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Letter to the Editor

The Role of Atrial Cardiopathy as a Potential Cause of Embolic Stroke of Undetermined Source

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Dear Sir:

Atrial cardiopathy (AC), which refers to left atrial (LA) structural and functional disorders (independent of atrial fibrillation [AF]),[1,2] is increasingly considered a potential mechanism for embolic stroke of undetermined source (ESUS).[3] AC has been independently associated with silent AF detection and stroke recurrence,[4,5] suggesting an etiopathogenic role. Most studies on AC in ESUS were conducted before the recently proposed ESUS construct update.[6] Given the heterogeneous definition of ESUS, etiological misclassification may have limited our understanding of the link between AC and ESUS. After applying the proposed ESUS construct update, we first assessed whether any differences existed in the prevalence of AC in patients with ESUS classified according to the traditional versus revised criteria. After focusing on the revised classification, we investigated the clinical and radiological differences between ESUS with AC (AC(+)/ESUS) versus without AC (AC(-)/ESUS). Additionally, we investigated the association between AC and stroke severity and outcome and the role of AC in stroke recurrence and AF detected after stroke (AFDAS).[7]

This retrospective single-center study included all consecutive patients with acute ischemic stroke (AIS) diagnosed as ESUS (according to standard criteria).[8] These patients were admitted to our stroke unit between January 2018 and December 2022. All diagnostic evaluations were reviewed for each patient, and recently proposed changes to the ESUS construct[6] were applied to redefine the ESUS classification. We excluded patients with (1) high-risk patent foramen ovale (PFO), (2) high-risk non-stenosing (<50%) ipsilateral supracardiac atherosclerosis, and (3) probable cancer-related hypercoagulability (see Supplementary Methods for details).

AC was defined as LA enlargement (LAE), measured using the LA volume index (LAVI) based on the standard criteria: LAVI >34 mL/m^2. The entire cohort was divided based on the presence of AC (AC(+)/ESUS if LAVI >34 mL/m^2) versus its absence (AC(–)/ESUS if LAVI ≤34 mL/m^2). AC was also categorized according to severity as mild (LAVI 35–41 mL/m^2) or moderate/severe (LAVI ≥42 mL/m^2).[9]

Radiological data, including the analysis of stroke lesions by location and site, were also collected. Stroke severity (measured by the baseline National Institutes of Health Stroke Scale [NIHSS] score) and functional status at 90 days (modified Rankin Scale [mRS] score of 0–2 and 0–3) were considered as clinical outcomes. Stroke recurrence and AFDAS were considered long-term follow-up outcomes.

Statistical analysis was performed using Stata statistical software (Version 17; StataCorp., College Station, TX, USA), with the significance level set at P<0.05. Univariate and multivariate logistic (or ordered logistic) regression analyses were performed to evaluate the association between AC (considered both continuous [LAVI] and dichotomous variables [AC(+) vs. AC(-); moderate/severe AC vs. mild AC/AC(-)]) and stroke severity, 90-day mRS score, stroke recurrence, and AFDAS. This study was approved by the local ethics committee (Comitato Etico Milano Area 3, n. 346-18052022), and informed consent was obtained from patients upon admission. Detailed information regarding the study population, diagnostic evaluations, and statistical analyses can

be found in Supplementary Methods.

Among the 414 eligible ESUS patients (with available LAVI measurements), 116 (28%) were reclassified and excluded per the ESUS construct update, resulting in a final sample of 298 ESUS patients (Supplementary Figure 1). The prevalence of AC was higher in ESUS cases classified according to the revised criteria than in those classified according to the traditional criteria (42.0% vs. 36.2%) and significantly different from excluded ESUS cases (42.0% vs. 21.5%; P<0.001) (Table 1). The excluded patients with ESUS had a lower LAVI, were younger with fewer vascular risk factors, experienced milder strokes, and had better 3-month outcomes (Supplementary Table 1). The general characteristics of the final ESUS cohort (revised criteria) are presented in Table 2. Patients with AC(+)/ESUS were older and had more hypertension, coronary artery disease, and non-stenosing ipsilateral supra-cardiac atherosclerosis. Additionally, they suffered more frequently from cortico-subcortical strokes and had fewer small-isolated cortical lesions compared to patients with AC(-)/ESUS.

