The role of intracranial artery calcification (IAC) in stroke subtype and risk of vascular events

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Objective: To test the hypothesis that intracranial arterial calcification (IAC) is associated with intracranial large artery stenosis (ILAS) and a higher risk of vascular events and mortality. *Method:* We leveraged data from two cohorts, the New York-Presbyterian Hospital/Columbia University Irving Medical Center Stroke Registry Study (NYP/CUIMC-SRS) and the Northern Manhattan Study (NOMAS) to test our hypotheses. We measured IAC using CT scans of participants in both cohorts and expressed IAC as present (vs not) and in tertiles. For the CUIMC-SRS, demographic, clinical and ILAS status was collected retrospectively. In NOMAS, we used research brain MRI and MRA to define asymptomatic ILAS and covert brain infarcts(CBI). We built models adjusted for demographics and vascular risk factors for cross-sectional and longitudinal analyses. *Results:* Cross-sectionally, IAC was associated with ILAS in both cohorts (OR 1.78, 95% CI: 1.16-2.73 for ILAS-related stroke in the NYP/CUIMC-SRS and OR 3.07, 95%CI 1.13-8.35 for ILAS-related covert brain infarcts in NOMAS). In a meta-analysis of both cohorts, IAC in the upper (HR 1.25, 95%CI 1.01-1.55) and middle tertile (HR 1.27, 95%CI 1.01-1.59) was associated with higher mortality compared with participants with no IAC. There were no longitudinal associations between IAC and risk of stroke or other vascular events. *Conclusion:* In these multiethnic populations, IAC is associated with symptomatic and asymptomatic ILAS as well as higher mortality. IAC may be a useful marker of higher mortality, the role of IAC as an imaging marker of risk of stroke is less certain.

Keywords: Calcification—Stroke—Intracranial artery—Atherosclerosis

Abbreviations: IAC, intracranial arterial calcification; ILAS, intracranial large artery stenosis; CAD, coronary artery disease; AFib, atrial fibrillation; NYP/CUIMC-SRS, New York-Presbyterian Hospital/Columbia University Irving Medical Center Stroke Registry Study; NOMAS, Northern Manhattan Study; SPARCS, New York State Statewide Planning and Research Cooperative System

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Introduction

Strokes can result from various mechanisms that include intracranial atherosclerosis, one of the most common causes of ischemic stroke worldwide.[1] Intracranial atherosclerosis has been identified as an important risk factor for stroke in the Asian, the Hispanic and the non-Hispanic Black populations. Despite advances in the management of intracranial atherosclerosis[2], the risk of stroke recurrence attributed to Intracranial large artery stenosis (ILAS) remains > 10% per year even with well-controlled vascular risk factors.[3] Therefore, there is a need to better understand what additional tools may be available to clinicians to identify patients at highest risk.

Intracranial arterial calcification (IAC) is often assumed diagnostic of atherosclerosis, but not all IAC is atherosclerotic.[4,5] In the case of validated pathology calcification, non-atherosclerotic fibrotic degeneration of the arterial wall and aberrant bone marrow formation have been identified.[6,7] Intracranial arterial calcification is often seen in elderly patients with stroke, using computed tomography (CT),[8] and it is most commonly seen in the Internal Carotid Artery (ICA), Vertebral Artery, and Basilar Artery.[9] IAC has been associated with vascular risk factors[8,10] and stroke in white populations,[11] but there is less data related to IAC in multi-ethnic cohorts. Furthermore, brain CT remains more widely available in middle and low-income countries where arterial imaging using contrasted CTA or magnetic resonance angiography is less generalized. Therefore, clarifying the diagnostic value of IAC as seen in brain CT may be helpful in these situations.

In this study, we tested the hypothesis that IAC is associated with intracranial large artery stenosis and that by virtue of this association; IAC is associated with higher risk of vascular events and mortality.

Methods

New York Presbyterian Hospital/Columbia University Irving Medical Center Stroke Registry Study (NYP/CUIMC-SRS)

The study population included adult patients admitted to the NYP/CUIMC in New York City with initial clinical suspicion of stroke or transient ischemic attack (TIA), between 1999 and 2020 and from whom we were able to extract their brain CT from the clinical Picture Archiving and Communication System (PACS) for IAC quantification at the time of this analysis (1322/~19,000 patients). We prioritized these 1322 cases based on availability of genetic and blood biomarkers from a separate study as well as completed stroke subtype adjudication. Four clinical researchers reviewed 1322 patients' charts to extract demographic, clinical and stroke subtype data. All 1322 received brain CT scans at NYP-CUIMC. Of the 1322 charts analyzed for that period, 913 patients ultimately had a confirmed diagnosis of stroke or TIA and 409 had a final diagnosis that was neither stroke nor TIA. We selected these 409 patients as the reference group. We excluded from this list NOMAS participants who may have come to NYP/CUIMC for clinical care.

