Heart and Vessels (2019) 34:1936–1943
https://doi.org/10.1007/s00380-019-01445-7

ORIGINAL ARTICLE

Left atrial remodeling index is a feasible predictor of poor prognosis in patients with acute ischemic stroke

Naoto Hashimoto[1] · Tetsu Watanabe[1] · Harutoshi Tamura[1] · Hayato Tsuchiya[1] · Masahiro Wanezaki[1] · Shigehiko Kato[1] · Satoshi Nishiyama[1] · Takanori Arimoto[1] · Hiroki Takahashi[1] · Tetsuro Shishido[1] · Masafumi Watanabe[1]

Received: 17 December 2018 / Accepted: 31 May 2019 / Published online: 5 June 2019

Abstract
Left atrial (LA) functional remodeling as well as LA structural remodeling are associated with incident LA appendage (LAA) thrombus formation. This study aimed to elucidate whether combined assessment of LA functional and structural remodeling can predict LAA dysfunction and recurrent cerebrovascular events in patients with acute ischemic stroke. We performed transthoracic and transesophageal echocardiography in 196 patients within 7 days after acute ischemic stroke. Peak systolic LA strain was evaluated using 2D speckle tracking imaging. We defined the ratio of LA peak systolic strain to LA volume index (LAVI) as the LA remodeling index (LARI). All patients were prospectively followed for recurrent cerebrovascular events. We divided patients into four groups according based on the LARI quartile. LAA dysfunction increased with decreasing LARI. In total, 52 recurrent cerebrovascular events were noted during the median follow-up period of 700 days. Patients with recurrent cerebrovascular events had lower LARI than those without recurrent events (0.50 ± 0.45 vs. 1.10 ± 0.95, $P < 0.001$). Kaplan–Meier analysis showed that patients with lower LARI were more susceptible to recurrent cerebrovascular events than those with higher LARI. Multivariate Cox proportional hazard regression analysis showed that LARI was an independent predictor of recurrent cerebrovascular events after adjustment for confounding factors. Net reclassification index improved with the addition of LARI to basic predictors. LARI is a novel feasible parameter for LAA dysfunction and can predict recurrent cerebrovascular events in patients with acute ischemic stroke.

Keywords Left atrial remodeling · Left atrial strain · 2D speckle tracking · Ischemic stroke · Transthoracic echocardiography

Introduction

Cardioembolic stroke has been characterized as an important clinical issue, as it is the most common cause of death in patients with acute ischemic stroke [1, 2]. Left atrial appendage (LAA) is a major source of thromboembolism in patients with stroke and atrial fibrillation (AF) [3–5]. Moreover, the presence of spontaneous echocardiographic contrast (SEC) and decreased LAA emptying flow velocity (LAA eV), evaluated by transesophageal echocardiography (TEE), can predict thromboembolism in patients with AF [6]. However, TEE is a semi-invasive procedure. It is well known that left atrial (LA) dilatation, as LA structural remodeling, is associated with LAA thrombus formation [6–8]. Recently, we and others reported that LA peak systolic strain by two-dimensional speckle tracking imaging can evaluate LAA dysfunction and predict thrombus formation in patients with acute ischemic stroke [9–12]. It was reported that LA functional remodeling is feasible to predict cardiovascular outcomes as well as LA structural remodeling [13]. However, whether the combined assessment of LA functional and structural markers can predict clinical outcome in patients with ischemic stroke is still unclear. Therefore, we investigated whether the combined marker of LA peak systolic strain and LA size more accurately predicts LAA dysfunction and recurrent cerebrovascular events.

✉ Tetsu Watanabe
tewatana@med.id.yamagata-u.ac.jp

[1] Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

Methods

Study patients

We enrolled 216 consecutive patients with acute ischemic stroke who underwent transthoracic echocardiography (TTE) and TEE between April 2010 and December 2016. TTE and TEE were performed at a median of 7 days after stroke onset. All patients underwent cerebral computed tomography and/or magnetic resonance imaging, after which neurologists diagnosed the category of clinical ischemia. Clinical ischemic stroke category was defined by the National Institute of Neurological Disorders and Stroke (NINDS) [1]. Patients with malignant tumors or severe infections, and those who failed to undergo TEE were excluded, and the remaining 196 patients were enrolled in the study and followed up prospectively.

