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ORIGINAL ARTICLE

Italian symptomatic intracranial atherosclerosis study (ISIDE)

A multicenter transcranial ultrasound evaluation

Claudio Baracchini[1] · Gian Paolo Anzola[2] · Silvia Cenciarelli[3] · Marina Diomedi[4] · Rita Bella[5] · Agnese Tonon[6] · Massimiliano Braga[7] · Maria Luisa Zedde[8] · Carla Zanferrari[9] · Massimo Del Sette[10] · Pietro Caliandro[11] · Carlo Gandolfo[12] · Stefano Ricci[3] · Giorgio Meneghetti[1]

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Abstract There are currently no data available on the prevalence of symptomatic intracranial atherosclerosis (ICAS) in Italy. The aim of this prospective, multicenter, hospital-based, transcranial ultrasound study was to establish the prevalence of ICAS among patients hospitalized with acute ischemic stroke. At 11 stroke centers across Italy, patients consecutively admitted for their first ever acute ischemic stroke were assessed prospectively over a 24-month period either with transcranial color-coded Doppler sonography (TCCS) or transcranial Doppler (TCD) according to validated criteria. ICAS was diagnosed when there was an evidence of a cerebral infarction in the territory of a ≥50 % stenosis detected by TCCS/TCD and confirmed by magnetic resonance angiography or computed tomography angiography. A total of 1134 patients were enrolled, 665 of them (58.6 %) men, with a mean age of 71.2 ± 13.3 years. ICAS was recorded in 99 patients (8.7 % of the whole sample, 8.9 % among Caucasians), most commonly located in the anterior circulation (63 of 99, 5.5 %). After adjusting for potential confounders, multivariate analysis identified carotid/vertebral ≥50 % stenosis [odds ratio (OR) 2.59, 95 % (confidence interval) CI 1.77–6.33; $P = 0.02$] and hypercholesterolemia (OR 1.38, 95 % CI 1.02–1.89; $P = 0.02$) as being independently associated with ICAS. ICAS is a surprisingly relevant cause of ischemic stroke in Italy, identified in almost 9 % of first-ever stroke patients. It is more prevalent in the anterior circulation and independently associated with hemodynamically significant cervical vessel atherosclerosis and hypercholesterolemia. These findings support the systematic use of transcranial ultrasound to identify ICAS in patients presenting with acute ischemic stroke and in cases with ≥50 % cervical vessel stenoses.

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✉ Claudio Baracchini
claudiobaracchini@gmail.com

[1] Stroke Unit and Neurosonology Laboratory, Department of Neuroscience, University of Padua School of Medicine, Via Giustiniani 5, 35128 Padua, Italy

[2] Neurologic Clinic and Rehabilitation Department, Casa di Cura Villa Barbarano, Salò, Italy

[3] UO Neurologia, USL Umbria 1, Ospedale di Città di Castello (PG), Città di Castello, Italy

[4] UOC Stroke Unit, Dipartimento di Neuroscienze, Fondazione Policlinico Tor Vergata, Rome, Italy

[5] UOS Malattie Cerebrovascolari Acute, University of Catania, Catania, Italy

[6] Divisione di Neurologia, Ospedale SS. Giovanni e Paolo, Venice, Italy

[7] Stroke Unit, Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy

[8] Stroke Unit, Department of Neuromotor Physiology, Arcispedale Santa Maria Nuova IRCCS Reggio Emilia, Reggio Emilia, Italy

[9] Neurosonology Service, Department of Neuroscience, University of Parma, Parma, Italy

[10] Divisione di Neurologia, Ospedale Galliera, Genoa, Italy

[11] Department of Geriatrics, Neuroscience, Orthopedics and Physiatrics, Institute of Neurology, Catholic University, Rome, Italy

