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PERIPHERAL ARTERIAL DISEASE PREVALENCE AND ASSOCIATED RISK FACTORS IN THE MEDITERRANEAN POPULATION

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¨This thesis is dedicated to my parents, Rose and Moises, if it wasn't for their constant love, support and sacrifice, I would not be where I am today. Pai e mom, this is for you¨

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Abbreviations

AAA	Abdominal Aortic Aneurysm
ABI	Ankle Brachial index The ankle brachial index
ACC	American College of Cardiology
AHA	American Heart Association
AIS	area of treatment, health- integrated area
ALI	Acute limb ischemia
ARIC	Atheroesclerotic Risk in Communities
BASIL	Bypass versus Angioplasty in Severe Ischemia of the Leg
BEST-CLI	Best Endovascular vs Best Surgical Therapy for Patients with Critical Limb Ischemia"
BMI	Body mass index
BMS	Bare metal stent
CAD	Coronary artery disease
CKD	Chronic kidney disease
CLI	Critical limb ischemia
CLTI	Critical limb threatening ischemia
COBEST	Covered versus Balloon Expandable Stent Trial
CTA	Computer tomography angiography
CTLI	Critical Threatening Limb Ischemia
CV	Cardiovascular
DCB	Drug coated balloon
DES	Drug Eluding Stent
DPP-4	Dipeptidyl peptidase 4
DSA	Digital subtraction angiography
ESCA	EnQuest Catalunya de Salut 2018
ESVS	European Society of Vascular Surgery
GFR	Glomerular filtrate rate
GH	Growth Hormone
GLP-1	Glucagon like peptide 1
HbA1c	Haemoglobin A1c
HDL	High Density Lipoprotein
HDL-C	High Density Lipidprotein Cholesterol

HICs	High-Income Countries
HMG-CoA	Hydroxymethylglutaryl-CoA
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HRT	Hormone Replace Therapy
IC	Intermittent claudication
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LDL	Low-Density Lipoprotein
LMICs	Low-and Middle Income Countries
MACE	Major Adverse Cardiac Events
MALE	Major Adverse Limb Events
MESA	Multi-ethnic Study of Atherosclerosis
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAT	Pedal Acceleration Time Pedal acceleration time
PCSK9	Proprotein convertase subtilisin/kexin type 9
POBA	Plain Old Balloon Angioplasty
PTA	Percutaneous Transluminal Angioplasty
RAS	Renal Artery Stenosis
REACH	Reduction of Atherothrombosis for continued Health Registry
REGICOR	Registri Gironi del Cor
SD	Standard Deviation
SDPS	San Diego Population Study
SET	Supervised exercise therapy
SGLT-2	Sodium -Glucose cotransporter -2
TASC	Transatlantic Intersociety Consensus
TBI	Toe brachial index
WMD	Weighted Mean Difference

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Abstract

Introduction

The manifestation of atherosclerosis in the lower extremities is known as peripheral arterial disease (PAD), this disease leads to a narrowing of the artery thus restricting blood flow to this area. PAD is one of the leading causes of cardiovascular pathology and an important indicator of cardiovascular risks due to its association to other cardiovascular diseases.
It is estimated that after 5 years, 20% of patients with PAD have associated coronary heart disease or cerebrovascular events with mortality rates between 10-15%. Therefore, PAD is an important indicator of cardiovascular morbid mortality.
The overall global prevalence of PAD has shown an increase of 17% from 2010-2015 estimating 237 million cases worldwide, with PAD screening suggested at 65 years old in American guidelines. This expresses the importance of early diagnosis in these subjects to aid and prevent associated cardiovascular diseases.

Justification

An overall worldwide increase in prevalence of PAD has been observed in the last few years creating a general concern because of the associated risk with other cardiovascular disease and mortality. PAD can be asymptomatic in most cases and present with atypical symptoms as seen in women, delaying its diagnosis. We also know due to its atherosclerotic nature; its prevalence increases with age and varies with demographic region. Being aware of the prevalence of PAD in your region can be an important tool to help develop preventative strategies and provide an early and perhaps more effective diagnosis and treatment.

Hypothesis and Objective

We hypothesize that the prevalence of PAD will be higher than shown in other studies in our region because these studies tend to include younger age groups who consequently have fewer risk factors. We believe these studies might not reflect our current reality in Barcelona Nord due to our population base, being of a higher age.

Our primary objective: is to determine the overall prevalence of PAD in 65-year-olds in our area of treatment, Barcelona Nord.

Secondary objectives: are to determine the difference in prevalence's in males and females as well as to identify their associated risk factor and assess their cardiovascular risk in the next 10 years.

Study Design

A single center, population based, cross sectional in which we analysed all asymptomatic men and women of 65 years in age in our area of treatment, Barcelona Nord. We evaluated common cardiovascular risk factors, performed a physical exam evaluating distal pulses and in all participants an ankle brachial index (ABI) was performed. Those ABI$\leq$ 0.9 mmHg were considered to have peripheral arterial disease.

All participants whom an ABI could not be performed due to skin ulcers or limb amputations were excluded.

Results

A total of 2.808 subjects were 65 years old during the time of recruitment, 1.174 subjects were finally included, 59.2% male and 40.8% females. The prevalence for PAD in Barcelona Nord in individuals of 65 years was 6.2% (95% CI: 4.8–7.6%), male 7.9% (95% CI: 5.9–9.9%) and female 3.8% (95% CI: 2.1–5.5%). Male subjects who were smokers and diabetic were more likely to have PAD ($p = 0.017$) and female subjects who were smokers and had hypertension ($p = 0.026$).

Conclusion

Overall prevalence of PAD in our region was relatively lower than the prevalence in other parts of Europe and concurred with prevalence's estimated in other Catalunya regions. We found that in our population base study, hypertensive smoking women and diabetic smoking men had a strong association for developing PAD. These results shift our focus in these subgroups of individuals, knowing that in these cases perhaps ABI screening programs and secondary preventive measures could have an important role in diagnosing and preventing this pathology in our area of treatment.

Resumen

Introducción

La enfermedad arterial periférica (EAP) es la manifestación del ateroesclerosis en las extremidades inferiores. Esta produce el estrechamiento de las arterias que lleva a la disminución del flujo sanguíneo a las extremidades. Es la tercera manifestación más común de patología cardiovascular y un importante predictor de eventos cardio y cerebrovascular.

Se estima que después de 5 años, 20% de los pacientes con EAP tiene enfermedad coronaria asociado y /o eventos cerebrovasculares, con una mortalidad entre el 10 -15%.

La prevalencia global de EAP ha aumentado 17% desde 2010 a 2015, estimando un total de 237 millones de casos mundial. En Norte América se ha visto que 1 de cada 5 sujetos padecerán de EAP a partir de los 65 años, sugiriendo programas de screening a partir de esta edad.

Justificación.

Un aumento global en a la prevalencia de EAP se ha observados en los últimos años, causando una preocupación general debido a su asociación con otras enfermedades cardiovasculares. EAP puede ser asintomático en la mayoría de los casos o presentarse con síntomas atípicos, como se observa en las mujeres, demorando así su diagnóstico. También sabemos que debido a su naturaleza ateroesclerótica, que su prevalencia aumenta con la edad y varia con cada región demográfica.

Conociendo la prevalencia de EAP de su región demográfica es importante para el desarrollo de estrategias preventivas secundarias además de ofrecer un diagnóstico y tratamiento precoz y efectivo.

Hipótesis y objetivo

Nuestra hipótesis es que la prevalencia de EAP en nuestra región será más alta de las demostrada en la demás literatura de nuestra área, ya que la mayoría de los estudios en nuestra zona incluye sujetos más jóvenes y por ende con menos factores de riesgo. Pensamos que estos estudios no reflejan nuestra realidad en Barcelona Nord debido a nuestra añosa población.

Nuestro objetivo Primario: es determinar la prevalencia global de EAP en sujetos asintomáticas de 65 años en Barcelona Nord.

Nuestros objetivos secundarios: Son determinar la diferencia en prevalencia en hombres y mujeres, identificar factores de riesgos asociados y determinar su riesgo cardiovascular en los próximos 10 años.

Diseño del estudio

Unicéntrico poblacional, transversal en el que se analiza todos los hombres y mujeres asintomáticas de 65 años de edad en nuestra población a tratar, Barcelona Nord. Evaluamos factores de riesgos comunes, se realizó un examen físico evaluando la presencia de pulsos distales y en todo los participantes se realizó un índice tobillo brazo (ITB). ITB $\leq$ 0.9 mmHg fueron considerados patologicos.

Todos los participantes a los que no se puede realizar ITB debido a lesiones extensas o amputaciones mayores fueron excluidos.

Resultados.

Total, de 2.808 sujetos tenían 65 años durante el tiempo del estudio. Se incluyeron finalmente 1.174 sujetos, 59.2% hombres y 40.8% mujeres. La prevalencia de EAP in Barcelona Nord en sujetos de 65 años fue 6.2% (95% CI: 4.8–7.6%), hombres 7.9% (95% CI: 5.9–9.9%) en mujeres 3.8% (95% CI: 2.1–5.5%).

Los hombres fumadores y diabéticos tenían mayor asociación con EAP (p = 0.017) y las mujeres fumadoras e hipertensas (p = 0.026).

Conclusión

En general la prevalencia de EAP en nuestra área eran relativamente menor que la prevalencia en otras partes de Europa y nuestro resultado son parecidos al estudio de prevalencia EAP en Catalunya. Encontramos que en nuestra población las mujeres fumadoras hipertensas y los hombres fumadores diabéticos tenían una asociación fuerte con el desarrollo de PAD. Estos resultados cambian nuestro enfoque a estos subgrupos de individuos, sabiendo que en esto casos se beneficiarían de programas de screening y prevención secundaria.

1.Introduction

1.1. Definition of PAD

PAD is defined as the narrowing of blood vessels in the lower extremities, restricting blood flow to this area (1). Atherosclerosis is the underlying cause in 95% of the cases and 5% of the cases, other ethiologies can be observed such as: vasculitis, lower limb aneurysms, popliteal entrapment, cystic adventitial disease, hereditary conditions, trauma and/or undiagnosed past embolism or local thrombosis (2).

PAD is one of the leading causes of cardiovascular disease, third only to coronary artery disease and stroke. It is also an important predictor of cardiovascular risk morbidity and mortality (3). These subjects are seen to have a three to six fold increase risk of cardiovascular mortality compared to those male and females without PAD (4). About 20% of patients with PAD have associated coronary heart disease or cerebrovascular events after 5 years as well as mortality rates between 10-15% (5). Despite universal efforts to diagnose, treat and prevent this pathology a significant increase in prevalence has been seen worldwide (2).

1.2. Epidemiology

Prevalence of PAD was estimated at 237 million cases globally by the Global Peripheral Artery Disease study, showing a 17 % increase worldwide of PAD from 2010-2015(6). Due to our aging population, a continued increase in prevalence is expected especially in low- and middle-income countries.The American Heart Association (AHA) estimates that approximately more than 12 million North Americans have PAD (7). This number is significantly higher in Europe, with some studies suggesting a total of 40 million Europeans out of 750 million suffer with PAD (8,9). Prevalence varies considerable with demographic region, age, race/ethnicity, gender as well as with socioeconomic background. This is important when considering the burden of this disease in our healthcare system.

1.3. Risk factors

Associated risk factor for PAD are the same as the traditional cardiovascular risk's factors, such as; smoking, hyperlipidaemia, hypertension, diabetes mellitus and chronic kidney disease. The presence of three or more of these risk factors confers a 10-fold increase in risk for PAD (10). Crique et al, showed the strongest predictor for PAD in those 65 years and younger was smoking and diabetes (11). Therefore, one of the fundamental pillars in preventing PAD is the treatment and control of these risk factors as well as being able to identify individuals who are at a higher risk, this way allowing for the implement of preventative measures not only from the vascular surgeons but starting from the primary care facilities.

1.3.1. Tobacco

Smoking is the leading risk factor for PAD. Cardiovascular mortality in PAD smokers is almost doubled compared to PAD non-smokers (12). It is associated with progression of the disease and a higher risk for amputation (13). It is one of the few preventable risks factor that is entirely dependent on the patient, yet one of the most difficult to control. In Catalunya the prevalence of smoking was 24.1% in 2022 according to the statistical institute of Catalunya. According to SIDIAP (*Sistema de Informaciòn para el Desarrollo de la Investigación en Atención Primaria*) and CMBD (*Conjunto Mínimo Básico de Datos de las Altas Hospitalarias*) database, 58% of individuals with PAD in Catalunya were smokers or former smokers (14).

Young et al, showed a dose dependent relationship between the amount of smoking pack/years to PAD, in a retrospective review in 2019 where they evaluated smoking intensity in all subjects who underwent lower limb revascularization. They observed a 1.48 (95% CI, 1.01-2.16) times increase in risk for major adverse limb events (MALEs) at 1 year in subjects who smoked more than one pack/day compared to those who smoked less (13).

Not only is smoking associated with a doubled risk for PAD and other cardiovascular events (15), but smoke cessation is associated with reduction of risk for PAD, improvement in leg symptoms and in revascularization success as well as a reduction in amputation rates and overall cardiovascular mortality (16,17).

Thus, it's inevitable that smoking is one of the major risk factors that needs to be controlled in subjects with PAD and in those considered high risk. Counselling should be encouraged, and pharmacotherapy can be provided in order to help aide our patients. Educational resources should be easily available to the general population in an attempt to avoid starting smoking.

1.3.2. Diabetes mellitus

Diabetes Mellitus is another one of the major cardiovascular risk factor for PAD, it also poses a higher risk for critical limb threatening ischemia CLTI, worst prognosis limb amputation and high mortality (18). Aside from smoking, diabetes is one of the strongest risk factors for PAD with 2 - 4 odds ratio (11).With the estimating global prevalence of Diabetes on the rise, this can impose an important problem (19).

Diabetes is diagnosed with 2 accounts of Haemoglobin A1c (HbA1c) >6.5% or 2 accounts of fasting glucose level >126mg/dL or an altered oral glucose tolerance test of 200mg/dL (20). Because Diabetes is not only a risk factor for developing PAD, but it generates a worse limb prognosis due to more distal artery affectations, this can lead to limited surgical options and higher risk of major amputations in these individuals.

The pathophysiology behind PAD in diabetes is atherosclerotic, chronic hyperglycaemia can create a series of inflammatory responses that produce vascular injury and consequently promote platelet activation and adhesion as well as endothelial dysfunction due to the increased oxidative stress, all of which leads to atheroma formation and subsequently PAD (21).

Different in hospital-based studies show that PAD is more prevalent in subjects with diabetes than in those without, with a 9% prevalence in those without Diabetes and a 55% prevalence in those with diabetes (22–24).

PAD with diabetes also ranked high for progression of PAD, perioperative complications, hospital stay and mortality in a German systematic review (25). All of these can generate an important healthcare cost as well as an emotional and psychological burden in our subjects. The importance of a multidisciplinary approach in treating these subjects, with the help of an endocrinologist is essential in order to be able to better control the catastrophic effects of this disease.

1.3.3. Hyperlipidaemia

When referring to hyperlipidaemia, we mean total cholesterol levels that include high density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides and how all of these associates with PAD. High cholesterol levels can cause fatty build up in your bloodstream adhering to arterial walls leading to narrowing of the blood vessels, making this another important risk factor for PAD and other cardiovascular diseases such as heart disease (26). In a logistic regression analysis of the Framingham Heart study a relative risk of 1.2 for claudication (95% CI 1.1-1.3) was seen for every 40mg/dL increase in total cholesterol observed in participants (27). Correlation between high total cholesterol and altered ABI have also been observed in different studies (28). On another hand, an inverse correlation between HDL and PAD (29) is observed in multiples studies, HDL levels < 35 mg/dL was associated with incident of PAD (OR: 0.7; 95% CI: 0.5-0.8) in the Rotterdam Study (29).

This inverse correlation is also seen in the Framingham Offspring Study that showed a 10% increase in risk for PAD for every 5mg/dL decrease in HDL (28,30), suggesting a protective effective over PAD. Further studies have assessed the ratio of total cholesterol to HDL cholesterol (TC: HDL-C) with PAD, MESA studies concluded that a ratio > 5.0 was associated with an almost 60% increased risk of ABI ≤ 0.90 compared to TC: HDL-C ≤ 5.0 (31), showing these to be a significant risk determinant.

Correlation between LDL levels and PAD are not as clear (32), this is also true for triglycerides levels and PAD. Although high levels of triglycerides can be associated with atherosclerotic disease, its direct correlation with incident of PAD is uncertain, although an association with PAD progression has been noted. Smith I et al, described a 70% greater risk of ABI decrease with triglyceride level ≥ 195 mg/dL ($p = 0.003$) (33), and the Speedwell Study showed higher triglyceride levels in those participants who developed claudication over the control group ($p < 0.01$)(34).

Controlling these factors with lipid lowering therapy, is an important branch of treatment for PAD, in order to better control incidence and progression of this disease.

1.3.4. Hypertension

Hypertension is a risk factor present in more than half of PAD subjects (35), it is also added mortality and morbidity in those with PAD, being a concomitant risk factor for other cardiovascular diseases. About 5 % of hypertensive subjects have intermittent claudication (36).

Meijer et al evaluated PAD risk factor determinants in 6.450 subjects, finding an odds ratio for PAD of 1.3 (95% CI: 1.2–1.5) per 10 mmHg systolic pressure (37). Hypertension is a modifiable risk factor and optimal medical treatment should be evaluated taking into consideration other associated cardiovascular disease present. The aim target threshold is <140/85 mmHg and of <130/80 mmHg in those subjects with diabetes or chronic renal disease (38).

When treating hypertension in PAD we should also be aware of related or coexisting renal-vascular disease such as renal artery stenosis (RAS), Constantinious et al observed a 4 times greater incidence of renal artery stenosis in subjects with 3 to 4 peripheral artery affectation (39). Watchell et al, found that 81% of patients with severe peripheral ischemia with RAS had hypertension. We should suspect RAS in difficult to treat hypertension cases of subjects with severe peripheral arterial disease.

1.3.5. Chronic kidney disease

Chronic Kidney disease (CKD) is another well-known risk factor for PAD, due to its pro calcification state, chronic inflammation as well as hypoalbuminemia and albuminuria, all of which favours arterial disease, making these subgroup of patients most likely to develop PAD then those with normal kidney function (40). The National Health and Nutrition Examination Survey (NHANES) showed a 6 fold higher prevalence rate of PAD in those subjects with CKD described as creatinine clearance of <60 mL/min/1.73m^{2}compared to those with creatinine clearance of >60 mL/min/1.73m^2 (41).

Keatiyoat et al, analysed kidney function and PAD within the data obtained in the ARIC study, with a mean follow up of 13.1 years, they found incidence rates of PAD to be 8.6 in CKD groups compared to 4.7 in those with normal kidney function. When adjusted with age, race and gender, a relative risk for PAD was 1.82 (95% CI: 1.34 to 2.47) in those with CKD compared to 1.04 (95% CI: 0.91 to 1.18) in those without (42).

