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Complete List of Authors:	Ovesen, Christian; Copenhagen University Hospital - Bispebjerg, Department of Neurology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Abild, Annemette; Copenhagen University Hospital - Bispebjerg, Department of Radiology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Christensen, Anders; Copenhagen University Hospital - Bispebjerg, Department of Radiology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Rosenbaum, Sverre; Copenhagen University Hospital - Bispebjerg, Department of Neurology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Krarup, Christine; Copenhagen University Hospital - Bispebjerg, Department of Neurology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Havsteen, Inger; Copenhagen University Hospital - Bispebjerg, Department of Radiology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Nielsen, Jens; Copenhagen University Hospital - Bispebjerg, Department of Radiology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre Christensen, Hanne; Copenhagen University Hospital - Bispebjerg, Department of Neurology; Copenhagen University Hospital - Bispebjerg, Copenhagen Stroke Research Centre
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Prevalence and Long Term Clinical Significance of Intracranial Atherosclerosis after Ischemic Stroke or Transient Ischemic Attack: A Cohort Study

Christian Ovesen[1], Annemette Abild[2], Anders Fogh Christensen[2], Sverre Rosenbaum[1], Christine Krarup[1], Inger Havsteen[2], Jens Kellberg Nielsen[2], Hanne Christensen[1]

[1] Department of Neurology, Copenhagen University Hospital - Bispebjerg & Copenhagen Stroke Research Centre.

[2] Department of Radiology, Copenhagen University Hospital - Bispebjerg & Copenhagen Stroke Research Centre.

Corresponding author: Christian Ovesen BSc, Copenhagen Stroke Research Centre, Copenhagen University Hospital - Bispebjerg, Bispebjerg Bakke 23, DK-2400 Copenhagen NV, Denmark. Email: Christian.Aavang.Ovesen@regionh.dk, Phone: (0045)-31376351, Fax: (0045)-35313733.

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ABSTRACT:

Objectives: We investigated the prevalence and long-term risk associated with intracranial atherosclerosis identified during routine evaluation.

Design: This study presents data from a prospective cohort of patients admitted to our stroke unit for thrombolysis evaluation.

Setting and Participants: We included 652 with a final diagnosis of ischemic stroke or transient ischemic attack (TIA) from April 2009 to December 2011. All patients were acutely evaluated with cerebral CT and CT-angiography (CTA). Acute radiological examinations were screened for intracranial arterial stenosis (IAS) or intracranial artery calcifications (IAC). Intracranial stenosis was grouped into 30-50%, 50-70% and >70% lumen reduction. The extent of IAC was graded as number of vessels affected.

Primary and Secondary Outcome Measure: Patients were followed until July 2013. Recurrence of ischemic event (stroke, ischemic heart disease (IHD), TIA) was documented through the national chart system. Poor outcome was defined as death or recurrence of ischemic event.

Results: 101 (15.5%) patients showed IAS (70: 30-50%, 29: 50-70%, 16: >70%). 215 (33%) patients had no IAC, 339 (52%) in 1-2 vessels and 102 (16%) in >2 vessels. During follow-up, 53 strokes, 20 TIA and 14 IHD occurred, and 95 patients died. The risk of poor outcome was significantly different among different extents of both IAS and IAC (Log-rank test $p<0.01$ for both). In unadjusted analysis IAS and IAC predicted poor outcome and recurrent ischemic event. When adjusted, IAS and IAC independently increased the risk of a recurrent ischemic event (IAS: HR1.67; CI: 1.04-2.64 and IAC: HR 1.22; CI: 1.02-1.47).

Conclusion: Intracranial atherosclerosis detected during acute evaluation predicts an increased risk of recurrent stroke.

Article Focus:

- Establishing the incidence of intracranial arterial stenosis and calcifications in an acute stroke population.
- Identifying potential modifiable risk factors for intracranial atherosclerosis.
- Assessing if intracranial atherosclerosis identified during acute stroke evaluation could predict poor long-term outcome.

Key Messages:

- Radiological markers of intracranial atherosclerosis are prevalent in North European patients with symptoms of acute stroke or TIA.
- Intracranial atherosclerosis is linked to atherosclerotic disease in other extracranial vascular beds.
- Intracranial artery stenosis or calcifications independently increase the risk of recurrent ischemic event.

Strengths and Limitations of this Study:

- The primary strength is the high degree of generalizability due to the unselected patient population.
- Another important strength of this study was the consistent use of CT-angiography.
- Limitations include the acute CTA performance that might lead to an underestimation of the true prevalence of intracranial arterial stenosis due to thrombus formation.

INTRODUCTION:

Ischemic stroke remains a leading cause of disability and death worldwide, and one of six persons suffers a stroke during their lifetime. Intracranial atherosclerosis represents a risk factor of stroke, however, varying incidence and significance worldwide have been reported [1-6]. Even though intracranial artery atherosclerosis is traditionally assumed most prevalent in patients of Asian descent, limited evidence is available as to the prevalence and prognostic significance of intracranial atherosclerosis in a European stroke population.

Overall, two markers of intracranial atherosclerotic changes are recognized on CT-based imaging of stroke patients: intracranial arterial stenosis (IAS) and diffuse intracranial arterial calcifications (IAC).

