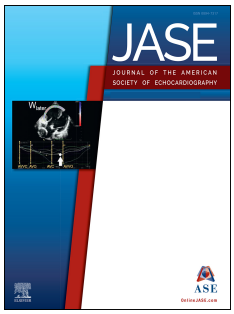
Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Journal Pre-proof



Diagnostic And Prognostic Value Of Left Atrial Function In Identification Of Cardioembolism And Prediction Of Outcomes In Patients With Cryptogenic Stroke

Aditya Bhat, MBBS, BMedSc, MPH, DDU, FRACP, Henry H.L. Chen, MBBS, BMedSc, FRACP, Shaun Khanna, MBBS, MMed, Vipul Mahajan, MBBS, Arnav Gupta, MD, Camelia Burdusel, RN, Nigel Wolfe, BSc (Med), MBBS, FRACP, Lina Lee, MBBS, BSc, MSc, FRACP, Gary C.H. Gan, MBBS, BSc, FRACP, Timothy Dobbins, BMath, PhD, C. Raina MacIntyre, MBBS, FRACP, FAFPHM, M App Epid, PhD, Timothy C. Tan, MBBS, BSc, PhD, FRACP

PII: S0894-7317(22)00291-7

DOI: https://doi.org/10.1016/j.echo.2022.05.018

Reference: YMJE 4976

To appear in: *Journal of the American Society of Echocardiography*

Received Date: 28 September 2021

Revised Date: 15 May 2022

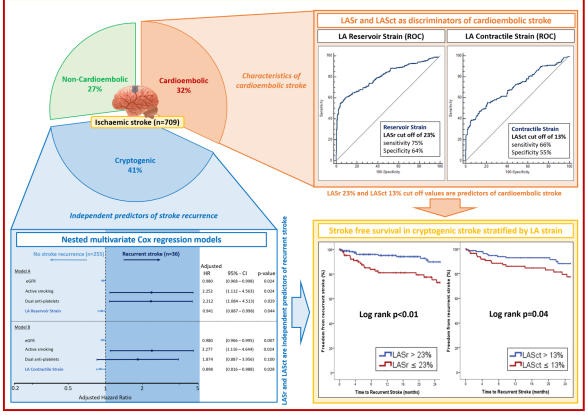
Accepted Date: 23 May 2022

Please cite this article as: Bhat A, Chen HHL, Khanna S, Mahajan V, Gupta A, Burdusel C, Wolfe N, Lee L, Gan GCH, Dobbins T, MacIntyre CR, Tan TC, Diagnostic And Prognostic Value Of Left Atrial Function In Identification Of Cardioembolism And Prediction Of Outcomes In Patients With Cryptogenic Stroke, *Journal of the American Society of Echocardiography* (2022), doi: https://doi.org/10.1016/j.echo.2022.05.018.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

2022 Published by Elsevier Inc. on behalf of the American Society of Echocardiography.

CENTRAL ILLUSTRATION: Diagnostic and prognostic value of left atrial function in identification of cardioembolism and prediction of outcomes in patients with cryptogenic stroke.



Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

DIAGNOSTIC AND PROGNOSTIC VALUE OF LEFT ATRIAL FUNCTION IN IDENTIFICATION OF CARDIOEMBOLISM AND PREDICTION OF OUTCOMES IN PATIENTS WITH CRYPTOGENIC STROKE

Aditya Bhat MBBS, BMedSc, MPH, DDU, FRACP [a,b,c], Henry H.L. Chen MBBS, BMedSc, FRACP [a], Shaun Khanna MBBS, MMed [a], Vipul Mahajan MBBS [a], Arnav Gupta MD [a], Camelia Burdusel RN [d], Nigel Wolfe BSc (Med), MBBS, FRACP [d], Lina Lee MBBS, BSc, MSc, FRACP [d], Gary C.H. Gan MBBS, BSc, FRACP [a,b,c], Timothy Dobbins BMath, PhD [b], C. Raina MacIntyre MBBS, FRACP, FAFPHM, M App Epid, PhD [b], Timothy C. Tan MBBS, BSc, PhD, FRACP [a,b,c]

a. Department of Cardiology, Blacktown Hospital, Sydney, NSW 2148, Australia
b. School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW 2052, Australia
c. School of Medicine, Western Sydney University, Sydney, NSW 2148, Australia
d. Stroke, Rehabilitation & Aged Care Services, Blacktown Hospital, Sydney, NSW 2148, Australia

Corresponding Author: Professor Timothy C. Tan,
Department of Cardiology,
Blacktown Hospital, 18 Blacktown Road,
Blacktown, NSW 2148, Australia
Phone: +61 402 075 550
Fax: +612 8078 3800
Email: timothy.tan9@gmail.com

Article Type: Original article

Tables / Figures: 8 Tables / Figures

Word count: Body with references (6076 words) and abstract (265 words)

References: 39

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

ABSTRACT

Diagnostic and prognostic value of left atrial function in identification of cardioembolism and prediction of outcomes in patients with cryptogenic stroke.

Background: Strokes of undetermined source, commonly termed cryptogenic stroke (CS), account for a significant proportion of ischemic stroke etiology and have high rates of stroke recurrence. The heterogeneous etiology of CS makes decisions regarding treatment for such patients challenging. We sought to evaluate the diagnostic and prognostic value of left atrial (LA) function in identification of cardioembolism and prediction of outcomes in patients with CS.

Methods: Consecutive patients admitted to our tertiary institution with ischemic stroke or transient ischemic attack (TIA) who underwent transthoracic echocardiography were recruited with comprehensive evaluation of LA metrics including LA strain. Ischemic strokes / TIAs were classified as non-cardioembolic, cryptogenic and cardioembolic. A total of 709 patients (66.0±15.1 years, 55% male) were recruited. 291 patients had CS, 189 had non-cardioembolic stroke and 229 had cardioembolic stroke. Patients with CS were followed for 20.0±13.8 months for recurrent ischemic stroke / TIA.

Results: Receiver-operating characteristic curves showed LA reservoir (LASr) and contractile (LASct) strains to be strong discriminators of cardioembolic strokes and log rank tests showed both measures to be significantly associated with the distribution of time to recurrent ischemic stroke / TIA in patients with CS. Multivariable hazards models showed LASr and LASct to be independent predictors of recurrent ischemic stroke / TIA in CS patients in addition to eGFR and active smoking.

Conclusions: LASr and LASct were strong discriminators of cardioembolic stroke and independently predicted recurrent ischemic stroke / TIA in patients with CS. Use of LA strain may improve risk stratification and decision-making in patients with CS, with particular regards to prolonged ambulatory heart rhythm monitoring and/or empiric anticoagulation.

Key Words: Stroke; Cardioembolism; Echocardiography; Heart Atria; Prognosis.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

INTRODUCTION

Ischemic stroke is the leading cause of severe long-term disability and one of the largest contributors to mortality globally (1). It can be classified according to the *Trial of ORG 10172 in Acute Stroke Treatment* (TOAST) classification system, and the corresponding secondary prevention and treatment plan is given according to its etiology (2). However, about one third of acute ischemic strokes have no identified etiology after standardized evaluation and are commonly identified as 'cryptogenic' stroke (CS) (3).

CS comprise a large proportion of all ischemic strokes and are associated with a high rate of recurrence (4-6). These strokes are thought to be due to sources of uncertain risk, including occult paroxysmal atrial fibrillation, other cardioembolic sources, undiagnosed malignancy, arteriogenic emboli, and paradoxical emboli through interatrial shunting (8). The CS population has significant etiological heterogeneity and given the differential etiology and thus mechanism of stroke development, broad initiation of anticoagulation in this group for secondary stroke prevention has not been found to be beneficial and has evidence of harm (8,9). The challenge remains in identification of the subset of CS patients with a cardioembolic source of stroke, who would most benefit from anticoagulation rather than anti-platelet therapies.

With advances in technology, novel markers of LA function are now able to be measured using echocardiography and as such represent a potential source of differentiation between cardioembolic and non-cardioembolic etiologies of CS. Assessment of early LA dysfunction via measurement of LA strain is now appreciable using speckle-tracking echocardiography (STE), a novel technique for characterization and quantification of myocardial deformation. Small mechanistic studies have demonstrated alterations in LA strain in patients with CS without traditional cardiovascular risk factors when compared to age-matched healthy controls, suggestive of tissue substrate as a causative factor of stroke development and biomarker of cardioembolic stroke risk (10,11).

We hypothesise that impaired LA function as assessed by reduced LA strain is associated with cardioembolic stroke subtypes and provides independent predictive value above traditional echocardiographic and clinical factors for prediction of recurrent ischemic strokes and transient ischemic attacks (TIA) in CS patients.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study population and design. In this retrospective analysis of prospectively collected data, consecutive patients admitted to our institution between 1st January 2016 to 1st January 2020 with a clinical and/or radiological diagnosis of ischemic stroke or TIA who underwent transthoracic echocardiography were appraised. An ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction which required the presence of ischemic brain injury on radiologic investigation whereas a transient ischemic attack was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without evidence of acute infarction on radiologic investigation (12).

Patients over 18 years of age with ischemic stroke or TIA were targeted for recruitment. The primary diagnosis of ischemic stroke / TIA was adjudicated by the patient's treating stroke physician. Stroke classification was then performed in accordance with the TOAST classification system by two independent clinicians blinded to the patient's novel echocardiographic data or the initial classification at diagnosis based on information available from the index hospitalization. Exclusionary criteria included patients with non-stroke condition as a primary diagnosis, valvular heart disease including presence of prosthetic heart valves or moderate and greater mitral stenosis, or those without a transthoracic echocardiogram with adequate quality images available as part of their stroke workup (**Figure 1**).

Informed consent was obtained from all subjects, with consent by next of kin or guardian obtained for patients who were cognitively incapacitated or unconscious. The study protocol was approved by the Western Sydney Local Health District Human Research and Ethics Committee.

Included patients underwent detailed clinical history and physical examination and were investigated with computed tomography and/or magnetic resonance imaging of the brain, as well as vascular imaging of the aortic arch, neck and cerebral vessels performed with either computed tomographic angiography, magnetic resonance angiography or carotid duplex sonography. Diagnosis of acute ischemic stroke via computed tomography was based on the loss of grey-white matter differentiation and presence of cortical hypo-attenuation whereas magnetic resonance imaging criterion included that of an increased diffusion weight imaging signal with a low apparent diffusion coefficient.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Resting electrocardiography was performed at admission and all patients underwent at least 24 hours of telemetry monitoring. Included patients also underwent comprehensive transthoracic echocardiography and a subset (n=167, 23.6%) underwent transesophageal echocardiography. In the event of a finding of patent foramen ovale, blinded clinicians utilised the Risk of Paradoxical Embolism score (13) to determine the probability of causality with the index stroke event. A total of 123 patients (17.3%) had assessment of hypercoagulability via collection of serum pathology. Management strategies on discharge, in particular the use of anti-platelet agents, anticoagulants, statins, anti-hypertensives, and vasoactive medications were also recorded.

