The International Journal of Cardiovascular Imaging (2019) 35:603–613
https://doi.org/10.1007/s10554-018-1485-z

ORIGINAL PAPER

Prognostic value of global left atrial peak strain in patients with acute ischemic stroke and no evidence of atrial fibrillation

Andrea Sonaglioni[1,6] · Antonio Vincenti[1] · Massimo Baravelli[1] · Elisabetta Rigamonti[1] · Elena Tagliabue[2] · Pietro Bassi[3] · Gian Luigi Nicolosi[4] · Claudio Anzà[5] · Michele Lombardo[1]

Received: 15 August 2018 / Accepted: 24 October 2018 / Published online: 30 October 2018

Abstract

Prognostic stratification of acute ischemic stroke (AIS) patients without atrial fibrillation (AF) remains a challenge. Two-dimensional speckle tracking echocardiography (2D-STE) has recently been introduced for dynamic evaluation of left atrial function. However only few data are actually available regarding the application of 2D-STE in AIS patients. The aim of our study was to assess the prognostic role of global left atrial peak strain (GLAPS), measured by 2D-STE, in AIS patients without AF history. Eighty-five AIS patients (mean age 74.1 ± 12.1 years, 49 males) with normal sinus rhythm on ECG and without AF history were enrolled in the prospective study. All patients underwent a complete echocardiographic study with 2D-STE. At 1 year follow-up, we evaluated the occurrence of a composite endpoint of all-cause mortality plus cardiovascular re-hospitalizations. GLAPS was markedly reduced in AIS patients (15.71 ± 4.70%), without any statistically significant difference between the stroke subtypes. At 1-year follow-up, 14 deaths and 17 hospital readmissions were detected in AIS subjects. On a multivariate Cox model, variables independently associated with the occurrence of the composite endpoint were the "Rankin in" Scale (HR 1.69, p = 0.001), GFR (HR 0.98, p = 0.03) and the GLAPS value (HR 0.78, p < 0.0001). A GLAPS value ≤ 15.5% predicted the composite endpoint with sensitivity of 100% and specificity of 80%. A GLAPS value ≤ 15.5% reflects a more advanced atrial cardiomyopathy and might provide a reliable and useful prognostic risk stratification of AIS patients without AF history.

Keywords Acute ischemic stroke · Atrial fibrillation · Speckle tracking echocardiography · Global left atrial peak strain

Introduction

Stroke is the third leading cause of death after cardiovascular diseases and cancer, and is the major cause of long-term disability in Europe and in the United States, with a considerable socio-economic impact worldwide [1].

It occurs more frequently in older people, and the risk of stroke increases with age. The stroke mortality rate ranges between 15 and 40% at 1 year [2]. Additionally, early after stroke one-third to one-half of the patients are partially or totally dependent in activities of daily living [3].

The prognostic stratification of acute ischemic stroke (AIS) patients remains a challenge. Echocardiography is the most commonly used tool for the cardiovascular evaluation of these patients. Although several studies [4–8] adopted volumetric assessment of left atrium for correlation with or prediction of adverse cardiovascular events, only few authors [9, 10] have demonstrated that left atrial (LA) enlargement

✉ Andrea Sonaglioni
sonaglioniandrea@gmail.com

1 Department of Cardiology, Ospedale San Giuseppe MultiMedica, Via San Vittore 12, 20123 Milan, Italy

2 Biostatistical Unit, MultiMedica IRCCS, Via Fantoli 16/15, 20138 Milan, Italy

3 Department of Neurology, Ospedale San Giuseppe MultiMedica IRCCS, Via San Vittore 12, 20123 Milan, Italy

4 Cardiology Clinic, Policlinico San Giorgio, Via Agostino Gemelli 10, 33170 Pordenone, Italy

5 Cardiovascular Department, MultiMedica IRCCS, Via Milanese 300, 20099 Sesto San Giovanni, Milan, Italy

6 Ospedale San Giuseppe Multimedica IRCCS, Via San Vittore 12, 20123 Milan, Italy

is independently associated with new neurological events and with all-cause mortality in patients with first-ever AIS.

Since the majority of AIS patients are frail with multiple comorbidities, it is complex obtaining an echocardiographic risk assessment based only on the traditional morphological echocardiographic parameters. In fact, the coexistent increase in LA size remains a nonspecific marker, difficult to interpret in patients with concomitant comorbidities, such as hypertension, valvular disease and diastolic dysfunction.

Two-dimensional speckle tracking echocardiography (2D-STE) has recently been introduced to evaluate dynamic LA function [11]. Impaired global LA peak strain (GLAPS) may suggest reduced LA compliance and might provide a better insight into LA function.

However, currently very few data are available regarding the application of this technique in AIS patients [12], especially with no evidence of atrial fibrillation (AF) [13].

The aim of our study was to evaluate the prognostic value of GLAPS in AIS patients without AF history, for predicting the occurrence of death and cardiovascular re-hospitalizations in the medium and short-term follow-up.

Materials and methods

We performed a prospective single-center observational study, carried out on 85 AIS patients (mean age 74.1 ± 12.1 years, 49 males), hospitalized in the Neurology Department at San Giuseppe MultiMedica Hospital (Milan, Italy) from October 2016 to February 2017.

According to the World Health Organization criteria [14], acute stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than of vascular origin".

The following patients' data were collected from hospital charts: age, gender, BSA, incidence of coronary risk factors (i.e. cigarette smoking, hypertension, type 2 diabetes mellitus and dyslipidemia), history of coronary artery disease (prior myocardial infarction and/or percutaneous coronary intervention and/or coronary artery bypass graft) and/or of cerebrovascular events [prior stroke and/or transient ischemic attacks (TIAs)], electrocardiographic data, long-term medical treatment and blood tests, such as hemoglobin, serum creatinine and lipid profile.

Hypertension criteria included the use of antihypertensive drugs, persistent systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg.

Type 2 diabetes mellitus was defined by the use of antidiabetic medications or fasting plasma glucose levels ≥ 126 mg/dl confirmed by several tests done on different days (fasting was defined as no caloric intake for at least 8 h).

