The Association of Peripheral Arterial Occlusive Disease with Major Coronary Events in a Mediterranean Population with Low Coronary Heart Disease Incidence

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Objectives: The association of peripheral arterial occlusive disease (PAD) association with major coronary events (MCE) has been well documented, nevertheless data are lacking for populations with a low incidence of coronary heart disease (CHD). We aimed to assess the association of PAD with MCE in a Mediterranean population.

Design: Prospective survey of 699 55–74 year-old men representative of an urban district near Barcelona (Spain).

Methods: Baseline cardiovascular risk factors, CHD and PAD (ankle/brachial index < 0.9) were recorded. MCE were evaluated during the 5-year follow-up.

Results: At recruitment 94 subjects (13.4%) had PAD. During follow-up (mean 69.3 months), 35 (5%) subjects suffered a MCE, of whom 12 had PAD, 9 previous symptomatic CHD and 1 subject both conditions. Higher CHD related mortality (8.6% vs 1.4%; p < 0.001) and lower MCE-free survival (78.67% vs 93.26%; p < 0.001) was observed for PAD subjects. On Cox regression analysis PAD (RR = 3; p = 0.003) and previous symptomatic CHD (RR = 4.1; p < 0.001) were associated independently with MCE during follow-up.

Conclusions: Even in a population with a low incidence of CHD there is a strong relationship between PAD and future MCE. Screening for PAD may improve the selection of patients targeted for cardiovascular risk prevention.

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Introduction

Peripheral artery occlusive disease (PAD) has been associated with coronary heart disease (CHD) morbidity and mortality in prospective epidemiological studies performed in populations with a high incidence of cardiovascular disease. In those studies, subjects with PAD, as measured by clinical or hemodynamic criteria, showed a 20% to 60% increased risk of myocardial infarction and a 2- to 6-fold increased risk of cardiac related death.1-8 However, little is known about the magnitude of these relationships in populations with low incidence of CHD, as in the case of the Mediterranean population. Several epidemiological studies have found that the incidence of coronary morbidity and mortality in Southern Europe is 2- to 4-fold lower than in Northern countries.9-11 Primary prevention within populations with low CHD incidence is costly and the addition of new risk factors to existing scoring systems may enhance cost-effective strategies for primary prevention.

The Pubilla-Casas Artery Study12,13 was a study of prevalence and risk factors of PAD in 699 adult-old men from an urban district nearby Barcelona, Spain. In this study the prevalence of PAD and cardiovascular risk factors were similar to that observed in other countries with higher incidence of CHD. The aim of the present analysis was to evaluate the risk of major coronary events (MCE) in patients with PAD after 5 years of follow-up.

Subjects and Methods

Study population

The target population comprised all 55- to 74-year-old men of Pubilla Casas, an urban neighbourhood of Barcelona, Spain. At the time of recruitment (1996–7), 3500 of all inhabitants in Pubilla Casas were men in this age category, of whom 85% were registered with the Pubilla Casas Primary Care Centre, attended by 14 general practitioners. All male subjects (excluding those with mental disorders or terminal illnesses) attended by 4 of these general practitioners were recruited. To improve generalisability, a random sample of 15% of the registered male population of the same age from 4 other practitioners was added. This sampling method yielded 900 eligible men for the study, of whom 708 agreed to participate. Informed consent was obtained from all participants.

Measurements

Cardiovascular risk factors, symptomatic CHD and PAD were evaluated at the time of recruitment by the 4 general practitioners who regularly attended the population of study. Risk factors assessed included age, exposure to cigarette smoking, alcohol intake, hypertension, diabetes, body mass index, cholesterol and its fractions and triglycerides. Previous symptomatic CHD or cerebrovascular events were defined by well documented previous episodes (hospital discharge sheets or a confirmative cardiologist/neurologist evaluation).

PAD was assessed by rest ankle/brachial pressure indexes (ABI). ABIs were performed by the 4 principal general practitioners, using a calibrated mercury sphygmomanometer and a handheld Doppler device. Present or previous symptoms suggestive of PAD were also recorded from all subjects. Subjects presenting with an ABI below 0.9 or present or past PAD symptoms were referred to the vascular surgery department of the Hospital del Mar. In all such causes, clinical history was verified by a vascular surgeon and ABIs performed in the vascular laboratory. Definitive diagnosis of PAD was established when an ABI < 0.9 was confirmed, regardless of symptoms. Nine participants had an abnormally high ABI (>1.5) suggestive of arterial calcification and were excluded from the study.

Follow-up

According to standard clinical criteria, subjects were followed-up by their four general practitioners. Standard care was provided with the aim of limiting all cardiovascular risk factors, including tobacco consumption. Subjects lost to follow-up, usually because of change of address, were contacted by telephone. All coronary events were confirmed by hospital discharge sheets or cardiologist evaluations. Criteria to define fatal or non-fatal myocardial infarction (MI) were adapted from those proposed by the American Heart Association.14 Coronary deaths were confirmed by death certificates or hospital records. Sudden death was considered to be coronary related in all those cases with previous CHD and no other reasonable cause. Major coronary events (MCE) were defined as myocardial infarction (MI) (fatal or non-fatal) or suspected coronary sudden death.

