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The Barcelona-Asymptomatic Intracranial Atherosclerosis study: Subclinical intracranial atherosclerosis as predictor of long-term vascular events

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ABSTRACT

Background and aims: Symptomatic intracranial atherosclerosis (ICAS) is associated with a high risk of stroke recurrence and occurrence of other vascular events. However, ICAS has been poorly studied from its asymptomatic stage. The objective of our study was to determine if subclinical intracranial atherosclerosis is associated with long-term incident vascular events in Caucasians.

Methods: The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) Study is a population-based study that enrolled 933 subjects with a moderate-high vascular risk and without history of stroke or coronary disease, and determined the prevalence of asymptomatic ICAS and associated risk factors. At baseline visit, carotid atherosclerosis and ICAS were screened by color-coded duplex ultrasound, and moderate-severe stenosis was confirmed by magnetic resonance angiography. At baseline, 8.9% of subjects had asymptomatic ICAS, of whom 3.3% were moderate-severe. In the longitudinal phase, subjects were prospectively followed-up to assess the incidence of a combined primary endpoint of vascular events (stroke, acute coronary syndrome and/or vascular death).

Results: After 7.17 years of follow-up, there were 51 incident cerebrovascular events (16 transient ischemic attacks, 27 ischemic, 8 hemorrhagic strokes), 63 incident coronary events and 23 vascular deaths. After multivariate Cox regression analyses adjusted by age, sex, vascular risk and presence of carotid plaques, ICAS was an independent predictor for overall vascular events (HR 1.83 [1.10–3.03], $p = 0.020$), and moderate-severe intracranial stenosis was also an independent predictor for cerebrovascular events (HR 2.66 [1.02–6.94], $p = 0.046$).

Conclusions: Asymptomatic ICAS is independently associated with the incidence of future vascular events in our population. These findings might have implications for the development of primary prevention strategies.

1. Introduction

Intracranial atherosclerosis (ICAS) is one of the most important causes of stroke worldwide, accounting for 5–10% of ischemic strokes in Caucasians and up to 50% in Asians [1]. Symptomatic ICAS is one of the stroke etiologies with a higher stroke recurrence risk despite aggressive medical therapy [2]. Furthermore, subjects with stroke due to ICAS are also exposed to an elevated risk of having a stroke in other territories and other vascular events (e.g. coronary events or vascular death) [3,4], especially when ICAS is associated with atherosclerosis in other vascular beds [5].

Compared to carotid atherosclerosis, studies focused on asymptomatic or subclinical ICAS are still scarce and primary prevention trials are lacking. In the past two decades, several population-based studies

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including asymptomatic subjects have evaluated the prevalence of subclinical ICAS, using non-invasive tools as transcranial ultrasound or magnetic resonance angiography. According to these studies, the prevalence of asymptomatic ICAS is up to 24.5% [6–9] in Asian populations, 8–9% in Whites [10,11] and 12% in African-Americans [11]. However, the natural history and long-term prognosis of asymptomatic ICAS have been rarely evaluated. In prior studies in Asian cohorts, presence of intracranial stenosis was independently associated with incident stroke [12–14], acute coronary syndrome and vascular death [12]. Among Caucasians, the population-based Rotterdam Study found that intracranial carotid artery calcification on computed tomography scans (found in 80% of subjects) was an independent predictor of any stroke after a mean follow-up of 6 years [15]. However, intracranial carotid calcification on CT scans may be a surrogate marker of ICAS but not a direct measure of intracranial stenosis.

Our aim was to determine whether the presence of subclinical ICAS predicts a higher risk for long-term incident vascular events in Caucasians in the population-based Barcelona-Asymptomatic Intracranial Atherosclerosis study (AsIA study).

2. Materials and methods

2.1. Setting

The Barcelona-AsIA study is a prospective and population-based study aimed to determine the prevalence of asymptomatic intracranial atherosclerosis, its associated clinical, molecular and genetic risk factors, and its prognostic impact. The complete study protocol [16] and main results on ICAS prevalence and associated risk factors have been reported in detail elsewhere [10,17]. Briefly, Barcelona-AsIA study included from March 2007 to June 2010 a random population sample of 933 Caucasian subjects older than 50 years with a moderate-high vascular risk (assessed by REGICOR score [18], which is the Framingham risk score validated for the Spanish population and calculated based on age, sex, diabetes, smoking, blood pressure and cholesterol levels) and without history of stroke, coronary disease or severe disability. This study was approved by the Ethics Committee of our Institution (Germans Trias i Pujol University Hospital, Barcelona), and all patients gave their written consent to participate in the study.