PAD risk increases as glomerular filtrate rate (GFR) decreases, with an impaired kidney function, different metabolic changes occur (43). Albuminuria is one of the main associations described between CKD with PAD, its known as a marker for endothelial dysfunction as well as medial arterial calcification, causing stiffening of the arterial wall which does not only favour development of PAD but also can impair ABI results, causing a false normal result in these subjects, delaying PAD diagnosis.(44) (45)

The delay in diagnosis and worst outcomes in surgical revascularization of these subjects, especially those in dialysis, lead to higher risk of amputation as well as overall mortality.

1.3.6. Hyperhomocysteinemia

Elevated homocysteine is considered pro thrombotic in concentrations > 15 umol/L. Rong et al, observed in their study that patients with PAD had higher total homocysteine than the control subjects (20.4±11.5 vs 17.2±8.7) and a 3% higher risk of PAD associated with a 1μmol/L increase in total serum homocysteine. In the same study hyperhomocystenemia was considered an independent risk factor for PAD. Although an association between hyperhomocystenemia and PAD is observed in some studies, the mechanism behind it is still not well understood and its actual role as risk factor remains controversial.

All risk factors exposed above have a unique individual risk for developing PAD as well as associated morbidly and mortality in these subjects. Knowing that subjects with PAD don't usually have just one risk factors but most likely have at least two risk factors, emphasize the importance and the burden of impact of PAD on the population. Especially since the association with other cardiovascular diseases is also prevalent in these subjects leading to high morbid-mortality rates. It is of uttermost importance to be able to adequately treat these modifiable risk factors in order to prevent possible catastrophic events in these subjects

1.4. Symptoms

PAD can vary in symptoms. Some subjects are asymptomatic, and the disease can go by undiagnosed in the early stages. Others have symptoms that can be acute o chronic and vary with the progression of the disease or with complication of the atherosclerotic plaque(77,78). Symptoms for PAD all derive from the restricted blood flow to the lower extremities. Intermittent claudication is the usual initial symptom and is defined by

exercise induced pain relieved by rest (2) in the lower extremities. Described as dull, calf discomfort or fatigue (46). In 70-80% of patient's claudication remains stable and about <20% are seen to worsen (47).

As the disease progresses, symptoms can become worse, with critical limb ischemia (CLI) known as rest /nocturnal pain and skin ischemic lesions (46). Table 1 shows symptom classification of PAD according to Fontaine Classification.

Table 1: Fontaine classification

Grade	Symptoms
Stage I	Asymptomatic, incomplete blood vessel obstruction
Stage II	Mild claudication pain in limb
Stage IIA	Claudication at a distance > 200 m
Stage IIB	Claudication at a distance < 200 m
Stage III	Rest pain, mostly in the feet
Stage IV	Necrosis and/or gangrene of the limb

1.5. Clinical diagnosis

1.5.1. Patient history

Patient history is the first step in diagnosing any pathology and it is just as important when accessing for PAD. When evaluating patients history it is important to note past medical history (family history of PAD) as well as current risk factors such as smoking, diabetes, among others. Just with this information we can be more aware of potencial at risk subjects for PAD and potential asymptomatic subgroups that could benefit from screening test with ABI. AHA/ACC evaluated potential high risk subjects for PAD and recommend screening in the following subjects (48):

-Age ≥65 years old

-Age 50–64 years old, with risk factors for atherosclerosis or family history of PAD

-Age <50 years, with diabetes mellitus and 1 additional risk factor for Atherosclerosis

-Individuals with known atherosclerotic disease in another vascular bed (coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aorta aneurysm AAA)

These are the potential high-risk subjects we should be aware of when suspecting PAD.

1.5.2. Physical examination

When performing a physical examination in PAD patients, start with the subject laying down in the supine position at rest for a couple of minutes. We should start the exam with the inspection of the lower extremity: observing color such as pallor or erythema, the presence of skin lesions, necrosis/gangrene as well as the temperature of the extremity to touch, noting that these can be subjected to the temperature of the room as well as other underlying pathologies such as venous abnormalities or rheumatoid entities such as vasculitis.

We should proceed with palpation to detect abnormal lower extremity pulses (femoral, popliteal, tibial artery pulses, radial, brachial and axillary) as well as abdominal palpation to exclude pulsating abdominal mass. In the case of absence of any pulses, PAD should be suspected.

Mobility and sensitivity of the lower extremity should also be assessed. And lastly, auscultation, listening for any vascular bruits that could suggest an underlying arterial cause (48). Through a thorough and correct physical examination we are able to know at which stage a PAD subject is in, thus proceed accordingly.

1.6. Diagnostic tests

1.6.1. Ankle brachial index

The ankle brachial index (ABI), is a well-known and used non-invasive diagnostic test that helps us screen for PAD as well as classify the stage of symptomatic subjects. It is an inexpensive simple procedure that is available at the majority of primary care centers. A high sensitivity rate is reported for detecting >50% stenosis in those with ABI <0.9 (49).

ABI is also known to have a prognostics role, helping identify those subjects at a higher cardiovascular risk (50) Leng et al, showed a nonlinear inverse correlation between mortality, cardiac events and ABI values (51).

ABI is performed in the supine position in a subject at rest for a minimum of 5 min, a continuous wave Doppler probe and blood pressure cuff is used to measure the systolic blood pressure of both lower and upper extremities. The cuff is initially placed at the level of the malleoli and the pressure for the anterior and posterior tibial arteries as well as for both brachial arteries is taken. ABI is the ratio of highest systolic pressure of the tibial arteries to the highest brachial artery measurement (52).

A normal ABI is considered an index of 1.0-1.4. Those with index $\leq$0.9 is suggestive of PAD, as shown in the table below.

ABI is strictly dependent on the compressibility of the artery being evaluated and there are some cases with severe arterial stiffness, generating ABI results >1.4. This is common in subjects with diabetes mellitus and end stage renal disease. In such cases, interpretation of these results can be undetermined and further analysis should be conducted in order to rule out PAD.

Table 2: ABI results and PAD

ABI range	Diagnosis
ABI $\leq$ 0.9	Abnormal
ABI 1.0-1.4	Normal
ABI $\geq$1.4	Undetermined/Uncompressible

1.6.2. Stradness test

For those subjects with borderline ABI with a high suspicion of PAD, ABI measurements after exercise can be useful. During exercise peripheral resistance decreases in order to provide more blood flow to the peripheral musculature, in those subjects with important atherosclerotic plaque a decrease in blood flow and in pressure can be seen during exercise, revealing a possible PAD in subjects with otherwise normal or borderline ABI at rest (53).

Overall, ABI as mentioned, is an effective, noninvasive diagnostic tool that can provide us with important information in our PAD subjects as well as aide as a differential diagnostic tool in those subjects with other possible causes of intermittent claudication and serve as a screening test that can help us diagnose PAD in asymptomatic subject.

1.6.3. Toe pressure and toe brachial index

Toe brachial index is a good alternative in the cases in which ABI results are inconclusive due to uncompressible distal arteries. Distal arteries of the toes tend to be less affected by arterial stiffness. The exam is performed after 10min rest, where a mini cuff is placed around the patient's great toe and systolic pressure is measured through a Doppler wave, photoplethysmography or laser Doppler method. A quotient of systolic toe and brachial pressure is calculated. Index < than 0.7 is considered abnormal (54). Absolute toe pressure is also measured through this mechanism and an absolute toe pressure < than 30mmHg is considered abnormal. Various systematic reviews have evaluated the reliability of Toe brachial index (TBI) in diagnosis PAD (55,56). Tehan et al, found a sensitivity of 81% (95% CI 70 – 94) and a specificity of 77% (95% CI 66 – 90) in TBI for detecting stenosis >50% (57). TBI is noninvasive diagnostic option in the cases where ABI results are undetermined.

1.6.4. Treadmill testing

Treadmill testing in another diagnostic tool than can give us information on claudication distance. It's a test that can provide us with initial information on the patients walking distance as well as serve as an important tool during follow up controls to evaluate the patient's progressions. The test can also be used in conjunction with ABI pre, and post treadmill as described before.

1.6.5. Pedal acceleration time

Pedal acceleration time (PAT) provides physiological hemodynamic information on pedal flow with direct duplex imaging of the pedal arteries (58). It is non-invasive test that can be done with a standard duplex imaging, that is available in almost all vascular labs. With PAT we can evaluating collateral pathways of the foot and determine flow distribution. Silva et al, in a recient study, evaluated the correlation between PAT and ABI, suggesting an inverse correlation among the two. With mean ABI in Fontaine I of 0.94 ± 0.17 and mean PAT of 82.0 ± 27.4 ms; Fontaine stage IIa 0.69 ± 0.21 and 141.3 ± 57.8 ms; Fontaine stage III 0.43 ± 0.15 and 216 ± 33.2 ms; and Fontaine stage IV 0.49 ± 0.17 and 206.7 ± 78.1 ms, respectively(59), showing the use of PAT in helping evaluate the severity in PAD.

PAT is an important tool and should be considered in those patients with uncompressible arteries and or skin ulcerations where an ABI exam might not be conclusive.

1.7. Imaging tests

Imaging test is generally solicited when a surgical treatment is being assessed, since most of PAD diagnosis can be easily done through physical examination and other diagnostic tools mentioned before. When planning revascularization treatment, a complete leg assessment all the way down to pedal arches is recommended to provide direct blood flow.

1.7.1. Duplex ultrasound

Duplex ultrasound can provide us with valuable information on arterial disease. Although it is highly dependent on the operator, now a days most vascular surgeons are trained in identifying vascular lesions through duplex ultrasound. Its diagnostic accuracy decreases in below the knee lesions with study showing sensitivity range of 41 – 96% and specificity range 80 – 99%, respectively. Therefore, additional imaging should be considered in those where below the knee stenosis/occlusion is suspected. Although ultrasound is a great initial tool for vascular surgeons, its limitation is in heavily calcified arteries and obese patients, other diagnostic tools should be considered in those cases (60).

1.7.2. Digital subtraction angiography

Digital subtraction angiography (DSA) used to be the gold Standard for diagnosing PAD. Questionably replaced by Computed tomography angiography and computed tomography angiography. DSA not only provides a direct and thorough method for diagnosis PAD it's also an important aide in treatment. One of the important down falls of DSA is the radiation exposure, the entire surgical team should be aware of the dangers of exposure and preventive measures and strategies should be implemented to protect the entire team as well as the patient. The use of contrast agents is another downfall of the exam, favouring acute kidney failures, alternative options such as carbon dioxide can be used and should be contemplated in those patients at a higher risk for renal failure.

1.7.3. Computer tomography angiography

Computer tomography angiography (CTA) has taken the place of DSA for gold standard diagnostic tool for PAD. Sensitivity and specificity are shown to be over 90% for detecting arterial Stenosis (60,61). Although it is a good tool for proximal aortic, femoral, popliteal lesions, more distal affectation can impose a more challenging diagnosis especially in those

lesions that are highly calcified and may overestimate the degree of stenosis. We should also be aware of our patient's kidney functions since contrast is also used in this study.

1.7.4. Magnetic resonance angiography

Like CTA, magnetic resonance angiography is considered gold standard in diagnosis PAD with same specificity and sensitivity rates of >90% for detecting stenosis (61). It is an option to consider in those subjects allergic to iodine contrast and are unable to do have a CTA performed. Careful should be taken in ferromagnetic implants as well as those patients who are claustrophobic.

The different specificity and sensitivity rates are shown in the Table 5 among the different imaging modalities described in ESVS guidelines.

Table 3: Advantages and disadvantages of different imaging modalities in detecting PAD compared to digital subtraction angiography

Imaging modality	Sensitivity	Specificity	Advantages	Disadvantages
Duplex US	> 85%	> 95%	Low cost, no radiation exposure, non-invasive	Interobserver variability, accuracy affected by patient characteristics, time consuming and lower accuracy below the knee
CTA	> 90%	> 90%	Imaging of whole vascular tree, relatively short imaging time, non-invasive	Radiation exposure, misinterpretation in heavily calcified lesions, contrast agent nephrotoxicity
MRA	> 90%	> 90%	Imaging of whole vascular tree, non-invasive, no radiation	Relatively expensive, contraindications include ferromagnetic implants, and claustrophobia, risk of gadolinium induced nephrogenic systemic fibrosis
DSA	–	–	Imaging of the entire vascular tree, option for immediate intervention	Relatively expensive, invasive, radiation exposure, nephrotoxicity of contrast agents

US = ultrasound; CTA = computed tomography angiography; MRA = magnetic resonance angiography; DSA = digital subtraction angiography.

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1.7. Treatment

The general goal in treating PAD is not only avoiding the progression of the disease or adverse limb outcomes but to also prevent and treat associated CV events/diseases. There are two main lines of treatment in peripheral arterial disease. One is preventative strategies, aimed at treating modifiable risk factors in order to prevent the development and progression of PAD as well as concomitant CV events and second, is the treatment of PAD once established, in order to avoid major adverse limb loss and overall cardiovascular death.

1.7.1 Preventative treatment

This goal is to prevent the development of PAD or progression of the disease in those at most risk, by treating the common cardiovascular risk factors, already mentioned before. It is important to generate awareness in our society of the prevalence and possible outcomes of this disease in order to reach those subjects at risk and to be able to provide them with the necessary tools to aide them. These preventative strategies usually start from a primary care standpoint, since these are the medical providers that first encounter these patients and are usually the ones to early detect, diagnose and start medical treatment.

All modifiable risk factors should be treated:

Tobacco

Smoke cessation is the pillar in treating this disease, not only is this the number one risk factor associated with PAD, but it also can lead to progression and worst outcomes, as mentioned before. Smoke cessation as also been associated with improved outcomes.

As for pharmacological therapy, Bupropion and Vareniclina are the two approved drugs to help with smoking cessation. Bupropion is dopamine and norepinephrine re-uptake inhibitor and Vareniclina is a partial agonist of α-4 and β-2 nicotinic acetylcholine receptor, these drugs used alone or in association with each other or with nicotine patches have shown to be effective in smoke cessation. Vareniclina being the best in aiding smoke abstinence of up to three months (62).

Apart from pharmacological therapy and counselling provided for these subjects the European society stresses the importance of following up with the patients, since most of them relapse in the first week according to The ACC Expert Consensus on Tobacco Cessation Treatment (62). Therefore, providing pharmacological treatment, counselling, and regular follow ups should be the aim in our vascular clinicians.

Exercise

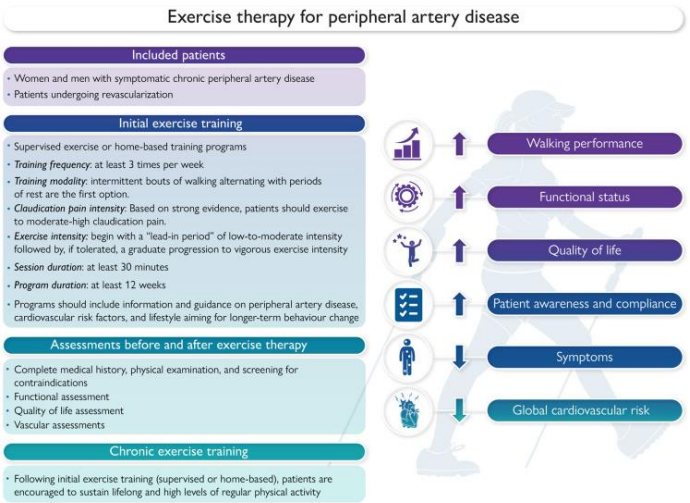
Physical activity is not only important to help with weight loss but is also recommended for those with PAD. There is lack of substantial evidence as to how much or what type of physical activity is recommended in *asymptomatic* PAD, since most studies to this day include small groups and mixed populations (63,64). Nonetheless, with all the evidence associating PAD with cardiovascular disease, ESVS recommends with Class IC

recommendation, 150 – 300 minutes a week of moderate intensity or 75 – 150 minutes a week of vigorous intensity aerobic physical activity, to reduce all cause and cardiovascular mortality and cardiovascular morbidity, in subjects with PAD (2,65,66) .

When it comes to *symptomatic* PAD with intermittent claudication (IC), physical activity does play an important role in improving walking impairment as shown in multiple different studies over the years. A standard supervised exercise program can promote vasodilation, reduce inflammatory markers as well as changes in gastrocnemius muscles this way improving walking distance in these subjects (67,68).

Supervised exercise therapy (SET) is the common exercise method used, it consists of intermittent walking exercise performed on a treadmill for a total of 30-60 minutes, three times a week for 3-6 months (67). A meta-analysis showed that SET was superior for maximum pain free walking distance compared to no exercise and unsupervised home-based exercise programs (69). Even though there are many studies comparing different exercise modalities, SET till this day seems to be the method of choice for improving IC, although different alternatives should be considered for those subjects who are unable to complete walking exercises. AHA/ACC provides a summarized exercise modality guidelines for PAD subjects, shown in Figure below.

Figure A. Exercise Therapy Guidelines for patients with lower extremity PAD



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Overall, an individual supervised exercise program that fits each subject's personal habits, ability and capacity should be considered for better adherence to these programs. Perhaps the future lies in cardiac rehabilitation programs, with some studies reporting improvement in PAD subjects who concluded such programs (70,71), although further studies are needed to confirm results. Either way, it is safe to say, that constant physical activity is beneficial for PAD, for improving claudication on set time, distance, and overall cardiovascular risk, in metabolic syndrome.

Antidiabetic therapy

Diabetes as mentioned before is one of the main risk factors for PAD other than smoking having an important effect on progression of plaque atheroma thus leading to worst outcomes. Not only is diabetes an important risk that should be medically controlled but preventative treatment should be offered in those subjects with hyperglycaemia and or pre-diabetes.

Regulating glucose levels can be controlled at these stages with dietary changes, physical activity, and consequently pharmacological therapy. The common glucose lowering drugs are metformin, dipeptidyl peptidase 4 (DPP-4) ,glucagon linked transporter 2 inhibitors (SGLT-2) and glucagon like peptide 1 (GLP-1). Palmer et al, in a meta-analysis performed, concluded that there was no combination or alone therapy with these drugs that was more effective in reducing cardiovascular risk or all-cause mortality in type 2 diabetes. They did however notice lower HbA1c levels with metformin alone (72).

Although accordingly to this meta-analysis there is no one anti diabetic drug that provides more benefit than the other in type 2 Diabetes, it is to note that, some demonstrate higher benefits in associated cardiovascular disease. For example, GLP-1 and SGLT-2 drugs demonstrate renal and cardiovascular benefits and should be considered in those diabetic subjects with associated CKD and or heart disease (73,74).

