# Prevalence of peripheral artery disease and its associated risk factors in Spain: The ESTIME Study

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***Aim.*** **Several studies have demonstrated that patients with peripheral arterial disease (PAD), are at an increased risk of morbidity and mortality compared with those without PAD. However, few population-based studies have addressed the prevalence of PAD and intermittent claudication (IC). We assessed the prevalence of and the factors associated with PAD and IC in the Spanish population.**
***Methods.*** **A cross sectional study with 1324 participants aged 55 to 84 years randomly selected from the census was conducted in 12 Spanish regions. The presence of PAD and IC was determined by an ankle-brachial index (ABI) <0.90 in either leg and by means of the Edinburgh questionnaire, respectively, fulfilled together with a detailed past history. All participants had blood pressure, body mass index, glycemia, and lipid profile measured.**
***Results.*** **The response rate was 63.9% (846/1 324). ABI prevalence of PAD was 8.03% The prevalence of symptoms of definite or atypical IC was 6%. Subjects with an ABI <0.9 were more likely to be older, men, diabetics, current smokers, with coronary heart disease, with higher systolic pressure and with higher triglyceride levels than participants with ABI ≥0.9.**
***Conclusion.*** **ESTIME study confirms the high prevalence of asymptomatic PAD, and its relation with typical cardiovascular risk factors. ABI provides early diagnosis before claudication symptoms in a high proportion of patients. ABI could contribute to developing early prevention programmes.**
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Peripheral arterial disease (PAD) is a manifestation of systemic arterial disease and can present as intermittent claudication (IC), occasionally as critical ischemia, or may remain asymptomatic. The general population prevalence of asymptomatic PAD varies between 0.9% and 22%, with a symptomatic/asymptomatic ratio of between 1/0.9 and 1/6.

A detailed analysis of the available data suggests that for each patient with IC there are three with asymptomatic PAD.[1] The most important consequence of PAD, in terms of morbidity and mortality, is that it serves as an indirect marker for arteriosclerotic disease in other vascular territories, is associated with other factors of cardiovascular disease risk, and a higher morbidity-mortality relative to the general population.[2] As IC is a subjective symptom, the validity of different questionnaires for its detection, such as that of Rose *et al*. and the Edinburgh questionnaire, has been placed in doubt.[3, 4] Since asymptomatic PAD has similar prognostic implications as that of symptomatic, the ankle-brachial index (ABI) is used to detect its presence. An ABI value of <0.9 has a sensitivity of 95% and a specificity of 100% for arterial stenosis ≥50%.[5]

Despite its importance, there is a paucity of population studies, and even less in Spain, on the prevalence of symptomatic and asymptomatic PAD, and on the associated risk factors.[6, 7] Hence we carried out the ESTIME (*ESTudio de la Isquemia de Miembros Inferiores en España;* Study of Lower Limb Ischemia in Spain).

The aim of our study was to determine the prevalence of PAD in the general population using a

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*On behalf of the ESTIME study investigators.

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clinical questionnaire together with the ABI. We analyzed as well, the factors associated with PAD development in Spain, and the predictive capacity of the Edinburgh questionnaire to identify subjects with an abnormal ABI <0.9.

## Materials and methods

A cross-sectional study with random selection of participants aged 55 to 84 years from the local census of populations in the participating centres was designed by the ESTIME Study investigators.

### *Inclusion criteria*

A sample was randomly selected in 12 areas from Spain. The study sample was stratified by gender and age that reflected the distributions in the general population. The selected participants were notified in their own towns by a letter informing them of the aims of the study, and the tests to be performed. Participants were requested to attend, after an overnight fast, the local participating health centre for a complete a physical examination and to have a blood sample taken for biochemical analyses. A telephone number for inquiries was provided. If the participants had a telephone, they were contacted one week before the examination to confirm the attendance. Examinations were performed by a trained vascular surgeon in an outpatient clinic of the reference hospital in the area.

All participants had ABI, blood pressure, body mass index measured. A venous blood sample was taken for glucose and lipid profile determinations.

The level of physical activity (PA) was recorded from a questionnaire that noted the type, frequency and average time devoted to typical leisure-time physical activities undertaken every week. The oxygen consumption per minute of each activity was used to classify the type of physical activity into low (<6 kcal/min) and moderate/intense (≥ 6 kcal/min). The proportions of participants undertaking such weekly types of physical activity were recorded.

The Edinburgh questionnaire was administered, together with a questionnaire on the subject's history of comorbidity, leisure-time PA, smoking and alcohol consumption in the outpatient clinic. Alcohol consumption was considered excessive (alcohol abuse) if the intake was >40 g/day in men and 24 g/day in women.