IAS has in recent years received much attention in relation to possible treatment interventions especially with regard to endovascular procedures [7] and pharmacological treatment [8]. Though most attention has been focused on stenosis with severe lumen reduction, post mortem studies have shown that even lumen reductions of 30% can potentially give rise to embolism or thrombus [9]. This finding indicates that patients with 30% stenosis could potentially be at increased risk of recurrent stroke.

IAC is assumed to reflect the atherosclerotic burden and can be assessed by means of simple non-contrast CT [10, 11]. Even though these lesions do not necessarily cause lumen reduction and may represent a more diffuse atherosclerotic process – limited evidence suggests their link to recurrent ischemic event in stroke patients [12].

Because intracranial atherosclerosis may represent an important and potentially modifiable risk factor for recurrent ischemic event in an European stroke population, we aimed at: (1) establishing the incidence of intracranial arterial stenosis and calcifications in an acute Northern European thrombolysis population identified during acute radiological examination; (2) identifying potential modifiable risk-factors; and (3) assessing whether intracranial atherosclerosis identified during acute stroke evaluation predicts poor long-term outcome.

METHODS:

This study is based on a prospective cohort of stroke or TIA (transitory ischemic stroke) patients admitted to Copenhagen University Hospital - Bispebjerg with symptoms of acute stroke within 4.5 hours and worked up for recanalization therapy. The hospital has a catchment area for acute stoke of 1.7 mill inhabitants on even dates, sharing the function with another hospital.

Patients admitted from April 2009 to December 2011 with a computed tomography angiography (CTA) of diagnostic quality on admission and a discharge diagnosis of stroke or TIA were prospectively included in the cohort.

Upon arrival, all patients underwent physical and neurological examination, and National Institute of Health Stroke Scale (NIHSS) score was obtained along with standard biochemistry, ECG and vital values. All patients underwent non-contrast CT - and in patients without contra indications, CTA was performed. I.V. thrombolysis was administered according to general guidelines. In all non- thrombolysed patients with stroke or TIA, 300 mg of aspirin was administered.

Radiological Imaging:

Acute CT-scans were performed using 64-section MDCT (Philips Brilliance 64 TM; Philips Medical Systems, Best, the Netherlands) with non-contrast CT cerebrum (120 kVp, 500 mAs, 5mm slice thickness reconstruction). CT angiography was performed from aortic arch to vertex (120 kVp, 295 mAs, collimation 64x0.625mm (isotropic voxel resolution)) with contrast injection, Omnipaque 350 mg/ml, 5 ml/s, monitored by bolus tracking in the descending aorta and scanned with fixed 3 seconds post tracking delay (0.9 mm slice reconstruction).

All images during the study period were reviewed by a consultant neuro-radiologist (AC) blinded to all clinical data using a standardized method. Thoraco-cervicale and intracranial arteries from the aortic arch and cranially were evaluated. An extracranial carotid artery stenosis was considered significant, if a lumen reduction >70% was demonstrated.

All major intracranial vessels (ICA, ACA, MCA, PCA, B and V) were screened for stenosis stratified into three categories of lumen reduction (30-50%, 50-70% and >70%) in accordance to standard WASID criteria for grading of intracranial arterial stenosis [13]. We defined percent stenosis of an intracranial artery as follows: percent stenosis = [(1 - (D(stenosis)/D(normal)))] x 100, where D(stenosis) = the diameter of the artery at the site of the most severe stenosis and D(normal) = the diameter of the proximal normal artery [13]. If the proximal segment was diseased, contingency sites were chosen to measure D(normal): distal artery (second choice) or feeding artery (third choice). IAS was graded as symptomatic, if supplying a vascular area with radiological signs of acute ischemia and no other obvious cause (e.g. acute occlusion) was present.

We employed a semi-quantitative score for the number of vessels calcified according to a presence or absence of calcified foci [12].

Data Extraction and Definitions:

Data were prospectively collected from all patients on a daily basis from charts and by direct interview. All previous concurrent medical conditions (stroke/TIA, ischemic heart disease, congestive heart failure, periphery artery disease) were confirmed by registrations in previous medical charts.

Hypertension was defined as either use of antihypertensive medication or at least 3 blood pressure measurements above 140/90 mmHg taken at least 1 hour apart and at least 24 hours after stroke onset - or a diagnosis of hypertension in the outpatient clinic. Diabetes was defined as use of anti-diabetic medication, or a fasting glucose >9mmol/L - or HgA1c >6.5%. Hypercholesterolemia was defined as use of lipid-lowering medication - or plasma cholesterol > 5.0mmol/L. Ischemic heart disease was defined as prior myocardial infarction or prior coronary by-pass surgery - or prior percutaneous coronary intervention. Atrial fibrillation was defined as a history of atrial fibrillation or at least 30 seconds of atrial fibrillation documented by telemetry or ECG in 12 leads. A history of smoking was defined as present use of tobacco in any form or a previous smoking history of at least 3 pack years. Excessive use of alcohol was defined as consumption of more than 250 g alcohol per week for men and 170 g for women. Glomerular filtration rate was estimated on the basis of the creatinine-level: eGRF (ml/min/1.73m^2)=175 x (Creatinine level/88.4)$^{-1.154}$ x Age$^{-0.203}$ x (0.742 for women) [14].