[12] Stroke Unit, University of Genoa, DINOGMI, Genoa, Italy

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Introduction

Intracranial atherosclerosis is a major cause of ischemic stroke worldwide [1, 2], and commonly believed to have a poor prognostic impact due to a high recurrence rate; the risk of recurrence is highest for 70–99 % stenosis and during the first 2–3 weeks after the initial event [3]. ICAS consequently needs to be identified promptly in ischemic stroke patients. Noninvasive neuroimaging methods like transcranial ultrasound, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) are effective in detecting ICAS and relatively risk-free. The prevalence of ICAS is strongly influenced by ethnicity, being much more common among Asian (54 %), Afro-American (11 %) and Hispanic (6 %) stroke patients than in Caucasians (with rates reportedly as low as 1 % in the United States) [4–7]. However, ICAS in Caucasians might be underestimated, as suggested by the very different prevalence rates documented in various reports, ranging between 1 % and 43 % [5, 8]. Only few studies have assessed the prevalence of ICAS in European ischemic stroke patients, and its associated risk factors [9–13]. The lack of facilities for diagnosing ICAS and/or their underuse in practice, may contribute to the apparently low frequency of this condition in European ischemic stroke patients [14]. As there are no published data on the prevalence of ICAS in Italy, we conducted a prospective, multicenter, hospital-based, transcranial ultrasound study (the ISIDE, Italian Symptomatic Intracranial atherosclerosis and Doppler Evaluation) on acute stroke patients.

Methods

General study protocol

Patients consecutively admitted for their first-ever acute ischemic stroke at 11 stroke centers throughout Italy (Stroke Unit, University of Padua, Padua—208 patients; Neurological Clinic, Città di Castello (PG)—224 patients; Stroke Unit, University Tor Vergata, Roma—158 patients; Neurological Clinic, University of Catania—127 patients; Neurological Clinic, "SS. Giovanni e Paolo" Hospital, Venice—118 patients; Stroke Unit, Desio-Vimercate Hospital (MB)—72 patients; Stroke Unit, "Santa Maria Nuova" IRCCS, Reggio Emilia—59 patients; Neurosonology Service, University of Parma, Parma—55 patients; Neurological Clinic, La Spezia Hospital—41 patients; Neurological Clinic, Catholic University, Rome—40 patients; Stroke Unit, University of Genoa, Genoa—32 patients) were prospectively assessed during a 2-year study period adopting standardized diagnostic and therapeutic procedures as recommended by the European Stroke Organization [15], including treatment with intravenous recombinant tissue plasminogen activator in eligible patients. The chosen stroke centers had well-trained and experienced neurosonologists and committed to enrolling patients during the study period (September 2011–September 2013). Some, but not all centers were university hospitals and this was reflected by the number of patients they recruited. All patients details were entered in a computerized database provided free of charge to all participating centers, recording their demographic characteristics, vascular risk factors and routine blood tests. Patients were diagnosed as having arterial hypertension, if they had a systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg or if they were or had been on antihypertensive medication at any time before enrollment. Diabetes mellitus was defined as fasting serum glucose $\geq$7.0 mmol/L ($\geq$126 mg/dl), non-fasting serum glucose $\geq$11.1 mmol/L ($\geq$200 mg/dl), glycated hemoglobin (HbA1C) $\geq$48 mmol/mol ($\geq$6.5 % by the Diabetes Control and Complications Trial) or the use of glucose-lowering drugs before enrollment. Hypercholesterolemia was defined as total cholesterol >6.2 mmol/L (>240 mg/dl) or use of lipid-lowering drugs before enrollment. Any history of angina pectoris, myocardial infarction, coronary treatment (angioplasty/stenting, or bypass surgery), peripheral arterial disease, previous transient ischemic attack (TIA) was also recorded. Any cardiac arrhythmia, such as atrial fibrillation was diagnosed on the basis of at least one electrocardiogram (ECG) before or during the study period. Smoking habit was defined as current or cessation within the past 5 years. Clinical and functional status was assessed with the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS), respectively, both on admission and at discharge. Territorial distribution was evaluated in all patients with magnetic resonance imaging (MRI) or repeat computed tomography (CT) and with the Oxfordshire Community Stroke Project (OCSP) classification system [16]. The diagnostic workup included standard blood tests, routine ECG, cervical vessel ultrasound, transcranial ultrasound, transthoracic echocardiography (TTE), and 24-h ECG monitoring, plus coagulation studies, and transesophageal echocardiography (TEE) if appropriate. This study was approved by the Clinical Research and Ethics Committees of all participating centers.