Ethics

The study protocol was approved by the institutional ethics committee of Yamagata University School of Medicine, and all participants provided written informed consent. All procedures were performed in accordance with the Declaration of Helsinki.

Echocardiography

TTE and TEE were performed using a Vivid E9 ultrasound instrument (GE Healthcare, Wauwatosa, WI, USA) equipped with a sector transducer (carrier frequency 2.5 or 3.75 MHz). A 5-MHz phased array multiplane probe was used for TEE. All images were stored digitally for playback and analysis. All echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography [14]. Left ventricular ejection fraction (LVEF) and LA volume were calculated using the biplane disc method, with apical two- and four-chamber views. The peak velocities of early (*E*) and late (*A*) transmitral flow, early diastolic deceleration time, early diastolic mitral annular velocity (*E*′), and the ratio of peak early mitral annular velocity to *E* wave (*E*/*E*′) were measured using a standard technique by Doppler imaging. LA volume was indexed to body surface area (LAVI) [15]. Atrial septal aneurysm, patent foramen ovale, SEC, LAA thrombus, and LAA emptying flow velocity (LAA eV) were evaluated by TEE. SEC was considered present when dynamic "smoke-like" echoes were observed within the atria that could not be eliminated by changes in gain settings [15]. LAA thrombus was diagnosed when a fixed or mobile echogenic mass could be clearly differentiated from the wall of the left atrium or LAA. LAA eV was measured using pulsed wave Doppler, with the sample volume placed 1 cm distal to the mouth of the appendage by TEE. As previously reported, LAA dysfunction was defined as the presence of LAA thrombus and/or severe SEC [16, 17].

Measurement of LA strain and LARI

LA strain was measured by two-dimensional speckle tracking echocardiography, as previously reported [9, 18]. We calculated the average value for LA peak systolic strain obtained from the apical four-chamber, two-chamber, and apical long axis views.

We defined the ratio of LA peak systolic strain and LAVI as LA remodeling index (LARI = [LA peak systolic strain/LAVI]).

Hemostatic markers

Blood samples were collected at the time of the echocardiographic studies. General biochemical parameters were measured using routine laboratory methods. Estimated glomerular filtration rate (eGFR) was calculated using the following equations: eGFR in male patients = $194 \times \text{creatinine}^{-1.094} \times \text{Age}^{-0.287}$; eGFR in female patients = $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ [19].

Endpoints

We prospectively followed the patients until the occurrence of recurrent cerebrovascular events, including ischemic stroke that required rehospitalization, and cerebrovascular death. No patients were lost to follow-up after discharge.

Statistical analysis

The results were expressed as means ± standard deviation (SD) for continuous variables including LARI, and as percentages of the total number of patients for categorical variables. Data for skewed variables are presented as medians with interquartile range. The *t* test and Chi-square test were used for comparison of continuous and categorical variables, respectively. When the data were not normally distributed, the Mann–Whitney *U* test was used. Significant variables in the univariate analysis were entered into the multivariate analysis. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses with Cox proportional hazards regression were used to determine significant predictors of recurrent cerebrovascular events. Multicollinearity was checked by variance inflation factor. Logarithm-transformed brain natriuretic peptide (BNP) levels were used in the Cox analysis. The net reclassification index (NRI)

and integrated discrimination index (IDI) were calculated to measure the quality of improvement for the correct reclassification following the addition of LARI to the baseline model. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using a standard statistical program package (JMP version 11.0; SAS Institute Inc. Cary, NC, USA and R 3.0.2 with additional packages including Rcmdr, Epi, pROC, and PredictABEL).

Results

Association between LAA dysfunction and LARI

Table 1 shows the baseline clinical characteristics of the patients with acute ischemic stroke. The mean age of the patients was 72 ± 11 years; 66% of them were male, and 75 had AF (37, paroxysmal AF; 38, chronic AF). In total, 64 patients each (33%) had cardioembolic and atherothrombotic stroke, and 9 (5%) had lacunar stroke. Among patients with paroxysmal AF, 12 (32%) patients underwent TTE and TEE during AF rhythm.

There was a fair correlation between LARI and LAA eV, irrespective of the heart rhythm ($R = 0.483$, $P < 0.001$, Fig. 1a). We divided the patients into four groups according to the quartile of LARI. The prevalence of LAA dysfunction was found to increase with decreasing LARI (Fig. 1b).

