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Left Atrial Volume Index is Associated with Cardioembolic Stroke and Atrial Fibrillation Detection after ESUS

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Abstract

BACKGROUND AND PURPOSE—Left atrial enlargement has been shown to be associated with ischemic stroke but the association with embolic stroke mechanisms remains unknown. We aim to study the associations between left atrial volume index (LAVI) and embolic stroke subtypes and atrial fibrillation (AF) detection on cardiac event monitoring in patients with embolic stroke of unknown source.

METHODS—Data was collected from a prospective cohort of consecutive ischemic stroke patients admitted to a comprehensive stroke center over 18 months. Stroke subtype was classified

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into cardioembolic stroke (CES), non-cardioembolic stroke of determined mechanism (NCE), or Embolic Stroke of Undetermined Source (ESUS). Univariate and pre-specified multivariable analyses were performed to assess associations between LAVI and stroke subtype and atrial fibrillation (AF) detection in patients with ESUS.

RESULTS—Of 1224 consecutive patients identified during the study period, 1020 (82.6%) underwent transthoracic echocardiography (TTE) and had LAVI measurements. LAVI was greater in patients with CES than NCE (41.4 mL/m2 ± 18.0 versus 28.6 mL/m2 ± 12.2, p < 0.001) but not in ESUS vs. NCE (28.9 mL/m2 ± 12.6 vs. 28.6 mL/m2 ± 12.2, p =0.61). In multivariable logistic regression models, LAVI was greater in CES vs. NCE (adjusted OR per mL/m2 1.07, 95% CI 1.05–1.09, p < 0.001), but not in ESUS vs. NCE (adjusted OR per mL/m2 1.00, 95% CI 0.99–1.02, p = 0.720). Among 99 patients with ESUS who underwent cardiac monitoring, 18.2% had AF detected; LAVI was independently associated with AF detection in ESUS (adjusted OR per mL/m2 1.09, 95% CI 1.02–1.15, p = 0.007).

CONCLUSION—LAVI is associated with cardioembolic stroke as well as AF detection in patients with ESUS, two subsets of ischemic stroke that benefit from anticoagulation therapy. Patients with increased LAVI may be a subgroup where anticoagulation may be tested for stroke prevention.

Keywords

Ischemic stroke; embolic stroke of undetermined source; left atrial volume index; atrial fibrillation; atrial cardiopathy

Introduction

Nearly 30% of ischemic strokes are categorized as cryptogenic[1] many of which are thought to be related to a distant embolic source.[2–4] A subtype of cryptogenic stroke, embolic stroke of undetermined source (ESUS), is used to describe non-lacunar cryptogenic strokes in which embolism is a likely underlying mechanism.[5,6] Recent evidence suggests a relatively high stroke recurrence rates after ESUS, with pooled data from several cohorts showing an annualized rate of 4.5%.[6, 7] Therefore, secondary prevention strategies are essential in reducing the risk of recurrent stroke in ESUS patients.

Left atrial enlargement has been shown to be associated with ischemic stroke[8], stroke recurrence[9], and covert brain infarcts.[10] One limitation of these studies however is that they used left atrial diameter or left atrial index which do not fully represent the true 3-dimensional size of the left atrium. [8, 9, 11, 12] In fact, recent studies have shown that left atrial volume indexed to the subjects body surface area (LAVI) [13, 14] is a superior metric of left atrial dimension in terms of predicting cardiovascular outcomes.[15]

In this study, we aim to determine the association between LAVI and cardioembolic stroke and ESUS subtypes. We furthermore seek to understand the association between LAVI and the detection of AF on outpatient monitoring in ESUS.

Methods

This study was approved by the Lifespan Institutional Review Board. Informed consent was waived as this is a retrospective study. Data from this study are available upon request to the corresponding author.