Over a median follow-up of 20 months (interquartile range [IQR] 8–32; available for 290 patients), recurrent stroke occurred in 17 patients (5.9%) and AFDAS in 28 patients (9.7%). The median time between the index and recurrent stroke was 5 months (IQR 3–20). In both univariate and multivariate logistic regression analyses, no significant associations were observed between the AC parameters (presence, severity, and LAVI), stroke severity, 90-day mRS, and stroke recurrence. The AFDAS was independently associated with all AC parameters (Table 3). Further analyses and results are reported in the Supplementary Results, including Kaplan-Meier survival analysis for the risk of stroke recurrence (Supplementary Figure 2).

In our study, we found that, following the recent ESUS update, patients classified as non-ESUS exhibited a significantly different echocardiographic profile than ESUS patients, with a higher AC incidence in the latter group (42.0%). This finding highlights the substantial heterogeneity in the echocardiographic profiles within these two groups and underscores the importance of precise ESUS patient classification.

The prevalence of AC varies in published studies, depending on the criteria used for its definition. Various AC biomarkers, categorized as electrophysiological, structural, hemodynamic, and serological, have been associated with stroke risk.[2] Our study defined AC as LAE by measuring the LAVI, which is now considered a superior indicator of LA dimensions compared to LA diameter. The LAVI has been demonstrated to be better associated with new-onset AF[4] and stroke recurrence[10] in patients with ESUS.

Consistent with previous studies, our findings indicate that patients with AC tended to be older and have a higher atherosclerotic burden. This finding aligns with the pathogenetic evidence indicating that LAE results from progressive cardiac wall remodeling due to aging, inflammation, oxidative stress, and stretching from pressure and volume overloads.[1,2]

Additionally, the infarction pattern differs; AC(+)/ESUS exhibits more cortical-subcortical infarcts and fewer small isolated cortical lesions, suggesting a potential connection to the formation of larger thrombi in the larger left atria. Our study revealed no significant differences in stroke recurrence rates. However, given the limited sample size and recurrence rates, our results may be underpowered to draw meaningful conclusions. Notably, we found that AC was independently associated with AFDAS. This finding aligns with those of previous studies[4,7] and supports the adoption of the LAVI in future trials assessing the role of anticoagulant therapy in selected patients with ESUS at high risk of AFDAS.

Our study had several strengths. First, we focused on a carefully "selected" ESUS population, following the recently proposed update, and utilized LAVI measurement as a superior marker of LAE. However, acknowledging certain limitations is important. This was a retrospective, observational, single-center study. We restricted our analysis to structural cardiopathy, defining AC as LAE without measuring other markers of LA dysfunction. Further studies should include serological and electrophysiological biomarkers to ensure a more comprehensive evaluation of AC

Table 1. Differences in echocardiographic characteristics between ESUS patients classified according to traditional and revised ESUS criteria

TTE characteristics	Entire ESUS cohort (n=414, 100%)	ESUS included (n=298, 72%)	ESUS excluded (n=116, 28%)	*P*
AC	150 (36.2)	125 (42.0)	25 (21.5)	<0.001
AC moderate/severe	75 (18.1)	64 (21.5)	11 (9.5)	<0.001
LAVI (mL/m^2)	30 (24–38)	32 (25–40)	27 (21–33)	<0.001
LVDD grade 2–3	46 (11.1)	39 (13.1)	7 (6.0)	0.040
LVEF (%)	59 (56–63) [n=397]	59 (56–62) [n=285]	60 (57–63) [n=112]	0.122
LVEF ≤50%	31 (7.5)	24 (8.0)	7 (6.0)	0.483

Values are presented as n (%) or median (interquartile range).
ESUS, embolic stroke of undetermined source; TTE, transthoracic echocardiography; AC, atrial cardiopathy; LAVI, left atrial volume index; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction.

Table 2. Differences in clinical, radiological, and echocardiographic characteristics between ESUS patients with versus without AC (defined as LAVI >34 mL/m^2)