Ultrasound protocol

All patients presenting with their first ever acute ischemic stroke underwent a complete cervical and intracranial ultrasound assessment by specialized stroke neurologists experienced in the use of cerebrovascular ultrasound, as soon as possible after hospitalization, at discharge and 3 months later. All cervical vessels were examined using high-resolution color-coded duplex sonography scanners with a high-frequency (5–10 MHz) linear probe. Carotid and vertebral plaques were recorded and stenoses were graded according to validated criteria [17, 18].

The intracranial arteries were examined with either a low frequency (1–3 MHz) phased-array transcranial color-coded Doppler sonography (TCCS) probe or a 2-MHz power-motion or single-channel transcranial Doppler (TCD). The system settings were adjusted for the analysis of middle-high velocity signals, with an appropriate pulse repetition frequency for arterial vessel detection. Patients were examined in a supine position, first through the transtemporal bone window and then through the transforaminal bone window. The middle cerebral artery (MCA), the anterior cerebral artery (ACA), the posterior cerebral artery (PCA) and the top of the basilar artery (BA) were examined through the transtemporal bone window, while the intracranial segment of the vertebral arteries (VAs) and the BA were assessed through the transforaminal bone window. After correctly identifying all these vessels, hemodynamic data were collected (blood flow direction, peak systolic velocity, and end diastolic velocity). The maximum achievable flow velocity without angle correction was recorded, unless a straight vessel segment of at least 1.5–2.0 cm was visualized. The pulsatility index (P.I.), which reflects downstream intracranial arterial resistance, was calculated for all patients according to the following formula: (peak systolic velocity − end diastolic velocity)/mean flow velocity. Cerebral artery stenosis was diagnosed qualitatively based on aliasing phenomenon (only visible on TCCS in a short segment of the vessel), increased flow velocities in the area of the stenosis, and flow disturbances upstream and downstream from the lesion. Previously validated criteria were used to detect ≥50 % intracranial stenosis with TCCS [19] and TCD [20, 21]. Symptomatic ICAS was diagnosed when there was evidence of a cerebral infarction on repeat brain CT or MRI in the territory of a ≥50 % stenosis detected by TCCS or TCD and confirmed within a week by either CTA or MRA, at the treating physician's discretion. Neuroradiologists were always blind to the ultrasound findings. Digital subtraction angiography (DSA) was performed only when there was not a full agreement between TCD/TCCS and CTA/MRA findings. The degree of intracranial stenosis was calculated and graded by the neuroradiologist according to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study method and criteria [22]. The prevalence of ICAS was estimated after excluding patients with no or inadequate temporal windows, patients with potential cardiac sources of emboli (as in atrial fibrillation), and patients with other non-atherosclerotic causes of intracranial stenosis, such as dissection, vasospasm, or vasculitis. Only patients with persistent intracranial stenosis at 3 months were diagnosed with ICAS.

Statistical analyses

Using the common statistical calculations (alpha 0.01, prevalence 5 % and precision 1.5), 811 patients would have been needed to obtain significant results. We aimed to recruit at least 1000 patients to account for data dispersion and incompleteness. The statistical analysis was performed with the SSPS statistical software (SPSS Inc. version 13.0 for Windows, Chicago, IL, USA). Patients' demographic and clinical characteristics are given as means ± standard deviations (SD) or as medians and ranges. Non-continuous variables are presented as percentages. Frequencies and categorical data of patients with and without ICAS were compared with Chi-square or Fisher's exact tests, as appropriate, calculating the odds ratios (OR) with the 95 % confidence intervals (CI). Significance was assumed at $p < 0.05$. Cox's proportional hazards analysis was used to identify factors with statistical or marginal significance on an univariate analysis as potential predictors of ICAS.

Results

During a 2-year study period, a total of 1526 patients were hospitalized with their first ever acute ischemic stroke, and had a first ultrasound examination 3.7 ± 1.5 days later. The temporal bone window was inadequate in 122 (8 %) patients, who were consequently excluded from the sample. These patients did not differ in baseline characteristics from those with adequate temporal windows. After completing the diagnostic workup, 270 patients were also excluded from this study due to atrial fibrillation or other cardiac sources of emboli ($n = 258$, 16.9 %), dissection ($n = 2$, 0.13 %) or vasculitis ($n = 10$, 0.7 %). The criteria for inclusion in the ISIDE study were thus met by 1134 patients, comprising 665 (58.6 %) men and 469 (41.4 %) women, with a mean age 71.2 ± 13.3 years; 1100 (97 %) were Caucasians, and the sample demographic and clinical details are displayed in Table 1. All 1134 patients were assessed by TCCS/TCD and by at least another imaging modality; in particular, 290 by CTA, 844 by MRA and 113 by DSA. ICAS was first detected by ultrasound in 119 patients (10.5 %) and later confirmed in 99 patients