Table 1 Baseline clinical characteristics of the study population

	$n = 196$
Age, years	72 ± 11
Gender (male/female)	130 / 66
Heart rate (bpm)	68 ± 15
Atrial fibrillation, n (%)	75 (38)
Paroxysmal, *n*	37
Chronic, *n*	38
Hypertension, *n* (%)	152 (78)
Diabetes mellitus, *n* (%)	63 (32)
Dyslipidemia, *n* (%)	102 (52)
Smoking, *n* (%)	106 (54)
Chronic heart failure, *n* (%)	32 (16)
CHA_2DS_2VASc score (at discharge)	5.2 ± 1.5
NIHSS	1.0 (0−3.0)
NINDS clinical categories	
Cardioembolic stroke, *n* (%)	64 (33)
Atherothrombotic stroke, *n* (%)	64 (33)
Lacunar stroke, *n* (%)	9 (5)
Other or undetermined, *n* (%)	59 (30)

Data was expressed as mean ± SD, number (percentage) of subjects or median (interquartile range)

bpm beats per minute, *NIHSS* National Institute of Health Stroke Scale, *NINDS* the US National Institute of Neurological Disorders and Stroke

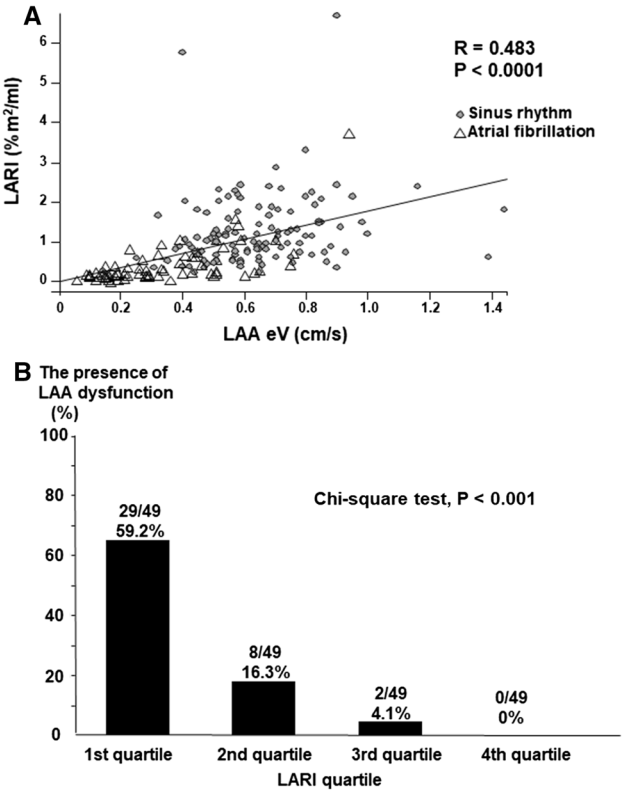

Fig. 1 Relationship between LARI and echocardiographic parameters for LAA function. **a** Correlation of LARI and LAA eV. **b** Proportion of patients with LAA dysfunction according to the quartile of LARI. The quartiles of LARI were the 1st quartile (< 0.30% m^2/mL), 2nd quartile (0.30–0.74% m^2/mL), 3rd quartile (0.75–1.23% m^2/mL), and 4th quartile (> 1.23% m^2/mL). LAA dysfunction was defined as severe SEC and/or LAA thrombus. *LARI* left atrial remodeling index, *LAA dysfunction* left atrial appendage dysfunction, *LAA eV* left atrial appendage emptying flow velocity, *SEC* spontaneous echocardiographic contrast

Figure 2 shows the ROC curve analysis for predicting LAA dysfunction. Each cut-off value of LARI and LA peak systolic strain for LAA dysfunction was 0.39 and 21%, respectively. The C index of LARI was significantly higher than that of LA peak systolic strain.

Clinical characteristics of patients with and without recurrent cerebrovascular events

During the median follow-up period of 700 (interquartile range, 439−1170) days, 52 patients experienced recurrent cerebrovascular events; 40 patients who developed ischemic stroke required hospitalization, and 12 patients with cerebrovascular deaths.

