ESC European Society of Cardiology

European Heart Journal Open (2023) **3**, 1–10
https://doi.org/10.1093/ehjopen/oead039

ORIGINAL ARTICLE
Vascular and cardiac imaging

Left atrial appendage strain predicts subclinical atrial fibrillation in embolic strokes of undetermined source

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Received 8 February 2023; revised 19 March 2023; accepted 13 April 2023; online publish-ahead-of-print 21 April 2023

Handling Editor: Frank A. Flachskampf

Aims Left atrial (LA) strain is promising in prediction of clinical atrial fibrillation (AF) in stroke patients. However, prediction of subclinical AF is critical in patients with embolic strokes of undetermined source (ESUS). The aim of this prospective study was to investigate novel LA and left atrial appendage (LAA) strain markers in prediction of subclinical AF in ESUS patients.

Methods and results A total of 185 patients with ESUS, mean age 68 ± 13years, 33% female, without diagnosed AF, were included. LAA and LA function by conventional echocardiographic parameters and reservoir strain (Sr), conduit strain (Scd), contraction strain (Sct), and mechanical dispersion (MD) of Sr were assessed with transoesophageal and transthoracic echocardiography. Subclinical AF was detected by insertable cardiac monitors during follow-up. LAA strain was impaired in 60 (32%) patients with subclinical AF compared to those with sinus rhythm: LAA-Sr, 19.2 ± 4.5% vs. 25.6 ± 6.5% ($P < 0.001$); LAA-Scd, −11.0 ± 3.1% vs. −14.4 ± 4.5% ($P < 0.001$); and LAA-Sct, −7.9 ± 4.0% vs. −11.2 ± 4% ($P < 0.001$), respectively, while LAA-MD was increased, 34 ± 24 ms vs. 26 ± 20 ms ($P = 0.02$). However, there was no significant difference in phasic LA strain or LA-MD. By ROC analyses, LAA-Sr was highly significant in prediction of subclinical AF and showed the best AUC of 0.80 (95% CI 0.73–0.87) with a sensitivity of 80% and a specificity of 73% ($P < 0.001$). LAA-Sr and LAA-MD were both independent and incremental markers of subclinical AF in ESUS patients.

Conclusion LAA function by strain and mechanical dispersion predicted subclinical AF in ESUS patients. These novel echocardiographic markers may improve risk stratification in ESUS patients.

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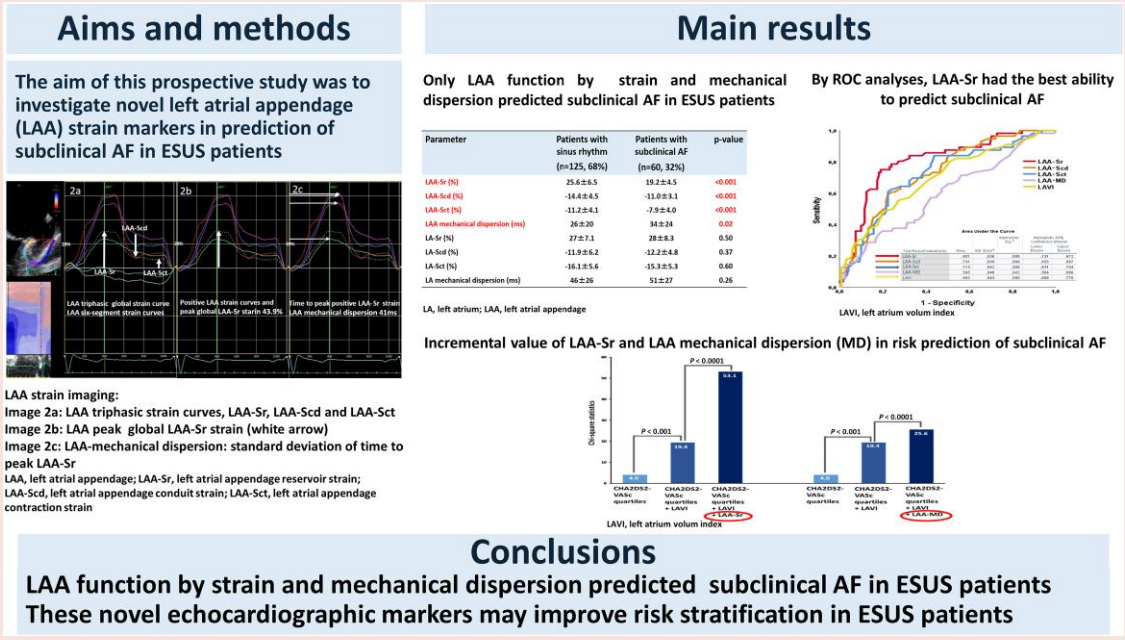
Graphical Abstract



Keywords Embolic stroke of undetermined source • Subclinical atrial fibrillation • Cardiac embolism • Atrial strain

Introduction

High rates of recurrent stroke and mortality in cryptogenic cerebrovascular events support the need of proper diagnostic work-up and risk stratification in this large group of patients.[1] Identifying the underlying causes is crucial to reduce stroke disability and mortality. The lack of consensus for cryptogenic stroke and transient ischemic attack (TIA) has prompted proposal of a new concept: 'embolic strokes of undetermined source' (ESUS),[2] frequently associated with atrial cardiomyopathy.[3] ESUS makes up to one-third of all ischemic strokes/TIA.[4] Most cases of ESUS are thromboembolic,[2] and subclinical atrial fibrillation (AF) occurs in approximately one-third of these patients, detected by insertable cardiac monitors (ICMs).[5,6] Consequently, ESUS patients may be at higher risk for recurrent stroke due to subclinical AF.[3,4,7] Without anticoagulation, these patients have a yearly stroke recurrence rate of 3–6%.[2] It is therefore of uppermost importance to develop new diagnostic tools to identify ESUS patients at high risk to develop AF and consecutive recurrent stroke.

