuse in sport	Transfusion (accepted, in press)	*22/71* *Q2* *HEMATOLOGY*	*3.423*
2	**Manfredini F**, Lamberti N, Guerzoni F, Napoli N, Gasbarro V, Zamboni P, Mascoli F, Manfredini R, Basaglia N, Rodriguez Borrego MA, Lopez Soto PJ	Rehabilitative exercise reduced the impact of peripheral artery disease on vascular outcomes in elderly patients with claudication: a 3-year single centre retrospective study	J Clin Med. 2019 Feb 7;8(2). pii: E210. doi: 10.3390/jcm8020210	15/154 Q1 MEDICINE, GENERAL & INTERNAL	5,583
3	Straudi S, **Manfredini F*,** Lamberti N, Martinuzzi C, Maietti E, Basaglia N. *Co-first author	Robot-assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the RAGTIME study): A randomized controlled trial.	Mult Scler. 2019 Mar 4:1352458519833901. doi: 10.1177/1352458519833901. [Epub ahead of print] in press	22/197 Q1 Clinical Neurology	5,280
4	Lamberti N, **Manfredini F**, Tessari M, Menegatti E, Nardi F, Basaglia N, Zamboni P. *Co-first author	A near-infrared spectroscopy-assisted test discriminates patients with peripheral arterial disease and venous insufficiency with changes of foot oxygenation following light elastic compression therapy	VASA - European Journal of Vascular Medicine 2019 Mar 6:1-7. doi: 10.1024/0301-1526/a000780. [Epub ahead of print] in press	53/57 Q4 PERIPHERAL VASCULAR DISEASE	1,210
5	Manfredini R, Lamberti N, **Manfredini F,** Straudi S, Fabbian F, Rodríguez-Borrego MA, Basaglia N, Carmona-Torres J, López-Soto P.	Gender Differences in Outcomes Following a Pain-Free, Home-Based Exercise Program for Claudication.	J Womens Health (Larchmt). 2018 Sep 15. doi: 10.1089/jwh.2018.7113. [Epub ahead of print] in press	4/42 Q1 WOMENS STUDIES	2,097
6	Lamberti N, Straudi S, Lissia E, Cavazzini L, Buja S, Manfredini R, Basaglia N, **Manfredini F.**	Home-based exercise for elderly patients with intermittent claudication limited by osteoarticular disorders - feasibility and effectiveness of a low-intensity programme	Vasa. 2018 Apr;47(3):227-234. doi: 10.1024/0301-1526/a000692. Epub 2018 Feb 21.	53/57 Q4 PERIPHERAL VASCULAR DISEASE	1,210

Table A. Publications/products that the doctoral student has carried out in the period 2018-2019 (2/2)

	Authors	**Title**	**Journal, year**	**Rank Quartile (Q) ISI Branch**	**Impact factor ISI 2017**
7	Baggetta R, D'Arrigo G, Torino C, Abd ElHafeez S, **Manfredini F**, Mallamaci F, Zoccali C, Tripepi G * and on behalf of the EXCITE Working group.	Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: a secondary analysis of the EXCITE trial	BMC Geriatr. 2018 Oct 20;18(1):248. doi: 10.1186/s12877-018-0938-5.	27/53 Q3 GERIATRICS AND GERONTOLOGY	2,866
8	López-Soto PJ, Fabbian F, Cappadona R, Zucchi B, **Manfredini F**, García-Arcos A, Carmona-Torres JM, Manfredini R, Rodríguez-Borrego MA.	Chronotype, nursing activity, and gender: A systematic review.	J Adv Nurs. 2019 Apr;75(4):734-748 doi: 10.1111/jan.13876.	7/118 Q1 NURSING	2,267
9	Marchetti G, Ziliotto N, Meneghetti S, Baroni M, Lunghi B, Menegatti E, Pedriali M, Salvi F, Bartolomei I, Straudi S, **Manfredini F,** Voltan R, Basaglia N, Mascoli F, Zamboni P, Bernardi F	Changes in expression profiles of internal jugular vein wall and plasma protein levels in Multiple Sclerosis	Mol Med. 2018 Aug 9;24(1):42. doi: 10.1186/s10020-018-0043-4.	50/133 Q2 MEDICINE, RESEARCH & EXPERIMENTAL	3,340
10	Ziliotto N, Baroni M, Straudi S, **Manfredini F**, Mari R, Menegatti E, Voltan R, Secchiero P, Zamboni P, Basaglia N, Marchetti G, Bernardi F	Coagulation Factor XII Levels and Intrinsic Thrombin Generation in Multiple Sclerosis	Front Neurol. 2018 Apr 20;9:245. doi: 10.3389/fneur.2018.00245.	84/259 Q2 NEUROSCIENCES	3,552
11	Lamberti N, Finotti A, Gasparello J, Lampronti I, Zambon C, Cosenza LC, Fabbri E, Bianchi N, Dalla Corte F, Govoni M, Reverberi R, Gambari R, **Manfredini F.**	Changes in hemoglobin profile reflect autologous blood transfusion misuse in sports	Intern Emerg Med. 2018 Jun;13(4):517-526. doi: 10.1007/s11739-018-1837-7.	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2,453

