Presence of intracranial artery calcification is associated with mortality and vascular events in patients with ischemic stroke after hospital discharge: a cohort study.

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Presence of Intracranial Artery Calcification Is Associated With Mortality and Vascular Events in Patients With Ischemic Stroke After Hospital Discharge

A Cohort Study

Jean-Marc Bugnicourt, MD*; Claire Leclercq*; Jean-Marc Chillon, PharmD, PhD; Momar Diouf; Hervé Deramond, MD, PhD; Sandrine Canaple, MD; Chantal Lamy, MD; Ziad A. Massy, MD, PhD; Olivier Godefroy, MD, PhD

Background and Purpose—Although intracranial artery calcification (IAC) has been reported to be a risk factor for ischemic stroke, the prognostic implications of IAC in stroke outcome are unknown. The purpose of this study was to determine the association between IAC and risk of vascular events and death in patients with stroke after hospital discharge.

Methods—All patients with ischemic stroke over a 1-year period were included (n=302). IAC, assessed by multidetector CT, was defined as hyperdense foci (peak density >130 Hounsfield units) and assessed in the 7 major cerebral arteries. The IAC scores ranged from 0 (no calcification) to 7. Follow-up information on major clinical events (including fatal or nonfatal ischemic stroke, cardiac and peripheral artery events, and all-cause death) was obtained by means of a structured phone interview.

Results—IAC was present in 260 patients (83%). With a mean follow-up of 773±223 days, 88 major clinical events occurred in 67 patients (22%): 45 new ischemic vascular events (ischemic stroke: n=22; cardiac event: n=15; peripheral artery event: n=8) and 43 deaths from any cause. Patients with the highest IAC scores had significantly higher rates of death and vascular events than those with the lowest IAC scores (log rank test, $P=0.029$). In the Cox proportional hazards regression model, the IAC score was significantly associated with major clinical events (hazard ratio, 1.34; 95% CI, 1.11–1.61; $P=0.002$).

Conclusions—In patients with ischemic stroke, IAC detection may constitute a simple marker of a high risk of future major clinical events. **(*Stroke*. 2011;42:3447-3453.)**

Key Words: acute stroke ■ all-cause mortality ■ calcifications ■ cardiovascular risk ■ outcome ■ stroke

Atherosclerosis is the leading cause of death and a major cause of ischemic stroke and cardiac events in industrialized countries.[1–4] Arterial calcifications are considered to be an integral part of this active process, occurring in up to 90% of atheromatous lesions,[5] and may be used as a noninvasive marker of atherosclerosis, because calcium deposits can now be easily detected with the development of several imaging techniques such as multidetector CT. For example, a strong correlation has been demonstrated between coronary calcifications and coronary plaques[6] and between aortic calcification and aortic atherosclerosis.[7] However, to the best of our knowledge, the relationship between carotid artery calcification and carotid plaque burden has not been examined. Furthermore, although intracranial artery calcification (IAC) is a relatively sensitive and specific marker of intracranial atherosclerosis, it is not always associated with intracranial stenosis.[8]

Brain CT imaging frequently reveals IAC in patients admitted for acute ischemic stroke. The prevalence of IAC is high in Chinese[9] and white[10] individuals, and IAC has also been found to be a risk factor for ischemic stroke.[9,10] We have also previously shown a strong correlation between IAC and significant carotid atherosclerosis[10] and between IAC and complex atherosclerotic plaques in the proximal aorta

Received February 23, 2011; final revision received June 14, 2011; accepted July 6, 2011.

From the Service de Neurologie (J.-M.B., C.L., S.C., C.L., O.G.), Service de Biostatistiques (M.D.), Service de Radiologie (H.D.), Services de Pharmacologie Clinique et Néphrologie (Z.A.M.), CHU Amiens, Amiens, France; Laboratoire de Neurosciences Fonctionnelles et Pathologies EA 4559 (J.-M.B., C.L., O.G.), Amiens, France; INSERM ERI12 (J.-M.B., J.-M.C., Z.A.M.), Amiens, France; and Université de Picardie Jules Verne (J.-M.C., Z.A.M.), Amiens, France.

The online-only Data Supplement is available at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.111.618652/-/DC1.

*J.-M.B. and C.L. equally contributed to this work.

Correspondence to Jean-Marc Bugnicourt, MD, Service de Neurologie, CHU Amiens, France, Place Victor Pauchet, F-80054 Amiens Cedex 1, France. E-mail bugnicourt.jean-marc@chu-amiens.fr

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.111.618652**

(≥4 mm in thickness) in patients referred for ischemic stroke,[11] suggesting that IAC is a marker of widespread systemic atherosclerosis in this population. However, no data are currently available concerning the prognostic significance of IAC relative to the outcome of these patients after hospital discharge. In particular, it is unknown whether IAC has an additional value to predict future vascular events and/or mortality.