Study Population

We analyzed data from our prospective ischemic stroke database that included all consecutive patients admitted to Rhode Island Hospital with a diagnosis of ischemic stroke over an 18-month period. All patients underwent standard ischemic stroke evaluation including laboratory testing, neuroimaging, 12-lead EKG, transthoracic echocardiography (TTE), cardiac telemetry monitoring for at least 24 hours. Stroke subtype was prospectively assigned by the inpatient vascular neurology attending based on the ESUS consensus criteria.[5]

Primary Predictor

Our primary predictor was LAVI as measured on TTE. 2-D TTE was performed within 3 months of ischemic stroke onset as part of routine clinical care. Studies were performed by licensed echocardiography technicians and measurements were acquired in accordance with the guidelines of the American Society of Echocardiography.[16] Staff cardiologists at our institution provided measurement of LAVI as part of routine clinical care. In cases where no left atrial volume was reported, two readers (K.J and C.S.) reviewed each TTE and provided LAVI measurements using the biplane method of disks (modified Simpson's rule).[17] To ascertain these measurements, the left atrium was traced in the apical four-chamber and two-chamber views at the level of the mitral valve in end-systole, with care taken to exclude the left atrial appendage and pulmonary veins.

Outpatient Cardiac Event Monitoring & Atrial Fibrillation Detection

As part of routine post-stroke care, patients with cryptogenic stroke underwent 4-week outpatient cardiac event monitoring. The cardiac event monitors were reviewed and reports were generated by staff cardiologists with a subspecialty in electrophysiology. Presence of atrial fibrillation defined as more than 30 seconds of AF detected on event monitoring was extracted for this study.

Covariates

Covariates were extracted from the database including the following – clinical and demographic data including age, sex, history of hypertension, diabetes mellitus, coronary artery disease, prior history of stroke, congestive heart failure, smoking status, and NIHSS score. Laboratory and echocardiogram covariates were also collected including presence of elevated troponin (troponin > 0.1 ng/mL) and left ventricular ejection fraction.

Outcome

The primary outcome of interest was ischemic stroke subtype, which was determined by the primary attending vascular neurologist at time of discharge using the ESUS criteria divided

into three categories: embolic stroke of unknown source (ESUS), cardioembolic (CES), and non-cardioembolic (NCE). Adjudication of stroke subtype in our dataset has previously been described.[18]

Statistical Analysis

Study participants were divided by their ESUS classification. We compared demographic, clinical characteristics, and laboratory data between the two groups using t-tests for continuous variables and fisher tests for categorical variables. To determine the association between LAVI and stroke sub-type we performed a multivariable regression analyses adjusting for covariates with 3 separate pre-specified models. Our first model was adjusted for age and sex. The second model was adjusted for covariates in model 1 plus HTN, HLD, DM, CAD, prior stroke, CHF, smoking, and NIHSS. Our third model adjusted for covariates in model 2 plus left ventricular ejection fraction and troponin level. To assess the association between LAVI and detection of atrial fibrillation in patients with ESUS we performed a multivariate regression analysis adjusting for age. Our analysis was performed using SPSS, version 18.0 (Chicago, IL) using a p-value < 0.05 as statistical significance.

Results

Baseline Characteristics

Over an 18-month period, a total of 1224 consecutive patients with ischemic stroke and stroke subtype adjudicated were included in our cohort for analysis. The mean age in the cohort was 71.1 years, and 53.7% were men. TTE was performed on 1197 patients (97.8%) patients within three months of their stroke diagnosis, with 1020 (85.2%) having LAVI successfully measured. Clinical characteristics between patients with and without LAVI measurement were similar with the exception of prior stroke history (20.9% vs 27.9%, $p = 0.026$) and admission NIHSS (9 ± 8 vs.11 ± 9, $p = 0.049$) (Table 1). The proportion of patients who had LAVI measurement did not differ significantly among stroke subtypes; 84.9% (412/485) in the ESUS group, 83.6% (336/402) in the CES group, and 80.7% (272/337) in the NCE group ($p = 0.273$) (Table 1).

Baseline demographics and clinical characteristics of this cohort are listed in table 2. Within our cohort, stroke subtype frequencies were as follows: 39.6% ESUS (485/1224), 32.8% CES (402/1224), and 27.5% NCE (337/1224).

There were 35 patients (7.2%) with a history of AF who were adjudicated as ESUS subtype. In these patients, it is likely that the AF was self reported and could not be confirmed or the AF history was a remote history or transient following cardiac surgery. In addition, there were 38 patients (11.3%) with self-reported history of AF or chart review evidence of AF history who were adjudicated as non-cardioembolic subtypes (2 adjudicated as hypercoagulability in the setting of malignancy, 16 adjudicated as large artery atherosclerosis, and 20 adjudicated as small vessel disease). This is consistent with previous studies that showed that up to 17% of strokes in patients with a history of AF may be related to a non-cardioembolic mechanism.[19]

Among ESUS subtypes with available LAVI measurement, 24.0% (99/412) completed outpatient cardiac event monitoring. The baseline characteristics between patients with or without cardiac monitoring obtained were similar except for patients being monitored having a lower median NIHSS score (5 vs. 6, p = 0.004).