	Entire ESUS cohort (n=298, 100%)	AC(+)/ESUS (n=125, 42%)	AC(-)/ESUS (n=173, 58%)	*P*
Baseline characteristics				
Age (yr)	71 (61–80)	76 (69–82)	68 (57–76)	<0.001
Female sex	136 (45.6)	63 (50.4)	73 (42.2)	0.161
Pre-mRS score	0 (0–0)	0 (0–0)	0 (0–0)	0.096
NIHSS score	5 (2–11)	6 (3–10)	5 (2–12)	0.567
Prior stroke	36 (12.1)	14 (11.2)	22 (12.7)	0.692
Current smoking	73 (24.5)	24 (19.2)	49 (28.3)	0.071
Hypertension	234 (78.5)	114 (91.2)	120 (69.4)	<0.001
Diabetes	59 (19.8)	30 (24.0)	29 (16.8)	0.122
Dyslipidemia	176 (59.1)	67 (53.6)	109 (63.0)	0.103
Obesity	63 (21.1)	27 (21.6)	36 (20.8)	0.869
CAD	52 (17.4)	33 (26.4)	19 (11.0)	0.001
Supra-cardiac atherosclerosis	136 (45.6)	69 (55.2)	67 (38.7)	0.005
Acute reperfusion therapy				
IVT	85 (28.5)	40 (32.0)	46 (26.6)	0.309
EVT +/- IVT	108 (36.2)	44 (35.2)	63 (36.4)	0.829
None	152 (51.0)	59 (47.2)	93 (53.8)	0.264
Stroke pattern and location				
Anterior circulation	232 (77.8)	97 (77.6)	135 (78.0)	0.929
Posterior circulation	80 (26.8)	34 (27.2)	46 (26.6)	0.907
Multi-territory	21 (7.0)	10 (8.0)	11 (6.4)	0.585
Cortical (small isolated lesions)	19 (6.4)	2 (1.6)	17 (9.8)	0.004
Cortical-subcortical	252 (84.5)	112 (89.6)	140 (80.9)	0.041
Deep (white/grey) matter	27 (9.1)	11 (8.8)	16 (9.2)	0.894
Intracranial vessel occlusion	192 (64.4)	84 (67.2)	108 (62.4)	0.396
LVO	102 (34.2)	44 (35.2)	58 (33.5)	0.764
MeVO	90 (30.2)	40 (32.0)	50 (28.9)	0.565
TTE characteristics				
LAVI (mL/m^2)	32 (25–40)	42 (38–48)	26 (22–30)	<0.001
AC moderate/severe	64 (21.5)	64 (51.2)	NA	
LVDD grade 2–3	39 (13.1)	37 (29.6)	2 (1.2)	<0.001
LVEF (%)	59 (56–62) [n=285]	58 (55–62) [n=120]	60 (57–63) [n=165]	0.019
LVEF ≤50%	24 (8.0)	12 (9.6)	12 (6.9)	0.404
90-day outcome				
mRS score	1 (0–3) [n=295]	1 (0–3) [n=124]	1 (0–2) [n=171]	0.742
mRS 0–2	215 (72.9)	86 (68.8)	129 (74.6)	0.487
mRS 0–3	251 (85.1)	107 (86.3)	144 (84.2)	0.621
Death	15 (5.0)	5 (4.0)	10 (5.8)	0.747
Long-term follow-up				
Follow-up (mo)	20 (8–32) [n=290]	20 (8–32) [n=123]	20 (8–33) [n=167]	0.848
Implantable loop recorder	52 (17.9)	22 (17.9)	30 (18.0)	0.986
AFDAS	28 (9.7)	21 (17.1)	7 (4.2)	<0.001
Stroke recurrence	17 (5.9)	10 (8.1)	7 (4.2)	0.158

Values are presented as n (%) or median (interquartile range).
ESUS, embolic stroke of undetermined source; AC, atrial cardiopathy; LAVI, left atrial volume index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease; IVT, intravenous thrombolysis; EVT, endovascular treatment; LVO, large vessel occlusion; MeVO, medium vessel occlusion; TTE, transthoracic echocardiography; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; AFDAS, atrial fibrillation detected after stroke.

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Table 3. Univariate and multivariate logistic regression analysis for the association between AC related variables and stroke severity, 90-day functional outcome, and follow-up variables