2.2. Baseline procedures and assessment of ICAS

At baseline visit sociodemographic and clinical variables were collected, anthropometric variables measured and blood samples obtained. Most subjects received a complete neuropsychological study at baseline. In order to determine the presence and grade of extracranial and intracranial atherosclerosis all subjects underwent a complete cervical and transcranial color-coded duplex (TCCD) ultrasound study. Subjects with moderate-severe carotid or intracranial stenosis ($\geq$50%) detected in ultrasound study were also invited to undergo a magnetic resonance angiography (MRA).

2.3. Follow-up

All Barcelona-AsIA study participants were contacted via phone calls every 6 months after baseline visit and electronic medical records checked to evaluate the incidence of vascular events and/or death. The type and date of vascular event were collected and event was finally adjudicated by a committee blinded to clinical/atherosclerosis data. If no records were found to be able to confirm an event this was not included in the study. Follow-up for incident vascular events was conducted until May 30, 2017. Between April 2016 and May 2017 participants were also invited via phone call to come to our stroke center to undergo an in-person follow-up visit, where they underwent a new complete cervical and TCCD ultrasound study and a new neuropsychological study.

Primary outcome was defined as the occurrence of any vascular event (cerebrovascular event, coronary event and/or vascular death) and secondary outcome as the occurrence of cerebrovascular event. The cerebrovascular events included cerebral infarction, transient ischemic attack (TIA), intracerebral hemorrhage and subarachnoid hemorrhage that required hospitalization. TIA was defined as focal neurological dysfunction lasting less than 24 h; all TIA events were studied by neurologists and patients underwent either MRI or CT scan. Coronary event included angina and myocardial infarction that required hospitalization. Vascular death was defined as death due to stroke (ischemic or hemorrhagic), systemic hemorrhage, myocardial infarction, congestive heart failure, pulmonary embolism, sudden death, or arrhythmia, or other cardiovascular conditions or procedures.

2.4. Subject groups

According to presence of intracranial stenosis (ICAS) at baseline visit, subjects were categorized in 2 groups: (1) non-ICAS group (n = 853) and (2) ICAS group (n = 80). Secondly, according to severity of intracranial stenosis at baseline visit, subjects were classified into 3 groups: (1) non-ICAS group (n = 853), (2) mild ICAS group-stenosis < 50% (n = 49) and (3) moderate-severe ICAS group-stenosis $\geq$ 50% (n = 31).

2.5. Statistical analyses

Quantitative variables were expressed as mean (SD) in cases of normal distribution or median (interquartile range [IQR]) otherwise. Qualitative variables were expressed as frequencies (percentages). Bivariate comparisons were made using the *t*-test or Mann-Whitney *U* test for quantitative variables and the $\chi 2$ test for categorical variables. Patient characteristics and 7-year outcomes were compared between patients with and without ICAS at baseline. First event was considered as outcome. Survival analysis for the combination of major vascular events and for stroke were performed with the Kaplan-Meier curves according to the presence/absence of ICAS and its severity. Cox multivariate regression models were used to check the association between the incidence of vascular events and the presence of ICAS. The hazards ratios (HR) were given with their corresponding 95% confidence intervals. Statistics were performed with Stata 15.1 statistical package.

3. Results

The mean follow-up period of the entire cohort was 7.17 [6.92–7.75] years. From the initial cohort of 933 participants recruited between 2007 and 2010, 114 subjects (12.2%) had died at the end of follow-up (May 2017), and 23 deaths were considered of vascular origin; 51 participants had a cerebrovascular event (16 TIA, 27 ischemic strokes and 8 haemorrhagic strokes) and 63 participants had coronary events. Overall, 118 (12.6%) subjects had any vascular event and/or vascular death during follow-up. Baseline clinical and sonographic characteristics of participants in the whole population and according to incidence of any vascular event are summarized in Table 1. Participants that had vascular events at follow-up were significantly older, had higher vascular risk score (REGICOR) and higher prevalence of classical vascular risk factors. Regarding subclinical atherosclerosis at baseline, those with incident vascular events had higher carotid intima-media thickness (IMT), and more frequently carotid plaques, carotid stenosis > 50%, intracranial stenosis and moderate-severe intracranial stenosis (Table 1).