Northern Manhattan Study subsample

The Northern Manhattan Study (NOMAS) is a population-based study ongoing since 1993. Detailed procedures for NOMAS are found elsewhere.[12] Briefly, individuals were eligible for enrollment if they resided in Northern Manhattan at the time of enrollment, were ≥ 40 years old and were stroke-free. Participant selection was done randomly by telephone. From 2003 to 2008, 1290 stroke-free participants were invited to undergo a brain MRI/MRA. Because NOMAS participants received most of their clinical care at NYP/CUIMC, we linked NOMAS participants to the NYP/CUIMC medical records to identify those who had a brain CT scan performed but no acute stroke (on brain MRI) to maintain the NOMAS sample as "stroke-free". Covariates related to demographics and vascular risk factor were coded at the time of brain MRI.

Calcification measurement

Noncontrast CT scans were performed by using a 32-slice CT scanner (Somatom Sensation, SIEMENS; Lightspeed pro or Prospeed 16, GE MEDICAL SYSTEM; or Aquilion, TOSHIBA). Image acquisition parameters were as follows: slice thickness was 5 mm, tube voltage was either 120 or 130 kV, and tube current was between 83 and 400 mAs. A trained physician reader quantified IAC using ImageJ software (Version 1.46r) in all patients with a customized plug-in in the cavernous segment of the carotid and basilar arteries and the V4 segment of the vertebral arteries. The cut-off value for calcifications in the arteries was identified as ≥130 Hounsfield units.[8] Calcification was scored semi-automatically by drawing regions of interest on CT scans. The software calculated the number of pixels above the cut-off value of 130 Hounsfield units in consecutive slices and multiplied it by pixel size and slice thickness to obtain the total calcium volume as cubic millimeters (mm^3). With these procedures, we achieved similar sensitivity and specificity in detection of calcifications and their volume in images acquired with different CT scanners. The reliability of these intracranial artery calcification measurement protocols has been established in previous studies.[13,14]

Covert brain infarcts (in NOMAS) and stroke subtypes (NYP/CUIMC) adjudication for cross-sectional analyses

In NOMAS, stroke free participants were evaluated for detection of covert brain infarcts. Two vascular neurologist ascertained possible covert brain infarcts mechanisms by consensus using information from concomitant brain

MRA, carotid Doppler, echography or EKG plus self-reported history of atrial fibrillation (AFib).[15] With this information, covert brain infarcts were classified as likely caused by (1) ILAS, (2) cardioembolic, (3) isolated small artery disease and (4) cryptogenic. If there was a competing etiology, we chose the presumed mechanism most likely to guide clinical management (for example, in people with AFib and small artery disease, we chose cardioembolic as mechanisms given primacy of anticoagulation as specific therapy for stroke risk reduction).

In the NYP/CUIMC-SRS, only stroke subtypes were adjudicated using the medical team impression based on the inpatient workup. Stroke etiologies were classified as follows: (1) ILAS, (2) cardioembolic, (3) isolated small artery disease, (4) cryptogenic, (5) other etiologies, (6) cervical carotid or aortic plaque. The prevalence of covert brain infarcts or stroke subtypes related to IAC was compared to individuals with no covert brain infarcts or stroke, respectively.

Longitudinal outcomes

The outcomes for these analyses were death, any stroke, ischemic stroke, myocardial infarction, and a composite of any vascular events (any stroke, any Myocardial Infarction, any vascular death). NOMAS participants were followed annually since their enrollment with loss to follow up $< 3\%$ over > 10 years. When an event was detected via phone interview, the event was adjudicated by reviewing medical records at NYP/CUIMC or at other institutions where the event occurred. Two vascular neurologists adjudicated events related to stroke or vascular death independently and a third neurologist resolved disagreements. Myocardial infarction was adjudicated according to the Cardiac Arrhythmia Suppression Trial and the Lipid Research Clinics Coronary Primary Prevention Trial by a study cardiologist.(24,25) For the purpose of this manuscript, we used NOMAS follow-up data collected up to July 2020.