Table 1 Demographic and clinical characteristics of the study population

Variables, *n* (%)	Total ($n = 1134$)	ICAS ($n = 99$)	No ICAS ($n = 1035$)	*p* value
Age, years (±SD)	71.2 (13.3)	68.1 (13.7)	71.5 (13.2)	0.01
Male	665 (58.6)	58 (58.5)	607 (58.6)	NS
Caucasian race	1100 (97.0)	98 (98.9)	1002 (96.8)	NS
Height, cm (±SD)	167.1 (9.0)	167.6 (8.8)	167.0 (9.0)	NS
Weight, kg (±SD)	73.9 (14.7)	75.7 (14.1)	73.6 (14.7)	NS
BMI, kg/m^2 (±SD)	26.4 (4.4)	27.0 (3.9)	26.3 (4.4)	NS
Hypertension	800 (70.5)	68 (68.8)	732 (70.7)	NS
Diabetes mellitus	247 (21.8)	30 (30.3)	217 (20.9)	0.03
Hypercholesterolemia	467 (41.1)	51 (51.5)	416 (40.2)	0.02
Smoking	361 (31.8)	30 (30.3)	331 (31.9)	NS
Cardiovascular Diseases	192 (16.9)	16 (16.1)	176 (17.0)	NS
PVD	48 (4.2)	4 (4.1)	44 (4.2)	NS
Previous TIA	150 (13.2)	20 (20.2)	130 (12.5)	0.03
ESR, mm/h (±SD)	30.3 (24.3)	35.9 (23.6)	29.6 (24.0)	0.01
CRP, mg/dL (±SD)	10.1 (22.2)	15.5 (25.6)	9.4 (22.5)	NS
Carotid/vertebral atherosclerosis	218 (19.2)	27 (27.3)	191 (18.4)	0.03
Median NIHSS (range)	6 (3–20)	7 (5–20)	6 (3–20)	NS

BMI body mass index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ICAS* symptomatic intracranial atherosclerosis, *NIHSS* National Institutes of Health Stroke Scale, *PVD* peripheral vascular disease, *SD* standard deviation, *TIA* transient ischemic attack

p values <0.05 are reported, otherwise they are defined as *NS* not significant

(8.7 %). Therefore, 20 (1.8 %) false positives were excluded. Considering only the Caucasian patients (1100), ICAS was detected in 98 patients (8.9 %). There was no significant difference in the prevalence of ICAS among the study centers. Overall, ICAS was most commonly located in the anterior circulation [63 (5.6 %)], and especially in the MCA (45.5 % of the ICAS population). The prevalence of ICAS according to the different location is given in Table 2. When patients with and without ICAS were compared, the two groups did not differ significantly in terms of their demographic and clinical characteristics, except that patients with ICAS were more likely to have diabetes mellitus (30.3 vs 20.9 %, $p = 0.03$), hypercholesterolemia (51.5 vs 40.2 %, $p = 0.02$), a history of TIA (20.2 vs 12.5 %, $p = 0.03$), a high erythrocyte sedimentation rate (ESR) (35.9 vs 29.6 %, $p = 0.01$), and more concomitant asymptomatic carotid/vertebral ≥50 % stenoses (27.3 vs 18.4 %, $p = 0.03$) than patients without ICAS (Table 1). Among all the prognostic patient variables included in the univariate analysis as potential predictors of ICAS (age, gender, race, height, weight, BMI, hypertension, diabetes mellitus, hypercholesterolemia, smoking, cardiovascular disease, atrial fibrillation, peripheral vascular disease, previous TIA, ESR, C-reactive protein, carotid/vertebral atherosclerosis and median NIHSS score on admission), only hypercholesterolemia (OR 1.38; 95 % CI 1.02–1.89, $p = 0.02$) and ≥50 % carotid/vertebral atherosclerosis (OR 2.59; 95 % CI 1.77–6.33, $p = 0.02$) emerged on multivariate analysis as independent predictors of ICAS (Table 3).