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Stroke severity*				
+1 point in baseline NIHSS score				
LAVI	1.01 (0.99–1.02)	0.501	1.01 (0.99–1.03)	0.226
AC	1.12 (0.75–1.67)	0.569	1.17 (0.78–1.75)	0.442
Moderate/severe AC	1.01 (0.63–1.62)	0.973	0.92 (0.56–1.49)	0.731
Baseline NIHSS score >5				
LAVI	1.01 (0.99–1.03)	0.515	1.01 (0.98–1.03)	0.525
AC	1.17 (0.74–1.86)	0.493	1.11 (0.63–1.95)	0.715
Moderate/severe AC	1.10 (0.63–1.92)	0.732	0.92 (0.47–1.83)	0.821
90-day functional outcome†				
90-day mRS 0–2				
LAVI	1.00 (0.98–1.02)	0.912	1.02 (0.99–1.05)	0.203
AC	0.92 (0.53–1.57)	0.750	2.48 (0.97–6.31)	0.056
Moderate/severe AC	1.14 (0.59–2.21)	0.699	1.77 (0.76–4.13)	0.184
90-day mRS 0–3				
LAVI	1.00 (0.98–1.03)	0.525	1.04 (0.99–1.08)	0.101
AC	1.18 (0.61–2.28)	0.621	1.60 (0.77–3.30)	0.205
Moderate/severe AC	1.26 (0.55–2.88)	0.578	1.94 (0.65–5.76)	0.234
Follow-up‡				
AFDAS				
LAVI	1.05 (1.02–1.08)	0.001	1.04 (1.01–1.08)	0.009
AC	4.71 (1.93–11.47)	0.001	4.63 (1.77–12.14)	0.002
Moderate/severe AC	3.77 (1.68–8.43)	0.001	3.15 (1.30–7.64)	0.011
Stroke recurrence				
LAVI	1.03 (0.99–1.07)	0.097	1.03 (0.99–1.07)	0.169
AC	2.02 (0.75–5.47)	0.165	1.56 (0.53–4.64)	0.420
Moderate/severe AC	1.14 (0.36–3.63)	0.824	0.88 (0.25–3.03)	0.834

AC, atrial cardiopathy; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; NIHSS, National Institutes of Health Stroke Scale; LAVI, left atrial volume index; mRS, modified Rankin Scale; AFDAS, atrial fibrillation detected after stroke; LVO, large vessel occlusion; MeVO, medium vessel occlusion; AIS, acute ischemic stroke; IVT, intravenous thrombolysis; EVT, endovascular treatment.
*Multivariate analysis adjusted for: site of vessel occlusion (no occlusion/LVO/MeVO) and vascular territory (anterior circulation/posterior circulation/multi-territory); †Multivariate analysis adjusted for: age, female sex, baseline NIHSS score, pre-AIS mRS score >2, site of vessel occlusion (no occlusion/LVO/MeVO) and vascular territory (anterior circulation/posterior circulation/multi-territory), arterial hypertension, diabetes, coronary artery disease, dyslipidemia, acute-phase treatment (IVT alone/EVT alone/IVT+EVT); ‡Multivariate analysis adjusted for: age, female sex, arterial hypertension, diabetes, coronary artery disease, dyslipidemia, obesity, implantable loop recorder.

in ESUS. Finally, the initiation of anticoagulation therapy might have occurred after AFDAS, potentially influencing the observed stroke recurrence rate.

Despite these limitations, our study provides valuable insights for a deeper understanding of the role of AC in ESUS. Although we found an independent association between AC and AFDAS, no significant associations were observed with stroke severity, 90-day outcome, and stroke recurrence. Considering the recent failure of the ARCADIA trial (NCT03192215), our results may prove instrumental in the design of future trials aimed at demonstrating the benefits of anticoagulation therapy in these patients.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.00031.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: ACR, GS, AM, ECA. Study design: ACR, GS. Methodology: ACR, GS, AB, BDC, AM, ECA. Data collection: ACR, GS, AB, ADP, MDP, FA, BDC. Investigation: ACR, GS, AB, BDC. Statistical analysis: ACR, GS. Writing—original draft: ACR, GS. Writing—review & editing: ACR, GS, AB, BDC, AM, ECA, CM. Approval of final manuscript: all authors.

References

1. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke. *Stroke* 2016;47:895-900.
2. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: a mechanism of cryptogenic stroke. *Expert Rev Cardiovasc Ther* 2017;15:591-599.
3. Jalini S, Rajalingam R, Nisenbaum R, Javier AD, Woo A, Pikula A. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology* 2019;92:e288-e294.
4. Jordan K, Yaghi S, Poppas A, Chang AD, Mac Grory B, Cutting S, et al. Left atrial volume index is associated with cardioembolic stroke and atrial fibrillation detection after embolic stroke of undetermined source. *Stroke* 2019;50:1997-2001.
5. Tan BYQ, Ho JSY, Sia CH, Boi Y, Foo ASM, Dalakoti M, et al. Left atrial volume index predicts new-onset atrial fibrillation and stroke recurrence in patients with embolic stroke of undetermined source. *Cerebrovasc Dis* 2020;49:285-291.
6. Diener HC, Easton JD, Hart RG, Kasner S, Kamel H, Ntaios G. Review and update of the concept of embolic stroke of undetermined source. *Nat Rev Neurol* 2022;18:455-465.
7. Sposato LA, Chaturvedi S, Hsieh CY, Morillo CA, Kamel H. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke* 2022;53:e94-e103.
8. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429-438.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-271.
10. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, et al. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke* 2015;46:1488-1493.

