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Echocardiographic parameters versus CHA_2DS_2-VASc score in prediction of overall cardiac events, heart failure, and stroke in non-valvular atrial fibrillation

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Abstract

Background: *Apart from stroke, atrial fibrillation (AF) is associated with higher mortality and heart failure (HF), in which risk stratification scheme is lacking. Therefore this investigation examined the prognostic value of echocardiographic predictors against CHA_2DS_2-VASc score in permanent non-valvular AF (NVAF).*

Methods: *In 252 asymptomatic or mildly symptomatic consecutive patients with NVAF, comprehensive echocardiography was performed. Left atrial deformation parameters were also obtained by two-dimensional speckle tracking echocardiography. End-points pertaining to HF deterioration, ischemic stroke and cardiac death were recorded.*

Results: *There were 74 cardiovascular events, including 44 deterioration of HF, 22 ischemic strokes and 8 cardiovascular deaths during an average follow-up period of 20.8 ± 13.5 months (interquartile range, 8–31 months). For prediction of overall prognosis and HF, left ventricular mass index, peak early filling velocity (E), and E to tissue Doppler mitral annular early diastolic velocity ratio (E/e') outperformed CHA_2DS_2-VASc score in multivariate analysis, area under curve, and stepwise nested regression models. Left ventricular hypertrophy and E/e' > 8 showed worse overall and heart-failure free survival in Kaplan-Meier curves. For prediction of ischemic stroke, the addition of E or E/e' to CHA_2DS_2-VASc score provides extra prognostic value.*

Conclusions: *Echocardiographic parameters offer incremental value over CHA_2DS_2-VASc score for prediction of future cardiac events in NVAF.* (Cardiol J 2018; 25, 1: 60–71)

Key words: atrial fibrillation, echocardiography, heart failure, prognosis, stroke

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias confronted in daily practice; affecting 1.5–2% of the general population in the developed world [1]. It is notorious for undermining the quality of life and increasing relevant cardiovascular risks including a 5-fold risk of stroke, a 3-fold incidence of congestive heart failure (HF), and higher mortality [1]. In the aging population, AF is emerging as a major public health burden. Currently, most efforts have been dedicated to

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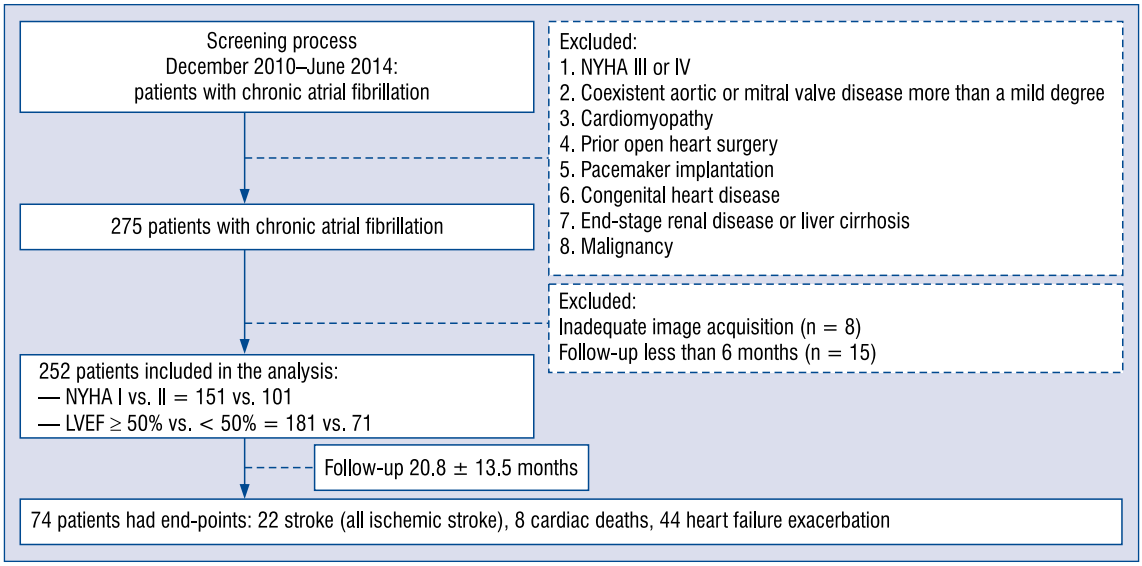

Figure 1. The study flow diagram; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association.

stroke prediction and prevention on the basis of CHA_2DS_2-VASc score. On the other hand, AF associated cardiac mortality and HF exacerbation are clinically challenging issues which are frequently encountered. The analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) study by Marijon et al. [2] surprisingly pointed out that cardiac death, but not stroke-associated death, is responsible for 37% of death in AF. Among which, progressive HF is an important determinant. It suggests that studying the contributors of AF-related adverse cardiac events and HF is as paramount as that of stroke. Although CHA_2DS_2-VASc score appears to be helpful in this aspect by some studies [3, 4], it was not generally applied for this purpose. In addition, current guidance does not stress HF prediction and there lacks a risk scheme to tackle this conundrum [5]. Since cardiac ultrasound is a noninvasive and easily assessable tool, the possibility of implementing echocardiographic parameters in risk assessment for AF related adverse cardiac events is of particular interest and needs further characterization. Indeed, several echocardiographic indexes pertaining to stroke risk stratification in AF have already been reported, namely the left atrial (LA) volume index (LAVi), LA appendage flow velocity, or LA deformation analysis [6–8]. This implies that incorporation of echocardiographic parameters to a clinical risk scheme to lower disease burden is of potential benefit. Also, CHA_2DS_2-VASc score is almost routinely obtained in every patient with AF, rendering comparison to echocardiographic indexes feasible.