Association between LAVI and ESUS Stroke Subtype

On univariate analyses, there was no difference in LAVI between patients with ESUS versus those with NCE stroke (28.9 ± 12.6 mL/m^2 vs. 28.6 ± 12.2 mL/m^2, p = 0.61). Multivariable analyses reflected these finding, demonstrating no significant association between ESUS subtypes and LAVI on both unadjusted (Odds Ratio [OR] per mL/m2 increase, 1.00; 95% Confidence Interval [CI], 0.99–1.01; p = 0.844) and fully adjusted models (adjusted OR per mL/m2 increase, 1.00, 95% CI 0.99–1.02, p = 0.720; Table 3).

Association between LAVI and CES Subtype

On univariate analysis of patients with CES vs. NCE there was a statistically significant difference in LAVI between the two groups (41.4 ± 18.0 mL/m^2 versus 28.6 ± 12.2 mL/m^2, p < 0.001). Multivariable analyses also demonstrated greater LAVI were associated with increased odds of having CES subtype compared to NCE subtype (OR per mL/m2 increase, 1.06; 95% CI, 1.05–1.08; p < 0.001). This association persisted across all adjusted models, including those adjusting for elevated troponin and left ventricular ejection fraction (adjusted OR per mL/m2 increase, 1.07; 95% CI 1.05–1.09; p < 0.001; Table 3).

Sensitivity analyses

Since there remains a chance that some of the patients with a history of AF who were not adjudicated as cardioembolic stroke subtype were erroneously adjudicated, we performed sensitivity analyses adding these patients to the cardioembolic stroke category. In these analyses, there was an association between LAVI and cardioembolic stroke (adjusted OR per mL/m2 increase, 1.06; 95% CI, 1.04–1.08; p<0.001) but not ESUS (adjusted OR per mL/m2 increase, 1.01; 95% CI 0.99–1.02; p=0.604).

Multivariable Analysis of Association of AF detection in patients with ESUS subtype

Of the 99 patients with ESUS who completed outpatient cardiac event monitoring, we detected AF in 18 patients (18.2%). Among patients with ESUS subtypes, LAVI was noted to be higher in those with AF detected on outpatient cardiac monitoring compared to those without evidence of AF (33.0 ± 10.1 mL/m^2 vs. 25.5 ± 8.4 mL/m^2, p = 0.001). On multivariable analysis adjusting for age, LAVI was independently associated with AF detection in ESUS (adjusted OR per mL/m2 increase, 1.09; 95% CI, 1.02–1.15; p = 0.007).

Discussion

Our study suggests an association between LAVI and cardioembolic stroke subtype, but not ESUS subtype, when compared to NCE stroke subtypes. We also demonstrate that LAVI is associated with AF detection in ESUS patients who underwent outpatient cardiac event monitoring. These findings highlight the important interplay between left atrial volume, atrial fibrillation, and cardioembolic stroke.

Mechanism of Association

At face value, the association between LAVI and cardioembolic stroke appears intuitive, but the exact mechanism of this association remains unclear. Left atrial enlargement (LAE) is hypothesized to lead to cardioembolic stroke but promoting stasis, endothelial injury, and thrombus formation.[9] In fact, studies showed an association between LAE, spontaneous echocardiographic contrast, and embolic events.[11] Furthermore, as LAVI increases, patients are more likely to develop AF[20] or higher cardiac thromboembolic risk irrespective of AF.[21] In addition, other studies suggest that AF may contribute to left atrial enlargement (LAE), and that reducing AF burden via ablation may cause remodeling and eventual reduction in left atrial size.[22] Furthermore, there is emerging evidence suggesting that atrial dysfunction or "cardiopathy" may itself be an independent cardioembolic stroke risk factor, and AF may not be the only prerequisite for atrial thromboembolism.[23] It is hypothesized that atrial cardiopathy starts with fibrotic changes in the left atrium and these changes over time are a precursor to the development of AF. Atrial fibrosis is best detected by cardiac MRI and was shown to occur more frequently in ESUS vs. non-cardioembolic subtypes.[24] Studies suggest that fibrotic changes of the atrium may be responsible for premature atrial complexes, increased PR interval, and increased p-wave terminal force in V1 on ECG. [21, 25] On the other hand, LAE is likely to be found at a more advanced stage of atrial cardiopathy and co-exist with AF. This fact is highlighted by our finding that LAVI was associated with AF detection in patients with ESUS. In addition, our finding that LAVI was not associated with ESUS is unsurprising due to the heterogeneous nature of ESUS that may include sources of thromboembolism such as patent foramen ovale, non-stenotic atherosclerotic plaques, aortic arch atheroma, and other such etiologies all of which are not associated with LAE.[1]

