Prevalence of carotid stenosis and silent myocardial ischemia in asymptomatic subjects with a low ankle-brachial index

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Objective: **Subjects with symptomatic peripheral artery disease (PAD) have an elevated prevalence of carotid stenosis and of silent myocardial ischaemia. As such, clinical guidelines advocate the detection of sub-clinical vascular disease in this population. However, the prevalence of occult vascular disease in asymptomatic patients with a low ankle-brachial index (ABI) has not been previously evaluated.**

Methods: **Cross-sectional study in five primary care centres for patients' selection and two University Hospitals for further assessment. Subjects were 1070 asymptomatic individuals between 60 and 80 years of age with at least two cardiovascular risk factors, selected for ankle-brachial index measurement. Eighty five subjects with an ABI <0.9 and an equal number of controls, matched for age, gender, diabetes, and smoking habit, and with a normal ABI, were referred to the Hospital for carotid ultrasound and exercise stress tests (EST). Main outcome measures were prevalence of a carotid stenosis >50% and an abnormal EST.**

Results: **The prevalence of a low ABI in the overall population was 9.1%. A carotid stenosis >50% was detected in 14.3% of the subjects with a low ABI and in 4.7% of the control subjects (Odds Ratio [OR]: 3.37; 95% Confidence Interval [CI]: 1.04-10.93, $P = .033$). The prevalence of a positive EST test was 16.2% in those with a low ABI and 10.5% in control subjects (OR: 1.65; 95% CI: 0.63-4.29, $P = .309$). These prevalences were higher in older subjects, in those with hypertension or diabetes, or in those with dyslipidemia.**

Conclusion: **Our results indicate that in high-risk asymptomatic subjects >60 years of age, the presence of an ABI <0.9 identifies a subgroup of the population with an increased prevalence of carotid stenosis and of silent myocardial ischemia and, as such, are candidates for closer follow-up. (J Vasc Surg 2008;■■:■■■.)**

Subjects with symptomatic peripheral artery disease (PAD) have an elevated rate of cardiovascular morbidity and mortality[1] and, as such, they are candidates for intensive treatment of their cardiovascular risk factors.[2] Due to this high risk, some authors and consensus documents have recommended the systematic search for occult coronary and cerebrovascular disease in this population.[3-7]

Asymptomatic subjects with PAD also have an elevated risk of cardiovascular disease which, in some studies, parallels that of symptomatic individuals.[8] For that reason, and in order to improve risk stratification, ankle-brachial index (ABI) measurement has been recommended in subjects of intermediate risk.[2,5] This has come to a widespread use of ABI measurement in daily clinical practice and to the identification of a high number of asymptomatic individuals with PAD. However, the prevalence of occult coronary and cerebrovascular disease in this asymptomatic population has not been investigated previously and, for that reason, specific recommendations on the screening for carotid stenosis or coronary artery disease cannot be made at present.

The objective of the present study was to evaluate the prevalence of significant carotid artery disease and of silent myocardial ischemia in subjects >60 years of age with asymptomatic PAD and without known cardiovascular disease. We compared these patients with a control group, matched for age, gender, diabetes, and smoking habit and with a normal ABI.

PATIENTS AND METHODS

Five health-care centers, two in Madrid and three in Santiago de Compostela (Spain), were selected for the study. Between January 2007 and June 2007, subjects between 60 and 80 years of age and with at least two cardiovascular risk factors (being male, current smoker, hypertension, diabetes, or low density lipoprotein (LDL)-cholesterol ≥4.1 mmol/L) were invited to participate. Those individuals who had a previous diagnosis of coronary, cerebrovascular, or PAD, or those who were being investigated because of chest pain, clinical manifestations compatible with stroke, or transient ischaemic attack (TIA) or who had clinical symptoms suggestive of typical inter-

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Competition of interest: none.