Antihypertension therapy

The European Society of Vascular Surgery (ESVS) recommends, with a Class 1 A, blood pressure of $\leq$ 120 – 129/80 mmHg in patients < 70 years and $\leq$ 130 – 139/80 mmHg in patients $\geq$ 70 years in those with PAD to reduce MACE (2). Apart from dietary restrictions and lifestyle changes, antihypertensive are usually needed and recommended to reduce blood pressure. Standard approach is usually offered by single pill with a dual combination therapy,

usually consistent of angiotensin converting enzyme inhibitor/ angiotensin receptor blocker plus dihydropyridine calcium channel blocker (75). In some cases, added diuretic therapy might be required.

A study trial, showed benefits of Ramipril therapy in reducing risk of myocardial infarction, stroke, or death from cardiovascular causes in those subjects with symptomatic and asymptomatic PAD(76), an antihypertensive therapy choice perhaps to be considered in those subjects at a high risk of CV disease.

Lipid lowering therapy

Lipid lowering agents, should be considered in all subjects with PAD, not only to decrease levels of cholesterol but to treat underlying concomitant CV diseases. LDL target values are recommended at ≤ 1.4 mmol/L (55 mg/dL) (77) to reduce MACE and major adverse limb events (MALE) in symptomatic PAD. Benefits for asymptomatic PAD are understudied, but lipid lowering agents are also recommended to avoid associated cardiovascular events. ESVS guidelines recommend high intensity statin treatment in both subgroups, symptomatic and asymptomatic PAD in order to reduce CV events, limb events and progression of the disease, with recommendations Class 1A and Class I C subsequently (2).

Statins, inhibitors of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme are the main pharmacological therapy used in PAD. Studies have demonstrated the benefit of simvastatin in reducing major vascular events, relative reduction rate of 22% (95% CI: 15 – 29) (78) and the use of simvastatin has also been shown to improve total walking distance and pain free walking distance with a weighted mean difference (WMD) 152 m; (95% CI:32.11 to 271.88) and WMD 89.76 m (95% CI:30.05 to 149.47) in a Cochrane Review (79). Newer statins, such as , atorvastatin and rosuvastatin, have been shown more effective in lowering lipid levels and are now becoming the statin of choice in treating PAD subjects, with recommended doses of 40-80 mg atorvastatin and 20-40 mg Rosuvastatin (80).

Ezetimibe is another lipid lowering therapy that acts inhibiting the absorption of cholesterol in the intestines. When used with statins, generates in added benefit, especially in those subgroups of PAD with coronary artery disease (CAD). Christopher et al, in a double blinded randomized trial with more than 18,000 patients hospitalized for CAD, compared simvastatin+ezetimibe versus simvastatin alone for overall reduction of cardiac events. A

32.7% Kaplan-Meier event rate in the simvastatin-ezetimibe group was observed, compared with 34.7% in the simvastatin alone (HR, 0.936; 95% CI: 0.89 to 0.99; P=0.016) (81).

Overall, high intensity statins is recommended as first line treatment in PAD and in those subjects who are unable to reduce lipid level despite statin treatment, the addition of ezetimibe is recommended (2).

Recent studies have been focusing on PCSK9 inhibitors such as evolocumab, alirocumab and its possible effect on cardiovascular events when added with statins, but further studies must be performed for clear conclusions (82).

Antithrombotic therapy

Multiple studies have shown the benefit of antiplatelet therapy in PAD in reducing MACE and it is strongly recommended for all patients with PAD to be on antiplatelet therapy. Initially studies favoured low dose aspirins, 75-150 mg daily, that proved to be effective and at a low risk of bleeding(83). Yet in the recent years more studies have been conducted in reviewing alternatives to aspirin, such as clopidogrel, ticagrelor and vorapaxar. All of these have shown to reduce MACE although some are associated with elevated bleeding risk, such as vorapaxar that showed an increased risk for intracranial haemorrhage (84). Despite all of these showing benefits in preventing MACE, none of them have shown to be superior to clopidogrel and, in a recent meta-analysis, clopidogrel in monotherapy was found to be the safest and most effective (85).

Antiplatelet agents also have a role in secondary prevention after surgical treatment, which will be described further on.

As for systemic anticoagulation in PAD, it is not recommended in *asymptomatic* PAD. But more studies are beginning to evaluate low dose of rivaroxaban of 2.5mg, twice a day with antiplatelet agents, showing initial benefits in preventing MACE (86). The recent Voyager Trial, was one of them and evaluated rivaroxaban and aspirin in PAD who had undergone revascularization, and lower incidence of MALE and MACE was observed in the rivaroxaban+aspirin group compared to aspirin as monotherapy (87). Primary efficacy at 3 years were 17.3% in the rivaroxaban groups and 19.9% in the placebo group, (HR, 0.85, 95% CI, 0.76 to 0.96; P=0.009). Although efficacy is higher in rivaroxaban group, so was the risk of bleeding, with mayor bleeding occurring in 5.94% and 4.06% respectively; (HR, 1.42; 95% CI, 1.10 to 1.84; P=0.007) (87).

Once the diagnose of PAD is made (ABI ≤0.9) and general lifestyle modifications have been advised; treatment of PAD symptoms is initiated. There are different strategy of treatments, pharmacological and surgical, that are offered between Fontaine classification I and II and Fontaine classification III-IV or CLI.

1.7.2. Pharmacotherapy

Pharmacotherapy in treating IC is aimed to improve walking capacity and distance. The most common drugs used are pentoxifylline, cilostazol and naftidrofuril.

Pentoxifylline is xanthine derivative and acts by reducing blood viscosity through different mechanisms. This improves blood flow to muscle helping with IC. Although it is still widely used, it seems to be the least effective of the three, shown in different comparison studies. A 2015 Cochrane review concluded there was no high quality dated to confirm the effects of pentoxifylline in IC (88). Similar conclusions were affirmed in a more recent review (89).

Cilostazol is a phosphodiesterase inhibitor with antiplatelet and vasodilator properties. It has been shown to be effective in IC by improving walking distance but common side effects such as headaches are to be advised when taking this medication (90).

Naftidrofuril serotonin 5-HT2 receptor antagonist. It is shown to be the most effective drug on maximum pain free walking distance when compared to cilostazol and pentoxifylline in systematic review by Stevens et al (91). Recommended dosage is of 300 to 600mg/day (92).

In summary, guidelines recommend nafdtidrofuryl or cilostazol to improve IC symptoms, in the case that improvement is not observed, treatment should be stopped after three to six months (2).

1.7.3. Surgical treatment

Surgical treatment in intermittent claudication

Invasive surgical treatment in PAD are usually reserved for CLTI or certain cases of disabling limited IC and after exhausting other medical treatment options. The aim of vascular surgical intervention is limb salvage and the best surgical option can vary depending on the type and location of lesion (TASC) and the patient's individual characteristics.

Surgical treatment in chronic ischemia Fontaine II, should only be considered after exhausting all other medical treatment options and should be carefully evaluated. ESVS guidelines provides us with a list of principal factors that should be carefully evaluated before deciding on surgical intervention, these factors include general diagnosis and patient education on their disease, to risk factor assessment and treatment, as well as expected surgical benefits, general surgical risk and possible long term complications , among others (2)

Surgical treatment in critical limb threatening ischemia

Surgical revascularization should be considered in all patients with critical limb threatening ischemia (CLTI) in an attempt to provide direct blood flow to the foot, targeting angiosomes if possible. CLTI is classified as Fontaine classification III and IV and are at a higher risk for limb loss, hence the importance of evaluating revascularization. The WIFI classification has been proposed to help stratify patients with rest pain and lesion in order to help assess risk of amputation(93).

The “Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL 1)” trial. Initially, showed no difference in terms of amputation free survival between endovascular versus bypass at 2 years, but a higher survival and amputation free rate was seen at 5 years in the bypass group (94). BASIL 2 trial favoured endovascular treatment in infra popliteal lesions, which showed higher amputation free rates compared to open surgery (95).

The “Best Endovascular versus Best Surgical Therapy for Patients with Critical Limb Ischemia” (BEST-CLI), a more recent multicenter prospective trial, showed better results in the surgical group than ¨endovascular first¨ approach when suitable anatomy was present, with a higher MALE events or all-cause mortality seen in endovascular group, 57.4%, versus 42.6% in surgical group ($P < 0.001$). Fewer re intervention rates, fewer medical events related to CLTI and fewer above the ankle amputations were also observed in the surgical group, (65%, 32%, and 27%) (96).

With all the different treatment options and data available, there is still no ¨one fits all¨ treatment for CLTI patients. Treatment options can depend on many factors, such as suitable anatomy, patient’s characteristics, surgeon skill, hospital resources and many more. Various approaches can be available for each case and the decision on how to treat personalized to each patient.

2. Justification

Justification

An important increase in PAD prevalence has been observed over the years, with 237 million cases worldwide in 2015 and over 17 million of them are asymptomatic (2,5). Higher morbid-mortality rates are seen in PAD subjects due to its correlation with associated cardiovascular disease, with 40 % of those with PAD dying from coronary artery disease and up to 20% of cerebrovascular disease (3).

In Europe, prevalence's of up to 18% have been seen in age groups as young as 45 years old (3). However, in Spain, relatively lower prevalence's have been described, the ESTIME study, estimated prevalence of PAD to be 8.03% and in Barcelona, Alzamora et al, showed a prevalence of 7.6% in those subjects 49 years and older (97,98).

Prevalence of PAD can be influenced by many factors as shown before and even underdiagnosed in some cases, it can also vary significantly in age and demographic region.

Due to the nature of presentation of this disease and its important correlation with other cardiovascular diseases, an early diagnosis and prompt treatment is important for preventing associated cardiovascular morbid mortality.

AHA ACC guidelines states that North Americans at 65 years in age have a 1 in 5 chance of developing PAD and consider recommend screening with ABI in this age group (99).

We believe it's important to know the prevalence of PAD as well as its associated risk factors in our area of treatment in order to identify those groups at a higher risk, this way being able to provide effective treatment plans as well as screening programs and secondary preventative strategies that are focused on these subgroups. Identifying these subjects, is the first step in controlling the progression of this disease and its associated morbid mortality.

To our knowledge, most studies of prevalence of PAD in our region were inclusive of younger age groups and perhaps underestimate our current reality

3. Hypothesis

Hypothesis

We hypothesized that the prevalence of PAD in our area of treatment will be higher than the estimated prevalence in the Catalunya region, due to the older age population base in our region of treatment. We believe since most Catalunya studies include younger age groups, thus fewer risk factors, it might have underdiagnosed our population's prevalence of PAD and this study might not reflect our current reality, in Barcelona Nord.

4. Objective

Objective:

4.1. Main objective:

- Identify the overall prevalence of PAD in asymptomatic males and females of 65 years old in age, in Barcelona Nord.

4.2. Secondary objectives:

-Identify associated risk factors in male and female subjects in our region of treatment, Barcelona Nord.

-Determine difference of prevalence PAD in females and males subjects of Barcelona Nord.

-Determine the risk of cardiovascular event in 10 years with REGICOR in Barcelona Nord.

5. Method and material

Method and material

Study design:

This thesis is based on a single – center, population – based, cross – sectional study that was part of a larger pilot screening program, also evaluating abdominal aortic aneurysm(100).

Patient selection:

This study was performed in our hospitals designated area of treatment, health- integrated area (AIS) Barcelona Nord, with a population base of 400,000 inhabitants.

Inclusion criteria

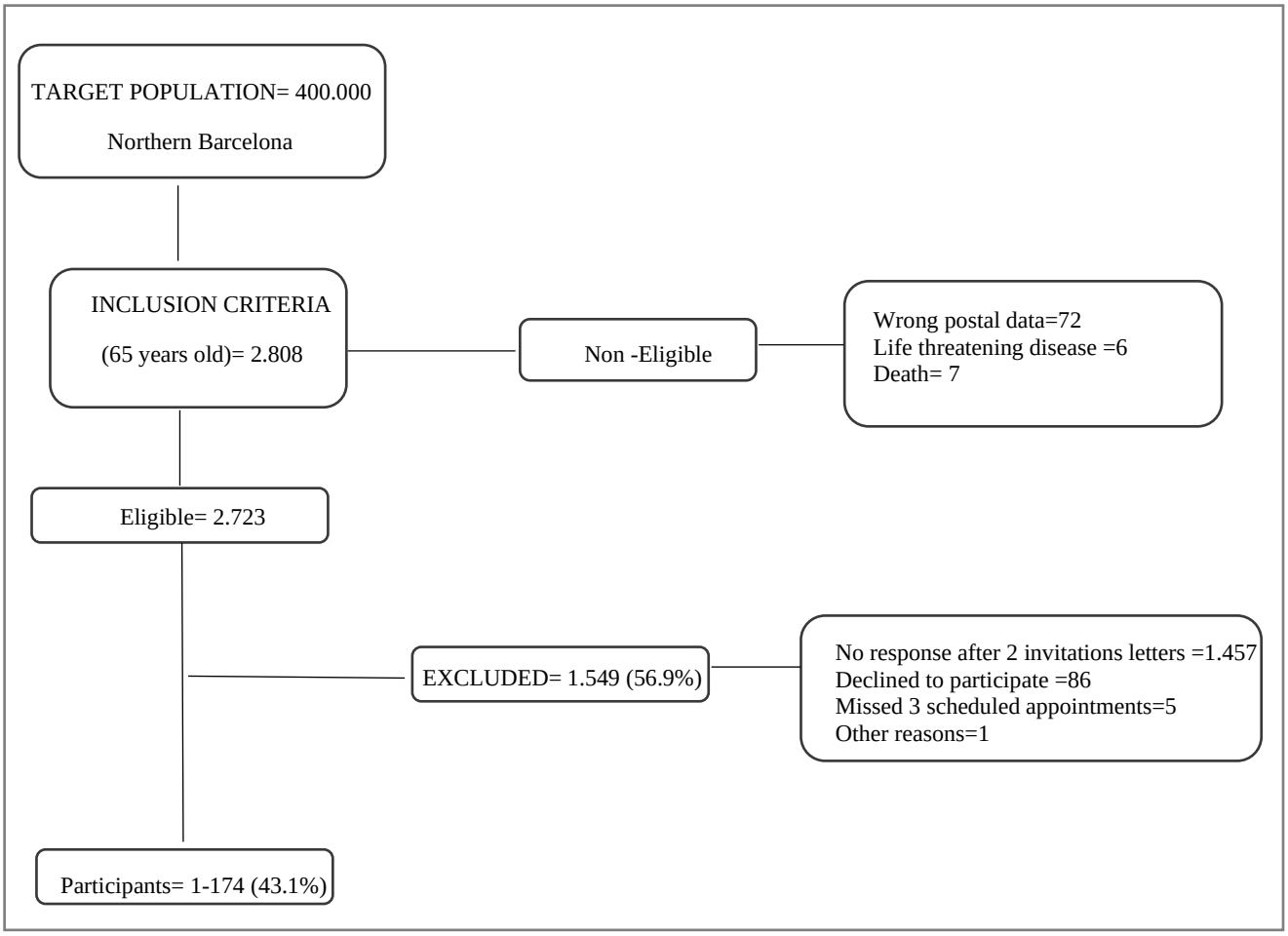
We included all asymptomatic, noninstitutionalized males and females of 65 years in age, who were healthcare cardholders during the time of recruitment and resided for a minimum of 6 months in the designated area.

Inhabitants contact information were previously authorized and obtained through our public health census registry and those eligible, were sent invitation letters to participate in our study. Incase no response was received with the first letter; a second letter was sent again at 1 month. Those who agreed to participate were scheduled an appointment at our center's outpatient Vascular lab, with one of our five trained vascular surgeon residents. Attendance was confirmed 48 hours before scheduled appointment, and in the case of a cancelation, three more attempts were made before excluding the subject. At our outpatient Vascular lab, a full vascular interview was conducted, and vascular physical exam was performed as well as an ABI. Description of initial inclusion is described in Figure B.

Exclusion criteria

We excluded those subjects who had an incorrect postal address, terminal disease or were deceased, as well as those who did not respond to the invitation letters after both tries. Those who did not wish to participate were also excluded and those who an ABI exam could not be performed due to major amputation or extensive skin ulcerations.

Figure B: Flowchart of inclusion criteria



Gonçalves-Martins G, Gil-Sala D, Tello-Díaz C, Tenezaca-Sari X, Marrero C, Puig T, Gayarre R, Fité J, Bellmunt-Montoya S. Prevalence of Peripheral Arterial Disease and Associated Vascular Risk Factors in 65-Years-Old People of Northern Barcelona. J Clin Med. 2021 Sep 28;10(19):4467. doi: 10.3390/jcm10194467. PMID: 34640483; PMCID: PMC8509737.

Vascular lab evaluation

Upon arrival at our vascular lab outpatient setting, a signed consent formed was provided and signed by each participant before proceeding. Afterwards, a complete history was taken evaluating the following risk factors:

-Cigarette smoking: active, former (≥ 1 year without smoking) or non-smoker.

-Hypertension: considered those with systolic blood pressure ≥140/90mmHg or those with antihypertensive medication.

-Hyperlipidaemia: considered with the presence of at least one of the following, total blood cholesterol >200mg/dL, LDL cholesterol >100mg/dL, and/or triglycerides levels >150mg/dL or those subjects with lipid lowering agents.

-Diabetes: diagnosed and/or with anti-hyperglycaemic treatment.

-History of cerebrovascular disease (stroke or transient ischemic cerebral accident).

-History of cardiac ischemia (coronary artery disease or previous myocardial infarction).

-Chronic renal disease: (Glomerular filtration rate<60mL/min).

-History of any aortic aneurysmatic disease.

After complete history was taken, anthropometric measurements were also noted, such as subject's height (m), weight (kg), waist circumference (cm) and body mass index (BMI). A REGICOR (Girona Heart Registry)(101) score was calculated in these subjects. REGICOR is a computer-generated score obtained through a serious of data info, such as age, sex, history of smoking, presence of diabetes, blood pressure, total cholesterol and HDL levels, this generates a score that assess the risk of presenting a cardiovascular event in the following 10 years (101,102). The results are as follows; scores <5%: low risk, 5-9% moderate risk, and scores >10% are considered at a high risk. A REGICOR score was determined for each individual discarding those who already had presented with a cardiovascular event.

Physical exam

A complete vascular physical exam was performed in each participant where the presence of distal pulses was palpated. The presence of at least one distal tibial artery pulse per limb was considered adequate. Furthermore, and ABI exam was performed in a standard fashion in all participants.

ABI exam

An ankle brachial index was performed in all participants after a 5 min rest in the supine position. An arterial pressure cuff was places above the malleoli and the systolic blood pressure was measured at the level of anterior and posterior tibial arteries as well as at the level of both brachial arteries with a continuous wave Doppler probe (Flowsoft 7 angiolab Spread Doppler Systeme,Kehl,Germany). The ratio between the systolic pressure of the tibial arteries and highest brachial systolic pressure was calculated and recorded for both extremities. ABI of $\leq$0.9 in one or both lower extremities were considered pathological and an indication of PAD. ABI > 1.4 were registered for future studies.

After each assessment a signed report was given to each participant with their ABI results, those ABI considered pathological were also given recommendations for treating modifiable risk factors as well as an indication for follow up with their primary care center. In those subjects who presented with critical limb ischemia considered as, rest pain or ischemic lesions were immediately sent to vascular emergency room for evaluation.