Diagnostic criteria for dyslipidemia were the following: serum total cholesterol ≥ 200 mg/dl, serum HDL-cholesterol ≤ 40 mg/dl and triglycerides ≥ 150 mg/dl.

Glomerular filtration rate (GFR) was estimated through the Modification of Diet in Renal Disease (MDRD) equation.

Exclusion criteria were the following: history of AF (also excluded by a continuous telemetry monitoring during hospitalization), hemorrhagic stroke and patients with transient neurological symptoms and without acute ischemic lesions on brain magnetic resonance imaging (MRI), classified as TIA patients. The latter were excluded from the study on the basis of the negative results of the latest-generation brain MRI, able to detect even very small ischemic lesions. Thus, we selected and examined a more homogenous patient population (AIS patients). Patients with poor echocardiographic images unsuitable for LA size measurement were also excluded.

During hospitalization all patients underwent accurate anamnesis, complete physical and neurological examination comprehensive of computed tomography (CT), brain MRI scans, blood analysis, ultrasound evaluation of carotid arteries, a 12-lead electrocardiogram (ECG) and an echocardiographic study with pulsed-wave tissue Doppler imaging (PW-TDI) and 2D-STE.

The primary endpoint of our study was a composite endpoint of all-cause mortality plus cardiovascular re-hospitalizations. The latter were defined as hospital re-admissions for surgical procedures or adverse cardiovascular events such as recurrence of stroke/TIA, arrhythmias associated with hemodynamic instability, heart failure, acute coronary syndromes and/or major bleedings.

The annual follow-up consisted of a clinical visit together with telephone interview and re-evaluation of the patients' clinical charts in order to detect the above-mentioned endpoint.

All procedures performed in the present study were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A written and informed consent was obtained from all individual participants and/or their relatives included in the study and the protocol was approved by the local Ethics Committee. No extramural funding was used to support this work. The authors are solely responsible for the structure and direction of the study, investigations and analyses, drafting and editing of the paper.

Patient evaluation

Clinical measures

The cardioembolic risk of each patient was assessed by the CHA_2DS_2-VASc (congestive heart failure, hypertension,

age ≥ 75 years [doubled], diabetes, stroke/TIA/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–74 years, sex category [female]) Risk Score [15].

The subtypes of ischemic stroke were classified according to the TOAST criteria: (1) large-artery atherosclerosis (LAA), (2) small vessel occlusion (SVO), (3) cardioembolism (CE), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology [16]. Additionally, all patients underwent complete neurological examination, and the modified Rankin Scale (mRS) [17–19] was used to measure the degree of disability or dependence at three specific moments: before the hospital admission, at the Neurology Department admission (Rankin "in" Scale) and at the hospital discharge. The mRS is a 7-level ordered categorical scale describing levels of patient functional independence following a stroke, with scores ranging from 0 (fully independent) to 6 (dead).

Standard echocardiographic measurements

Transthoracic echocardiography was performed in all patients by the same cardiologist (A.S.), by using the portable Philips Sparq ultrasound machine with a 2.5 mHz transducer.

All measurements were performed according to the Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [20, 21].

The following echo M-mode and 2D parameters were recorded: left ventricular (LV) end-diastolic and end-systolic diameters indexed, ventricular septal thickness and LV posterior wall thickness, from the parasternal long-axis 2-dimensional guided M-mode examination; relative wall thickness (RWT), calculated with the formula RWT = 2 posterior wall thickness/LV internal diameter at end-diastole; LV mass indexed (LVMi), calculated by the Devereux's formula; LV end-diastolic and end-systolic volumes indexed (LVEDVi and LVESVi respectively); LV ejection fraction (LVEF) by the modified biplane Simpson's method; LA anteroposterior diameter in parasternal short axis view at the aortic valve level; LA longitudinal diameter in apical four-chamber view; LA end-systolic volume indexed (LAVi) measured from biplane method of disks (modified Simpson's rule) using apical four-chamber and apical two-chamber views at ventricular end-systole; right ventricular (RV) inflow tract, measured in a RV focused apical view; longitudinal systolic function of RV, measured by tricuspid annular plane systolic excursion from four-chamber view [22] and finally inferior vena cava (IVC) diameter by a subcostal longitudinal view.

Doppler measurements included: transmitral flow velocities by pulsed wave (PW) Doppler technique, i.e. velocities of early (E) and late (A) filling wave (the latter due to atrial contraction) and the E/A ratio; early diastolic myocardial relaxation velocities, assessed by PW-TDI, placing the sample volume in the ventricular myocardium immediately adjacent to the medial (e′ sep) and lateral (e′ lat) mitral annulus in order to calculate the average E/e′ ratio, as an index of the LV filling pressures (LVFP); tricuspid regurgitation was searched and assessed in parasternal RV inflow, parasternal short-axis, and apical or subcostal four-chamber views, in order to achieve an optimized continuous-wave Doppler echocardiographic sampling of tricuspid regurgitation peak velocity (TRV), which was used to estimate the RV-to-right atrial systolic pressure gradient calculated with the modified Bernoulli equation ($4 \times [TRV]^2$) [23]. Right atrial pressure, estimated by both IVC diameter and its inspiratory collapse, was added to that calculated value, to estimate the systolic pulmonary artery pressure.

The echocardiographic grading of valvular regurgitation was assessed by standard color Doppler criteria, the aortic valve area by the continuity equation [24] and the transvalvular gradients by the simplified Bernoulli equation [25].

Speckle tracking echocardiography

Two-dimensional STE was performed immediately after conventional echocardiography, during the same examination, by using the Philips QLAB 10.3.1 ultrasound software. All acquired images were then analyzed offline by the same cardiologist (A.S.). To calculate LA strain, we employed the same software that is used for the analysis of ventricular function. At first, we manually traced the atrial endocardium by using three reference points, the first one placed at the medial mitral annulus, the second one at the lateral mitral annulus and the third one at the atrial roof. The epicardial surface was automatically calculated, and after manually reducing the region of interest to the atrial thickness, to include only the atrial wall, the software automatically divided the atrial wall into six segments. We repeated these steps from each of the two apical views: four-chamber (six segments) and two-chamber (six segments) using a 12-segments model ("biplane method"); the apical three-chamber view was excluded. Then, the system processed the data and after finishing tracing and auto processing of the two views, the global LA strain and Bull's eye report was obtained.

