The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study: Prevalence and risk factors

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A B S T R A C T

Background and purpose: The ongoing population-based Barcelona-Asymptomatic Intracranial Atherosclerosis (Barcelona-AsIA) study is a prospective study that plans to investigate the natural history of asymptomatic intracranial atherosclerosis (AsIA) in a Caucasian–Mediterranean population, which remains unknown until now. The present study aims to determine the prevalence of AsIA and associated risk factors in the final study cohort.

Methods: Crossover, population-based study of a representative sample (randomly selected from our reference population) older than 50 with a moderate-high vascular risk assessed by the vascular equation REGICOR and prior history of neither stroke nor ischemic heart disease. Anthropometric, demographic, clinical data and blood samples were collected at baseline. All individuals underwent a complete extracranial and transcranial color-coded duplex (TCCD) examination. TCCD criteria were used to identify and classify the degree of intracranial stenoses.

Results: A total of 933 subjects (64% men, mean age 66.3 years) were included in the study. One or more intracranial stenoses were detected at baseline in 80 subjects (8.6%) of whom 31 (3.3%) had moderate-severe lesions. The higher the REGICOR scores the greater the prevalence of AsIA (6.6%, 10.2% and 25% for REGICOR scores 5–9, 10–14 and >15, p<0.001). Diabetes (OR 2.95; 95% CI 1.68–5.18; p<0.001), age (OR 1.05; 95% CI 1.02–1.08; p=0.001) and hypertension (OR 1.78; 95% CI 1.02–3.13; p=0.04) were independently associated with any degree of AsIA, while diabetes (OR 2.85; 95% CI 1.16–6.96; p=0.02) and age kept independently associated with moderate-severe AsIA.

Conclusion: The prevalence of AsIA and moderate-severe AsIA in stroke-free Caucasians with a moderate-high vascular risk were 8.6% and 3.3% respectively. Diabetes and age were independently associated with moderate-severe AsIA.

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1. Introduction

Large artery intracranial atherosclerosis disease (ICAD) is a major public health problem as it is a major cause of ischemic stroke worldwide [1] and consequently, a main cause of long-term disability and mortality. It may account for 8–10% of ischemic strokes in whites [2–4] and up to 50% in Oriental Asians [5,6]. Extended use of new non-invasive tests, like transcranial color-coded-duplex (TCCD), computed tomography angiography (CTA) or magnetic resonance angiography (MRA) have led to an increased number of studies involving an assessment of ICAD in the past two decades. Even so, ICAD is still an understudied disease when compared to extracranial atherosclerosis.

Atherosclerotic lesions develop silently over years until they become symptomatic. Identification of markers of latent ICAD could be useful in the setting of stroke primary prevention and may provide an opportunity for early preventive interventions [7,8]. Nevertheless, studies of natural history of ICAD from its asymptomatic stage are limited. Large population studies aimed
to determine its prevalence and related vascular risk factors in stroke-free individuals have only been conducted in Asia [9–13].

To clarify the prevalence and natural history of asymptomatic ICAD in whites, we designed a population-based, prospective, long-term follow-up observational study called the Barcelona-AsIA study (Asymptomatic Intracranial Atherosclerosis study), whose main objectives have been described elsewhere [14]. After having concluded the recruitment phase, the present study was conducted to determine the prevalence of asymptomatic intracranial atherostenoses in the final Barcelona-AsIA cohort and to identify risk factors associated with this condition.

2. Materials and methods

2.1. Study sample selection and inclusion criteria

Complete study protocol has been reported in detail elsewhere [14]. From our reference population of 600,000 inhabitants that are registered in a database of the Primary Care Information Technology System containing demographic and contact details of all subjects covered by our Public National Health System, an initial sample of 3010 subjects older than 50 years was randomly selected within the peripheral arterial disease (PERART) study [15]. This is an ongoing study coordinated in 28 primary health centers of our region that aims to study the prevalence and prognosis impact of peripheral artery disease. After phone contact and agreement to participate, subjects were given an appointment to perform an interview with Primary Care physicians. In this baseline visit, blood sample extraction and anthropometric measurements, including ankle–arm index, were performed. A validated questionnaire called Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) [16] was used to assess self-reported vascular risk factors, history of stroke/TIA and history of coronary disease (angina or myocardial infarction). This questionnaire has shown a ~90% sensibility, specificity, VPP and VPN in assessment of cardiovascular disease. Moreover, clinical history recordings were also checked to confirm diagnoses of stroke/TIA and coronary disease (positive hospital dischargeing report and/or coded as CIE-10 164, G45, 120 or 125), REGICOR and Framingham vascular risk functions (short protocol) were thereafter calculated, taking into account all the information obtained in the baseline visit.

