

# Determinants and Outcomes of Asymptomatic Intracranial Atherosclerotic Stenosis



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## ABSTRACT

**BACKGROUND** Intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of stroke worldwide and confers a high risk of stroke recurrence, despite aggressive management of risk factors.

**OBJECTIVES** This study identified the role of risk factors and risk of vascular events in subjects with asymptomatic ICAS for improved risk stratification.

**METHODS** Stroke-free participants in the NOMAS (Northern Manhattan Study), prospectively followed since 1993, underwent a brain magnetic resonance angiogram from 2003 to 2008. The study rated stenosis in 11 brain arteries as: 0: no stenosis; 1: <50% or luminal irregularities; 2: 50%-69%; and 3: ≥70% stenosis or flow gap. The study ascertained vascular events during the post-magnetic resonance imaging (MRI) period. Proportional odds regression quantified the association of pre-MRI exposures, and proportional hazard adjusted models were built to identify the risk of events in the post-MRI period.

**RESULTS** The included sample included 1,211 participants from NOMAS (mean age: 71 ± 9 years; 59% women; 65% Hispanic; 45% had any stenosis). Older age (OR: 1.02 per year; 95% CI: 1.01 to 1.04), hypertension duration (OR: 1.01 per year; 95% CI: 1.00 to 1.02), higher number of glucose-lowering drugs (OR: 1.64 per each medication; 95% CI: 1.24 to 2.15), and high-density lipoprotein (OR: 0.96 per mg/dL; 95% CI: 0.92 to 0.99) were associated with ICAS. The highest event risk was noted among participants with ICAS ≥70% (5.5% annual risk of vascular events; HR: 2.1; 95% CI: 1.4 to 3.2; compared with those with no ICAS).

**CONCLUSIONS** ICAS is an imaging marker of established atherosclerotic disease in stroke-free subjects, and incidental diagnosis of ICAS should trigger a thorough assessment of vascular health. (J Am Coll Cardiol 2021;78:562-571)

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Intracranial atherosclerotic stenosis (ICAS) is one of the most common causes of stroke worldwide (1-3). The proportion of strokes caused by ICAS varies depending on the intensity of the diagnostic

workup and on the underlying demographics of the populations studied. For example, in a population-based racially and ethnically diverse urban cohort in New York City, 8% of all ischemic strokes were caused



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by ICAS, the risk being higher for non-Hispanic Blacks and Hispanics (1,4). In hospital-based samples and in samples from Asia, the proportion of ICAS-related stroke is even greater (12%-46%) (2,5-7). Risk factors for ICAS and ICAS-related stroke include older age (7,8), higher systolic blood pressure (8), dyslipidemia (8-10), diabetes mellitus (10,11), and limited physical activity (12). In addition, post hoc data from clinical trials have demonstrated that achieving strict risk factor control can decrease the risk of recurrent vascular events among people with ICAS, including stroke and other noncerebral vascular events (eg, myocardial infarction [MI]) (12). The systemic benefit of vascular risk factor control may relate to the almost certain coexistence between ICAS and systemic atherosclerosis, including coronary atherosclerosis (13-16).

Nonetheless, even with aggressive medical therapy, the annual rate of stroke recurrence remains >10% in ICAS cases with stenosis  $\geq 70\%$  (17) and up to 20% among those with occlusions and  $\geq 3$  vascular risk factors (7). The high rate of recurrent vascular events in patients with stroke caused by ICAS underscores the need for a greater focus on primary prevention and targeted interventions among stroke-free individuals at the highest risk of ICAS-related stroke and vascular events. In this context, we leveraged longitudinal data acquired through decades of follow-up in the NOMAS (Northern Manhattan Study) to test the hypothesis that the presence of

asymptomatic ICAS might help identify stroke-free subjects at a high risk of stroke and vascular events. We also aimed to provide observational data supporting the premise that mid-life exposure and degree of control of modifiable vascular risk factors are high priority targets for primary prevention of vascular disease.