The aim of the present study was to examine whether the presence of IAC, assessed by multidetector CT, could be predictive of all-cause mortality and ischemic vascular events in a cohort of patients with acute ischemic stroke.

Subjects and Methods

Study Population

This study included all consecutive patients between January and December 2007 who were referred to our Stroke Unit for acute cerebral ischemia, including transient ischemic attack and cerebral infarct (n=375). Thirty-one of these patients died in the hospital. Thrombolyzed patients (n=12) and foreigners (n=5) were excluded from the study as well as 15 patients who refused follow-up. For each patient, clinical data were prospectively collected according to a standardized protocol.[12] CT, electrocardiogram, cervical Doppler ultrasonography, transthoracic echocardiography, and standard laboratory tests were performed in all patients on admission. Transesophageal echocardiography, specialized laboratory tests, Holter electrocardiographic monitoring, MRI, and/or angiography were performed in selected patients. The following variables concerning the acute stage of ischemic stroke were collected: age, gender, type of ischemic stroke (according to the Oxfordshire Community Stroke Project Classification),[13] cause of ischemic stroke (according to the Trial of ORG 10172 in Acute Stroke Treatment criteria with the addition of aortic atheroma ≥2 mm[14] and intracranial atherosclerotic disease, defined as a focally narrowed [but still visible] lumen or the segmental nonvisualization of a brain artery in magnetic resonance angiography), and previously identified stroke risk factors or those discovered during hospitalization, including hypertension (antihypertensive treatment or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg before hospitalization), diabetes (insulin or oral antidiabetic therapy or fasting blood glucose >7 mmol/L on 2 occasions during hospitalization), hypercholesterolemia (lipid-lowering treatment or low-density lipoprotein cholesterol >1 g/L), coronary artery disease (defined as a history of myocardial infarction or angina), current smoking, regular alcohol consumption (>2 alcoholic drinks daily), peripheral artery disease, and body mass index (kg/m^2). The glomerular filtration rate was estimated using the 4-component Modification of Diet in Renal Disease equation based on age, gender, race, and serum creatinine concentration determined on admission. Chronic kidney disease was defined as a glomerular filtration rate <60 mL/min/1.73 m^2 in accordance with the National Kidney Foundation criteria.[15] Serum C-reactive protein and low-density lipoprotein cholesterol concentrations were also collected. Finally, the severity of neurological deficits of the index stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS).[16] The study was approved by the hospital's ethics review committee.

Assessment of IAC

IAC score was determined by a simple head CT scan as previously described.[10] Briefly, all CT examinations were performed on a 64-slice multidetector CT scanner (slice thickness 0.625 mm with no intersection gap) from the skull base to the vertex. Images were reviewed on a dedicated workstation. A method that scores the number of calcified arteries rather than the severity of calcification of individual arteries was used. Calcification was defined as hyperdense foci along the artery considered with a peak density >130 Hounsfield units. Grade 0 corresponds to the absence of calcifications or tiny scattered calcification foci seen on only 1 slice and Grade 1 corresponds to thick contiguous calcification, thick interrupted calcification, thin confluent calcification, or tiny, scattered calcification foci seen on at least 2 adjacent slices. This semiquantitative scoring system was applied to 7 intracranial arteries: right and left internal carotid arteries, right and left middle cerebral arteries, right and left vertebral arteries, and the basilar artery. IAC scores therefore ranged from 0 (no calcification) to 7 (calcification in all 7 intracranial arteries examined). A trained neurologist, blinded to clinical data, examined the CT scan to detect and grade calcifications.

Follow-Up and Outcome Measures

All survivors were contacted by phone at least 2 years after their stroke. Follow-up information was obtained by means of a structured phone interview with the patient or, if necessary, the caregiver. All telephone interviews were performed by a stroke specialist using a standardized questionnaire, and the interviewer was blinded to the IAC score. Quality assessment was performed in 243 patients (80%) examined by a stroke specialist during a standard outpatient visit. There was perfect agreement between the data gathered by telephone on 1 hand and the data from medical and imaging files on the other. In 40 patients (14%), follow-up information obtained by phone was corroborated with hospital medical records by means of an electronic database (DxCARE for clinical information and DxMM for imaging analysis); again, the agreement was perfect. In 19 cases (6%), additional information was only obtained after contacting their relatives or their general practitioner.