Accordingly, an undertaking with this study had interests focused on echocardiographic indexes in predicting: (1) overall adverse cardiac events, (2) HF progression and, (3) ischemic stroke against CHA_2DS_2-VASc score in permanent non-valvular AF (NVAF).

Methods

Study population

Between December 2010 and June 2014, we screened 950 consecutive patients who had permanent NVAF (no coexistent aortic or mitral valve disease more than a mild degree) and had undergone a clinically indicated echocardiography in the outpatient clinic of National Cheng Kung University Hospital (Fig. 1). Permanent AF was diagnosed according to the guidelines described by the European Society of Cardiology and European Heart Rhythm Association [1]. Serial electrocardiograms, Holter recordings, and the medical records were used to confirm that AF had lasted for more than 1 year. Patients excluded were those with: (1) New York Heart Association functional classification (NYHA) III or IV, (2) infiltrative cardiomyopathy, (3) prior open heart surgery, (4) pacemaker implantation, (5) congenital heart disease, (6) end-stage renal disease or liver cirrhosis, and (7) malignancy. Patients with incomplete image acquisition and less than 6-month follow-up were not enrolled (Fig. 1). Every 1 to 3 months, patients were followed up by their original care physicians blinded to the study in the clinic where symptoms and signs of HF as well as ischemic stroke events

were carefully evaluated. The baseline functional classification, medication, as well as comorbid conditions for calculation of the CHA_2DS_2-VASc score (including congestive HF or left ventricular [LV] dysfunction, hypertension, diabetes, history of stroke and vascular disease) were obtained from the medical records. The study end-points during the follow-up period were also obtained from the medical records or telephone interview and were adjudicated by two cardiologists. The end-points were designated as: (1) a composite of sudden cardiac death, ischemic stroke, and HF exacerbation (symptom progression with evidence of pulmonary congestion by the X-ray either requiring hospitalization or identified in the outpatient clinic), (2) HF exacerbation, and (3) ischemic stroke. Ischemic stroke was confirmed by a focal neurologic deficit of sudden onset and the computed tomography imaging findings. During the follow-up period, the time to each end-point was recorded separately and the time to the first end-point (if the patient had more than 1) was used for analysis. If patients experienced any cardiac events eventually leading to cardiovascular death, the end-point was denoted as that cardiac event but not death. All patients were followed until death or until the last contact. The minimal follow-up period was 6 months. The follow-up rate was 94% as of January 2015.

The study adhered to the Declaration of Helsinki and received approval from the Human Research and Ethics Committee (A-ER-102-322) of National Cheng Kung University Hospital, where the informed consent was waived due to the retrospective nature of this study.

Standard echocardiography

Standard echocardiography was performed with Doppler studies (Vivid 7, GE-VingMed, Horten, Norway) with a 3.5-MHz multiphase array probe in individuals lying in a left lateral decubitus position to obtain electrocardiogram-gated images. Standard M-mode, two-dimensional (2D), color, pulsed and continuous wave Doppler images were recorded and saved in a cine-loop format for five cardiac cycles with a frame rate of 50–90 frames per second. The images were analyzed offline with a dedicated software (EchoPac PC 09, GE-VingMed, Horten, Norway). The mean of measurements for 5 beats was used for analysis.

All chamber quantification was aligned with the American Society of Echocardiography [9]. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), which were measured from the apical 4- and 2-chamber views using Simpson's biplane method, were indexed by the body surface area to obtain LVEDV index (LVEDVi) and LVESV index (LVESVi) [10]. LV mass was measured at end-diastole on M-mode recordings obtained in the parasternal long-axis view and calculated with the Devereux formula [3]. LV hypertrophy (LVH) was defined as LV mass index (LVMi) ≥ 115 g/m^2 in men and ≥ 95 g/m^2 in women [10]. The maximal LA volume during LV end-systole (LAVs) and the minimal LA volume during LV end-diastole (LAVd) were used to calculate LA total emptying fraction (LAEF), signified as [(LAVs – LAVd) / LAVs] × × 100% [3]. LAVi was obtained by LAVs indexed by body surface area. The sphericity of LA was assessed by LA eccentricity index (LAEi) [11]. Parameters of LV diastolic function were determined from transmitral inflow velocities using pulsed wave Doppler recordings in the apical 4-chamber view. Early mitral inflow velocity (E) was measured and peak mitral annular tissue Doppler velocity (e') was obtained from septal and lateral mitral annulus to calculated mean e'. Subsequently, E/e' ratio was derived with a normal value signified as E/e' ≤ 8 [12].

Deformation analysis of LV and LA by speckle-tracking echocardiography

The global longitudinal stain (GLS) of LV was measured from three apical views by automated function imaging software as reported in detail previously with very low intra-observer and inter-observer variability [13]. The method for LA deformation analysis by speckle tracking echocardiography has been described in detail in our previous studies [14, 15]. In patients with AF, we analyzed only the peak systolic positive strain ($LA\varepsilon_R$) and strain rate ($LASR_R$) during LA filling (reservoir phase), and the peak negative conduit strain rate ($LASR_{CD}$) in LV early filling while discarding the contractile strain and strain rate (peak negative strain and strain rate after the P-wave) [14]. The LA wall was further divided into 8 segments including basal septal, middle septal, basal lateral, and middle lateral segments on a 4-chamber view and basal inferior, middle inferior, basal anterior, and middle anterior segments on a 2-chamber view. The averages of the $LA\varepsilon_R$, $LASR_R$, and $LASR_{CD}$ in 8 segments were recorded. The mean of measurements for 5 cardiac cycles was used for analysis.