For the NYP/CUIMC-SRS, long-term outcomes were determined by interrogation of the New York State Statewide Planning and Research Cooperative System (SPARCS) dataset for up to 18 years after patients' admission. SPARCS is a comprehensive data reporting system, which captures all hospital admissions and emergency department visits. To determine the presence of the outcomes of interest, we used codes of the International Classification of Diseases, 9th and 10th editions, previously validated (any stroke: 325, 430-436; myocardial infarction: 410 and 412; any vascular event: 325, 410,412, 430-436, 930, 437.3, 440, 441, 443.1, 443.2,443.8, 443.9, 447.1, 557.1,557.9, 434). We obtained death dates from the Social Security Administration's Death Master File (SSDMF), last accessing it in April 2021.

Covariates adjudication

For NOMAS participants, data was collected in person during study or home visits by research staff. A structured questionnaire was used to collect medical history and demographic data. For CUIMC-SRS participants, all data was collected from the NYP/CUIMC electronic medical records. Age, sex and race/ethnicity were gathered by self-report for both cohorts. Hypertension, diabetes and hypercholesterolemia were detected by self-reported medical history and medication use or by using blood pressure measurement, glucose level or cholesterol level, all obtained during admission at NYP/CUIMC or during study visits (NOMAS participants). For our study, participants with two separate blood pressure measurements $\geq$ 140/90 mm Hg were considered hypertensive; participants with fasting glucose level $\geq$ 126mg/dl were considered diabetic; participants with total cholesterol level $\geq$ 240 were considered as having hypercholesterolemia. Only participants with active smoking (at the time of study visit for NOMAS or hospital admission for CUIMC-SRS) were considered smokers.

Statistical analyses

Descriptive characteristics were reported from either the time of hospital admission (CUIMC-SRS) or the study visit (NOMAS). We first investigated cross-sectional associations between IAC and demographics and vascular risk factors with logistic regressions. Two different models were established for each cohort: model 1 included vascular risk factors as binary variables, and model 2 includes aspects of these risk factors expressed as continuous measures related to intensity and control of these risk factors. We then investigated the association between IAC and stroke mechanisms (or CBI mechanism for the NOMAS cohort). Lastly, we categorized IAC by location in the brain circulation (anterior, posterior and both anterior and posterior) and volume (lower, middle and upper tertile). We investigated the risk of death, any stroke, ischemic events, and any vascular events by these categories using Cox proportional hazards regressions to obtain hazard ratios (HR) and their corresponding 95% confidence intervals (CI) by cohort. We then meta-analyzed the HRs for each event from both cohorts. Heterogeneity was tested by using the Cochran Q test and I^2 statistic. $P < .10$ and $I^2 > 50\%$ were considered statistically significant. Ultimately, random and fixed effect model meta-analyses were conducted using Review Manager Version 5.4, The Cochrane Collaboration, 2020. The outcomes of fixed and random model meta-analyses are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). P value <0.05 was considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

Demographic and clinical characteristics (Table 1)

We included 1322 CUIMC-SRS patients (mean age 66 ± 17 years, 51% women, 39% Hispanic). The majority of participants had at least one vascular risk factor (Table 1). Calcification was present in 49% (32% anterior circulation only, 5% posterior circulation only and 12% in both).

We included 489 NOMAS participants (mean age 78 ± 9 years, 64% women, 66% Hispanic). The majority of participants had at least one vascular risk factor (Table 1). Calcification was present in 54% (41% anterior circulation only, 3% posterior circulation only and 10% in both) (Fig. 1).

Cross-sectional associations with IAC

IAC was associated with older age in both cohorts, in addition to vascular risk factors, although the significance for each risk factor varied by cohort (Table 2). In both cohorts, IAC was associated with ILAS-related covert brain infarcts (OR: 3.07, 95% CI: 1.13-8.35, in NOMAS) and ILAA-related stroke (OR: 1.78, 95% CI: 1.16-2.73, in the NYP/CUIMC-SRS) but not with other stroke mechanisms (Table 3).