Statistical analysis

Statistical analysis was performed through IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

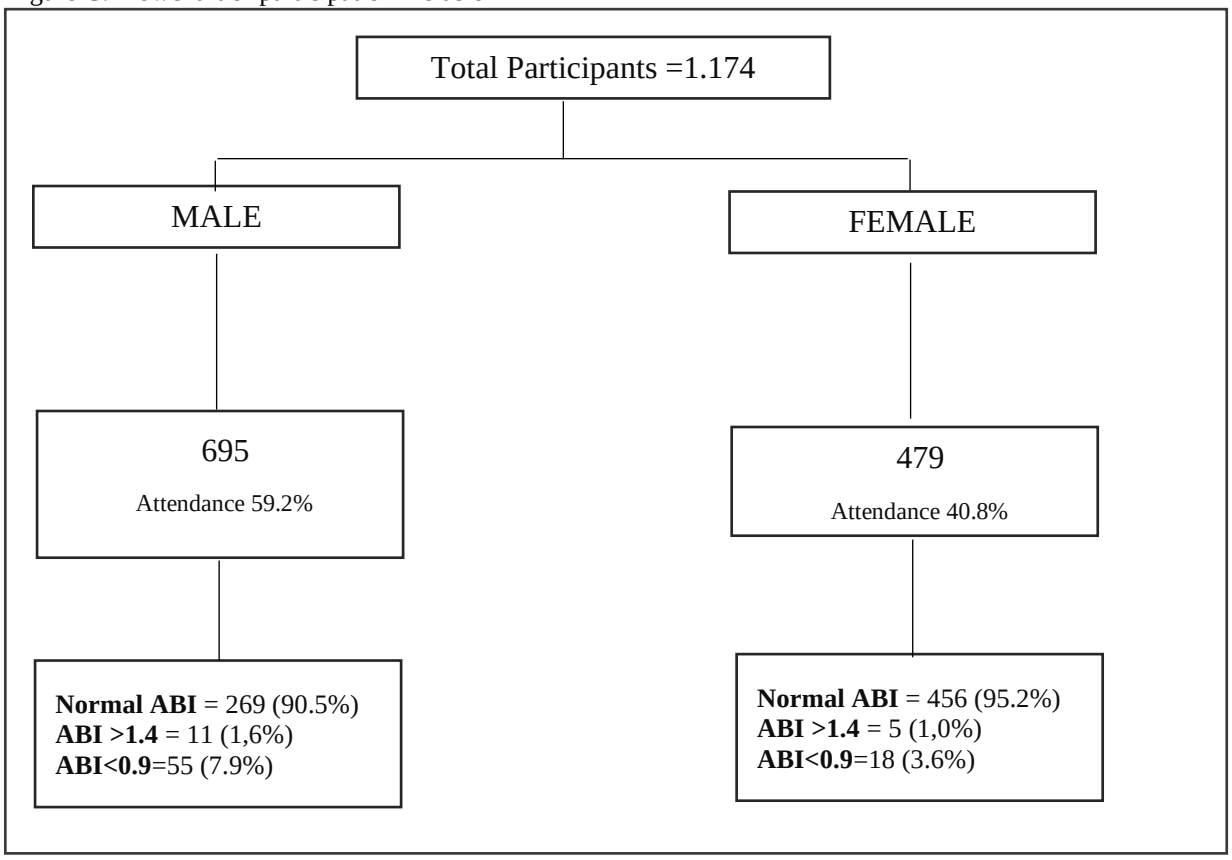
A descriptive analysis was performed and a prevalence of PAD with 95% confidence interval was obtained. Pearsons chi-square test or Fisher s exact test was used to analyse dichotomous variables. For those risk factors who were significant in the bivariate analysis, a logistic regression model was used to obtain independent associated risk factors for PAD. Interaction effect was also evaluated among these risk factors. And statistically significant results were considered in those values of p <0.05.

6. Results

Results

A total of 2.808 subjects were 65 years old during the time of the recruitment and were invited. A total of 1.174 individuals were finally included, mostly males, 695 (59.2%) male and 479 (40.8%) females. Higher participation rates were seen in females (46.7%) compared to males (40.9%) with a total participation rate of 43.1%. Flow chart of initial selection can be seen in Figure C.

Figure C: Flowchart of participation inclusion



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In our study, fewer women were smokers ($p<0.001$), and our male participants had more risk factors, presenting with higher percentages of diabetes ($p<0.001$), high blood pressure ($p<0.0001$), cardiac ischemia ($p<0.001$) and chronic renal disease ($p=0.001$). The major clinical manifestation was of Fontaine I classification, (n = 53, 72.6%), 20.5% IIA (n = 15), 5.5% IIB (n = 4) and 1.4% (n = 1). Characteristics of all participants can be seen in Table 4.

Table 4 Means and proportions of selected characteristics in the screened population separated by sex.

	TOTAL (n=1 174)	MALE (n=695)	FEMALE (n=479)
CARDIOVASCULAR RISK FACTORS% (N)			
Non-Smokers [a]	48.6% (570)	35.0% (243)	68.3% (327)
Active smoker	14.8% (174)	71.8% (124)	10.4% (50)
Former smoker	36.6% (430)	47.2% (328)	21.3% (102)
Relative's history of AAA	3.0% (35) *	2.3% (16)	4% (19) *
First Degree	74.3% (26)	87.5% (14)	63.2% (12)
Second Degree	14.3% (5)	12.5% (2)	15.8% (3)
Diabetes Mellitus [a]	17.7% (208)	23.2% (161)	9.8% (47)
Dyslipidaemia	46.3% (544)	45.9% (319)	47% (225)
Hypertension [a]	47.8% (561)	52.9% (368)	40.3% (193)
Chronic Renal Disease [a]	4.1% (48)	5.8% (40)	1.7% (8)
CARDIOVASCULAR EVENTS % (N)			
Cardiac Ischemia [a]	6.4% (75)	9.8% (68)	1.5% (7)
Cerebrovascular events	4.3% (50)	4.9% (34)	3.3% (16)
Intermittent claudication	3.8% (45)	4.5% (31)	2.9% (14)

ANTHROPROMETIC MEASUREMENTS % (N)

Waist circumference (cm) [b] (SD)	99.5 (12)	102.4 (10.9)	95.3 (12.3)
Mean BMI (kg/m^2) (SD)	27.7 (4.3)	27.8 (3.8)	27.6 (4.9)
Normal weight [a] (BMI 18.5-24.9)	28.3 % (332)	24.2% (168)	34.2% (164)
Overweight (BMI 25-30)	46.3% (543)	51.4% (357)	38.8% (186)
Obesity (BMI >30)	25.5% (299)	24.5% (170)	26.9% (129)

* 4 of these, unknown degree [a] P value <0.001. Pearson´s Chi Square [b] P value <0.001 Student´s T Test Percentage (n). Mean and standard deviation

The overall prevalence of PAD in 65-year-old of Barcelona Nord, was 6.2% (95% CI: 4.8-7.6%), 7.9% (95% CI: 5.9-9.9%) in males and 3.8% (95% CI: 2.1-5.5%) in females. Difference in prevalence in male and female was statistically significant (p=0.006), with male subjects presenting a higher risk for PAD, with an OR of 2.2 (95% CI:1.3–3.8).

There was a total of 18 ABI >1.4 and two of them had ABI <0.9 in the contralateral leg, of the remaining 16 (ABI >1.4), 6 had diabetes and none had chronic renal disease, all but one had a palpable distal pulse, and all were asymptomatic.

Diabetic male subjects (p=0.017), were more likely to have PAD along with hypertensive female participants (p=0.026). Table 5: shows risk factors presented in PAD and non-PAD separated by gender.

Table 5: Relationship between PAD and Non-Pad risk factors separated by gender. Logistic regression model with OR and CI 95% of the potential variables associated with PAD

	Male					Female				
	Non-PAD (n = 640)	PAD (n = 55)	Total (n = 695)	OR * (95% CI: **)	p [a]	Non-PAD (n = 461)	PAD (n = 18)	Total (n = 479)	OR (95% CI: **)	p [a]
Non-smoker	237 (37.0%)	6 (10.9%)	243 (35.0%)	1	<0.001	320 (69.4%)	7 (38.9%)	327 (68.3%)	1	0.02
Former smoker	299 (46.7%)	29 (52.7%)	328 (47.2%)	3.8 (1.6–9.40)	0.003	96 (20.8%)	6 (33.3%)	102 (21.3%)	2.9 (0.9–8.7)	0.065
Active smoker	104 (16.3%)	20 (36.4%)	124 (17.8%)	7.6 (3.0–19.5)	<0.001	45 (9.8%)	5 (27.8%)	50 (10.4%)	5.1 (1.5–16.7)	0.007
Cardiovascular risk factors n (%)										
Diabetes	141 (22.0%)	20 (36.4%)	161 (23.2%)	2.0 (1.1–3.6)	0.017	43 (9.3%)	4 (22.2%)	47 (9.8%)	2.8 (0.9–8.8)	0.083
Dyslipidemia	293 (45.8%)	26 (47.3%)	319 (45.9%)	1.1 (0.6–1.8)	0.831	215 (46.6%)	10 (55.6%)	225 (47.0%)	1.4 (0.6–3.7)	0.459
Hypertension	340 (53.1%)	28 (50.9%)	368 (52.9%)	0.9 (0.5–1.6)	0.752	181 (39.3%)	12 (66.7%)	193 (40.3%)	3.1 (1.1–8.4)	0.026
Chronic Renal Disease	37 (5.8%)	3 (5.5%)	40 (5.8%)	0.9 (0.3–3.2)	0.920	8 (1.7%)	0 (0%)	8 (1.7%)	0	0.9
Cardiac Ischemia	59 (9.2%)	9 (16.4%)	68 (9.8%)	1.9 (0.9–4.1)	0.092	6 (1.3%)	1 (5.6%)	7 (1.5%)	4.5 (0.5–39.1)	0.177
Cerebrovascular Events	31 (4.8%)	3 (5.5%)	34 (4.9%)	1.1 (0.3–3.8)	0.840	16 (3.5%)	0 (0%)	16 (3.3%)	0	0.9
Anthropometric measurements mean (SD)										
Waist Circumference (cm)	102.4 (SD 11.0)	103.6 (SD 9.4)	102.5 (SD 10.9)	1.01 (0.99–1.04)	0.410	95.1 (SD 12.1)	102.4 (SD 15.9)	95.3 (SD 12.3)	1.05 (1.01–1.09)	0.018

Data are expressed as n (%) or mean (standard deviation); * OR: odds ratio; ** CI: confidence interval; [a] Wald test's p-values of logistic regression.

In the logistic regression model an independent association for PAD was seen in male smokers, with an OR of 7.2 (95% CI:2.8–18.6) in active smokers,3.5 (95% CI:1.4–8-7) in former smokers, compared to non –smokers.

An association with diabetes and PAD was also seen in our male participants, OR of 1.8 (95% CI: 1.0–3.3).

In our female participants, there was also a relation with PAD and smoking: (>OR of 5.2 (95% CI:1.6–17.3) in active smokers, 3.1 (95% CI:1.0–9.6) in ex-smokers, compared to non-smokers. And PAD was also seen in higher in hypertensive female participants OR of 3.3 (95% CI:1.2–9.0). No mediation effect was observed with gender and no interaction effect was observed among the variables. Table 6: shows the logistic regression analysis of PAD risk.

Table 6. Logistic regression risk of PAD.

Male		Female	
Variables	OR (95% CI)	Variables	OR (95%CI)
Non smokers	1	Non smokers	1
Former Smokers	3.5 (1.4-8.7)	Former Smokers	3.1 (1.0-9.6)
Active Smokers	7.2 (2.8-18.6)	Active Smokers	5.2 (1.6-17.3)
Diabetes	1.8 (1.0-3.3)	High blood pressure	3.3 (1.2-9.0)

*CI: Confidence interval. OR: Odds Ratio

In regard to REGICOR score, 157 participants had already presented with cardiovascular event and were discarded and 4 were eliminated due to missing data, therefore a total of 1.013 participants were evaluated for their REGICOR score. A 51.4% (*n* = 500) were at low risk, 40.4% (*n* = 393) were at a moderate risk and 8.1% (*n* = 79) were at a high-risk for developing a cardiovascular event in the next 10 years. Male subjects presented with higher REGICOR score ($p<0.001$) than our female participants.

Finally, our studies total participation rate was due to a less than 50% participation rate, we decided to further analyze our data risk factors with those obtained from the Official health department database-2018 Catalan Health Survey ¨*EnQuest Catalunya de Salut 2018*¨ (ESCA) ages 65-74 years old and primary care centers located in our region of treatment, Barcelona Nord. In table 7, risk factors from our study and those from ESCA database and from primary care centers can be seen. Similar risk factors were seen among all three data bases demonstrating how our sample was representative of Barcelona Nord population at 65years.

Our article with our explained findings can be found in the Annex section.

Table 7. Characteristics of our study participants and participants of Catalunya health survey 2018 (ESCA) and Primary care centres of our region of study separated by sex.

	Our Study Participants (65 Years Old)			**ESCA 2018 (65–74 Years Old)**			**Primary Care Centers (65 Years Old)**		
	Male (*n* = 695)	**Female (*n* = 479)**	**Total (*n* = 1 174)**	**Male (*n* = 206)**	**Female (*n* = 224)**	**Total (*n* = 430)**	**Male (*n* = 1653)**	**Female (*n* = 1994)**	**Total (*n* = 3647)**
Active smoker	17.8% (15.0–20.7)	10.4% (7.7–13.2)	14.8% (12.8–16.9)	18.0% (12.7–23.2)	8.0% (4.5–11.6)	12.8% (4.5–11.6)	20.8% (18.8–22.7)	13.4% (11.9–14.9)	16.8% (15.5–17.9)
Diabetes mellitus	23.2% (20.0–26.3)	9.8% (7.2–12.5)	17.7% (15.5–19.9)	27.2% (21.1–33.3)	20.1% * (14.8–25.3)	23.5% * (19.5–27.5)	23.1% (21.0–25.1)	12.8% * (11.4–14.3)	17.5% (16.2–18.7)
Dyslipidemia	45.0% * (42.2–49.6)	47.0% (42.5–51.4)	46.3% (43.5–49.2)	34.5% * (28.0–41.0)	46.0% (39.5–52.5)	40.5% * (35.8–45.1)	39.4% * (37.1–41.8)	41.7% * (39.5–43.8)	40.7% * (39.1–42.3)
Hypertension	53.0% (49.2–56.7)	40.3% (35.9–44.7)	47.8% (44.9–50.6)	50.5% (43.7–57.3)	48.2% * (41.7–54.8)	49.3% (44.6–54.0)	53.8% (51.4–56.2)	62.9% * (60.8–65.1)	58.8% * (57.2–60.4)
Chronic renal disease	5.8% (4.0–7.5)	1.7% (0.5–2.8)	4.1% (3.0–5.2)	5.8% (2.6–9.0)	6.3% * (3.1–9.4)	6.1% * (3.8–8.3)	4.1% (3.1–5.0)	2.3% (1.6–2.9)	3.1% (2.5–3.6)
Cardiac ischemia	9.8% (7.6–12.0)	1.5% (0.4–2.5)	6.4% (5.0–7.8)	7.3% (3.7–10.8)	2.2% (0.3–4.2)	4.7% (2.7–6.6)	8.1% (6.8–9.4)	1.8% (1.2–2.4)	4.7% * (3.9–5.4)
Cerebrovascular events	4.9% (3.3–6.5)	3.3% (1.7–5.0)	4.3% (3.1–5.4)	5.8% (2.6–9.0)	2.7% (0.6–4.8)	4.2% (2.3–6.1)	3.1% (2.3–3.9)	1.4% (0.9–1.9)	2.1% * (1.7–2.6)
Overweight (BMI 25–30)	51.4% (47.7–55.1)	38.8% (34.5–43.2)	46.3% (43.4–49.1)	46.6% (39.8–53.4)	42.0% (35.5–48.4)	44.2% (39.5–48.9)	38.2% * (35.8–40.5)	30.9% * (28.9–33.0)	34.2% * (32.7–35.8)
Obesity (BMI >30)	24.5% (21.3–27.7)	26.9% (23.0–31.0)	25.5% (23.0–28.0)	27.2% (21.2–33.3)	17.4% * (12.4–22.4)	22.1% (18.2–26.0)	27.7% (25.6–29.7)	29.5% (27.5–31.5)	28.7% * (27.2–30.2)

Values are presented as percentages (95% Confidence Interval); Pearson's chi-square analysis; * Difference in values among both studies.

7. Discussion

Discussion

The overall prevalence of PAD in asymptomatic subjects at 65 years was 6.2% (95% CI: 4.8-7.6%). In male subjects prevalence of PAD was 7.9% (95% CI: 5.9–9.9%) and in females 3.8% (95% CI: 2.1–5.5%) in Barcelona Nord. As mentioned before, the prevalence of peripheral arterial disease varies among different age groups, gender, economical background, ethnicities and even demographic regions, and its association with common risk factor and other important cardiovascular disease makes for an important socio economical health burden. In today's aging population, it is important to be aware of this pathology. We believe prevention is key in treating this disease. Identifying those of risk in your hospitals area of treatment can be helpful in providing an early diagnosis and treatment of modifiable risk factors, thus lowering future limb complications as well as overall cardiovascular morbid- mortality.

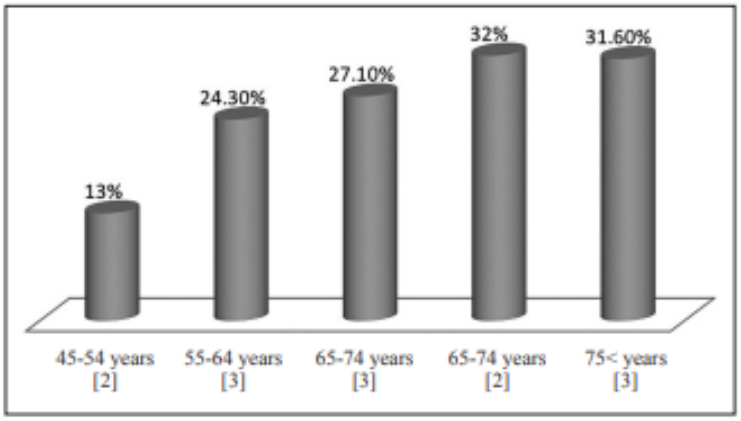
7.1. Prevalence

7.1.2.Demographic region and age

Across Europe the prevalence of PAD varies considerably. The PANDORA study showed prevalence across 6 European countries, estimating the highest prevalence of 28% in Greece followed by Italy with 22.9% and the lowest prevalence was seen in Belgium with only 7% (3). It also showed an overall estimated PAD in Europe at 17.8% (99% CI: 16.8–18.8%) between the ages of 45-55 in the northern region of Europe (3).

