

Supplementary Online Content

Hoshino T, Sissani L, Labreuche J, et al. Prevalence of systematic atherosclerosis burdens and overlapping stroke etiologies and their associations with long-term vascular prognosis in stroke with intracranial disease. *JAMA Neurol*. Published online December 26, 2017. doi:10.1001/jamaneurol.2017.3960

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Transcranial Doppler Ultrasound Examination of Intracranial Arteries¹

Stenosis $\geq 50\%$ was defined as a peak systolic velocity increase >150 cm/s for proximal middle cerebral artery (MCA), >120 cm/s for vertebral artery (VA) or basilar artery (BA), and >100 cm/s for carotid artery (CA) or a difference $>30\%$ compared with the contralateral artery. MCA occlusion was diagnosed if all other basal arteries were detectable or if the asymmetry index of the symptomatic MCA was $<-21\%$ compared with that of the contralateral MCA. CA occlusion was diagnosed if all basal arteries except the CA and the ipsilateral MCA were not detected. BA occlusion was diagnosed if there was a high-resistance flow pattern at depths of 85 to 95mm in the BA, possibly combined with a sudden loss of flow signals when increasing the examination depth, or retrograde flow in the distal BA. Intracranial VA occlusion was diagnosed if there was a resistance flow profile in 1 side whereas normal or even compensatory elevated flow velocity was seen on the other side.

Outcome

Vascular death included fatal stroke, fatal myocardial infarction, and other cardiovascular death. Other cardiovascular death included any sudden death, including unobserved and unexpected death (e.g., while sleeping) unless proven otherwise by autopsy; death after a vascular surgery, vascular procedure, or amputation (except for trauma or malignancy); death ascribed to heart failure; death after a visceral or limb infarction. Any myocardial infarction or stroke followed by death, whatever the cause, in the subsequent 28 days was considered as a fatal myocardial infarction or fatal stroke. Cardiac events included myocardial infarction, resuscitation after cardiac arrest, and hospitalization for unstable angina or cardiac insufficiency. Major peripheral events included all events related to noncoronary or cervicocerebral artery disease leading to hospitalization or revascularization (e.g., new or worsening of claudication leading to revascularization, surgery for ruptured aneurysm, cholesterol emboli syndrome).

eTable 1. Prevalence of ICAD by Site and Severity									
	Anterior Circulation				Posterior Circulation				Any
	Any	Infraclinoid	Supraclinoid	MCA	Any	BA	VA	PCA	
Severity									
Non-significant, No. (%)	299 (74.2)	377 (93.5)	396 (98.3)	371 (92.1)	325 (80.6)	271 (94.4)	373 (92.6)	378 (93.8)	257 (63.8)
Stenosis \geq 50%, No. (%)	51 (12.7)	17 (4.2)	4 (1.0)	21 (5.2)	53 (13.6)	16 (5.6)	26 (6.4)	25 (6.2)	97 (24.1)
Occlusion, No. (%)	25 (6.2)	9 (2.2)	3 (0.7)	11 (2.7)	23 (5.7)	0 (0.0)	4 (1.0)	0 (0.0)	49 (12.2)
Stenosis \geq 50% or occlusion, No. (%)	76 (18.9)	26 (6.4)	7 (1.7)	32 (7.9)	76 (18.9)	16 (5.6)	30 (7.4)	25 (6.2)	146 (36.2)

Abbreviations: BA, basilar artery; ICAD, intracranial atherosclerotic disease; MCA, middle cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery.

No. of patients = 403.

eTable 2. Baseline Characteristics of Patients with Symptomatic and Asymptomatic Significant ICAD