The specified outcomes were a major clinical event (MCE), including death (vascular death, nonvascular death, and death of undetermined cause) or vascular ischemic events: cerebral ischemic event (ischemic stroke/transient ischemic attack), cardiovascular ischemic event, and peripheral artery event. Cardiovascular death was defined as fatal stroke, fatal myocardial infarction, or any sudden death that could not be definitely attributed to a nonvascular cause. Multiple overlapping methods, including contact with the patient's general practitioner and/or family members, were performed to more clearly determine the circumstances surrounding all out-of-hospital deaths. Unclear or uncertain information about cause of death was classified as unknown cause. The diagnosis of stroke was documented on the basis of clinical and neurological examination including the patient's history and evaluation of symptoms surrounding the episode and CT (or MRI). A cardiovascular ischemic event was documented by a history of at least 1 of the following conditions: acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery, or myocardial infarction. These diagnoses were based on the diagnosis reported on the discharge summary by the attending physician. Peripheral artery events included surgical or endovascular revascularization procedure. Time to follow-up and time to event were calculated as the period between hospital discharge and the phone interview and between hospital discharge and the event, respectively. All vascular ischemic events followed by death from any cause over the next 28 days were considered to be fatal vascular ischemic events.

Statistical Analysis

In line with previous results showing that almost 15% of patients with ischemic stroke die or experience another clinical event at 1 year,[12] the study power was calculated by considering an expected MCE rate of 25% in the IAC group and 5% in patients without IAC. A sample including at least 92 patients (46 in each group) was calculated to achieve 80% power to detect a significant association (α error=0.05) between IAC and the MCE incidence rate.

Baseline characteristics (patients with IAC versus patients without IAC) were compared by Student t tests for continuous variables and χ^2 tests for categorical variables. Dependent variables were: age, gender, main risk factors (hypertension, diabetes mellitus, hypercholesterolemia, ischemic heart disease, smoking, alcohol, peripheral artery disease, and body mass index), previous stroke or transient ischemic attack, chronic kidney disease, and causes of ischemic stroke. A second series of analyses examined baseline characteristics

between patients developing MCEs and patients without MCEs. In survival analysis, event-free curves were generated using Kaplan–Meier analysis and compared using the log rank test. The Cox proportional hazards regression function was used to estimate the impacts of possible determinants of MCEs in terms of risk ratios, taking into account the time variable. The first step consisted of Cox regression analyses for outcome by considering all risk factors. Cox regression analyses were then performed for outcome by considering causes and severity of ischemic stroke and by considering different variables known to be associated with outcome. The analysis was repeated by considering patients who experienced only cardiovascular death and ischemic vascular events and patients who were regularly reviewed. Associations are presented as hazard ratios with corresponding 95% CIs. A P value <0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS statistical software (SPSS Inc, Chicago, IL).

Results

Patient Characteristics at Baseline

A total of 312 eligible patients were admitted during the study period (men: n=173; women: n=139), 260 (83%) of whom had IAC. Patients with IAC were older (70.5±12.2 versus 49.9±16.0 years, $P<0.001$) and more frequently had hypertension (69.2% versus 23.1%, $P<0.001$), diabetes mellitus (26.5% versus 9.6%, $P=0.007$), peripheral artery disease (11.9% versus 1.9%, $P=0.025$), and chronic kidney disease (31.9% versus 5.8%, $P<0.001$). Patients with IAC also had more significant carotid atherosclerotic disease (16.5% versus 3.8%, $P=0.016$), cardioembolic stroke (32.7% versus 13.5%, $P=0.005$), and proximal aortic plaques (24.7% versus 2.9%, $P=0.002$). Baseline C-reactive protein level was significantly higher in patients with IAC (6.96±9.57 mg/L versus 4.07±4.20 mg/L, $P=0.001$).

Patient Outcome

Ten patients (3.2%) were lost to follow-up after hospital discharge. The mean follow-up time was 773±223 days (median follow-up time, 831 days; range, 49–1021 days) and the mean time to event was 715±276 days (median time to event, 808 days; range, 27–1013 days). Eighty-eight MCEs occurred in 67 patients (22.2%) during this follow-up period. Men and women were equally affected, although deaths of unknown causes were more frequent in women (Supplemental Table I; http://stroke.ahajournals.org). The MCEs were mainly new cerebral ischemic events followed by cardiovascular events and peripheral vascular events (Table 1). At last follow-up, 43 patients (14%) had died from the following causes: myocardial infarction (n=4), recurrent stroke (n=3), peripheral artery disease (n=1), pulmonary embolism (n=4), sudden death (n=7), malignancy (n=3), pneumonia or sepsis (n=6), fatal hemorrhagic stroke (n=3), and death from unknown causes (n=12). Baseline and recurrent cerebral ischemic events are detailed in Supplemental Figure I and Table I.

Baseline characteristics of patients with stroke according to the presence or absence of an MCE are shown in Table 2. Age, hypertension, NIHSS score at hospital discharge, and presence of IAC were associated with MCEs. Patients with MCEs were also less likely to be active smokers. In addition, baseline C-reactive protein was higher in patients with MCEs, whereas glomerular filtration rate and low-density lipoprotein cholesterol levels were higher in patients without MCEs. Finally, patients with the highest IAC scores had the highest rates of MCEs (Figure).