Left atrial (LA) function by strain is promising to predict clinical AF in patients at risk and after cerebral ischemia;[8,9] however, knowledge of this novel approach is more limited in prediction of subclinical AF. Thus, we aimed to investigate if LA and left atrial appendage (LAA) function by strain and mechanical dispersion may improve prediction of subclinical AF in ESUS patients. As thrombus formation mostly occurs in the LAA, our hypothesis was that LAA function by these novel markers may be superior to LA function to predict subclinical AF in ESUS patients at risk of thromboembolic events.

Methods

Study design and population

In this prospective study, consecutive ESUS patients from the PROACTIA study[10] were referred to the Department of Cardiology, Akershus University Hospital, from 2016 to 2018. Patients above 18 years of age, hospitalized for the first time with non-disabling stroke or acute ischemic stroke syndrome (TIA), were screened according to the TOAST criteria[11] and ESUS criteria[2] by two neurologists and a cardiologist. Eligible ESUS patients with complete transthoracic (TTE) and transoesophageal echocardiographic (TOE) examinations (Vivid E9 and E95, GE Vingmed, Horten, Norway) and written informed consent were included, without upper age limit.

This prospective study was conducted according to the Declaration of Helsinki and was approved by the Regional Ethics Committee with reference number 2014/1260.

Clinical examination and detection of subclinical AF

All study patients underwent clinical examination and recording of medical history (*Table 1*) and were screened with 12-lead resting ECG for clinical AF >30 s, according to ESC AF guidelines 2020[12] and excluded if clinical AF was detected.

Furthermore, all patients were also screened for paroxysmal AF prior to inclusion by 24 h Holter ECG by OxyHolter® Recorder (Maynard, MA, USA). Only patients without detected paroxysmal AF were included, and ICMs (Reveal LINQ; Medtronic Inc., Minneapolis, MN, USA) were implanted to detect subclinical AF, defined as episodes of irregular heart rhythm with variable RR interval and without detectable *P* waves, lasting more than 30 s,[12] adjudicated by two cardiologists (LSS, HK). Home monitoring analyses were performed once weekly during the follow-up.

CT and MRI

All study patients underwent neurovascular imaging by CT, MRI, or both to verify ESUS according to the TOAST and ESUS criteria,[3,11] as described previously.[10]

Acquisition of transthoracic and transoesophageal echocardiography

All study patients underwent comprehensive transthoracic and transoesophageal echocardiographic examination after index ESUS [median 4 days (IQR 3–6 days)]. Data were digitally stored for off-line analysis (EchoPAC® software version 203, GE Healthcare). Echocardiographic analyses were performed blinded to clinical data by three operators (JS, EBO, LSS). We performed standard TTE and TOE echocardiography according to current recommendations.[13,14] Focused 2D TOE monoplane and multiplane and 3D LAA views with a narrow image sector to increase frame rate (40–60 frames/s) were achieved at mid-oesophageal TOE views with imaging axis at 0–135 degrees of three consecutive, regular beats. Under 3D imaging guidance, the largest dimension of the LAA (depth and diameter) was acquired by 2D TOE, preferably at imaging axis planes of 45, 90, and 135 degrees.[14] Evaluation of LAA structure and function by conventional imaging parameters was performed (*Figure 1*).

Table 1 Clinical characteristics in 185 study patients with embolic strokes of undetermined source (ESUS)

Clinical parameter	
Age at diagnosis (years)	68 ± 13
Female gender (*n*/%)	61/33
Body mass index (kg/m2)	27.7 ± 4.3
Heart rate (bpm)	65 ± 11
Cryptogenic stroke (*n*/%)	133/72
Cryptogenic TIA/(*n*/%)	52/28
CHA2DS2-VASc score (*n*)	4.2 ± 1.5
Hypertension (*n*/%)	113/61
Heart failure (*n*/%)	7/4
Diabetes mellitus (*n*/%)	11/22
Smoking, including previous (n/%)	75/41
Current smoking (*n*/%)	20/11
Recurrent stroke/TIA (*n*/%)	14/8
Death (*n*/%)	3/2
Subclinical AF (*n*/%)	60/32

TIA, transient ischemic attack; AF, atrial fibrillation.

Left atrial speckle tracking strain echocardiography

Triphasic LA strain by LA reservoir strain (LA-Sr), LA conduit strain (LA-Scd), and LA contraction strain (LA-Sct) was assessed by LA-focused four-chamber view, according to EAVCI recommendations.[15] The resulting LA strain curves provided two peaks consistent with LA-Sr and LA-Sct, and the difference between these was LA-Scd. LA-Sr was defined as LA strain to assess LA mechanical dispersion: peak-positive LA-Sr values from all available LA segments were averaged as global LA-Sr strain. Time to peak LA-Sr strain was defined as the time from onset of R on ECG to peak-positive LA-Sr strain. LA mechanical dispersion was defined as the standard deviation of time to peak global LA-Sr strain.