In the same PANDORA study, a 13% increase in prevalence's was seen in those 65-74 years old, age being an independent risk factor for PAD in this study and 17.8% of those with PAD, were asymptomatic(3). Similar increases with age were also seen in a French study, where Cacoub et al, showed an increase from 24.3% to 27.1% to 31.6% in those 55-64 years old , 65-74 years old and over 75 years old respectively(4) Figure D.

Figure D : Prevalence's of PAD with increase in age.



Olinic DM, Spinu M, Olinic M, Homorodean C, Tataru DA, Liew A, Schernthaner GH, Stanek A, Fowkes G, Catalano M. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. Int Angiol. 2018 Aug;37(4):327-334. doi: 10.23736/S0392-9590.18.03996-2. PMID: 29936722.

In Germany, prevalence as low as 3% are seen in subjects between the ages of 45-49 years in age, yet an increase of almost 6 times is seen in ages between 70-75 years, showing an estimated 18% prevalence in this age group (103). The same prevalence was also seen in age group, 60-90 years, in Sweden (104). In the Edinburg Artery study, 9% prevalence in those 55-74years with 84% without exertional leg symptoms (105).

The estimated prevalence of PAD in Spain, is considerably lower compared to other regions in Europe. The ESTIME Study, a cross -sectional study that included 12 different Spanish regions, with participants in ages 55-84 years old, found overall prevalence to be 8.03% (97). In Catalunya, Velescu et al, in the REGICOR study, reported prevalence's as low as 4.5%, in age groups 35-79 years old and Alzamora et al in the Perart/Artper study, described prevalence of 7.6% in those >45 years(98,102).

It is well demonstrated across all these different epidemiological studies, how PAD increase with age and its variability in each demographic region.

Our studies do concur with prevalence's observed in Spain and throughout some of Catalunya studies, despite our initial doubt due to the younger age groups included in most of Catalunya Studies.

Our overall prevalence at 65 years old was a 6.2% (95% CI: 4.8-7.6%), similar to other Catalunya's studies. As we age, the longer the exposure to risk factors that lead to cellular damage that promote atherosclerosis and its diseases therefore an increase in prevalence would be expected in older age groups. But perhaps it would also be interesting to evaluate the prevalence of PAD in our region in younger age groups. The earlier we identify PAD and its associated risk factors the earlier we can start prevention that can help lower the incidence of limb and cardiovascular complications.

7.1.3.Gender

Although PAD is initially thought to occur predominantly in male subjects, women are just as affected by this pathology as their male counterparts. Traditional risk factors are common among both genders, but male subjects are associated with a higher all-cause mortality (107,108). Studies also suggest better surgical outcomes in treatment for PAD in males' subjects compared to females (108).

PAD in women tend to be asymptomatic or presents with atypical symptoms leading to a late diagnosis. In some studies PAD in women presented 10-20 years later than in men (109). Rotterdam study showed an increase in PAD in males from 6.6% to 52, 0% from the age's 55-59years to 85 years and in women an increase from 9.5% to 59.6% in the same corresponding age groups (29).

The reason for this late presentation is thought to be the loss of estrogen with aging women. Estrogen is known to have vascular protective effect that helps with vasodilation and anti-oxidative property (110). As estrogen levels go down in perimenopause, women lose their protective role leading to a higher incidence of PAD during this time. Some studies even suggest treatment with hormone replace therapy (HRT) in preventing PAD in older women. Rotterdam study initially showed a decrease of 52% of PAD in women who had taken HRT for >1 year (29). Although in other studies this benefit was not shown (111–113).

Sigvant et al showed higher prevalence's in women with asymptomatic PAD, 12.6% versus 9.4% in males (p=.03) and in CLI with 1.5% versus 0.8% (p<.008) respectively, it is to note this study included ages between 60 and 90 years old (114).

An increase of prevalence has been observed in elderly women with some studies suggesting a 30% increase in women over 70 years old (108,115). The presence of atypical symptoms also plays a role in the delayed diagnosis in women.

Although PAD in male patients have been associated with a higher all-cause mortality (HR 1.13; 95% CI:1.10-1.16;P < .001) and MACE (HR,1.10; 95% CI:1.06-1.14;P < .001) shown in a systematic review presented by Parvars group (108), women patients tend to present with a faster decline in quality-of-life developing symptoms of depression and even tend to have worst outcomes than their male counterparts (114).

In our study, 3.8% (95% CI: 2.1–5.5%) females at 65 years old presented with a diagnosis of PAD compared to a 7.9% (95% CI: 5.9–9.9%) in males. Curiously we had a higher participation rate from females (46.7%) than males (40.9%).

The lack of awareness among our population, its late onset of the disease as well as its atypical symptoms are possibly what contributes to the worst outcome present in our female patients. We believe that educating our population about this disease and emphasizing on the atypical symptoms presentation in women might be a way for us to diagnose this disease more effectively and early on in our women patients.

It would be interesting to re-evaluate our female participants in 5 to 10 years to see any new onset of PAD.

7.1.4.Race

Disparity between PAD and race is also observed. A meta-analysis review showed higher prevalence's of PAD among the black race ($p < 0.001$), than in whites and Asians, with PAD prevalence of 6.7%, 3.5% and 3.6% respectively (116). In the same meta-analysis this was also true for diabetic subject with PAD, showing a higher prevalence in Blacks diabetics 25.3% and in diabetic Asian population the lowest prevalence compared to whites ($p < 0.001$) (116).

In the United States, three major ethnic cohorts, The National Health and Nutrition Examination Survey (NHANES) (117), San Diego Population Study (SDPS) (118), and Multi-ethnic Study of Atherosclerosis (MESA) (31), also observed higher prevalence of

PAD in Black Americans, 7.8% in NHANES, 7.8% SDPS and 7.2% MESA followed by European Americans, 4.5%, 3.9% and 3.6% respectively (119). Black Americans also debut with a more severe PAD than other races and worst outcomes (120). This can be in part because of higher prevalence's of cardiovascular risk factor seen in the Black population as well as social economic factors that play a role (121,122).

In European studies, Caucasians show the highest prevalence's, and the lowest values are seen in the south Asian population, yet this group have the highest mortality for ischemic heart disease than Europeans (123).

7.1.5.Socioeconomical and educational background

Educational levels and economical resources all play a role in preventing, diagnosing and treating PAD early on. Stoecker et al, showed a strong association between incidence of PAD with annual household income, female sex and black race (124).

Lower income societies are an underprivileged group with lesser educational background, less access to healthcare preventative/screening programs and less likely to live a healthy lifestyle due to financial constraints. All these factors can make these individuals at a higher risk for PAD.

Low economic status is also shown to be associated with cardiovascular risk and different studies have analysed how Socio-economic inequality impacts prevalence of PAD.

Although in early ages lower income countries can be associated with a higher PAD, studies show that as the population ages, higher incidences prevail in higher income countries.

An updated systematic review and meta- analysis studied the prevalence of PAD in the general population at global, regional and national levels, comparing the prevalence of PAD in high-income countries (HICs), low-and middle income countries (LMICs) in the population diagnosed with PAD in 2015 (6). The study showed a higher prevalence in LMICs in younger subjects: (4.32% vs. 3.54% at 40–44 years) compared to HICs, this was reversed in older subjects, showing higher prevalence's of PAD in HICs (21.24% vs. 12.04% at 80–84 years) compared to LMICs (6).

Similar results were observed in 2019 systematic analysis, which showed global prevalence of 1.52% (95% CI 1.33–1.72), in which 42.6% were LMICs in subjects 40 years and older, with an increase in prevalence HICs as the population got older (125).

Even though Spain's prevalences for PAD is relatively lower than its neighbouring European countries, cardiovascular disease is the number one cause of mortality in Spain, accounting for 33.71% of total deaths, cardiac ischemia being the first cause in men and cerebrovascular disease in women (106). Therefore, we believe in the importance of cardiovascular risk prevention in those with PAD due to its association with other cardiovascular diseases.

7.2. Risk factors

Cardiovascular risk factors are another important tool when assessing PAD, although common risk factors are generally known, the importance of identifying the most common ones in your area of treatment can help in developing preventative strategies. Literature suggest that the strongest predictor of PAD is diabetes and smoking in those younger than 65 years old (11), this was also evident in our study in our male participants but not so much in our female participants. After logistic regression analysis an independent risk factor association was seen between our female smokers and hypertension OR 5.2 (95% CI:1.6–17.3) and 3.3 (95% CI:1.2–9.0) and concurring with the literature, our male smokers and diabetes 7.2 (95% CI:2.8–18.6) and 1.8 (95% CI: 1.0–3.). The results identify our potential at risk subgroups in Barcelona Nord.

PAD is also an indirect assessment of cardiovascular risk, since most cardiovascular diseases are of an atherosclerotic nature and depend on the same cardiovascular risk factors. Just the presence of PAD alone can suggest a 6.6-fold increase in cardiovascular disease (2).

The association of PAD and other atherosclerotic disease has been shown in various studies (105,126). FRENA study showed increase incidence of cardiac events and cerebrovascular disease in those with PAD as well as correlation with the severity of PAD symptoms. An increase in incidences as high as 42 patient years (95% CI: 24-67) were seen in Fontaine stage IV(127). In the REACH study, major vascular events were twice as high in those with more than one arterial bed involved (128). The correlation between ischemic cardiac events and PAD is important since more than half of PAD patients died from a cardiac event. The significance of this correlation means we can possibly identify those subjects with potential higher risk of cardiac disease with an easy assessable test such as ABI exam. This is especially important in a society where the number of mortalities is caused by cardiac events.

In our study, 13.6% of our participants had associated history of ischemic heart disease and a small few of ischemic cerebrovascular disease at the time of our evaluation.

An attempt to stratify cardiovascular Risk in our study was also done through REGICOR Score. We found that 14.8% of participants with PAD, compared to 12.7% participants without PAD, had a high REGICOR Score (>10%) and were at a higher risk of developing cardiovascular event in 10 years. We also found that these scores were higher in our male participants. ($p<0.001$). This shows the importance of implementing secondary cardiovascular preventative measures.

Overall, our results concur with literature which show lower prevalence's of PAD in Spain compared to other parts of Europe (3,129), with this study we were also able to identify our potential high risk subjects: Male smokers and diabetic as well as females smokers with hypertension, this way being able to focus on developing screening programs in our primary care facilities aimed at these subgroups of patients as well as developing preventative measure and educations resources that reach out to those at a higher risk.

Educating our population is another important factor and tool to help in early PAD diagnosis and to help our population better understand and control modifiable risk factors. The risk factor with the most association with PAD is smoking and, in our study, more than 50% of our participants had a history of smoking. Providing counselling and a close follow up with primary care units dedicated in tobacco prevention is another important tool in treating PAD.

The use of Risk score stratification can also be of utility when trying to identify those of higher risk to implement secondary prevention especially since the high association among PAD and other atherosclerotic diseases.

Our goal, we believe in this disease is to provide limb salvage, as well as overall quality of life and reduce cardiovascular morbid-mortality and recognizing your area PAD prevalence and potential group of higher risk can helps achieve this goal.

Therefore, we propose:

Health care awareness provided to our primary care center in order to develop screening programs in those high-risk subgroups detected in this study. Preventative strategies and specialized units to help treat modifiable risk factor such as tobacco cessation, glycaemic levels and blood pressure control, providing counselling and close monitorized follow ups. Population education of PAD and its risk factors aiming towards potential female patients since diagnosis in women tend to be more difficult due to its uncommon and late presentation of symptoms. And to provide secondary cardiovascular prevention in those with a higher stratifications risk score.

7.3. Limitations

Our study was part of a larger pilot screening program evaluating abdominal aortic aneurysm and PAD at 65 years old (146), hence our age and method of selection. Perhaps focusing on just one age group instead of a range in ages could have provided limited data. Our study also, included an urban population base and might not be presentative of entire Catalunya population. But with this in mind, we did compare our study population with ESCA database 65-74 years old as well as primary care centers data base of those 65 years old, we analysed risk factors among all three and found our study population to be similar in risk factors and believe that our sample is a true representation of our population. Another limitation was our participation rate of 43.1%, but this seems to be consistent with participation rates from other screening studies from our area, 43.6% in colon cancer screening in Barcelona and 54.7% breast cancer screening and seeing that these programs have a wider range of media diffusion than our study yet similar participation rates. Finally, another limitation of this study is that there is no follow up to this date, and we are unaware of the possible prognostic impact these factors could have.

8. Future lines

Future lines

- Evaluate cardiovascular morbid mortality at 10 years of our analysed group in order to see how many suffered a cardiovascular event in this time and what preventative measure and treatment they received.

- This data also correlates with today's literature in PAD being predominantly in male subjects and it would be interesting to see if the incidence of PAD in our women group increases with age by re-evaluated these subjects in 5-10 years.

- Evaluate which of those asymptomatic PAD, evolved to CTLI despite treating modifying risk factor.

- Follow-up on those inconclusive ABI 1,4 .

9. Conclusions

Conclusions

1. We conclude that the overall prevalence of PAD in Barcelona Nord in asymptomatic 65-year-old is 6.2% (95% CI:4.8–7.6%).

2. Our prevalence was higher in males 7.9% (95% CI:5.9–9.9%) compared to females 3.8% (95% CI:2.1–5.5%).

3. A strong association between PAD and cardiovascular risk factor was seen between male smokers and diabetes as well as female smokers and hypertension.

4. Our male subjects presented with a higher risk REGICOR score ($p<0.001$), being at a higher risk for developing a cardiovascular event in the next 10 years.

10. Bibliography

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). 2007;

2. Nordanstig J, Behrendt CA, Baumgartner I, Belch J, Bäck M, Fitridge R, et al. Editor's Choice – European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. European Journal of Vascular and Endovascular Surgery. 2024 Jan 1;67(1):9–96.

3. Cimminiello C, Kownator S, Wautrecht JC, Carvounis CP, Kranendonk SE, Kindler B, et al. The PANDORA study: Peripheral arterial disease in patients with non-high cardiBlanes, J. I., M. A. Cairols, and J. Marrugat. 20"Epidemiology, Risk Factors, and Natural History of Lower Extremity Peripheral Artery Disease - UpToDate." n.d. Accessed Novembe. Intern Emerg Med. 2011 Dec;6(6):509–19.

4. Cacoub PP, Abola MTB, Baumgartner I, Bhatt DL, Creager MA, Liau CS, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Atherosclerosis. 2009 Jun;204(2):e86–92.

5. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Vol. 39, European Heart Journal. Oxford University Press; 2018. p. 763–816.

6. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019 Aug;7(8):e1020–30.

7. Allison MA, Armstrong DG, Goodney PP, Hamburg NM, Kirksey L, Lancaster KJ, et al. Health Disparities in Peripheral Artery Disease: A Scientific Statement From the American Heart Association. Circulation. 2023 Jul 18;148(3):286–96.

8. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. The Lancet. 2013;382(9901):1329–40.

9. Olinic DM, Spinu M, Olinic M, Homorodean C, Tataru DA, Liew A, et al. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. International Angiology. 2018 Jun;37(4).

10. firnhaber.

11. Criqui MH, Aboyans V. Epidemiology of Peripheral Artery Disease. Circ Res. 2015 Apr 24;116(9):1509–26.

12. Amrock SM, Abraham CZ, Jung E, Morris PB, Shapiro MD. Risk Factors for Mortality Among Individuals With Peripheral Arterial Disease. Am J Cardiol. 2017 Sep 1;120(5):862–7.

13. Young JC, Paul NJ, Karatas TB, Kondrasov SA, McGinigle KL, Crowner JR, et al. Cigarette smoking intensity informs outcomes after open revascularization for peripheral artery disease. J Vasc Surg. 2019 Dec 1;70(6):1973-1983.e5.

14. Forés R, Alzamora MT, Boixadera-Planas E, Vázquez A, Pera G, Torán P. Evolución de la prevalencia de arteriopatía periférica en la práctica clínica: Estudio descriptivo poblacional con bases de datos reales (SIDIAP-CMBD). Aten Primaria. 2022 Sep;54(9):102437.

15. Lu L, Mackay DF, Pell JP. Meta-analysis of the association between cigarette smoking and peripheral arterial disease. Heart. 2014 Mar 1;100(5):414–23.

16. He Y, Jiang Y, Wang J, Fan L, Li X, Hu FB. Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China. J Vasc Surg. 2006 Aug;44(2):333–8.

17. WHAT IS PAD?

18. Singh M V., Dokun AO. Diabetes mellitus in peripheral artery disease: Beyond a risk factor. Front Cardiovasc Med. 2023 Apr 17;10.

19. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes. Diabetes Care. 2004 May 1;27(5):1047–53.

20. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539–53.

21. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047–53.

22. Soyoye DO, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: A review. World J Diabetes. 2021 Jun 15;12(6):827–38.

23. Arora E, Maiya AG, Devasia T, Bhat R, Kamath G. Prevalence of peripheral arterial disease among type 2 diabetes mellitus in coastal Karnataka. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2019 Mar;13(2):1251–3.

24. Ikem R, Ikem I, Adebayo O, Soyoye D. An assessment of peripheral vascular disease in patients with diabetic foot ulcer. The Foot. 2010 Dec;20(4):114–7.

25. Stoberock K, Kaschwich M, Nicolay SS, Mahmoud N, Heidemann F, Rieß HC, et al. The interrelationship between diabetes mellitus and peripheral arterial disease. Vasa. 2021 Sep;50(5):323–30.

26. Aday AW, Everett BM. Dyslipidemia Profiles in Patients with Peripheral Artery Disease. Curr Cardiol Rep. 2019 Jun 22;21(6):42.

27. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997 Jul 1;96(1):44–9.

28. Curb JD, Masaki K, Rodriguez BL, Abbott RD, Burchfiel CM, Chen R, et al. Peripheral artery disease and cardiovascular risk factors in the elderly. The Honolulu Heart Program. Arterioscler Thromb Vasc Biol. 1996 Dec;16(12):1495–500.

29. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE, et al. Peripheral Arterial Disease in the Elderly The Rotterdam Study From the Department of Epidemiology [Internet]. 1998 [cited 2019 Nov 17]. Available from: http://ahajournals.org

30. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW f. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002 Jun;143(6):961–5.

31. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2006 Sep 19;48(6):1190–7.

32. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. Circulation. 2018 Nov 20;138(21):2330–41.

33. Smith I, Franks PJ, Greenhalgh RM, Poulter NR, Powell JT. The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. European Journal of Vascular and Endovascular Surgery. 1996 May;11(4):402–8.

34. Bainton D, Sweetnam P, Baker I, Elwood P. Peripheral vascular disease: consequence for survival and association with risk factors in the Speedwell prospective heart disease study. Br Heart J. 1994 Aug;72(2):128–32.

35. Lane DA, Lip GYH. Treatment of hypertension in peripheral arterial disease. Cochrane Database Syst Rev. 2013 Dec 4;(12):CD003075.