Longitudinal outcomes

In CUIMC-SRS, anterior and posterior arterial IAC was associated with mortality (HR: 1.42, 95% CI: 1.03-1.94). In NOMAS, posterior circulation IAC was associated with any vascular event (HR: 2.41, 95% CI: 1.07-5.41, Supplemental Table 1). In a pooled sample analysis using fixed model meta-analysis, individuals in the upper tertile (HR: 1.25, 95% CI: 1.01-1.55) and middle tertile of IAC volume (HR: 1.27, 95% CI: 1.01-1.59) or IAC on both anterior and posterior circulations (HR: 1.30, 95% CI 1.10-1.53) had a

Table 1. *Characteristics of the studied cohorts*

	CUIMC-SRS *N* = 1322	NOMAS MRI subsample *N* = 489
Enrollment period	1999-2020	2003-2008
Follow-up time (in years, median, IQR)	12.2 (4.4-14.3)	6.10 (2.3-10.7)
Age (mean ± SD)	66.1 ± 16.8	77.5 ± 9.4
Men (%)	49	36
Ethnicity (%)		
Non-Hispanic white	32	16
Non-Hispanic black	19	18
Hispanic	39	66
Other/mixed	10	-
Hypertension (%)	74.4	84.7
Systolic blood pressure (mmHg)	135.4 ± 17.3	138.1 ± 17.7
Diastolic blood pressure (mmHg)	78 ± 9.6	78 ± 9.8
Use of antihypertensives(%)	56	68
Diabetes(%)	23	29
Glucose (mg/dl),	101 ± 34 *	102 ± 35 **
Use of hypoglycemic drugs (%)	16.6	25
Hypercholesterolemia (%)	88	93
LDL (mg/dl)	118.1 ± 34*	110.8 ± 37.3**
HDL (mg/dl)	53.6 ± 17)*	52.9 ± 17.2**
Triglycerides (mg/dl)	125.6 ± 81.8*	128.2 ± 71.5**
Statins use (%)	55	68
Active smoking (%)	20	11
History of CAD (%)	20	31
History of AFib (%)	4	6
Chronic kidney disease (%)	19	24
Creatinine (mg/dl),	0.9 ± 0.3*	1 ± 0.5**
C-reactive protein (mg/dl)	4.3 ± 6.3*	5 ± 9.8**
Any brain arterial calcification (%)	49	54
Anterior circulation only	32	41
Posterior circulation only	5	3
Both circulations	12	10

*The percentages of data available in the sample are 96.1% for blood glucose level, 96.4% for LDL, 96.5% for HDL 96.5% for Triglycerides, 96.3% for creatinine and 50% for C-reactive protein.

**The percentages of data available in the sample are 94.3% for blood glucose level, 94.9% for LDL, 94.88% for HDL 94.9% for triglycerides, 94.2% for creatinine and 50.1% for C-reactive protein.