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Supplementary Methods

Inclusion criteria

Embolic stroke of undetermined source (ESUS) was defined, according to standard criteria,[1] as a non-lacunar stroke in the absence of (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (2) major-risk cardio-embolic sources of embolism (permanent or paroxysmal atrial fibrillation (AF), sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent [<4 weeks] myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis); and (3) any other specific cause of stroke identified.

All patients underwent a comprehensive minimum diagnostic assessment, as specified in ESUS criteria. This assessment included: brain computed tomography (CT) or magnetic resonance imaging (MRI), 12-lead electrocardiogram (ECG), precordial echocardiography, cardiac monitoring for ≥24 hours with automated rhythm detection, and imaging of both the extracranial and intracranial arteries supplying the area of brain ischemia (catheter, MR or CT angiography, or cervical duplex plus transcranial Doppler ultrasonography).

Exclusion criteria

According to the revised ESUS-construct update,[2] we excluded: (1) patients aged <60 years with high-risk patent foramen ovale (PFO) (clinical and anatomical features), categorized as probably or possibly associated with stroke according to the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system;[3] (2) patients with high-risk (plaque ulceration, endoluminal or mobile thrombus) non-stenosing (<50%) ipsilateral (in an intra- or extracranial artery supplying the ischemic field, including the aortic arch) supra-cardiac atherosclerosis;[4–6] and (3) patients with probable cancer-related hypercoagulability (defined as active cancer with or without other concurrent arterial-venous thrombosis).[7]

Echocardiographic parameters

Transthoracic echocardiography (TTE) was performed on each patient during hospitalization. All tests were conducted, and measurements were acquired in accordance with the American Society of Echocardiography guidelines.[8] All data were reviewed by three cardiologists (AB, BDC, and AM). Parameters such as left atrial (LA) volume, LA volume index (LAVI), left ventricular ejection fraction (LVEF), and LV diastolic function were obtained from previous reports. LV diastolic dysfunction (LVDD) was defined according to the American Society of Echocardiography guidelines,[9] using the mitral valve inflow pattern with pulsed-wave Doppler, e'-wave at tissue Doppler of the lateral and septal mitral annulus, tricuspid regurgitation velocity, and LAVI.

PFO diagnosis

For patients aged <60 years, transcranial Doppler (TCD) was performed, both at rest and during provocative maneuvers using an intravenous injection of agitated saline, to identify the presence of a right-to-left shunt (RLS). Among patients aged ≥60 years, a PFO search was conducted in selected cases. In cases where RLS was detected, patients underwent further evaluation using transesophageal echocardiography (TEE) to confirm the presence of a PFO. TEE was also used to further assess the anatomical characteristics of the shunt, including the presence of an atrial septal aneurysm (ASA). A large shunt was defined as >30 bubbles at rest on TCD[10] and/or >20 bubbles in the left atrium after TEE.[11] In the presence of a PFO, the Risk of Paradoxical Embolism (RoPE)[12] was also calculated. High-risk PFO was defined based on anatomical features (large shunt and/or ASA) and/or clinical features (RoPE score ≥7).[3]

Non-stenosing supra-cardiac atherosclerosis

Head and neck CT angiography images obtained during admission were reviewed for each patient to evaluate the presence of non-stenosing (<50%) supracardiac atherosclerosis in the aortic arch and the intra- or extracranial arteries supplying the ischemic field. The degree of carotid stenosis was determined according to the NASCET criteria (North American Symptomatic Carotid Endarterectomy Trial).[13] High-risk plaque was defined as any ulcerated or "soft" plaque or any plaque with endoluminal thrombus, causing <50% of luminal narrowing in an intra- or extracranial artery supplying the ischemic field, including the aortic arch (ascending aorta or proximal arch).

AF detection after stroke

Atrial fibrillation detected after stroke (AFDAS) was defined as any occurrence of AF detected after a stroke in patients without known AF, excluding AF detected during admission.[14] During admission, each patient underwent a 12-lead ECG and cardiac monitoring for ≥24 hours with automated rhythm detection. Outpatient cardiac monitoring, including Holter monitoring (ranging from 24 hours to 30 days) and/or an implantable loop recorder (ILR), was performed for all patients at the discretion of the treating physician.