Claudication was defined according to the answers to the Edinburgh questionnaire.[4] The questionnaire includes the following questions:

1. Do you get any pain or discomfort in your legs when you walk?
2. Does this pain ever occur when you are standing still or sitting? (No)
3. Do you get this pain if you walk uphill or hurry? (Yes)
4. Do you get this pain if you walk at an ordinary pace on level ground? (No=mild, Yes=moderate/severe)
5. What happens to the pain if you stand still? (It goes away)
6. Does the pain disappear within 10 minutes or less when you stand still (Yes)
7. Where do you get the pain or discomfort? (a schematic representation of a leg is presented to the patient)

Based on the response we classified patients into the following categories:

1) Definite claudication. All the following conditions needed to be fulfilled.
- Yes to question 1
- No to question 2
- Yes to question 3
- Yes or No to question 4
- And "usually the pain disappears after 10 or less minutes rest", to question 5
- And the calf area marked on the diagram of the leg.

2) Atypical claudication.
- Yes to question 1
- No to question 2
- Yes to question 3
- Yes or No to question 4
- And "usually the pain disappears after 10 or less minutes rest", to question 5
- And the thigh or the buttock marked on the diagram of the leg, and in the absence of calf pain

3) No claudication. Any other combination of responses.

### *Statistical analysis*

Prevalence rates were standardized for the overall population distribution. Differences in categorical variables among patients segregated by PA quartiles were assessed with the $\chi^2$ test and $?\chi^2$ for trends. ANOVA with orthogonal polynomial coef-

TABLE I.—*Age-standardized prevalence, in Spanish population aged 55 to 84 years, of PAD segregated by ankle-brachial index <0.9, by definite category defined by the Edinburgh questionnaire , and by definite or atypical categories of the Edinburgh questionnaire.*

| | Men (*/**) | Women (*/**) | All (*/**) |
|---|---|---|---|
| 1 | 11%/ (8.6-15.0) | 6.6% (4.9-9.8) | 8.03% (6.9-10.8) |
| 2 | 1.1% (0.8-3.4) | 0.7% (0.5-2-7) | 0.8% (0.6-2.0) |
| 3 | 9.5% (7.3-13.4) | 3.5% (2.4-6.2) | 6.0% (4.8-8.1) |

1) Ankle-brachial index <0.9; 2) definite claudication; 3) definite or atypical claudication; *prevalence; **95%CI.

ficients was used to test linear trends of the means of the continuous variables of the PA quartiles.

Differences in categorical variables among patients without claudication, definite claudication by questionnaire, and ABI <0.9 alone were assessed with the $\chi^2$ test and $\chi^2$ for trends. Student's t-test or the Mann-Whitney U test were used as appropriate for continuous variables and the $\chi^2$ test for categorical variables were used to compare means and proportions, respectively, between non-claudication and definite claudication based on the questionnaire or on the ankle-brachial index of <0.9. The concordance between the classification of the ABI and the Edinburgh questionnaire was assessed by the statistic. Adjusted odds ratio of ABI <0.9 for definite or atypical claudication by questionnaire, as compared with the non-claudication group (ABI ≥0.9) was estimated using unconditional logistic regression. To control for different characteristics between claudication groups, all variables which met the criteria for being a confounding factor (i.e. those factors which, in categories of ABI, that were statistically different at an risk level of 0.05 in bivariate analysis, and which were, as well, associated with definite claudication defined by the questionnaire) were included in the models, together with age and gender.

TABLE II.—*Characteristics of the participants aged 55 to 84 years segregated with respect to PAD as defined by ankle-brachial index <0.9.*

| | ABI≥00.9 N.=778 | ABI<0.9 N.=68 | P value |
|---|---|---|---|
| Age; years* | 67.2 (7.5) | 71.3 (8) | <0.001 |
| Gender; % women | 57.4 | 39.7 | 0.005 |
| History | | | |
| Diabetes; % | 16.7 | 26.9 | 0.036 |
| Current smokers; % | 10.1 | 22.1 | 0.002 |
| Hypercholesterolemia; % | 41.3 | 46.2 | 0.451 |
| Hypertension; % | 43.2 | 50 | 0.284 |
| Other chronic diseases; % | 68.8 | 66.2 | 0.662 |
| Coronary heart disease; % | 8.5 | 19.4 | 0.003 |
| Cerebrovascular disease; % | 3.8 | 8.8 | 0.056 |
| *Physical activity Intensity* | | | |
| None/low | 87.9 | 94.1 | 0.125 |
| Moderate/intense | 12.1 | 5.9 | |
| *Edinburgh questionnaire* | | | |
| Without claudication | 97.2 | 89.7 | 0.006 |
| Atypical claudication | 1.7 | 7.4 | |
| Definite claudication | 1.2 | 2.9 | |
| ABI* | 1.07 (0.12) | 0.72 (0.18) | <0.001 |
| BP* | | | |
| Systolic BP* (mmHg) | 143 (20) | 151 (23) | 0.001 |
| Diastolic BP (mmHg)* | 81 (13) | 84 (11) | 0.133 |
| *Blood sample determinations* | | | |
| Total cholesterol* | 222 (38) | 210 (33) | 0.059 |
| HDL-cholesterol* | 61 (48) | 81 (116) | 0.033 |
| Triglycerides** | 84 (60-117) | 98 (64-121) | 0.262 |
| Glycaemia** | 96 (86-109) | 98 (82-119) | 0.626 |
| Body Mass Index | | | |
| Body Mass Index (kg/m2)* | 28.6 (4.4) | 28.3 (3.5) | 0.615 |
| Body Mass Index >30; % | 34.5 | 28.4 | 0.309 |
| CVD risk REGICOR** | 23 (16.5-30.9) | 27 (17.7-38.4) | 0.187 |