From this initial random sample population included in PERART study, we selected all the 1503 subjects that met our inclusion criteria: (1) no history of stroke or transient ischemic attack; (2) no history of coronary disease (angina and/or myocardial infarction); (3) exposure to a moderate-high vascular risk, assessed by a REGICOR ≥ 5 (see below); (4) absence of institutionalization or severe disability.

All these subjects were first contacted by regular mail warning them about the AsIA project and the chance of being called to take part in it. Thereafter they were contacted by phone from our tertiary stroke center to confirm participation and to program the baseline visit in our center. Our study protocol was approved by the Ethics Committee of our institution.

2.2. Baseline procedures

All subjects accepting to participate were visited at our public health tertiary stroke center, the Germans Trias i Pujol University Hospital (Badalona, Barcelona, Spain). At baseline visit and after signing written informed consent, subjects underwent a complete questionnaire performed by a neurologist and including sociodemographic variables (age, sex, socioeconomic status, education status, and employment) and clinical variables (smoking and alcohol habits, physical activity level, personal and family history of hypertension, diabetes and dyslipidemia, current drug intake, intermittent claudication, etc.). Hypertension, diabetes and dyslipidemia were defined based on personal history of these diagnoses and/or on current diet or medical treatment intake for these disorders. Smoking was considered to be present in current smokers or if the time interval since abstinence was <5 years. The neurologist also re-assessed personal history of coronary disease and stroke/TIA to exclude any incident case between PERART study sample selection and our baseline visit. Anthropomorphic variables were also measured (waist circumference, height, and weight) during this visit. Collected data was prospectively stored in paper Case Report Forms and also in the AsIA main electronic dataset (SPSS format).

Fasting blood samples (serum, plasma and total blood) were drawn, processed and stored in a biobank at −80°C. After finishing the complete subject recruitment (June 2010), serum from this biobank was obtained and analyzed to measure fasting glycemia, cholesterol and triglyceride levels. Framingham and REGICOR scores were previously calculated within the PERART cohort study. REGICOR is the Framingham function adapted and validated for the Spanish population [17] and evaluates the 10-year risk (%) of having cardiovascular events based on a compute of traditional risk factors (sex, age, diabetes, smoking, blood pressure and cholesterol levels). REGICOR <5% indicates low risk, 5–9% moderate risk, 10–14% high risk and ≥15% very high risk [18]. Framingham and REGICOR scores had a very high correlation (Spearman coefficient, 0.98) in our population.

2.3. Diagnosis of intracranial stenosis

All ultrasonographic studies were performed at baseline in the same lab, by two experienced neurologists, with a General Electric Vivid/Pro (Horton, Norway). First, a complete duplex extracranial study was performed to determine the presence and grade of carotid and vertebral atherosclerosis. Significant carotid atherosclerosis was considered when the stenosis was ≥50% (peak systolic velocity > 125 cm/s) [19].

After that, a TCCD examination was set using contrast agents if necessary, by transtemporal and transforaminial windows, following consensus recommendations for an optimal exploration [20]. Intracranial stenosis was diagnosed following previous published criteria for TCCD [21]. First, color-mode is used to observe distribution and flow direction of the main intracranial arteries, looking for appearance of segmental narrowing of the color signal and/or color aliasing phenomena. After that, a complete spectral study is set along every artery, assessing not only focal increases in velocity but also the presence of spectral changes (low-frequency high-intensity signals, spectral widening or musical murmurs). Number, location and severity of intracranial stenosis were recorded in every subject. Stenosis severity by TCCD was classified following Baumgartner cut-off values of PSV for mild/moderate-severe stenosis [21]: ≥155/≥220 cm/s for middle cerebral artery; ≥120/≥155 cm/s for anterior cerebral artery; ≥100/≥145 cm/s for posterior cerebral and basilar arteries and ≥90/≥120 cm/s for vertebral artery.

Prevalence of asymptomatic intracranial atherosclerosis (AsIA) was calculated based on neurosonological study, with the exception of 5 subjects with a poor quality TCCD study who underwent a complementary MRA study to rule out the diagnosis. Moderate-severe asymptomatic intracranial atherosclerosis was defined as having at least one moderate-severe stenosis by TCCD velocity criteria.