Neuroimaging assessment

Brain CT and/or MRI scans were thoroughly reviewed for each patient. Stroke lesions were analyzed based on (1) location (an-

terior circulation, posterior circulation, and multi-territory [both anterior and posterior circulation or bilateral anterior circulation]) and (2) site (cortical [small isolated cortical lesions], cortico-subcortical [lesions located across cortical and subcortical areas], and deep [involving deep white/grey matter such as the corona radiata, basal ganglia, brainstem, and deep cerebellum]). The occlusion site on CT angiography was also recorded, and large vessel occlusions (LVO) were defined as occlusion of the intracranial internal carotid artery, M1, M2-dominant, A1, P1, basilar, and vertebral arteries; meanwhile, medium vessel occlusions (MeVO) were defined as occlusion of the A2, A3, M2 non-dominant, M3, P2, and P3 segments.[15]

Outcomes definition

Stroke severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score, considering either a 1-point increase from the baseline score or an NIHSS score >5. Ninety-day functional status was defined based on the modified Rankin Scale (mRS) score of 0–2 and 0–3. For patients with a pre-ischemic stroke mRS >2 or >3, achievement of mRS 0–2 and 0–3, respectively, was considered in cases of return to baseline mRS. Ischemic stroke recurrence and AFDAS from discharge to the last available follow-up were considered as long-term follow-up outcomes.

Standard protocol approval, registration, and patient consent

This study was approved by the local ethics committee (Comitato Etico Milano Area 3, n. 346-18052022). Upon admission, patients were duly apprised that all data obtained during routine clinical practice would be utilized for research endeavors and subsequently granted their written informed consent. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Statistical analysis

Baseline characteristics, acute-phase therapy, radiological sites of the ischemic lesions, echocardiographic features, and 3-month outcomes were evaluated in the included patients. Differences in variables between the AC(+)/ESUS and AC(-)/ESUS groups were analyzed through univariate analysis (including χ^2, Fisher's exact test, and Wilcoxon-Mann-Whitney test, as appropriate). The association between AC (considered as continuous [LAVI] and dichotomous variable [AC(+) vs. AC(-); moderate/severe AC vs. mild AC/AC(-)]) and various outcomes, such as stroke severity (measured by baseline NIHSS score), 90-day mRS 0–2 and 0–3, stroke recurrence, and AFDAS, was assessed through univariate and multivariate logistic (or ordered logistic, as appropriate) regression analyses. The latter were adjusted for pre-specified baseline variables. The association between AC and stroke severity was adjusted for site of vessel occlusion (no occlusion/LVO/MeVO) and vascular territory (anterior circulation/posterior circulation/multi-territory); 90-day mRS adjusted for age, sex, baseline NIHSS score, pre-AIS mRS score >2, site of vessel occlusion, vascular territory, arterial hypertension, diabetes, coronary artery disease (CAD), dyslipidemia, and acute-phase treatment; stroke recurrence and AFDAS adjusted for age, sex, arterial hypertension, diabetes, CAD, dyslipidemia, obesity, and ILR. Moreover, the association between time to stroke recurrence was evaluated using Kaplan–Meier survival analysis stratified according to the presence of AC. Subsequently, the significance of the differences was evaluated using the log-rank test. Additionally, a sensitivity Kaplan–Meier survival analysis was performed, excluding patients discharged on anticoagulant therapy. Statistical analyses were performed using Stata statistical software (Version 17; StataCorp., College Station, TX, USA). The significance level was set at $P<0.05$.

Supplementary Results

Among the 2,050 patients with acute ischemic stroke admitted to our stroke unit during the study period (between 2018 and 2022), 21.3% (436 patients) were classified as having ESUS. LAVI measurements were available for 95% (414 patients) of ESUS cases, with 22 patients (5%) having no available LAVI due to a poor echo acoustic window. A total of 116 patients (28%) were reclassified and excluded as per the ESUS construct update, resulting in a final cohort of 298 patients with ESUS. A flowchart of the study is shown in Supplementary Figure 1. In the final ESUS cohort (revised criteria), the median age was 71 years (IQR 61–80), the baseline NIHSS score was 5 (IQR 2–11), and 45.6% of the patients were women. Three-months mRS data were available for 295 patients (1% lost at follow-up), with 215 patients (72.9%) achieving an mRS score of 0–2 at 90 days. No significant differences were observed in the location of infarcts (multi-territorial, anterior, or posterior circulation) or intracranial vessel occlusions between AC(+)/ESUS versus AC(-)/ESUS.