Table 2 shows a comparison of patients with and without cerebrovascular events. Compared to patients without

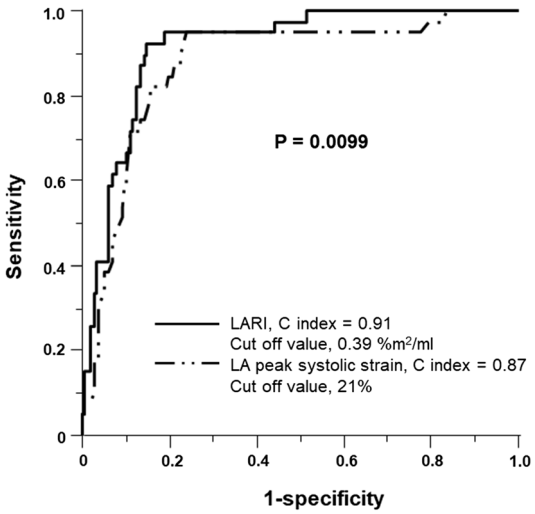

Fig. 2 ROC curve analysis for predicting LAA dysfunction. *ROC curve* receiver operating characteristic curve, *LAA* left atrial appendage, *LARI* left atrial remodeling index

cerebrovascular events, those with cerebrovascular events were older and had higher CHA_2DS_2VASc scores at discharge from the first hospitalization. There were no significant differences in the prevalence of hypertension, diabetes mellitus, dyslipidemia, and smoking history between patients with and without cerebrovascular events. Compared to patients without cerebrovascular events, those with cerebrovascular events had higher prevalence of chronic heart failure, had higher levels of high-sensitivity C-reactive protein, BNP, and had lower level of eGFR. Compared to patients without cerebrovascular events, those with cerebrovascular events showed larger LAVI, higher *E*/*E*′, and lower LA peak systolic strain. There were no significant differences in LV volume, LVEF, presence of atrial septal aneurysm, and patent foramen ovale between patients with and without cerebrovascular events. Patients with cerebrovascular events had lower LAA eV, and higher prevalence of severe SEC and LAA thrombus. Moreover, compared to patients without cerebrovascular events, those with cerebrovascular events had significantly lower LARI.

LARI and recurrent cerebrovascular events

Kaplan–Meier analysis revealed that the prevalence of recurrent cerebrovascular events increased with decreasing LARI (log-rank test, $P = 0.0001$; Fig. 3).

Univariate cox proportional hazards analysis revealed that age, atrial fibrillation, CHA_2DS_2VASc score, eGFR, log BNP levels, LAVI, LA peak systolic strain, *E*/*E*′, and LARI were significantly associated with recurrent cerebrovascular events (Table 3). Multivariate analysis revealed that LARI was independently associated with cerebrovascular events after adjustment for age, eGFR, log BNP levels, and *E*/*E*′.

Improvement of reclassification after addition of LARI to predict recurrent cerebrovascular events

We evaluated NRI and IDI to examine whether model fit and discrimination improve with the addition of LARI to basic predictors for cardioembolic stroke such as age, atrial fibrillation, CHA_2DS_2VASC score, BNP, eGFR, and *E*/*E*′. NRI and IDI were significantly improved by adding LARI to the basic predictors (Table 4).

Discussion

Main findings

The present study showed for the first time that LARI is a novel TTE parameter reflecting LA structural and functional remodeling. LARI is useful for predicting the long-term recurrence of cerebrovascular events in patients with acute ischemic stroke. The main findings from the present study were: (1) LARI was significantly associated with LAA eV and the presence of LAA dysfunction; (2) patients with lower LARI were more susceptible to recurrent cerebrovascular events than those with higher LARI; (3) LARI was an independent predictor of recurrent cerebrovascular events; and (4) the prediction model with LARI had improved prognostic capacity for patients with ischemic stroke. In the present study, a composite LA parameter LARI, which reflects both LA enlargement and LA dysfunction, was more significantly associated with the presence of LAA dysfunction compared with LA strain alone. Therefore, we used LARI as a feasible parameter to predict recurrent cerebrovascular events.