Follow-up:

Prior to discharge, all patients with ischemic stroke or TIA were prescribed an antiplatelet treatment regime (clopidogrel - or aspirin and dipyridamol in combination). Patients with diagnosed atrial fibrillation were prescribed oral anti-coagulation treatment, mainly warfarin, but dabigatran was used in some cases. All patients with thrombotic stroke were prescribed a statin and antihypertensives aiming at a maximum systolic value of 130 mmHg.

All patients were followed up after discharge through the national online chart system until 1st July 2013. Recurrent event was defined as ischemic stroke, TIA or ischemic heart diseases (IHD) as documented by discharge cards. Recurrent stroke or TIA were considered present, if diagnosed by radiographic imaging studies, or if a consultant neurologist in the patient's discharge card confirmed the diagnosis. Recurrent ischemic heart disease was defined as either myocardial infarction (STEMI or NSTEMI) diagnosed by ECG change or enzyme level increase, unstable angina pectoris, coronary by-pass surgery or percutaneous coronary intervention. Poor outcome was defined as either recurrent event or death within the follow-up period. The registry was approved by the Danish Data Protection Agency file no. 2010-41-5205 in accordance with Danish law.

Statistics:

No formal sample size calculations were performed. The patient-flow in the study period determined the sample size.

Categorical data were compared among groups using Chi^2-test. Ordinal or discrete risk factors were represented using median values and compared using Mann-Whitney-U-test. If variables were

normally distributed, they were compared using Students-t-test, otherwise using a non-parametric alternative (Mann-Whitney U test). Missing values were excluded from the calculations.

To assess the association between risk factors and the presence of intracranial atherosclerosis, multi-nominal logistic regression model was used. All risk-factors from table 2 that proved a group difference of $p < 0.1$ were entered in a backward stepwise multi-nominal logistic regression.

Survival was assessed using Kaplan-Meyer curves. In order to ensure sufficient group size in the Kaplan Meier curves, we grouped 50-70% and >70% stenosis as >50%. Calcifications were grouped into three groups: one without, and two groups with calcifications divided by the total median number of calcified arteries in the cohort. We conducted univariate Cox Proportional Hazard Model analysis of characteristics in table 2 (not including medical history - prior stroke, TIA or myocardial infarction - due to potential interaction with other characteristics). We transferred characteristics that in the univariate model proved a $p < 0.1$ to the multivariate model. Patients lost to follow-up were censured the day they were lost. A general significance level of $p < 0.05$ was employed. Statistical analysis was performed using SPSS 20 statistical software (IBM Corp., Armonk, NY).

RESULTS:

Study Population:

During the study period, 924 patients were admitted with acute stroke symptoms. The final population thus comprised 652 patients with ischemic stroke or ischemic attack (TIA) (Figure 1). Only 34 patients (5.2%) had other ethnicity than Scandinavian, of whom 3 (0.5%) of Asian descent.

Prevalence of Intracranial Atherosclerosis:

A total of 115 IAS were observed in 101 (15.5%) patients (table 1). 45 (39%) had a severe lumen reduction of >50%. Only one patient underwent endovascular procedures with stenting of a >70% basilar artery stenosis. This patient remained in the cohort due to failure of revascularisation. Three patients had a symptomatic stenosis (all above 50% lumen reduction and all in the MCA). IAC in one or more vessels was observed in 441 (68%) (Figure 2), and median number of vessels involved was 2. This number was used to group patients with moderate calcifications (1-2 vessels calcified) from patients with extensive lesions (>2 vessels calcified).

Risk Factors:

Based on the baseline characteristics (table 2), a multi-nominal logistical regression was performed to determine the risk factor profile of IAC and IAS (table 3). Age was an independent predictor of both IAC and IAS. In addition, atherosclerotic lesions in the aorta and former IHD were independent predictors in both IAC and IAS. Hypertension, former stroke, hypercholesterolemia and extracranial carotid stenosis were independent predictors of IAS (table 3).

Outcome after Stroke:

Of the 652 patients included in this analysis, 13 were lost to follow-up after hospital discharge – all foreign citizens, who had a stroke while visiting Copenhagen. The median (IQR) follow-up time was 815.5 days (607-1124 days). During the follow-up time, 87 ischemic events were registered (53 strokes, 20 TIA and 14 IHD), and 95 patients died. Kaplan Meier curves for poor outcome (death or ischemic events) are presented in Figure 3 (A+B). A significant difference in risk of poor outcome was present when stratified for the extent of both IAS and IAC (Log Rank test $P<0.01$ in both A and B). The probability of poor outcome past the first year after index event for patients with no

IAS (0.16 CI: 0.10-0.22) and no IAC (0.10 CI: 0.03-0.22) was substantially lower than in patients with >50% IAS (0.27 CI: 0.09-0.49) and >2 vessels IAC (0.30 CI: 0.18-0.43). In crude estimates, both the burden of IAC (per vessels increase) and lumen reduction of any significant degree (IAS>30%) were associated with recurrent ischemic event and poor outcome (table 4). When adjusted for other risk factors, the burden of IAC emerged as an independent predictor for recurrent event or death (HR 1.18; CI: 1.03-1.36 per vessel increase). If only recurrent ischemic events (stroke, TIA and MI) were considered, both IAC and IAS emerged as independent risk factors for recurrent event (HR1.67; CI: 1.04-2.64 and HR 1.22; CI: 1.02-1.47 respectably).