Table 1. Clinical Events Observed in the 67 Patients With Ischemic Stroke Who Experienced Major Clinical Events During Follow-Up

	No. of Patients(%)
Cerebrovascular events	22 (32.8)
Transient ischemic attack	5 (7.5)
Ischemic stroke	17 (25.4)
Lacunar	2 (3.0)
Nonlacunar	15 (22.4)
Fatal stroke	3 (4.5)
Cardiovascular events	15 (22.4)
Acute coronary syndrome	9 (13.4)
Myocardial infarction	4 (6.0)
Coronary artery bypass surgery	2 (3.0)
Fatal cardiovascular event	4 (6.0)
Peripheral artery events	8 (11.9)
Fatal event	1 (1.5)
Deaths	43 (64.2)
Cardiovascular causes	19 (28.4)
Nonvascular causes	12 (17.9)
Unknown causes	12 (17.9)

Patients may have ≥1 major clinical event.

Patients who received regular follow-up (80%) had a higher rate of active smoking (24% versus 9%, $P=0.004$) and peripheral artery disease (12% versus 3%, $P=0.023$) but a lower rate of hypertension (58% versus 75%, $P=0.008$). These individuals had a significantly lower modified Rankin Scale score at hospital discharge than patients who were not followed up (1.45±1.5 versus 2.54±1.8, respectively; $P<0.001$) and presented a lower MCE rate (16% versus 39%, respectively; $P<0.001$), although the presence of IAC was similar (82% versus 87%, $P=0.46$). In the subgroup of patients with brain MRI data (n=111), we showed that individuals with MCEs had more intracranial atherosclerotic disease than those without MCEs (36% versus 5%, respectively; $P<0.001$); similarly, patients who experienced recurrent ischemic stroke tended to have intracranial atherosclerotic disease more frequently than patients with no recurrence (30% versus 9%, respectively, $P=0.075$).

In the Cox proportional hazards regression model, the adjusted hazard ratio for MCEs in the presence of IAC was 1.34 (95% CI, 1.11–1.61; $P=0.002$; Table 3). Other independent predictors of MCEs were age and NIHSS score at hospital discharge and C-reactive protein depending on several factors included in the model. When considering only cardiovascular death and ischemic vascular events (hazard ratio, 1.39; 95% CI, 1.10–1.76; $P=0.007$) or only patients who were regularly followed (hazard ratio, 1.35; 95% CI, 1.04–1.74; $P=0.021$), the IAC score remained significantly associated with MCEs.

Table 2. Baseline Demographic, Clinical, and Laboratory Factors of the Stroke Population According to the Presence or Absence of Major Clinical Events (MCEs)

	All Patients (n=302)	MCEs (n=67)	No MCEs (n=235)	*P*
Age, y	67.0±15.0	72.7±13.1	65.1±15.0	<0.001
No. of males	168 (55.6)	36 (53.7)	132 (56.2)	0.78
Previous main risk factors				
Hypertension	186 (61.6)	51 (76.1)	135 (57.4)	0.007
Previously treated	164 (54.3)	45 (67.2)	119 (50.6)	0.018
Discovered during hospitalization	22 (7.3)	6 (8.9)	16 (6.8)	0.594
Diabetes mellitus	73 (24.2)	21 (31.3)	52 (22.1)	0.14
Hypercholesterolemia	104 (34.4)	24 (35.8)	80 (34.0)	0.77
Active smoking	63 (20.9)	7 (10.4)	56 (23.8)	0.017
CAD	41 (13.6)	13 (19.4)	28 (11.9)	0.15
PAD	32 (10.6)	9 (13.4)	23 (9.8)	0.38
Stroke/TIA	61 (20.2)	19 (28.4)	42 (17.9)	0.08
BMI ≥25 kg/m^2	156 (51.7)	36 (53.7)	120 (51.1)	0.78
Chronic kidney disease	84 (27.8)	25 (37.3)	59 (25.1)	0.063
TIA	38 (12.6)	9 (13.4)	29 (12.3)	0.83
Ischemic stroke	264 (87.4)	58 (86.6)	206 (87.7)	0.83
Causes of ischemic stroke	44 (14.6)	14 (20.9)	30 (12.8)	0.12
Atherosclerosis ≥50%	90 (29.8)	24 (35.8)	68 (28.9)	0.30
Cardioembolic	30 (9.9)	6 (8.9)	24 (10.2)	1.00
Lacunar	118 (39.1)	25 (37.3)	92 (39.1)	1.00
Undetermined	21 (6.9)	3 (4.5)	17 (7.2)	1.00
Other	40 (13.2)	8 (11.9)	32 (13.6)	0.84
Aortic plaques (Grades III–IV)*	12 (11)	8 (36)	4 (5)	<0.001
Intracranial atherosclerotic disease†				
Intracranial artery calcification				
Presence of IAC	251 (83.1)	65 (97.0)	186 (79.1)	<0.001
IAC score	2.20±1.4	2.84±1.3	1.98±1.4	<0.001
Laboratory parameters				
C-reactive protein, mg/L‡	6.47±8.94	11.26±13.24	4.97±6.66	<0.001
LDL-C, mg/L	1.21±0.34	1.12±0.33	1.22±0.34	0.041
GFR, mL/min/1.73 m^2	75.2±25.7	69.6±26.7	76.7±25.4	0.047
NIHSS score at hospital discharge	3.0±4.8	4.1±4.9	2.7±4.7	0.037
Antihypertensive treatment at hospital discharge	231 (76.5)	54 (80.6)	177 (75.3)	0.417