Long-term follow-up data were available for 290 patients (3 patients [1.0%] were lost to follow-up and 5 [1.7%] died during the acute phase) (Supplementary Table 1).

Kaplan–Meier analysis (Supplementary Figure 2) revealed no difference in stroke recurrence among patients stratified according to AC (log-rank test, $P=0.149$). Further, we conducted a sensitivity Kaplan–Meier analysis, excluding patients discharged on anticoagulant therapy (n=9 patients), which led to consistent results.

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Supplementary References

1. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429-438.
2. Diener HC, Easton JD, Hart RG, Kasner S, Kamel H, Ntaios G. Review and update of the concept of embolic stroke of undetermined source. *Nat Rev Neurol* 2022;18:455-465.
3. Kent DM, Saver JL, Kasner SE, Nelson J, Carroll JD, Chatellier G, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021;326:2277-2286.
4. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005;58:688-697.
5. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). *Cerebrovasc Dis* 2013;36:1-5.
6. Ntaios G, Wintermark M, Michel P. Supracardiac atherosclerosis in embolic stroke of undetermined source: the underestimated source. *Eur Heart J* 2021;42:1789-1796.
7. Navi BB, Kasner SE, Elkind MSV, Cushman M, Bang OY, DeAngelis LM. Cancer and embolic stroke of undetermined source. *Stroke* 2021;52:1121-1130.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-271.
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321-1360.
10. Spencer MP, Moehring MA, Jesurum J, Gray WA, Olsen JV, Reisman M. Power M-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* 2004;14:342-349.
11. Lao AY, Sharma VK, Tsivgoulis G, Frey JL, Malkoff MD, Navarro JC, et al. Detection of right-to-left shunts: comparison between the International Consensus and Spencer Logarithmic Scale criteria. *J Neuroimaging* 2008;18:402-406.
12. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619-625.
13. Bartlett ES, Walters TD, Symons SP, Fox AJ. Quantification of carotid stenosis on CT angiography. *AJNR Am J Neuroradiol* 2006;27:13-19.
14. Sposato LA, Chaturvedi S, Hsieh CY, Morillo CA, Kamel H. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke* 2022;53:e94-e103.
15. Saver JL, Chapot R, Agid R, Hassan A, Jadhav AP, Liebeskind DS, et al. Thrombectomy for distal, medium vessel occlusions: a consensus statement on present knowledge and promising directions. *Stroke* 2020;51:2872-2884.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453-1457.

Supplementary Table 1. Differences in clinical, radiological and echocardiographic characteristics between ESUS patients classified per traditional versus revised criteria

	Entire ESUS cohort (n=414)	ESUS included 298 (72%)	ESUS excluded 116 (28%)	*P*
Baseline characteristics				
Age (yr)	67 (54–77)	71 (61–80)	52 (44–60)	<0.001
Female sex	184 (44.4)	136 (45.6)	48 (41.4)	0.434
Pre-mRS score	0 (0–0)	0 (0–0)	0 (0–0)	0.181
NIHSS score	5 (2–11) [n=413]	5 (2–11)	3 (2–9) [n=115]	0.004
Prior stroke	43 (10.4)	36 (12.1)	7 (6.0)	0.070
Current smoking	105 (25.4)	73 (24.5)	32 (27.6)	0.516
Hypertension	276 (66.7)	234 (78.5)	42 (36.2)	<0.001
Diabetes	70 (16.9)	59 (19.8)	11 (9.5)	0.012
Dyslipidemia	215 (51.9)	176 (59.1)	39 (33.6)	<0.001
Obesity	79 (19.1)	63 (21.1)	16 (13.8)	0.088
CAD	59 (14.2)	52 (17.4)	7 (6.0)	0.003
Supra-cardiac atherosclerosis	169 (40.8)	136 (45.6)	33 (28.4)	0.001
Acute reperfusion therapy				
IVT	115 (27.8)	85 (28.5)	30 (25.9)	0.587
EVT +/- IVT	141 (34.1)	108 (36.2)	33 (28.4)	0.133
None	220 (53.1)	152 (51.0)	68 (58.6)	0.163
Stroke pattern and location				
Anterior circulation	314 (75.8)	232 (77.8)	82 (70.7)	0.126
Posterior circulation	119 (28.7)	80 (26.8)	39 (33.6)	0.171
Multi-territory	28 (6.8)	21 (7.0)	7 (6.0)	0.713
Cortical (small isolated lesions)	28 (6.8)	19 (6.4)	9 (7.8)	0.615
Cortical-subcortical	346 (83.6)	252 (84.5)	94 (81.0)	0.486
Deep (white/grey) matter	40 (9.7)	27 (9.1)	13 (11.2)	0.507
Intracranial vessel occlusion	254 (61.3)	192 (64.4)	62 (53.4)	0.039
LVO	130 (31.4)	102 (34.2)	28 (24.1)	0.047
MeVO	127 (30.7)	93 (31.2)	34 (29.3)	0.707
TTE characteristics				
AC	150 (36.2)	125 (42.0)	25 (21.5)	<0.001
AC moderate/severe	75 (18.1)	64 (21.5)	11 (9.5)	<0.001
LAVI (mL/m^2)	30 (24–38)	32 (25–40)	27 (21–33)	<0.001
LVDD grade 2–3	46 (11.1)	39 (13.1)	7 (6.0)	0.040
LVEF (%)	59 (56–63) [n=397]	59 (56–62) [n=285]	60 (57–63) [n=112]	0.122
LVEF ≤50%	31 (7.5)	24 (8.0)	7 (6.0)	0.483
Outcome 3-months				
mRS	1 (0–2) [n=411]	1 (0–3) [n=295]	1 (0–2)	<0.001
mRS 0–2	316 (76.9) [n=411]	215 (72.9) [n=295]	101 (87.1)	0.002
Death	22 (5.3)	15 (5.0)	7 (6.0)	0.700
Long-term follow-up				
Follow-up (month)	21 (8–33) [n=405]	20 (8–32) [n=290]	23 (9–35) [n=115]	0.101
Stroke recurrence	21 (5.1)	17 (5.9)	4 (3.4)	0.338