Clinical Implications

The association between LAE and cardioembolic stroke may serve to improve our risk stratification for cardioembolic stroke risk and may help guide secondary prevention strategies. Recent studies hypothesize that patients with atrial cardiopathy, but not known AF, may benefit from anticoagulation therapy as opposed to current risk stratification models that emphasize AF as a major risk factor for thromboembolic risk and disregard structural and functional abnormalities of the left atrium.[21] Given our findings that LAVI is associated with cardioembolic stroke subtype, anticoagulation therapy may be beneficial for primary stroke prevention in patients with increased LAVI and secondary stroke prevention in patients with ESUS and LAE. Several prospective randomized control trials have sought to understand the efficacy of anticoagulation after ESUS. The Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial demonstrated that rivaroxaban was not superior to aspirin with regarding to prevention of recurrent stroke in ESUS.[26] Furthermore, the Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RESPECT ESUS) trial testing dabigatran vs. aspirin in ESUS patients yielded similar findings. A post-hoc analysis of NAVIGATE ESUS, however, demonstrated a 74% risk reduction in recurrent stroke with rivaroxaban vs. aspirin in patients with ESUS and moderate to severe LAE (HR 0.26 95% CI 0.07 – 0.94).

The Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trial is currently underway and is randomizing patients with cryptogenic stroke and evidence of biomarkers of atrial cardiopathy to either aspirin or apixaban, with the primary endpoint being recurrent stroke or death.[27] The results of the ARCADIA trial will help guide our discussion of anticoagulation in ESUS, a population that remains high risk for stroke recurrence despite current standard of care with antiplatelet therapy.

Strengths and limitations

Our study has several limitations. First our data was extracted from a single-center prospective database, which limits generalizability of our findings. Second, only 24% of ESUS patients completed outpatient cardiac event monitoring, and AF was detected in only 18 of those patients. This association may be limited by the small sample size, and our inability to control for possible confounders between those who completed outpatient cardiac event monitoring and those who did not. Second, AF detection on outpatient event monitoring was defined as AF lasting > 30 seconds in our study which perhaps may be too sensitive in diagnosing clinically significant sub-clinical atrial fibrillation (SCAF). Data from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing (ASSERT) trial demonstrated that patients with SCAF >24 hours had a significantly increased risk of subsequent stroke or systemic embolism (HR 3.24, 1.51–6.95, P=0.003). However those with SCAF lasting 6 min to 24 hours did not have rates of stroke or systemic embolization different from those without SCAF.[28] The patient population enrolled in ASSERT, however, is different from the one in our study and therefore the threshold of AF duration, if any, that warrants anticoagulation therapy after ESUS remains controversial. Third, LAVI measurement was missing on 16.7% of patients. Finally, patients with LAVI measurement demonstrated lower admission NIHSS and less prevalence of prior stroke history compared to those without LAVI measurement. This raises a question whether TTE was deferred in patients with prior stroke because their stroke subtype classification had already been determined and TTE seemed redundant. Patients with higher NIHSS also may have earlier mortality or transition to comfort measures only, which may have precluded the acquisition of TTE.

On the other hand, our study has several strengths, including a large sample size extracted from a prospective ischemic stroke database. In addition, we were able to obtain LAVI measurements for most patients in our database (85.2%) and there was little difference between patients with and without LAVI measurement. Our use of indexed left atrial volume is also a strength, as it has been cited as the most superior method for measuring left atrial dimensions when analyzing cardiac outcomes.[15] This is in contrast to multiple prior studies that analyzed the association between left atrial dimensions and various stroke endpoints using left atrial diameter or area. Lastly, prospective stroke subtype adjudication by attending vascular neurology faculty at our institution provided assurance of data quality.