36. Clement DL, De Buyzere ML, Duprez DA. Hypertension in peripheral arterial disease. Curr Pharm Des. 2004;10(29):3615–20.

37. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med. 2000 Oct 23;160(19):2934–8.

38. Singer DRJ, Kite A. Management of Hypertension in Peripheral Arterial Disease: Does the Choice of Drugs Matter? European Journal of Vascular and Endovascular Surgery. 2008 Jun;35(6):701–8.

39. Missouris CG, Buckenham T, Cappuccio FP, MacGregor GA. Renal artery stenosis: A common and important problem in patients with peripheral vascular disease. Am J Med. 1994 Jan;96(1):10–4.

40. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004 Mar 22;164(6):659–63.

41. O'Hare AM, Glidden D V, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. Circulation. 2004 Jan 27;109(3):320–3.

42. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007 Feb;18(2):629–36.

43. Chen J, Mohler ER, Xie D, Shlipak MG, Townsend RR, Appel LJ, et al. Risk Factors for Peripheral Arterial Disease Among Patients With Chronic Kidney Disease. Am J Cardiol. 2012 Jul;110(1):136–41.

44. Selvin E, Köttgen A, Coresh J. Kidney function estimated from serum creatinine and cystatin C and peripheral arterial disease in NHANES 1999-2002. Eur Heart J. 2009 Aug;30(15):1918–25.

45. Garimella PS, Hirsch AT. Peripheral artery disease and chronic kidney disease: clinical synergy to improve outcomes. Adv Chronic Kidney Dis. 2014 Nov;21(6):460–71.

46. Hardman R, Jazaeri O, Yi J, Smith M, Gupta R. Overview of Classification Systems in Peripheral Artery Disease. Semin Intervent Radiol. 2014 Nov 14;31(04):378–88.

47. Gul F, Janzer SF. Peripheral Vascular Disease. 2024.

48. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: Executive Summary: A report of the American college of cardiology/American Heart Association task force on clinical practice guidelines. Vol. 135, Circulation. Lippincott Williams and Wilkins; 2017. p. e686–725.

49. Bhat M, Parry A, Maqsood S, Ganie F. Utility of ankle brachial index in the diagnosis of peripheral arterial disease in a resource limited setting. Indian Journal of Vascular and Endovascular Surgery. 2022;9(1):22.

50. Rac-Albu M, Iliuta L, Guberna SM, Sinescu C. The role of ankle-brachial index for predicting peripheral arterial disease. Maedica (Bucur). 2014 Sep;9(3):295–302.

51. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley C V. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ. 1996 Dec 7;313(7070):1440–4.

52. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and Interpretation of the Ankle-Brachial Index. Circulation. 2012 Dec 11;126(24):2890–909.

53. Alqahtani KM, Bhangoo M, Vaida F, Denenberg JO, Allison MA, Criqui MH. Predictors of Change in the Ankle Brachial Index with Exercise. Eur J Vasc Endovasc Surg. 2018 Mar;55(3):399–404.

54. Høyer C, Sandermann J, Petersen LJ. The toe-brachial index in the diagnosis of peripheral arterial disease. J Vasc Surg. 2013 Jul;58(1):231–8.

55. Herraiz-Adillo Á, Cavero-Redondo I, Álvarez-Bueno C, Pozuelo-Carrascosa DP, Solera-Martínez M. The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: A systematic review and meta-analysis. Atherosclerosis. 2020 Dec;315:81–92.

56. Brouwers JJWM, Willems SA, Goncalves LN, Hamming JF, Schepers A. Reliability of bedside tests for diagnosing peripheral arterial disease in patients prone to medial arterial calcification: A systematic review. EClinicalMedicine. 2022 Aug;50:101532.

57. Tehan PE, Santos D, Chuter VH. A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral artery disease. Vasc Med. 2016 Aug;21(4):382–9.

58. Sommerset J, Teso D, Karmy-Jones R, Vea Y, Feliciano B. Pedal Flow Hemodynamics in Patients With Chronic Limb-Threatening Ischemia. Journal for Vascular Ultrasound. 2020 Mar 5;44(1):14–20.

59. Silva E, Lima P, Iglésias J, Constâncio V, Nunes C, Baldaia L, et al. Pedal Acceleration Time a New Method to Assess Peripheral Arterial Disease. EJVES Vasc Forum [Internet]. 2024;61:S22–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2666688X24000339

60. Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. Health Technol Assess. 2007 May;11(20):iii–iv, xi–xiii, 1–184.

61. Jens S, Koelemay MJW, Reekers JA, Bipat S. Diagnostic performance of computed tomography angiography and contrast-enhanced magnetic resonance angiography in patients with critical limb ischaemia and intermittent claudication: systematic review and meta-analysis. Eur Radiol. 2013 Nov;23(11):3104–14.

62. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018 Dec 25;72(25):3332–65.

63. McDermott MM, Tiukinhoy S, Greenland P, Liu K, Pearce WH, Guralnik JM, et al. A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication. J Cardiopulm Rehabil. 2004;24(3):187–96.

64. LASLOVICH S, ALVAR BA, ALLISON M, RAUH MJ. Effects of Lifestyle Physical Activity on Vascular Function in Asymptomatic Peripheral Arterial Disease. Med Sci Sports Exerc. 2020 Jan;52(1):8–15.

65. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, et al. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. Med Sci Sports Exerc. 2019 Jun;51(6):1270–81.

66. Powell KE, King AC, Buchner DM, Campbell WW, DiPietro L, Erickson KI, et al. The Scientific Foundation for the *Physical Activity Guidelines for Americans* , 2nd Edition. J Phys Act Health. 2019 Jan;16(1):1–11.

67. Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, et al. Optimal Exercise Programs for Patients With Peripheral Artery Disease: A Scientific Statement From the American Heart Association. Circulation. 2019 Jan 22;139(4).

68. Rodrigues E, Silva I. Supervised exercise therapy in intermittent claudication: a systematic review of clinical impact and limitations. Int Angiol. 2020 Feb;39(1):60–75.

69. Gommans LNM, Saarloos R, Scheltinga MRM, Houterman S, de Bie RA, Fokkenrood HJP, et al. Editor's Choice – The Effect of Supervision on Walking Distance in Patients with Intermittent Claudication: A Meta-analysis. European Journal of Vascular and Endovascular Surgery. 2014 Aug;48(2):169–84.

70. Siercke M, Jørgensen LP, Missel M, Thygesen LC, Møller SP, Sillesen H, et al. Cardiovascular Rehabilitation Increases Walking Distance in Patients With Intermittent Claudication. Results of the CIPIC Rehab Study: A Randomised Controlled Trial. European Journal of Vascular and Endovascular Surgery. 2021 Nov;62(5):768–76.

71. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol. 2021 May 14;28(5):460–95.

72. Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes. JAMA. 2016 Jul 19;316(3):313.

73. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2021*. Diabetes Care. 2021 Jan 1;44(Supplement_1):S111–24.

74. Escobar C, Barrios V, Cosín J, Gámez Martínez JM, Huelmos Rodrigo AI, Ortíz Cortés C, et al. SGLT2 inhibitors and GLP1 agonists administered without metformin compared to other glucose-lowering drugs in patients with type 2 diabetes mellitus to prevent cardiovascular events: A systematic review. Diabetic Medicine. 2021 Mar 4;38(3).

75. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020 Jun;75(6):1334–57.

76. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J. 2004 Jan;25(1):17–24.

77. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111–88.

78. Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007 Apr;45(4):645–54; discussion 653-4.

79. Aung PP, Maxwell H, Jepson RG, Price J, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database of Systematic Reviews. 2007 Oct 17;

80. High-Intensity Statin Therapy Is Associated With Improved Survival in Patients With Peripheral Artery Disease. J Am Heart Assoc. 2019 May 21;8(10):e002305.

81. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015 Jun 18;372(25):2387–97.

82. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. Circulation. 2018 Jan 23;137(4):338–50.

83. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71–86.

84. Bonaca MP, Scirica BM, Braunwald E, Wiviott SD, Goto S, Nilsen DW, et al. New ischemic stroke and outcomes with vorapaxar versus placebo: results from the TRA 2 °P-TIMI 50 trial. J Am Coll Cardiol. 2014 Dec 9;64(22):2318–26.

85. Katsanos K, Spiliopoulos S, Saha P, Diamantopoulos A, Karunanithy N, Krokidis M, et al. Comparative Efficacy and Safety of Different Antiplatelet Agents for Prevention of Major Cardiovascular Events and Leg Amputations in Patients with Peripheral Arterial Disease: A Systematic Review and Network Meta-Analysis. PLoS One. 2015;10(8):e0135692.

86. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018 Jan 20;391(10117):219–29.

87. Rymer J, Anand SS, Sebastian Debus E, Haskell LP, Hess CN, Jones WS, et al. Rivaroxaban Plus Aspirin Versus Aspirin Alone After Endovascular Revascularization for Symptomatic PAD: Insights From VOYAGER PAD. Circulation. 2023 Dec 12;148(24):1919–28.

88. Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. Cochrane Database of Systematic Reviews. 2015 Sep 29;

89. Broderick C, Forster R, Abdel-Hadi M, Salhiyyah K. Pentoxifylline for intermittent claudication. Cochrane Database of Systematic Reviews. 2020 Oct 16;2020(10).

90. Bedenis R, Stewart M, Cleanthis M, Robless P, Mikhailidis DP, Stansby G. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014 Oct 31;2014(10):CD003748.

91. Stevens JW, Simpson E, Harnan S, Squires H, Meng Y, Thomas S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. British Journal of Surgery. 2012 Nov 6;99(12):1630–8.

92. Barradell LB, Brogden RN. Oral Naftidrofuryl. Drugs Aging. 1996 Apr;8(4):299–322.

93. Mills JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on Wound, Ischemia, and foot Infection (WIfI). J Vasc Surg. 2014 Jan;59(1):220-234.e2.

94. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. The Lancet. 2005 Dec;366(9501):1925–34.

95. Bradbury AW, Moakes CA, Popplewell M, Meecham L, Bate GR, Kelly L, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. The Lancet. 2023 May;401(10390):1798–809.

96. Menard MT, Rosenfield K, Farber A. The BEST-CLI Trial: Implications of the Primary Results. European Journal of Vascular and Endovascular Surgery. 2023 Mar;65(3):317–9.

97. Blanes JI, Cairols MA, Marrugat J. Prevalence of peripheral artery disease and its associated risk factors in Spain: The ESTIME study. International Angiology. 2009;

98. Alzamora MT, Forés R, Baena-Díez JM, Pera G, Toran P, Sorribes M, et al. The Peripheral Arterial disease study (PERART/ARTPER): Prevalence and risk factors in the general population. BMC Public Health. 2010;10.

99. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2024 Jun 11;149(24). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001251

100. Fite J, Gayarre-Aguado R, Puig T, Zamora S, Escudero JR, Solà Roca J, et al. Feasibility and Efficiency Study of a Population-Based Abdominal Aortic Aneurysm Screening Program in Men and Women in Spain. Ann Vasc Surg [Internet]. 2020 Dec; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0890509620311055

101. Amor AJ, Serra-Mir M, Mart ınez-Gonz alez MA, Corella D, Salas-Salvad J, Fit M, et al. Prediction of Cardiovascular Disease by the Framingham-REGICOR Equation in the High-Risk PREDIMED Cohort: Impact of the Mediterranean Diet Across Different Risk Strata. [cited 2020 Jan 1]; Available from: http://www.Controlled-trials.com.

102. Velescu A, Clara A, Peñafiel J, Grau M, Degano IR, Martí R, et al. Peripheral Arterial Disease Incidence and Associated Risk Factors in a Mediterranean Population-based Cohort. the REGICOR Study. European Journal of Vascular and Endovascular Surgery. 2016;51(5):696–705.

103. Kröger K, Stang A, Kondratieva J, Moebus S, Beck E, Schmermund A, et al. Prevalence of peripheral arterial disease - results of the Heinz Nixdorf recall study. Eur J Epidemiol. 2006;21(4):279–85.

104. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. J Vasc Surg. 2007 Jun;45(6):1185–91.

105. FOWKES FGR, HOUSLEY E, CAWOOD EHH, MACINTYRE CCA, RUCKLEY C V, PRESCOTT RJ. Edinburgh Artery Study: Prevalence of Asymptomatic and Symptomatic Peripheral Arterial Disease in the General Population. Int J Epidemiol [Internet]. 1991;20(2):384–92. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/20.2.384

106. Bertomeu V, Castillo-Castillo J. Situación de la enfermedad cardiovascular en España. Del riesgo a la enfermedad. Revista Española de Cardiología Suplementos [Internet]. 2008 Jan;8(5):2E-9E. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1131358708761016

107. Schramm K, Rochon PJ. Gender Differences in Peripheral Vascular Disease. Semin Intervent Radiol. 2018;35(1):9–16.

108. Parvar SL, Thiyagarajah A, Nerlekar N, King P, Nicholls SJ. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. J Vasc Surg. 2021 Apr;73(4):1456-1465.e7.

109. Nguyen L, Liles DR, Lin PH, Bush RL. Hormone Replacement Therapy and Peripheral Vascular Disease in Women. Vasc Endovascular Surg. 2004 Nov 18;38(6):547–56.

110. Jelani Q ul ain, Petrov M, Martinez SC, Holmvang L, Al-Shaibi K, Alasnag M. Peripheral Arterial Disease in Women: an Overview of Risk Factor Profile, Clinical Features, and Outcomes. Curr Atheroscler Rep. 2018 Aug 2;20(8):40.

111. Teodorescu VJ, Vavra AK, Kibbe MR. Peripheral arterial disease in women. J Vasc Surg. 2013 Apr;57(4):18S-26S.

112. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002 Jul 3;288(1):49–57.

113. Hsia J, Simon JA, Lin F, Applegate WB, Vogt MT, Hunninghake D, et al. Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/Progestin Replacement Study. Circulation. 2000 Oct 31;102(18):2228–32.

114. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. J Vasc Surg [Internet]. 2007 Jun;45(6):1185–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S074152140700290X

115. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985 Mar;71(3):510–5.

116. Vitalis A, Lip GYH, Kay M, Vohra RK, Shantsila A. Ethnic differences in the prevalence of peripheral arterial disease: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther. 2017 Apr 3;15(4):327–38.

117. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004 Aug 10;110(6):738–43.

118. Criqui MH, Vargas V, Denenberg JO, Ho E, Allison M, Langer RD, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. Circulation. 2005 Oct 25;112(17):2703–7.

119. Forbang NI, Hughes-Austin JM, Allison MA, Criqui MH. Peripheral artery disease and non-coronary atherosclerosis in Hispanics: another paradox? Prog Cardiovasc Dis. 2014;57(3):237–43.

120. Collins TC, Johnson M, Henderson W, Khuri SF, Daley J. Lower Extremity Nontraumatic Amputation Among Veterans With Peripheral Arterial Disease. Med Care. 2002 Jan;40(Supplement):I-106-I–116.

121. Hackler EL, Hamburg NM, White Solaru KT. Racial and Ethnic Disparities in Peripheral Artery Disease. Circ Res. 2021 Jun 11;128(12):1913–26.

122. Havranek EP, Mujahid MS, Barr DA, Blair I V., Cohen MS, Cruz-Flores S, et al. Social Determinants of Risk and Outcomes for Cardiovascular Disease. Circulation. 2015 Sep;132(9):873–98.

123. Balarajan R. Ethnic differences in mortality from ischaemic heart disease and cerebrovascular disease in England and Wales. BMJ. 1991 Mar 9;302(6776):560–4.

124. Stoecker JB, Cohen JB, Belkin N, Chen JC, Townsend RR, Xie D, et al. The Association Between Socioeconomic Factors and Incident Peripheral Artery Disease in the Chronic Renal Insufficiency Cohort (CRIC). Ann Vasc Surg. 2022 Mar;80:196–205.

125. GBD 2019 Peripheral Artery Disease Collaborators. Global burden of peripheral artery disease and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Glob Health. 2023 Oct;11(10):e1553–65.

126. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). The Lancet [Internet]. 1996 Nov;348(9038):1329–39. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673696094573

127. Monreal M, Alvarez L, Vilaseca B, Coll R, Suárez C, Toril J, et al. Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA). Eur J Intern Med [Internet]. 2008 May;19(3):192–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0953620507002609

128. Sabouret P, Cacoub P, Dallongeville J, Krempf M, Mas JL, Pinel JF, et al. REACH: International prospective observational registry in patients at risk of atherothrombotic events Results for the French arm at baseline and one year. Arch Cardiovasc Dis [Internet]. 2008 Jan;101(2):81–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1875213608702638

129. Cacoub P, Cambou JP, Kownator S, Belliard JP, Beregi JP, Branchereau A, et al. Prevalence of peripheral arterial disease in high-risk patients using ankle-brachial index in general practice: a cross-sectional study. Int J Clin Pract. 2009 Jan;63(1):63–70.

11. Annexes

11.1.Publication

Gonçalves-Martins G, Gil-Sala D, Tello-Díaz C, Tenezaca-Sari X, Marrero C, Puig T, Gayarre R, Fité J, Bellmunt-Montoya S. ***Prevalence of Peripheral Arterial Disease and Associated Vascular Risk Factors in 65-Years-Old People of Northern Barcelona****. J Clin Med. 2021 Sep 28;10(19):4467. doi: 10.3390/jcm10194467. PMID: 34640483; PMCID: PMC8509737.*

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Prevalence of Peripheral Arterial Disease and Associated Vascular Risk Factors in 65-Years-Old People of Northern Barcelona

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Abstract: Objective: To determine the prevalence and risk factors associated with peripheral arterial disease (PAD) in Northern Barcelona at 65 years of age. Methods: A single-center, cross-sectional study, including males and females 65 years of age, health care cardholders of Barcelona Nord. PAD was defined as an ankle–brachial index (ABI) < 0.9. Attending subjects were evaluated for a history of common cardiovascular risk factors. A REGICOR score was obtained, as well as a physical examination and anthropometric measurements. Results: From November 2017 to December 2018, 1174 subjects were included: 479 (40.8%) female and 695 (59.2%) male. Overall prevalence of PAD was 6.2% (95%CI: 4.8–7.6%), being 7.9% (95%CI: 5.9–9.9%) in males and 3.8% (95%CI: 2.1–5.5%) in females. An independent strong association was seen in male smokers and diabetes, with ORs pf 7.2 (95% CI: 2.8–18.6) and 1.8 (95% CI: 1.0–3.3), respectively, and in female smokers and hypertension, with ORs of 5.2 (95% CI: 1.6–17.3) and 3.3 (95% CI: 1.2–9.0). Male subjects presented with higher REGICOR scores ($p < 0.001$). Conclusion: Higher-risk groups are seen in male subjects with a history of smoking and diabetes and female smokers and arterial hypertension, becoming important subgroups for our primary healthcare centers and should be considered for ABI screening programs.