DISCUSSION:

In this study, intracranial atherosclerosis was not an unusual finding in North European ischemic stroke and TIA patients. The process of developing atherosclerotic lesions seemed to be part of a global and time-dependent process of atherosclerotic development in the body, marked by progressing age along with accompanying lesions in the aortic arch and former myocardial infarction. In addition, more severe atherosclerotic lesions (lesions with lumen reduction - IAS) were linked to a more severe risk-profile accompanied by extracranial carotid stenosis as well as traditional stroke risk factors as hypertension and hypercholesterolemia. We furthermore observed that the risk of a poor outcome increased with the burden of intracranial atherosclerotic disease being highest in patients with >50% IAS and >2 vessels IAC. Both IAS (>30%) and IAC-burden were independently associated with risk of recurrent ischemic event.

The primary strength of this study is the high degree of generalizability due to the unselected patient population. This cohort of unselected patients further allows us to compare consecutive stroke or TIA patients with intracranial atherosclerosis against a control group comprised of similar

stroke or TIA patients without intracranial atherosclerosis. Further, our national online chart system made sure that all patients with permanent stay in Denmark could be followed up, and recurrent events could be assessed from discharge cards. Only patients not seeking medical help for recurrent events have been missed. Another important strength of this study is the consistent use of CT-angiography in the population and the blinded standardised imaging evaluation.

The primary limitations of this study are that the true prevalence of intracranial arterial stenosis probably is underestimated due to the acute setting, in which the CTA was performed. IAS may have been mistaken as acute vascular occlusions due to superimposed thrombus. However, in the present study, the aim is to assess the impact of stenosis identified during acute evaluation and their implication and signal value on the prognosis of the patients.

CTA has been shown to process a sensitivity and specificity of 97% and 99.5% respectively in detecting IAS >50% compared to DSA and to be superior to magnetic resonance angiography [15, 16]. A number of studies have used transcranial Doppler to detect stenosis. Although TCD is non-invasive and perform well in the middle cerebral artery, it is highly observer dependent and has poor sensitivity and specificity in the posterior vasculature [17].

It is known that the prevalence of intracranial atherosclerosis varies with ethnicity. In direct comparison between ethnic groups in the population on Manhattan, persons with Caucasian ancestry have a lower burden of large vessel disease compared to people of Hispanic and Afro-American descent [4, 18]. This is supported by studies reporting the prevalence of intracranial artery stenosis to be as high as 30-50% in Asian stroke populations [1, 3, 5, 6] and 7-12% in asymptomatic populations [19, 20]. The incidence of documented symptomatic intracranial stenosis

in populations of Europe is reported to be 2.2-6.5% [21-23]. This number may represent the top of the iceberg. A newer cross sectional CTA based study elaborated by Homburg et al revealed a prevalence of stenotic lesions of 23% (30-99% stenosis) [2]. Our finding of a prevalence of 15.5% is in accordance with Homburg et al. revealing that intracranial atherosclerotic disease is a relevant and prevalent problem in European stroke population. The reason for this ethnic difference in prevalence is likely due to genetic and lifestyle differences between ethnic groups.

The direct comparison of the prevalence of intracranial artery calcification among studies is hampered by differences in the methods of quantifying its extent [11, 24-26]. However, intracranial artery calcifications are likely to reflect atherosclerotic burden [10, 11].

Our finding that age is a risk factor for atherosclerotic disease is in accordance with almost all previous studies [2, 11, 19, 24, 26, 27]. It is likely that the process of atherosclerosis in the intracranial vasculatures is of progressive nature and linked to on-going atherosclerotic processes in other body-parts [24, 28, 29]. In this study, we identified hypertension and hypercholesterolemia as risk factors for only intracranial artery stenosis, and not calcifications. This finding is not in accordance with other studies identifying especially hypertension as an important risk-factor for intracranial artery calcifications [26]. However, we believe that the pooling of patients with various degrees of IAC - from patients with one vessel calcified and thus a weak risk-factor profile together with patients with more extensive IAC burden and thus a heavier risk factor profile - may have led to this conclusion.

In the present study, we were not able to identify diabetes as a risk factor for intracranial atherosclerosis. Diabetes is in general believed to be a risk factor for both intracranial artery

calcifications and intracranial artery stenosis [2, 9, 20, 26, 27]. This finding may be due to ethnic differences in the incidence of diabetes [30].

Prognostic studies of patients with IAS have predominantly been focusing on symptomatic lesions [22, 31] and thus contain an ill-fitting prognostic value on the general stroke population with varying degree of intracranial atherosclerosis and with a low prevalence of symptomatic stenosis. Studies on prognosis in more general stroke populations have been performed in Asian stroke patients with a much higher rate of IAS [32] showing a clear link to recurrent ischemic event.

In order to prevent further ischemic events in patients with intracranial artery stenosis, efforts as balloon angioplasty and stenting have been attempted. The recent SAMMPRIS trial found no benefit of stenting the intracranial stenotic lesions compared to aggressive medical therapy especially due to an unacceptable rate of periprocedural complications [7]. This finding is further supported by results from the WASID-trial proposing that the recurrence rate in patients with symptomatic artery stenosis can be reduced by strict risk-factor modification [33]. This suggests a possible beneficial effect of stricter risk factor control and aggressive medical prophylaxis in patients with lumen-reducing lesions (IAS).