Observer variability

The intra- and inter-observer variability of echocardiographic parameters were assessed in 20 randomly selected patients and presented as the

percent variability (percentage of the absolute difference divided by the mean of repeated measurements) and intraclass correlation coefficient (ICC).

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, Illinois) or JMP version 11.0 (SAS Institute Inc, Cary, NC). All data were presented as mean ± standard deviation unless otherwise stated. By using the χ^2 test for categorical variables, and independent-samples t-test for continuous variables, we first identified factors with significant correlations to enter multivariate logistic regression analysis ($p < 0.05$). To determine whether echocardiographic parameters could predict the end-points as compared to CHA_2DS_2-VASc score while avoiding colinearity between them, separate multivariate Cox regression models were employed for each echocardiographic parameter. Incremental model performance was assessed by the change in the χ^2 value using sequential Cox analysis with nested models. The Kaplan-Meier method was used with a log-rank test to demonstrate differences between strata in terms of end-points. A p value of < 0.05 was considered to be statistically significant.

Results

A total of 252 patients (mean age 67.8 ± 13.5 years, 68% men) with NVAF formed our study group (Fig. 1, Table 1). Antiplatelet or anticoagulant use in the population is 54% and 25%, reflecting a general under-use of anticoagulant therapy as stated in a nationwide study in Taiwan [16]. Trivial tricuspid regurgitation with faint trans-tricuspid valve continuous wave Doppler tracings occurred in 30 patients, causing inaccuracy in estimating pulmonary arterial systolic pressure (PASP), hence PASP was not included in analysis. After a mean follow-up period of 20.8 ± 13.5 months (interquartile range, 8–31 months), 74 (29%) patients reached the composite end-point of cardiovascular death (n = 8, all sudden cardiac death), HF exacerbation (n = 44) and ischemic stroke (n = 22).

Table 1. Baseline characteristics of 252 patients.

Age [years]	67.8 ± 13.5
Body mass index [kg/m^2]	25.6 ± 4.74
Men	172 (68%)
Hypertension	175 (69%)
Diabetes mellitus	61 (24%)
Hyperlipidemia	136 (54%)
Current smoker	25 (10%)
Peripheral arterial occlusive disease	10 (4%)
Coronary artery disease	22 (9%)
NYHA I	151 (60%)
NYHA II	101 (40%)
Antiplatelet agents	136 (54%)
Anticoagulants	63 (25%)
Beta-blockers	102 (41%)
ACEI and/or ARBs	124 (49%)
Statins	37 (15%)
Diuretic use	96 (38%)
Heart rate [bpm]	83.5 ± 18.5
Systolic BP [mm Hg]	129.4 ± 17.1
Diastolic BP [mm Hg]	77.9 ± 12.7
LVEDVi [mL/m^2]	41.10 ± 16.46
LVESVi [mL/m^2]	19.14 ± 12.79
LVMi [g/m^2]	101.72 ± 34.45
LVEF [%]	55.39 ± 12.69
LV GLS [%]	–12.47 ± 4.66
E [m/s]	1.00 ± 0.25
DT [ms]	144.60 ± 41.66
E/e'	10.40 ± 4.31
LAVi [mL/m^2]	46.40 ± 18.04
LAEi	1.28 ± 0.15
LAEF [%]	23.81 ± 11.70
$LA\varepsilon_R$ [%]	15.35 ± 7.53
$LASR_R$ [1/s]	1.37 ± 0.43
$LASR_{CD}$ [1/s]	–1.86 ± 0.67
CHA_2DS_2-VASc score	2.90 ± 1.63
$CHADS_2$ score	2.00 ± 1.34

Data are expressed as mean ± standard deviation or number (%). NYHA — New York Heart Association; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; BP — blood pressure; DT — deceleration time; LA — left atrial; LV — left ventricular; LVEDVi — LV end-diastolic volume index; LVESVi — LV end-systolic volume index; LVMi — LV mass index; LVEF — LV ejection fraction; LV GLS — global LV peak systolic longitudinal strain; E — transmitral peak early filling velocity; E/e'— early trans-mitral velocity to tissue Doppler mitral annular early diastolic velocity ratio; LAVi — LA volume index; LAEi — LA eccentricity index; LAEF — LA ejection fraction; $LA\varepsilon_R$ — LA reservoir strain; $LASR_R$ — LA reservoir strain rate; $LASR_{CD}$ — LA conduit strain rate

Differentiation of patients with or without end-points

Patients with composite end-points had more severe LVH, higher E, E/e', LAV, and CHA_2DS_2-VASc score. Patients with HF progression had more severe LVH and higher E/e'. On the other hand, patients with ischemic stroke had higher E, E/e' and CHA_2DS_2-VASc score. Age, NYHA classification, anticoagulant use, heart rate, blood pressure, LAEF, LAEi, LA deformation parameters, LV

ejection fraction (LVEF), LV volume and GLS were similar between the groups (Table 2).

Echocardiographic parameters versus CHA_2DS_2-VASc score in risk stratification of adverse events

Table 3 shows how each echocardiographic parameter was tested against CHA_2DS_2-VASc score in separate multivariate Cox regression models. For overall adverse cardiac events (a composite of cardiac death, HF exacerbation and ischemic stroke), LVMi, E/e', E, and LAVi remain independent discriminators and outperform CHA_2DS_2-VASc score. For HF exacerbation, E, E/e' and LVMi, but not CHA_2DS_2-VASc score, possess abilities in risk stratification. As for ischemic stroke, E and E/e' show added value to CHA_2DS_2-VASc score.