Once the longitudinal atrial strain curves were obtained, the following measurements were performed: positive global atrial strain (GSA +), during the reservoir phase, plotted as a positive curve at the aortic valve closure; negative global atrial strain (GSA −), during the LA systole, plotted as a negative curve with a peak after the P wave on ECG; peak to peak strain (TGSA): the sum of the two peaks; time to peak positive strain (TPPS): the time interval from the

beginning of P wave to the time of the peak of the positive strain (Fig. 1a).

GLAPS value was calculated from the sum of the values of GSA +, during the reservoir phase, obtained in each of the two apical echocardiographic views, divided by the total number of segments (12).

From the 2D atrial strain, strain rate (SR) curves were derived, which permitted the measurement of atrial SR during the three phases: the first positive global strain rate (GSR +), from the beginning of ventricular systole; global early-diastolic strain rate (GSRE); global late-diastolic strain rate (GSRL); time to peak positive strain rate (TPPSR +), measured from the beginning of P-wave to the peak of the first positive SR (Fig. 1b).

Finally, we calculated: GLAPS/LAVI ratio and two echocardiographic indices of LA stiffness, i.e. E/GLAPS ratio and E/e′/GLAPS ratio.

Ultrasound assessment of carotid arteries

All patients underwent carotid ultrasound imaging. Grading of carotid stenosis was primarily based on morphological information. In addition to the degree of narrowing, plaque thickness, plaque length, and residual lumen diameter were reported. Velocity measurements in stenosis (peak systolic velocity and carotid ratio) were used to differentiate a moderate from a severe (> 70%) stenosis, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [26].

Statistical analysis

For all patients, continuous data were summarized as mean ± standard deviation (SD), while categorical data were given as frequency and percentage. The non-parametric

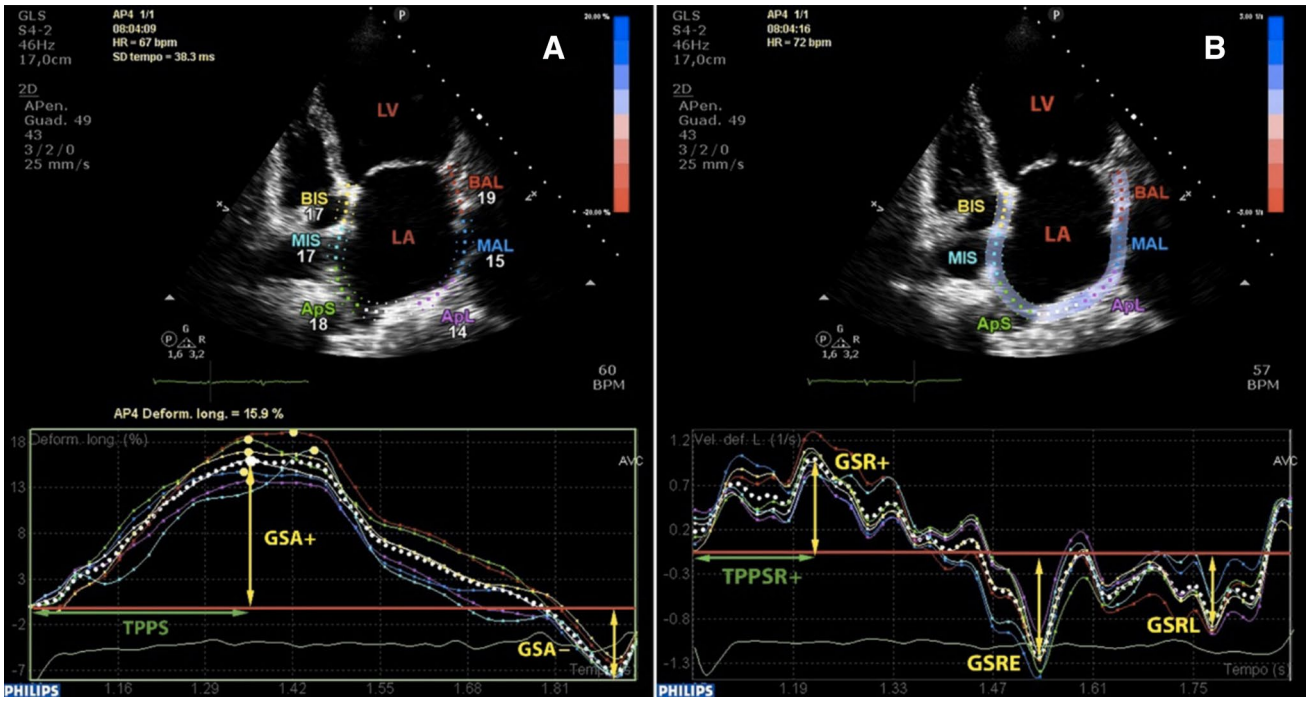

Fig. 1 **a** Example of measurement of longitudinal LA strain by two-dimensional speckle tracking echocardiography, obtained from the apical four-chamber view in a stroke patient enrolled in the study. Longitudinal strain curves of the six atrial segments are depicted with different colors. The dotted line indicates the average atrial longitudinal strain. Positive curves indicate the atrial strain of the reservoir during ventricular systole, which coincides with aortic valve closure. GSA + (%): positive global atrial strain (yellow arrow from the positive peak of the dotted line to the red line). Negative curves represent atrial strain during the LA systole with a peak after the P wave of the ECG. GSA − (%): negative global atrial strain (yellow arrow from the negative peak of the dotted line to the red line). TPPS (ms), time to peak positive strain, the time interval from the beginning of P wave to the time of peak positive strain (green arrow). *AVC* aortic valve closure, *LA* left atrial. **b** Left atrial longitudinal SR. The dotted line indicates the average SR. Positive curves, indicate atrial lengthening (relaxation) during the periods of isovolumic contraction, ventricular ejection and isovolumic relaxation (reservoir SR). GSR + (%), the first positive global strain rate, from the beginning of ventricular systole (yellow arrow from the positive peak of the dotted line to the red line). Negative curves indicate atrial SR during rapid ventricular filling (E) and atrial systolic SR (A), which is seen after the P wave of the ECG. GSRE (%), global early-diastolic strain rate (yellow arrow from the first negative peak of the dotted line to the red line). GSRL (%), global late-diastolic strain rate (yellow arrow from the second negative peak of the dotted line to the red line). TPPSR + (ms), time to peak positive strain rate, measured from the beginning of P-wave to the peak of the first positive strain rate (green arrow). *AVC* aortic valve closure, *SR* strain rate

Wilcoxon test was used to estimate the difference between the means, since Kolmogorov–Smirnov test showed a not normally distribution for all continuous variables, while categorical variables were compared using the Chi square test or the Fisher's exact test, as appropriate.