Left atrial appendage speckle tracking strain echocardiography

A comprehensive TOE evaluation of LAA function by speckle tracking strain analysis was performed. Specific software for evaluating LAA strain by speckle tracking is not yet available; therefore, we analysed LAA strain by EchoPAC® software, developed for the LV four-chamber view. All four LAA types, except cauliflower, have a dominant lobe.[16] Thus, we have performed our measurements on the main lobe by standardized acquisition of the whole length of the main LAA lobe in the long-axis view. A six-segment LAA strain model was established (*Figure 1*) by standardized acquisition of the whole length of the LAA (long-axis view), taking into account the morphologic variability of the LAA.[14]

Similar to LA strain analysis, the onset of the QRS complex was used as a reference point (*Figure 2A*). Endocardial LAA border was traced manually by a point-and-click technique. The region of interest was adjusted with a default width of 3 mm, given the thin wall of the LAA, and the imaging software automatically identified the six LAA segments. Segmental and global LAA strain curves were then generated. All strain analyses were performed off-line from digitally stored cine-loops with manual adjustment of region of interest whenever necessary to optimize speckle tracking. The resulting LAA strain curves provided, similar to LA strain, triphasic LAA strain curves and were characterized with three measurements: two peaks consistent with LAA reservoir strain (LAA-Sr) and LAA contraction strain (LAA-Sct). The difference between these was defined as LAA conduction strain (LAA-Scd). LAA strain analyses by peak-positive LAA-Sr strain, peak-negative LAA-Scd, peak-negative LAA-Sct strain, and LAA mechanical dispersion were generated, measured, and reported.

Strain curves from all six LAA segments were averaged as global LAA-Sr strain (*Figure 2B*). LAA mechanical dispersion was defined as the standard deviation of time from mitral valve opening/R on ECG to peak-positive longitudinal LAA-Sr from all available LAA segments (*Figure 2C*).

Only LAA strain curves with > 75% positive concordance were included, according to the GE imaging software strain algorithm and to overcome

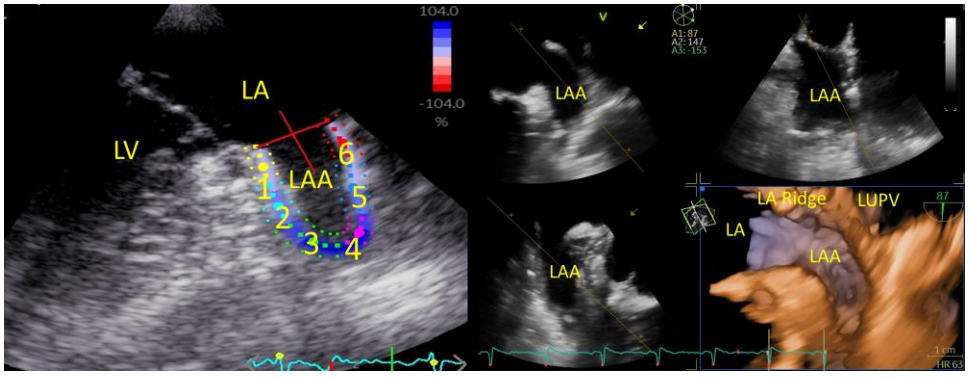


Figure 1 Examples of LAA six-segment strain model and LAA multiplane and 3D imaging. LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LUPV, left upper pulmonic vein.