Table 2 Site of Symptomatic Intracranial Atherosclerosis

Location	Patients with ICAS *n* (% of study population)
Anterior circulation	63 (5.5)
MCA	45
TICA	16
ACA	2
Posterior circulation	36 (3.2)
VA	20
BA	10
PCA	6
Total	99 (8.7)

ACA anterior cerebral artery, *BA* basilar artery, *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *TICA* terminal internal carotid artery, *VA* vertebral artery

Table 3 Univariate and multivariate analyses of the variables associated with symptomatic intracranial atherosclerosis

Predictor	Univariate analysis OR (95 % CI), p value	Multivariate analysis OR (95 % CI), p value
Age	3.39 (1.73–6.67), $p = 0.01$	NS
Diabetes mellitus	1.63 (1.01–2.63), $p = 0.03$	NS
Hypercholesterolemia	1.58 (1.92–2.43), $p = 0.02$	1.38 (1.02–1.89), $p = 0.02$
Prior TIA	1.76 (1.00–3.05), $p = 0.03$	NS
ESR	2.19 (1.84–5.23), $p = 0.01$	NS
Carotid/vertebral ≥50 % stenosis	1.65 (1.00–2.71), $p = 0.03$	2.59 (1.77–6.33), $p = 0.02$

CI confidence interval, *ESR* erythrocyte sedimentation rate, *OR* odds ratio, *TIA* transient ischemic attack
p values <0.05 are reported, otherwise they are defined as *NS* not significant

Discussion

This Italian nationwide, prospective, hospital-based, multicenter ultrasound-driven ISIDE study, found ICAS responsible for first-ever ischemic stroke in 8.7 % of our study population, and 8.9 % of the Caucasians. The most common site of ICAS was the anterior circulation and the MCA in particular. After adjusting for potential confounders including demographic and baseline clinical characteristics, hypercholesterolemia and concomitant carotid/vertebral ≥50 % stenosis were independently associated with a higher probability of ICAS.

To the best of our knowledge, this is the first study to provide data on the prevalence of ICAS in an Italian ischemic stroke population. Previous population- or hospital-based studies on stroke epidemiology in Italy provided no data on the prevalence of ICAS among Italian patients with cerebrovascular disease [23]. This study fills this gap and consistently with many reports [1, 2, 8], it demonstrates that besides carotid and/or vertebral arteries, the intracranial vessels should not be ignored as a potential site of atherosclerosis causing stroke syndromes.

Few European studies have investigated the prevalence of ICAS among Caucasian patients presenting with acute cerebral ischemia [9–13, 24]. ICAS was reportedly the cause of TIA or ischemic stroke in 2.3 % of Dutch patients, 6.5 % of Germans, 7.4 % of Norwegians, 9.2 % of Greeks, 12.4 % of Spanish patients. Therefore, an overall 8.7 % ICAS prevalence (8.9 % among Caucasians) detected in our study is consistent with mounting evidence of the important role of ICAS in Europe. However, there are several differences between the ISIDE study and the other above-mentioned studies. First, we did not include patients with TIA to avoid attributing the cause of the ischemic event to the wrong vessel, and consequently risking to overestimate the prevalence of ICAS. Second, we considered only first-ever ischemic strokes for much the same reasons. Third, we excluded strokes due to branch occlusion because they involve a different mechanism from strokes due to a stenosis of a main intracranial artery. Fourth, the ISIDE study relied entirely on transcranial ultrasound (TCD/TCCS), using MRA/CTA and occasionally DSA, to confirm cases of ≥50 % intracranial stenosis. Even with all these restrictions, the prevalence of ICAS in our sample is consistent with the figure (9.2 %) found in another ultrasound study (using TCD alone) conducted in Greece, which also included patients with TIA's [12]. Interestingly, in another ultrasound-driven investigation conducted systematically on French patients with acute TIA, ICAS was detected in 8.8 % of all screened patients [13]. Despite their diversity, these three Mediterranean studies reached very similar results and all support the systematic use of transcranial ultrasound in the early management of patients presenting with symptoms of acute cerebral ischemia.