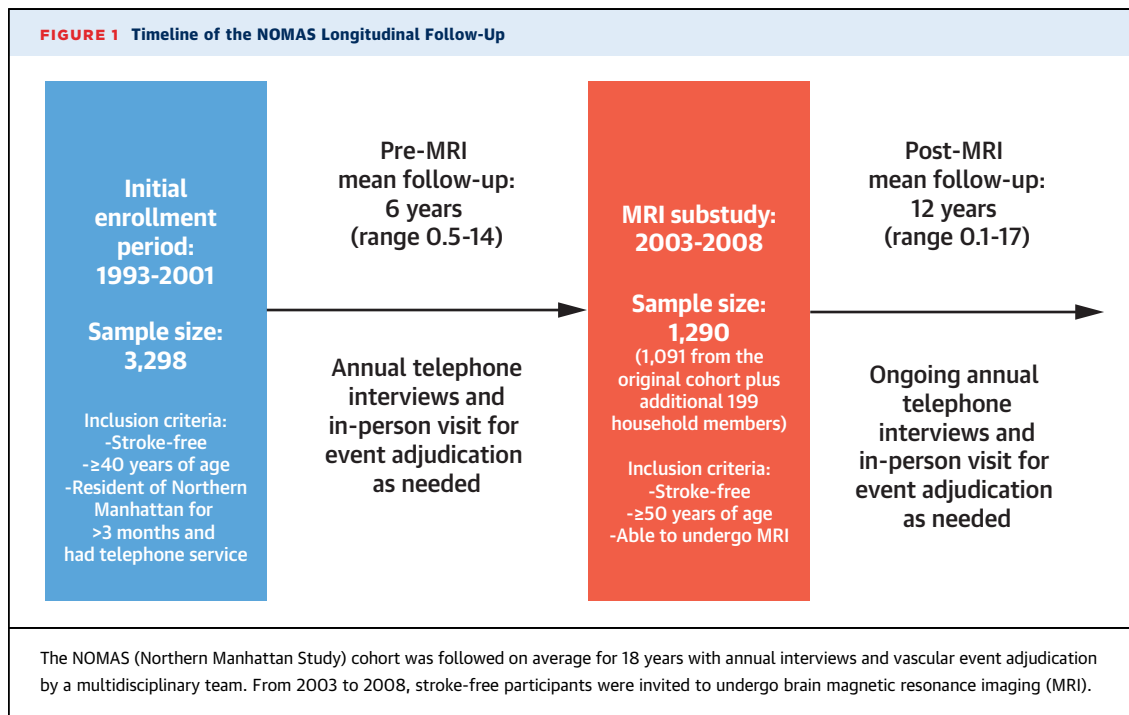
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**METHODS**

**SAMPLE DESCRIPTION.** NOMAS is an ongoing urban, population-based, racially and ethnically diverse epidemiological study that began following its 3,298 participants in 1993 (Figure 1). Participants were identified via random selection among people living in northern Manhattan who had a telephone at home, were 40 years or older, and were stroke-free (self-reported). The methods of this study were previously described (18). In 2003-2008, surviving NOMAS participants were invited to undergo brain magnetic resonance imaging (MRI) if they remained stroke-free, were 50 years or older, and had no contraindications. Between 2006 and 2008, an additional 199 household members of the original NOMAS participants were invited to enroll in the MRI substudy, to supplement the cohort, thus bringing the total enrollment to 1,290 participants. Participants were followed annually since 1993 by telephone

**ABBREVIATIONS AND ACRONYMS**

- ICAS** = intracranial atherosclerotic stenosis
- LDL** = low-density lipoprotein
- MI** = myocardial infarction
- MRA** = magnetic resonance angiography
- MRI** = magnetic resonance imaging
- OR** = odds ratio
- PMD** = primary medical doctor



using a structured interview. Among the MRI cohort, only 3 (0.38%) subjects were lost to follow-up, and 11 (1.4%) withdrew from active participation. Participants signed written informed consent, and the study was approved by the Institutional Review Boards at Columbia University and the University of Miami.

**COVARIATES ADJUDICATION.** Age, sex, race/ethnicity, and years of education were obtained at the time of baseline enrollment by self-report. Enrollment visits occurred in person in the Columbia University Irving Medical Center or in the participant's home. During this visit, participants underwent a structured questionnaire for their baseline characteristics and medical history. Participants had blood sampled to evaluate fasting glucose and a lipid profile (at baseline enrollment and at the time of MRI). Prevalent hypertension, diabetes, and hypercholesterolemia were captured at the enrollment visit by a combination of direct measures of risk factors, self-reported diagnosis, or self-reported medication use to treat any of these risk factors. For hypertension, we used a cutoff of  $\geq 140/90$  mm Hg averaged from at least 2 separate measures of brachial blood pressure taken by trained research personnel; for diabetes, a cutoff of fasting glucose of  $\geq 126$  mg/dL was used, and for hypercholesterolemia, we used a cutoff of total cholesterol of  $\geq 240$  mg/dL. Participants with prevalent risk factors were asked for the duration of their diagnoses. We noted the number and class of all medications used by the participants, and from this survey, we derived the number of medications used to treat a given risk factor. For smoking, we asked the duration of smoking and the number of packs per year smoked. We defined established care under their primary medical doctor (PMD) at the time of MRI if participants self-reported seeing their PMD at least 80% of their scheduled visits at the time of MRI or in the pre-MRI period.