Association between LARI and LAA dysfunction

It is well known that there are three types of LA mechanical function: reservoir, conduit, and booster function [20, 21]. LA peak systolic strain reflects LA reservoir function and can be measured regardless of the heart rhythm. We previously reported that LA peak systolic strain is a feasible predictor of LAA dysfunction in patients with acute ischemic stroke [9]. Although TEE parameters such as SEC and low LAA eV were reported as reliable markers for LAA thrombus formation in patients with AF [6], TEE procedure is semi-invasive and could not be repeatedly performed in patients with ischemic stroke. Since LA strain imaging is a novel noninvasive method for predicting LAA function, repeated measurements can be performed [22]. Several studies reported that LA function evaluated by LA strain

Table 2 Comparison of patients with and without recurrent cerebrovascular events

	Event free ($n=144$)	Cerebrovascular event ($n=52$)	P values
Age (years)	70 ± 11	76 ± 10	0.0011
Gender (male/female)	94/50	36/16	0.6034
Heart rate (bpm)	70 ± 13	63 ± 11	0.3536
Atrial fibrillation, *n* (%)	41 (38)	34 (65)	< 0.0001
Paroxysmal, *n*	23	14	
Chronic, *n*	18	20	
Hypertension, *n* (%)	111 (77)	41 (79)	0.7931
Diabetes mellitus, *n* (%)	43 (30)	20 (38)	0.2595
Dyslipidemia, *n* (%)	75 (52)	27 (52)	0.9842
Smoking, *n* (%)	76 (53)	30 (56)	0.1077
Chronic heart failure, *n* (%)	17 (12)	15 (29)	0.0064
CHA_2DS_2VASc score (at discharge)	3.4 ± 1.6	4.4 ± 1.6	0.0003
Medications (at discharge)			
Antiplatelet drugs, *n* (%)	86 (60)	29 (56)	0.6205
Anticoagulants, *n* (%)	60 (42)	23 (44)	0.7487
Warfarin, *n*	31	13	
DOAC, *n*	29	10	
Blood markers			
hs-CRP (mg/dl) (IQR)	0.105 (0.044–0.26)	0.140 (0.041–0.792)	0.0347
eGFR (ml/min/1.73m^2)	73 ± 24	65 ± 21	0.0236
BNP (pg/ml) (IQR)	37.7 (11.2–137.0)	91.4 (26.7–445.5)	0.0440
TTE parameters			
LAVI (ml/m^2)	38 ± 18	58 ± 37	< 0.0001
LA peak systolic strain (%)	30.2 ± 13.8	18.7 ± 12.9	< 0.0001
LVEDV (ml)	93 ± 35	93 ± 35	0.9935
Simpson LVEF (%)	62 ± 10	59 ± 11	0.0934
E/*E*′	11.3 ± 4.5	13.3 ± 5.8	0.0109
LARI (% m^2/ml)	1.10 ± 0.95	0.50 ± 0.45	< 0.0001
TEE parameters			
Atrial septal aneurysm, *n* (%)	12 (8.2)	1 (2.0)	0.0751
Patent foramen ovale, *n* (%)	24 (16.6)	4 (7.7)	0.0878
LAA eV (cm/s)	56.0 ± 24.2	44.8 ± 24.3	0.0074
Severe SEC, *n* (%)	19 (13)	14 (27)	0.0005
LAA thrombus, *n* (%)	13 (9)	13 (25)	0.0024

Abbreviations as in Table 1. *DOAC* direct oral anticoagulants, *hs-CRP* high-sense C-reactive protein, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *TTE* transthoracic echocardiography, *LAVI* left atrial volume index, *LAEF* left atrial emptying fraction, LA peak systolic strain left atrial peak systolic strain, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *E*/*E*′ the ratio of the early transmitral flow velocity and the early mitral annular velocity, *LARI* left atrial remodeling index, *TEE* transesophageal echocardiography, *LAA eV* left atrial appendage emptying flow velocity, *SEC* spontaneous echo contrast, *LAA thrombus* left atrial appendage thrombus

can predict LAA thrombus formation in patients with acute ischemic stroke [10, 23–25]. A retrospective study using magnetic resonance imaging reported that mechanical dyssynchrony of the LA during sinus rhythm is associated with a history of stroke in patients with AF [26].