Intracranial atherosclerosis has been associated with several risk factors, and particularly diabetes mellitus [5, 12, 24–28] and arterial hypertension [12, 26, 28, 29]. In this ISIDE study, diabetes mellitus was also more prevalent among patients with ICAS (30.3 vs 20.9 %, $p = 0.03$), as younger age ($p = 0.01$), a history of TIA (20.2 vs 12.5 %, $p = 0.03$), and ESR (23.6 vs 24 %, $p = 0.01$), but only hypercholesterolemia (OR 1.38; 95 % CI 1.02–1.89, $p = 0.02$) and concomitant hemodynamically significant cervical vessel stenosis (OR 2.59; 95 % CI 1.77–6.33, $p = 0.02$) emerged as risk factors independently associated with ICAS. Hypercholesterolemia reportedly predicted intracranial atherosclerosis in the Northern Manhattan Stroke Study too [5], although it was slightly more prevalent in Blacks than in Caucasians, partly accounting for the racial disparity in the incidence of ICAS. More recently, hypercholesterolemia was also found associated with a higher likelihood of underlying intracranial atherosclerotic disease as a cause of intracranial arterial occlusion [30]. Carotid/vertebral ≥50 % stenosis was the stronger predictor of ICAS in our sample. Previous studies have not reported on this association, though it seems intuitive to think that patients suffering a stroke secondary to intracranial atherosclerosis are likely to have significant cervical vessel atherosclerosis, given that this disease is

systemic. In fact, extracranial carotid atherosclerotic stenosis is the most common vascular lesion identified in Caucasian stroke patients [5, 7]. A few studies have already reported a higher risk of death and vascular events in patients with ICAS associated with extracranial carotid disease [10, 31].

The ISIDE study has some limitations. First, operator-dependence is an issue (as with all ultrasound studies), and this is the reason why the recruiting centers were selected among those with specialized training and experience in cerebrovascular ultrasound. Second, as this study was planned to be adherent to the current practice, we did not have the same ultrasound technique (TCD or TCCS) and/or equipment to perform uniformly all ultrasound studies. In doing so, our study represents a more real picture of standard hospital care, and therefore, a true estimate of ICAS occurrence. Third, we are also aware that in contrast to the accuracy reported by single-center studies, a multi-center study with variable experience in TCD and TCCS might have a lower accuracy of TCD/TCCS for intracranial stenosis compared with intra-arterial digital subtraction angiography. Even so, our ICAS prevalence would be at worst an underestimation of the true value. Fourth, ICAS diagnosis might have been missed in some patients because DSA was performed only in cases with discordant findings between TCD/TCCS and CTA/MRA. However, many studies have already shown that transcranial ultrasound is a valid alternative for detecting symptomatic intracranial stenosis, and it carries a high negative predictive value for $\geq$50 % intracranial stenosis [20, 32–34]. Here again, the worst-case scenario of a false negative ultrasound finding would have resulted in an underestimation of the prevalence of ICAS. Fifth, ruling out patients with no or inadequate acoustic windows might have biased our findings. Finally, mild (<50 %) intracranial atherosclerosis could determine a stroke just as in mild carotid disease, and this type of patients are currently excluded by most studies, including ours. Using a lower threshold ($\geq$30 %) for detection of ICAS, a higher prevalence (up to 17.8 %) was documented [8, 35]. Noteworthy, most of the above-mentioned limitations of the ISIDE study could actually be interpreted as strengths, since they could only give rise to an underestimation of the prevalence of ICAS. In other words, the nearly 9 % prevalence identified here is not only robust, but already much higher than hitherto reported in Caucasians [5].

In conclusion, the results of the ISIDE study show that ICAS is a surprisingly relevant cause of ischemic stroke in Italy, identified in almost 9 % of first ever stroke patients and independently associated with carotid/vertebral $\geq$50 % stenosis and hypercholesterolemia. These findings support the systematic use of transcranial ultrasound to detect ICAS in the early management of patients presenting with symptoms of acute cerebral ischemia and in patients with cervical vessel atherosclerosis.

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Compliance with ethical standards

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Ethical statement This study has been approved by the local ethics committee of every recruitment center and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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