**BRAIN MRI AND ICAS ASSESSMENT.** Imaging was performed on a 1.5-T MRI system (Philips Medical Systems, Best, Netherlands) at the Columbia University Irving Medical Center following a standardized protocol. We used 3-dimensional, time-of-flight magnetic resonance angiography (MRA) with the following parameters: field of view of 15 cm; 1-mm effective slice thickness; acquisition matrix interpolated to a  $256 \times 228$  matrix; flip angle of  $25^\circ$ ; and TR/TE of 20 and 2.7 ms, respectively. Each major intracranial large artery was visually inspected to decide whether further diameter measurements were indicated. If arterial stenosis was identified, we measured the narrowest lumen area to define stenosis and selected the immediate preceding segment with

**TABLE 1** Characteristics of the Northern Manhattan Study MRI Cohort (N = 1,290)

	Available MRA (n = 1,211)	No MRA (N = 79)	P Value
Age, y	71 $\pm$ 9	73 $\pm$ 10	0.04
Men	41	18	<0.001
Ethnicity			
Non-Hispanic White	15	6	0.02
Non-Hispanic Black	18	13	
Hispanic	65	78	
Insured	85	82	0.50
High school completed	47	24	<0.001
Hypertension	78	83	0.24
Diabetes	25	41	0.001
Hypercholesterolemia	81	81	0.98
Current smoking	11	19	0.03

Values are mean  $\pm$  SD or %.  
MRA = magnetic resonance angiography; MRI = magnetic resonance imaging.

normal lumen (or the next normal appearing lumen if the stenosis was at the arterial origin) (19). Stenosis of each artery was ascertained as: 0: no stenosis; 1: <50% (or luminal irregularities); 2: 50%-69%; and 3:  $\geq 70\%$  stenosis or flow gap. These categories were consistent with frequent clinical cutoffs for ICAS used in the literature (8,17,19). A neurologist and a vascular neurologist rated the MRAs independently, blinded to the participant's identity and to each other's reads. The intraclass correlation coefficient for the ICAS ordinal scale was  $>0.90$  for single and average measures. Categorizing the stenosis into  $>50\%$  stenosis yielded  $\kappa = 0.93$ . For the analysis, a consensus variable between the 2 reads was used, and the vascular neurologist read took precedence if a discrepancy of  $>1$  point existed.

**POST-MRI DEATH AND VASCULAR EVENT ADJUDICATION.** Participants in the study were screened annually with standardized telephone interviews and/or in-person visits for a predefined outcome. The outcomes included vascular death, myocardial infarction, ischemic stroke, cardioembolic stroke, intracranial artery disease stroke (which combined intracranial small and large artery disease strokes), and any vascular events (defined as a composite of vascular death, any stroke, or MI, as described previously) (20). We combined intracranial small and large artery disease into a single outcome based on epidemiological and genetic evidence suggestive of the overlapping nature of these 2 stroke phenotypes (21-23). We did not consider cryptogenic strokes as a separate category in this study, but cryptogenic strokes were included in the ischemic stroke category. Briefly, death and vascular events were adjudicated by

**TABLE 2 Pre-MRI Vascular Risk Factor Exposure Relationship With Asymptomatic Intracranial Large Artery Stenosis (Ordinal Categories)**

	Model 1	Model 2	Model 3
Age at MRI, y	<b>1.05 (1.03-1.06)</b>	<b>1.05 (1.03-1.06)</b>	<b>1.02 (1.01-1.04)</b>
Male	1.08 (0.84-1.40)	1.18 (0.91-1.53)	0.87 (0.67-1.14)
Ethnicity			
Non-Hispanic White	Reference group	Reference group	Reference group
Non-Hispanic Black	1.11 (0.75-1.68)	1.03 (0.68-1.58)	1.00 (0.67-1.451)
Hispanic	1.03 (0.69-1.52)	0.89 (0.60-1.34)	1.04 (0.72-1.52)
High school completed (yes/no)	0.85 (0.62-1.15)	0.86 (0.63-1.18)	1.12 (0.84-1.49)
Visits to PMD during pre-MRI follow-up	1.06 (0.55-2.04)	1.00 (0.51-1.96)	0.77 (0.38-1.57)
Hypertension (yes/no) at MRI		<b>1.74 (1.22-2.49)</b>	
SBP (per each 5 mm Hg)			1.03 (0.99-1.07)
DBP (per each 5 mm Hg)			0.98 (0.91-1.06)
No. of antihypertensives at MRI			1.03 (0.88-1.22)
Hypertension duration at MRI, y			<b>1.01 (1.001-1.025)</b>
Diabetes at MRI (yes/no)		<b>1.60 (1.21-2.13)</b>	
Fasting glucose (per each 5 mg/dL)			1.00 (0.98-1.01)
No. of glucose-lowering drugs at MRI			<b>1.64 (1.24-2.15)</b>
Diabetes duration, y			0.99 (0.96-1.02)
Hypercholesterolemia at MRI (yes/no)		<b>2.03 (1.19-3.46)</b>	
LDL (per each 5 mg/dL)			1.01 (1.00-1.03)
HDL (per each 5 mg/dL)			<b>0.96 (0.92-0.99)</b>
Triglycerides, mg/dL			1.01 (0.99-1.02)
No. of cholesterol-lowering drugs at MRI			1.02 (0.81-1.34)
Smoking at MRI (yes/no)		1.21 (0.81-1.82)	
Smoking duration, y			<b>1.01 (1.00-1.01)</b>
Packs per day (per each 5)			0.95 (0.76-1.19)

Values are odds ratio (95% CI). **Bold** values are the model that included all variables with a valid  $\beta$  estimate in each column.  
DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein PMD = primary medical doctor; SBP = systolic blood pressure; other abbreviations as in Table 1.