	Intracranial Stenosis \geq 50% or Occlusion		P Value
	Asymptomatic (n = 74)	Symptomatic (n = 72)	
Age, mean (SD), y	64 (14)	65 (13)	.58
Men, No. (%)	55 (74.3)	53 (73.6)	.92
Body mass index, mean (SD), kg/m ²	27.1 (4.5)	26.3 (4.4)	.27
Medical history, No. (%)			
Hypertension	58 (78.4)	63 (87.5)	.14
Diabetes	16 (21.6)	16 (22.2)	.93
Dyslipidemia	33 (44.6)	37 (51.4)	.41
Current smokers	24 (32.4)	29 (40.3)	.32
History of stroke	7 (9.5)	8 (11.1)	.74
History of coronary heart disease	14 (18.9)	12 (16.7)	.72
History of peripheral artery disease	6 (8.1)	9 (12.5)	.38
History of atrial fibrillation	11 (14.9)	3 (4.2)	.03
Examination findings			
Systolic BP, mean (SD), mm Hg	142 (22)	142 (18)	.91
Diastolic BP, mean (SD), mm Hg	79 (12)	78 (11)	.40
Total cholesterol, mean (SD), mg/dL	199 (42)	197 (49)	.84
LDL-C, mean (SD), mg/dL	121 (38)	120 (44)	.85
HDL-C, mean (SD), mg/dL	54 (14)	51 (15)	.23
TG, median (IQR), mg/dL	110 (88-139)	128 (93-175)	.22 ^a
TG/HDL-C ratio, median (IQR)	2.1 (1.5-3.4)	2.4 (1.8-3.9)	.13 ^a
Glucose, median (IQR), mg/dL	97 (88-108)	96 (90-117)	.55 ^a
HbA1c, median (IQR), %	5.7 (5.4-6.4)	5.8 (5.4-6.4)	.65 ^a
Metabolic syndrome, No. (%)	14 (20.9)	18 (29.5)	.26
Atherogenic dyslipidemia, No. (%)	5 (6.8)	10 (13.9)	.16
ASCOD grade ^b , No. (%)			
Atherothrombosis			<.001
A0	0 (0.0)	0 (0.0)	
A3	28 (37.8)	0 (0.0)	
A2	9 (12.2)	4 (5.6)	
A1	37 (50.0)	68 (94.4)	
Cardiac pathology			.005
C0	27 (36.5)	38 (52.8)	
C3	9 (12.2)	12 (16.7)	
C2	8 (10.8)	9 (12.5)	
C1	28 (37.8)	8 (11.1)	

eTable 2. Baseline Characteristics of Patients with Symptomatic and Asymptomatic Significant ICAD (continued)			
	Intracranial Stenosis \geq50% or Occlusion		P Value
	Asymptomatic (n = 74)	Symptomatic (n = 72)	
Small vessel disease			.62
S0	12 (16.2)	7 (9.7)	
S3	54 (73.0)	59 (81.9)	
S2	0 (0.0)	0 (0.0)	
S1	4 (5.4)	3 (4.2)	

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ICAD, intracranial atherosclerotic disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

^a Calculated after log-transformation of data.

^b ASCOD phenotyping assigns a degree of causality between the index stroke and each category as follows: 1 = potential cause; 2 = causality is uncertain; 3 = the disease is present but is unlikely a direct cause; 0 = the disease is absent.

eTable 3. Baseline Characteristics According to Localization of Significant ICAD				
	Circulation			P Value
	Anterior (n = 68)	Posterior (n = 42)	Both (n = 36)	
Age, mean (SD), y	63 (15)	65 (12)	68 (11)	.15
Men, No. (%)	43 (63.2)	35 (83.3)	30 (83.3)	.02
Body mass index, mean (SD), kg/m ²	26.7 (4.9)	27.2 (4.2)	25.9 (3.8)	.45
Medical history, No. (%)				
Hypertension	56 (82.3)	35 (83.3)	30 (83.3)	.99
Diabetes	14 (20.6)	10 (23.8)	8 (22.2)	.92
Dyslipidemia	31 (45.6)	19 (45.2)	20 (55.6)	.57
Current smokers	22 (32.3)	21 (50.0)	10 (27.8)	.08
History of stroke	9 (13.2)	3 (7.2)	3 (8.3)	.61
History of coronary heart disease	8 (11.8)	8 (19.0)	10 (27.8)	.12
History of peripheral artery disease	8 (11.8)	4 (9.5)	3 (8.3)	.94
History of atrial fibrillation	12 (17.6)	1 (2.4)	1 (2.8)	.008
Examination findings				
Systolic BP, mean (SD), mm Hg,	142 (21)	140 (18)	145 (22)	.52
Diastolic BP, mm Hg, mean (SD)	79 (12)	79 (13)	78 (22)	.83
Total cholesterol, mean (SD), mg/dL	198 (42)	198 (39)	198 (56)	1.00
LDL-C, mean (SD) mg/dL	120 (39)	122 (34)	120 (53)	.95
HDL-C, mean (SD), mg/dL	52 (15)	53 (13)	52 (15)	.88
TG, median (IQR), mg/dL	116 (91-165)	109 (81-138)	127 (104-164)	.43 ^a
TG/HDL-C ratio, median (IQR)	2.3 (1.5-3.5)	2.1 (1.4-3.2)	2.4 (1.5-4.1)	.48 ^a
Glucose, mg/dL, median (IQR)	97 (86-104)	101 (94-122)	94 (88-113)	.10 ^a
HbA1c, median (IQR), %	5.6 (5.4-6.0)	6.0 (5.5-6.4)	6.1 (5.4-6.4)	.54 ^a
Metabolic syndrome, No. (%)	14 (24.6)	9 (21.9)	9 (30.0)	.74
Atherogenic dyslipidemia, No. (%)	8 (11.8)	3 (7.1)	4 (11.1)	.77
ASCOD grade ^b , No. (%)				
Atherothrombosis				.03
A0	0 (0.0)	0 (0.0)	0 (0.0)	
A3	13 (19.2)	13 (30.9)	2 (5.6)	
A2	6 (8.8)	5 (11.9)	2 (5.6)	
A1	49 (72.1)	24 (57.1)	32 (88.9)	
Cardiac pathology				.15
C0	29 (42.6)	18 (42.9)	18 (50.0)	
C3	5 (7.3)	7 (16.7)	9 (25.0)	
C2	9 (13.2)	7 (16.7)	1 (2.8)	
C1	21 (30.9)	8 (19.0)	7 (19.4)	