It is known that LA enlargement is also a feasible parameter for ischemic stroke associated with thrombus formation in the LAA [6–8, 27–29]. It was reported that LA strain decreases with increasing LA enlargement [30]. Conversely, it was reported that decreased LA peak systolic strain predisposes before LA enlargement in patients with LV diastolic dysfunction [31]. LA peak systolic strain is reportedly associated with the degree of LA fibrosis evaluated using cardiac magnetic resonance imaging in patients with AF [32]. Allessie et al. revealed that there are three types of LA remodeling induced by AF: electrical, functional, and structural remodeling. LA remodeling progresses with different mechanisms and time courses while affecting each other,

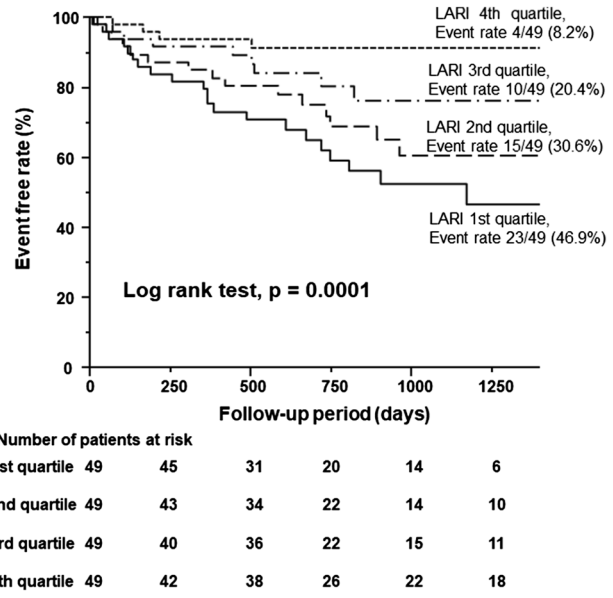

Fig. 3 Kaplan–Meier event-free curves for recurrent cerebrovascular events according to the quartiles of LARI. The quartiles of LARI are divided as Fig. 1b. *LARI* left atrial remodeling index

and may facilitate new onset of AF [33]. Therefore, it is difficult to evaluate the severity of LA remodeling by a single echocardiographic parameter. The present study revealed that LARI could simultaneously evaluate LA functional and structural remodeling, and that LARI was feasible for risk stratification of patients with LAA dysfunction.

LARI and long-term prognosis of patients with acute ischemic stroke

Once AF develops, the dysrhythmia causes LA contractile dysfunction and stasis, which further increases the risk of thromboembolism [34, 35]. It was reported that alterations in LA structure and function during sinus rhythm are causally related to thromboembolism even in patients without AF [36]. Aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or LA enlargement, which results in new onset of AF and/or thromboembolism.

The development of stroke transiently increases the development of AF owing to autonomic changes and post-stroke inflammation [37]. Recently, Kamel et al. [38] reported that systemic and atrial substrate as well as rhythm are associated with thromboembolic stroke. This report suggested that it is important to evaluate LA remodeling mainly for predicting the prognosis of patients with cerebrovascular events regardless of the heart rhythm. The results of our study suggested that LARI can sensitively detect decreased LA function prior to the development of severe LA structural enlargement, and that LARI may be a feasible predictor to reflect LA substrate including the development of potential AF. LARI can be easily measured during routine clinical echocardiography. The results of our study will help us to consider additional anticoagulation for primary prevention of cerebrovascular events in patients with LA remodeling. Therefore, LARI is a noninvasive feasible marker for detecting patients at high risk of ischemic stroke.

Table 3 Univariate and multivariate Cox proportional hazard analyses for predicting recurrent cerebrovascular events

Variables	Hazard ratio	95% CI	P-value
Univariate analysis			
Age (per 1 year increase)	1.749	1.256–2.527	0.0006
Female	1.197	0.613–2.411	0.6034
Atrial fibrillation	2.733	1.535–4.749	0.0009
CHA_2DS_2VASc score (per 1 increase)	1.321	1.084–1.620	< 0.0001
eGFR (per 1 SD increase)	0.756	0.568–0.999	0.0489
log BNP (per 1 SD increase)	1.512	1.156–1.984	0.0026
LAVI (per 1 SD increase)	2.259	1.578–3.363	< 0.0001
LA peak systolic strain (per 1 SD increase)	0.369	0.237–0.551	< 0.0001
Simpson LVEF (per 1 SD increase)	0.770	0.562–1.051	0.0992
E/*E*′ (per 1 SD increase)	2.255	1.183–4.482	0.0134
LARI (per 1 SD increase)	0.238	0.117–0.436	< 0.0001
Multivariate analysis			
Age (per 1 year increase)	1.037	1.004–1.075	0.0291
eGFR (per 1 SD increase)	0.902	0.660–1.212	0.4997
log BNP (per 1 SD increase)	1.063	0.640–1.388	0.7580
E/*E*′ (per 1 SD increase)	1.319	0.659–2.461	0.4191
LARI (per 1 SD increase)	0.411	0.195–0.789	0.0050