Furthermore, the following analyses were performed. Investigated outcome was a composite endpoint of all-cause mortality plus cardiovascular re-hospitalizations, herein called major adverse cardiovascular events (MACE). Univariate Cox regression was performed to evaluate the effect of the clinical, Doppler-echocardiographic and 2D-STE variables on the occurrence of MACE at 1-year follow-up. Correspondent hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Furthermore, the most clinically relevant variables were then evaluated in an overall multivariate Cox proportional hazard model to test their effect on the occurrence of MACE.

The correlation between GLAPS score and conventional clinical parameters was assessed by Spearman Correlation Coefficient.

The receiver operating characteristics (ROC) curve was drawn for GLAPS value in predicting MACE and the best cut-off for GLAPS was found by maximizing the sum of sensitivity (SE) and specificity (SP). Area under the ROC curve (AUC) was calculated.

Finally, survival curves were drawn to evaluate whether there was a difference between strata of GLAPS comparing values lower vs greater than the best cut-off. The comparison of the survival curves of the two groups was assessed by using the log-rank test.

Values of $p < 0.05$ were considered statistically significant.

Statistical analysis was performed using the SAS software (SAS version 9.4, Cary, N.C., USA) and R (R version 3.4.4), with Hmisc and pROC libraries (Hmisc and pROC libraries: http://cran.r-project.org/).

Results

Stroke patients enrolled in the study showed a duration of hospital stay of 5 ± 2 days, at continuous ECG monitoring. The main demographic and clinical characteristics of the study population are reported in Table 1. As expected, hypertension, dyslipidemia and type 2 diabetes mellitus were the most common cardiovascular risk factors. The thromboembolic risk score resulted being very high in AIS patients, suggesting a considerable burden of atherosclerosis; furthermore, a moderate-to-severe neurological disability was detected in these patients at hospital admission.

Table 2 lists the basal conventional echocardiographic data obtained among AIS patients. As compared to reference range values [20, 27], the RWT and the LVMi were markedly increased in AIS patients, while, the LVEF was generally found within the normal range. Moreover, the linear and volumetric measurements of LA size were significantly increased in AIS patients if compared with normal ranges; impaired diastolic function was quite common; we detected an impaired relaxation pattern of LV diastolic filling (grade 1 diastolic dysfunction) with echocardiographic signs of increased LVFP (average E/e′ ratio > 13).

Table 3 shows the most important functional parameters of the global LA systolic strain, echocardiographically obtained from the two apical views (four-chamber and two-chamber views) in the whole patient population. As compared to the accepted reference values [28, 29], GSA+, TGSA and GSR + values were significantly decreased in AIS patients in both the echocardiographic apical views. Consequently, the GLAPS value and the GLAPS/LAVi ratio were also markedly reduced, whereas, the E/GLAPS ratio and the

Table 1 The main demographic and clinical characteristics of the study population

Clinical parameters	AIS patients (n = 85)
Age (years)	74.1 ± 12.1
Males (%)	49 (57.7)
BSA (m^2)	1.8 ± 0.2
GFR (ml/min/m^2)	75.3 ± 22.1
Smokers (%)	14 (16.5)
Type 2 diabetes mellitus (%)	22 (25.9)
Hypertension (%)	66 (77.7)
Dyslipidemia (%)	45 (52.9)
Prior stroke (%)	20 (23.5)
> 40% carotid artery stenosis (%)	26 (30.6)
History of IHD (%)	25 (29.4)
CHA_2DS_2-VASc Risk Score	5.4 ± 1.4
Rankin "in" Scale	3.0 ± 1.6
Ace-i/ARBs tp (n, %)	64 (75.3)
Beta-blocker tp (n, %)	33 (38.8)
Diuretic tp (n, %)	10 (11.8)
Statin tp (n, %)	55 (64.7)
Antiplatelet tp (n, %)	77 (90.6)
Anticoagulant tp (n, %)	11 (12.9)

Data are expressed as mean ± SD or as a count and percentage

Ace-i/ARBs tp therapy with angiotensin-converting-enzyme (ACE)-inhibitors or Angiotensin II receptor blockers (ARBs); *AIS patients* acute ischemic stroke patients; *BSA* body surface area; *CHA2DS2-VASc Score* congestive heart failure (included left ventricular dysfunction), hypertension, aged 75 or more, diabetes, stroke/TIA/thromboembolism, vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), aged 65–74, sex category: female; *GFR* glomerular filtration rate; *IHD* ischemic heart disease; *Pts* patients; *Rankin "in" Score* modified Rankin Scale, measured at the admission to the Neurology Department; *SD* standard deviation; *Tp* therapy

Table 2 Basal conventional echocardiographic data of all study population

Echo-parameters	Reference range in women	Reference range in men	AIS pts (n = 85)
RWT	0.22–0.42	0.24–0.42	0.5 ± 0.1
LVMi (g/m^2)	43–95	49–115	107.4 ± 27.3
LVEDVi (ml/m^2)	29–61	34–74	42.9 ± 14.0
LVEF (%)	54–74	52–72	59.4 ± 10.8
LA A-P diam (mm)	2.7–3.8	3.0–4.0	43.2 ± 5.5
LAVi (ml/m^2)	16–34	16–34	39.7 ± 13.7
E/A ratio	0.99 ± 0.31 (0.53–1.80)[a]	0.96 ± 0.27 (0.53–1.80)[a]	0.9 ± 0.4
Average E/e′ ratio	8.6 ± 2.2 (4.6–13.5)[a]	8.4 ± 2.2 (4.6–13.5)[a]	14.1 ± 5.7