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Table I. Characteristics of the study population (n = 1070) separated by normal (n = 973) or low (n = 97) ankle-brachial index

Characteristic	*Total*	*Low ABI (<0.9) 9.1%*	*Normal ABI (≥0.9) 90.9%*	P
Gender; % males	52.9	54.6	52.7	.715
Age; years	66.7 (6.5)	69.3 (6.7)	66.1 (6.8)	.01
Smokers or ex-smokers; %	26.1	40.2	24.4	.002
Hypertension: %	62.4	64.6	62.6	.645
Diabetes; %	35.2	39.2	34.7	.383
BMI; kg/m^2	29.3 (4.3)	29.7 (4.6)	29.8 (4.4)	.84
SBP; mmHg	146 (20)	151 (19)	145 (19)	.005
DBP; mmHg	81 (10)	80 (13)	81 (10)	.30
LDL-cholesterol; mmol/L	3.56 (.90)	3.72 (.90)	3.56 (.91)	.11
HDL-cholesterol; mmol/L	1.37 (.33)	1.30 (.33)	1.37 (.33)	.04
Triglycerides; mmol/L	1.45 (.88)	1.53 (.94)	1.45 (.85)	.365
BP lowering drugs; %	49.5	53.4	49	.475
Lipid lowering drugs; %	37.1	35.3	37.3	.746

BMI, body mass index; *DBP,* diastolic blood pressure; *HDL,* high density lipoprotein; *LDL,* low density lipoprotein; *SBP,* systolic blood pressure.

mittent claudication were excluded. Also excluded were those patients with atrial fibrillation or receiving treatment with drugs that could alter the basal ST segment such as digoxin, or who were incapable of understanding the protocol and of providing informed consent to participation. On recruitment, all subjects had a complete clinical history and physical examination that included height, weight, and blood pressure measurement. A blood sample was taken for analysis of glucose, total cholesterol, LDL-cholesterol, high density lipoprotein (HDL)-cholesterol, and total triglycerides.

The diagnosis of hypertension required a blood pressure ≥140/90 mmHg, ≥130/80 mmHg for subjects with diabetes or chronic kidney disease, or being on treatment with anti-hypertensive drugs. The diagnosis of diabetes was established in accordance with the criteria of the American Diabetes Association.[9]

All subjects had an ABI measurement performed with a bi-directional portable echo-Doppler of 8 MHz (Minidoppler HADECO ES-100, Kawasaki, Japan) and a calibrated mercury sphygmomanometer. The systolic blood pressure (SBP) was measured in the posterior tibial and pedal arteries of both lower limbs and the brachial artery of both upper limbs. The value of the ABI for each limb was calculated dividing the greater systolic blood pressure (SBP) obtained in each limb by the SBP of whichever was the higher in the upper limbs. The lowest value obtained was considered the ABI for that individual.

All patients with a low ABI (<0.9) and one control subject for each patient (1:1) matched for age (within five years), gender, diabetes, and smoking status were invited to continue in the study in one of the referral hospitals (Hospital Carlos III de Madrid or the Hospital Universitario de Santiago de Compostela) in which a carotid duplex scan and a EST were performed in all participants.

Carotid duplex protocol. Carotid ultrasound was evaluated with an Aplio 50 ultrasound scanner (Toshiba Medical Systems, Tokyo, Japan) with a PLT-704 AT transducer of 7.5 MHz. The patient was explored in the supine decubitus position with the head rotated away from the side being evaluated. The evaluation of carotid plaques (mode B) was performed in longitudinal and transversal planes at the level of the common, bulb, and internal carotid. The presence of a plaque was defined as a thickening of the arterial wall >1.5 mm.[10] Two measurements (longitudinal/transversal) were made to determine the grade of stenosis at the point of greater acceleration, applying the criteria of Grant et al.[11] Stenosis >50% was defined as a peak systolic velocity in the internal carotid artery >125 cm/s, an end-diastolic velocity >40 cm/s, and an internal carotid artery/common carotid artery ratio >2.

EST protocol. The EST was performed according to the modified protocol of Bruce.[12] A positive test was defined as a decrease in the ST segment of at least 1 mm measured at 80 ms from the J point.