The prognostic value of IAC has only been investigated in a smaller single centre study elaborated by Bugnicourt et al [12]. This study found that IAC provided an independent risk factor for recurrent vascular event and death. This finding is supported by our data and indicates that the burden of IAC should be assessed as a factor in post-stroke risk assessment similar to artery stenosis and atrial fibrillation.

To our knowledge, this is the first study to investigate the impact of radiological finding of intracranial atherosclerosis (IAS and IAC) detected during acute evaluation on recurrent vascular events and death in a large well-defined cohort of patients admitted within 4.5 hours of stroke onset. With the results of the present study in hand, it seems that the problem of preventing recurrent ischemia in patients with intracranial atherosclerosis is still very much alive.

In summary, this study shows that radiological markers of intracranial atherosclerosis are prevalent in North European patients with symptoms of acute stroke and appear linked to a global process of atherosclerotic disease. Our results suggest that intracranial atherosclerosis in consecutive stroke or TIA patients entail a dramatic increase in risk of poor outcome compared to stroke or TIA patients without intracranial atherosclerosis. Furthermore, intracranial artery stenosis or calcifications independently increases the risk of recurrent ischemic event. So far, risk factor modification and aggressive medical therapy remain first line treatment in this patient group.

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TABLES:

Table 1: Prevalence of intracranial arterial stenosis (IAS).

Vascular segments	Degree of stenosis			Total
	30-50%	50-70%	>70%	
ICA	18 (16%)	6 (5%)	2 (2%)	26 (23%)
MCA	17 (15%)	17 (15%)	8 (7%)	42 (37%)
ACA	3 (3%)	0 (0%)	0 (0%)	3 (3%)
PCA	21 (18%)	5 (5%)	3 (3%)	29 (25%)
Basilar	2 (2%)	1 (1%)	2 (2%)	5 (4%)
Vertebral	9 (8%)	0 (0%)	1 (1%)	10 (9%)
Total	70 (61%)	29 (25%)	16 (14%)	115 (100%)

ICA: internal carotid artery – in this context the intracranial segment, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, PCA: Posterior cerebral artery.

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Table 2: Baseline characteristics between groups

	IAS	No IAS	P	IAC	No IAC	P
Age, years	72.6 (11.9)	66.0 (14.3)	<0.0001	71.7 (11.2)	57.7 (14.9)	<0.0001
Male	65 (62%)	303 (55%)	0.200	252 (57%)	116 (54%)	0.452
Index stroke:						
Ischemic	82 (78%)	409 (74%)	0.462	340 (77%)	151 (70%)	0.068
TIA	23 (22%)	142 (26%)		101 (23%)	64 (30%)	
NIHSS, units	5 (2-11)	4 (2-9)	0.141	4 (2-9)	3 (1-8)	0.013
Onset until CTA, minutes	155.4 (120.6)	148.5 (118.0)	0.655	148.7 (100.9)	151.4 (148.3)	0.115
Medical history:						
Prior stroke	27 (26%)	91 (17%)	0.026	95 (22%)	23 (11%)	0.001
Prior TIA	12 (12%)	39 (7.1%)	0.159	39 (8.9%)	12 (5.6%)	0.163
Ischemic heart disease	22 (21%)	56 (10%)	0.003	69 (16%)	9 (4.2%)	<0.0001
Congestive heart failure	9 (8.7%)	23 (4.2%)	0.076	29 (6.6%)	3 (1.4%)	0.003
Stroke risk factors:						
Hypertension	85 (81%)	312 (57%)	<0.0001	308 (70%)	89 (42%)	<0.0001
Diabetes	11 (11%)	46 (8.3%)	0.453	47 (11%)	10 (4.7%)	0.011

Hypercholesterolemia	79 (78%)	333 (64%)	0.008	294 (71%)	118 (57%)	0.001
Atrial fibrillation	20 (19%)	136 (25%)	0.260	118 (27%)	38 (18%)	0.011
Smoking history	52 (53%)	263 (51%)	0.743	222 (54%)	93 (48%)	0.033
Alcohol abuse	16 (17%)	60 (12%)	0.176	63 (15%)	13 (6.4%)	0.002
Laboratory values:						
Cholesterol, mmol/l*	5.2 (1.1)	5.3 (1.1)	0.364	5.31 (1.1)	5.32 (1.1)	0.901
LDL, mmol/l*	3.2 (1.0)	3.3 (1.0)	0.224	3.3 (1.0)	3.3 (0.9)	0.737
HDL, mmol/l*	1.3 (0.3)	1.4 (0.5)	0.812	1.4 (0.4)	1.4 (0.5)	0.787
Triglycerides, mmol/l*	1.5 (0.9)	1.4 (0.8)	0.838	1.4 (0.9)	1.3 (0.7)	0.516
Glucose, mmol/l	6.5 (1.8)	6.4 (2.0)	0.116	6.5 (1.9)	6.2 (2.1)	0.001
eGFR, ml/min/1.73m^2	70.4 (20.4)	77.8 (21.1)	0.001	74.4 (21.6)	81.2 (19.7)	<0.0001
Radiological observations:						
Extracranial carotid stenosis	20 (19%)	48 (8.7%)	0.003	60 (14%)	8 (3.7%)	<0.0001
Atherosclerotic carotid lesions	80 (76%)	251 (46%)	<0.0001	288 (65%)	43 (20%)	<0.0001
Atherosclerotic aorta lesions	75 (71%)	237 (43%)	<0.0001	275 (48%)	37 (17%)	<0.0001

*Only patients not on pre-stroke statin-treatment. LDL: Low density lipoprotein, HDL: High density lipoprotein, eGRF: estimated glomerular filtration rate.