Keywords: peripheral arterial disease; cardiovascular risk factors; asymptomatic; ankle–brachial index; prevalence; screening

1. Introduction

Peripheral arterial disease (PAD) is the manifestation of atherosclerotic disease in the lower extremities, resulting in narrowing of the blood vessels and diminishing blood flow to the limbs. It is the third leading cause of cardiovascular pathology after coronary and cerebrovascular disease and an important indicator of cardiovascular risk [1]. The mere presence of PAD can indicate a 6.6-fold increased risk of cardiovascular disease association [2], becoming, therefore, an important indicator of the coexistence of other cardiovascular pathologies.

Associated risk factors are common for cardiovascular diseases, such as smoking, diabetes, dyslipidemia and hypertension, among others. Active smoking has the strongest

association, doubling the risk of PAD in these patients [3]. Therefore, early diagnosis and treatment of modifiable risk factors is an important tool in preventing and treating this disease, consequently lowering associated cardiovascular disease morbidity and mortality.

The ankle–brachial index (ABI) is an effective, easy and first-line noninvasive method in screening PAD [4–6], with an overall 69–79% sensitivity and 83–99% specificity for detecting >50% arterial stenosis [7]. Despite the feasibility of this technique, this pathology is well known to be underdiagnosed and undertreated [4,5].

In the United States, 8 to 12 million Americans suffer from PAD, with an overall prevalence of 3–10%, which increases to almost 50% in those greater than 85 years old [8,9]. As for Europe, prevalence as high as 17.8% (99% CI: 16.84–18.83%) was observed in some studies, especially in the northern region [10].

PAD is also influenced by gender and age, predominantly being associated with the male gender. Age is also an important factor, with a 20% increase observed in those older than 75 [11,12]. In a global aging society, this can present an important social and economic burden.

To our knowledge, most studies focused on the prevalence of PAD performed in our region were inclusive of younger age groups, some including ages as young as 35 years old [13,14]. This perhaps explains the low prevalence results achieved in these studies. Due to the important variety of factors that influence the prevalence of this pathology, age being one of them, we decided to perform a study including individuals of 65 years old in order to analyze if an increase of prevalence was seen in these groups and, as such, evaluate if there were differences in our gender groups with this increase in age, as well as associated risk factors. This way perhaps allows pinpointing a target group that requires a more detailed initial evaluation and opportunistic screening (with ABI) in our primary care centers in order to prevent and/or diagnose PAD.

Thus, the aim of our study was to determine the prevalence of peripheral arterial disease through ABI in 65-year-old men and women in Northern Barcelona (Spain), as well as its associated risk factors.

2. Materials and Methods

This is a single-center, populational-based, cross-sectional study, part of a larger pilot screening program evaluating abdominal aorta aneurysm [15]. The protocol was approved by the ethics committee of Hospital Vall d'Hebron with code PR(AG)221/2017.

2.1. Patient Selection

The study was carried out in a health-integrated area AIS-Barcelona Nord, with a population base of 400,000 inhabitants, which corresponds to the area of treatment of our center. Inclusion criteria were all noninstitutionalized males and females of 65 years of age during the time of recruitment who were health care cardholders and resided for at least 6 months in the referred area.

Contact information of the population was authorized and obtained through our public health census registry, and all eligible subjects received invitation letters informing them of the present study and tests to be performed. Those with incorrect postal data, terminal disease and deceased subjects were considered ineligible (Figure 1).

Nonresponders to the first letter were invited again within 1 month. Those who agreed to participate were scheduled an appointment at our Vascular Lab Center with one of five trained vascular surgeon residents. Participants were contacted 48 h before the appointment to confirm attendance. Those who did not show up for the scheduled appointment after 3 occasions, those who did not wish to participate and subjects who did not respond to both invitation letters were excluded.

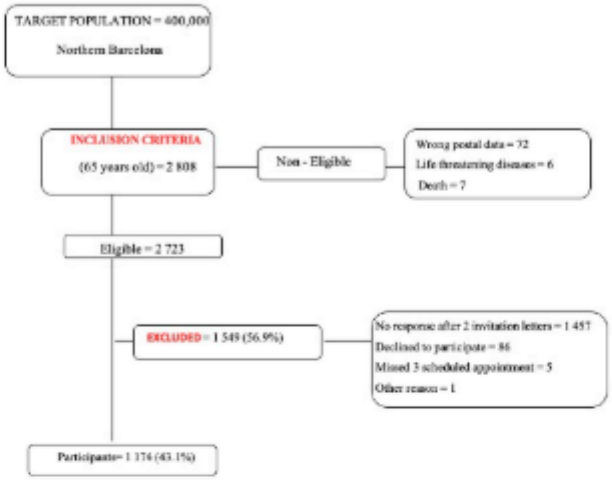

Figure 1. Flowchart of initial inclusion description.

2.2. Variables Evaluated

After arrival, prior to questioning, a signed consent form was required from each participant. All subjects were questioned for a history of risk factors, such as: cigarette smoking: active, former (more than a year without smoking) or nonsmoker; hypertension, defined as systolic blood pressure ≥140/90 mmHg or subjects under antihypertensive treatment; dyslipidemia, defined as one or all of total blood cholesterol >200 mg/dL, low-density lipoprotein (LDL) cholesterol >100 mg/dL or triglycerides >150 mg/dL or subjects under treatment for dyslipidemia; diabetes, defined as those diagnosed and/or under antidiabetic treatment; history of cerebrovascular disease (previous stroke or transient ischemic cerebral accident); history of cardiac ischemia (diagnosed coronary artery disease or previous myocardial infarction); chronic renal disease (glomerular filtration <60 mL/min) and history of any aortic aneurismatic disease. Anthropometric measurements were also recorded: height (m), weight (kg), waist circumference (cm) and body mass index (BMI). A REGICOR score [16] was determined for each individual to evaluate primary prevention, discarding those subjects who had already presented a previous cardiovascular event. Cholesterol levels and blood pressure required for scoring were obtained through medical records. The REGICOR (Girona Heart Registry) research group focuses on ischemic heart disease and associated risk factors in order to improve preventive strategies. This score assesses the risk of presenting a cardiovascular event in the following 10 years through a computer-generated calculation that evaluated age, sex, history of smoking, presence of diabetes and blood pressure, total cholesterol and high-density lipoprotein (HDL) levels. Low risks are considered to be scores <5%, moderate risk between 5 and 9% and high-risk subjects >10%.

2.3. Physical Assessment

To complete the assessment, a physical exam was performed, evaluating distal pulses through palpation. The presence of a pulse in one or both tibial arteries was considered adequate. Afterward, an ABI was performed in a standard manner [7]: after a 5 min rest, with the subjects in a supine position, systolic blood pressure was measured at the level of the posterior and anterior tibial arteries of both lower extremities and at the level of the brachial artery of both upper extremities, with a continuous wave Doppler probe

(Flowsoft 7 Angiolab1 Spead Doppler Systeme, Kehl, Germany) and an arterial pressure cuff that was placed just above the malleoli. ABI was calculated through the ratio of systolic pressure of the tibial arteries to the highest brachial systolic pressure. ABI of both extremities was recorded. Those with an ABI < 0.9 in one or both lower extremities were considered pathological with an indication of PAD. All ABI > 1.4 were registered. In the case that a patient presented with critical limb ischemia, considered as rest pain or presence of ischemic lesions, they were sent to the vascular emergency room for evaluation. At the end of each assessment, the patient was given a signed report indicating the result of their ABI exam, and if the exam was pathological, recommendations of the modifiable risk factors were given in order to prevent the progression of PAD.

For better analysis and interpretation of our results, we reviewed common risk factors among our study participants and those obtained from the official health department database, 2018 Catalan Health Survey "Enquesta Catalunya de Salut 2018" (ESCA) (ages 65–74 years old), and our primary care clinics (65 years old), with previous authorization from our health department.

2.4. Statistical Analysis

Descriptive analysis was performed, and prevalence of PAD was obtained with the 95% confidence interval. Dichotomous variables were analyzed through Pearson's chi-square test or Fisher's exact test. Logistic regression models were used to obtain independent associated risk factors for PAD that were previously significant in the bivariate analysis. Interaction effect was also evaluated among these risk factors. Statistical significance results were considered for a value of $p < 0.05$. Statistical analysis was performed through IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

From November 2017 to December 2018, a total of 2808 subjects were 65 years old during the time of recruitment. A total of 1174 subjects were finally included, 695 (59.2%) male and 479 (40.8%) female. Total participation rate was 43.1%, with higher participation from females (46.7%) than males (40.9%). A flow chart of initial screening with main results separated by sex is shown in Figure 2.

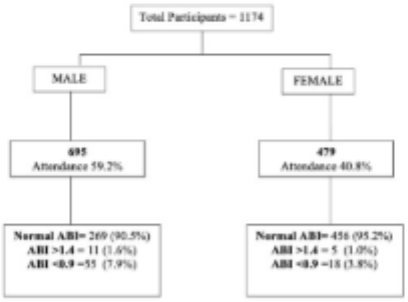

Figure 2. Flowchart screening results.

The overall prevalence of PAD was 6.2% (95% CI: 4.8–7.6%), male 7.9% (95% CI: 5.9–9.9%) and female 3.8% (95% CI: 2.1–5.5%), most of them corresponding to the Fontaine I classification ($n = 53$, 72.6%), 20.5% IIA ($n = 15$), 5.5% IIB ($n = 4$) and 1.4% ($n = 1$). The difference in prevalence between male and female was statistically significant ($p = 0.006$). Male subjects presented at higher risk for PAD, with an OR of 2.2 (CI: 1.3–3.8).

There was a total of 18 ABI > 1.4, of which two of these had contralateral ABIs < 0.9 considered PAD. Of the other 16 ABIs > 1.4 (6 were diabetic subjects, and none had chronic

renal disease), all subjects except for one had palpable distal pulses and none referred to intermittent claudication.

Diabetes male subjects were more likely to have PAD ($p = 0.017$) and female subjects hypertension ($p = 0.026$) and waist circumference ($p = 0.018$). No association was seen with a family history of abdominal aortic aneurysm, probably due to the small number of cases detected. Table 1 compares risk factors presented in PAD and non-PAD divided by gender.

Table 1. Relationship between PAD and risk factors divided by gender. Logistic regression model with OR and CI 95% of the potential variables associated with PAD.

	Male					Female				
	Non-PAD (n = 640)	**PAD (n = 55)**	**Total (n = 695)**	**OR * (95% CI: **)**	**p ª**	**Non-PAD (n = 461)**	**PAD (n = 18)**	**Total (n = 479)**	**OR (95% CI: **)**	**p ª**
Non-smoker	237 (37.0%)	6 (10.9%)	243 (35.0%)	1	<0.001	320 (69.4%)	7 (38.9%)	327 (68.3%)	1	0.02
Former smoker	299 (46.7%)	29 (52.7%)	328 (47.2%)	3.8 (1.6–9.40)	0.003	96 (20.8%)	6 (33.3%)	102 (21.3%)	2.9 (0.9–8.7)	0.065
Active smoker	104 (16.3%)	20 (36.4%)	124 (17.8%)	7.6 (3.0–19.5)	<0.001	45 (9.8%)	5 (27.8%)	50 (10.4%)	5.1 (1.5–16.7)	0.007
Cardiovascular risk factors n (%)										
Diabetes	141 (22.0%)	20 (36.4%)	161 (23.2%)	2.0 (1.1–3.6)	0.017	43 (9.3%)	4 (22.2%)	47 (9.8%)	2.8 (0.9–8.8)	0.083
Dyslipidemia	293 (45.8%)	26 (47.3%)	319 (45.9%)	1.1 (0.6–1.8)	0.831	215 (46.6%)	10 (55.6%)	225 (47.0%)	1.4 (0.6–3.7)	0.499
Hypertension	340 (53.1%)	28 (50.9%)	368 (52.9%)	0.9 (0.5–1.6)	0.752	181 (39.3%)	12 (66.7%)	193 (40.3%)	3.1 (1.1–8.4)	0.026
Chronic Renal Disease	37 (5.8%)	3 (5.5%)	40 (5.8%)	0.9 (0.3–3.2)	0.920	8 (1.7%)	0 (0%)	8 (1.7%)	0	0.9
Cardiac Ischemia	59 (9.2%)	9 (16.4%)	68 (9.8%)	1.9 (0.9–4.1)	0.092	6 (1.3%)	1 (5.6%)	7 (1.5%)	4.5 (0.5–39.1)	0.177
Cerebrovascular Events	31 (4.8%)	3 (5.5%)	34 (4.9%)	1.1 (0.3–3.8)	0.840	16 (3.5%)	0 (0%)	16 (3.3%)	0	0.9
Anthropometric measurements mean (SD)										
Waist Circumference (cm)	102.4 (SD 11.0)	103.6 (SD 9.4)	102.5 (SD 10.9)	1.01 (0.99–1.04)	0.410	95.1 (SD 12.1)	102.4 (SD 15.9)	95.3 (SD 12.3)	1.05 (1.01–1.09)	0.018

Data are expressed as n (%) or mean (standard deviation); * OR: odds ratio; ** CI: confidence interval; ª Wald test's p-values of logistic regression.

A multilogistic regression model was performed from the significant bivariate analysis variables. In our male model, an independent association between PAD and smoking was shown. PAD in male subjects was higher in ex-smokers, with an OR of 3.5 (95% CI: 1.4–8-7) and in active smokers 7.2 (95% CI: 2.8–18.6) in comparison with nonsmokers. An association with diabetes and PAD was also seen in our male participants, with an OR of 1.8 (95% CI: 1.0–3.3)

As for our female model, an association was also seen in relation to PAD and smoking, with an OR of 3.1 (95% CI: 1.0–9.6) in ex-smokers and 5.2 (95% CI: 1.6–17.3) in active smokers compared with nonsmokers. PAD was also higher in those female subjects with hypertension, with an OR of 3.3 (95% CI: 1.2–9.0) (Table 2). No significant association was seen between hypertension and PAD in male subjects nor diabetes and PAD in our female subjects. Therefore, no interaction effect was observed among these variables, and no mediation effect was observed with gender.

Table 2. Multiple logistic regression analysis of PAD risk.

Male		Female	
Variables	**OR (95% CI)**	**Variables**	**OR (95% CI)**
Non-smokers	1	**Non-smokers**	1
Former Smokers	3.5 (1.4–8.7)	**Former Smokers**	3.1 (1.0–9.6)
Active Smokers	7.2 (2.8–18.6)	**Active Smokers**	5.2 (1.6–17.3)
Diabetes	1.8 (1.0–3.3)	**High blood pressure**	3.3 (1.2–9.0)

CI: confidence interval. OR: odds ratio.

Discarding 157 subjects who had already presented a previous cardiovascular event, 1013 subjects were classified according to their cardiovascular risk at 10 years with the REGICOR scale. In this regard, 51.4% (n = 500) of our population were at low risk of developing a cardiovascular event in the following 10 years, 40.4% (n = 393) were at moderate risk and 8.1% (n = 79) were at a high-risk score. Four subjects were excluded from REGICOR analysis due to missing data. Male subjects presented with higher REGICOR scores ($p < 0.001$), putting them at a higher risk for developing a cardiovascular event in the following 10 years compared to our female subjects. Table 3 illustrates the REGICOR score in our general population divided by sex and PAD.

Table 3. REGICOR results in general population separated by sex and PAD.

	Non-PAD			PAD		
	TOTAL (n = 972)	**MALE (n = 543)**	**FEMALE (n = 429)**	**TOTAL (n = 41)**	**MALE (n = 27)**	**FEMALE (n = 14)**
Low risk <5%	51.4% (500)	33.1% (180)	74.6% (320)	48.8% (20)	40.7% (11)	64.3% (9)
Moderate risk 5–9%	40.4% (393)	54.1% (294)	23.1% (99)	41.5% (17)	44.4% (12)	35.7% (5)
High risk >10%	8.1% (79)	12.7% (69)	2.3% (10)	9.8% (4)	14.8% (4)	0% (0)

Pearson's chi-square analysis; 4 subjects without REGICOR.

Characteristics of our 1174 studied men and women are best shown in Table 4. Overall, fewer women were smokers ($p < 0.001$), and our male subjects had higher percentages of diabetes ($p < 0.001$), high blood pressure ($p < 0.001$), chronic renal insufficiency ($p = 0.001$) and cardiac ischemia ($p < 0.001$), presenting with more risk factors than our female participants. Regarding the history of aneurysmal disease, 3% (n = 35) had a family history of abdominal aneurismatic disease, with 26 of them being a first-degree family member.

Table 4. Means and proportions of selected characteristics in the screened population separated by sex.

	Total (n = 1174)	**Male (n = 695)**	**Female (n = 479)**
Cardiovascular Risk Factors% (N)			
Non-smokers [a]	48.6% (570)	35.0% (243)	68.3% (327)
Active smoker	14.8% (174)	71.8% (124)	10.4% (50)
Former smoker	36.6% (430)	47.2% (328)	21.3% (102)
Relative's history of AAA	3.0% (35) *	2.3% (16)	4% (19) *
First degree	74.3% (26)	87.5% (14)	63.2% (12)
Second degree	14.3% (5)	12.5% (2)	15.8% (3)
Diabetes mellitus [a]	17.7% (208)	23.2% (161)	9.8% (47)
Dyslipidemia	46.3% (544)	45.9% (319)	47% (225)
Hypertension [a]	47.8% (561)	52.9% (368)	40.3% (193)
Chronic renal disease [a]	4.1% (48)	5.8% (40)	1.7% (8)

Table 4. *Cont.*

	Total (n = 1174)	Male (n = 695)	Female (n = 479)
Cardiovascular events % (N)			
Cardiac ischemia [a]	6.4% (75)	9.8% (68)	1.5% (7)
Cerebrovascular events	4.3% (50)	4.9% (34)	3.3% (16)
Intermittent claudication	3.8% (45)	4.5% (31)	2.9% (14)
Anthropometric measurements % (N)			
Waist circumference (cm) [b] (SD)	99.5 (12)	102.4 (10.9)	95.3 (12.3)
Mean BMI (kg/m²) (SD)	27.7 (4.3)	27.8 (3.8)	27.6 (4.9)
Normal weight [a] (BMI 18.5–24.9)	28.3 % (332)	24.2% (168)	34.2% (164)
Overweight (BMI 25–30)	46.3% (543)	51.4% (357)	38.8% (186)
Obesity (BMI >30)	25.5% (299)	24.5% (170)	26.9% (129)

[a] 4 of these, unknown degree; [a] $p < 0.001$ Pearson's chi-square; [b] $p < 0.001$ Student's t-test; Percentage (n). Mean and standard deviation.

Characteristics of our participants with those obtained from the 2018 Catalan Health Survey "Enquesta Catalunya de Salut 2018" (ESCA) and primary care centers located in our area of treatment of Barcelona Nord were reviewed in order to better assess the representation of our sample participants with our overall area of treatment population, as shown in Table 5.

Table 5. Characteristics of our study participants and participants of Catalunya Health Survey 2018 (ESCA) and primary care centers of our region of study separated by sex.