NOMAS investigators using review of medical records from our institution (where most our participants obtained medical care) or review of medical records from outside institutions (which included records from foreign hospitals, if needed). Vascular death was attributed when the cause of death was MI, stroke, heart failure, pulmonary embolus or cardiac arrhythmia. Two study vascular neurologists (blinded to the study MRA) adjudicated stroke subtypes independently. A study cardiologist using the criteria from the Cardiac Arrhythmia Suppression Trial and the Lipid Research Clinics Coronary Primary Prevention Trial adjudicated MI (24,25). For the purpose of this paper, we used follow-up data collected up to July 2020.

**STATISTICAL ANALYSES.** Descriptive statistics were used to calculate the demographic characteristics and vascular risk factors of the study participants. Chi-square and Student's *t*-tests were used to compare the characteristics of the MRI cohort with available MRAs versus those without MRAs. The first part of the analyses focused on risk factors for asymptomatic ICAS at the time of MRA, and we used data collected

up to the time of MRI (Figure 1). For this part of the analysis, we carried out proportional odds models with the ICAS ordinal variable as the dependent variable to obtain the odds ratios (ORs) and their 95% CIs. We used the 4 categories of stenosis as the main exposure: 0: no stenosis; 1: luminal irregularities with <50% stenosis in at least 1 artery; 2: 50%-69% stenosis in at least 1 artery; and 3:  $\geq$ 70% stenosis or flow gap in at least 1 artery. We used risk factors in various forms, including prevalent risk factors with or without addition of direct measures of intensity and control of such risk factors.

The second part of the analysis focused on the post-MRI vascular event outcomes. We obtained the crude incidence rate of first-occurring vascular events per 1,000 person-years using the 4 categories of ICAS severity. We calculated cumulative incidence for events other than death using Fine and Gray regression to account for competing risk of death using the %pshreg SAS macro (26). To calculate the adjusted risk of events by category of stenosis, we used adjusted Cox proportional hazards regression models to estimate HRs and their 95% CIs with robust

**TABLE 3** Incidence Rate of Events per 1,000 Person-Years of Follow-Up by Asymptomatic Intracranial Large Artery Stenosis Category in the Northern Manhattan Study Cohort (N = 1,211)

	n	Incidence Rate per 1,000 Person-Years (95% CI)			
		No Stenosis (n = 667)	<50% Stenosis (n = 447)	50%-69% Stenosis (n = 37)	≥70% Stenosis or Flow Gap (n = 70)
Death	454	28 (25-33)	32 (27-36)	53 (34-82)	63 (46-88)
Vascular death	200	12 (9-14)	14 (11-17)	32 (18-56)	35 (23-54)
Myocardial infarction	61	4 (2-5)	6 (0.5-19)	3 (0.5-19)	8 (3-21)
Stroke	122	6 (4-8)	11 (9-14)	16 (7-35)	17 (9-33)
Ischemic stroke	104	5 (3-7)	9 (7-36)	16 (7-36)	15 (7-30)
Cardioembolic	39	2 (1-4)	3 (2-4)	8 (3-25)	5 (2-17)
Intracranial (small or large) artery disease	36	1 (0.5-2)	4 (2-6)	5 (1-21)	7 (3-19)
Small artery disease	25	1 (0.5-2)	3 (2-5)	3 (0.5-19)	2 (0.5-13)
Intracranial atherosclerosis	11	0.3 (0.1-1)	0.8 (0.3-2)	3 (0.5-18)	5 (2-17)
Cryptogenic	19	1 (0.5-2)	2 (1-3)	—	—
Any vascular event	324	19 (16-22)	27 (24-32)	38 (22-64)	55 (38-80)

sandwich error variance (27). To evaluate the survival bias because of any death, we modeled the adjusted risk of events using Fine and Gray regression using the same covariates. The statistical analyses were carried out with SAS software, version 9.4 (SAS Institute Inc.).

## RESULTS

Of 1,290 NOMAS participants in the MRI study, we included 1,211 in these analyses (mean age:  $71 \pm 9$  years; 59% women; 65% Hispanic). Participants without MRAs were older and more likely to be women, Hispanic, have diabetes, or to be smokers (Table 1).

The prevalence of any stenosis in any assessed intracranial large artery was 45% (37% had at least 1 artery with <50% stenoses or luminal irregularities, 3% had at least 1 artery with 50%-69% stenosis, and 5% had at least 1 artery with ≥70% stenosis or flow gap).

**Pre-MRI risk factor exposure.** From enrollment to the brain MRI, NOMAS participants were followed on average for 6 years (Figure 1). Using a simple model with risk factor prevalence expressed categorically, older age (OR: 1.05 per year; 95% CI: 1.03-1.06), hypertension (OR: 1.74; 95% CI: 1.22-2.49), diabetes (OR: 1.60; 95% CI: 1.21-2.13), and dyslipidemia (OR: 2.03; 95% CI: 1.19-3.46) were associated with ICAS prevalence and incremental severity (Table 2). Further adjustment for measures of risk factor severity and chronicity revealed that older age (OR: 1.02 per year; 95% CI: 1.01-1.04), longer duration of hypertension (OR: 1.01 per year; 95% CI: 1.00-1.02), higher number of glucose-lowering drugs (OR: 1.64 per each medication; 95% CI: 1.24-2.15), and high-density lipoprotein (OR: 0.96 per mg/dL; 95% CI: 0.92-0.99) were

associated with ICAS prevalence and severity. There were no racial or ethnic differences in ICAS score (Table 2).