Table 3: Multinomial logistical regression.

	No Lesions:	IAS (≥30%):		IAC (≥1 vessels):	
	OR	OR	95% CI	OR	95% CI
Age (per 10 years)	1	2.08	1.54-2.82	1.56	1.56-2.38
Hypercholesterolemia	1	2.62	1.36-5.05	1.49	0.95-2.34
Ischemic heart disease	1	3.50	1.14-10.7	2.83	1.01-7.91
Former stroke	1	2.53	1.18-5.43	1.80	0.95-3.40
Hypertension	1	3.29	1.61-6.71	1.44	0.91-2.26
Atherosclerotic aorta lesions	1	4.88	2.45-9.75	3.86	2.28-6.54
Extracranial carotid stenosis	1	2.91	1.03-8.26	1.75	0.68-4.51

Atherosclerotic carotid lesions, eGRF and congestive heart failure were entered in the model.

Nagelkerke $R^2 = 0.40$.

Table 4: Multivariate Cox Proportional Hazard model for the predictive value of stenosis and calcifications

	IAS (≥30%):		IAC (Per vessels):	
	HR	95% CI	HR	95% CI
Poor outcome (Ischemic event or Death):				
Crude estimate	1.73	1.21-2.48	1.41	1.26-1.58
Adjusted estimate[1]	1.25	0.86-1.81	1.18	1.03-1.36
Ischemic event alone:				
Crude estimate	2.13	1.34-3.38	1.39	1.19-1.61
Adjusted estimate[2]	1.67	1.04-2.64	1.22	1.02-1.47

[1]Adjusted for Age, NIHSS, mRS before, hypertension, atrial fibrillation, Extracranial carotid stenosis and Atherosclerotic aorta lesions.

[2]Adjusted for Age, hypertension, Extracranial carotid stenosis and Atherosclerotic aorta lesions.

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COMPETING INTEREST:

None to declare

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ETHICS:

The Danish Data Protection Agency (file no. 2010-41-5205) has approved the registry

CONTRIBUTORS:

CO designed the study, gathered data, performed statistical analysis, interpreted the results and drafted the manuscript. AMA, CKH, JKN, IH gathered data. AFA gathered data and interpreted the results. SR interpreted results. HC designed the study and interpreted the results.

DATA SHARING STATEMENT:

No additional data are available

FIGURE LEGENDS:

Figure 1: Patient-flow

Figure 2: Prevalence of intracranial artery calcifications (IAC) graded by the number of calcified vessels.

Figure 3: Kaplan-Meier curves showing the proportion of patients alive and free of recurrent event. P-value indicates log-rank test.

REFERENCES:

1. De Silva DA, Woon FP, Lee MP, et al. South Asian patients with ischemic stroke: intracranial large arteries are the predominant site of disease. *Stroke*. 2007;38:2592-2594.

2. Homburg PJ, Plas GJ, Rozie S, et al. Prevalence and calcification of intracranial arterial stenotic lesions as assessed with multidetector computed tomography angiography. *Stroke*. 2011;42:1244-1250.

3. Suri MF, Johnston SC. Epidemiology of intracranial stenosis. *J Neuroimaging*. 2009;19 Suppl 1:11S-16S.

4. White H, Boden-Albala B, Wang C, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation*. 2005;111:1327-1331.

5. Wong KS, Huang YN, Gao S, et al. Intracranial stenosis in Chinese patients with acute stroke. *Neurology*. 1998;50:812-813.

6. Wong KS, Li H, Chan YL, et al. Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. *Stroke*. 2000;31:2641-2647.

7. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365:993-1003.

8. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352:1305-1316.

9. Mazighi M, Labreuche J, Gongora-Rivera F, et al. Autopsy prevalence of intracranial atherosclerosis in patients with fatal stroke. *Stroke*. 2008;39:1142-1147.

10. Kassab MY, Gupta R, Majid A, et al. Extent of intra-arterial calcification on head CT is predictive of the degree of intracranial atherosclerosis on digital subtraction angiography. *Cerebrovasc Dis*. 2009;28:45-48.

11. Sohn YH, Cheon HY, Jeon P, et al. Clinical implication of cerebral artery calcification on brain CT. *Cerebrovasc Dis*. 2004;18:332-337.

12. Bugnicourt JM, Leclercq C, Chillon JM, et al. Presence of intracranial artery calcification is associated with mortality and vascular events in patients with ischemic stroke after hospital discharge: a cohort study. *Stroke*. 2011;42:3447-3453.

13. Samuels OB, Joseph GJ, Lynn MJ, et al. A standardized method for measuring intracranial arterial stenosis. *AJNR Am J Neuroradiol*. 2000;21:643-646.

14. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247-254.

15. Bash S, Villablanca JP, Jahan R, et al. Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. *AJNR Am J Neuroradiol*. 2005;26:1012-1021.