Data are expressed as mean ± SD

AIS pts acute ischemic stroke patients; *LA* left atrial; *LA A-P diam* left atrial anteroposterior diameter; *LAVI* left atrial volume indexed; *LV* left ventricular; *LVEDVI* left ventricular end-diastolic volume indexed; *LVEF* left ventricular ejection fraction; *LVMI* left ventricular mass indexed; *Pts* patients; *RWT* relative wall thickness

[a]Data expressed as mean ± SD (95% confidence interval) and referred to subjects aged > 60 years

Table 3 The main left atrial functional parameters obtained in AIS patients

STE variables	AIS patients (n = 85)
GSA + (%) 4C	15.69 ± 5.40
GSA + (%) 2C	15.64 ± 5.03
TGSA (%) 4C	20.54 ± 6.57
TGSA (%) 2C	20.45 ± 6.14
TPPS (s) 4C	1.26 ± 0.18
TPPS (s) 2C	1.28 ± 0.19
GSR + (1/s) 4C	0.98 ± 0.31
GSR + (1/s) 2C	1.00 ± 0.32
TPPSR (s) 4C	1.06 ± 0.19
TPPSR (s) 2C	1.08 ± 0.18
GLAPS (%)	15.71 ± 4.70
GLAPS/LAVI (%/ml/m^2)	0.45 ± 0.21
E/GLAPS (m/s)	5.51 ± 2.73
E/e′/GLAPS	1.07 ± 0.93

Data are expressed as mean ± SD

AIS patients acute ischemic stroke patients; *GLAPS* global left atrial peak strain; *LAVI* left atrial volume indexed; *GSA +* positive global atrial strain; *GSR +* the first positive global strain rate; *Pts* patients; *STE* speckle tracking echocardiography; *TGSA* the sum of the peak positive and of the peak negative strain; *TPPS* time to peak positive strain; *TPPSR* time to peak positive strain rate; *4C* four-chamber apical view; *2C* two-chamber apical view

E/e′/GLAPS ratio were significantly increased, suggesting a pathologic LA chamber stiffness.

Moreover, the GLAPS value resulted being reduced in the whole population of stroke patients regardless of the stroke subtypes (p = 0.81 for CE stroke vs. LAA stroke, p = 0.27 for CE stroke vs. SVO stroke and p = 0.06 for LAA stroke vs. SVO stroke).

Finally, Spearman correlation coefficients showed a significant negative correlation between GLAPS and both Rankin "in" Scale (Rho − 0.31, p = 0.004) and CHA_2DS_2-VASc Risk Score (Rho − 0.44, p < 0.0001).

Predictors of outcome in stroke patients

At 1 year follow-up (330 ± 60 days), 14 deaths and 17 hospital readmissions for cardiovascular causes were detected in the whole population of AIS patients. Eight patients underwent surgical procedures, such as carotid endarterectomy (three patients) and cardiac surgery (five patients), while nine patients were hospitalized because of recurrent stroke (three patients), heart failure (four patients), arrhythmias associated with hemodynamic instability (one patient) and major bleeding (one patient).

At the univariate Cox analysis (Table 4), the variables associated with the occurrence of MACE at 1-year follow-up, were age, GFR, the Rankin "in" Scale, SVO stroke, Ace-i/ARBs therapy (as clinical variables) and LVEF, LAVI, average E/e′ ratio and GLAPS (as morphological and functional echo variables) with HR ranging from 0.39 to 1.59. At the multivariate analysis, GLAPS, GFR and Rankin "in" Scale confirmed their significance with HR (95% CI) of 0.78 (0.70–0.86), 0.98 (0.95–0.99) and 1.69 (1.25–2.29), respectively. Age and LAVi were no more significant.

The ROC curve analysis highlighted that a GLAPS value ≤ 15.5% predicted the occurrence of MACE at 1-year follow-up with sensitivity of 100% and specificity of 80%. AUC was 0.8981.

The Kaplan–Meier survival curves for the two strata of the GLAPS value (> vs. ≤ 15.5%) are depicted in Fig. 2. Log-Rank test for the differences between the two curves showed a significant p value < 0.0001.

Table 4 Univariate and multivariate Cox proportional hazard ratio models

Variables	Univariate Cox regression model			Multivariate Cox regression model		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	**1.05**	**1.01–1.09**	**0.01**	0.96	0.92–1.00	0.07
Male sex	1.03	0.51–2.11	0.93			
BSA	0.33	0.05–2.25	0.26			
GFR	**0.97**	**0.95–0.98**	**< 0.0001**	**0.98**	**0.95–0.99**	**0.03**
Smokers	0.71	0.25–2.02	0.51			
Diabetes mellitus	1.61	0.76–3.43	0.22			
Hypertension	1.34	0.55–3.26	0.52			
Dyslipidemia	0.72	0.35–1.46	0.36			
Prior stroke	1.06	0.47–2.37	0.89			
History of IHD	0.67	0.29–1.57	0.36			
CHA2DS2-VASc Risk Score	1.26	0.96–1.65	0.10			
Rankin "in" Scale	**1.59**	**1.22–2.07**	**0.001**	**1.69**	**1.25–2.29**	**0.001**
CE stroke	1.56	0.72–3.39	0.26			
SVO stroke	**0.39**	**0.18–0.85**	**0.02**			
LAA stroke	2.00	0.98–4.08	0.06			
AC E-i/ARBs tp	**0.45**	**0.22–0.95**	**0.03**			
Beta-blocker tp	1.20	0.59–2.46	0.61			
Statin tp	0.59	0.29–1.20	0.14			
LVMi	1.01	0.99–1.02	0.12			
LVEF	**0.96**	**0.93–0.98**	**0.001**			
Average E/e′ ratio	**1.11**	**1.05–1.17**	**0.0003**			
LAVi	**1.03**	**1.01–1.05**	**0.01**	1.02	0.99–1.05	0.06
GLAPS	**0.78**	**0.72–0.84**	**< 0.0001**	**0.78**	**0.70–0.86**	**< 0.0001**