Figure 2 shows the ability of LVMi, E/e', E, LAVi and CHA_2DS_2-VASc score to predict overall cardiac events, HF progression and stroke. In general, although the discriminative power of echocardiographic parameters was modest based on the area under curve, yet they retain superiority when compared to CHA_2DS_2-VASc score in: (1) overall prognosis (LVMi, E/e', E and LAVi), (2) HF exacerbation (LVMi, E/e'), and (3) ischemic stroke prediction (E/e') ($p < 0.05$).

Incremental value of echocardiographic parameters over CHA_2DS_2-VASc score for predicting future cardiac events

For overall cardiac events, the sequential addition of LAVi, E, E/e' and LVMi to the previous model improved the predictive power in nested regression analysis (Fig. 3A). For HF progression, the addition of E/e' and LVMi to CHA_2DS_2-VASc score based model offered significant incremental value (Fig. 3B). As for ischemic stroke, whether the addition of E or E/e' on top of CHA_2DS_2-VASc score based model provided additional value (Fig. 3C).

Kaplan-Meier analysis showed better overall event-free survival among patients without LVH, without elevated LV filling pressure (E/e' ≥ 15), and with normal LV filling pressure (E/e' < 8), as well as those with less enlarged LA (LAVi < median value, 43.8 mL/m^2) (all Log-rank $p < 0.05$; Fig. 4). As for HF, the presence of LVH or abnormal LV filling pressure (E/e' ≥ 8) displayed poor survival (**Supplementary Figure 1**). For ischemic stroke, the presence of E/e' ≥ 15 predicted worse event-free survival (**Supplementary Figure 2**).

Subgroup analyses were also performed by stratifying all patients by the CHA_2DS_2-VASc score into: ≤ 1 (n = 48), 2–4 (n=163), and ≥ 5 (n = 41) to see whether echocardiographic parameters provide additional value (Table 4). For overall prognosis, E and E/e' are significant factors in patients with low (≤ 1) CHA_2DS_2-VASc score; LVEDVi, LVMi, E, E/e' and LAVi are significant in patients with intermediate CHA_2DS_2-VASc score (between 2 and 4). LVMi is the most powerful factor in this intermediate group (adjusted for age, LVEDVi, E, and LAVi). For HF progression, E is significant in low (≤ 1) CHA_2DS_2-VASc score group; LVEDVi, LVESVi, LVMi, and E/e' are significant in the intermediate group. LVMi is again the most powerful factor in this intermediate group (adjusted for age, LVEDVi, and E/e'). As for ischemic stroke prediction, E/e' and $LA\varepsilon_R$ are significant factors in the low CHA_2DS_2-VASc score group. LAVi is significant in the intermediate group. In patients with high (≥ 5) CHA_2DS_2-VASc score, no echocardiographic indexes remain significant for any prognosis.

Reproducibility

Intraobserver variability values for echocardiographic parameters were 6.4–8.8%. The ICCs were 0.92–0.97. Corresponding interobserver variability values were 7.5–11.0% with an ICC of 0.90–0.96.

Discussion

There were three major findings in the present study: (1) echocardiographic parameters outperform CHA_2DS_2-VASc score in prophesying overall cardiac events and HF progression, therefore compensate the deficiency of CHA_2DS_2-VASc score in this regard; (2) E/e' and LVMi are the most powerful indexes to discriminate overall cardiac events and HF; (3) although CHA_2DS_2-VASc score performs well in stroke prediction, the addition of E and E/e' further strengthens risk stratification. E/e' is particularly useful in low CHA_2DS_2-VASc score (≤ 1). Patients with E/e' ≥ 15 are at higher risk.

Previous studies

Atrial fibrillation independently adds risks to future cardiac events including death, stroke, myocardial infarction and HF exacerbation [3]. Most efforts have been exerted on stroke prediction and prevention, leading to the refinement of $CHADS_2$ score to CHA_2DS_2-VASc score as well as the emergence of new-generation oral anticoagulants. On the other hand, the incidence of HF in AF patients varies from 1.7% to more than 10% per year, meaning that AF related HF is an important clinical comorbid condition which deserves more

Table 2. Differences between patients with and without end-points.