Results are expressed as either mean±SD (age, NIHSS score at hospital discharge, IAC score, C-reactive protein, LDL-C, and GFR) or as no. (%) with no.=no. of patients and %=% of patients in the group.

CAD indicates coronary artery disease; PAD, peripheral artery disease; TIA, transient ischemic attack; BMI, body mass index; IAC, intracranial artery calcification; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate estimated according the Modification of Diet in Renal Disease formula; NIHSS, National Institutes of Health Stroke Scale.

*n=196 (transesophageal echocardiography was not performed in all patients).

†n=111 (brain MRI was not performed in all patients).

‡n=292 (after excluding patients in whom C-reactive protein was not assayed, n=3, and those with pulmonary infection at admission, n=7).

Discussion

This study demonstrates that the IAC score is a strong and independent predictor of all-cause mortality and ischemic vascular events after hospital discharge, even after adjustment for other possible predictors. This finding indicates that a simple determination of IAC using multidetector CT allows identification of patients with ischemic stroke at high risk of subsequent MCEs; patients with the highest IAC scores had the highest risk.

A meta-analysis of prospective studies reporting calcifications and cardiovascular end points was recently published.[17] The authors reported various imaging modalities to assess calcifications of the arterial wall or cardiac valves in populations with various baseline risk levels. They showed that the presence of calcifications in any arterial wall was associated with a 3- to 4-fold higher risk for cardiovascular events and death. Furthermore, noncontrast CT scans were more predic-

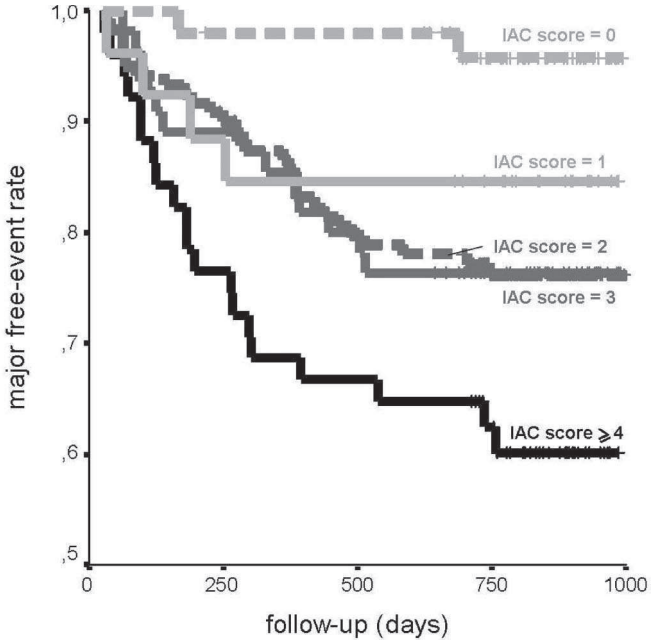

Figure. Kaplan–Meier analysis of the incidence of major clinical events in patients with ischemic stroke according to the intracranial artery calcification (IAC) scores. Patients with the highest IAC scores had significantly higher rates of death and vascular events than those with the lowest IAC scores (log rank test, $P=0.029$).

Cumulative events

IAc score = 0	0	1	1	2	2
IAC score = 1	0	4	4	4	4
IAC score = 2	0	12	25	28	28
IAC score = 3	0	7	13	13	13
IAC score ≥ 4	0	13	17	19	20

tive of subsequent events than radiographic studies, probably due to more reliable identification of small amounts of calcification. However, no published study has specifically addressed outcome in patients with arterial calcifications of intracranial arteries. A few studies have tried to address the association between IAC and subsequent risk of stroke. Most of these studies reported that IAC does not appear to play a major role in the development of cerebral infarcts.[18,19] Only Erbay et al showed a relationship between small deep cerebral infarcts and severe IAC located in carotid arteries.[20] More recently, in a study based on a small sample size, no significant difference was demonstrated between severity of carotid atherosclerotic calcification and stroke incidence in a 3-year clinical follow-up.[21]