Subjects with moderate-severe intracranial stenosis detected by TCCD study at baseline were invited to undergo a MRA study with a 1.5 T Philips and a time-off-flight (TOF) sequence if no contraindications were present. All MRA studies were analyzed by a neuroradiologist blind to clinical and sonographic data.
2.4. Statistical analyses

Statistics were performed with the SPSS 18.0 statistical package. Our sample calculation assumed that: (1) at least 50% of subjects older than 50 years in our population would have a REGICOR >5% [22]; (2) 10% of subjects would be excluded for failure to fulfill the inclusion criteria; (3) 20% of subjects would be uncontactable or refuse participation; (4) a prevalence of intracranial stenosis of 8%. To obtain this value, we assumed that the differences in prevalence of asymptomatic intracranial atherosclerosis between Asians and Caucasians would be similar to those observed in symptomatic patients (around 3 to 4 times more prevalent in Asians). Thus, our expected prevalence was obtained by dividing the reported prevalence of asymptomatic intracranial stenosis in Asians by 24.5% [12] by three.

Accepting an alpha error of 0.05, a sample size of more than 900 individuals and a prevalence of intracranial stenosis of 8% ensured a statistical power of 80% to detect as statistically significant an odds ratio equal or higher than 2 in the study of risk factors associated to the presence of AsIA. Therefore, the projected sample size was around 1000 individuals with moderate–high vascular risk with neither prior stroke nor ischemic heart disease selected from 3010 subjects randomly included in the PERART study [14].

The association of vascular risk factors with the presence and severity of intracranial stenoses, was analyzed by Pearson’s χ² test, Mann–Whitney test or Student’s t-test when appropriate. Multivariate logistic regression models were performed to identify risk factors independently associated with the presence of asymptomatic intracranial atherostenoses of any degree, including in the model those variables with values of p < 0.20 in previous univariate analysis. A multinomial regression analysis was conducted to identify the factors associated to the severity of intracranial atherosclerosis, comparing the groups without AsIA (reference group), with mild AsIA and with moderate–severe AsIA. Statistical significance was defined as p value < 0.05.

3. Results

Prospective subject enrolment took place between March 2007 and June 2010. From the initial random sample of 1503 subjects, 229 subjects were not located after 5 phone calls, 316 declined to participate for several reasons, 5 were excluded for having suffered a stroke after initial sample randomization and 20 died during the recruitment period. Finally, a total of 933 subjects were included in baseline visit at our center and comprise the final Barcelona-AsIA cohort. All subjects were of Spanish origin, with the exception of eight subjects natives of different Latino-American countries. Mean age was 66.3 years (8.1 SD) and 64% were males. Regarding vascular risk factors, 56% had hypertension, 39.5% had dyslipidemia, 27% were diabetic and 18% active smokers. Age, sex and vascular risk scores were similar between the final AsIA cohort and the group of subjects not located or who declined to participate, although mean age of not located subjects was lower, probably because phone calls were performed during working hours. Subjects who died during recruitment phase (n = 20) were older and more frequently men (see supplemental Table e-1).

3.1. Prevalence of asymptomatic intracranial atherostenoses

Asymptomatic intracranial atherostenoses were found at baseline in 80 out of 933 individuals. The prevalence of AsIA in the total population was 8.6% (95% CI, 6.8–10.4), and the prevalence of moderate–severe AsIA was 3.3% (95% CI, 2.1–4.4). Echo–contrast agents were used in 234 (25%) subjects due to a poor acoustic window.

Of those subjects with AsIA, 33 (41.3%) had a unique intracranial stenosis and 47 had two or more stenoses. A total of 187 intracranial stenoses were detected at baseline and were located as follows: 60 in terminal ICA/siphon, 55 in middle cerebral artery, 31 in anterior cerebral artery, 20 in posterior cerebral artery, 11 in vertebral artery and 10 in basilar artery. Regarding distribution of intracranial stenosis in each patient, 46 subjects (57.5%) had isolated anterior circulation stenosis, 11 (13.8%) had isolated posterior circulation stenosis and 23 (28.7%) showed stenoses in both anterior and posterior circulations.

In extracranial duplex study, 466 subjects (50%) were found to have one or more carotid plaques and 29 subjects (3.1%) had a significant internal carotid artery stenosis >50%.