Abbreviations as in Tables 1 and 2. *CI* confidence interval, *per 1 SD* per 1 standard deviation, *95% CI* 95 percent confidence interval

Table 4 Addition of LARI for predicting recurrent cerebrovascular events with non-invasive baseline model

	Baseline model	Baseline model + LARI
C index (*P* value)	0.743	0.764 (0.2606)
NRI (95% CI, *P* value)	Reference	0.3248 (0.0164–0.6332, 0.0390)
IDI (95% CI, *P* value)	Reference	0.0256 (0.0021–0.0491, 0.0331)

Baseline model includes age, atrial fibrillation, CHA_2DS_2VASC score, BNP, eGFR, and E/E'

IDI integrated discrimination index, *NRI* net reclassification index. Other abbreviations as in Tables 1, 2 and 3

Limitations

This study has several limitations. First, the study population was relatively small, and this study included patients with various types of stroke. Second, this study was a single-center study. Third, we could not investigate whether all study patients had received adequate anticoagulation after their first stroke, because some patients might have had undocumented AF. However, there was no significant difference in medications between patients with and without cerebrovascular events in this study. Fourth, we did not repeatedly evaluate LARI during the follow-up period. Fifth, we could not investigate the interpatient difference in LA strain between AF and sinus rhythm, since we performed TTE and TEE at the only one time point. Further studies with a large number of participants are required to adequately assess the feasibility of LARI in patients with acute ischemic stroke.

Conclusions

Compared to other single echocardiographic markers, LARI had superior prognostic value in patients with ischemic stroke. LARI may be a noninvasive feasible predictor for poor prognosis in patients with ischemic stroke.

Acknowledgements We would like to thank the staff at the Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine for their cooperation during this study. We would like to thank Editage (www.editage.jp) for English language editing.

Compliance with ethical standards

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

References

1. National Institute of Neurological Disorders and Stroke (1990) Special report from National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 21:637–676
2. Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, Hogelin G, Marler J, McGovern P, Morosco G, Mosca L, Pearson T, Stamler J, Stryer D, Thom T (2000) Trend and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation 102:3137–3147
3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D (1998) Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98:946–952
4. Takada T, Yasaka M, Nagatsuka K, Minematsu K, Yamaguchi T (2001) Blood flow in the left atrial appendage and embolic stroke in non-valvular atrial fibrillation. Eur Neurol 46:148–152
5. García-Fernández MA, Torrecilla EG, San Román D, Azevedo J, Bueno H, Moreno MM, Delcán JL (1992) Left atrial appendage Doppler flow patterns: implications on thrombus formation. Am Heart J 124:955–961
6. Kamp O, Verhorst PM, Welling RC, Visser CA (1999) Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation. Eur Heart J 20:979–985
7. Verhorst PM, Kamp O, Visser CA, Verheugt FW (1993) Left atrial appendage flow velocity assessment using transesophageal echocardiography in nonrheumatic atrial fibrillation and systemic embolism. Am J Cardiol 71:192–196
8. Sparks PB, Mond HG, Vohra JK, Yapanis AG, Grigg LE, Kalman JM (1999) Mechanical remodeling of the left atrium after loss of atrioventricular synchrony: a long-term study in humans. Circulation 100:1714–1721
9. 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
10. Cameli M, Lunghetti S, Mandoli GE, Righini FM, Lisi M, Curci V, Tommaso CD, Solari M, Nistor D, Gismondi A, Focardi M, Favilli R, Mondillo S (2017) Left atrial strain predicts pro-thrombotic state in patients with non-valvular atrial fibrillation. J Atr Fibrillation 10:1641
11. Kupczynska K, Michalski BW, Miskowiec D, Kasprzak JD, Wejner-Mik P, Wdowiak-Okrojek K, Lipiec P (2017) Association between left atrial function assessed by speckle-tracking echocardiography and the presence of left atrial appendage thrombus in patients with atrial fibrillation. Anatol J Cardiol 18:15–22
12. Tamura H, Watanabe T, Nishiyama S, Sasaki S, Arimoto T, Takahashi H, Shishido T, Miyashita T, Miyamoto T, Nitobe J, Hirono O, Kubota I (2011) Increased left atrial volume index predicts a poor prognosis in patients with heart failure. J Card Fail 17:210–216
13. Hoit BD (2014) Left atrial size and function: role in prognosis. J Am Coll Cardiol 63:493–505
14. 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. Eur Heart J Cardiovasc Imaging 16:233–270
15. Itoh T, Kimura M, Tomita H, Sasaki S, Owada S, Horiuchi D, Sasaki K, Ishida Y, Kinjo T, Okumura K (2016) Reduced residual conduction gaps and favourable outcome in contact force-guided circumferential pulmonary vein isolation. Europace 18:531–537

16. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger PW, Hart RG (1998) Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 31:1622–1626
17. Fatkin D, Kelly RP, Feneley MP (1994) Relationship between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. J Am Coll Cardiol 23:961–969
18. 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 22:299–305
19. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, Collaborators developing the Japanese equation for estimated GFR (2009) Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53:982–992
20. Russo C, Jin Z, Liu R, Iwata S, Tugcu A, Yoshita M, Homma S, Elkind MS, Rundek T, Decarli C, Wright CB, Sacco RL, Di Tullio MR (2013) LA volumes and reservoir function are associated with subclinical cerebrovascular disease: the CABL (cardiovascular abnormalities and brain lesions) study. JACC Cardiovasc Imaging 6:313–323
21. To AC, Flamm SD, Marwick TH, Klein AL (2011) Clinical utility of multimodality LA imaging: assessment of size, function, and structure. JACC Cardiovasc Imaging 4:788–798
22. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z (2004) Two-dimensional strain — a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 17:1021–1029
23. Leung M, van Rosendael PJ, Abou R, Ajmone Marsan N, Leung DY, Delgado V, Bax JJ (2018) Left atrial function to identify patients with atrial fibrillation at high risk of stroke: new insights from a large registry. Eur Heart J 39:1416–1425
24. Zhu MR, Wang M, Ma XX, Zheng DY, Zhang YL (2018) The value of left atrial strain and strain rate in predicting left atrial appendage stasis in patients with nonvalvular atrial fibrillation. Cardiol J 25:87–96
25. Kim D, Shim CY, Hong GR, Kim MH, Seo J (2016) Clinical implications and determinants of left atrial mechanical dysfunction in patients with stroke. Stroke 47:1444–1451
26. Ciuffo L, Inoue YY, Tao S, Gucuk Ipek E, Balouch M, Lima JAC, Nazarian S, Spragg DD, Marine JE, Berger RD, Calkins H, Ashikaga H (2018) Mechanical dyssynchrony of the left atrium during sinus rhythm is associated with history of stroke in patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging 19:433–441
27. 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 92:835–841
28. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, Roman MJ, Devereux RB (2006) Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 151:412–418
29. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, Cha SS, Seward JB (2006) Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 47:1018–1023
30. Sirbu C, Herbots L, D'hooge J, Claus P, Marciniak A, Langeland T, Bijnens B, Rademakers FE, Sutherland GR (2006) Feasibility of strain and strain rate imaging for the assessment of regional left atrial deformation: a study in normal subjects. Eur J Echocardiogr 7:199–208
31. Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, Marquez E, Krisper M, Lindhorst R, Osmanoglou E, Boldt LH, Blaschke F, Haverkamp W, Tschöpe C, Edelmann F, Pieske B, Pieske-Kraigher E (2018) Potential usefulness and clinical relevance of adding left atrial strain to left atrial volume index in the detection of left ventricular diastolic dysfunction. JACC Cardiovasc Imaging 11:1405–1415
32. 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 3:231–239
33. Allessie M, Ausma J, Schotten U (2002) Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 54:230–246
34. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR (1996) Short-term predictors of incident stroke in older adults. The Cardiovascular Health Study. Stroke 27:1479–1486
35. Lodder J, Bamford JM, Sandercock PA, Jones LN, Warlow CP (1990) Are hypertension or cardiac embolism likely causes of lacunar infarction? Stroke 21:375–381
36. Piccini JP, Daubert JP (2011) Atrial fibrillation and stroke: it's not necessarily all about the rhythm. Heart Rhythm 8:1424–1425
37. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S (2014) Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res 114:1500–1515
38. Kamel H, Okin PM, Elkind MS, Iadecola C (2016) Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke 47:895–900