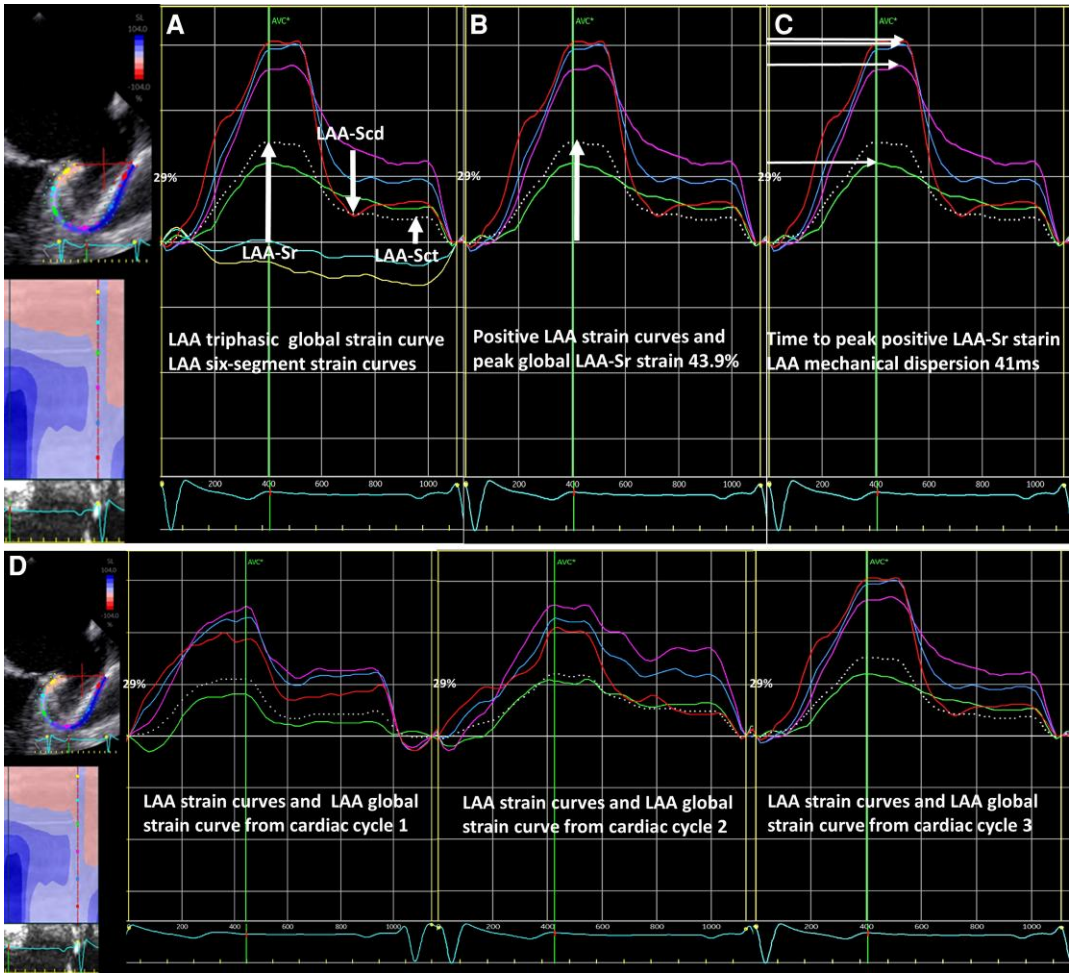


Figure 2 (*A–C*) LAA strain imaging, different image examples from one cardiac cycle. (*A*) LAA triphasic strain curve, vertical white arrows indicate the amplitudes of LAA-Sr, LAA-Scd, and LAA-Sct. (*B*) LAA-positive triphasic strain curves, vertical white arrow indicates peak global LAA-Sr strain. (*C*) LAA mechanical dispersion, horizontal white arrows indicate time to peak LAA-Sr strain. The standard deviation of time to peak LAA-Sr ewas dfined as LAA mechanical dispersion, reflecting contraction inhomogeneity. LAA, left atrial appendage; LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain. (*D*) LAA strain imaging of three different, independent cardiac cycles recorded in the same patient but briefly after each other.

LAA strain measurement failure caused by LV myocardial deformation pattern close to LAA, as shown in *Figure 2A–C*.

Statistical analysis

Data were presented as mean ± SD or median with IQR, as appropriate. Differences between groups were assessed by Chi-square test and Fisher's exact test for categorical variables and unpaired Student's *t*-test, the analysis of variance (ANOVA), or Kruskal–Wallis test for continuous variables, as appropriate (SPSS 26.0 Inc., Chicago, Illinois). We performed univariable logistic regression to access predictors of subclinical AF. Multivariable logistic models with significant covariates from univariable analyses were performed to assess the primary endpoint. C-statistics were calculated by receiver operating characteristic (ROC) curves to assess the parameters' ability to predict subclinical AF. Two-sided *P*-values < 0.05 were considered significant.

The incremental value of LAA strain and mechanical dispersion for prediction of subclinical AF was assessed in modelling steps using nested logistic regression models. Covariate selection for model entry was based on significant results from univariable logistic regression. The change in overall log-likelihood ratio Chi-square was used to estimate the incremental value after the addition of significant parameters from univariable logistic regression.

Inter- and intraobserver variability was expressed by intraclass correlation coefficients. Two-sided *P*-values < 0.05 were considered statistically significant.

Results

Baseline clinical characteristics and conventional echocardiography

Of 236 ESUS patients in the main study, 185 who were eligible for analysis (mean age 68 ± 13years, 33% female) with complete TTE and TOE examinations were included in the present study, with a median follow-up of 849 days (IQR 663–1045 days). Clinical characteristics of the 185 study patients are shown in *Table 1*, while left atrial strain, left atrial appendage strain, and mechanical dispersion are outlined in *Table 2*.

Table 2 Left atrial and left atrial appendage strain and mechanical dispersion in 185 study patients with ESUS

Echocardiographic characteristics	
Echocardiography in SR (*n*/%)	185/100
LAA strain echocardiography (*n*/%)	180/97
Mean LAA segments analysed (*n*)	4.7 ± 0.9
LA strain echocardiography (*n*/%)	152/82
Mean LA segments analysed (*n*)	4.4 ± 0.7
LAA-Sr (%)	23.5 ± 6.6
LAA-Scd (%)	−13.3 ± 4.4
LAA-Sct (%)	−10.1 ± 4.3
LAA-MD (ms)	29 ± 21
LA-Sr (%)	27.5 ± 7.2
LA-Scd (%)	−12.0 ± 5.8
LA-Sct (%)	−15.6 ± 5.0
LA-MD (ms)	47 ± 27

LAA, left atrial appendage; LA, left atrium; LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; LAA-MD, left atrial appendage mechanical dispersion; LA-Sr, left atrial reservoir strain; LA-Scd, left atrial conduit strain; LA-Sct, left atrial contraction strain; LA-MD, left atrial mechanical dispersion.

One hundred thirty-three (71.9%) of all patients experienced stroke and 52 (28.1%) TIA. No significant differences were found in frequency of subclinical AF or in LA and LAA function by strain and mechanical dispersion in patients with stroke compared to TIA (all ns). Moreover, there were no differences in frequency of subclinical AF or in LA and LAA function by strain and mechanical dispersion in patients with thrombolysis ($n = 24$, 13%) compared to those without. Recurrent stroke or TIA occurred in 14 (7.6%) during follow-up (median 396 days, IQR 152–649 days), and three patients (2%) died.

Of the 185 included patients, 60 (32.4%) developed subclinical AF after median 149 days (IQR 33–379 days), detected by ICM during follow-up. Patients with subclinical AF were older and had more hypertension and increased NT pro-BNP and CHA2DS2-VASc score by quartiles compared to patients with sinus rhythm (*Table 3*). All parameters which predicted subclinical AF in univariable analysis are shown in *Table 4*. Systolic blood pressure was significantly higher in patients with subclinical AF (146 ± 19 vs. 139 ± 20 mmHg, $P = 0.034$), but diastolic blood pressure did not differ significantly (78 ± 19 vs. 77 ± 11, $P = 0.5$). However, in multivariable analysis, adjusted for blood pressure, LAA-Sr remained significantly reduced in patients with subclinical AF (*Table 5*). Other clinical characteristics are shown in *Table 3*. Cumulative subclinical AF burden was < 6 min in 12 (20%), > 6 min and < 6 h in 20 (33%), and > 6 h in 28 (47%) of study patients.