Statistical analyses. The quantitative variables are presented as means with standard deviation and the qualitative variables are presented as percentages. Comparisons between the quantitative variables were with the Student *t* test and between the qualitative variables were with the χ^2 test. The comparisons between cases (those with a pathologically low ABI) and control subject were with the McNemar test. Logistic regression analyses were performed to evaluate the independent contribution of the ABI and of each of the cardiovascular risk factors to the risk of carotid stenosis and of an abnormal EST. The software program used for all statistical analyses was the SPSS package (version 13.0; SPSS, Inc, Chicago, Ill).

All subjects gave written informed consent, and the study was approved by the Committee on Ethics and Research of the Hospital Carlos III in Madrid.

RESULTS

There were 1070 subjects included in the study (706 in Madrid and 364 in Santiago de Compostela). The overall mean ABI for the population sample was 1.06 (±0.14), ranging from 0.51 to 1.56. The overall prevalence of a low ABI was 9.1%. A 1.5% of all participants have an ABI >1.4. The characteristics of the population are presented in Table I.

Table II. Characteristics of cases (n = 85) and control subjects (n = 85)

Characteristic	*Cases*	*Controls*	P
Gender; % males	56.5	56.5	Matched
Age; years	70.1 (6.1)	69.9 (6.2)	Matched
Smokers or ex-smokers; %	38.8	38.8	Matched
Diabetes; %	36.5	36.5	Matched
BMI; kg/m^2	29.3 (4.5)	29.3 (4.3)	.865
Hypertension; %	67.9	64.7	.665
SBP; mmHg	152 (18)	142 (19)	.0001
DBP; mmHg	80 (13)	79 (9)	.841
LDL-cholesterol; mmol/L	3.79 (.92)	3.72 (.90)	.318
HDL-cholesterol; mmol/L	1.33 (.33)	1.32 (.32)	.958
Triglycerides; mmol/L	1.58 (1.0)	1.44 (.66)	.23
BP lowering drugs; %	55.7	45.8	.175
Lipid lowering drugs; %	34.5	26.2	.327
ABI	0.78 (0.11)	1.10 (0.11)	.0001

ABI, ankle-brachial index; *BMI,* body mass index; *BP,* blood pressure; *DBP,* diastolic blood pressure; *HDL,* high density lipoprotein; *LDL,* low density lipoprotein; *SBP,* systolic blood pressure.

Subjects with a low ABI were older, had a higher SBP, and a higher prevalence of smoking habit. Also, they had a lower concentration of HDL-cholesterol.

Of the 97 cases with an ABI <0.9, 12 did not give their consent to continue in the study. These individuals did not differ from the rest of participants in relation to age, gender, risk factors, and mean ABI values. The characteristics of the 85 subjects with a low ABI together with their corresponding 85 controls are presented in Table II. Both groups were well matched with respect to age, gender, diabetes, and smoking habit. There were no differences with respect to other risk factors except that SBP was higher in cases.

Carotid ultrasound. Carotid plaques were present in 53.6% of the cases compared to 43.5% of the controls. The prevalence of a stenosis >50% was 14.3% ± 5.9% in cases and 4.7% ± 2.3% in controls (Odds Ratio [OR]: 3.37; 95% Confidence Interval [CI]: 1.04-10.93, P = .033). There was only one individual case with stenosis >70%. The association between a low ABI and carotid stenosis lost its significance in the multivariate analysis (OR: 2.5; 95% CI: 0.75-8.4) after adjusting for SBP and other cardiovascular risk factors.

Considering only subjects with a low ABI, those with a stenosis >50% were more frequently women, older, active smokers, hypertensives, and with higher mean concentrations of LDL-cholesterol and plasma triglycerides (Fig 1).

Exercise stress test. The EST was valid in 75 subjects. In 10, there were basal alterations either in the ST segment or a left bundle branch block (five cases), failure to reach sub-maximum heart rate (three cases), or problems with the adaptation to the treadmill (two cases). The prevalence of a positive EST was 16.2% ± 4.2% in cases and 10.5% ± 3.5% in controls (OR: 1.65; 95% CI: 0.63-4.29, P = .309).