For the purposes of the study, participants were segregated into three groups (cardioembolic, non-cardioembolic and CS) based upon the independent stroke classification performed in accordance with the TOAST criteria (2). Cardioembolic strokes were defined to include patients with arterial occlusions presumed to be due to an embolus arising in the heart. Non-cardioembolic strokes included those with strokes / TIA secondary to small vessel occlusion, large artery atherosclerosis and strokes of other determined etiology. CS was defined as those classified to have stroke of undetermined etiology.

A total of 709 patients (mean age 66.0±15.1 years, 55% male) were recruited which was comprised of 291 patients (mean age 63.1±14.6 years, 54% male) with CS, 189 patients (mean age 63.2±14.7 years, 55% male) with non-cardioembolic stroke and 229 patients (mean age 72.1±14.3 years, 56% male) with cardioembolic stroke. **Figure 2** demonstrates the breakdown of patient groups in the study population.

Enrolled patients with CS were followed up for up to two years for the primary outcome of recurrent ischemic stroke / TIA. This was defined as a new neurological deficit befitting the definitions for ischemic stroke / TIA, occurring after a period of neurological stability or improvement lasting ≥ 24 hours and not attributable to peri-infarctional edema, mass effect, or hemorrhagic transformation of the index cerebral infarct. Clinical data was censored following development of the primary outcome or if the patient died. Adverse events were corroborated from hospital, specialist physician and general practitioner medical records.

Transthoracic echocardiogram. Transthoracic echocardiography was performed using commercial ultrasound systems (EPIQ, Philips Medical Systems, Andover, MA; GE-E95, GE Healthcare, Milwaukee, WI), in keeping with recommendations of the American Society of Echocardiography (14).

LV end-diastolic and end-systolic volumes were obtained and LV ejection fraction (LVEF) was calculated by the Simpson's biplane method. Normal LVEF was defined as ≥54% for women and ≥52% for men. LV mass was calculated using the Devereux formula and indexed to body

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

surface area (BSA) to derive the indexed LV mass (LVMI). LV hypertrophy was defined as LVMI of ≥95 g/m^2 for females and ≥115 g/m^2 for males (14).

Diastolic function was evaluated from transmitral E and A velocities, E/A ratio, average of the septal and lateral annular e' velocity, E/e', peak tricuspid regurgitant velocity, and indexed LA volume (LAVI). Diastolic grade was evaluated as per current guidelines (15). Biplane LA volume was evaluated from apical 4- and 2-chamber views by the area-length method and indexed to body surface area (14). LA emptying volume was determined by the difference between LA maximum and LA minimum volume, and LA emptying fraction (LAEF) was calculated by the LA emptying volume divided by the LA maximum volume.

Speckle-tracking echocardiography. Two-dimensional speckle tracking strain analysis was performed offline using vendor independent software (TomTec Arena, Germany v4.6).

For LV global longitudinal strain (GLS), the LV endocardium was traced at end-systole in the three apical views. An 18-segment LV model (6 segments in each apical view) was obtained and GLS was calculated as the average of the 18 segments of the left ventricle (16).

For LA strain, the endocardium of the left atrium was manually traced at end-systole with automatic tracking throughout the cardiac cycle using R-to-R gating with LV strain software. The left atrium was divided into six segments (basal, mid-, and apical segments) in the apical 4- and 2-chamber views. LA reservoir strain (LASr) was the average of the peak systolic strain from 12 segments, LA contractile strain (LASct) the peak positive strain following the p wave (representative of atrial contraction) and LA conduit strain (LAScd) was the difference between the peak reservoir and contractile strain (16).

Intra- and inter-observer variability. Intra- and inter-observer variability were assessed by repeating LASr and LASct in 5% of the study population chosen at random from the cohort at least one month apart by the same investigator and by a second independent investigator. The investigators had independently selected and analysed different loops from 3 cardiac cycles for each subject.

Statistical analysis. Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). All tests were 2-tailed with a p-value <0.05 considered statistically significant. Continuous variables were presented as mean ± standard deviation and categorical variables were presented as number and percentage. Differences between groups was evaluated by Students T tests or its non-parametric equivalent the Mann Whitney test for continuous variables and chi-square analyses for categorical variables. Comparison of multiple groups were assessed by Chi-squared trend tests for ordered categorical variables

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

and one-way ANOVA with Bonferroni correction or its non-parametric equivalent, the Kruskal-Wallis test, for continuous variables.

Receiver operating characteristic (ROC) curves and the area under the curve (AUC) was used to quantify the global performance of LA strain and other echocardiographic parameters of interest in discriminating cardioembolic stroke. DeLong tests were used for pairwise comparisons of the AUC. A discriminatory cut-off was derived from this analysis and used to dichotomize the population.

Log rank tests were used to test for univariable associations between clinical and echocardiographic variables and distributions of time to the primary outcome. Time to adverse outcomes from baseline assessment were graphically illustrated using Kaplan-Meier estimates of the associated survival distributions. Multivariable Cox proportional hazards models were used to identify the independent predictors of the study outcome in a backward stepwise manner. Variables were first tested for proportional hazards assumption with time-dependent Cox regression. Variables with $p<0.05$ on univariable analysis were considered as candidates for inclusion in the models. Collinearity assessment was undertaken with regression collinearity diagnostics. The estimated hazard ratios (HR) and their 95% confidence intervals (95% CI) were used to quantify the strength of the associations.

RESULTS

Study population. At enrolment, of the total study cohort (709 patients), 158 (22%) patients had ischemic heart disease, 48 (7%) had heart failure and 147 (21%) had atrial fibrillation. There was an expected prevalence of modifiable cardiovascular risk factors in the cohort with 284 (40%) patients having comorbid diabetes mellitus, 487 (69%) with hypertension and 358 (50%) with hypercholesterolemia. 190 (27%) patients were active smokers, and 235 (33%) patients were obese with a calculated body mass index of ≥ 30 kg/m^2.

Cardioembolic versus non-cardioembolic stroke groups. Of the 229 patients with cardioembolic strokes, 147 (64%) had a history of atrial fibrillation and 54 (24%) had evidence of atrial fibrillation on resting electrocardiography captured during hospitalization. Overall, patients with cardioembolic strokes were older with a higher prevalence of ischemic heart disease and heart failure ($p<0.01$ for both) (**Table 1**). These patients also had a lower estimated glomerular filtration rate (eGFR) ($p<0.01$), lower hemoglobin levels ($p=0.01$) as well as lower total cholesterol and LDL-C levels ($p<0.01$ for both). Of the modifiable cardiovascular risk factors, a higher proportion of hypertension ($p=0.05$) and lower proportion of active smokers ($p<0.01$) were observed amongst patients with cardioembolic strokes. No difference

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

was noted in the proportion of comorbid diabetes mellitus (p=0.84) and hypercholesterolemia (p=0.70) between groups. Further, patients with cardioembolic strokes were more likely to receive beta-blockers (p<0.01) and anticoagulant therapy (p<0.01) while patients with non-cardioembolic strokes showed greater use of angiotensin converting enzyme inhibitors / angiotensin II receptor blockers (p<0.01) and dual anti-platelet therapy (p<0.01). Lipid-lowering therapy was prescribed in similar rates between groups.

On echocardiography, patients with cardioembolic strokes had larger LV end-systolic volumes, lower LVEF, greater LVMI and lower LVGLS (p<0.01 for all). These patients also had higher LV filling pressures reflected by a higher E/e ratio (p<0.01), higher rates of diastolic dysfunction (p<0.01) and decreased right ventricular systolic function with lower tricuspid annual plane systolic excursion (TAPSE) and tissue Doppler–derived tricuspid lateral annular systolic velocity (S') (p<0.01 for both). Differences in LA metrics were also present and are further discussed in the section entitled LA mechanics.

Cardioembolic vs CS groups. Compared to patients with cardioembolic stroke, CS patients were younger (p<0.01) with higher body mass index (p=0.02) (**Table 1**). These patients were less likely to have ischaemic heart disease, heart failure and hypertension (p<0.01 for all). They also had better renal function as reflected by higher eGFR, higher haemoglobin levels, higher total cholesterol levels and LDL-C levels (p<0.01 for all). There was lower use of beta-blockers (p<0.01) and anticoagulants (p<0.01) amongst CS patients but higher rates of dual anti-platelet therapy (p<0.01) compared to patients with cardioembolic stroke.

On echocardiography, patients with CS strokes had smaller LV end-systolic volumes, higher LVEF, smaller LVMI and higher LVGLS (p<0.01 for all). These patients also had lower LV filling pressures, lower rates of diastolic dysfunction (p<0.01) and better right ventricular systolic function with higher tricuspid annual plane systolic excursion (TAPSE) and tissue Doppler–derived tricuspid lateral annular systolic velocity (S') (p<0.01 for both). The differences in LA metrics between groups are further discussed in the section entitled LA mechanics.

CS versus non-cardioembolic stroke groups. Apart from lower diastolic blood pressures in patients with CS, there was no major differences in the baseline demographics and comorbidities between CS and non-cardioembolic stroke patients (**Table 1**). CS patients were less likely to receive beta-blockers (p=0.01), angiotensin converting enzyme inhibitors / angiotensin II receptor blockers (p=0.03) and dual anti-platelet therapy (p=0.03) compared to non-cardioembolic stroke patients. There was no difference in hematology and biochemistry parameters between groups including eGFR and lipid profiles.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Similarly, no major differences were observed in LV metrics on echocardiography, including LV volumes, LV mass or parameters of LV systolic and diastolic function including LVGLS. There was also no difference in right ventricular parameters between groups.

LA mechanics. Compared to patients with CS and non-cardioembolic strokes, patients with cardioembolic strokes had evidence of greater LA structural remodelling with larger LAVI ($p<0.01$). These patients also had greater LA functional remodelling as reflected by lower LAEF ($p<0.01$) and lower LASr, LAScd and LASct ($p<0.01$ for all) (**Table 1**).

Of interest, though there was no difference in LA volumes (LAVI; $p=0.73$) and conventional parameters of LA mechanical function (LAEF; $p=0.14$), patients with CS were observed to have reduced LA reservoir and contractile function when compared to non-cardioembolic strokes, with lower LASr ($p=0.05$) and LASct ($p=0.04$).