Table 3 Clinical and echocardiographic characteristics in 185 study patients with embolic strokes of undetermined source (ESUS), sinus rhythm vs. subclinical AF

Parameter	SR (*n* 125)	Subclinical AF (*n* 60)	*P*-value
Age at diagnosis (years)	67 ± 14	71 ± 11	0.02
Female gender (*n*/%)	42/34	18/30	0.55
Body mass index (kg/m2)	27.3 ± 4.2	28.6 ± 4.5	0.06
Heart rate (beats/minute)	65 ± 11	65 ± 10	0.70
CHA2DS2-VASc score (*n*)	4.1 ± 1.5	4.5 ± 1.4	0.05
CHA2DS2-Vasc score by quartiles (*n*)	2.1 ± 1.2	2.5 ± 1.1	<0.05
Hypertension (n/%)	16/27	44/73	0.02
Systolic BP (mmHg)	139 ± 20	146 ± 19	0.03
Diastolic BP (mmHg)	77 ± 11	78 ± 19	0.54
Diabetes mellitus (n/%)	14/11	8/13	0.68
NT-pro-BNP (ng/L)	280 ± 577	719 ± 1811	0.02
LAVI (mL/m2)	35 ± 9	42 ± 11	<0.001
LV end-diastolic diameter (mm)	52 ± 7	55 ± 7	0.02
LV mass index (g/m2)	94 ± 28	103 ± 26	0.03
LVEF (%)	63 ± 8	63 ± 8	0.97
LAA emptying velocity (cm/s)	81 ± 22	80 ± 23	0.71
LAA neck diameter (mm)	14.7 ± 3.2	16.2 ± 3.6	<0.01
LAA EDV 2D (ml)	4.0 ± 2.0	4.8 ± 2.2	0.02
LAA ESV 2D (ml)	1.1 ± 0.6	1.4 ± 0.8	<0.01
LAA-Sr (%)	25.6 ± 6.5	19.2 ± 4.5	<0.001
LAA-Scd (%)	−14.4 ± 4.5	−11.0 ± 3.1	<0.001
LAA-Sct (%)	−11.2 ± 4.1	−7.9 ± 4.0	<0.001
LAA-MD (ms)	26 ± 20	34 ± 24	0.02
LA-Sr (%)	27.4 ± 7.1	28.0 ± 8.3	0.50
LA-Scd (%)	−11.9 ± 6.2	−12.2 ± 4.8	0.37
LA-Sct (%)	−16.1 ± 5.6	−15.3 ± 5.3	0.60
LA-MD (ms)	46 ± 26	51 ± 27	0.26

BP, blood pressure; ESV, end-systolic volume; EDV, end-diastolic volume; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; LAA, left atrial appendage; LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; LAA-MD, left atrial appendage mechanical dispersion; LA, left atrium; LA-Sr, left atrial reservoir strain; LA-Scd, left atrial conduit strain; LA-Sct, left atrial contraction strain; LA-MD, left atrial mechanical dispersion.

Transthoracic LA strain and transoesophageal LAA strain by speckle tracking

One hundred fifty-two (82%) and 180 (97%) of the study patients were eligible for LA and LAA strain analysis, respectively (*Tables 2* and *3*). Mean numbers of analysed LA strain and LAA strain segments were 4.4 ± 0.7 and 4.4 ± 0.5, respectively. Transthoracic and transoesophageal echocardiographic results from 60 patients with subclinical AF vs. 125 patients in sinus rhythm are described in *Table 3*.

LAA function by triphasic LAA strain was reduced, and LAA mechanical dispersion was increased in patients with subclinical AF compared to those with sinus rhythm (*Table 3*). However, LA function by triphasic strains and mechanical dispersion were not different in these two patient groups (*Table 3*). Furthermore, LA strain was impaired in ESUS patients compared to established normal and age-adjusted LA strain values[17] (*Table 2*). LAA triphasic strain showed a strong bivariable correlation between LAA-Sr and LAA-Scd ($R = 0.80$, $P < 0.001$) and LAA-Sr and LAA-Sct ($R = 0.77$, $P < 0.001$). Hence, we defined LAA function by LAA-Sr. By ROC analyses, LAA triphasic strain, LAA mechanical dispersion, and left atrial volume index (LAVI) were significant in prediction of subclinical AF detected during follow-up by ICM (*Figure 3*).

LAA-Sr showed the best AUC of 0.80 (95% CI 0.73–0.87) with a cut-off value of 22.2%, sensitivity of 80%, and specificity of 73% ($P < 0.001$),

Table 4 Univariable analyses to predict subclinical AF in 185 ESUS patients

Risk factors for subclinical AF	OR	95% CI	*P*-value
Age	1.03	1.00–1.06	0.03
Hypertension	2.23	1.14–4.37	0.02
CHA2DS2-VASc by quartiles	1.32	1.00–1.73	0.048
LAVI (mL/m2)	1.07	1.04–1.11	<0.001
LAA-Sr (%, positive values)	0.80	0.74–0.87	<0.001
LAA-Scd (%, negative values)	1.29	1.16–1.43	<0.001
LAA-Sct (%, negative values)	1.24	1.13–1.37	<0.001
LAA-MD (ms)	1.02	1.00–1.03	0.03

LAVI, left atrial volume index; LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; LAA-MD, left atrial appendage mechanical dispersion.