It has been suggested for a long time that intracranial atherosclerosis may be a potential marker of extensive systemic atherosclerotic disease. Marzewski et al first reported that long-term outcome of patients with intracranial carotid artery stenosis was marked by ischemic cerebral events as well as cardiac events.[22] Similarly, in a stroke-free population, the presence of calcified carotid plaque was shown to be an independent predictor of ischemic cerebrovascular but also cardiac events.[23] In light of our previous studies showing a strong association between IAC and significant carotid atherosclerosis (ie, carotid stenosis ≥50%),[10] and between IAC and significant plaques of the proximal aorta (ie, plaques ≥4 mm thick),[11] we hypothesize that the poor outcome of patients with IAC might be attributed to the burden of atherosclerosis. Thus, despite the lack of strong association between IAC and risk of cerebrovascular events, IAC may be an accurate marker of the extent and vulnerability of atherosclerotic plaques in other vascular beds. Furthermore, it appeared that patients with the highest IAC scores had the highest risk of MCEs, although this relationship must be confirmed in a specifically designed study.

However, atherosclerosis can only explain the vascular events and deaths observed in this population. The association between IAC and other causes of mortality in these patients suggests that IAC is a marker of a more generalized process. One likely explanation is that the presence of IAC reflects inflammation, because there is evidence to suggest that systemic inflammation is predictive of poor outcome after stroke.[24] For example, we have demonstrated a significant association between IAC and baseline C-reactive protein level. We have also shown that baseline C-reactive protein is predictive of MCEs. A previous study has shown similar results: C-reactive protein was associated with risk of death from a nonvascular cause in a similar population.[24] More recently, Whiteley et al showed that C-reactive protein level was associated with both vascular and nonvascular deaths after stroke, independently of initial stroke severity.[4] Finally, we cannot rule out that another as yet unidentified mechanism could contribute to this association.

We also observed that the NIHSS score at hospital discharge was also predictive of MCEs. It is not surprising to find an association between stroke severity as measured by

Table 3. Multivariate Analysis With Cox Proportional Hazards Models Showing Predictive Value of Several Factors for MCEs

	Major Clinical Events		
	Hazard Ratio	95% CI	*P*
Vascular risk factors			
Age, y	1.02	0.99–1.04	0.18
Male gender	1.01	0.60–1.70	0.96
Hypertension	1.25	0.67–2.35	0.48
Active smoking	0.64	0.27–1.51	0.31
Hypercholesterolemia	0.80	0.47–1.36	0.42
Diabetes mellitus	1.09	0.62–1.88	0.76
Coronary artery disease	1.47	0.76–2.84	0.25
Chronic kidney disease	1.09	0.64–1.85	0.75
IAC score	1.34	1.11–1.61	0.002
Causes and severity of stroke (NIHSS)			
Age, y	1.03	1.01–1.06	0.011
Male gender	1.18	0.70–1.99	0.53
NIHSS score at hospital discharge	1.05	1.01–1.10	0.035
Carotid atherosclerosis ≥50%	1.59	0.81–3.11	0.17
Cardioembolic stroke	1.04	0.57–1.91	0.89
Lacunar stroke	1.05	0.38–2.88	0.92
Stroke of undetermined cause	1.51	0.84–2.73	0.17
Stroke of other cause	1.83	0.60–5.64	0.29
Aortic plaques (Grades III–IV)	0.57	0.26–1.24	0.16
IAC score	1.38	1.14–1.67	0.001
Clinical and laboratory parameters in patients with ischemic stroke			
Age, y	1.01	0.98–1.03	0.59
Male gender	1.08	0.62–1.88	0.79
NIHSS score at hospital discharge	1.03	0.98–1.08	0.25
Hypertension	1.57	0.79–3.12	0.20
LDL–C	0.48	0.21–1.11	0.085
Diabetes mellitus	0.85	0.47–1.56	0.61
GFR	1.001	0.99–1.01	0.89
C-reactive protein	1.04	1.02–1.06	0.001
IAC score	1.32	1.07–1.64	0.01

MCEs indicates major clinical events; NIHSS, National Institutes of Health Stroke Scale; IAC, intracranial artery calcification; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; CI, confidence interval.

NIHSS and long-term outcome, because the volumes of infarct lesions are closely correlated with NIHSS and there is evidence to suggest that NIHSS is associated with final outcome after a stroke in terms of length of stay, survival, and discharge destination.[25,26]