Conclusions

Our study demonstrates an independent association between LAVI and cardioembolic stroke, as well as an independent association between LAVI and AF detection in ESUS.

These two associations raise the question whether patients with LAE, even in the absence of AF, may benefit from anticoagulation for secondary stroke prevention.

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References

1. McTaggart RA, Yaghi S, Baird G, Haas RA, Jayaraman MV. Decreasing procedure times with a standardized approach to elvo cases. Journal of neurointerventional surgery. 2017;9:2–5 [PubMed: 27402859]
2. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: The pfo-asa study. Atrial septal aneurysm. Stroke. 2002;33:706–711 [PubMed: 11872892]
3. Nah HW, Lee JW, Chung CH, Choo SJ, Kwon SU, Kim JS, et al. New brain infarcts on magnetic resonance imaging after coronary artery bypass graft surgery: Lesion patterns, mechanism, and predictors. Ann Neurol. 2014;76:347–355 [PubMed: 25111072]
4. Sacco RL, Ellenberg JH, Mohr JP, Tatemichi TK, Hier DB, Price TR, et al. Infarcts of undetermined cause: The nincds stroke data bank. Ann Neurol. 1989;25:382–390 [PubMed: 2712533]
5. 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 [PubMed: 24646875]
6. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: A systematic review and clinical update. Stroke. 2017;48:867–872 [PubMed: 28265016]
7. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Vemmou A, Koroboki E, et al. Embolic strokes of undetermined source in the athens stroke registry: An outcome analysis. Stroke. 2015;46:2087–2093 [PubMed: 26159795]
8. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke. 1999;30:2019–2024 [PubMed: 10512901]
9. 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 [PubMed: 25908460]
10. Yaghi S, Bartz TM, Kronmal R, Kamel H, Gottdiener J, Longstreth WT, Jr., et al. Left atrial diameter and vascular brain injury on mri: The cardiovascular health study. Neurology. 2018;91:e1237–e1244 [PubMed: 30158157]
11. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The framingham heart study. Circulation. 1995;92:835–841 [PubMed: 7641364]
12. Karas MG, Devereux RB, Wiebers DO, Whisnant JP, Best LG, Lee ET, et al. Incremental value of biochemical and echocardiographic measures in prediction of ischemic stroke: The strong heart study. Stroke. 2012;43:720–726 [PubMed: 22207511]
13. Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, et al. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. Mayo Clin Proc. 2004;79:1008–1014 [PubMed: 15301328]
14. Russo C, Jin Z, Liu R, Iwata S, Tugcu A, Yoshita M, et al. La volumes and reservoir function are associated with subclinical cerebrovascular disease: The cabl (cardiovascular abnormalities and brain lesions) study. JACC Cardiovasc Imaging. 2013;6:313–323 [PubMed: 23473112]

15. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of cardiovascular outcomes with left atrial size: Is volume superior to area or diameter? J Am Coll Cardiol. 2006;47:1018–1023 [PubMed: 16516087]
16. Picard MH, Adams D, Bierig SM, Dent JM, Douglas PS, Gillam LD, et al. American society of echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr. 2011;24:1–10 [PubMed: 21172594]
17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463 [PubMed: 16376782]
18. Yaghi S, Chang AD, Ricci BA, Jayaraman MV, McTaggart RA, Hemendinger M, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. Stroke. 2018;49:121–126 [PubMed: 29167390]
19. Kim SJ, Ryoo S, Kwon S, Park YK, Kim JP, Lee GY, et al. Is atrial fibrillation always a culprit of stroke in patients with atrial fibrillation plus stroke? Cerebrovascular diseases (Basel, Switzerland). 2013;36:373–382
20. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997;96:2455–2461 [PubMed: 9337224]
21. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: A mechanism of cryptogenic stroke. Expert review of cardiovascular therapy. 2017;15:591–599 [PubMed: 28718666]
22. Wozakowska-Kaplon B Changes in left atrial size in patients with persistent atrial fibrillation: A prospective echocardiographic study with a 5-year follow-up period. Int J Cardiol 2005;101:47–52 [PubMed: 15860382]
23. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: Time for a new model. Stroke. 2016;47:895–900 [PubMed: 26786114]
24. Fonseca AC, Alves P, Inacio N, Marto JP, Viana-Baptista M, Pinho EMT, et al. Patients with undetermined stroke have increased atrial fibrosis: A cardiac magnetic resonance imaging study. Stroke. 2018;49:734–737 [PubMed: 29371431]
25. Kamel H, Hunter M, Moon YP, Yaghi S, Cheung K, Di Tullio MR, et al. Electrocardiographic left atrial abnormality and risk of stroke: Northern manhattan study. Stroke. 2015;46:3208–3212 [PubMed: 26396031]
26. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med. 2018;378:2191–2201 [PubMed: 29766772]
27. Kamel H, Longstreth WT Jr., Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, et al. The atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: Rationale and methods. Int J Stroke. 2019;14:207–214 [PubMed: 30196789]
28. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in assert. Eur Heart J. 2017;38:1339–1344 [PubMed: 28329139]