To evaluate the clinical utility of LASr and LASct in discriminating cardioembolic strokes from non-cardioembolic strokes, we computed ROC curves of LASr and LASct and compared it to LAVI and LVGLS. This showed both LASr and LASct to be significant discriminators of cardioembolic stroke (**Figure 3**). A threshold LASr value of 23% yielded a sensitivity of 75% and specificity of 64% in discriminating cardioembolic strokes while a threshold LASct value of 13% had a sensitivity of 66% and specificity of 55% in discriminating cardioembolic strokes. DeLong tests showed the AUC for LASr to be significantly higher than the AUC for LAVI and LVGLS. The AUC for LASct was significantly higher than the AUC for LVGLS but was comparable to the AUC for LAVI.

Predictors of recurrent stroke / TIA in patients with CS. A total of 285 CS patients were followed up over a mean follow-up period of 20.03±13.81 months; 6 patients died during their index hospitalization and therefore could not be followed up. During the follow-up period, 36 (12.6%) CS patients developed the primary endpoint of recurrent ischemic stroke / TIA with 12 TIAs and 24 radiologically confirmed ischemic strokes. To determine factors associated with the endpoint, we divided CS patients into two groups based on those who suffered recurrent ischemic stroke / TIA and those who were free of events (**Table 2**). Those who suffered events were more likely to be active smokers ($p=0.05$) with lower eGFR ($p=0.04$) and lower LASr ($p=0.01$) and LASct ($p=0.01$).

Based on the discriminatory cut-off for LASr and LASct of 23% and 13%, 38% of patients with CS had impaired LASr and 43% had impaired LASct at baseline. This proportion was significantly higher in those who experienced recurrent stroke / TIA with 66% with impaired LASr and 62% with impaired LASct (**Figure 4**). On log rank tests, LASr ($p<0.01$) and LASct ($p=0.04$) using the discriminatory cut-offs was significantly associated with the distribution of time to the primary composite outcome (**Figure 5**). Other significant univariate predictors

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

included older age (p=0.03), reduced eGFR (p<0.01), active smoking (p=0.02), elevated LDL-C (p=0.01) and use of dual anti-platelet therapy on discharge from index hospitalization (p=0.03).

Using the univariate predictors of the composite outcome identified on log rank tests, we performed multivariable Cox regression analysis (**Table 3**). No variables violated the assumption of proportional hazards. To avoid overfitting, we performed 'nested' models with clinical variables (Model 1a and 1b) followed by independent clinical and echocardiographic variables (Model 2). Separate models were performed for LASr (Model 2a) and LASct (Model 2b). There was no collinearity between variables in the models assessed with all variation inflation figures <2 on collinearity diagnostics. In addition to eGFR and active smoking which are known factors associated with vascular thrombosis and stroke, LASr and LASct were independent predictors of recurrent stroke / TIA in CS patients.

To assess the predictive value of LASr and LASct, we repeated log rank tests using the current guideline recommended lower limit of normal reference value of 26.1% and 7.7% (17) which similarly showed freedom from recurrent ischemic stroke / TIA to be significantly lower in patients with LASr and LASct below these cut-off values (**Supplementary Figure 1**).

LA strain in patients with non-cardioembolic strokes and cardioembolic strokes. To assess the clinical utility of LA strain in non-cardioembolic and cardioembolic strokes, we performed survival analysis using a similar approach to CS patients.

Over the mean follow-up period, 15 (8%) patients with non-cardioembolic stroke suffered recurrent ischemic stroke / TIA. Significant univariate associations of the primary endpoint included age (p=0.01), previous stroke (p=0.03) and E/e' (p=0.03). Of note, metrics of LA size and function including LA strain (LASr, p=0.54; LAScd, p=0.75; LASct, p=0.07) did not show a significant association. Given the small number of events, multivariable analysis was not able to be performed.

Amongst patients with cardioembolic strokes, 25 (11%) patients suffered recurrent ischemic stroke / TIA over the mean follow-up period. Increased LAVI (p=0.01) and reduced LASr (p=0.02) were both associated with the primary endpoint on log rank tests. On multivariable Cox regression analysis, LASr (HR 0.94, 95% CI 0.88 – 1.00, p=0.03) had an independent association with recurrent ischemic stroke / TIA after adjusting for LAVI.

Intra- and inter-observer variability. Reproducibility of these measurements was represented by the intraclass correlation coefficient and coefficient of variation using the logarithmic method. For intraobserver LASr measurements, the intraclass correlation was 0.97 (95% CI 0.95 to 0.98) with a coefficient of variation of 5.6% (95% CI 4.6 to 6.6). For

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

interobserver LASr measurements, the intraclass correlation was 0.94 (95% CI 0.91 to 0.96) with a coefficient of variation of 7.9% (95% CI 6.5 to 9.3). For intraobserver LASct measurements, the intraclass correlation was 0.98 (95% CI 0.96 to 0.99) with a coefficient of variation of 5.8% (95% CI 4.8 to 6.8). For interobserver LASct measurements, the intraclass correlation was 0.96 (95% CI 0.79 to 0.99) with a coefficient of variation of 8.5% (95% CI 7.0 to 10.0).

DISCUSSION

In this study, we identified anatomical cardiac substrates associated with cardioembolic stroke subtypes and evaluated the prognostic role of these substrates with regards to ischemic stroke / TIA recurrence in patients with CS. LASr and LASct were both strong discriminators of cardioembolic stroke beyond conventional LA volumetric parameters. In addition to established clinical associates of ischemic stroke / TIA, both measures also demonstrated independent predictive value for recurrence of ischemic stroke / TIA in patients with CS. The findings of our study add evidence to the growing body of work implicating adverse LA remodelling in the pathogenesis of ischemic stroke and atrial fibrillation, two disease states which share a complex causal relationship.

LA strain as a discriminator of cardioembolic stroke. Previous studies have shown an association between elevated LA volumes and impaired LV systolic function in cardioembolic stroke subtypes when compared to those with non-cardioembolic strokes (18-20). In our study we appreciated that LASr had incremental value over LAVI and LVGLS in discrimination of cardioembolic strokes, suggestive of its greater sensitivity in identification of this stroke subtype. We also found that LASct had superior discriminatory value when compared to LVGLS and was comparable to LAVI. These findings were similar to that of the I-LASER study which also demonstrated an association between reduced LA reservoir and contractile functions and cardioembolic stroke subtypes (21).

LAVI is an established echocardiographic parameter of adverse LA remodelling and has shown prognostic value across normal and diseased populations (22). Its derived volumetric indices, such as LAEF, provide quantification of LA mechanical functional however like LAVI have lower sensitivity in detection of LA dysfunction in early disease states when compared to LA strain (23-25). In keeping with these studies, our findings suggest myocardial LA analysis using STE represents an earlier window into the pathological stresses and extent of LA remodelling than volumetric changes, adding incremental value as a cardioembolic disease state biomarker in patients with ischemic stroke / TIA.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

LA strain in CS. Further supportive of its role as an early disease state biomarker, alterations in LA strain have also been appreciated in the CS population. Mechanistic studies have found reductions in LA strain in young patients with CS when compared to age and risk-factor matched controls (10,11), suggesting early subclinical changes to the left atrium in this population without primary causative risk factors. Other studies, including the I-LASER study (21) and work by Sade et al. (26), have evaluated the utility of LA strain in differentiation of stroke subtypes. Sade and investigators had found a relationship between reduced LASr and cryptogenic and embolic strokes of undetermined source, independent of measures of LA size and stroke risk algorithms such as the CHA_2DS_2VASc score. We similarly found reductions in LASr and LASct in our CS population compared to those with non-cardioembolic strokes. Although this finding was not apparent in the I-LASER study, we speculate that this may be secondary to the larger sample size in our study which lends itself to greater statistical power to detect these differences between groups.

Reduced LA strain has been associated with LA wall fibrosis (27) and shown to be a predictor of incident atrial fibrillation in the CS population, with studies finding incremental prognostic value above traditional clinical risk factors and echocardiographic parameters of left heart size and function (28-30). Occult paroxysmal atrial fibrillation has been proposed to be the cause of a significant proportion of cryptogenic ischemic strokes (31), however lacks temporality with embolic events (32) and has associations with non-cardioembolic stroke subtypes (33). Taken together, these findings suggest atrial fibrillation may act as a risk marker for stroke development rather than a pure causative factor. Emerging evidence has implicated a thrombogenic atrial substrate, often termed ‘atrial cardiopathy’, as a direct causative factor for ischemic stroke / TIA in addition to its role in promotion and maintenance of atrial fibrillation (33). Assessment of hard endpoints such as recurrent ischemic stroke / TIA in the CS population may therefore provide insight into at-risk patients with atrial cardiopathy without diagnosed comorbid atrial fibrillation.

LA strain as a predictor of recurrent ischemic stroke / TIA. To the best of our knowledge, this is the first study to show an association between impaired LA strain and prediction of recurrent ischemic stroke / TIA in patients with CS.

Our findings are in keeping with the published literature and bear biological plausibility. Studies have found an association between impaired LA strain and LA appendage stasis and thrombus formation in patients with atrial fibrillation (34) and acute ischemic stroke (35). Further, studies have found an association with LAVI and stroke recurrence in general ischemic stroke populations (36,37), however have yet to assess this end-point in CS and non-atrial fibrillation populations. Moreover, as mentioned earlier, LAVI is a late measure of

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

LA remodelling and therefore lacks sensitivity in those with atrial cardiopathy with early LA dysfunction. Interestingly, we found LA strain also predicted stroke recurrence in patients with cardioembolic stroke but not those with non-cardioembolic strokes, again suggestive of pathophysiological differences in stroke mechanisms between the two groups.

Similar to previous reports (38,39), active smoking and lower eGFR both showed independent prognostic value for ischemic stroke / TIA recurrence in patients with CS. Interestingly, dual antiplatelet therapy demonstrated an independent association to ischemic stroke / TIA recurrence in the nested model with LASr. We postulate that this may be related to physician choice for dual antiplatelet therapy in patients deemed to have possible higher thrombotic risk than those discharged on single anti-platelet therapy.

Clinical implications. Transthoracic echocardiography is a routine part of diagnostic evaluation of ischemic stroke / TIA and represents a potential tool in the differentiation of stroke etiology. Use of LA strain imaging via STE may therefore identify CS patients who would most benefit from prolonged ambulatory heart rhythm monitoring and anticoagulation initiation for secondary stroke prevention.