eTable 3. Baseline Characteristics According to Localization of Significant ICAD (continued)				
	Circulation			P Value
	Anterior (n = 68)	Posterior (n = 42)	Both (n = 36)	
Small vessel disease				.81
S0	6 (8.8)	6 (14.3)	7 (19.4)	
S3	55 (80.)	32 (76.2)	26 (72.2)	
S2	0 (0.0)	0 (0.0)	0 (0.0)	
S1	4 (5.9)	2 (4.8)	1 (2.8)	

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ICAD, intracranial atherosclerotic disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

^a Calculated after log-transformation of data.

^b ASCOD phenotyping assigns a degree of causality between the index stroke and each category as follows: 1 = potential cause; 2 = causality is uncertain; 3 = the disease is present but is unlikely a direct cause; 0 = the disease is absent

eTable 4. Prevalence of Non-Intracranial Atherosclerosis in Patients with Symptomatic and Asymptomatic Significant ICAD

	Intracranial Stenosis \geq 50% or Occlusion		<i>P</i> Value
	Asymptomatic (n = 41)	Symptomatic (n = 48)	
No. (%) with atherosclerosis in:			
Extracranial carotid artery	55 (76.4)	52 (73.2)	.66
Aortic arch	36 (60.0)	34 (61.8)	.84
Descending aorta	15 (25.0)	15 (27.3)	.78
Abdominal aorta	22 (34.9)	17 (27.4)	.36
Femoral artery	50 (74.6)	51 (78.5)	.60
Coronary artery	48 (71.6)	55 (82.1)	.15

Abbreviations: ICAD, intracranial atherosclerotic disease.

eTable 5. Prevalence of Non-Intracranial Atherosclerosis According to Localization of Significant ICAD

	Circulation			P Value
	Anterior (n = 35)	Posterior (n = 34)	Both (n = 20)	
No. (%) with atherosclerosis in:				
Extracranial carotid artery	27 (79.4)	25 (75.8)	16 (80.0)	.91
Aortic arch	17 (56.7)	14 (53.8)	12 (80.0)	.22
Descending aorta	7 (23.3)	9 (34.6)	5 (33.3)	.61
Abdominal aorta	11 (32.3)	11 (39.3)	4 (30.8)	.81
Femoral artery	29 (82.9)	25 (83.3)	11 (78.6)	.92
Coronary artery	25 (75.8)	27 (84.4)	16 (88.9)	.46

Abbreviations: ICAD, intracranial atherosclerotic disease.