Of the 31 subjects with moderate–severe intracranial stenoses detected by TCCD, only 23 gave informed consent to undergo a complementary MRA in the following 6 months that confirmed the presence of AsIA in 21 of them. The two subjects with no angiographic confirmation had both stenosis located in carotid siphon; after reviewing the MRA we considered the misdiagnosis due probably to movement and bone artifacts in the TOF sequence; moreover, both subjects underwent a new neurosonological study two years after inclusion that showed the same findings as in the first. For these reasons, these patients were considered as having AsIA. In one subject with a severe tandem extra-intracranial carotid stenosis a conventional arteriography was performed and confirmed both lesions.

3.2. Risk factors associated with AsIA

Variables potentially associated with AsIA of any degree and with a moderate–severe degree are shown in Table 1. AsIA was significantly associated with age but not with sex. Vascular risk assessed by REGICOR and Framingham scores was also associated with the presence of asymptomatic intracranial atherosclerosis (Table 1). The higher the REGICOR scores the greater the prevalence of AsIA (6.6%, 10.2% and 25% for REGICOR scores 5–9, 10–14 and ≥15 respectively, p < 0.001, Fig. 1 online).

Regarding individual vascular risk factors, diabetes mellitus, hypertension, dyslipidemia and higher fasting glycemia levels were significantly associated with the presence of any degree of AsIA. The median (IQR) duration of diabetes was 10 (5.5–20) years in the group with AsIA (n = 44) and 5 (2–10) years in subjects without AsIA (n = 206) (p < 0.001). A multivariate logistic regression model including variables showing a p < 0.20 in univariate analysis, identified diabetes (OR 2.95; 95% CI (1.68–5.18); p < 0.001), age (OR 1.05; 95% CI (1.02–1.08); p = 0.001) and hypertension (OR 1.78; 95% CI (1.02–3.13); p = 0.04) as independently associated with AsIA (Table 2). Multinomial regression analysis showed that the factors independently associated with moderate–severe AsIA were age (OR 1.05; 95% CI (1.004–1.1); p = 0.03) and diabetes (OR 2.85; 95% CI (1.16–6.96); p = 0.02) (Table 3).

Prevalence of AsIA was progressively higher with the combination of the independent risk factors age and diabetes (mean age of the group with AsIA was used to divide the subjects): from 3.8% among those subjects <70 years and without diabetes to 21% among those with the two risk factors. Percentage of subjects with moderate–severe AsIA also increased across these groups (Fig. 2 online).

4. Discussion

The major finding of our study was that the prevalence of AsIA assessed by TCCD in a Caucasian population with moderate–severe vascular risk is estimated in 8.6%. Prevalence of moderate–severe AsIA (3.3%) was similar to prevalence of significant carotid stenosis.
Table 1
Comparison of vascular risk factors between subjects with and without asymptomatic intracranial atherosclerosis (AsIA).

<table>
<thead>
<tr>
<th>Without AsIA (n = 853)</th>
<th>AsIA: any degree (n = 80)</th>
<th>p</th>
<th>AsIA: moderate-severe (n = 31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.9 (±8.1)</td>
<td>69.9 (±8.4)</td>
<td>&lt;0.001</td>
<td>69.7 (±9.7)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>63.8</td>
<td>62.5</td>
<td>0.44</td>
<td>61.3</td>
</tr>
<tr>
<td>REGICOR score</td>
<td>7 (5–9)</td>
<td>9 (7–13)</td>
<td>&lt;0.001</td>
<td>9 (7–11)</td>
</tr>
<tr>
<td>Framingham score</td>
<td>17 (13–25)</td>
<td>22 (16–32)</td>
<td>&lt;0.001</td>
<td>21 (19–30)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>54.5</td>
<td>75.6</td>
<td>&lt;0.001</td>
<td>80.6</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24.4</td>
<td>55.1</td>
<td>&lt;0.001</td>
<td>61.3</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>53.4</td>
<td>66.3</td>
<td>0.03</td>
<td>67.7</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>24.6</td>
<td>18.8</td>
<td>0.14</td>
<td>12.9</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>9.6 (±15)</td>
<td>8.3 (±13)</td>
<td>0.78</td>
<td>9.7 (±11)</td>
</tr>
<tr>
<td>Alcool &gt;20g/day (%)</td>
<td>12.3</td>
<td>8.8</td>
<td>0.34</td>
<td>12.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 (25.5–30.7)</td>
<td>28.5 (25.7–31.1)</td>
<td>0.53</td>
<td>28.2 (26.3–30.4)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>205.6 (±40)</td>
<td>204.8 (±43)</td>
<td>0.87</td>
<td>204.1 (±54)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>53 (46–60)</td>
<td>52 (46–62)</td>
<td>0.84</td>
<td>49 (44–64)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>131.1 (±35)</td>
<td>128.7 (±37.1)</td>
<td>0.57</td>
<td>126 (±47)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>108 (82–156)</td>
<td>113 (80–151)</td>
<td>0.85</td>
<td>147 (94–184)</td>
</tr>
<tr>
<td>Fasting glyceremia (mg/dl)</td>
<td>104 (95.2–118)</td>
<td>110 (98.9–138.2)</td>
<td>&lt;0.001</td>
<td>125.2 (105.3–165.6)</td>
</tr>
<tr>
<td>Current therapies use (baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives (%)</td>
<td>50.8</td>
<td>71.3</td>
<td>0.006</td>
<td>74.2</td>
</tr>
<tr>
<td>Hypoglycemians (%)</td>
<td>20.4</td>
<td>44.8</td>
<td>&lt;0.001</td>
<td>58</td>
</tr>
<tr>
<td>Hypolipidemias (%)</td>
<td>38.9</td>
<td>46.3</td>
<td>0.07</td>
<td>48.4</td>
</tr>
</tbody>
</table>