Table B. Conference presentations that the doctoral student has carried out in the period 2018-2019 (1/2)

N°	Authors	Conference, City, Date	Type	Title
1	Lamberti N, Straudi S, Borsato S, Baroni A, Donadi M, Biral GM, Tanaka H, Basaglia N, **Manfredini F**	1st Annual Meeting of Strength and Conditioning Society, Rome 18 November 2018	Poster/Oral	Effects of Low-intensity Interval Walking With Blood Flow Restriction on Functional Capacity in severe Multiple Sclerosis. Preliminary data from a pilot study
2	**Manfredini F**	59° Congresso Nazionale della Società Italiana di Nefrologia (SIN). Rimini 3 Ottobre 2018 Corso Educazionale "Promozione dell'esercizio fisico	Invited lecture	Fisiopatologia della ridotta capacità fisica nell'insufficienza renale
3	**F. Manfredini,** N Lamberti	DISTRESS nella malattia renale cronica Meeting Società Medico Chirurgica, Aula Magna Nuovo Arcispedale S. Anna - Cona, Ferrara, 10 novembre 2018	Invited Presentation	Qualità della Vita: l'esercizio fisico è terapia del distress?
4	Lamberti N, Tessari M, Spath P, Sibilla MG, Straudi S, Basaglia N, **Manfredini F**, Zamboni P.	European Society of Vascular Surgery ESVS 32nd Annual Meeting, Valencia-Spain 25-28 September 2018	Oral	A NIRS-assisted test discriminates patients with peripheral arterial disease and chronic venous insufficiency with improved foot oxygenation following low elastic compression therapy.
5	Lamberti N, **Manfredini F**.	14th Annual International Conference on Kinesiology and Exercise Sciences Athens, 30-31 July & 1-2 August 2018	Oral	Near-Infrared Spectroscopy as a valid tool to support the exercise physiologist interventions in chronic diseases.
6	**Manfredini F**, Lamberti N, Basaglia N, Manfredini R, Rodríguez Borrego MA, López Soto PJ.	9th IMIBIC YOUNG INVESTIGATOR MEETING, Cordoba,30-31 May 2018	Poster	The severity of peripheral arterial disease is not a barrier to exercise therapy in elderly patients with claudication: adherence, functional and clinical outcomes in a cohort of patients enrolled in a home-based pain-free program.

Table B. Conference presentations that the doctoral student has carried out in the period 2018-2019 (2/2)

N°	Authors	Conference, City, Date	Type	Title
7	Manfredini R, Lamberti N, **Manfredini F**, Fabbian F, Rodríguez Borrego MA, Carmona Torres JM, Lopez Soto PL.	9th IMIBIC YOUNG INVESTIGATOR MEETING, Cordoba,30-31 May 2018	Poster	Exercise is a gentleman: lack of gendere differences following a structured pain-free home based program for claudication.
8	**Manfredini F**	Incontri scientifici: Dipartimento Nefrologia Ospedale di Cona Ferrara, 4/5/2018	Invited Presentation	Progetto: esercizio fisico nella Malattia Renale Cronica