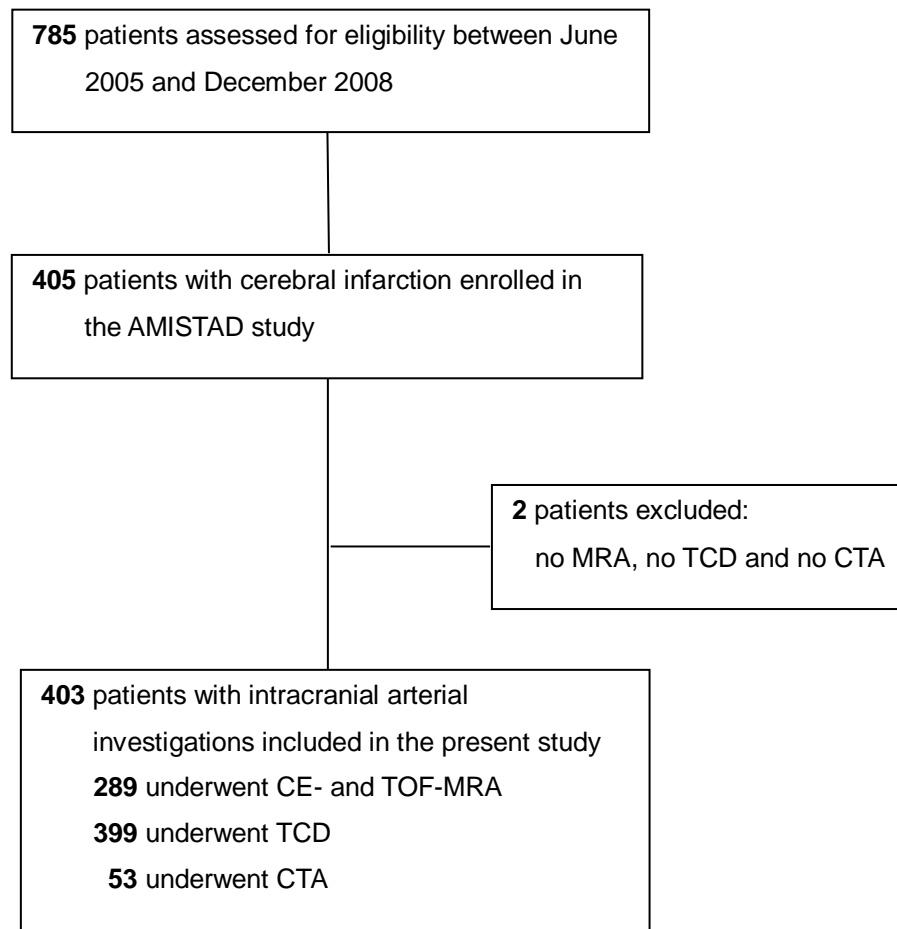
eTable 6. Four-Year Risk of Recurrent Vascular Events Associated with Coexisting Diseases in Patients with Significant ICAD

	MACE, N (%)	Log-Rank <i>P</i> Value	Hazard Ratio (95% CI) ^a	<i>P</i> Value
ECAS				
No (n = 36)	3 (9.0)	.08	1.00 (ref)	.24
Yes (n = 107)	24 (23.4)		2.12 (0.61-7.34)	
CAD				
No (n = 68)	8 (12.8)	.01	1.00 (ref)	.36
Yes (n = 66)	19 (29.9)		1.90 (0.48-7.53)	
Cardiac pathology				
C0 (n = 65)	7 (11.4)	.01	1.00 (ref)	.09
C1, 2, 3 (n = 74)	20 (28.2)		2.24 (0.87-5.73)	
Small vessel disease				
S0 (n = 19)	6 (34.6)	.05	1.00 (ref)	.008
S1, 2, 3 (n = 120)	20 (17.3)		0.23 (0.08-0.68)	

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ECAS, extracranial carotid artery stenosis; HR, hazard ratio; ICAD, intracranial atherosclerotic disease; MACE, major adverse cardiovascular events.

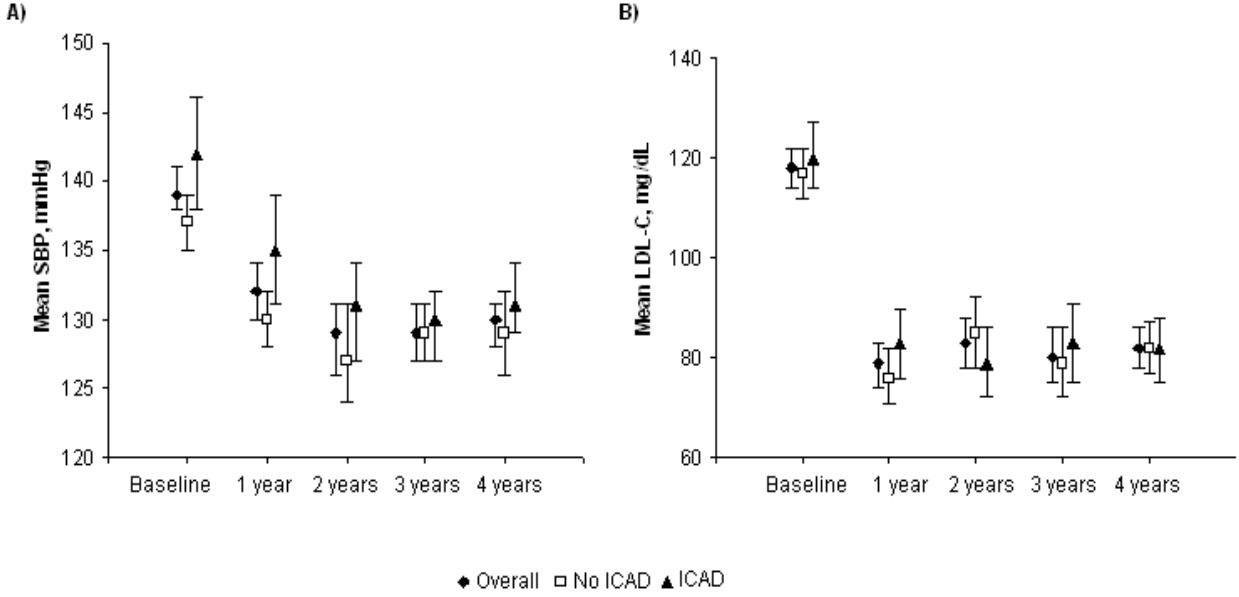
^a Adjusted for age, baseline systolic blood pressure, baseline high-density lipoprotein cholesterol, body mass index, and history of atrial fibrillation.