This study presents a number of limitations. Roughly 20% of patients were not regularly followed. In this subgroup of patients with a higher rate of MCEs, we were unable to check information obtained by phone in only 19 cases. On the basis of the phone interview data, it appeared that none of these patients had developed symptoms suggestive of ischemic vascular events (although death from unknown causes was frequent in this population). Hence, the involvement of recurrent vascular events cannot be ruled out. The cognitive status of the patients in this study was unknown, but there is substantial evidence to suggest that poststroke global cognitive decline and dementia are related to poor long-term survival.[27,28] We were also unable to evaluate the dental status of our patient. Because the common chronic inflammatory condition periodontitis is associated with cardiovascular risk in general and stroke risk in particular,[29] it will be important to evaluate this issue in future work. Furthermore, almost one third of our patients had chronic kidney disease; this represents an accelerated model of the active cardiovascular calcification process and may well account for the high prevalence of IAC seen in our population. However, we and others have found a similar high prevalence of chronic kidney disease in patients with cerebrovascular diseases.[10,30,31] Lastly, the large number of patients with C-reactive protein <0.5 mg/L (measured by standard assay) could not be stratified, because a highly sensitive C-reactive protein assay was not used. Nevertheless, this study also presents a number of strengths. A large number of consecutive patients was prospectively studied and the method used in this study to assess vascular calcification is widely available and is often the most common initial imaging study performed in patients with ischemic stroke. Because IAC was measured with no knowledge of the history of MCEs, an information bias is unlikely to have influenced our results. Furthermore, the majority of patients were regularly followed and multiple overlapping methods were used to ensure that all MCEs were detected. Finally, vital status was determined at the end of follow-up for the entire cohort and all MCE data were checked by the study clinicians either directly or by reviewing medical and imaging records.

In conclusion, the results of this study suggest that, in addition to well-defined risk factors, the IAC score is strongly predictive of MCEs in patients with ischemic stroke. IAC detection could therefore constitute a simple indicator to screen patients with ischemic stroke at high risk for vascular events and vascular death and also for nonvascular death. Before screening subjects with IAC in a more aggressive secondary prevention approach, these preliminary results should be replicated in a specifically designed study.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table 4. Relationship between the infarct site, the presumed cause of stroke and presence or absence of intracranial artery calcification in the affected territory at baseline and at stroke recurrence (n=22).

patient	gender	age (y)	IAC score	first stroke			stroke recurrence		
				infarct territory	cause of stroke	IAC in the affected territory	infarct territory	cause of stroke	IAC in the affected territory
1	male	26	0	L superficial Sylvian artery	cocaine use	-	L carotid TIA	cocaine use	-
2	male	65	4	TIA (posterior circ.)	ICA stenosis	+	L superficial Sylvian	AF, ICA stenosis	+
3	female	74	2	LACI	SVD	-	LACI	SVD	-
4	male	71	3	POCI (L posterior cerebral artery)	not determined	+	multiple (L and R superficial Sylvian arteries)	not determined	+
5	female	75	4	POCI (R posterior cerebral artery)	AF	+	POCI	AF	+
6	male	62	2	R superficial Sylvian artery	EICA stenosis	+	R superficial and deep Sylvian artery	EICA stenosis	+
7	male	79	2	R superficial Sylvian artery	EICA stenosis, IC stenosis	+	L carotid TIA	IC stenosis	+
8	male	79	2	R superficial Sylvian artery	AF	+	L deep Sylvian artery	AF	+
9	male	83	7	LACI	SVD	+	total POCI	not determined (deceased)	+
10	male	75	4	L anterior choroidal artery	EICA stenosis	+	L deep Sylvian artery	IC stenosis	+
11	female	81	4	R deep Sylvian artery	PAC (with ulcerated plaque)	+	R TACI	PAC (with ulcerated plaque)	+
12	male	80	5	L superficial Sylvian artery	AF, IC stenosis	+	L TACI	AF, IC stenosis, and EICA stenosis	+
13	male	79	2	R carotid TIA	EICA stenosis	+	L carotid TIA	EICA stenosis	+
14	female	82	2	R and L posterior cerebral arteries	paradoxical embolism	-	total POCI	not determined (deceased)	-
15	female	81	2	multiple (R superficial Sylvian and posterior arteries)	AF	-	L TACI	AF	-
16	female	81	6	L superficial Sylvian artery	AF	+	R carotid TIA and central	AF	+

							retinal artery occlusion		
17	Female	82	4	R superficial Sylvian artery	AF, PAC	+	R superficial and deep Sylvian artery	AF, PAC	+
18	female	65	2	R superficial Sylvian artery	not determined	+	R superficial Sylvian artery	not determined	+
19	male	76	2	LACI	SVD	+	L deep Sylvian artery	IC stenosis	+
20	female	82	2	L superficial Sylvian artery	not determined	+	L deep and superficial Sylvian artery	AF	+
21	male	50	2	LACI	SVD	+	LACI	SVD	+
22	male	58	1	R superficial Sylvian artery	Aortic dissection	+	L carotid TIA	Aortic dissection	-

AF: atrial fibrillation; EICA: extracranial internal carotid artery; IAC: intracranial artery calcification; IC: intracranial; L: left; PAC: proximal aortic plaques ≥ 4 mm; PACI: partial anterior cerebral infarct; POCI: posterior cerebral infarct; R: right; SVD: small vessel disease; TACI: total anterior cerebral infarct; TIA: transient ischemic attack.