*Mean (SD); **median (1st quartile-3rd quartile); ¶55 to 74 years in absence of CHD and CVD alone; ABI: ankle-brachial index; BP: blood pressure; HDL: high density lipoprotein.

## Results

The response rate to the invitation letter to participate in the study was 63.9% (846 of 1324 randomly selected individuals) in the 12 areas of Spain.

Participants in the claudication categories were older, more often men, had diabetes and with hypercholesterolemia. There were more current smokers in the group and there was a more frequent history of coronary heart disease (CHD) together with abnormal blood pressure, glycemia and lipid profile.

The age-standardized prevalence of claudication, according to the Edinburgh questionnaire and according to an ABI <0.9, are presented in Table I. The prevalence according to the Edin-

TABLE III.—*Characteristics of the participants aged 55 to 84 years segregated by claudication status and the definite or atypical category as defined by the Edinburgh questionnaire.*

| | Without claudication N.=796 | Atypical or definite claudication N.=50 | P value |
|---|---|---|---|
| Age; years* | 67.5 (7.6) | 67.8 (8.1) | 0.800 |
| Gender; % women | 57.5 | 30.0 | <0.001 |
| History | | | |
| Diabetes; % | 16.2 | 40.4 | <0.001 |
| Current smokers; % | 10.4 | 22.0 | 0.011 |
| Hypercholesterolemia; % | 40.6 | 60.9 | 0.007 |
| Hypertension; % | 43.1 | 53.1 | 0.174 |
| Other chronic diseases; % | 68.7 | 68.8 | 0.998 |
| Coronary heart disease; % | 9.2 | 12 | 0.456 |
| Cerebrovascular disease; % | 4.1 | 6 | 0.459 |
| *Physical activity Intensity* | | | |
| None/low; % | 88.1 | 92 | 0.410 |
| Moderate/intense; % | 11.9 | 8 | |
| ABI | | | |
| ABI* | 1.05 (0.15) | 0.96 (0.23) | <0.001 |
| ABI <0.9; % | 6.9 | 26.0 | <0.001 |
| BP* | | | |
| Systolic BP; mmHg * | 143 (21) | 147 (20) | 0.272 |
| Diastolic BP; mmHg* | 82 (13) | 81 (11) | 0.690 |
| *Blood sample determination* | | | |
| Total cholesterol* | 222 (38) | 211 (37) | 0.136 |
| HDL-cholesterol* | 64 (60) | 48 (19) | 0.177 |
| Triglycerides** | 84 (60-116) | 96 (65-152) | 0.173 |
| Glycemia** | 96 (86-109) | 96 (88-131) | 0.186 |
| Body Mass Index | | | |
| Body Mass Index; kg/m$^2$* | 28.6 (4.4) | 28.8 (4.2) | 0.687 |
| Body mass index >30; % | 33.7 | 38.0 | 0.535 |
| REGICOR CV risk** ¶ | 22.7 (16.5-31) | 26.8 (17.1-34) | 0.538 |

*: Mean (SD); **: Median (1st quartile-3rd quartile); ¶ 55 to 74 years in absence of CHD and CVD alone; ABI: ankle-brachial index; BP: blood pressure; HDL: high density lipoprotein.

burgh questionnaire was much lower than that defined by an ABI <0.9.

The characteristics of patients segregated by PAD status defined by an ABI <0.9 compared to the rest of the cohort are presented in Table II. Those with an ABI <0.9 were older, more often males, had diabetes, and were current smokers. CHD prevalence and 10-year cardiovascular disease risk were higher among patients with ABI <0.9. Systolic blood pressure, glycemia and triglycerides were also higher in these patients.

The characteristics of patients segregated by claudication status according to the definite or the atypical category definition of the Edinburgh questionnaire are presented in Table III. Those with definite claudication were more often male, had diabetes and hypercholesterolemia.