Limitations. Transthoracic echocardiography represents standard practice in near all patients admitted with a diagnosis of stroke / TIA at our institution. While this represents routine care, we acknowledge that inclusion of only patients with available transthoracic echocardiography may result in selection bias. In our study, we utilised standard 2- and 4-chamber views, rather than focused views, of the left atrium, which may represent a limitation for strain determination. Further, 53 patients were excluded due to low-quality echocardiographic images which did not allow for accurate LA strain measurement. Thirdly, given the observational nature of the trial, the investigative and management algorithms of the study participants was based on the discretion of their treating physician which may lead to variability in rates of transesophageal echocardiography, hypercoagulability screening and use of anti-platelet and anticoagulant regimens which poses a potential bias in the study. Further, stroke classification was performed based on information available from the index hospitalization by blinded clinicians; there is a potential for misclassification as information outside the hospitalization that was not available to the investigators could not be considered. Additionally, although all patients underwent 24 hours of telemetry monitoring, with most having 72 hours, this may be insufficient to exclude atrial fibrillation. Finally, utilised cut-off values for prediction of stroke recurrence were derived from this population; further studies are required in different independent populations to assess predictive capacity in these populations.

Despite these limitations, the study has several strengths. Firstly, our study includes a large sample size extracted from a prospective ischemic stroke database. Secondly, stroke subtype

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

adjudication was performed by independent clinicians blinded to the patient's novel echocardiographic data providing assurance of data quality. Finally, blinding of patient information to investigators involved in measuring parameters of cardiac size and function as well as test-retest between different investigators of the measured parameters helped ensure internal validity and reliability of the study findings.

CONCLUSIONS

Reduced LASr and LASct is associated with cardioembolic stroke subtypes and provides independent predictive value above traditional echocardiographic and clinical risk factors for prediction of recurrent ischemic stroke / TIA in patients with CS. Use of LA strain may improve risk stratification and decision-making in patients with CS, with particular regards to prolonged ambulatory heart rhythm monitoring and/or empiric anticoagulation.

Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

REFERENCES

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18:439-458.
2. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
3. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol. 2015;14:903-913.
4. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32:2735-40.
5. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31:1062-8.
6. 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;46:2087-93.
7. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke: Research and Practice. Circ Res. 2017;120:527-540.
8. 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.
9. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med. 2019;380:1906–1917.
10. Bhat A, Khanna S, Chen HH, Lee L, Gan CH, Negishi K, et al. Impairment of left atrial function and cryptogenic stroke: Potential insights in the pathophysiology of stroke in the young. Int J Cardiol Heart Vasc. 2019;26:100454.
11. Pirinen J, Järvinen V, Martinez-Majander N, Sinisalo J, Pöyhönen P, Putaala J. Left Atrial Dynamics Is Altered in Young Adults With Cryptogenic Ischemic Stroke: A Case-Control Study Utilizing Advanced Echocardiography. J Am Heart Assoc. 2020;9:e014578.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

12. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013; 44:2064-89.
13. 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.
14. 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. J Am Soc Echocardiogr. 2015;28:1-39.e14.
15. 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. J Am Soc Echocardiogr. 2016;29:277-314.
16. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018;19:591-600.
17. Sugimoto T, Robinet S, Dulgheru R, Bernard A, Ilardi F, Contu L, et al; NORRE Study. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging. 2018;19:630-638.
18. 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.
19. Kamel H, Okin PM, Merkler AE, Navi BB, Campion TR, Díaz I, et al. Relationship between left atrial volume and ischemic stroke subtype. Ann Clin Transl Neurol. 2019;6:1480-1486.
20. Shaikh Q, Ahmed B, Ahmed M, Mahar JH, Ahmad M, Ahmed A, et al. Left atrial volumes and associated stroke subtypes. BMC Neurol. 2013;13:149.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

21. Johansen MC, Doria de Vasconcellos H, Nazarian S, Lima JAC, Gottesman RF. The Investigation of Left Atrial Structure and Stroke Etiology: The I-LASER Study. J Am Heart Assoc. 2021; 10:e018766.
22. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014;63:493-505.
23. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, et al. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr. 2011;24:898-908.
24. Morris DA, Parwani A, Huemer M, Wutzler A, Bekfani T, Attanasio P, et al. Clinical significance of the assessment of the systolic and diastolic myocardial function of the left atrium in patients with paroxysmal atrial fibrillation and low CHADS(2) index treated with catheter ablation therapy. Am J Cardiol. 2013;111:1002-11.
25. Morris DA, Takeuchi M, Krisper M, Köhncke C, Bekfani T, Carstensen T, et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. Eur Heart J Cardiovasc Imaging. 2015;16:364-72.
26. Sade LE, Keskin S, Can U, Çolak A, Yüce D, Çiftçi O, et al. Left atrial mechanics for secondary prevention from embolic stroke of undetermined source. Eur Heart J Cardiovasc Imaging. 2022;23:381-391.
27. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging. 2010;3:231-9.
28. Pagola J, González-Alujas T, Flores A, Muchada M, Rodriguez-Luna D, Seró L, et al. Left atria strain is a surrogate marker for detection of atrial fibrillation in cryptogenic strokes. Stroke. 2014;45:e164-6.
29. Pathan F, Sivaraj E, Negishi K, Rafiudeen R, Pathan S, D'Elia N, et al. Use of Atrial Strain to Predict Atrial Fibrillation After Cerebral Ischemia. JACC Cardiovasc Imaging. 2018;11:1557-1565.
30. Deferm S, Bertrand PB, Churchill TW, Sharma R, Vandervoort PM, Schwamm LH, et al. Left Atrial Mechanics Assessed Early during Hospitalization for Cryptogenic Stroke Are Associated with Occult Atrial Fibrillation: A Speckle-Tracking Strain Echocardiography Study. J Am Soc Echocardiogr. 2021;34:156-165.
31. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al; Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366:120-9.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

32. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation. 2014;129:2094-9.
33. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke. 2016;47:895-900.
34. Providência R, Faustino A, Ferreira MJ, Gonçalves L, Trigo J, Botelho A, et al. Evaluation of left atrial deformation to predict left atrial stasis in patients with non-valvular atrial fibrillation - a pilot-study. Cardiovasc Ultrasound. 2013;11:44.
35. Kim D, Shim CY, Hong GR, Kim MH, Seo J, Cho IJ, et al. Clinical Implications and Determinants of Left Atrial Mechanical Dysfunction in Patients With Stroke. Stroke. 2016;47:1444-51.
36. 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;46:1488-93.
37. Ogata T, Matsuo R, Kiyuna F, Hata J, Ago T, Tsuboi Y, et al. Left Atrial Size and Long-Term Risk of Recurrent Stroke After Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 2017;6:e006402.
38. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 2016;15:913–24.
39. Dong K, Huang X, Zhang Q, Yu Z, Ding J, Song H. A lower baseline glomerular filtration rate predicts high mortality and newly cerebrovascular accidents in acute ischemic stroke patients. Medicine (Baltimore). 2017;96(5):e5868.

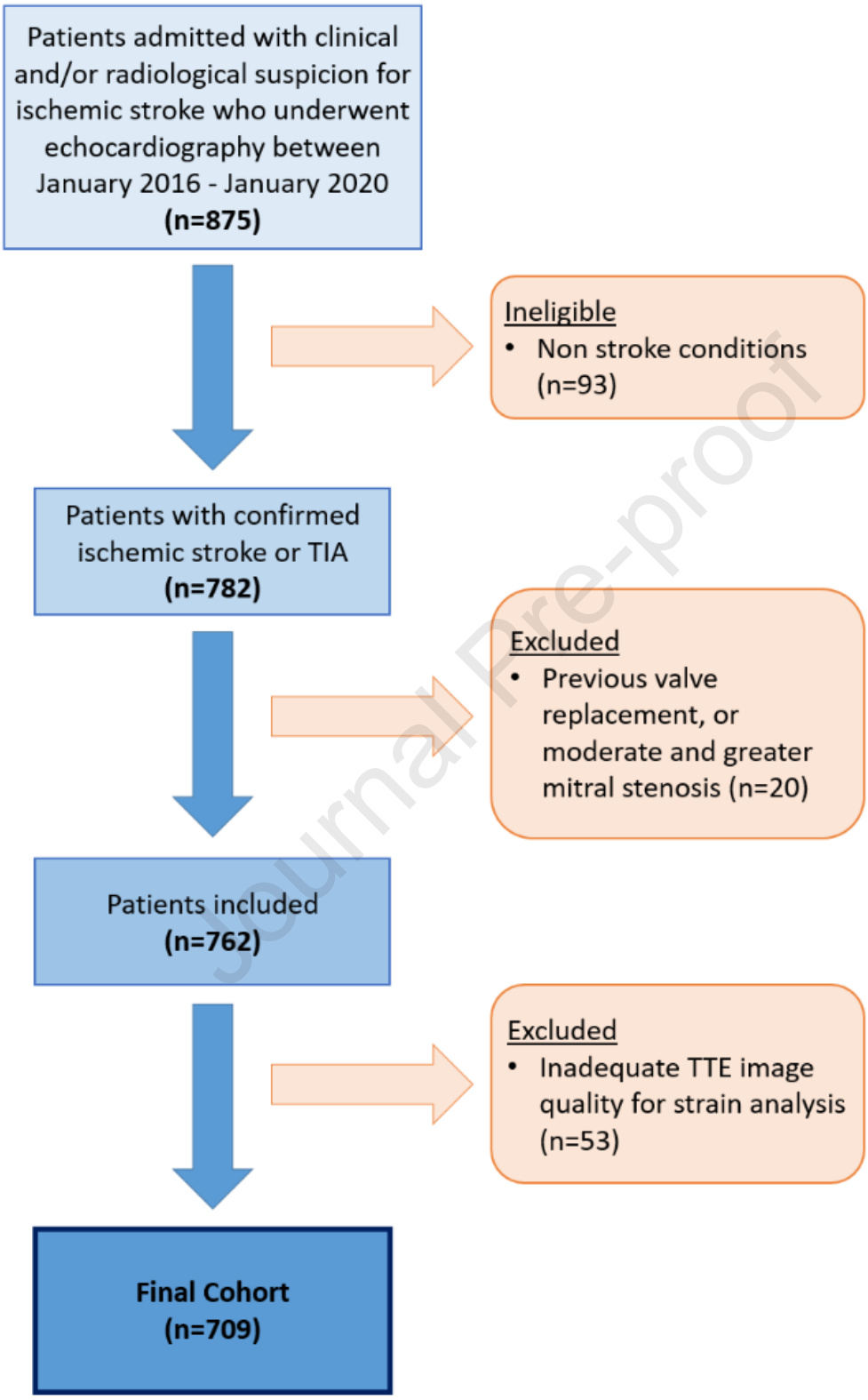
Sources of support: Dr Aditya Bhat is supported through the Australian Government Research Training Program Scholarship.