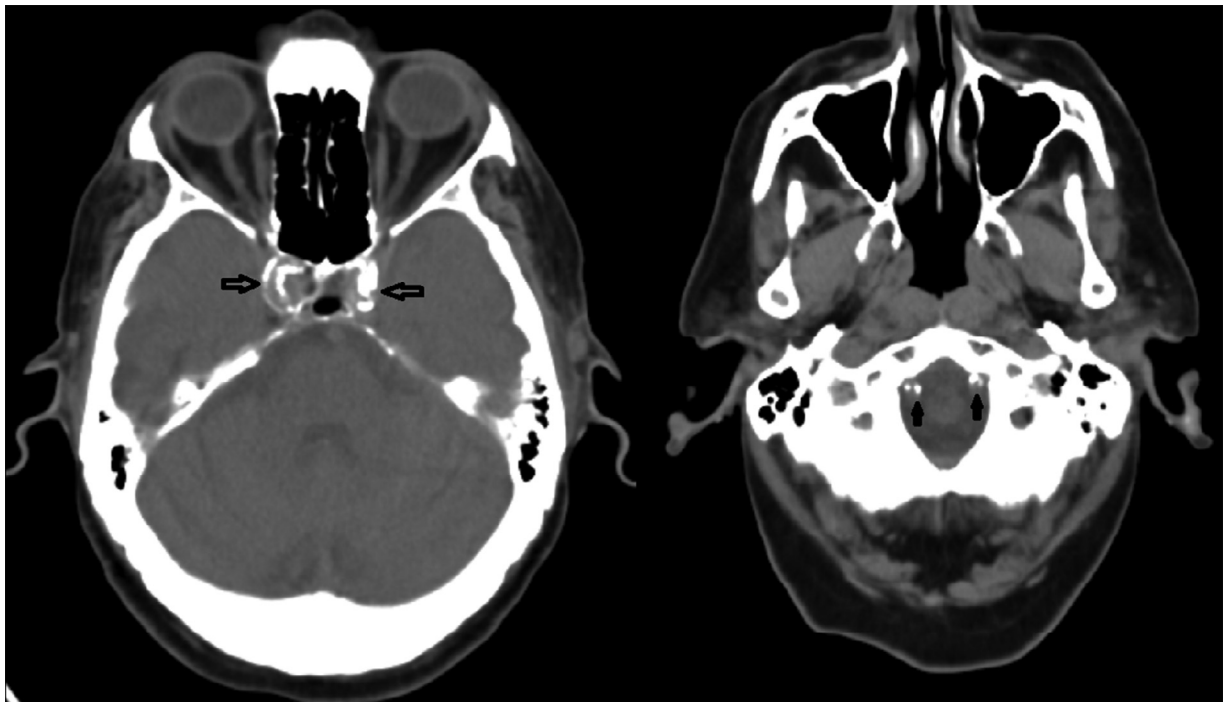

Fig. 1.

higher mortality risk. In either cohort or in the meta-analysis, the presence of any calcification was not associated with mortality (Table 4).

Discussion

In these two multi-ethnic cohorts, we found that IAC was associated with aging and vascular risk factors. Furthermore, IAC was cross-sectionally associated with strokes or CBIs attributable to ILAS. Prospectively, those with heavier IAC volumes and widespread IAC into the anterior and posterior circulation, had higher risk of death. Using a simpler binary definition for IAC was not enough to demonstrate an increased risk of death. These findings suggest that IAC may be a helpful addition to the risk-stratification of people at a high mortality and may be considered an imaging marker of brain arterial aging, although not necessarily of intracranial atherosclerosis. Specifically, the lack of association between IAC and stroke risk in these multi-ethnic samples suggests that IAC alone may lack the predictive power of other well-established measures of intracranial atherosclerotic disease such as luminal stenosis. Alternatively, the sample size might be underpowered to definitively rule out an association between IAC and stroke risk. Coronary artery calcification is a well-known hallmark of coronary atherosclerosis. Therefore, it came as no surprise that IAC was more likely associated with stroke from intracranial atherosclerosis than other stroke subtypes in our analyses. This is consistent with previous studies, which also showed that IAC is associated with both ILAS and ILAS-related stroke.

We found that IAC does not predict the future risk of stroke in these populations. Presence of IAC on CT scans is generally accepted as evidence of intracranial atherosclerosis. However, although calcification is part of the atherosclerotic process, it remains a matter of controversy whether calcification within arteries may stabilize plaques or promote embolization. Evidence has shown that plaques with microcalcification ($\leq$0.5 mm) are more unstable than plaques with macrocalcification (>0.5 mm) in carotid arteries. When calcified tissue in an atheromatous plaque grows and becomes more visible on CT scan, the atheroma plaque may then turn more resilient to rupture compared with "soft", cholesterol-rich plaques. Thus, calcification of atheroma plaques may have a protective effect against plaque rupture. Another histopathologic study posited that, although scattered calcifications were associated with intracranial large artery atherosclerosis, coalescent calcifications were not.[4] In addition, coalescent calcification are more visible on CT scan than scattered calcification. Consequently, IAC detected on CT scan would show more likely non-atherosclerotic calcified tissue. This finding may partially explain why IAC in and of itself is not a predictor of stroke. Nonetheless, other population-based studies have shown an association between IAC and risk of non-lacunar strokes.[11,16] Differences in population background and the extent of statistical modeling may partially explain these discrepancies.

Our results, suggestive of a higher risk of death but not stroke among participants with heavier burden of IAC, are similar to a previous study. The association between IAC and mortality could be related to an epiphenomenon

Table 2. *Adjusted associations between any brain arterial calcification with sample characteristics.*