Considering only subjects with a low ABI, the prevalence of a positive EST was higher in subjects with advanced age, hypertension, and diabetes, and in those with high triglycerides or low HDL-cholesterol (Fig 2).

DISCUSSION

Our results showed that subjects >60 years of age with a low ABI and without known vascular disease have a prevalence of carotid stenosis three-fold greater, and of silent myocardial ischaemia 1.6-fold greater, albeit statistically non-significant, than subjects with a normal ABI. Carotid stenosis was present in 14.3% of patients, a percentage that was greater in women, in smokers, in subjects with advanced age, in those with hypertension, and in those with elevated levels of triglycerides or LDL-cholesterol. Similarly, the prevalence of silent myocardial ischaemia was higher in subjects with hypertension, diabetes, advanced age, high triglyceride, or low HDL-cholesterol concentrations.

The prevalence of carotid stenosis and of silent myocardial ischemia found in our study can be used to estimate the efficiency of searching for occult vascular disease in this population. The results are relevant given that ABI is being increasingly used in primary-care health centers as well as in specialized outpatient clinics for improving the stratification of cardiovascular disease risk.[2]

The prevalence of a carotid stenosis >50% ranges between 2% and 11% depending on the characteristics of the population studied,[13-15] and is higher, between 14% and 36%, in patients with symptomatic PAD.[4,16-20] The prevalence found in our study is situated at the lower end of the range observed in patients with symptomatic disease. There is considerable debate regarding the value of population screening to detect the presence of asymptomatic carotid stenosis, and whether there is a specific subgroup that can benefit more from this strategy. The search for carotid stenosis has been recommended in populations in which the prevalence of stenosis >60% is higher than 4.5% and in which the annual rate of stroke is above 3.3% per year.[21] For this reason, several clinical guidelines recommend carotid duplex scanning in patients with symptomatic PAD.[5,7] Early detection of asymptomatic carotid stenosis is important for the identification of potential candidates for carotid endarterectomy and in order to select a group of subjects amenable to follow-up and evaluation of disease progression.

The association between a low ABI and carotid stenosis was reduced and lost its significance in multivariate analysis after adjusting for systolic blood pressure. Both PAD and carotid stenosis have been associated with hypertension[22,23] and this and other risk factors could be partially or totally responsible for this association.

The prevalence of a positive EST was 16%. The prevalence of myocardial ischemia in the general population depends on the techniques and the criteria employed, the age of the population evaluated, and the co-existence of cardiovascular risk factors. In subjects with symptomatic PAD and without clinical coronary disease, this prevalence is about 18% with Holter monitoring[24] and reaches 57% when thallium dipyridamol scintigraphy is used.[25] In patients with diabetes, the presence of PAD is the best predictive factor of a myocardial perfusion defect.[26,27] Also,

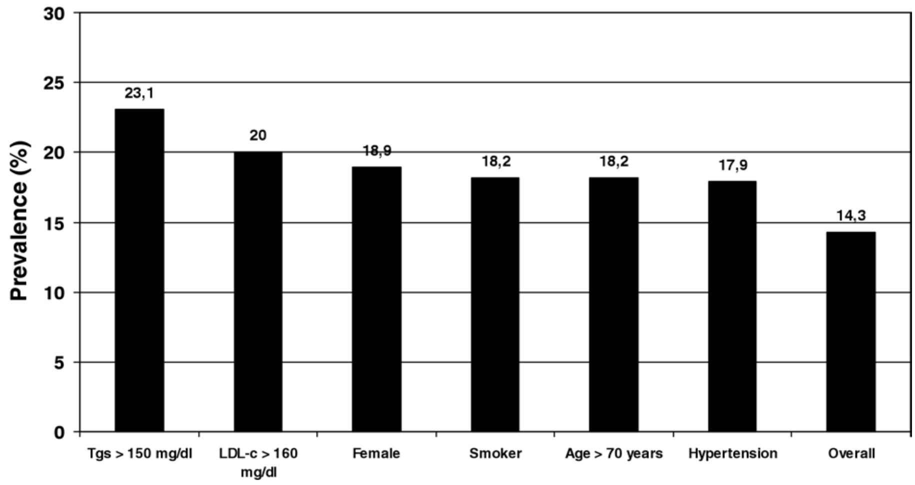

Fig 1. Prevalence of carotid stenosis in subjects with asymptomatic PAD and according to the presence of additional cardiovascular risk factors.