Values are presented as n (%) or median (interquartile range).
ESUS, embolic stroke of undetermined source; AC, atrial cardiopathy; LAVI, left atrial volume index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease; IVT, intravenous thrombolysis; EVT, endovascular treatment; LVO, large vessel occlusion; MeVO, medium vessel occlusion; TTE, transthoracic echocardiography; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; AFDAS, atrial fibrillation detected after stroke.

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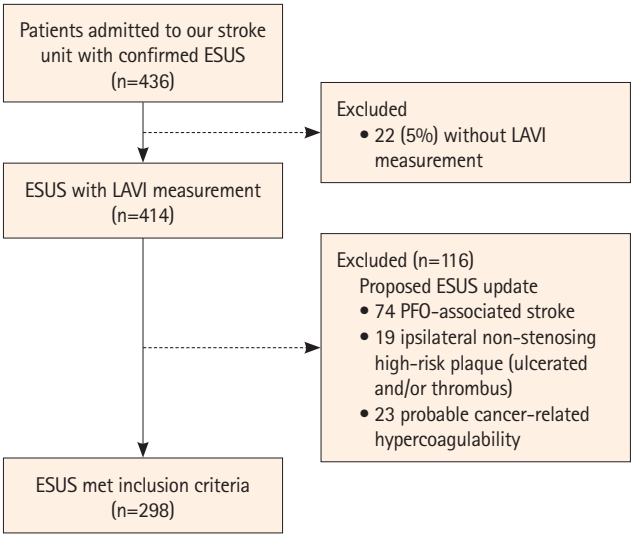
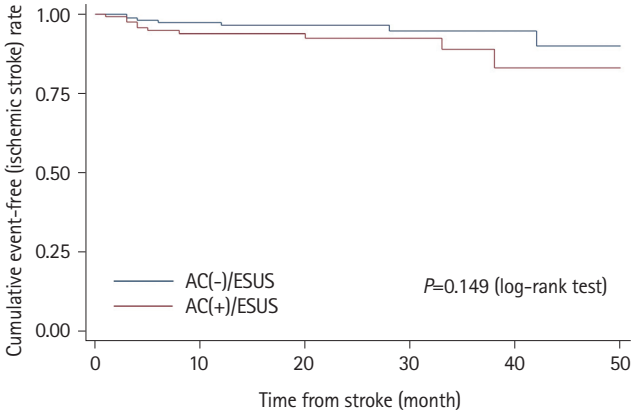


Supplementary Figure 1. Study flowchart. ESUS, embolic stroke of undetermined source; LAVI, left atrial volume index; PFO, patent foramen ovale.



Supplementary Figure 2. Kaplan-Meier survival analysis for risk of ischemic stroke recurrence according to the presence of atrial cardiopathy. AC, atrial cardiopathy; ESUS, embolic stroke of undetermined source.