	Model 1* Odds ratios (95% confidence intervals)		Model 2* Odds ratios (95% confidence intervals)	
	CUIMC-SRS	NOMAS	CUIMC-SRS	NOMAS
Age (in years)	1.06 (1.05-1.07)	1.06 (1.04-1.08)	1.06 (1.03-1.07)	1.06 (1.04-1.09)
Men	1.14 (0.90-1.45)	1.28 (0.89-1.84)	1.36 (0.81-2.27)	1.30 (0.82-1.86)
Non-white race/ethnicity	0.77 (0.61-0.98)	0.55 (0.32-0.91)	0.77 (0.46-1.24)	0.53 (0.31-0.86)
Hypertension	1.56 (1.11-2.16)	0.98 (0.58-1.64)		
Systolic blood pressure (per 10 mmHg)			1.00 (0.99-1.01)	1.01 (0.99-1.02)
Diastolic blood pressure (per 10 mmHg)			1.00 (0.99-1.02)	1.01 (0.99-1.04)
Use of antihypertensives			1.48 (0.85-2.60)	1.11 (0.73-1.69)
Diabetes	1.20 (0.90-1.59)	1.58 (1.08-2.31)		
Glucose (mg/dl)			1.00 (0.996-1.004)	1.003 (0.997-1.008)
Use of hypoglycemic drugs			1.18 (0.81-2.25)	1.33 (0.84-2.12)
Hypercholesterolemia	1.20 (0.90-1.59)	1.52 (0.75-3.08)		
LDL (mg/dl)			1.00 (1.00-1.01)	1.00 (0.99-1.01)
HDL (mg/dl)			1.00 (0.98-1.01)	1.00 (0.99-1.02)
Triglycerides (mg			1.00 (1.00-1.01)	1.00 (0.99-1.003)
Statins use			1.04 (0.0.63-1.70)	1.19 (0.81-1.77)
Active smoking	1.63 (1.14-2.06)	1.56 (0.89-2.71)	1.99 (1.06-3.73)	1.73 (0.99-3.05)
History of CAD	1.59 (1.16-2.19)	1.17 (0.80-1.74)	1.57 (0.89-2.78)	1.21 (0.82-1.80)
History of AFib	0.84 (0.61-1.16)	1.73 (0.82-3.62)	0.92 (0.52-165)	1.67 (0.79-3.53)
Chronic kidney disease	1.47 (1.05-2.07)	1.19 (0.79-1.80		
Creatinine (mg/dl)			0.90 (0.70-1.17)	1.07 (0.75-1.54)

Analytic notes:

Model 1 of CUIMC-SRS cohort was adjusted for age at the time of the brain CT, sex, ethnicity, hypertension, diabetes, hypercholesterolemia, active smoking, history of CAD, history of AFib and chronic kidney disease.

Model 2 of CUIMC-SRS cohort was adjusted for age at the time of the brain CT, sex, ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensive, blood glucose level, LDL, HDL, triglycerides and creatinine, Use of hypoglycemic drug and use of statins.

Model 1 of NOMAS cohort was adjusted for age at the time of the brain CT, sex, ethnicity, hypertension, diabetes, hypercholesterolemia, history of CAD and history of AFib.

Model 2 of NOMAS cohort was adjusted for age at the time of the brain CT, sex, ethnicity, systolic blood pressure, diastolic blood pressure, use of antihypertensives, blood

glucose level, LDL, HDL and triglycerides, use of hypoglycemic drugs, use of statins, history of CAD and history of AFib.

*Data are Odds ratio and 95% CI

of systemic biological aging. For example, smooth muscle cells and elastin-rich extracellular matrix are important determinants of arterial elasticity. During calcification, smooth muscle cells differentiate into osteoblast-like cells that produce calcium. Thus, arteries start losing their smooth muscle cells and elasticity, which leads to

Table 3. *Cross-sectional association between any IAC with CBIs (NOMAS) and stroke/TIA (CUIMC-SRS) subtypes.*

CUIMC-SRS		NOMAS MRI subsample	
	OR (95% CI)		OR (95% CI)
No stroke/TIA, *N* = 409	Referent group	No covert brain infarct *N* = 384	Referent group
Cryptogenic, *N* = 248	1.17(0.82-1.67)	Cryptogenic *N* = 60	1.47(0.86-2.51)
Cardioembolic, *N* = 288	0.84(0.57-1.23)	Cardioembolic, *N* = 16	2.19(0.69-6.86)
ILAS *N* = 112	1.78(1.16-2.73)	Intracranial large artery stenosis *N* = 16	3.07(1.13-8.35)
Isolated small artery disease *N* = 121	0.93(0.61-1.42)	Isolated small artery disease *N* = 13	1.68(0.55-5.10)
Other etiologies, *N* = 67	0.67(0.36-1.27)	Not ascertained	-
Cervical carotid or aortic plaque *N* = 77	0.96(0.58-1.58)	Not ascertained	-

The model of CUIMC-SRS cohort was adjusted for age at the time of the brain CT, sex ethnicity, hypertension, diabetes, hypercholesterolemia, active smoking, history of AFib, CAD and end stage renal disorder

The model of NOMAS cohort was adjusted for age at the time of the brain CT, sex, ethnicity, hypertension, diabetes, hypercholesterolemia, active smoking, history of AFib, coronary artery disease and chronic kidney disease

increased arterial stiffness. Both arterial stiffening and medial calcification are independent risk factors for cardiovascular mortality. In addition, arterial stiffness in the brain arteries may result in end-organ damage, as is the case with arteries in other organs.