Conflicts of interest: None.

Acknowledgement: We would like to thank the staff of the Departments of Cardiology, Neurology and Aged Care at Blacktown Hospital for their support in facilitating this project. We would also like to extend our sincere gratitude to our chief cardiac sonographer Fernando Fernandez and his team without whom this project would not have been possible.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Figure 1. Study pathway.

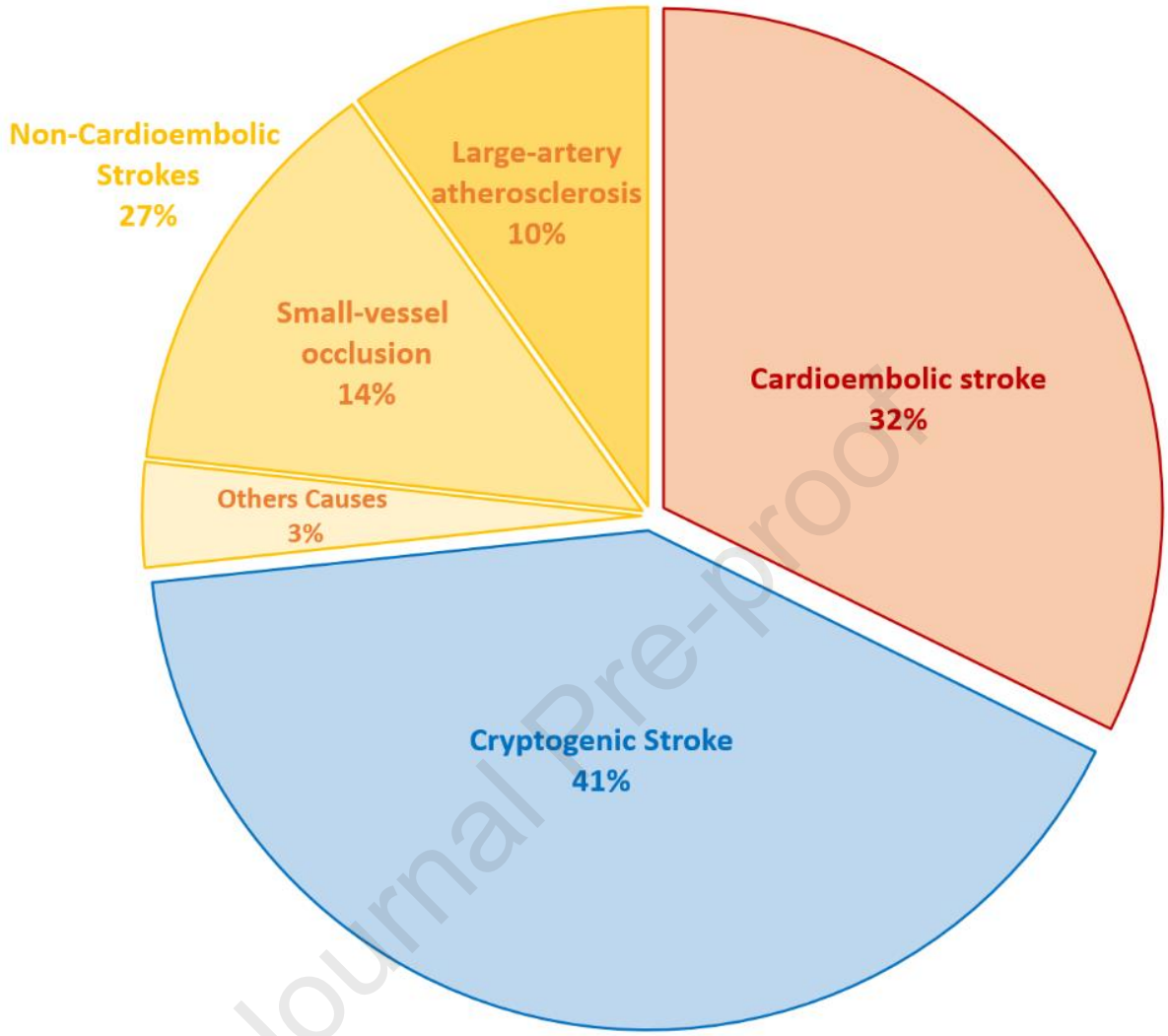


Of 875 patients screened, 709 patients met eligibility criteria and were included.

*Abbreviations: TIA = transient ischemic attack; TTE = transthoracic echocardiography.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

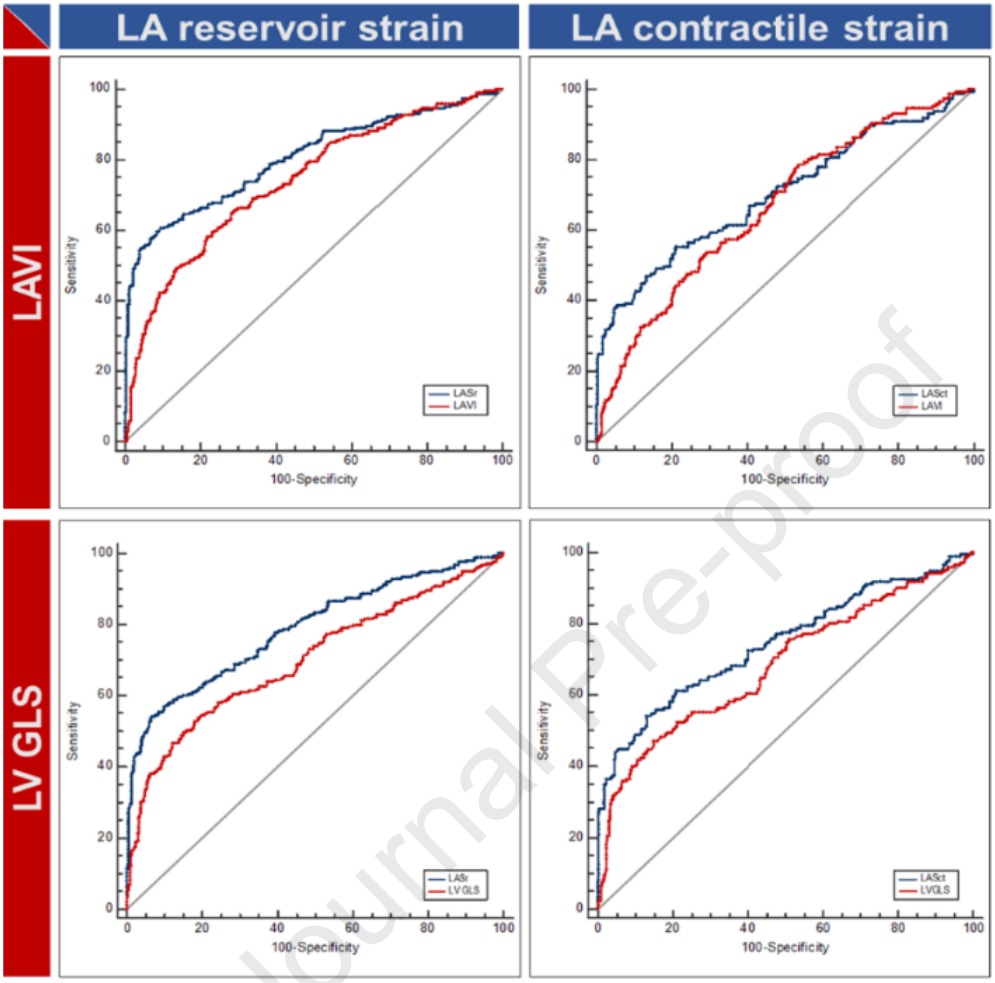
Figure 2. Study cohort.



Stroke subtype in the study cohort was classified by the TOAST classification system.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Figure 3. Receiver operating characteristic curves of LASr and LASct compared to LAVI and LVGLS in discrimination of cardioembolic stroke.



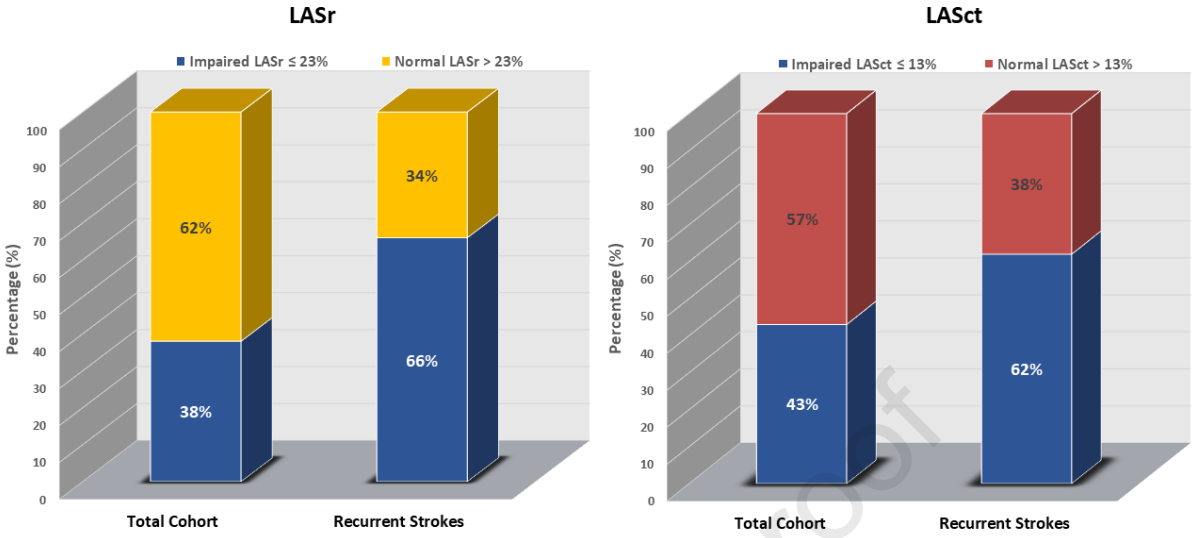
Variable	AUC	SE	95% CI	Sig (p-value)
LASr	0.804	0.020	0.772 – 0.833	p < 0.001
LAVI	0.730*	0.021	0.696 – 0.763	p < 0.001
LVGLS	0.684*	0.024	0.646 – 0.719	p < 0.001

Variable	AUC	SE	95% CI	Sig (p-value)
LASct	0.702	0.028	0.664 – 0.741	p < 0.001
LAVI	0.730	0.021	0.696 – 0.763	p < 0.001
LVGLS	0.684*	0.024	0.646 – 0.719	p < 0.001