16. Nguyen-Huynh MN, Wintermark M, English J, et al. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? *Stroke*. 2008;39:1184-1188.

17. Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. *Stroke*. 1994;25:1931-1934.

18. Sacco RL, Kargman DE, Gu Q, et al. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. *Stroke*. 1995;26:14-20.

19. Wong KS, Huang YN, Yang HB, et al. A door-to-door survey of intracranial atherosclerosis in Liangbei County, China. *Neurology*. 2007;68:2031-2034.

20. Wong KS, Ng PW, Tang A, et al. Prevalence of asymptomatic intracranial atherosclerosis in high-risk patients. *Neurology*. 2007;68:2035-2038.

21. von Weitzel-Mudersbach P, Johnsen SP, Andersen G. Intra- and extracranial stenoses in TIA - Findings from the Aarhus TIA-study: A prospective population-based study. *Perspectives in Medicine*. 2012;1:207-210.

22. Weber R, Kraywinkel K, Diener HC, et al. Symptomatic intracranial atherosclerotic stenoses: prevalence and prognosis in patients with acute cerebral ischemia. *Cerebrovasc Dis*. 2010;30:188-193.

23. Weimar C, Goertler M, Harms L, et al. Distribution and outcome of symptomatic stenoses and occlusions in patients with acute cerebral ischemia. *Arch Neurol*. 2006;63:1287-1291.

24. Chen XY, Lam WW, Ng HK, et al. The frequency and determinants of calcification in intracranial arteries in Chinese patients who underwent computed tomography examinations. *Cerebrovasc Dis*. 2006;21:91-97.

25. Chen XY, Lam WW, Ng HK, et al. Intracranial artery calcification: a newly identified risk factor of ischemic stroke. *J Neuroimaging*. 2007;17:300-303.

26. Koton S, Tashlykov V, Schwammenthal Y, et al. Cerebral artery calcification in patients with acute cerebrovascular diseases: determinants and long-term clinical outcome. *Eur J Neurol*. 2012;19:739-745.

27. Lopez-Cancio E, Dorado L, Millan M, et al. The Barcelona-Asymptomatic Intracranial Atherosclerosis (AsIA) study: prevalence and risk factors. *Atherosclerosis*. 2012;221:221-225.

28. Bugnicourt JM, Chillon JM, Tribouilloy C, et al. Relation between intracranial artery calcifications and aortic atherosclerosis in ischemic stroke patients. *J Neurol*. 2010;257:1338-1343.

29. Seo WK, Yong HS, Koh SB, et al. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. *Eur Neurol*. 2008;59:292-298.

30. McBean AM, Li S, Gilbertson DT, et al. Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: whites, blacks, hispanics, and asians. *Diabetes Care*. 2004;27:2317-2324.

31. Mazighi M, Tanasescu R, Ducrocq X, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology*. 2006;66:1187-1191.

32. Wong KS, Li H. Long-term mortality and recurrent stroke risk among Chinese stroke patients with predominant intracranial atherosclerosis. *Stroke*. 2003;34:2361-2366.

33. Chaturvedi S, Turan TN, Lynn MJ, et al. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. *Neurology*. 2007;69:2063-2068.

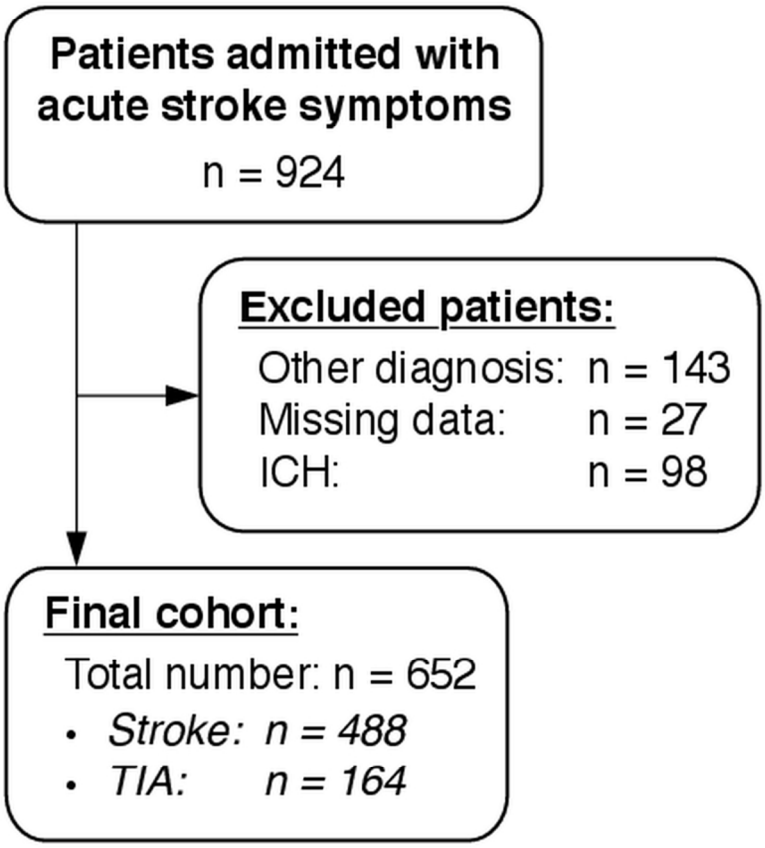

Figure 1: Patient-flow
90x96mm (300 x 300 DPI)