	Composite end-point			Heart failure			Ischemic stroke		
	+ (n = 74)	– (n = 178)	p	+ (n = 42)	– (n = 210)	p	+ (n = 22)	– (n = 230)	p
Baseline characteristics									
Age [years]	680.8 ± 120.4	670.4 ± 130.9	0.455	67.6 ± 13.6	67.8 ± 13.5	0.912	70.4 ± 11.1	67.5 ± 13.7	0.340
Body mass index [kg/m^2]	26.41 ± 5.08	25.29 ± 4.58	0.104	26.66 ± 5.83	25.40 ± 4.48	0.133	27.36 ± 6.04	25.45 ± 4.59	0.085
Men	51 (69%)	121 (68%)	0.884	27 (64%)	145 (69%)	0.545	14 (64%)	158 (69%)	0.626
NYHA I	39 (53%)	112 (63%)	0.163	20 (48%)	132 (63%)	0.201	13 (59%)	138 (60%)	0.915
NYHA II	34 (46%)	64 (36%)	0.117	21 (50%)	77 (37%)	0.162	9 (41%)	89 (40%)	0.851
Antiplatelet agents	40 (54%)	96 (54%)	0.986	22 (52%)	114 (54%)	0.821	15 (68%)	121 (53%)	0.161
Anticoagulants	17 (23%)	46 (26%)	0.632	9 (21%)	54 (26%)	0.558	3 (14%)	60 (26%)	0.198
Beta-blockers	27 (34%)	75 (42%)	0.405	15 (36%)	87 (41%)	0.491	8 (36%)	94 (41%)	0.681
ACEI and/or ARBs	41 (55%)	83 (47%)	0.204	22 (52%)	102 (49%)	0.652	13 (59%)	111 (48%)	0.332
Statins	9 (12%)	28 (16%)	0.466	2 (5%)	35 (17%)	0.047	6 (27%)	31 (13%)	0.081
Diuretic use	31 (42%)	65 (37%)	0.424	22 (52%)	74 (35%)	0.037	9 (41%)	87 (38%)	0.776
Heart rate [bpm]	84.1 ± 20.5	83.2 ± 17.7	0.728	84.4 ± 19.3	83.3 ± 18.4	0.736	85.7 ± 22.8	83.3 ± 18.1	0.577
Systolic BP [mm Hg]	130.8 ± 19.7	128.8 ± 15.9	0.421	129.8 ± 20.1	129.3 ± 16.5	0.869	128.3 ± 18.9	129.5 ± 17.0	0.754
Diastolic BP [mm Hg]	77.1 ± 12.9	78.3 ± 12.6	0.489	76.1 ± 12.5	78.3 ± 12.7	0.316	78.5 ± 10.6	77.8 ± 12.9	0.806
CHA_2DS_2-VASc score	3.2 ± 1.6	2.8 ± 1.6	0.038	3.0 ± 1.5	2.9 ± 1.6	0.592	3.7 ± 1.9	2.8 ± 1.6	0.012
Echocardiographic parameters									
LVEDVi [mL/m^2]	42.62 ± 16.41	40.50 ± 16.49	0.374	44.60 ± 18.94	40.40 ± 15.88	0.146	43.17 ± 13.12	40.91 ± 16.75	0.559
LVESVi [mL/m^2]	19.95 ± 11.20	18.82 ± 13.40	0.543	21.15 ± 12.46	18.74 ± 12.85	0.285	20.19 ± 10.50	19.05 ± 13.00	0.705
LVMi [g/m^2]	117.19 ± 39.55	95.39 ± 30.03	< 0.001	121.27 ± 42.44	97.81 ± 31.31	<0.001	113.42 ± 29.41	100.63 ± 34.74	0.113
LVEF [%]	54.10 ± 11.96	55.92 ± 12.98	0.302	52.92 ± 13.14	55.88 ± 12.58	0.169	54.72 ± 11.54	55.45 ± 12.82	0.797
LV GLS [%]	–12.15 ± 4.63	–12.60 ± 4.67	0.509	–12.33 ± 4.42	–12.50 ± 4.71	0.839	–11.23 ± 5.57	–12.59 ± 4.56	0.213
E [m/s]	1.08 ± 0.30	0.97 ± 0.23	0.002	1.07 ± 0.33	0.99 ± 0.23	0.053	1.11 ± 0.28	0.99 ± 0.25	0.035
DT [ms]	141.41 ± 44.63	145.89 ± 40.46	0.442	143.66 ± 48.71	144.77 ± 40.31	0.877	150.44 ± 38.20	144.03 ± 42.02	0.492
E/e'	12.22 ± 5.43	9.64 ± 3.48	< 0.001	12.45 ± 6.15	9.99 ± 3.71	0.001	12.69 ± 4.88	10.18 ± 4.19	0.009
LAVi [mL/m^2]	50.19 ± 19.76	44.88 ± 17.13	0.042	50.57 ± 22.26	45.57 ± 17.02	0.114	51.81 ± 13.72	45.89 ± 18.34	0.162
LAEi	1.26 ± 0.15	1.29 ± 0.15	0.119	1.27 ± 0.15	1.29 ± 0.15	0.661	1.28 ± 0.13	1.28 ± 0.15	0.908
LAEF [%]	24.85 ± 10.21	23.38 ± 12.26	0.363	25.42 ± 9.64	23.49 ± 12.06	0.330	23.44 ± 11.22	23.85 ± 11.76	0.876
$LA\varepsilon_R$ [%]	14.61 ± 5.90	15.66 ± 8.11	0.314	15.32 ± 6.39	15.35 ± 7.76	0.978	14.06 ± 4.95	15.47 ± 7.73	0.401
$LASR_R$ [1/s]	1.37 ± 0.44	1.38 ± 0.43	0.849	1.37 ± 0.48	1.38 ± 0.42	0.901	1.39 ± 0.35	1.37 ± 0.44	0.891
$LASR_{CD}$ [1/s]	–1.74 ± 0.71	–1.91 ± 0.64	0.062	–1.77 ± 0.80	–1.88 ± 0.64	0.309	–1.67 ± 0.43	–1.88 ± 0.68	0.153

Data are expressed as mean ± standard deviation or number (%). Abbreviations are the same as described in Table 1.