	Our Study Participants (65 Years Old)			ESCA 2018 (65–74 Years Old)			Primary Care Centers (65 Years Old)		
	Male (n = 695)	Female (n = 479)	Total (n = 1 174)	Male (n = 206)	Female (n = 224)	Total (n = 430)	Male (n = 1653)	Female (n = 1994)	Total (n = 3647)
Active smoker	17.8% (15.0–20.7)	10.4% (7.7–13.2)	14.8% (12.8–16.9)	18.0% (12.7–23.2)	8.0% (4.5–11.6)	12.8% (4.5–11.6)	20.8% (18.8–22.7)	13.4% (11.9–14.9)	16.8% (15.5–17.9)
Diabetes mellitus	23.2% (20.0–26.3)	9.8% (7.2–12.5)	17.7% (15.5–19.9)	27.2% (21.1–33.3)	20.1% * (14.8–25.3)	23.5% * (19.5–27.5)	23.1% (21.0–25.1)	12.8% * (11.4–14.3)	17.5% (16.2–18.7)
Dyslipidemia	45.0% * (42.2–49.6)	47.0% (42.5–51.4)	46.3% (43.5–49.2)	34.5% * (28.0–41.0)	46.0% (39.5–52.5)	40.5% * (35.8–45.1)	39.4% * (37.1–41.8)	41.7% * (39.5–43.8)	40.7% * (39.1–42.3)
Hypertension	53.0% (49.2–56.7)	40.3% (35.9–44.7)	47.8% (44.9–50.6)	50.5% (43.7–57.3)	48.2% * (41.7–54.8)	49.3% (44.6–54.0)	53.8% (51.4–56.2)	62.9% * (60.8–65.1)	58.8% * (57.2–60.4)
Chronic renal disease	5.8% (4.0–7.5)	1.7% (0.5–2.8)	4.1% (3.0–5.2)	5.8% (2.6–9.0)	6.3% * (3.1–9.4)	6.1% * (3.8–8.3)	4.1% (3.1–5.0)	2.5% (1.6–2.9)	3.1% (2.5–3.6)
Cardiac ischemia	9.8% (7.6–12.0)	1.5% (0.4–2.5)	6.4% (5.0–7.8)	7.3% (3.7–10.8)	2.2% (0.3–4.2)	4.7% (2.7–6.6)	8.1% (6.8–9.4)	1.8% (1.2–2.4)	4.7% * (3.9–5.4)
Cerebrovascular events	4.9% (3.3–6.5)	3.3% (1.7–5.0)	4.3% (3.1–5.4)	5.8% (2.6–9.0)	2.7% (0.6–4.8)	4.2% (2.3–6.1)	3.1% (2.3–3.9)	1.4% (0.9–1.9)	2.1% * (1.7–2.6)
Overweight (BMI 25–30)	51.4% (47.7–55.1)	38.8% (34.5–43.2)	46.3% (43.4–49.1)	46.6% (39.8–53.4)	42.0% (35.5–48.4)	44.2% (39.5–48.9)	38.2% * (35.8–40.5)	30.9% * (28.9–33.0)	34.2% * (32.7–35.8)
Obesity (BMI >30)	24.5% (21.3–27.7)	26.9% (23.0–31.0)	25.5% (23.0–28.0)	27.2% (21.2–33.3)	17.4% * (12.4–22.4)	22.1% (18.2–26.0)	27.7% (25.6–29.7)	29.5% (27.5–31.5)	28.7% * (27.2–30.2)

Values are presented as percentages (95% Confidence Interval); Pearson's chi-square analysis; * Difference in values among both studies.

4. Discussion

In the present study, the prevalence of PAD in asymptomatic patients was 6.2% at age 65, which is in accordance with previous studies carried out in the Mediterranean area [13,14,17]. Risk factors are commonly known to be associated with other atherosclerotic diseases, with predominant factors being those of active smoking and diabetes [14]. This was shown to be similar in our study, with associated risk factors being smoking, history of diabetes, cardiac ischemia and a large waist circumference, smoking being the strongest association. Independent risk factors were also seen in logistic regression analysis in male smokers who had a history of diabetes and in female smokers who had hypertension. Knowing the important association of PAD with high cardiovascular risk groups, nonscreening in these subjects could lead to an underdiagnosis or even underestimate the true cardiovascular risk of this disease, outlining the importance of screening in these subgroups.

4.1. Differences According to Geography and Age

The worldwide prevalence of PAD is estimated to be 3–12% [18], affecting 27 million people in America and Europe [19]. In Europe, the prevalence of PAD is estimated at around 17.8% (99% CI: 16.8–18.8%) in the ages of 45 and 55, seen in the PANDORA study [10].

In Spain, however, the prevalence of PAD is considerably lower. The ESTIME study [20] estimated an 8.03% prevalence in similar age groups as the PANDORA study [10] in Europe, and studies published in the Catalonia Region of Spain concur with these low results. In this sense, Velescu et al. [14] reported a prevalence as low as 4.5% in Girona, and the Perart/Artper group of Barcelona reported a 7.6% prevalence [17]. Although both results are relatively much lower than estimated in Europe and the USA, the observed difference amongst the two might be due in part to the difference in the studied age group, with the Velescu group including subjects as young as 35 years old. This demonstrates the increase in prevalence with age that has already been described previously and the variability of prevalence with geographic regions due to ethnicity and dietary lifestyle, which tend to be unique to each region of study [21,22].

4.2. Sex Differences

Traditionally PAD is thought to be a male-predominant disease [23], but in recent studies, this has been proven otherwise, with an increase of prevalence in elderly women. About 20–30% of women over 70 years old are affected by PAD [24]. Peripheral arterial disease is frequently underdiagnosed due to atypical symptoms and its late presentation in females, and some studies even suggest a 10 to 12 years delay in appearance. Our prevalence of PAD in women was 3.8% compared to 7.9% in males, perhaps partly, again, due to the age group selection, needing further studies to observe prevalence in older female groups.

4.3. Risk Factors

The association of PAD with coronary artery disease is observed in 50% of patients and in 20% of patients with cerebrovascular disease [25,26], becoming therefore an important indicator of the coexistence of other cardiovascular disorders [27]. Up to 40% of subjects with PAD die from coronary artery disease and 10–20% by cerebral artery disease [10]. This risk is not only high in asymptomatic subjects but has a straight relationship among symptomatic individuals and severe PAD measured through ABI [28]. Overall, only less than 40% of subjects with PAD do not have concomitant coronary or cerebrovascular disease. Therefore, the association of PAD with other cardiovascular diseases is one of the main concerns of this disease. In our study, 13.6% of our subjects with PAD had an associated history of ischemic heart disease, and only a small few had a history of ischemic cerebrovascular disease.

The strongest predictor of PAD in those 65 years and younger has been associated with diabetes and smoking [3], although our study concurs with this from the male sex

perspective. This was different in our study for females. After logistic regression analysis, we found an independent risk factor association between women who were smokers and had hypertension ORs of 3.3 (95% CI: 1.2–9.0) and 5.2 (95% CI: 1.6–17.3), showing a stronger association between smoking and hypertension than with diabetes in our female group.

Stratification of cardiovascular risk was also attempted through the REGICOR score to identify those who had a higher risk of developing a cardiovascular event in the following 10 years. Altogether, we found higher scores in males ($p < 0.001$) with a high-risk score (considered > 10%) in those with PAD at 14.8% versus those with non-PAD at 12.7%. Therefore, screening with ABI in these subjects we believe to be important for the early implementation of secondary cardiovascular prevention.

4.4. Limitations

It should be noted that this study is part of a larger pilot screening program evaluating abdominal aorta aneurysms [8], thus explaining the chosen method of selection. Nonetheless, in order to minimize any selection bias that could affect our results, we reviewed our study population with the 2018 Catalan Health Survey "Enquesta Catalunya de Salut 2018" (ESCA) [29], focusing on the population age group, 65–74 years of age, and to the data obtained from our primary care centers in 2018, focusing on 65 years of age. We looked into various risk factors among our participants and those of ESCA and our primary care centers shown previously. In general, our participants are similar, although some differences are to be expected due to the wider age group of the survey and different methods of obtaining participant data. All this could lead to some variations seen in our sample participants. Due to limitations in our resources, we were forced to focus on one specific age group in our study. Additionally, our participation rate was 43.1%, which is consistent with the participation rate of other screening programs performed in our region that have a wider broadcasting and media diffusion such as colon and breast cancer screening in Barcelona, which achieved participation rates of 43.6% and 54.7%, respectively [30]. Overall, we believe this is a correct representation of our population, although these limitations should be noted.

5. Conclusions

In summary, the overall prevalence of PAD in North Barcelona at 65 years old is still significantly low compared to other regions of Europe [10], and male subjects were still predominantly affected by this disease than females at this age.

Our results concur with the literature on this topic for our region [14,17] and outline the strong association between male smokers with diabetes and female smokers with hypertension, stressing the importance of our focus on these subgroups and perhaps emphasizing the need for ABI screening programs, as well as implementing secondary prevention if PAD is confirmed in these specific group of subjects. Additional follow-up studies would be interesting to further evaluate our initial results and differences in sex, as well as prevalence in older populations.

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Abbreviations

PAD	peripheral arterial disease
ABI	ankle–brachial index
OR	odds ratio
CI	confidence interval
AAA	abdominal aortic aneurysm
BMI	body mass index (kg/m^2)
SD	standard deviation

References

1. Aronow, W.S. Peripheral arterial disease of the lower extremities. *Arch. Med. Sci.* **2012**, *8*, 375–388. [CrossRef]
2. Fowkes, F.G.; Aboyans, V.; Fowkes, F.J.; McDermott, M.M.; Sampson, U.K.; Criqui, M.H. Peripheral artery disease: Epidemiology and global perspectives. *Nat. Rev. Cardiol.* **2017**, *14*, 156–170. [CrossRef]
3. Criqui, M.H.; Aboyans, V. Epidemiology of Peripheral Artery Disease. *Circ. Res.* **2015**, *116*, 1509–1526. [CrossRef]
4. Hirsch, A.T.; Haskal, Z.J.; Hertzer, N.R.; Bakal, C.W.; Creager, M.A.; Halperin, J.L.; Hiratzka, L.F.; Murphy, W.R.; Olin, J.W.; Puschett, J.B.; et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic). *Circulation* **2006**, *113*, e463–e654. [CrossRef]
5. Hirsch, A.T.; Criqui, M.H.; Treat-Jacobson, D.; Regensteiner, J.G.; Creager, M.A.; Olin, J.W.; Krook, S.H.; Hunninghake, D.B.; Comerota, A.J.; Walsh, M.E.; et al. Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care. *JAMA* **2001**, *286*, 1317–1324. [CrossRef]
6. Aboyans, V.; Ricco, J.B.; Bartelink, M.L.E.; Björck, M.; Brodmann, M.; Cohnert, T.; Desormais, I. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in Collaboration With the European Society for Vascular Surgery (ESVS): Document Covering Atherosclerotic Disease of Extracranial Carotid and Vertebral, Mesenteric, Renal, Upper and Lower Extremity arteries Endorsed By: The European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur. Heart J.* **2018**, *39*, e35–e41.
7. Aboyans, V.; Criqui, M.H.; Abraham, P.; Allison, M.A.; Creager, M.A.; Diehm, C.; American Heart Association Council on peripheral Vascular Disease; Council on Epidemiology and prevention; Council on clinical Cardiology; Council on Cardiovascular nursing; et al. Measurement and interpretation of the ankle-brachial index: A scientific statement from the American Heart Association. *Circulation* **2012**, *126*, 2890–2909. [CrossRef]
8. Benjamin, E.J.; Virani, S.S.; Callaway, C.W.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Muntner, P.; American Heart Association Council on Epidemiology; Prevention Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report from the American Heart Association. *Circulation* **2018**, *137*, e67–e492. [CrossRef]
9. Firnhaber, J.M.; Powell, C.S. Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. *Am. Fam. Physician* **2019**, *99*, 362–369.
10. Cimminiello, C.; Kownator, S.; Wautrecht, J.C.; Carvounis, C.P.; Kranendonk, S.E.; Kindler, B.; Borghi, C. The PANDORA study: Peripheral arterial disease in patients with non-high cardiovascular risk. *Intern. Emerg. Med.* **2011**, *6*, 509–519. [CrossRef]
11. SSchramm, K.; Rochon, P.J. Gender Differences in Peripheral Vascular Disease. *Semin. Interv. Radiol.* **2018**, *35*, 009–016. [CrossRef]
12. Norgren, L.; Hiatt, W.R.; Dormandy, J.A.; Nehler, M.R.; Harris, K.A.; Fowkes, F.G. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J. Vasc. Surg.* **2007**, *45*, S5–S67. [CrossRef]
13. Ramos, R.; Quesada, M.; Solanas, P.; Subirana, I.; Sala, J.; Vila-Domènech, J.S.; Masiá, R.; Cerezo, C.; Elosua, R.; Grau, M.; et al. Prevalence of Symptomatic and Asymptomatic Peripheral Arterial Disease and the Value of the Ankle-brachial Index to Stratify Cardiovascular Risk. *Eur. J. Vasc. Endovasc. Surg.* **2009**, *38*, 305–311. [CrossRef]
14. Velescu, A.; Clara, A.; Peñafiel, J.; Grau, M.; Degano, I.R.; Martí, R.; Ramos, R.; Marrugat, J.; Elosua, R. Peripheral Arterial Disease Incidence and Associated Risk Factors in a Mediterranean Population-based Cohort. The REGICOR Study. *Eur. J. Vasc. Endovasc. Surg.* **2016**, *51*, 696–705. [CrossRef]

15. Fite, J.; Gayarre-Aguado, R.; Puig, T.; Zamora, S.; Escudero, J.R.; Solà Roca, J.; Bellmunt-Montoya, S. Feasibility and Efficiency Study of a Population-Based Abdominal Aortic Aneurysm Screening Program in Men and Women in Spain. *Ann. Vasc. Surg.* **2021**, *73*, 429–437. [CrossRef]
16. Amor, A.J.; Serra-Mir, M.; Martínez-González, M.A.; Corella, D.; Salas-Salvad, J.; Fit, M.; Francisco, S. PREDIMED Investigators. Prediction of Cardiovascular Disease by the Framingham-REGICOR Equation in the High-Risk PREDIMED Cohort: Impact of the Mediterranean Diet across Different Risk Strata. *J. Am. Heart Assoc.* **2017**, *6*, e004803. [CrossRef]
17. Alzamora, M.T.; Forés, R.; Baena-Díez, J.M.; Pera, G.; Toran, P.; Sorribes, M.; Llussà, J. The Peripheral Arterial disease study (PERART/ARTPER): Prevalence and risk factors in the general population. *BMC Public Health* **2010**, *10*, 1–11. [CrossRef]
18. Harris, L.; Dryjski, M. Epidemiology, Risk Factors and Natural History of Lower Extremity Peripheral Artery Disease. *UpToDate* **2020**, *23*, 2020. Available online: https://www.uptodate.com/contents/epidemiology-risk-factors-and-natural-history-of-lower-extremity-peripheral-artery-disease (accessed on 15 January 2020).
19. Suárez, C.; Lozano, F.S.; Bellmunt, S.; Camafort, M.; Díaz, S.; Mancera, J.; Carrasco, E.; Lobos, J.M. *Documento de Consenso Multidisciplinar en Torno a la Enfermedad Arterial Periférica*, 1st ed.; Luzán 5, S.A.: Madrid, Spain, 2012.
20. Blanes, J.I.; Cairols, M.A.; Marrugat, J. Prevalence of peripheral artery disease and its associated risk factors in Spain: The ESTIME Study. *Int. Angiol.* **2009**, *28*, 20–25.
21. Dontas, A.S.; Zerefos, N.S.; Panagiotakos, D.B.; Vlachou, C.; Valis, D.A. Medieterranean diet and prevention of coronary heart disease in the elderly. *Clin. Interv. Aging.* **2007**, *2*, 109. [CrossRef]
22. McDermott, M.M.; Liu, K.; Criqui, M.H.; Ruth, K.; Goff, D.; Saad, M.H.; Sharrett, A.R. Ankle-Brachial Index and subclinical cardiac and carotid disease: The multi-ethnic study of atherosclerosis. *Am. J. Epidemiol.* **2005**, *162*, 33–41. [CrossRef]
23. Parvar, S.L.; Thiyagarajah, A.; Nerlekar, N.; King, P.; Nicholls, S.J. A systematic review and meta-analysis of gender differences in long-term mortality and cardiovascular events in peripheral artery disease. *J. Vasc. Surg.* **2021**, *73*, 1456–1465. [CrossRef]
24. Criqui, M.H.; Fronek, A.; Barrett-Connor, E.; Klauber, M.R.; Gabriel, S.; Goodman, D. The prevalence of peripheral arterial disease in a defined population. *Circulation* **1985**, *71*, 510–515. [CrossRef]
25. Fowkes, F.G.R.; Housley, E.; Cawood, E.H.H.; Macintyre, C.C.A.; Ruckley, C.V.; Prescott, R.J. Edinburgh Artery Study: Prevalence of Asymptomatic and Symptomatic Peripheral Arterial Disease in the General Population. *Int. J. Epidemiol.* **1991**, *20*, 384–392. [CrossRef]
26. Olinic, D.M.; Spinu, M.; Olinic, M.; Homorodean, C.; Tataru, D.A.; Liew, A.; Catalano, M. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. *Int. Angiol.* **2018**, *37*, 327–334. [CrossRef]
27. Venermo, M.; Sprynger, M.; Desormais, I.; Björck, M.; Brodmann, M.; Cohnert, T.; De Carlo, M.; Espinola-Klein, C.; Kownator, S.; Mazzolai, L.; et al. Editor's Choice—Follow-up of Patients After Revascularisation for Peripheral Arterial Diseases: A Consensus Document From the European Society of Cardiology Working Group on Aorta and Peripheral Vascular Diseases and the European Society for Vascular Surgery. *Eur. J. Vasc. Endovasc. Surg.* **2019**, *58*, 641–653.
28. Newman, A.B.; Shemanski, L.; Manolio, T.A.; Cushman, M.; Mittelmark, M.; Polak, J.F.; Siscovick, D. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arter. Thromb. Vasc. Biol.* **1999**, *19*, 538–545. [CrossRef] [PubMed]
29. Resultats de L'enquesta de Salut de Catalunya (ESCA). Departament De Salut, Generalitat De Catalunya. Available online: https://salutweb.gencat.cat/ca/el_departament/estadistiques_sanitaries/enquestes/esca/resultats_enquesta_salut_catalunya/ (accessed on 2 February 2021).
30. Burón, A.; Grau, J.; Andreu, M.; Augé, J.M.; Guayta-Escolies, R.; Barau, M.; Castells, A. Programa de Detección Precoz de Cáncer de Colon y Recto de Barcelona: Indicadores de la primera ronda de un programa con participación de la farmacia comunitaria. *Med. Clin.* **2015**, *145*, 141–146. [CrossRef]

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Conflicts of interest.

I have no conflict of interest to declare.