LASr and LASct were found to be significant discriminators of cardioembolic stroke. DeLong tests showed the AUC for LASr to be significantly higher than the AUC for LAVI and LVGLS. The AUC for LASct was significantly higher than the AUC for LVGLS but was comparable to the AUC for LAVI. *p<0.01 compared to ROC curve of LASr and LASct on DeLong test. *Abbreviations: LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAVI = left atrial volume index; LV GLS = left ventricular global longitudinal strain.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Figure 4. LA Strain Dichotomized by Stroke Recurrence in CS

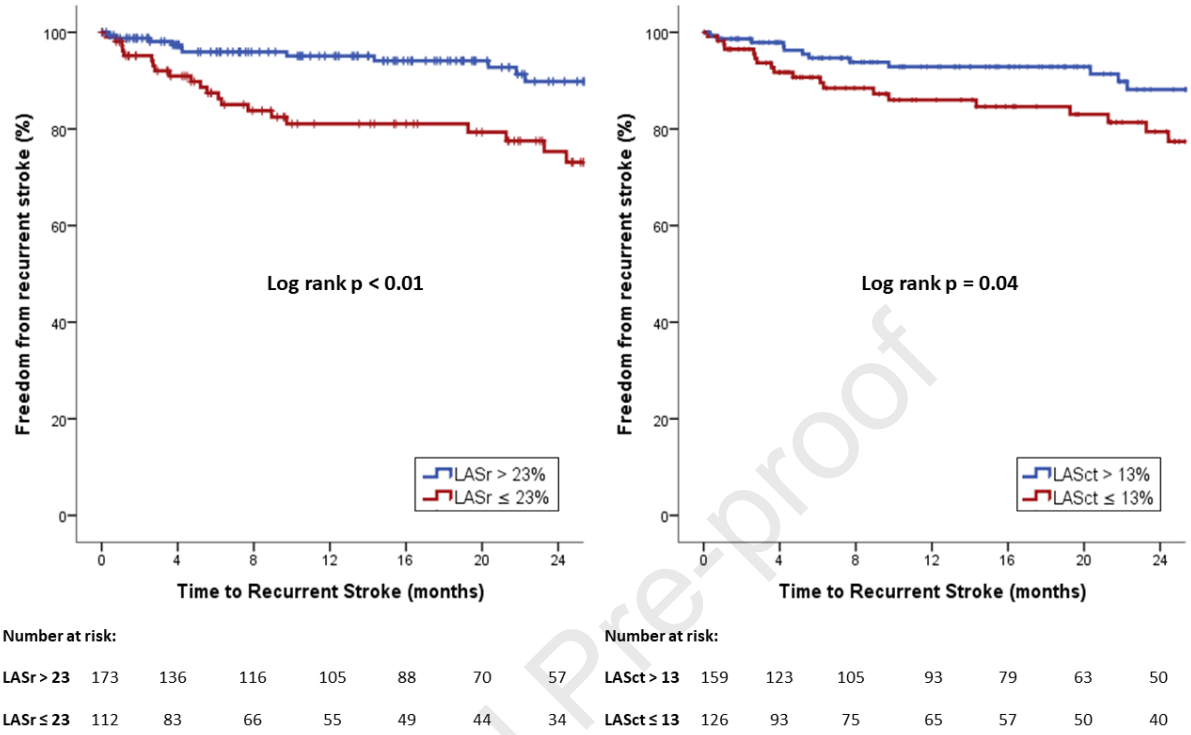


Based on the discriminatory cut-off for LASr and LASct of 23% and 13%, 38% of patients with cryptogenic stroke had impaired LASr and 43% had impaired LASct at baseline. This proportion was significantly higher in those who experienced recurrent stroke with 66% with impaired LASr and 62% with impaired LASct. *Abbreviations: LASct = left atrial contractile strain; LASr = left atrial reservoir strain.

Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

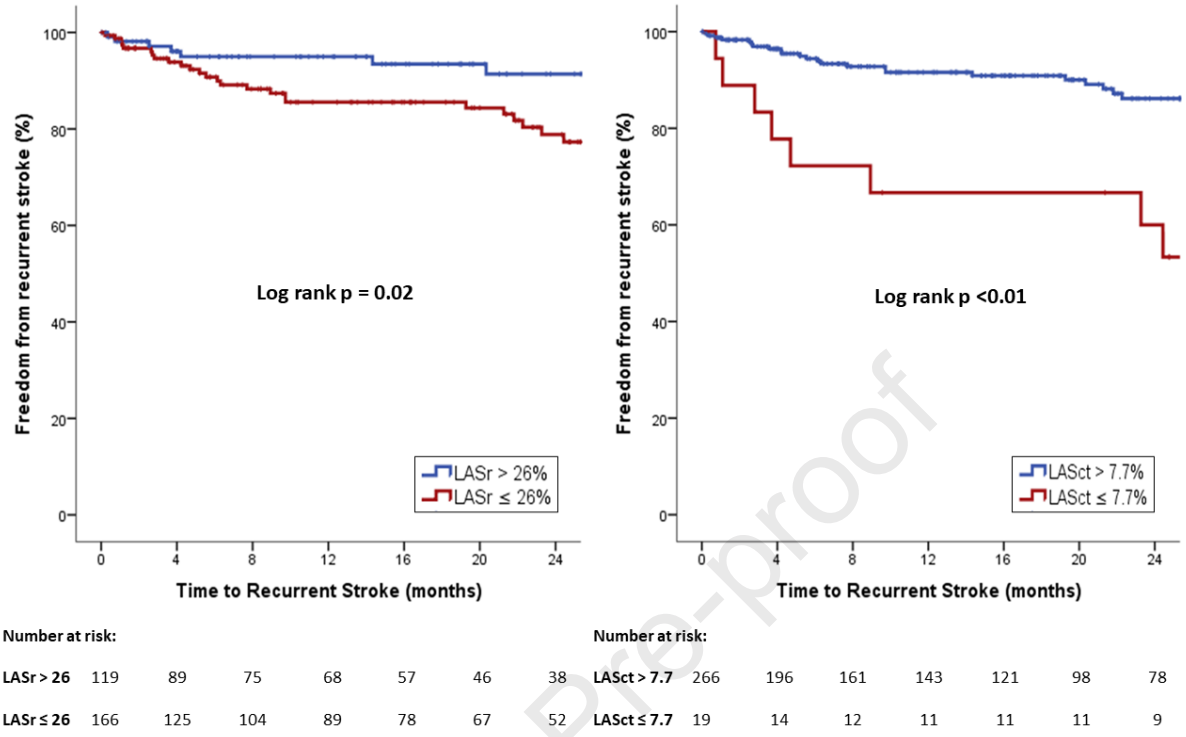
Figure 5. Kaplan Meier curve of LASr and LASct for recurrent ischemic stroke / TIA based on ROC discriminatory cut-offs.



Kaplan Meier curve evaluating freedom from recurrent ischemic stroke / TIA in patients with CS based on dichotomised discriminatory cut-off values of LASr and LASct established from the receiver operating characteristic curves. A reduction in freedom from recurrent ischemic stroke / TIA as a measure of time can be appreciated with LASr ≤23.0% and LASct ≤13.0%. *Abbreviations: LASct = left atrial contractile strain; LASr = left atrial reservoir strain.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Supplementary Figure 1. Kaplan Meier curve of LASr and LASct for recurrent ischemic stroke / TIA based on established normal cut-off values.



Kaplan Meier curve evaluating freedom from recurrent ischemic stroke / TIA in patients with CS based on dichotomised established normal cut-off values of LASr and LASct. A reduction in freedom from recurrent ischemic stroke as a measure of time can be appreciated with LASr ≤ 26.1% and LASct ≤ 7.7%. *Abbreviations: LASct = left atrial contractile strain; LASr = left atrial reservoir strain.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Table 1: Clinical and Echocardiographic characteristics

Variable	Non-cardioembolic stroke (n=189)	CS (n=291)	Cardioembolic stroke (n=229)	Sig (p value)
Demographics				
Age, mean (SD), yrs	63.2 (14.7)	63.1 (14.5)	72.1 (14.3)*°	<0.01
Male sex, n (%)	105 (55)	157 (54)	126 (56)	0.94
BMI, mean (SD), kg/m^2	28.6 (5.9)	29.3 (6.3)	27.9 (6.1)	0.05
SBP, mean (SD), mmHg	145.7 (28.5)	147.6 (26.7)	154.7 (27.5)*	<0.01
DBP, mean (SD), mmHg	84.0 (15.6)	80.5 (14.7)*	81.2 (17.7)	0.05
HR, mean (SD), bpm	76.0 (16.6)	76.0 (15.0)	78.7 (19.7)	0.17
Comorbidities and pharmacotherapy				
Ischemic heart disease, n (%)	35 (19)	45 (16)	78 (34)*°	<0.01
Heart failure, n (%)	3 (2)	8 (3)	37 (16)*°	<0.01
Atrial fibrillation	NA	NA	147 (64)	<0.01
Previous stroke, n (%)	33 (18)	49 (17)	53 (23)	0.13
Hypertension, n (%)	128 (68)	185 (64)	174 (76)*°	<0.01
Hypercholesterolemia, n (%)	99 (52)	144 (50)	115 (50)	0.82
Diabetes mellitus, n (%)	80 (42)	109 (38)	94 (41)	0.59
Peripheral vascular disease, n (%)	11 (6)	13 (5)	9 (4)	0.67
Obesity, n (%)	60 (32)	107 (37)	68 (30)	0.20
OSA, n (%)	6 (3)	8 (3)	7 (3)	0.82
Active smoking, n (%)	61 (32)	83 (29)	46 (20)*	0.02
Beta Blocker, n (%)	43 (23)	40 (14)	107 (46)*°	<0.01
ACEi/ARB, n (%)	113 (60)	142 (49)	93 (41)*	<0.01
Dual anti-platelets, n (%)	73 (39)	83 (29)	23 (10)*°	<0.01
Anticoagulation, n (%)	15 (8)	17 (6)	126 (55)*°	<0.01
Statin, n (%)	163 (86)	243 (84)	182 (80)	0.31
Ezetimibe, n (%)	9 (5)	11 (4)	14 (6)	0.45
Serum Biochemistry				
eGFR, mean (SD), mL/min/1.73m^2	74.2 (20.2)	75.8 (18.7)	67.8 (20.8)*°	<0.01
Hemoglobin, mean (SD), g/L	137.3 (21.1)	138.1 (21.0)	132.0 (20.9)*°	<0.01
Total cholesterol, mean (SD), mmol/L	4.5 (1.2)	4.4 (1.1)	3.9 (1.4)*°	<0.01