Statistical methods

Participants were classified according to the presence or absence of PAD at the beginning of the study. Associations of future MCE with baseline PAD, CHD and risk factors were assessed by crude event rates, Kaplan–Meier life tables and Cox proportional hazards models. In order to control for potential confounding factors, all variables related to PAD or MCE with p < 0.10 in the bivariate analyses (hypertension, diabetes mellitus, smoking history > 40 pack-years, LDL-cholesterol plasma levels > 160 mg/dl, HDL-cholesterol plasma levels < 35 mg/dl, triglyceride plasma levels > 200 mg/dl, previous cerebro-vascular events and previous symptomatic CHD) were considered in the multivariate model. Statistically non-significant variables not modifying beta-coefficients were retrieved from the model to increase statistical power. A p-value of < 0.05 was considered statistically significant. All analyses were performed using SPSS statistical software.

Results

The study included 699 men with a mean age of 64.7 years. Of these subjects 47.9% were previous smokers and 33.3% current smokers, 55.5% had hypertension, 20.9% diabetes, 33.8% LDL-cholesterol plasma levels > 160 mg/dl, 8% HDL-cholesterol plasma levels < 35 mg/dl, and 12.6%
triglyceride plasma levels > 200 mg/dl. Previous cerebrovascular and CHD events were recorded in 37 (5.3%) and 62 (8.9%) subjects, respectively.

At recruitment, 94 subjects (13.4%) had PAD, of whom 33 (4.7%) were asymptomatic and 61 (8.7%) were, or had been, symptomatic. Sixty (63.8%) patients had an ABI between 0.61 and 0.9, whereas the remaining 34 (36.2%) had an ABI of 0.6 or less.

Subjects with PAD were older and had an increased prevalence of cardiovascular risk factors (smoking exposure, diabetes, hypertension, low HDL-cholesterol and high triglycerides plasma levels) and CHD (14.9% vs 7.9%, \( p = 0.027 \)) (Table 1). At the recruitment, PAD subjects were more frequently prescribed angiotensin-converting enzyme inhibitors, diuretics and antiplatelet agents (\( p < 0.05 \)) (Table 2).

Mean follow-up of the cohort was 69.3 months. Within this period, 91 subjects died (22 CHD-related). Of the remaining 608 subjects, a minimum of 5-years follow-up was recorded in 90.1%. During follow-up, 35 (5%) subjects suffered a major coronary event, of which 21 (60%) were recorded in 90.1%. During follow-up, 35 (5%) subjects suffered a major coronary event, of which 21 (60%) were non-fatal MIs, 10 (28.6%) fatal MIs and 4 (11.4%) coronary artery bypass grafting (CABG).

Subjects with PAD at baseline had a lower MCE-free survival as compared with those without PAD (78.7% vs 93.3%; \( p < 0.001 \)) (Fig. 1). Similarly, CHD related mortality was higher within PAD subjects (8.6% vs 1.4%; \( p < 0.001 \)) (Fig. 2).

At 5-years, all-cause mortality was 15.3% in subjects without PAD, 27.2% in the asymptomatic PAD group and 37.7% in the symptomatic PAD group. Survival curves were calculated by Kaplan–Meier method, showing a 92.9% survival ratio at 5 years for subjects without PAD, 83.5% for asymptomatic and 72.6% for symptomatic PAD patients. Differences among survival curves were statistically significant (\( p < 0.01 \)) (Fig. 3).

To further evaluate the association between PAD and MCE, a proportional hazards Cox model was fitted. In the final model PAD (RR = 3; \( p = 0.003 \)) and previous symptomatic CHD (RR = 4.1; \( p < 0.001 \)) at baseline examination were independently associated with MCE during the follow-up after adjusting for diabetes mellitus, LDL-cholesterol plasma levels and age (Table 3). The relative risk of future MCE was 2.83 (\( p = 0.036 \)) for the group with ABI 0.61–0.9 ABI and 7.83 (\( p < 0.01 \)) for the group with ABI ≤0.6.

### Discussion

Over the last decade, much effort has been placed on identifying people at high risk of cardiovascular morbidity and mortality in Northern countries. Based on epidemiological studies, several formulae and scores to predict individuals’ cardiovascular risk according to conventional risk factors have been developed. Consequently, different primary and secondary preventive strategies have emerged. However, these strategies may raise unjustifiably high expenditures when applied in populations with low incidence of CHD, e.g. Mediterranean countries. With this purpose in mind, Marrugat et al. adapted the Framingham CHD risk score for the Girona population (Northeast of Spain).