Significant p values are in bold

ACE-i/ARBs tp therapy with angiotensin-converting-enzyme (ACE)-inhibitors or Angiotensin II receptor blockers (ARBs); *BSA* body surface area; *CE* cardio-embolic; *CHA2DS2-VASc Score* congestive heart failure (included left ventricular dysfunction), hypertension, aged 75 or more, diabetes, stroke/TIA/thromboembolism, vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), aged 65–74, sex category: female; *GFR* glomerular filtration rate; *GLAPS* global left atrial peak strain; *IHD* ischemic heart disease; *LAA* large artery atherosclerosis; *LAVI* left atrial volume indexed; *LVEF* left ventricular ejection fraction; *LVMI* left ventricular mass indexed; *Rankin "in" Score* modified Rankin Scale, measured at the admission to the Neurology Department; *SVO* small vessel occlusion; *Tp* therapy

Discussion

Extensive studies have highlighted the strong correlation between LA enlargement (assessed by echocardiography) and the incidence of adverse cardiovascular events [4–8].

For instance, the Atherosclerosis Risk in Communities (ARIC) Study fully described how the LA size affects both LA and LV functions, resulting a strong predictor of cardiovascular death, all-cause mortality and morbidity [4]. Furthermore, Framingham Heart Study (FHS) [5] demonstrated that LA size was a powerful predictor of stroke in males and death in both sexes, after adjusting for cardiovascular risk factors.

Several theories have been proposed to explain the mechanism underlying the correlation between LA size and the subsequent morbidity [5, 30].

One potential explanation is that blood stasis and thrombus formation might occur more often as the size of the LA increases [5]. Indeed, elevated intra-atrial pressure not only leads to LA enlargement but also to a decrease in LA flow velocity enhancing thrombus formation and possible embolic stroke [5, 31].

Moreover, LA enlargement is one of the main risk factors for the development of AF, which is a well-known risk factor for both embolic stroke and mortality [5, 31].

Additionally, LA enlargement represents a marker of structural heart disease, hypertension, or LV hypertrophy and it is thereby associated with a higher incidence of stroke and mortality [4].

Left atrial enlargement reflects the atrial remodeling process occurring secondary to pressure and/or volume overload [32].

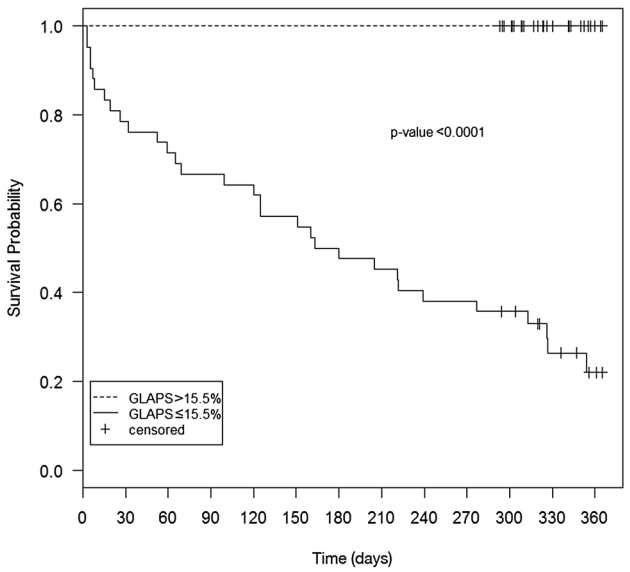

Fig. 2 Kaplan–Meier survival curves for the two strata of GLAPS value in stroke patients. A GLAPS value ≤ 15.5% was associated with significantly reduced event-free survival rates at 1-year follow-up, in patients with AIS. Dotted line represents event-free survival for patients with GLAPS > 15%. Straight line represents event-free survival for patients with GLAPS ≤ 15.5%. *GLAPS* global left atrial peak strain, *MACE* major adverse cardiovascular events

Hypertension [33], type 2 diabetes mellitus [34], hyperlipidemia [33] and ischemic heart disease [33] accelerate the LA remodeling process, through earlier development and more severe diastolic dysfunction, worsened by neurohormonal path activation as well as by development of atrial myopathy secondary to oxidative stress and lipoapoptosis [35]. LA remodeling may also arise as a consequence of increased arterial stiffness especially in elderly individuals [36].

Kamel et al. [37] demonstrated that aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or atrial cardiomyopathy, that can result in thromboembolism before AF develops.

Left atrial enlargement is usually associated with LA dysfunction, early detected by LA functional parameters, evaluated by 2D-STE. The latter, such as GLAPS, are a more direct measure of the intrinsic properties of the myocardium, while conventional morphological parameters, such as LAVi, just represent an indirect estimation of LA function.

GLAPS reflects the LA reservoir function. It's a rapid and simple measure that may elucidate the role of atrial function in several pathophysiological conditions, such as: mitral valve disease, supraventricular arrhythmias, hypertension, coronary heart disease, heart failure, atrial stunning and cardiomyopathy.

Currently, normal reference ranges for atrial function using speckle-tracking echocardiography are based on few studies, and remain to be established. Miglioranza et al. [28], i.e., identified normal average values of 19.7% for biplane GLAPS, while a recent meta-analysis of 40 studies [29] revealed a normal reference range for reservoir strain of 39% (95% CI 38–41%).

Several studies [12, 38, 39] described the reduced LA strain as a marker for identification of AF patients at high embolic risk. Moreover, it has been demonstrated a clear correlation between an impaired LA strain and the amount of LA wall fibrosis, as assessed by delayed-enhancement MRI [40]. Left atrial strain is inversely proportional to LA fibrosis, regardless of the presence or absence of AF [40–42] and a significant decrease in GLAPS value reflects a more advanced LA pathological remodeling [43, 44].

Few researchers, however, investigated LA functional parameters in AIS patients with no history of AF [13].