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

LDL-C, mean (SD), mmol/L	2.4 (1.0)	2.4 (1.0)	2.0 (1.1)*°	<0.01
HDL-C, mean (SD), mmol/L	1.3 (0.4)	1.3 (0.4)	1.3 (0.7)	0.82
Echocardiographic Parameters				
LVEDV, mean (SD), ml	77.5 (28.3)	76.6 (31.4)	82.4 (40.3)	0.13
LVESV, mean (SD), ml	32.2 (16.6)	30.6 (16.5)	41.2 (31.8)*°	<0.01
LVEF, mean (SD), %	59.7 (6.7)	60.1 (6.2)	53.6 (12.5)*°	<0.01
LVEDD, mean (SD), mm	42.7 (5.9)	43.6 (6.3)	46.7 (2.2)*°	<0.01
LVESD, mean (SD), mm	27.4 (5.3)	28.1 (5.7)	33.0 (1.9)*°	<0.01
IVSD, mean (SD), mm	11.1 (2.2)	10.6 (2.3)	11.6 (8.3)	0.07
PWD, mean (SD), mm	10.4 (2.4)	10.1 (2.0)	11.0 (7.8)°	0.05
LVMI, mean (SD), g/m^2	86.8 (31.1)	82.7 (26.7)	95.8 (29.6)*°	<0.01
LVGLS, mean (SD), -%	18.8 (3.3)	19.3 (3.1)	15.7 (4.8)*°	<0.01
Peak E, mean (SD), m/sec	0.7 (0.2)	0.7 (0.2)	0.9 (0.3)*°	<0.01
Peak A, mean (SD), m/sec	0.8 (0.2)	0.8 (0.2)	0.8 (0.3)*	0.02
E/A, mean (SD)	0.9 (0.3)	1.0 (0.9)	1.2 (0.7)*°	<0.01
e' Average, mean (SD), cm/s	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.15
E/e', mean (SD)	11.0 (4.8)	10.6 (4.3)	14.0 (6.7)*°	<0.01
Diastolic Grade				
*Normal, n (%)	125 (66)	211 (73)	87 (38)*°	<0.01
*Indeterminate, n (%)	23 (12)	27 (9)	41 (18)°	0.02
*Impaired, n (%)	41 (22)	51 (18)	101 (44)*°	<0.01
TAPSE, mean (SD), cm	2.3 (0.5)	2.3 (0.5)	2.1 (0.5)*°	<0.01
RVS', mean (SD), m/s	12.8 (3.1)	12.7 (3.0)	11.4 (2.9)*°	<0.01
LAVI, mean (SD), ml/m^2	27.4 (10.1)	28.0 (24.6)	38.2 (15.8)*°	<0.01
LAEF, mean (SD), %	51.7 (12.6)	50.0 (11.9)	33.5 (15.8)*°	<0.01
LASr, mean (SD), %	26.1 (5.5)	25.0 (6.1)	16.4 (8.2)*°	<0.01
LAScd, mean (SD), %	11.2 (4.7)	11.6 (4.9)	9.3 (4.6)*°	<0.01
LASct, mean (SD), %	14.7 (3.8)	13.9 (4.0)	10.6 (5.4)*°	<0.01

*p<0.05 to non-cardioembolic stroke; °p<0.05 to CS stroke

*Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CS = cryptogenic stroke; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = HDL cholesterol; HR = heart rate; IVSD = interventricular septal diameter; LDL-C = LDL cholesterol; OSA = obstructive sleep apnoea; LA = left atrial; LAScd = left atrial conduit strain; LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAEF = left atrial emptying fraction; LAVI = indexed left atrial volume; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVGLS = left ventricular global longitudinal strain; LVMI = indexed left ventricular mass; PWD = posterior wall diameter; RV = right ventricular; SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion.

Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Table 2. Comparison of clinical and echocardiographic parameters between CS patients with and without recurrent stroke

Variable	CS patients with recurrent stroke (n=36)	CS patients without recurrent stroke (n=249)	Significance (p value)
Demographics			
Age, mean (SD), yrs	65.1 (14.8)	62.9 (14.7)	0.38
Male sex, n (%)	18 (50)	115 (46)	0.72
BMI, mean (SD), kg/m^2	28.1 (4.8)	29.4 (6.6)	0.26
SBP, mean (SD), mmHg	144.4 (30.6)	147.9 (26.2)	0.47
DBP, mean (SD), mmHg	79.1 (16.2)	80.8 (14.6)	0.54
HR, mean (SD), bpm	76.9 (13.8)	76.0 (15.2)	0.74
Comorbidities and pharmacotherapy			
Ischemic heart disease, n (%)	8 (22)	37 (15)	0.33
Heart failure, n (%)	1 (3)	7 (3)	0.54
Previous stroke, n (%)	6 (17)	41 (17)	1.00
Hypertension, n (%)	23 (64)	158 (64)	1.00
Hypercholesterolemia, n (%)	20 (56)	122 (49)	0.48
Diabetes mellitus, n (%)	14 (39)	95 (38)	1.00
Peripheral vascular disease, n (%)	2 (6)	11 (4)	0.67
Obesity, n (%)	11 (31)	95 (39)	0.46
OSA, n (%)	2 (6)	6 (2)	0.27
Active smoking, n (%)	15 (42)	66 (27)	0.05

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Beta Blocker, n (%)	4 (11)	35 (14)	0.80
ACEi/ARB, n (%)	22 (61)	117 (47)	0.15
Aspirin, n (%)	25 (69)	189 (76)	0.41
Dual anti-platelets, n (%)	15 (18)	68 (27)	0.08
Anticoagulation, n (%)	4 (11)	12 (5)	0.13
Statin, n (%)	31 (86)	208 (84)	0.81
Serum Biochemistry			
eGFR, mean (SD), mL/min/1.73m^2	69.6 (23.6)	76.5 (17.8)	0.04
Hemoglobin, mean (SD), g/L	136.7 (24.4)	138.2 (20.2)	0.69
Total cholesterol, mean (SD), mmol/L	4.4 (1.1)	4.0 (1.2)	0.06
LDL-C, mean (SD), mmol/L	2.1 (1.1)	2.4 (1.0)	0.16
HDL-C, mean (SD), mmol/L	1.2 (0.3)	1.3 (0.4)	0.06
Echocardiographic Parameters			
LVEDD, mean (SD), mm	43.8 (6.1)	43.6 (6.3)	0.84
LVESD, mean (SD), mm	28.9 (5.0)	28.0 (5.8)	0.38
IVSD, mean (SD), mm	10.7 (2.9)	10.6 (2.2)	0.71
PWD, mean (SD), mm	10.2 (1.8)	10.0 (2.0)	0.50
LVMI, mean (SD), g/m^2	86.2 (28.6)	82.1 (26.2)	0.39
LVEDV, mean (SD), ml	76.9 (26.2)	76.7 (32.3)	0.97
LVESV, mean (SD), ml	29.9 (13.4)	30.8 (17.0)	0.77
LVEF, mean (SD), %	61.7 (6.9)	61.0 (6.2)	0.53
LV GLS, mean (SD), -%	19.6 (2.5)	19.2 (3.2)	0.50
Peak E, mean (SD), m/sec	0.7 (0.2)	0.7 (0.2)	0.73
Peak A, mean (SD), m/sec	0.8 (0.2)	0.8 (0.2)	0.75

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

E/A, mean (SD)	0.9 (0.3)	1.0 (1.0)	0.60
e' Average, mean (SD), cm/s	0.1 (0.0)	0.1 (0.0)	0.31
E/ e', mean (SD)	11.0 (4.6)	10.6 (4.5)	0.59
Diastolic Grade			
▪ Normal, n (%)	26 (72)	182 (73)	1.00
▪ Indeterminate, n (%)	2 (6)	25 (10)	0.55
▪ Impaired, n (%)	8 (22)	42 (17)	0.48
TAPSE, mean (SD), cm	2.2 (0.5)	2.3 (0.5)	0.10
RVS', mean (SD), m/s	12.3 (3.3)	12.7 (3.0)	0.50
LAVI, mean (SD), ml/m^2	26.8 (13.1)	28.3 (26.1)	0.74
LAEF, mean (SD), %	48.2 (11.7)	50.0 (12.0)	0.41
LASr, mean (SD), %	22.4 (6.1)	25.3 (6.1)	0.01
LAScd, mean (SD), %	10.1 (4.7)	11.8 (5.0)	0.08
LASct, mean (SD), %	12.2 (3.7)	14.1 (4.0)	0.01

*Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CS = cryptogenic stroke; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL-C = HDL cholesterol; HR = heart rate; IVSD = interventricular septal diameter; LDL-C = LDL cholesterol; OSA = obstructive sleep apnoea; LA = left atrial; LAScd = left atrial conduit strain; LASct = left atrial contractile strain; LASr = left atrial reservoir strain; LAEF = left atrial emptying fraction; LAVI = indexed left atrial volume; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVGLS = left ventricular global longitudinal strain; LVMI = indexed left ventricular mass; PWD = posterior wall diameter; RV = right ventricular; SBP = systolic blood pressure; TAPSE = tricuspid annular plane systolic excursion.

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Table 3. Multivariate models

Recurrent Stroke	Unadjusted Cox Regression		Multivariable Cox Regression Model	
Variables	Hazard Ratio (95% CI) Unadjusted	Sig (p value)	Hazard Ratio (95% CI) Adjusted	Sig (p value)
Model 1: Clinical variables				
Model 1a				
Age	1.011 (0.987 – 1.035)	0.364	1.001 (0.975 – 1.029)	0.918
eGFR	0.981 (0.967 – 0.996)	0.014	0.980 (0.965 – 0.994)	0.007
Active smoking	1.798 (0.926 – 3.492)	0.049	2.035 (1.023 – 4.049)	0.043
LDL-C	0.821 (0.583 – 1.155)	0.258	0.868 (0.617 – 1.221)	0.416
Model 1b				
eGFR	0.981 (0.967 – 0.996)	0.014	0.980 (0.966 – 0.994)	0.005
Active smoking	1.798 (0.926 – 3.492)	0.049	2.107 (1.076 – 4.125)	0.030
Dual anti-platelets	2.041 (1.050 – 3.967)	0.035	1.980 (1.014 – 3.867)	0.045
Model 2: Clinical and echocardiographic variables				
Model 2a (LASr)				
eGFR	0.981 (0.967 – 0.996)	0.014	0.983 (0.968 – 0.998)	0.024
Active smoking	1.798 (0.926 – 3.492)	0.049	2.252 (1.112 – 4.563)	0.024
Dual anti-platelets	2.041 (1.050 – 3.967)	0.035	2.212 (1.084 – 4.513)	0.029
LASr	0.934 (0.883 – 0.987)	0.016	0.941 (0.887 – 0.998)	0.044

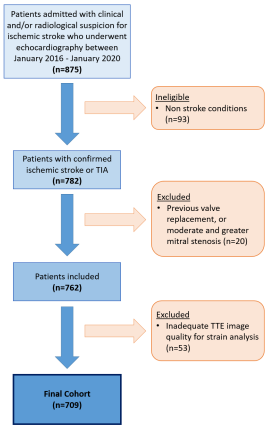
Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

Model 2b (LASct)				
eGFR	0.981 (0.967 – 0.996)	0.014	0.980 (0.966 – 0.995)	0.007
Active smoking	1.798 (0.926 – 3.492)	0.049	2.277 (1.116 – 4.644)	0.024
Dual anti-platelets	2.041 (1.050 – 3.967)	0.035	1.874 (0.887 – 3.956)	0.100
LASct	0.886 (0.804 – 0.976)	0.014	0.898 (0.816 – 0.988)	0.028

*Abbreviations: eGFR = estimated glomerular filtration rate; LASct = left atrial contractile strain; LASr = left atrial reservoir strain.