Table 5 Multivariable analysis of parameters to predict subclinical AF in 185 study patients with embolic strokes of undetermined source (ESUS), adjusted for blood pressure

Parameter	Odds ratio	95% CI	*P*-value
Age at diagnosis (years)	1.02	0.97–1.06	0.49
Female gender (1/0)	1.06	0.44–2.59	0.89
Systolic BP (mmHg)	1.00	0.97–1.03	0.96
Diastolic BP (mmHg)	1.01	0.96–1.06	0.81
LA-Sr (%)	1.03	0.98–1.09	0.26
LAA-Sr (%)	0.79	0.71–0.87	<0.001

BP, blood pressure; LA-Sr, left atrial reservoir strain; LAA-Sr, left atrial appendage reservoir strain.

while LAA mechanical dispersion showed an AUC of 0.60 (95% CI 0.50–0.69) with a cut-off value of 20 ms, sensitivity of 66%, and specificity of 50% ($P = 0.04$) (*Figure 4*). Importantly, by logistic multivariable regression analysis, LAA-Sr strain, LAA mechanical dispersion, and LAVI were independent markers of subclinical AF, while LAA-Scd, LAA-Sct, LA-Sr, and LA-MD were not (*Table 6A* and *B*).

Finally, by incremental Chi-square statistics, LAA-Sr strain and mechanical dispersion significantly improved prediction of subclinical AF when added to the conventional independent parameters CHA2DS2-VASc quartiles and LAVI, $P < 0.0001$ and $P < 0.001$, respectively (*Figure 4*).

Reproducibility

Intra- and interobserver intraclass correlation for the same recorded cardiac cycle in 10 random patients for LAA-Sr, LAA-Scd, LAA-Sct strain, and LAA-MD was 0.99 (95% CI 0.97–0.99) and 0.91 (95% CI 0.63–0.98), 0.97 (95% CI 0.88–0.99) and 0.92 (95% CI 0.66–0.98), 0.97 (95% CI 0.88–0.99) and 0.93 (95% CI 0.71–0.98), and 0.95 (95% CI 0.81–0.99) and 0.87 (95% CI 0.49–0.97), all respectively. Moreover, we performed reproducibility measurements by repeated semi-automated 2D strain measurements of different, independent cardiac cycles. These analyses confirm lower reproducibility of strain imaging in different, independent cardiac cycles recorded in the same patient but briefly after each other (*Figure 2D*). Intra- and interobserver intraclass correlation of different, independent recorded cardiac cycles for LAA-Sr, LAA-Scd, LAA-Sct strain, and LAA-MD was 0.89 and 0.90, 0.66 and 0.77, 0.99 and 0.97, and 0.65 and 0.69, all respectively.

Discussion

This prospective study for the first time presents a new approach to predict subclinical AF by LAA function by novel echocardiographic parameters in ESUS patients at risk. LAA function by strain and mechanical dispersion showed the ability to predict subclinical AF in ESUS patients, while LA strain and mechanical dispersion did not. Furthermore, LAA strain and mechanical dispersion predicted subclinical AF independently from CHA2DS2-VASc score quartiles, a surrogate of comorbidity, and conventional LAVI and added independent and incremental value to conventional clinical and echocardiographic parameters to improve diagnostic work-up, risk stratification, and outcome in ESUS patients.

Clinical characteristics, prediction of subclinical AF, conventional echocardiography, and outcome

At baseline, patients had moderate to high increased CHA2DS2-VASc score of > 4, which is strongly associated with AF and stroke risk.[18] Our results were compliant with the study by Bahit et al. and indicate that disease burden increases the risk of subclinical AF.[19] Thirty-two percent ($n = 60$) of all study patients developed subclinical AF in accordance with the CRYSTAL AF study.[5] Burden of subclinical AF > 6 min occurred in > 80% of all study patients with subclinical AF, which has shown to be associated with increased risk of recurrent stroke.[18] Eight percent ($n = 14$) of our ESUS patients developed recurrent stroke and TIA, which is in accordance with Bahit et al.[19]

AF burden in general is supposed to predict risk of adverse outcome, including stroke, recurrent stroke, and death. In patients with intermediate CHA2DS2-VASc scores of 3–4 and > 6 min of subclinical AF detected by ICM, stroke risk may shift above the threshold for recommended anticoagulation.[18] The interaction between subclinical AF duration and patients' clinical characteristics, evaluated by CHA2DS2-VASc score, can further risk-stratify this patient group and may be useful in guiding anticoagulation therapy.[12] Furthermore, conventional LA volume index (LAVI) is an established marker of clinical AF and was slightly increased in patients with subclinical AF compared to patients with sinus rhythm (*Table 3*). However, when added to LAVI, both LAA strain and LAA mechanical dispersion were independent and incremental markers in prediction of subclinical AF.

LA and LAA strain by speckle tracking imaging

In the present study, we demonstrated the impact of LAA function by strain and mechanical dispersion in risk stratification of ESUS patients. LAA function by strain was decreased, and LAA mechanical dispersion was increased in patients with subclinical AF compared to patients with sinus rhythm (*Table 3*). The present study extended the impact of strain and mechanical dispersion to LAA function in prediction of subclinical AF in ESUS patients.[8,9] By ROC analyses, LAA strain and mechanical dispersion predicted subclinical AF (*Figure 3*). Furthermore, by logistic regression, LAA strain and mechanical dispersion were markers of subclinical AF (*Table 6A* and *B*), independent of age, LAVI, body mass index, and CHA2DS2-VASc quartiles. Finally, by incremental Chi-square statistics, LAA strain and mechanical dispersion significantly improved prediction of subclinical AF, when added to independent