Incidence of the different vascular events during follow-up according to presence of ICAS at baseline is represented in Table 2. Incidence of all vascular events and all cause of death was significantly higher in ICAS group compared with non-ICAS group, with the exception of cerebrovascular events. However, considering ICAS severity at baseline, incidence of cerebrovascular events was significantly higher

Table 1
Baseline clinical and sonographic characteristics, according to incidence of vascular event.

	Overall (n = 933)	Without vascular event at follow-up (n = 815)	With any vascular event at follow-up (n = 118)	*p* value
Age (years), mean (SD)	66.4 (7.8)	65.9 (7.7)	69.9 (8.2)	< 0.001
Male sex	594 (63.7)	504 (61.8)	90 (76.3)	0.002
REGICOR score, median [IQR]	7 [5–10]	7 [5–9]	8 [7–13]	< 0.001
Hypertension	526 (56.4)	444 (54.6)	82 (69.5)	0.002
Diabetes	250 (26.8)	197 (24.2)	53 (45.9)	< 0.001
Dyslipidemia	509 (54.6)	442 (54.2)	67 (56.8)	0.604
Smoking habit	504 (54.0)	422 (51.8)	82 (69.5)	< 0.001
Carotid intima-media thickness (mm), mean (SD)	0.78 (0.16)	0.77 (0.15)	0.83 (0.17)	< 0.001
Carotid plaque	467 (50.1)	395 (48.5)	72 (61.5)	0.008
Carotid stenosis > 50%	29 (3.1)	19 (2.3)	10 (8.6)	< 0.001
Intracranial stenosis (ICAS)	80 (8.6)	59 (7.2)	21 (17.8)	< 0.001
Moderate-severe-ICAS	31 (3.3)	21 (2.6)	10 (8.5)	< 0.001

Data are presented as frequency (percentage) unless otherwise indicated.
SD: standard deviation; IQR: interquartile range.

Table 2
Vascular events in participants with and without intracranial stenosis (ICAS) at baseline.

	Overall (n = 933)	Without ICAS (n = 853)	With ICAS (n = 80)	*p* value
Months of follow-up, mean (SD)	85.6 (18.0)	85.9 (± 17.0)	82.6 (26.6)	0.060
Cerebrovascular event	51 (5.5)	44 (5.2)	7 (8.8)	0.177
Coronary event	63 (6.8)	48 (5.6)	15 (18.8)	< 0.001
All cause death	114 (12.2)	97 (11.4)	17 (21.3)	0.010
Vascular death	23 (2.5)	18 (2.1)	5 (6.3)	0.022
Any vascular event[a]	118 (12.7)	97 (11.4)	21 (26.3)	< 0.001

Data are presented as frequency (percentage) unless otherwise indicated.
SD: standard deviation.
[a] Cerebrovascular event, coronary event and/or vascular death.

in moderate-severe-ICAS group compared to non-ICAS group, especially cerebral ischemic events (Table 3). With regard to etiology of cerebrovascular events, 14 were considered cardioembolic, 7 atherothrombotic (3 due to intracranial stenosis and 4 due to extracranial carotid stenosis), 5 lacunar and 17 of undetermined origin. Regarding haemorrhagic strokes, 2 were hypertensive, 2 due to anticoagulant treatment, 2 amyloid related, 1 subarachnoid hemorrhage and 1 of undetermined origin.

Survival curves for vascular events with respect to presence and severity of intracranial stenosis at baseline are presented in Fig. 1. In the Cox regression analysis (Table 4), after adjusting for age, male sex, REGICOR score and presence of carotid plaques, ICAS was an independent predictor of vascular events in the follow-up with a HR 1.83 [1.10–3.03] and moderate-severe ICAS was an independent predictor of stroke with a HR 2.66 [1.02–6.94]. Interestingly, presence of carotid plaques were not independent predictors of incident vascular events in multivariable Cox regression analysis, and vascular risk score (REGICOR) was an independent predictor of any vascular event but not a predictor for incident stroke in our population. Similar results were observed when introducing in the Cox regression model presence of carotid stenosis > 50% instead of presence of carotid plaques (Supplementary table 1).