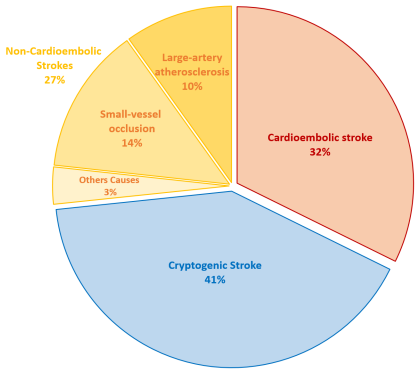
Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.



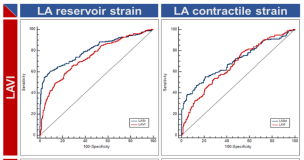
Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.



Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

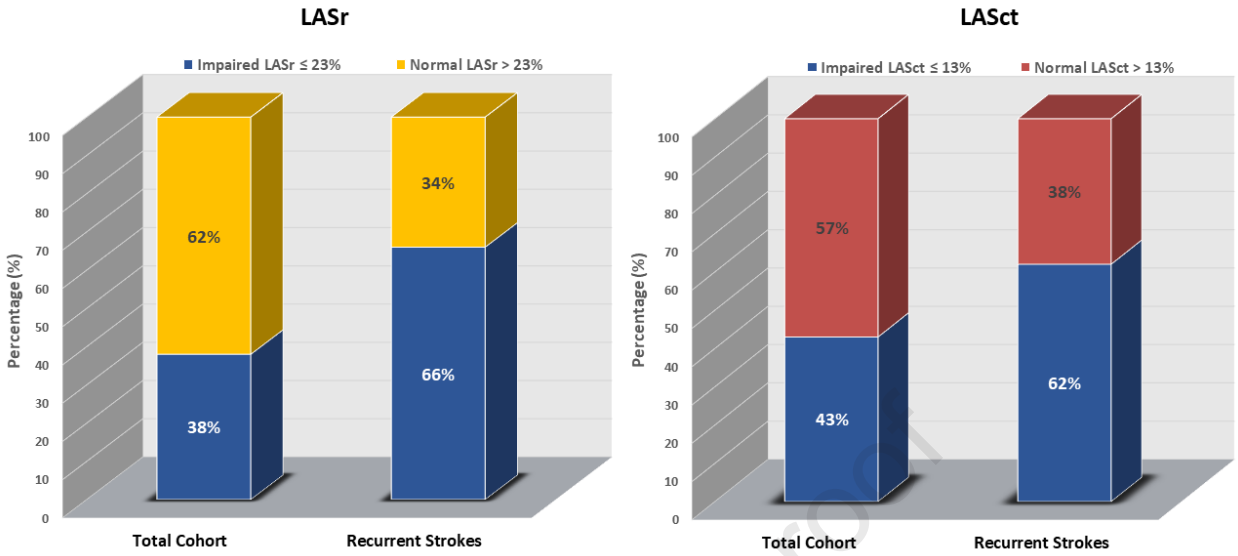


Variable	AUC	SE	95% CI	Sig (p-value)
LASr	0.804	0.020	0.772 – 0.833	p < 0.001
LAVI	0.736*	0.021	0.696 – 0.763	p < 0.001
LVGLS	0.664*	0.024	0.646 – 0.719	p < 0.001

Variable	AUC	SE	95% CI	Sig (p-value)
LASct	0.702	0.029	0.664 – 0.741	p < 0.001
LAVI	0.736	0.021	0.696 – 0.763	p < 0.001
LVGLS	0.664*	0.024	0.646 – 0.719	p < 0.001

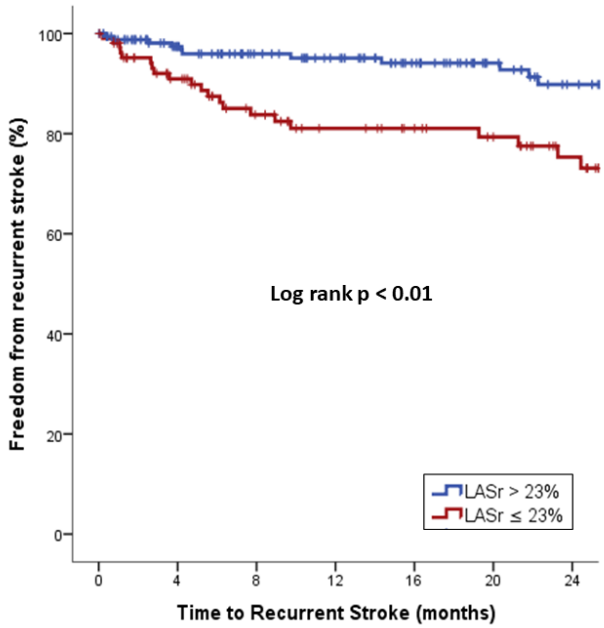
Journal Pre-proof

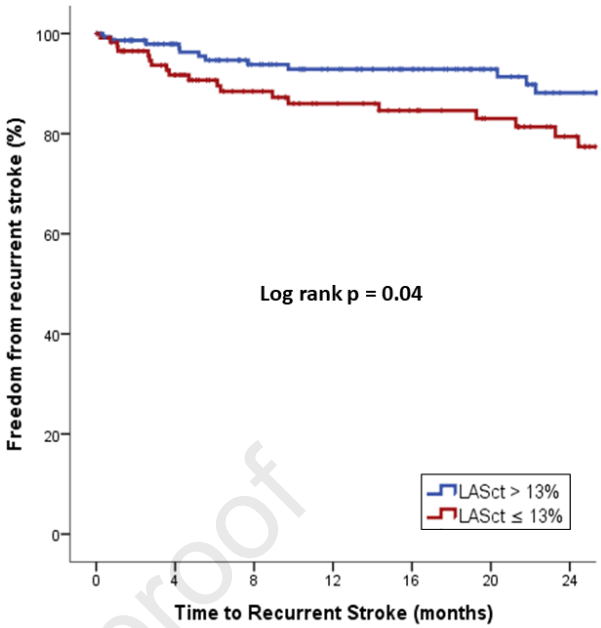
Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.



Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.





Number at risk:

LASr > 23	173	136	116	105	88	70	57
LASr ≤ 23	112	83	66	55	49	44	34

Number at risk:

LASct > 13	159	123	105	93	79	63	50
LASct ≤ 13	126	93	75	65	57	50	40

Journal Pre-proof

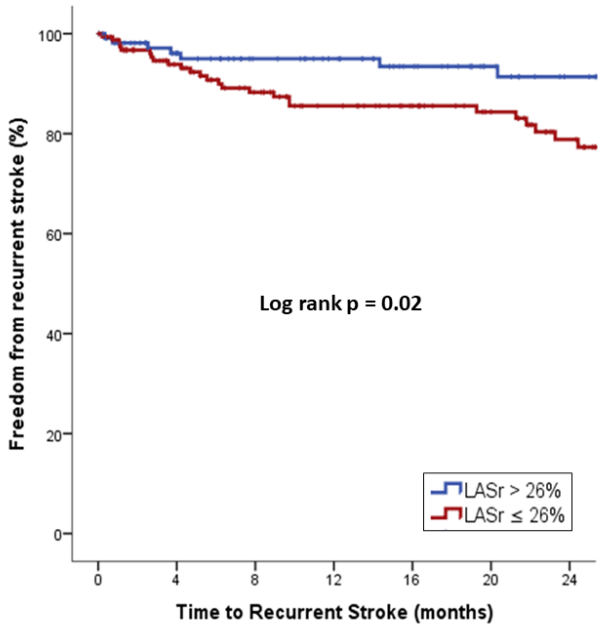
Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

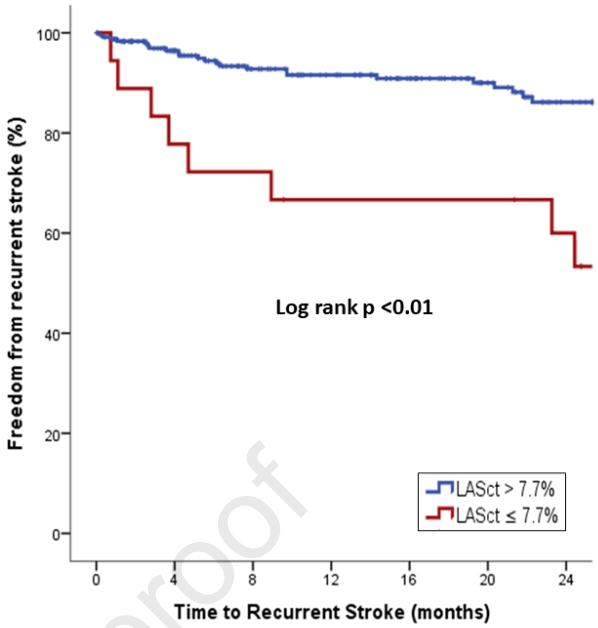
Highlights

- Cryptogenic strokes comprise a portion of ischemic strokes with high rates of recurrence
- Heterogeneous etiology of cryptogenic strokes makes treatment decisions challenging
- Reduced LA strain is a marker for cardioembolic stroke subtype and predicts recurrence
- LA strain may improve risk stratification in patients with cryptogenic stroke

Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.





Number at risk:

LASr > 26	119	89	75	68	57	46	38
LASr ≤ 26	166	125	104	89	78	67	52

Number at risk:

LASct > 7.7	266	196	161	143	121	98	78
LASct ≤ 7.7	19	14	12	11	11	11	9

Journal Pre-proof

Downloaded for Anonymous User (n/a) at Brazilian Society of Cardiology Department of Cardiovascular Imaging from ClinicalKey.com by Elsevier on June 10, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.