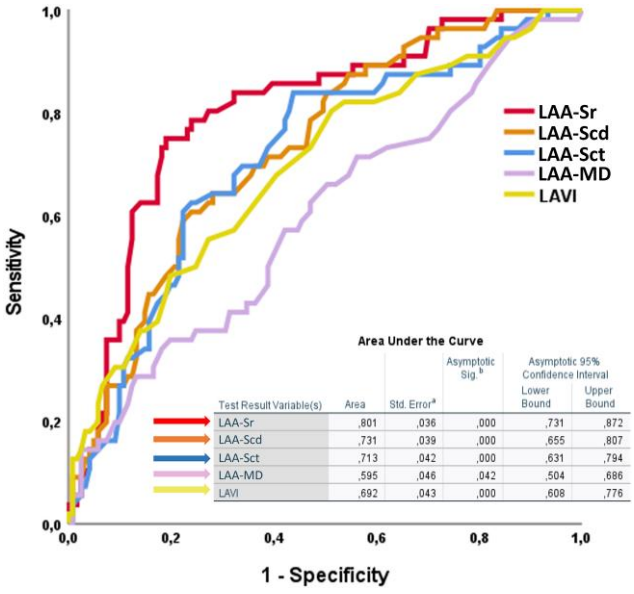


Figure 3 By ROC analyses, LAA-Sr showed the best ability to predict subclinical AF. LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; LAA-MD, left atrial appendage mechanical dispersion; LAVI, left atrial volume index; AF, atrial fibrillation.

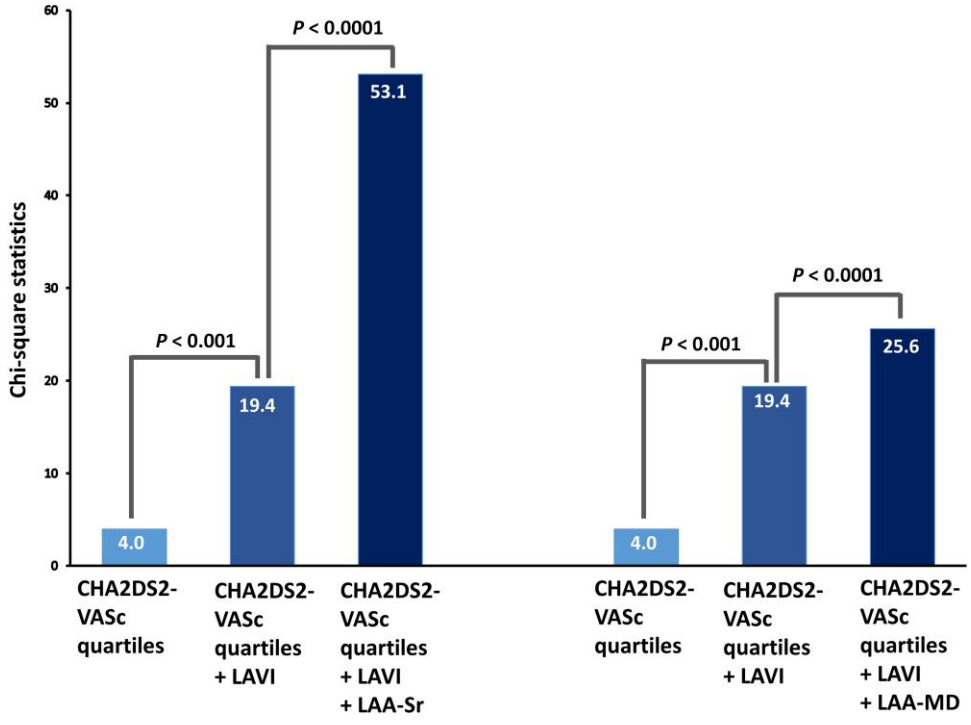


Figure 4 Independent and incremental predictive value of left atrial appendage strain and mechanical dispersion. The initial model with CHA2DS2-VASc quartiles was significantly improved by the addition of LAVI and further improved by adding LAA strain and LAA mechanical dispersion to predict subclinical AF in ESUS patients. AF, atrial fibrillation; ESUS, embolic strokes of undetermined source; LAA, left atrial appendage; LAA-Sr, left atrial appendage reservoir strain; LAA-MD, left atrial appendage mechanical dispersion; LAVI, left atrial volume index.

Table 6 Multivariable analysis of parameters to predict subclinical AF in 185 study patients with embolic strokes of undetermined source (ESUS)

A **Parameter, multivariable analysis model 1**	**Odds ratio**	**95% CI**	***P*-value**
LAA mechanical dispersion (ms)	1.02	1.00–1.04	0.02
Age at diagnosis (years)	1.02	0.98–1.06	0.25
LAVI (mL/m2)	1.07	1.03–1.11	<0.001
CHA2DS2-VASc quartiles	1.02	0.68–1.54	0.92
Parameter, multivariable analysis model 2	**Odds ratio**	**95% CI**	***P*-value**
LAA-Sr	0.84	0.75–0.93	0.001
Age at diagnosis (years)	1.01	0.97–1.06	0.64
LAA-Scd (%)	1.06	0.91–1.23	0.50
LAVI (mL/m2)	1.05	1.01–1.09	0.008
CHA2DS2-VASc quartiles	0.89	0.56–1.42	0.64
Parameter, multivariable analysis model 3	**Odds ratio**	**95% CI**	***P*-value**
LAA-Sr	0.83	0.75–0.92	<0.001
Age at diagnosis (years)	1.00	0.98–1.04	0.68
LAA-Sct (%)	0.97	0.86–1.10	0.68
LAVI (mL/m2)	1.05	1.01–1.09	< 0.01
B **Parameter, multivariable analysis model 1**	**Odds ratio**	**95% CI**	***P*-value**
Age at diagnosis (years)	1.01	0.96–1.07	0.65
Female gender (1/0)	0.83	0.30–2.32	0.72
CHA2DS2-VASc score by quartiles (*n*)	1.11	0.62–1.98	0.72
BMI (*n*)	1.13	1.02–1.25	0.02
LA-Sr (%)	1.05	0.99–1.11	0.14
LAA-Sr (%)	0.78	0.71–0.87	<0.001
Parameter, multivariable analysis model 2	**Odds ratio**	**95% CI**	***P*-value**
Age at diagnosis (years)	1.04	0.99–1.09	0.13
Female gender (1/0)	0.63	0.24–1.62	0.34
CHA2DS2-VASc score by quartiles (*n*)	1.34	0.80–2.25	0.27
BMI (*n*)	1.11	1.01–1.22	0.03
LA-Sr (%)	1.05	0.99–1.11	0.11
LAA-MD (ms)	1.02	1.00–1.04	0.04