Categorical variables presented in percentages. Continuous variables presented in mean (±SD) if normally distributed or median (interquartile range) in the rest. BMI: body mass index; HDL: high density cholesterol.

* Subjects with moderate-severe AsIA compared to those without AsIA.

Table 2
Logistic regression analyses: factors independently associated with the presence of asymptomatic intracranial atherosclerosis (any degree).

<table>
<thead>
<tr>
<th></th>
<th>Crude OR (95% CI)</th>
<th>p</th>
<th>Adjusted OR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.001</td>
<td>1.05 (1.02–1.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.68 (1.57–4.56)</td>
<td>&lt;0.001</td>
<td>1.78 (1.02–3.13)</td>
<td>0.042</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.83 (2.4–6.12)</td>
<td>&lt;0.001</td>
<td>2.95 (1.68–5.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.71 (1.05–2.77)</td>
<td>0.029</td>
<td>1.44 (0.86–2.41)</td>
<td>0.159</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.70 (0.39–1.26)</td>
<td>0.241</td>
<td>1.03 (0.55–1.91)</td>
<td>0.912</td>
</tr>
<tr>
<td>Fasting glyceremia (mg/dl)</td>
<td>1.01 (1.004–1.015)</td>
<td>&lt;0.001</td>
<td>1.00 (1.003–1.007)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

OR: odds ratios; CI: confidence interval.

* Logistic regression model adjusted for diabetes, sex, age, hypertension, dyslipidemia, smoking habit and fasting glyceremia.

(3.1%) in the same cohort. In previous Asian studies using transcranial Doppler (TCD), but using similar cut-off points of systolic peak velocity to define a stenosis, prevalence of asymptomatic intracranial atherosclerosis ranged from 6 to 24.5% [9–12], depending on number of arteries assessed. Principal results of these studies are summarized in supplemental Table e2 and compared to ours. In all these studies, subjects with poor acoustic windows were excluded of the analysis or classified as “non stenosis”, fact that could have led to an underestimation of the prevalence in stroke-free Asians. Contrary to Asian studies, we assessed intracranial and extracranial circulation globally and we used contrast agents to evaluate the whole sample. Therefore, according to our findings, asymptomatic intracranial atherosclerosis in Caucasians is not a rare entity and this finding could have important implications for general public health and for the design of primary prevention strategies in our setting.

From a primary prevention point of view, it is important to identify factors related to the presence of intracranial atherosclerosis in a stroke-free individual. In this setting, REGICOR score has shown a good correlation with subclinical intracranial atherosclerosis burden in our population. One of every four subjects with a very high risk score (REGICOR ≥ 15) had intracranial stenosis. Regarding individual risk factors, three were independently associated with asymptomatic intracranial atherosclerosis of any degree: diabetes, age and hypertension. These three risk factors have also been described in the Asian studies mentioned before. Thus, ethnic differences in the distribution of cerebral atherosclerosis between Asians and Caucasians may not be explained by a distinct vascular risk factor profile. These differences are probably related to other conditions, such as genetic, molecular or environmental factors. Further studies are needed to support this hypothesis. In this line, studies in stroke-free blacks and Hispanics (unreported until now) would be of great interest as they also have a higher prevalence of ICAD-stroke subtypes than Caucasians [3].