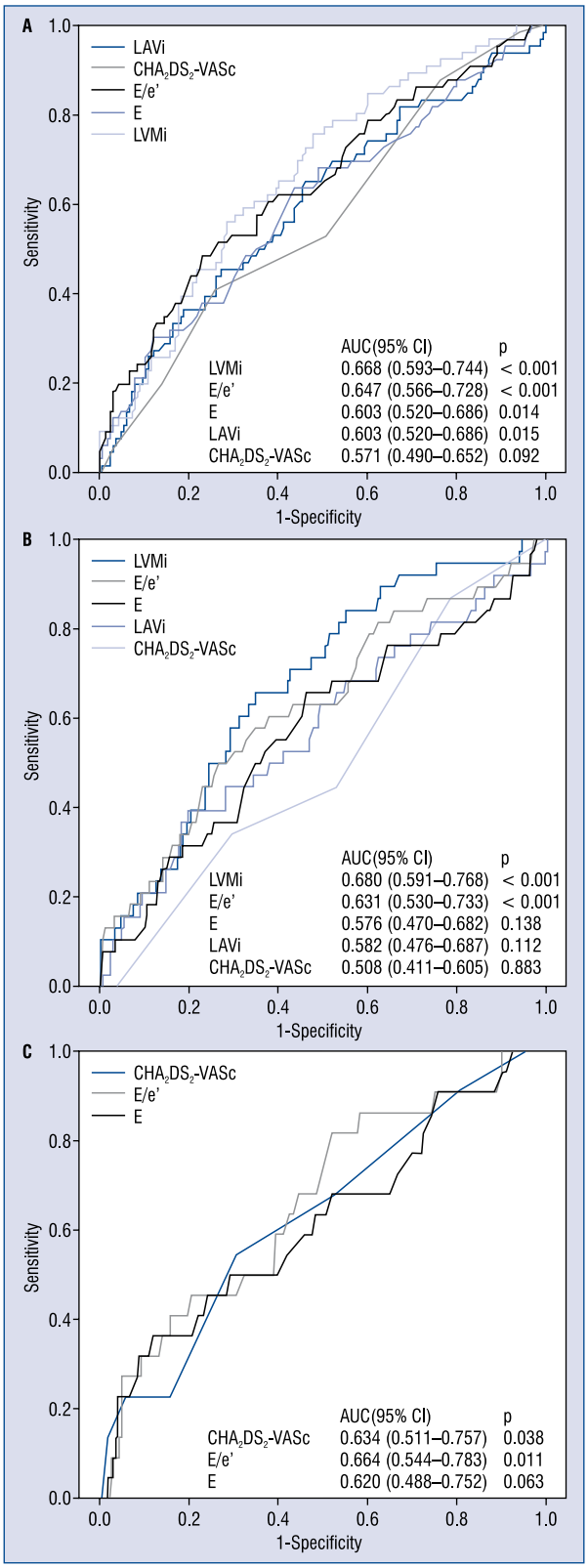

Figure 2. The predictive power of echocardiographic indexes and CHA_2DS_2-VASc score for future cardiovascular events. Receiver operating characteristic curves for prediction of overall adverse cardiac events (**A**), heart failure (**B**) and stroke (**C**); AUC — area under curve; CI — confidence interval.

attention [17]. Although the guideline does emphasize on preventing HF by rate and rhythm control, little is known about the risk stratifying model in gauging HF progression in AF [5].

Previous studies showed that CHA_2DS_2-VASc score has been reported to be of value in predicting AF-associated mortality, perioperative mortality, and cardiovascular hospitalization [3, 4, 18–20]. Nevertheless, its role in prediction of adverse outcome other than stroke was not established. Recently, a clinical risk score (ARC_2H score) for the prediction of HF was explored by a group of Japanese researchers by assigning points to age ≥ 72 years old, heart rate ≥ 80 bpm, hypertension, and history of HF [17]. In the same study, the $CHADS_2$ score was not found to be related to the incidence of HF.

Echocardiographic parameters are promising risk-stratification tools because of convenience, noninvasiveness, timeliness and reproducibility. In AF, several factors aggravate hemodynamic disarrangement, including rapid ventricular rate and loss of coordinated atrial contraction, leading to shortened LV filling, inefficient atrial emptying, a raised LA pressure, and impaired forward cardiac output with HF symptoms [21]. This effect is even more pronounced in patients with reduced LV compliance whose atrial contraction contributes significantly to LV filling. This implies that echocardiography may fill the diagnostic void in risk stratification. Several parameters have been reported useful in prognostication in AF, such as E/e', LAVi, and LVH [6, 9, 22–25]. Nonetheless, these indicators have not been tested directly against CHA_2DS_2-VASc score.

The present study

It was demonstrated that echocardiographic parameters (LVMi, E, E/e' and LAVi) outperform CHA_2DS_2-VASc score in predicting overall prognosis and HF progression. Also shown was their added value (E, E/e') on top of CHA_2DS_2-VASc score in stroke prediction, especially for patients with low CHA_2DS_2-VASc score (≤ 1). Patients having E/e' ≥ 15 are at higher risk of stroke. In other words, with similar heart rate, blood pressure, LV volume, LVEF and anticoagulant use, those with more advanced LVH, greater E, E/e' and LAVi suffered from detrimental prognosis in this study. The finding is reasonable and suggests factors reflecting adaptive consequences caused by increased hemodynamic load in AF bare prognostic value. Secondly, particular attention should be paid to AF related HF exacerbation. With an average CHA_2DS_2-VASc score 2.90 ± 1.63 and a nationwide underuse of