No matter what the incidence of CHD, risk prediction probably could be improved by incorporating new risk factors to existing scores. This possibility appears to be

### Table 1  Baseline characteristics of the population of study

<table>
<thead>
<tr>
<th></th>
<th>PAD (n = 94)</th>
<th>No PAD (n = 605)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>67.13 ± 5.1</td>
<td>64.39 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non smoker</td>
<td>1 (1.1)</td>
<td>130 (21.6)</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>39 (49.5)</td>
<td>296 (48.9)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>54 (57.4)</td>
<td>179 (29.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>22.78 ± 29.01</td>
<td>22.78 ± 33.14</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66 (70.2)</td>
<td>322 (53.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>35 (37.2)</td>
<td>111 (18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol &gt; 5.2 mmol/L</td>
<td>14 (14.9)</td>
<td>2 (7)</td>
<td>0.009</td>
</tr>
<tr>
<td>HDL-choles &lt; 0.9 mmol/L</td>
<td>18 (19.1)</td>
<td>200 (33.2)</td>
<td>ns</td>
</tr>
<tr>
<td>LDL-cholest &gt; 4 mmol/L</td>
<td>36 (38.3)</td>
<td>70 (11.6)</td>
<td>0.041</td>
</tr>
<tr>
<td>Triglycerides &gt; 2.3 mmol/L</td>
<td>14 (14.9)</td>
<td>48 (7.9)</td>
<td>0.027</td>
</tr>
<tr>
<td>Symptomatic CHD</td>
<td>8 (8.5)</td>
<td>29 (4.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.32 ± 3.86</td>
<td>27.32 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>

PAD, peripheral arterial occlusive disease; CHD, coronary heart disease.

* Mean ± SD.

### Table 2  Baseline medication of the population of study

<table>
<thead>
<tr>
<th></th>
<th>PAD (n = 94)</th>
<th>No PAD (n = 605)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>23 (24.4)</td>
<td>97 (16)</td>
<td>0.03</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>14 (14.2)</td>
<td>71 (11.7)</td>
<td>NS</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1 (1)</td>
<td>20 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>15 (15.9)</td>
<td>50 (8.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Antiplatelet aggregation agents</td>
<td>31 (32.9)</td>
<td>56 (9.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lipid lowering medicine</td>
<td>2 (2.1)</td>
<td>18 (1.3)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: \( \text{ABI} = \text{ankle-brachial index} \)
particularly attractive for those areas with lower incidence of CHD. Several epidemiological studies have demonstrated PAD to be a powerful predictor of both CHD and mortality. For this reason it has been suggested that PAD, which can be measured easily and non-invasively by ABI, might be used along with other classical risk factors to stratify individual risk and to screen and target older adults for more aggressive risk factor intervention. Nevertheless, the association between PAD and CHD has only been demonstrated in studies performed in settings with high incidence of cardiovascular events.

Our study was performed within a Mediterranean men population of the Northeast of Spain. In previous studies, CHD incidence in this area has been shown to be 2- to 4-fold lower than in Northern Europe or the USA. Our data confirm the low incidence of CHD in a Spanish population. However, the data also show a 3-fold higher risk of future MCE in subjects with PAD at baseline, which is similar to the findings. From Northern Europe and the USA. This is unlikely to be due to the under-treatment of those with PAD. The getABI study recently showed an association between PAD and all-cause mortality. Although the

![Figure 1](image1.png)  
**Figure 1** Kaplan–Meier coronary major event free survival rates for subjects with and without peripheral arterial occlusive disease (PAD).

![Figure 2](image2.png)  
**Figure 2** Kaplan–Meier coronary-related death free survival rates for subjects with and without peripheral arterial occlusive disease (PAD).
mortality in the getABI study was lower, probably because of the inclusion of women, the results were in the same direction as our study, suggesting that screening PAD could be indicated in elderly patients. In other populations, including those with very low CHD incidence, the association between PAD and CHD risk remains unknown.

The present study has two important limitations relating to the study population: sample size and age-sex characteristics. Our results are only applicable to older men. Further research is needed to evaluate the association of PAD with future CHD events in subjects with lower PAD incidence, such as women and younger subjects. However, our results clearly show that even in areas with low CHD incidence, PAD remains a strong predictive factor for future coronary events, as has been demonstrated in other populations. This finding may be particularly helpful to develop primary prevention strategies.

### References


### Table 3  Relative risk of MCE during follow-up according to risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>3</td>
<td>0.003</td>
</tr>
<tr>
<td>CHD</td>
<td>4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.9</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL-chol &gt; 4 mmol/l</td>
<td>1.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Age &gt; 70 years-old</td>
<td>1.8</td>
<td>0.06</td>
</tr>
</tbody>
</table>

MCE, coronary major event; RR, relative risk; PAD, peripheral arterial occlusive disease; CHD, coronary heart disease.