LAA, left atrial appendage; LV, left ventricle; LAVI, left atrial volume index; LAA-Sr, left atrial appendage reservoir strain; LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; BMI, body mass index; LA-Sr, left atrial reservoir strain; LA-MD, left atrial mechanical dispersion; LAA-Sr, left atrial appendage reservoir strain; LAA-MD, left atrial appendage mechanical dispersion.

conventional echocardiographic (LAVI) and clinical parameters (CHA2DS2-VASc quartiles) (*Figure 4*).

LA function by strain and mechanical dispersion have shown to predict clinical AF in patients at risk in several studies.[8,20,21] However, in the present study, LAA function by strain and mechanical dispersion independently predicted subclinical AF in ESUS patients, while LA function by strain and mechanical dispersion did not, which may seem to be different from previous studies.[8,9] In the present study, however, only strictly subclinical AF was detected by continuous rhythm monitoring by approximately 28 months of follow-up by ICM, similar to the CRYSTAL AF trial[5] and according to ESC AF guidelines 2020.[12] Previous studies predicting clinical AF have been performed in patient populations using standard 12-channel ECG or intermittent rhythm monitoring.[8,20,21] In the studies by Pathan et al. and Kawakami et al. with an older patient population with cryptogenic stroke and clinical AF, both studies detected only 11% AF under follow-up of 60 and 36 months, respectively.[8,9] The present prospective study presents younger ESUS patients with 30% subclinical AF and reflects a phenotypically different study population with lower disease burden compared to stroke patients with clinical AF.[6] Importantly, Sade and coworkers recently demonstrated impaired LA strain in ESUS patients compared to normal age-adjusted LA strain values, which is consistent with our results.[21] Hence, detection of subtle changes in LAA function by strain and mechanical dispersion may

be more sensitive in prediction of subclinical AF compared to LA strain in ESUS patients. However, additional studies are required to confirm our results.

Both LA and LAA function by strain and mechanical dispersion may constitute a surrogate of the new concept of atrial cardiomyopathy, defined as a complex of structural, functional, or electrophysiological changes, affecting the atria with the potential to produce clinically relevant manifestations.[22] Atrial cardiomyopathy has shown to be closely associated with ischemic stroke related to thromboembolism, AF, and atrial remodelling and may constitute one of the main mechanisms in ESUS.[3,6,23]

TOE is recommended in ESUS/stroke patients[3] with the opportunity to study LAA structure and function by novel risk markers and to evaluate early development of atrial cardiomyopathy as a marker of increased thromboembolic risk. We suggest TOE without any upper age limit as a routine examination in ESUS patients at risk. Further studies with regard to anticoagulant medication in ESUS patients with subclinical AF are needed to evaluate future treatment strategies.

Limitations

There are several limitations in this study. First, only ESUS patients were included without an age-adjusted control group to compare the LA strain and mechanical dispersion results. However, established normal LA strain values are available.[17] Second, normal LAA strain and mechanical dispersion values are not reported in the literature yet, and we could only present values in ESUS patients. Third, images of the LA were not always optimized; however, strain measurement was feasible in 82% of all patients. Fourth, variability in strain and mechanical dispersion measurements is vendor dependent, only few dedicated atrial strain software packages are available, and there is no specific software for evaluating LAA strain. Finally, LAA strain may be variable because of different LAA morphologies. Therefore, our study results need validation in further studies using different echocardiographic software packages.

Conclusions

Left atrial appendage function by strain and mechanical dispersion predict independently subclinical AF in ESUS patients and is superior and incremental to clinical and established echocardiographic risk parameters, including left atrial function by strain and mechanical dispersion. These novel echocardiographic markers, assessed by transoesophageal echocardiography, may be useful in ESUS patients at risk.

Lead author biographies

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Dr Skrebelyte-Strøm is currently working on her PhD degree in cardiology from the University of Oslo, Norway, and has a clinical position at the Department of Cardiology at the Akershus University Hospital (AHUS). Her research interests are within screening of atrial fibrillation and risk assessment in ESUS patients. Together with PhD supervisors, Associate Prof. Steine and coworkers, she initiated and conducted the PROACTIA study.[1] Their work resulted in the implementation of the research-guided best clinical practice at AHUS and development of the international cooperation in this area. Since 2019, she is the Norwegian representative in the European Society of Cardiology Council on Stroke.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgements

We thank the study nurses Vigdis Bakkelund and Annika Lorentzen for their valuable assistance in carrying out this study.

Funding

This work was supported by the Trust Foundation Dam (grant number 2016/FO82036, 2016) and Akershus University Hospital (project number 296908, 2016 and 2017).

Conflict of interest: None declared.

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