TABLE IV.—*Agreement between definite claudication and definite or atypical diagnosis with the Edinburgh questionnaire, and ankle-brachial index <0.9.*

| | ABI <0.9 | ABI ≥0.9 | Total |
|---|---|---|---|
| *Definite claudication* | | | |
| Positive | 3 | 4 | 7 |
| Negative | 65 | 774 | 839 |
| *Definite or atypical claudication* | | | |
| Positive | 13 | 37 | 50 |
| Negative | 55 | 741 | 796 |

The concordance between the definite category as determined by the Edinburgh questionnaire and the ABI <0.9 was=0.06. The sensitivity of definite claudication was only 4.4% (3 of 68 participants) and specificity was 99.5% (774 of 778 participants) as compared to the ABI<0.9. The positive predictive value was 42.9% (3 of 7 participants) and the negative predictive value was 92.3% (774 of 839 participants). The concordance between definite or atypical categories as defined by the Edinburgh questionnaire and ABI <0.9 was=0.16. The sensitivity of definite or atypical claudication defined by the Edinburgh questionnaire was 19.1% (13 of 68 participants) and specificity was 95.2% (741 of 778 participants) as compared to the ABI <0.9. The positive predictive value was 26% (13 of 50 participants) and the negative predictive value was 93.1% (741 of 796 participants). The distributions of the misclassification for definite, and definite or atypical, claudication are summarised in Table IV.

Following the adjustment for potential confounding factors (age, systolic blood pressure and gender), the odds ratio of ABI<0.9 was 3.08 (95% confidence interval 1.21 to 7.83) for the definite or atypical claudication category according to the Edinburgh questionnaire.

## Discussion

PAD is a vascular disease syndrome of high prevalence. When symptomatic, there are symptoms of intermittent claudication that can progress on

occasions to critical ischemia with the possible of loss of the limb. In patients with PAD, the prevalence of coronary disease varies between 20 and 60% depending on the clinical history, physical examination and electrography, and up to 90% in those undergoing coronary angiography. Similarly, cerbrovascular disease has been diagnosed in 40% to 50% of the patients with PAD.[8] Those patients with PAD have a greater cardiovascular morbidity-mortality than those who do not have PAD.[9] Despite its importance, there are very few population-based studies on the prevalence of PAD, especially in Spain, and this was the reason for conducting the present ESTIME study.

The rate of response to participate in the ESTIME study of 63.9% was within the range of other similar studies.[10]

The prevalence of PAD was 8.03%; 6.6% in females and 11% in males. Intermittent claudication, definite or atypical, as defined by the Edinburg questionnaire4, which theoretically increases the sensitivity of the classical questionnaire of Rose *et al*. adopted by the WHO,[3] was 6%; 3.5% in females and 9.5% in males. Of those with PAD, only 10.3% had signs/symptoms of claudication. These data confirm other published studies.[1, 10-12]

However, the validity of the questionnaires has been placed in doubt because of the method of evaluation of the symptoms and for being too subjective. On the one hand a minority of the patients with PAD have IC as a result of not taking enough exercise and, on the other, many of the patients with IC are elderly and, in whom, the symptoms encountered are considered to be expected with increased age. The occupations of the patients and their life-style habits have considerable influence on the presence/absence of the symptoms. Perhaps these explain the low sensitivity obtained in our study of the questionnaire compared to the gold standard which, in the present case, is the ABI. A resting ABI of 0.9 as a possible cut-off point has a sensitivity of 95% and a specificity of 100% for stenosis ≥50%; the values of <0.9 being considered evidence of arterial disease of the lower limbs and the lower values of this index indicating more severe obstruction5. Hence, the ABI is an excellent method in identifying PAD. Other studies have confirmed our findings, some in populations and others in groups of patients. The studies by Criqui *et al*.[13] and the San Luis Valley study [14] in patients with diabetes, and the most recent PARTNERS study indicate a higher prevalence of IC not only in patients with diabetes but also in those receiving attention in primary care centres.[15]

PAD is considered an indicator of generalised arteriosclerosis and, as with cardiovascular disease, is associated with other cardiovascular disease risk factors such as smoking, diabetes and hypertension.[10, 12]

## Conclusions

The ESTIME study confirms the high prevalence of asymptomatic PAD and the low prevalence of IC. The great majority of the individuals with PAD do not have symptoms of IC. In a high percentage of patients, the ABI<0.9 provides an early diagnosis even before the symptoms of IC appear. With the well-documented poor prognosis in this group of patients, a simple measurement as ABI is warranted as a screening tool in primary care centres, the objective being to identify those individuals who would benefit from early intervention programs against atherothrombotic complications.

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## Appendix I

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