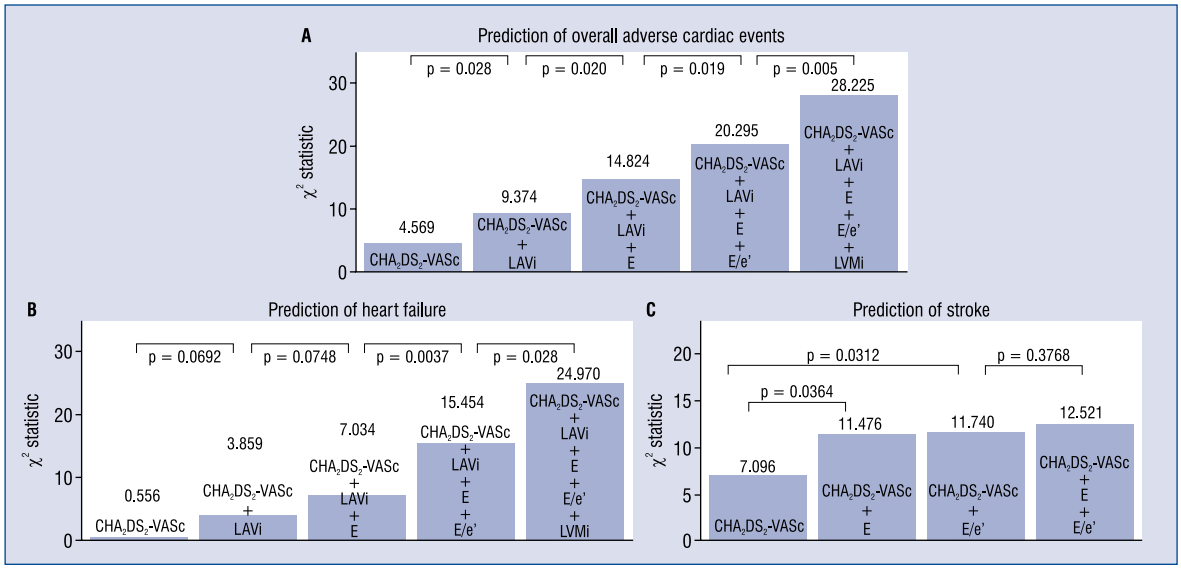

Figure 3. Incremental value of echocardiographic parameters for predicting future cardiovascular events. Nested regression models for predicting overall adverse cardiac events (**A**), heart failure (**B**), and ischemic stroke (**C**). The first step consisted of CHA_2DS_2-VASc score. Then left atrial volume index (LAVi), peak mitral early filling velocity (**E**), peak early filling velocity to tissue Doppler mitral annular early diastolic velocity ratio (E/e') and left ventricular volume index (LVMi) were successively included in the next steps.

anticoagulants, it was observed that there were more HF events than stroke. This implies that HF is as important as stroke in AF. Since CHA_2DS_2--VASc score is insufficient in the prediction of HF, echocardiographic indexes may offer more clues. Thirdly, deformation parameters (LV GLS and LA strain) failed to show prognostication in this study, although the degree of impaired deformation was in agreement with prior AF studies [26]. A plausible explanation was that different loading condition and disease process may affect the results. When compared to prior work, more advanced LVH, smaller LAVi, better LAEF and LA deformation were noted here, which may also explain the differences in prognostication provided by LA deformation parameters [14]. The usefulness of deformation imaging in well-controlled AF patients await more studies to confirm this. Lastly, we observed a high incidence of adverse cardiac events (29%). Due to the retrospective nature of this study, we can only presume that suboptimal medication use, patient compliance and a higher prevalence of hypertension may be possible reasons.

Clinical implications

The present findings offer several potential implications. First, refining risk assessment for future cardiovascular events is possible, particularly in HF progression, which contributed to the majority of the events that were observed. For ischemic stroke, elevated LV filling pressure signifies higher risk in addition to CHA_2DS_2-VASc score. While it is difficult to make blanket statements about individual risk, echocardiographic parameters may provide added information. Second, by improving multifaceted risk evaluation with the aid of noninvasive imaging, high risk population may warrant tailored and aggressive management (strict heart rate control, balance in volume status and anticoagulant use). Third, routine echocardiography is therefore needed because CHA_2DS_2-VASc score-guided anticoagulation therapy could not reduce HF progression. Notably, these indexes (LVMi, E, E/e', LAVi) are appealing in clinical practice given their generalization, vendor-independency, and easiness in measurement. These parameters might be used as surrogate markers for guiding aggressive treatment to prevent HF in AF. The presented findings also suggest that diastology may be a key mechanism for future outcome in AF. Further studies are required to confirm whether these parameters can guide treatment strategies.

Limitations of the study

First, this single-center study was limited in the number of participants and was not population based. Patients were excluded whose underlying disease might engender an adverse outcome, in-