The strength of our study consists in access to individual-level data of two different multi-ethnic cohorts, which allowed us to perform more detailed analyses while adjusting for several possible confounders, such as age, sex, race/ethnicity and vascular risk factors. One of the

Table 4. *Meta-analyses of the risk of death and vascular events by various phenotype of calcification.*

		DEATH	**ANY STROKE**	**ISCHEMIC STROKE OR MYOCARDIAL INFARCTION**	**ANY VASCULAR EVENT**
		HR (95% CI)			
Meta-analysis	Any calcification (yes vs no)	1.13 (0.95-1.35)	1.10 (0.80-1.53)	1.01 (0.75-1.36)	1.04 (0.82-1.33)
	Calcification burden				
	No calcification	Reference	Reference	Reference	Reference
	Lower tertile of calcification volume	0.93 (0.73-1.18)	0.94 (0.61-1.46)	0.99 (0.68-1.45)	0.92 (0.67-1.26)
	Middle tertile of calcification volume	1.27 (1.01-1.59)	1.39 (0.92-2.12)	1.11 (0.75-1.65)	1.27 (0.93-1.73)
	Upper tertile of calcification volume	1.25 (1.01-1.55)	1.06 (0.68-1.64)	0.90 (0.59-1.37)	0.98 (0.71-1.35)
	Calcification distribution				
	No calcification	Reference	Reference	Reference	Reference
	Anterior circulation only	1.10 (0.91-1.33)	1.01 (0.71-1.44)	0.97 (0.70-1.33)	0.99 (0.77-1.28)
	Posterior circulation only	0.97 (0.63-1.51)	1.15 (0.51-2.57)	1.18 (0.58-2.40)	1.62 (0.93-2.83)
	Both anterior and posterior	1.30 (1.10-1.53)	1.55 (0.96-2.49)	1.14 (0.71-1.81)	1.15 (0.79-1.66)

The models of CUIMC-SRS cohort were adjusted for age at the time of the brain CT, sex, ethnicity, hypertension, diabetes, hypercholesterimia, active smoking, history of AFib, CADand end stage renal disease

The models of NOMAS cohort were adjusted for age at the time of the brain CT, sex, ethnicity, hypertension, diabetes, hypercholesterimia, active smoking, history of AFib, CAD and chronic kidney disease

limitations in our study is the fact that the lipid component of atherosclerotic plaques cannot be seen on CT scan. This prevented us from distinguishing calcified atherosclerotic plaques from calcified non-atherosclerotic plaques to show the specificity of atherosclerotic calcification on long-term outcomes. Nevertheless, the imaging and clinical evidence analyzed allowed us to determine that IAC is not a predictor of future stroke, but high calcification burden does increase long-term mortality risk. Limitations that should be considered when interpreting these results include the relatively small sample size of each cohort, which undermines the power, and the selection of patients with hospital-based encounters that decreases the generalizability of the findings.

Better understanding of the mechanisms underlying IAC and how these relate to poorer outcomes may help planning future interventions to improve vascular health.

Author contributions

KG: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Calcification measurement, Writing original draft, Review & Editing). FK: Data curation. AS: Data curation. SR: Data curation. ML: Formal analysis, Methodology. EK: Methodology, Review & Editing. AB: Methodology, Writing, Review & Editing. TR: Review & Editing. ME: Review &Editing. RM: Review & Editing DB: Conceptualization, Methodology, Review & Editing. JG: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Review & Editing.

Statement of ethics

The CUIMC IRB approved the NYP/CUIMC-SRS and NOMAS. This research study was conducted ethically in accordance with World Medical Association Declaration of Helsinki. Informed consents were obtained from NOMAS participants. Informed Consent was not required for NYP/CUIMC-SRS due to retrospective study design.

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Data availability statement

The dataset generated or analyzed during this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2023.107185.

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