4. Discussion

This prospective population-based study examined the prognostic impact of asymptomatic ICAS in terms of incident stroke and vascular events. To our knowledge, this is the first population-based study among Caucasians to explore the prognosis of asymptomatic ICAS. Our findings indicate that asymptomatic ICAS is an independent risk factor for long-term vascular events and that moderate-severe asymptomatic ICAS is an independent risk factor for stroke.

Findings reported to date in Asian populations, where prevalence of ICAS is higher, have shown similar results as ours. In a Chinese hospital-based study including 2144 type 2 diabetic subjects without history of stroke at baseline, presence of asymptomatic middle cerebral artery (MCA) stenosis assessed by transcranial Doppler was independently associated with incident stroke, acute coronary syndrome and vascular death after a median follow-up of 14 years [12]. In a community-based study in China, participants with ICAS assessed by TCCD had a 3.6-fold greater risk of incident stroke than those without ICAS [13]. In another prospective study including 2807 healthy volunteers in Japan without history of stroke, presence of asymptomatic ICAS, assessed by MRA, was an independent risk factor of future stroke [14]. In Barcelona-AsIA study, ICAS was an independent predictor of cerebrovascular events

Table 3
Cerebrovascular events according to presence and severity of intracranial stenosis (ICAS) at baseline.

	Overall (n = 933)	Without ICAS (n = 853)	Mild ICAS (n = 49)	Moderate-severe ICAS (n = 31)	*p* value
Cerebrovascular events	51 (5.5)	44 (5.2)	1 (2.0)	6 (19.4)	0.002
Ischemic stroke/TIA	43 (4.6)	37 (4.3)	1 (2.0)	5 (16.1)	0.006
Hemorrhagic stroke	8 (0.9)	7 (0.8)	0 (0.0)	1 (3.2)	0.289

Data are presented as frequency (percentage).
TIA: transient ischemic attack.

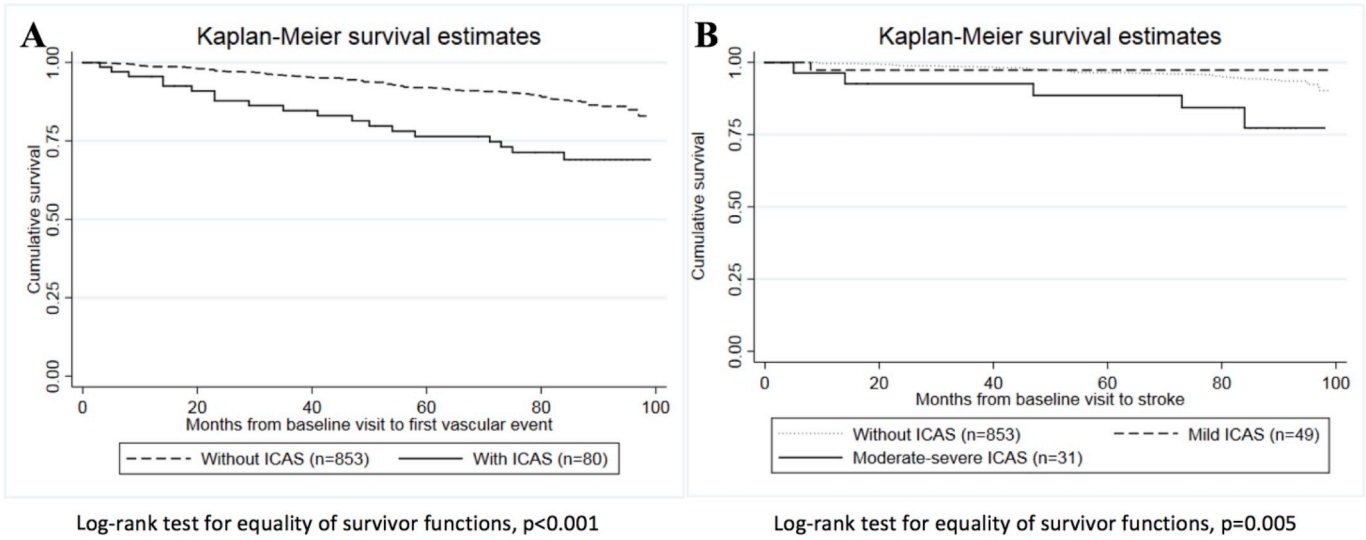

Fig. 1. Kaplan-Meier Survival curve for vascular events-free survival according to presence and severity of ICAS at baseline.
(A) Incident vascular event according to the presence of ICAS. (B) Incident cerebrovascular event according to severity of ICAS.