The present study was prospectively conducted on 85 AIS patients, without documented AF. They presented moderate disability, high thromboembolic risk score and a high incidence of the main cardiovascular risk factors, i.e. hypertension, dyslipidemia, type 2 diabetes mellitus, and several comorbidities (Table 1). GLAPS was found significantly impaired in each of the three subtypes of ischemic stroke, with no significant differences between subtypes. Consistent with previous studies [12, 38, 39], our findings confirmed that a reduced GLAPS value might identify patients at high cardio-embolic risk and with moderate-to-severe neurological disability.

We recognized that the main pathognomonic factors responsible for accelerating the LA remodeling process in AIS patients were aging, cardiovascular risk factors and comorbidities (i.e. chronic kidney disease). The pathophysiological process is characterized by the chamber's dilatation, fibrosis and stiffening, and, hence, impaired GLAPS value. Left atrial fibrosis, in turn, reduces LA compliance during the LA reservoir phase, leading to blood flow stasis in LA and LAA, dramatically augmenting the incidence of death and hospital readmissions for cardiovascular diseases at the 1-year follow-up.

Our findings suggest that the LA morpho-functional dysfunction is directly proportional to severity of clinical presentation and to patient's atherosclerotic burden.

The two-dimensional-STE allows a rapid and reliable prognostic stratification of AIS patients; a GLAPS value ≤ 15.5%, assessed by 2D-STE, might quickly reveal the AIS patients with high degree of hemodynamic impairment.

The potential clinical implications of our findings could be that in a stroke patient without AF history, a reduced GLAPS value could strengthen the indication for loop recorder implantation (to detect possible atrial arrhythmias) and/or for anticoagulation therapy (particularly in CE stroke patients) due to severe atrial cardiomyopathy.

The left atrium should be assessed by integrating the 2D-STE (for LA functional evaluation) and 2D-conventional echocardiography (for LA morphological measurements) together with clinical evaluation of thromboembolic risk by CHA2DS2-Vasc Risk Score.

The present study presented the advantage of prospectively selecting enough number of AIS patients in approximately 4 months.

LA longitudinal speckle tracking suffers from the same limitations of the conventional speckle tracking, such as the intervendor variability, the dependence on good image quality (all kinds of ultrasound noise reduce the tracking quality) and the temporal stability of tracking patterns [45]. Although we used the same software employed for the ventricular STE-analysis, it was able to clearly define LA deformation throughout the cardiac cycle and to obtain a rapid assessment of LA functional parameters.

Researchers have not reached an agreement concerning the method of choice for LA tracking modalities; some prefer using only the apical 4C-view [46], others the biplane method [47], others the triplane method [11]. Moreover, there is no consensus concerning the decision whether including or not the LA roof, since its motion is limited by the attachment of the four pulmonary veins [48]. Additionally, some researchers do not consider the strain of interatrial septum (consisting of fibromuscular tissue), paying attention only to the LA lateral wall [49].

Conclusions

LA strain and LA volume provide complementary information about the structural changes taking place in the left atrium.

Our data underline that a significantly reduced GLAPS value, compared to the traditional echo-parameters, might have an independent prognostic value. In particular, GLAPS values ≤ 15.5%, assessed by 2D-STE, suggest higher burden of cardiovascular disease and greater severity of atrial cardiomyopathy, regardless the stroke subtype and AF. This functional parameter seems to allow an additional quick and reliable prognostic risk stratification of the AIS patients with no evidence of AF in the medium and short-term follow-up. On the other hand, some conventional clinical parameters, like a more severe neurological and renal impairment, maintained their prognostic strength.

In conclusion, larger-scale prospective studies are necessary to identify the GLAPS cut-off value who can better stratify the patients with a higher risk of cerebrovascular accidents.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Libman RB, Sacco RL, Shi T, Tatemichi TK, Mohr JP (1992) Neurologic improvement in pure motor hemiparesis: implications for clinical trials. Neurology 42(9):1713–1716
2. Gresham GE, Kelly-Hayes M, Wolf PA, Beiser AS, Kase CS, D'Agostino RB (1998) Survival and functional status 20 or more years after first stroke: the Framingham Study. Stroke 29(4):793–797
3. Warlow CP (1998) Epidemiology of stroke. Lancet 352(Suppl 3):S1–S4
4. Nagarajarao HS, Penman AD, Taylor HA, Mosley TH, Butler K, Skelton TN, Samdarshi TE, Aru G, Fox ER (2008) The predictive value of left atrial size for incident ischemic stroke and all-cause mortality in African Americans: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 39(10):2701–2706
5. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D (1995) Left atrial size and the risk of stroke and death: the Framingham Heart Study. Circulation 92(4):835–841
6. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, Diamond PM, Marra MA, Gersh BJ, Wiebers DO, Petty GW, Seward JB (2001) Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc 76(5):467–475
7. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, Enriquez-Sarano M (2002) Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol 40(8):1425
8. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB (2004) Risks for atrial fibrillation and congestive heart failure in patients ≥ 65 years of age with abnormal left ventricular diastolic relaxation. Am J Cardiol 93(1):54–58
9. Ogata T, Matsuo R, Kiyuna F, Hata J, Ago T, Tsuboi Y, Kitazono T, Kamouchi M, FSR I (2017) Left atrial size and long-term risk of recurrent stroke after acute ischemic stroke in patients with nonvalvular atrial fibrillation. J Am Heart Assoc. https://doi.org/10.1161/JAHA.117.006402
10. Biteker M, Kayataş K, Başaran Ö, Dogan V, Özlek E, Özlek B (2017) The role of left atrial volume index in patients with a first-ever acute ischemic stroke. J Stroke Cerebrovasc Dis 26(2):321–326
11. Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP (2009) Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr 22(3):299–305
12. Sasaki S, Watanabe T, Tamura H, Nishiyama S, Wanezaki M, Sato C, Yamaura G, Ishino M, Arimoto T, Takahashi H, Shishido T, Miyamoto T, Kubota I (2014) Left atrial strain as evaluated by two-dimensional speckle tracking predicts left atrial appendage