eFigure 1. Study Flow Chart



Abbreviations: CE, contrast enhanced; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TCD, transcranial Doppler; TOF, time of flight.

eFigure 2. Mean Systolic Blood Pressure Levels and Low-Density Lipoprotein Cholesterol Concentrations at Baseline and Follow-Up Visits

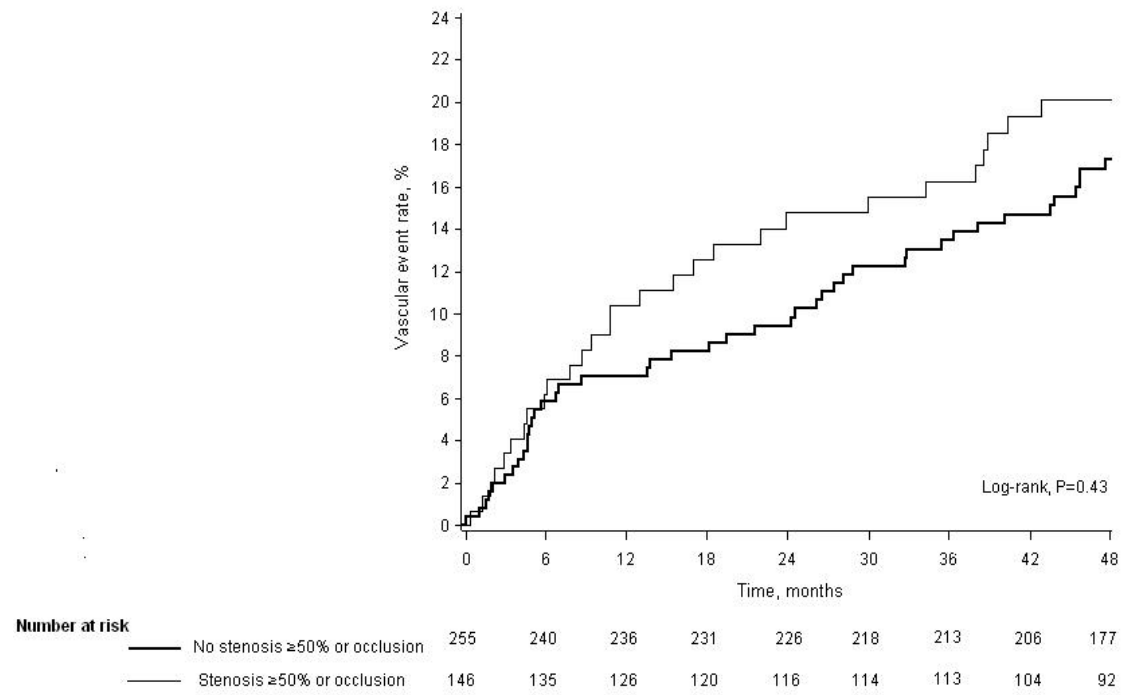


A. Mean SBP levels at baseline and follow-up visits.

B. Mean LDL-C concentrations at baseline and follow-up visits.

Abbreviations: ICAD, intracranial atherosclerotic disease; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

eFigure 3. Cumulative Incidence Curves of Major Vascular Events According to the Presence of Significant ICAD



Abbreviations: ICAD, intracranial atherosclerotic disease.

eReferences

1. Meseguer E, Lavallée PC, Mazighi M, et al. Yield of systematic transcranial Doppler in patients with transient ischemic attack. *Ann Neurol*. 2010;68(1):9-17.