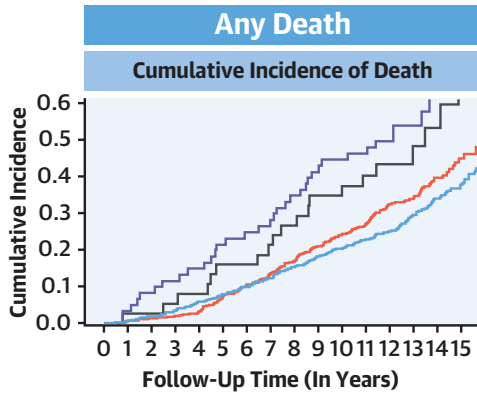
**POST-MRI FOLLOW-UP.** From the time of MRI, participants were followed, on average, for 12 years (Figure 1). Overall, the incidence of vascular events was higher with greater stenosis severity (Table 3, Central Illustration); the highest risk of vascular events was with ICAS ≥70% (5.5% annual risk of any vascular event). The risk of events increased linearly during follow-up after the brain MRI. The risk of vascular events was higher with greater stenosis severity (Table 4). After adjusting for demographics, vascular risk factors, use of antiplatelets or anticoagulation, and established PMD care, the risk of intracranial artery disease strokes and any vascular events remained significant among participants with ≥70% stenosis. Of the incident strokes initially classified as small artery disease, 80% occurred in participants who had evidence of ICAS (any degree) at their baseline MRI.

Among subjects with ICAS (any degree), an established PMD at the time of MRI was associated with a lower risk of events. Older age, longer pre-MRI duration of hypertension, and smoking were associated with a higher risk of vascular death, MI, and ischemic stroke (Table 5).

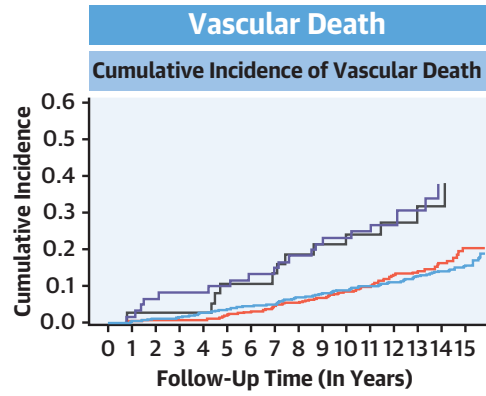
## DISCUSSION

ICAS is an important cause of stroke and a marker of systemic atherosclerosis. In this study of stroke-free subjects, we provided evidence that asymptomatic ICAS was a risk factor for cerebral and systemic vascular events and that the risk increased with greater stenosis severity. Furthermore, longer

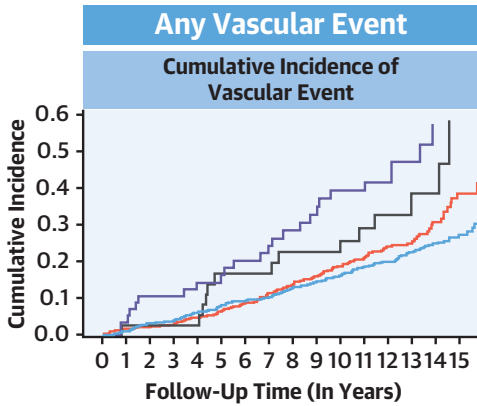
**CENTRAL ILLUSTRATION** Cumulative Incidence of Event Outcomes by Category of Stenosis



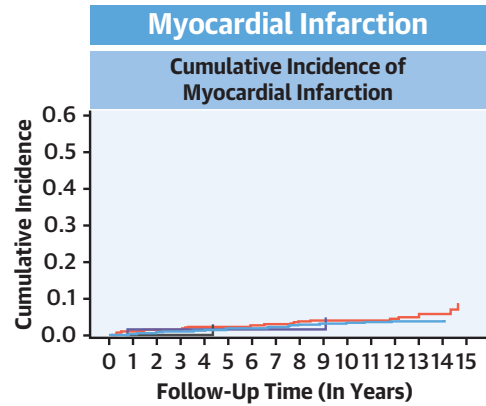
— No Stenosis, n = 667 — <50% Stenosis, n = 447  
 — 50%-69% Stenosis, n = 37 — ≥70% Stenosis, n = 60