In our study, diabetes mellitus has appeared like the most relevant risk factor associated with AsIA of any degree and also with moderate-severe AsIA, similar as previously described in the symptomatic phase of the disease [4,23]. Furthermore, the

Table 3
Multinomial regression analysis: severity of asymptomatic intracranial atherosclerosis and risk factors.

<table>
<thead>
<tr>
<th></th>
<th>Mild AsIA</th>
<th>p</th>
<th>Moderate-severe AsIA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted OR* (95% CI)</td>
<td></td>
<td></td>
<td>Adjusted OR* (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age (1 year)</td>
<td>1.06 (1.02–1.10)</td>
<td>0.004</td>
<td>1.05 (1.004–1.1)</td>
<td>0.034</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.140</td>
<td>0.072</td>
<td>0.285 (1.16–6.96)</td>
<td>0.022</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.001</td>
<td>0.910</td>
<td>1.92 (1.05–3.48)</td>
<td>0.023</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.013</td>
<td>0.132</td>
<td>1.50 (0.86–2.62)</td>
<td>0.159</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>0.673</td>
<td>0.109</td>
<td>0.77 (0.44–1.38)</td>
<td>0.351</td>
</tr>
<tr>
<td>Fasting glyceremia (mg/dl)</td>
<td>0.369</td>
<td>0.251</td>
<td>1.03 (0.86–1.23)</td>
<td>0.712</td>
</tr>
</tbody>
</table>

* Adjusted OR: age, hypertension, diabetes, dyslipidemia, tryglicerides and fasting glyceremia were introduced as covariables in the same multinomial regression analysis, using the group “without AsIA” as reference. OR: odds ratio; CI: confidence interval.

mean duration of the disease was significantly longer in diabetic patients with AsIA. We also found that higher levels of fasting glycemia and triglycerides, both related to insulin resistance, were significantly associated with moderate-severe AsIA. Diabetes may promote a more severe ICAD already from its early asymptomatic stage. Another important finding is that, in line with previous studies, some classical risk factors traditionally associated with carotid or coronary atherosclerosis like male sex, smoking habit or hypercholesterolemia, were not associated with intracranial atherosclerosis in our series. Intriguingly, we found a less smoking trend in patients with AsIA that has been previously reported either in the symptomatic or asymptomatic stage of intracranial atherosclerosis [4,10]. Intracranial arteries might have a different pattern of response to vascular deleterious stimuli as compared with other arterial beds. For instance, insulin resistance might promote a loss of the antioxidant potential of intracranial circulation favoring the development of atherosclerotic lesions in this location [24,25]. However, the basic mechanisms underlying this proneness of intracranial arteries to be selectively affected by diabetes remains largely unknown and deserves further study. Our projected AsIA-biomarker substudy may be able to shed some light into this issue.

To the best of our knowledge, this is the first large sample population-based study on asymptomatic intracranial atherosclerosis designed in a Caucasian population. However, our study has some limitations. First, as it was a cross-sectional study, evaluation of the real impact of risk factors in the development of intracranial atherosclerosis was not possible. Second, not all subjects with intracranial stenosis detected by TCCD underwent a simultaneous angiographic study to confirm the findings. However, the robust association of TCCD-detected intracranial stenoses with vascular risk factors supports the idea that they are true atherosclerotic stenoses. Finally, we did not obtain data on baseline creatinine clearance, so we may have missed the potential association of renal failure with the atherosclerotic burden.

In conclusion, the prevalence of asymptomatic intracranial atherosclerosis (AsIA) of any degree among stroke free Caucasians with moderate–high vascular risk was 8.6%, whereas moderate-severe AsIA was present in 3.3% of studied subjects. Diabetes, age and hypertension were independent risk factors for AsIA, being only diabetes and age independently associated with moderate-severe AsIA. AsIA is not a rare entity, and this finding may have important implications for stroke primary prevention in our setting. The real prognostic significance of AsIA will be evaluated in the ongoing longitudinal phase of our study.

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Conflicts of interest

None

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Appendix A. Supplementary data


References