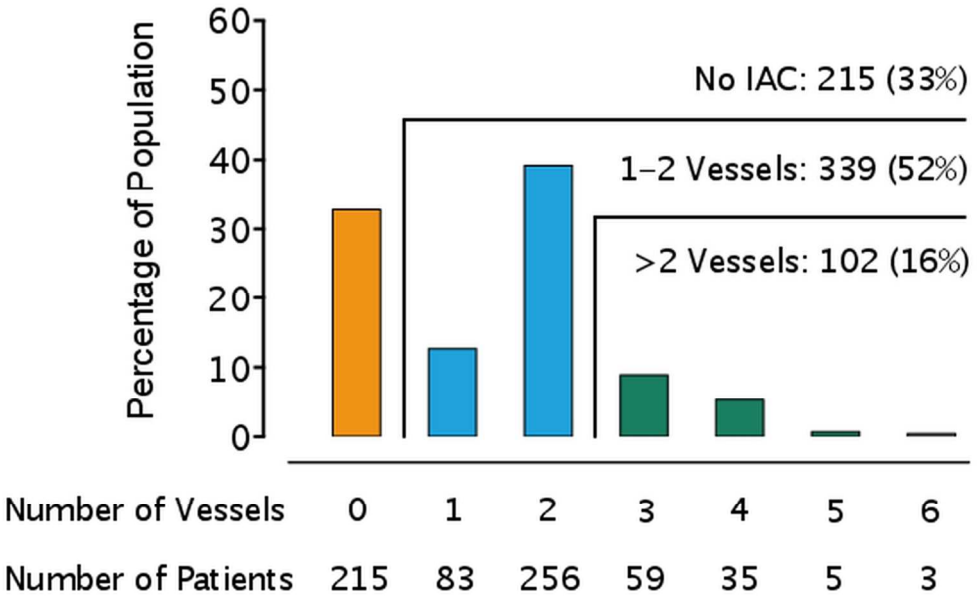

Figure 2: Prevalence of intracranial artery calcifications (IAC) graded by the number of calcified vessels.
142x90mm (300 x 300 DPI)

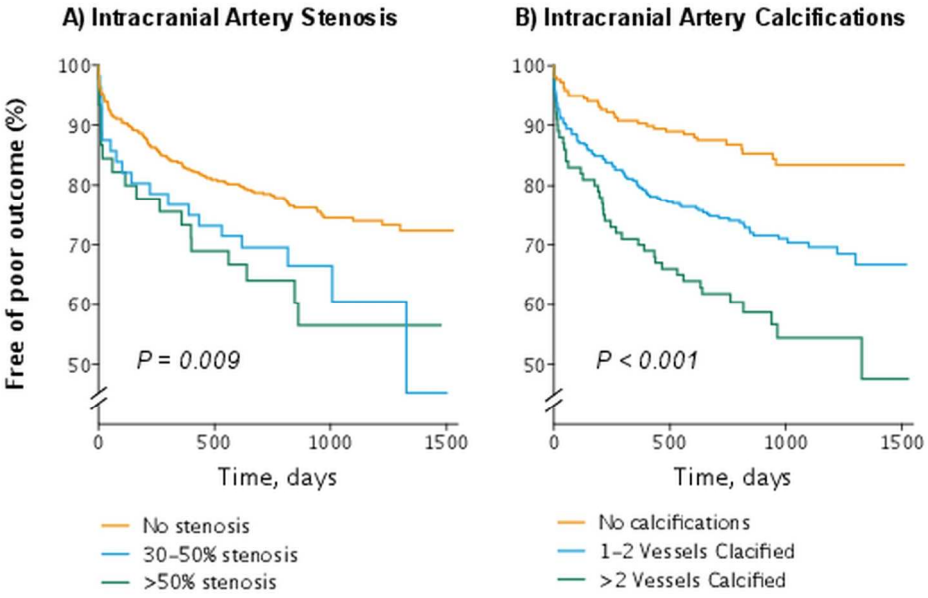

Figure 3: Kaplan-Meier curves showing the proportion of patients alive and free of recurrent event. P-value indicates log-rank test.
145x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - Done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - Done
Objectives	3	State specific objectives, including any prespecified hypotheses - Done
Methods		
Study design	4	Present key elements of study design early in the paper - Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Done
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - Done
Bias	9	Describe any efforts to address potential sources of bias -Done
Study size	10	Explain how the study size was arrived at - Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Done
		(*b*) Describe any methods used to examine subgroups and interactions - Done
		(*c*) Explain how missing data were addressed - Done
		(*d*) If applicable, explain how loss to follow-up was addressed - Done
		(*e*) Describe any sensitivity analyses - Done
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - Done
		(b) Give reasons for non-participation at each stage - Done
		(c) Consider use of a flow diagram – Included
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders – Done
		(b) Indicate number of participants with missing data for each variable of interest – Done
		(c) Summarise follow-up time (eg, average and total amount) – Done
Outcome data	15*	Report numbers of outcome events or summary measures over time – Done
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Done

		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - Done
Discussion		
Key results	18	Summarise key results with reference to study objectives - Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - Done
Generalisability	21	Discuss the generalisability (external validity) of the study results - Done
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - Done

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.