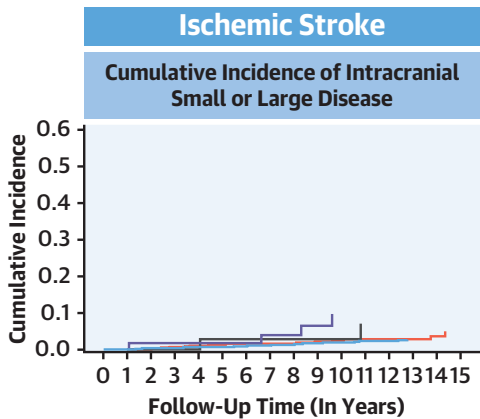
— No Stenosis, n = 667 — <50% Stenosis, n = 447  
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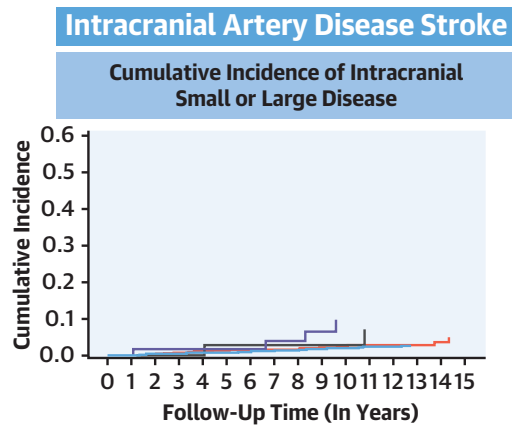
— No Stenosis, n = 667 — <50% Stenosis, n = 447  
 — 50%-69% Stenosis, n = 37 — ≥70% Stenosis, n = 60



— No Stenosis, n = 664 — <50% Stenosis, n = 444  
 — 50%-69% Stenosis, n = 37 — ≥70% Stenosis, n = 59



— No Stenosis, n = 665 — <50% Stenosis, n = 446  
 — 50%-69% Stenosis, n = 37 — ≥70% Stenosis, n = 59



— No Stenosis, n = 665 — <50% Stenosis, n = 446  
 — 50%-69% Stenosis, n = 37 — ≥70% Stenosis, n = 59

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The unadjusted cumulative incidence of event outcomes was higher in people with asymptomatic intracranial large artery stenosis compared with those with no stenosis. The highest risk of events was noted among those with ≥70% stenosis.

**TABLE 4 Risk of Vascular Events per Intracranial Large Artery Stenosis Category in Adjusted Models**

	Any Death	Vascular Death	Myocardial Infarction	Ischemic Stroke	Cardioembolic Stroke	Intracranial Small or Large Disease	Stroke, Myocardial Infarction, or Vascular Death
No. of events	454	200	61	122	39	36	324
Cox proportional models							
No stenosis	Referent group						
<50% stenosis	0.95 (0.77-1.17)	0.90 (0.65-1.25)	1.22 (0.71-2.09)	1.06 (0.69-1.62)	0.92 (0.75-1.13)	1.40 (0.67-2.89)	1.04 (0.81-1.32)
50%-69% stenosis	1.24 (0.77-1.99)	1.53 (0.81-2.89)	0.49 (0.07-3.69)	1.59 (0.65-3.90)	1.05 (0.65-1.69)	2.10 (0.45-9.68)	1.09 (0.62-1.92)
≥70% stenosis	1.31 (0.91-1.90)	1.60 (0.96-2.65)	1.22 (0.40-3.56)	1.50 (0.69-3.26)	1.22 (0.85-1.76)	<b>3.60 (1.17-11.14)</b>	<b>1.52 (1.003-2.31)</b>
Fine and Gray competing risk models							
No stenosis	Referent group						
<50% stenosis	—	0.8 (0.6-1.1)	1.2 (0.6-2.2)	1.0 (0.7-1.6)	0.9 (0.5-1.9)	1.4 (0.6-2.8)	1.0 (0.8-1.3)
50%-69% stenosis	—	1.7 (0.8-3.4)	0.6 (0.1-5.0)	2.1 (0.8-5.1)	2.4 (0.6-9.3)	2.4 (0.5-10.7)	1.3 (0.7-2.3)
≥70% stenosis	—	1.4 (0.8-2.4)	0.8 (0.2-4.1)	1.8 (0.8-3.7)	1.1 (0.3-3.9)	<b>3.9 (1.2-12.5)</b>	<b>1.7 (1.1-2.5)</b>

Values are n and HRs (95% CIs). Model adjusted for age, sex, ethnicity, prevalent risk factors at the time of MRI (hypertension, diabetes, dyslipidemia and smoking), self-reported medications to treat vascular risks at the time of MRI, use of oral antiplatelets or anticoagulants at the time of MRI, and established PMD care at the time of MRI. **Bold** values denote statistical significance. Abbreviations as in [Table 1](#).

exposure to vascular risk factors, specifically uncontrolled and/or more severe risk factors, had a direct impact on the presence of ICAS and ICAS-related vascular events. These results recapitulated the idea that the aggressive control of vascular risk factors is the cornerstone of secondary stroke prevention among subjects with ICAS and extended this same principle to those with asymptomatic ICAS. Subjects with stroke caused by ICAS had more severe stroke at presentation (median National Institute of Health Stroke Scale of 5 in those with ICAS vs median National Institute of Health Stroke Scale of 3 for other etiologies) (7), had a longer hospital stay, and had a higher risk of permanent disability (28). Therefore, the societal benefits of aggressively controlling risk factors in people with asymptomatic ICAS to prevent their first stroke might be greater than that after a stroke occurs.