Table 5. Types of major clinical event by gender

At baseline	**Men (n=173)**	**Women (n=139)**	p
Presence of calcification (n,%)	146 (84)	114 (82)	0.647
Follow-up	**Men (n=168)**	**Women (n=134)**	
Major clinical events (n,%)	36 (21)	31 (23)	0.781
Cerebrovascular event	13 (8)	9 (7)	0.826
Cardiovascular event	9 (5)	6 (4)	1.00
Peripheral artery event	7 (4)	1 (1)	0.137
Death	21 (12)	22 (16)	0.408
cardiovascular causes	11	4	0.189
non-vascular causes	7	9	0.439
unknown causes	3	9	0.038

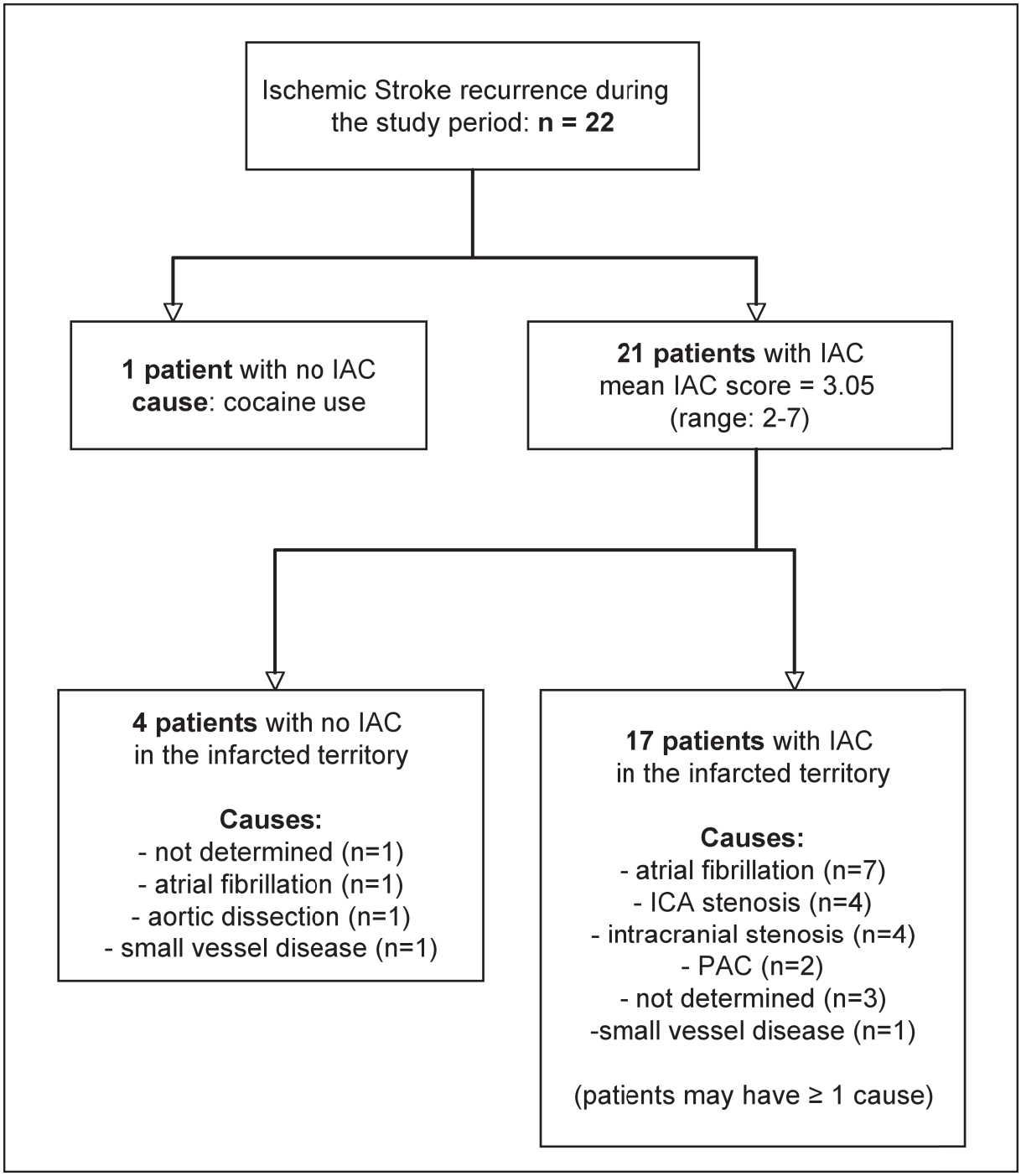

Figure. Causes of recurrent cerebral ischemic events and the relationship with intracranial artery calcification (n=22).