Table 4
Cox regression analysis of vascular events during follow-up.

	Adjusted HR (95% CI)	*p* value
INCIDENT VASCULAR EVENT (CORONARY, STROKE and/or VASCULAR DEATH)		
Age (years)	1.05 [1.02–1.07]	< 0.001
Male sex	1.54 [0.96–2.46]	0.071
REGICOR	1.06 [1.02–1.10]	0.004
Carotid plaque	1.11 [0.74–1.64]	0.619
ICAS	1.83 [1.10–3.03]	0.020
INCIDENT CEREBROVASCULAR EVENT		
Age (years)	1.09 [1.05–1.13]	< 0.001
Male sex	1.65 [0.81–3.37]	0.170
REGICOR	1.02 [0.95–1.09]	0.587
Carotid plaque	1.03 [0.56–1.88]	0.927
Moderate-severe ICAS	2.66 [1.02–6.94]	0.046

only in those subjects with moderate-severe stenosis, and cerebrovascular event (that included TIA, ischemic or hemorrhagic stroke) was not necessarily in the territory of intracranial stenosis. We cannot explain possible differences among Asian and Caucasian populations regarding incident stroke and stenosis degree because methodology and definition of cerebrovascular events varied among studies. In fact, in the Chinese hospital-based study [12] patients (all diabetics) are not categorized by stenosis degree, the only intracranial artery assessed was MCA, extracranial arteries were not studied, and stroke (including TIA) was defined as ischemic and associated with large-artery atherosclerosis (but not specifically in the territory of MCA stenosis); in the Chinese community-based study [13], all large intracranial and extracranial arteries were assessed with Doppler (similar to our study) but stenosis degree category was not clearly defined, classification of stroke included hemorrhagic stroke but excluded TIA, and location of ischemic stroke (related or not to intracranial stenosis) was not defined. Finally, in the Japanese study [14], intracranial stenosis were assessed by MRA and incident stroke included TIA but excluded intracerebral hemorrhage; in this study, incident stroke was associated both with mild and moderate degree of intracranial stenosis, and again, ischemic stroke was not defined in the territory of the stenosed artery.

Results from our study indicate that harboring asymptomatic intracranial stenosis confers a greater overall cardiovascular risk. Of note, 1 of every 4 subjects with ICAS developed a vascular event after 7 years of follow-up. These findings are important as asymptomatic subjects with ICAS can be considered a high-risk population and may be a population target for testing more intensive or aggressive primary prevention strategies. Our results reinforce the fact that intracranial atherosclerosis is not an isolated disease, but related to generalized atherosclerosis affecting other vascular territories, even from its asymptomatic stage.

One essential aim in primary prevention is to find tools to improve the evaluation of “the vulnerable patient” [19]. Therefore, the identification of new blood, genetic or instrumental biomarkers may be crucial to predict and prevent future ischemic events. Nowadays, classic vascular risk functions (as Framingham or REGICOR) are being combined with new markers of subclinical atherosclerosis (e.g carotid intima media thickness, coronary calcium, ankle-arm index or circulating inflammatory markers) to better classify subjects at high risk, although there are no universal strategies accepted yet [20]. Importantly, in our population, ICAS was a better predictor of long-term vascular events than vascular risk score (REGICOR) or than the presence of carotid plaques.

ICAS can be diagnosed easily with a non-invasive test as TCCD or MRA that may be applicable to large populations, but first we should evaluate if that screening is cost-effective, as primary prevention trials in subjects with subclinical ICAS are lacking. Further interventional preventive therapy studies are needed to elucidate whether any particular pharmacological or life-style modification could change the prognosis of asymptomatic ICAS.

Strengths of this study include the population-based setting and the longitudinal design. Moreover, complete study protocol including the main purpose of the present paper was previously published [16]. There were no subjects lost-to-follow-up and all medical histories could be reviewed. Limitations include the observational nature of the study that precludes the evaluation of different preventive therapy regimes.

In conclusion, our results confirm that the presence of asymptomatic intracranial stenosis is a strong independent predictor not only for stroke but also for a composite of stroke, acute coronary syndrome and death, with higher hazard ratios that those conferred by carotid plaques. These findings might have important practical implications for the design of specific primary prevention strategies or future trials.

Conflicts of interest

The authors declare that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.022.

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