The prevalence of any stenosis in NOMAS (45%) was similar to the prevalence reported in the ARIC (Atherosclerosis Risk In Communities) study (34%) (8,29), which was a comparable study to NOMAS in its design, other than ARIC did not include Hispanic populations. Historically, a cutoff of 50% stenosis was used in clinical studies of ICAS (19), and as we showed here, there was an incremental risk of vascular events with a higher degree of stenosis, thus justifying a cutoff as more clinically relevant than any stenosis. Using a ≥50% stenosis cutoff, the prevalence of ICAS was even more similar between ARIC (9%) (8) and NOMAS (8%). Compared with international studies, the prevalence of asymptomatic ICAS ≥50% stenosis in NOMAS was higher than it was reported in Japan (6%) (30), but it was lower

than that reported in the United Kingdom (11%) (31), Spain (9%) (32), or Hong Kong (13%) (33). These differences might be related to important differences in study design. For example, the Japanese study included healthy volunteers and reported low rates of hypertension and diabetes compared with NOMAS. The Oxford Vascular Study, the Barcelona-Asymptomatic Intracranial Atherosclerosis Study, and the Hong Kong cohorts focused on high-risk patients based on history of transient ischemic attack and/or or risk factor burden, which would expectedly select a population at a higher risk of ICAS. Furthermore, the Barcelona-Asymptomatic Intracranial Atherosclerosis Study and the Hong Kong study used transcranial Doppler imaging, as opposed to structural arterial imaging, which might have underestimated the prevalence of ICAS in these high-risk populations. The cumulative evidence presented by others and this study highlighted a hidden or clinically covert burden of ICAS across world populations that was not traditionally considered a therapeutic target.

Although the nature of these data prevented us from inferring a causative effect, extrapolation from other trials and the overall body of literature support the value of aggressive control of risk factors at this stage to prevent the occurrence of a first stroke and other vascular events. For secondary stroke prevention, in the SAMMPRIS (Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) trial, patients who achieved risk factor control targets had a lower risk of stroke recurrence (12). In the COSS (Carotid Occlusion Surgery Study) trial, which included patients with unilateral carotid occlusion

**TABLE 5** Role of Vascular Risks in Post-MRI Vascular Events in NOMAS Participants With Asymptomatic Intracranial Large Artery Stenosis

	Vascular Death	Myocardial Infarction	Ischemic Stroke
Age, y	<b>1.1 (1.1-1.1)</b>	<b>1.0 (1.0-1.0)</b>	<b>1.1 (1.1-1.1)</b>
Male	1.1 (0.8-1.5)	1.1 (0.6-2.0)	1.2 (0.8-1.8)
Ethnicity			
Non-Hispanic White	Reference	Reference	Reference
Non-Hispanic Black	0.8 (0.5-1.2)	0.8 (0.3-1.9)	0.9 (0.5-1.7)
Hispanic	0.6 (0.4-0.8)	0.6 (0.3-1.1)	1.2 (0.7-2.0)
PMD visits post-MRI	<b>0.3 (0.2-0.5)</b>	<b>0.2 (0.1-0.6)</b>	0.6 (0.2-1.5)
Antiplatelets exposure post-MRI, y	1.0 (0.7-1.3)	0.6 (0.3-1.2)	1.1 (0.7-1.6)
Anticoagulant exposure post-MRI, y	1.4 (0.6-3.0)	2.4 (0.6-9.5)	<b>3.4 (1.7-7.1)</b>
Hypertension at MRI or after	1.2 (0.8-2.0)	1.4 (0.4-4.1)	0.9 (0.5-1.8)
Antihypertensive use at the time of MRI	1.0 (0.7-1.5)	1.7 (0.7-4.1)	0.8 (0.5-1.5)
Hypertension duration before MRI, y	<b>1.0 (1.0-1.0)</b>	<b>1.0 (1.0-1.0)</b>	<b>1.0 (1.0-1.0)</b>
Diabetes at MRI or after	1.0 (0.5-1.8)	2.1 (0.9-5.1)	0.5 (0.2-1.0)
Hypoglycemic at the time of MRI	1.6 (0.8-3.2)	0.6 (0.2-1.7)	<b>3.4 (1.5-7.8)</b>
Diabetes duration before MRI, y	<b>1.0 (1.0-1.0)</b>	<b>1.0 (1.0-1.1)</b>	1.0 (0.9-1.0)
Hypercholesterolemia at MRI or after	0.6 (0.4-1.1)	0.9 (0.3-2.8)	1.4 (0.6-3.5)
Lipid-lowering drugs at the time of MRI	1.2 (0.9-1.7)	1.4 (0.8-2.7)	1.1 (0.7-1.8)
Smoking at the time of MRI	0.8 (0.5-1.5)	0.4 (0.1-1.3)	1.9 (0.9-4.1)
Smoking duration before MRI, y	<b>1.0 (1.0-1.0)</b>	<b>1.0 (1.0-1.0)</b>	<b>1.0 (1.0-1.0)</b>