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Table 1

Clinical characteristics of patients with and without LAVI measured

	LAVI measured	No LAVI measured	
	N = 1020	**N = 204**	**p-value**
Age (mean ± SD)	70.9 ± 15.0	72.4 ± 15.0	0.188
Sex (% men)	555 (54.4%)	102 (50%)	0.249
Hypertension (%)	780 (76.4%)	151 (74.0%)	0.454
Diabetes (%)	287 (28.1%)	60 (29.4%)	0.712
Hyperlipidemia (%)	501 (49.1%)	105 (51.5%)	0.539
CAD (%)	219 (21.5%)	43 (21.1%)	0.901
Prior Stroke (%)	213 (20.9%)	57 (27.9%)	**0.026**
CHF (%)	115 (11.3%)	20 (9.8%)	0.540
Current Smoker (%)	183 (17.9%)	43 (21.1%)	0.292
NIHSS (mean ± SD)	9.05 ± 8.39	10.55 ± 9.44	**0.049**

Table 2.

Baseline characteristics based on stroke subtype

	ESUS (n= 485)	CES (n= 402)	NCE (n= 337)
TTE Completed (%)	**412 (84.9%)**	**336 (83.6%)**	**272 (80.7%)**
Covariates			
Age (mean ± SD)	68.1 ±15.5	76.8 ±12.9	68.7 ± 14.6
Sex (% men)	252 (52.0%)	201 (50.0%)	204 (60.5%)
Hypertension (%)	353 (72.8%)	333 (82.8%)	245 (72.7%)
Diabetes (%)	143 (29.5%)	99 (24.6%)	105 (31.2%)
Hyperlipidemia (%)	234 (48.2%)	214 (53.2%)	158 (46.9%)
Atrial Fibrillation (%)	35 (7.2%)	272 (67.7%)	38 (11.2%)
Coronary Artery Disease (%)	91 (18.8%)	110 (27.4%)	61 (18.1%)
History of Stroke (%)	99 (20.4%)	93 (23.1%)	78 (23.1%)
Congestive Heart Failure (%)	36 (7.4%)	78 (19.4%)	21 (6.2%)
Current Smoker (%)	100 (20.6%)	50 (12.4%)	76 (22.6%)
Elevated Troponin (%)	53 (12.0%)	64 (17.3%)	17 (5.5%)
NIHSS (mean ± SD)	8.6 ± 8.1	12.1 ± 9.5	6.99 ± 7.2
LAVI (mean ± SD)	28.9 ±12.6	41.4 ± 18.0	28.6 ± 12.2
EF (mean ± SD)	62.0 ± 9.9	58.6 ± 13.8	62.6 ± 9.8

Table 3 -

Multivariate Model Showing Association between LAVI and Stroke Sub-Type

	CES*		ESUS*	
	OR (95% CI)	**P-Value**	**OR (95% CI)**	**P-Value**
Unadjusted	1.06 (1.05–1.08)	< 0.001	1.00 (0.99–1.01)	0.844
Model 1	1.06 (1.04–1.07)	< 0.001	1.00 (0.99–1.02)	0.582
Model 2	1.06 (1.04–1.07)	< 0.001	1.00 (0.99–1.01)	0.981
Model 3	1.07 (1.05–1.09)	< 0.001	1.00 (0.99–1.02)	0.720

*Compared with NCE stroke

Model 1: Adjusted for age, sex, and LAVI. Model 2: adjusted for model 1 plus HTN, HLD, DM, CAD, prior stroke, CHF, smoking, NIHSS. Model 3: Adjusted for model 2 plus ejection fraction and troponin.