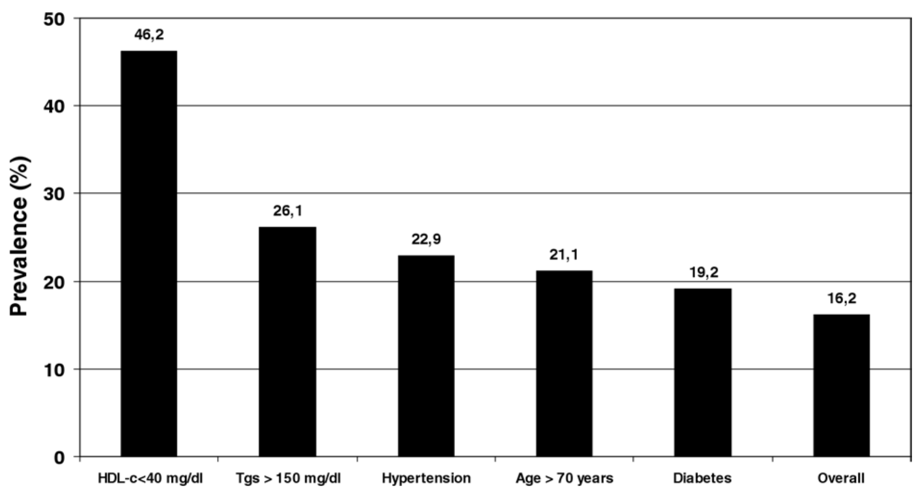

Fig 2. Prevalence of an abnormal exercise stress test in subjects with asymptomatic PAD and according to the presence of additional cardiovascular risk factors.

subjects with a low ABI have a greater risk of segmental wall motion abnormalities, as measured by echocardiography.[22] Despite this, the low sensitivity and specificity of the EST brings its usefulness into question. Generally, it is not recommended in asymptomatic subjects with a low pre-test probability, although it could provide valuable prognostic information in high risk subjects, such as patients with PAD.[28]

Our results indicate that in asymptomatic high-risk subjects >60 years of age and with an ABI <0.9, there needs to be between five and 12 duplex carotid scans and between five and eight EST performed to detect an abnormal clinically-relevant result. These numbers are less if subjects with a higher risk profile are selected (ie, those of more advanced age, with diabetes, or hypertension).

Our study has certain limitations. It is necessary to have available a considerable number of subjects free of cardiovascular disease to be able to detect a sufficient number of them with an abnormal ABI. As such, our sample size may be considered limited, which precludes a more precise estimation of the prevalence of carotid stenosis and silent myocardial ischemia in patients with asymptomatic PAD. A further limitation is not having performed additional tests in the subjects with a positive EST, which precludes us knowing the real prevalence of coronary artery disease in these subjects.

We conclude that, in subjects between 60 and 80 years of age and without clinical cardiovascular disease, the presence of an ABI <0.9 identifies a subgroup of the population with an elevated prevalence of asymptomatic carotid stenosis and of silent myocardial ischaemia. This prevalence is further elevated in those with advanced age, and in those with diabetes or hypertension.

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AUTHOR CONTRIBUTIONS

Conception and design: JM, JG, JC, CL
Analysis and interpretation: JM, JG, JC, JL, CL, FM
Data collection: JL, CL, FM
Writing the article: JM, JG, JC
Critical revision of the article: JM, JG, JC, JL, CL, FM
Final approval of the article: JM, JG, JC, JL, CL, FM
Statistical analysis: JM, CL
Obtained funding: JM, JG, JC
Overall responsibility: JM, JG, JC, JL, CL, FM

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