Values are HR (95% CI). Model adjusted for all variables listed in column one of this table. Estimates calculated with Fine and Gray regressions. **Bold** values denote statistical significance.  
NOMAS = Northern Manhattan Study; other abbreviations as in Tables 1 and 2.

and hemodynamic failure, those who achieved normotension had lower risks of stroke recurrence (34). This finding is particularly important in the setting of ICAS, because it can be hypothesized that relative hypertension could be beneficial to overcome the arterial flow resistance posed by luminal stenosis. There might be a role for permissive hypertension in some patients with ICAS in the acute stroke phase, but there is less evidence that permissive hypertension has a protective long-term role in ICAS (35). Data from the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial showed that among subjects with ICAS with >50% stenosis, higher blood pressure was associated with increased (not decreased) risk of ischemic stroke and stroke in the territory of the stenotic vessel (36).

Atherosclerosis is largely a cholesterol-mediated disease. Pathologically, atherosclerosis is diagnosed by the presence of atheroma (from the Greek, ἀθήρα [athera] or “gruel-like”) (37). The underlying assumed pathology of ICAS in most adult cases is atherosclerosis, especially in the setting of vascular risk factors. Other less common causes of ICAS include Moyamoya disease (38), infectious arteriopathies (eg, varicella zoster virus vasculitis) (39), focal cerebral arteriopathy in children (40), and so on. These etiologies of ICAS are not likely to be the cause of ICAS in our sample because of the asymptomatic status of the participants, their age, and vascular comorbidities. Nonetheless, it was difficult to determine the

underlying etiology with certainty using MRA. Contrary to what has been reported about coronary arteries, the relationship between atherosclerotic plaque burden and luminal stenosis in brain arteries is linear for the most part (41). Therefore, a higher degree of luminal stenosis implies a proportionally greater amount of cholesterol deposition and/or atherosclerotic plaque area. Robust evidence exists that statins decrease the risk of vascular events in primary prevention (42). Trials focused on noncardioembolic strokes (which include ICAS) demonstrated that high-dose statins reduce the risk of vascular events (43). In a subgroup analysis from the WASID trial that included participants with >50% stenosis, participants with a low-density lipoprotein (LDL) of ≤70 mg/dL had a risk of recurrent stroke of 7% compared with 23% among those with LDL ≥70 mg/dL (44). In SAMMPRIS, with a trial population that had 70%-99% stenosis, 47% achieved an LDL target of ≤70 mg/dL, and those without this target had an 80% greater risk of recurrent stroke. Similarly, aggressive control of diabetes and smoking cessation are opportunities to reduce vascular risk in the general population (45). Our study offered observational data supporting smoking cessation as a means of preventing ICAS because of the association between a greater number of packs per year and/or smoking duration and ICAS prevalence and ICAS-related vascular events. Similarly, the role of aggressive control of diabetes with a target glycosylated

hemoglobin of <7% appears applicable to subjects with asymptomatic ICAS (46). Finally, health care use, defined here as established PMD care at the time of MRI was associated with a lower risk of vascular events in the ICAS population. Frequent visits to primary care providers might imply better risk factor control and be related to other unmeasured confounders (health literacy, health care trust, health care access and availability, and so on).

**STUDY LIMITATIONS.** The results of this study should be interpreted in the context of its limitations. For example, the reliance on self-reported use of certain medications could be less reliable and subject to recall bias. The annual intervals for our telephone follow-up might have not been frequent enough to capture the variability in biological variables (eg, blood pressure or cholesterol levels), and therefore, underestimated other aspects of traditional risk factors that might play a role in ICAS and ICAS events. The lack of participants of Asian ancestry/ethnicities was also a limitation. Despite these limitations, the overall results were consistent with the extensive and well-established body of literature that supported aggressive control of risk factors as the main means to reduce vascular risks in the general population. Strengths of this work included its population-based design, the unique ethnically diverse stroke-free population with asymptomatic ICAS, the low rate of loss to follow-up, and the rigorous ascertainment of vascular outcomes in the population.

## CONCLUSIONS

The novel observations made in this study support a more aggressive primary prevention effort for vascular events in the general population. A targeted approach to identify high-risk community dwellers

who have asymptomatic ICAS may be desirable to test whether aggressive targets of risk factor control prevent stroke and vascular events. The data presented here support the notion that ICAS is an imaging marker of established atherosclerotic disease in stroke-free subjects, and that incidental diagnosis of ICAS should trigger thorough assessment of vascular health. Preventing a first-ever stroke at this asymptomatic stage may magnify the societal benefits of vascular prevention and decrease stroke-related disability and vascular death in our communities.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** ICAS is associated with high rates of initial and recurrent stroke and extracranial vascular events, proportionate to the severity of stenosis.

**TRANSLATIONAL OUTLOOK:** Additional research is needed to determine whether interventions that decrease recurrent stroke among patients with ICAS are helpful in asymptomatic subjects as well.

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