dysfunction in patients with acute ischemic stroke. BBA Clin 2:40–47
13. Kim D, Shim CY, Cho IJ, Kim YD, Nam HS, Chang HJ, Hong GR, Ha JW, Heo JH, Chung N (2016) Incremental value of left atrial global longitudinal strain for prediction of post stroke atrial fibrillation in patients with acute ischemic stroke. J Cardiovasc Ultrasound 24(1):20–27
14. WHO MONICA Project Principal Investigators (1988) The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. J Clin Epidemiol 41(2):105–114
15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137:263–272
16. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd (1993) 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 24(1):35–41
17. Rankin J (1957) Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 2(5):200–215
18. Bonita R, Beaglehole R (1988) Recovery of motor function after stroke. Stroke 19(12):1497–1500
19. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J (1988) Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19(5):604–607
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) 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 28:1–39
21. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD (2016) 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 29:277–314
22. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23:685–713
23. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E (1985) Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol 6:359–365
24. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS (1988) Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 61(1):123–130
25. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG (1997) Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation 95(9):2262–2270
26. North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, Eliasziw M (1991) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 325:445–453
27. Caballero L, Kou S, Dulgheru R, Gonjilashvili N, Athanassopoulos GD, Barone D, Baroni M, Cardim N, Gomez de Diego JJ, Oliva MJ, Hagendorff A, Hristova K, Lopez T, Magne J, Martinez C, de la Morena G, Popescu BA, Penicka M, Ozyigit T, Rodrigo Carbonero JD, Salustri A, Van De Veire N, Von Bardeleben RS, Vinereanu D, Voigt JU, Zamorano JL, Bernard A, Donal E, Lang RM, Badano LP, Lancellotti P (2015) Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. Eur Heart J Cardiovasc Imaging 16(9):1031–1041
28. Miglioranza MH, Badano LP, Mihăilă S, Peluso D, Cucchini U, Soriani N, Iliceto S, Muraru D (2016) Physiologic determinants of left atrial longitudinal strain: a two-dimensional speckle-tracking and three-dimensional echocardiographic study in healthy volunteers. J Am Soc Echocardiogr 29(11):1023–1034.e3
29. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K (2017) Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. J Am Soc Echocardiogr 30(1):59–70.e8
30. Di Tullio MR, Zwas DR, Sacco RL, Sciacca RR, Homma S (2003) Left ventricular mass and geometry and the risk of ischemic stroke. Stroke 34(10):2380–2384
31. Di Tullio MR, Sacco RL, Sciacca RR, Homma S (1999) Left atrial size and the risk of ischemic stroke in an ethnically mixed population. Stroke 30(10):2019–2024
32. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS (2006) Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 47(12):2357–2363
33. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB (2002) Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 90(12):1284–1289
34. Peterson LR, Waggoner AD, de las Fuentes L, Schechtman KB, McGill JB, Gropler RJ, Dávila-Román VG (2006) Alterations in left ventricular structure and function in type-1 diabetics: a focus on left atrial contribution to function. J Am Soc Echocardiogr 19(6):749–755
35. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, Benjamin EJ (2004) Obesity and the risk of new-onset atrial fibrillation. JAMA 292(20):2471–2477
36. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC (2005) The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail 11(3):191–195
37. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, Stein PK, deFilippi CR, Gottesman RF, Heckbert SR, Kronmal RA, Soliman EZ, Longstreth WT Jr (2018) Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). Stroke 49(4):980–986
38. Saha SK, Anderson PL, Caracciolo G, Kiotsekoglou A, Wilansky S, Govind S, Mori N, Sengupta PP (2011) global left atrial strain correlates with CHADS2 risk score in patients with atrial fibrillation. J Am Soc Echocardiogr 24:506–512
39. Shih JY, Tsai WC, Huang YY, Liu YW, Lin CC, Huang YS, Tsai LM, Lin LJ (2011) Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. J Am Soc Echocardiogr 24(5):513–519
40. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, Rao SN, Blauer J, Fish EN, Dibella EV, Macleod RS, McGann C, Litwin SE, Marrouche NF (2010) 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 3(3):231–239
41. Her AY, Choi EY, Shim CY, Song BW, Lee S, Ha JW, Rim SJ, Hwang KC, Chang BC, Chung N (2012) Prediction of left atrial fibrosis with speckle tracking echocardiography in mitral valve disease: a comparative study with histopathology. Korean Circ J 42(5):311–318
42. Longobardo L, Todaro MC, Zito C, Piccione MC, Di Bella G, Oreto L, Khandheria BK, Carerj S (2014) Role of imaging in assessment of atrial fibrosis in patients with atrial fibrillation: state-of-the-art review. Eur Heart J Cardiovasc Imaging 15(1):1–5
43. Tops LF, Delgado V, Bertini M, Marsan NA, Den Uijl DW, Trines SA, Zeppenfeld K, Holman E, Schalij MJ, Bax JJ (2011) Left atrial strain predicts reverse remodeling after catheter ablation for atrial fibrillation. J Am Coll Cardiol 57(3):324–331
44. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ (2014) Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr 27(5):463–478
45. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Kolias TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP (2015) Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 16:1–11
46. Pagola J, González-Alujas T, Flores A, Muchada M, Rodriguez-Luna D, Seró L, Rubiera M, Boned S, Ribó M, Alvarez-Sabin J, Evangelista A, Molina CA (2014) Left atrial strain is a surrogate marker for detection of atrial fibrillation in cryptogenic strokes. Stroke 45:e164–e166
47. Açar G, Bulut M, Arslan K, Alizade E, Ozkan B, Alici G, Tanboga IH, Yazicioğlu MV, Akcakoyun M, Esen AM (2013) Comparison of left atrial mechanical function in nondipper versus dipper hypertensive patients: a speckle tracking study. Echocardiography 30:164–170
48. Donal E, Behagel A, Feneon D (2015) Value of left atrial strain: a highly promising field of investigation. Eur Heart J Cardiovasc Imaging 16:356–357
49. Baltabaeva A, Marciniak M, Bijnens B, Parsai C, Moggridge J, Antonios TF, Macgregor GA, Sutherland GR (2009) How to detect early left atrial remodelling and dysfunction in mild-to-moderate hypertension. J Hypertens 27:2086–2093