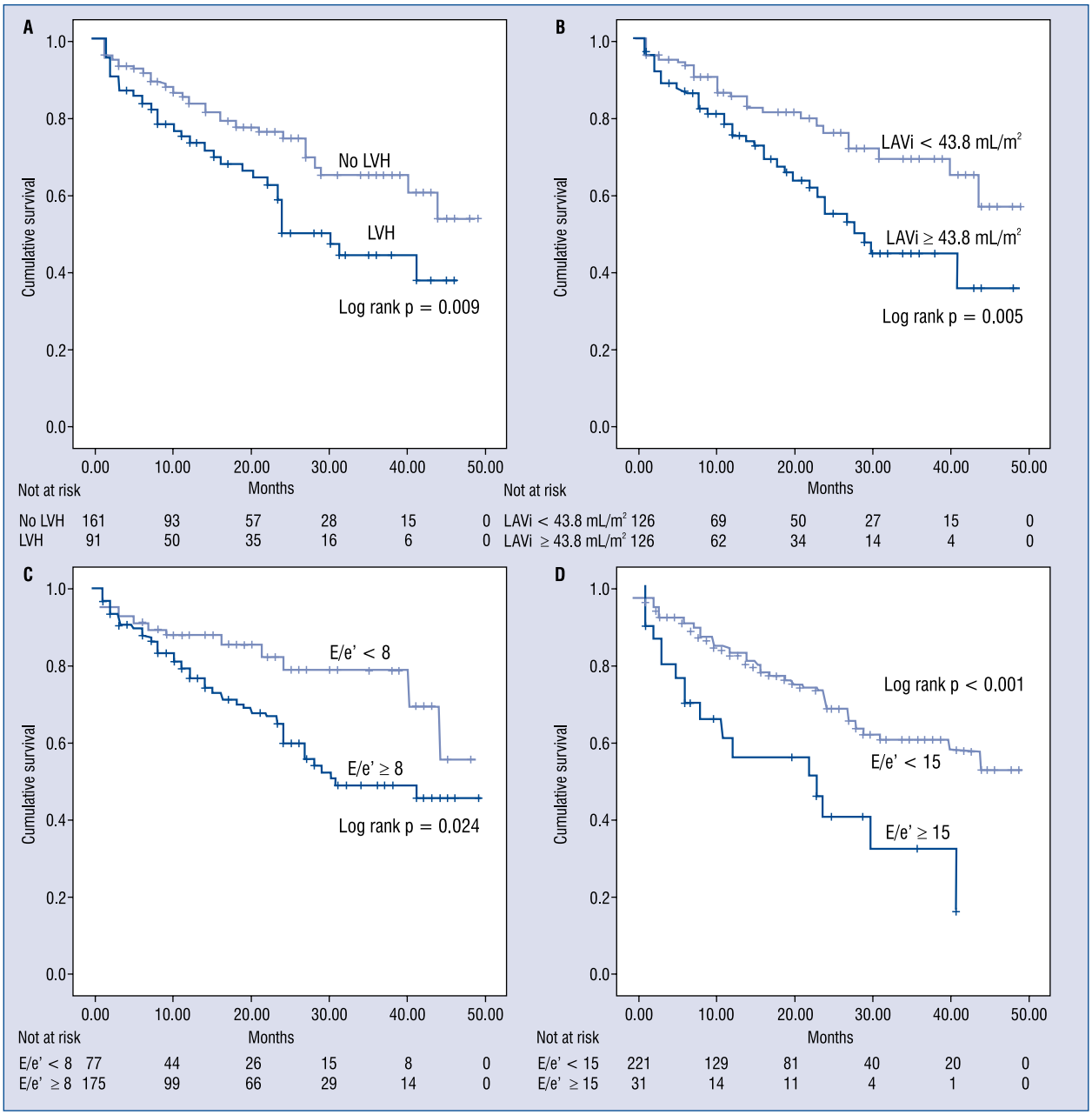

Figure 4. Kaplan-Meier curves for overall adverse cardiac events. Prognostic differences were shown between subgroups stratified by: **A.** The presence of left ventricular hypertrophy (LVH); **B.** The median value of left atrial volume index (LAVi) (43.8 mL/m²); **C.** E/e' with a cutoff of 8; **D.** E/e' with a cutoff of 15.

cluding significant valvular heart disease, cardiomyopathy, advanced HF, and major organ failure. Thus, the generalizability may be limited. Second, the duration of AF and HAS-BLED score wasnot taken into account, which may be a source of bias. Third, the medication was not randomly controlled, and the anticoagulation therapy was underused (reflecting real world status in Taiwan). Yet there was no association between all medication and outcome. Although the baseline heart rate showed no relevance in prediction of outcome in the studied population (average heart rate 83.5 ± 18.5 bpm), it is of interest whether rigorous heart rate control might help in preventing HF progression. Fourth, our samples included patients with NYHA functional classification I, II, and LV systolic dysfunction. However, NYHA functional classification and LVEF were similar in patients with or without

Table 3. Utility of echocardiographic parameters versus CHA_2DS_2-VASc score in multivariate analysis for prediction of end-points.

Composite end-points		Heart failure		Ischemic stroke	
Model 1		Model 1		Model 1	
E	**CHA_2DS_2-VASc score**	**E**	**CHA_2DS_2-VASc score**	**E**	**CHA_2DS_2-VASc score**
3.599 (1.606–8.065)	1.161 (1.002–1.344)	3.299 (1.140–9.548)	1.066 (0.873–1.301)	5.550 (1.269–24.261)	1.411 (1.087–1.832)
P = 0.002	P = 0.047	P = 0.028	P = 0.530	P = 0.023	P = 0.010
Model 2		Model 2		Model 2	
E/e'	**CHA_2DS_2-VASc score**	**E/e'**	**CHA_2DS_2-VASc score**	**E/e'**	**CHA_2DS_2-VASc score**
1.085 (1.041–1.132)	1.107(0.949–1.291)	1.100 (1.043–1.159)	1.001 (0.811–1.236)	1.092 (1.011–1.180)	1.357 (1.033–1.783)
P < 0.001	P = 0.194	P < 0.001	P = 0.990	P = 0.026	P = 0.028
Model 3		Model 3			
LVMi	**CHA_2DS_2-VASc score**	**LVMi**	**CHA_2DS_2-VASc score**		
1.013 (1.007–1.019)	1.143 (0.977–1.3380)	1.015 (1.008–1.023)	0.996 (0.801–1.239)		
P < 0.001	P = 0.095	P < 0.001	P = 0.971		
Model 4					
LAVi	**CHA_2DS_2-VASc score**				
1.013(1.002–1.025)	1.169 (1.002–1.364)				
P = 0.022	P = 0.047				

Abbreviations are the same as described in Table 1. Expressed as hazard ratio (95% confidence interval)

Table 4. The echocardiographic parameters in prediction of adverse outcome in subgroups stratified by the CHA_2DS_2-VASc score.

End-point	Composite end-point			Heart failure			Ischemic stroke		
CHA_2DS_2-VASc score	**≤ 1 (n = 8/48)**	**2–4 (n = 51/163)**	**≥ 5 (n = 15/41)**	**≤ 1 (n = 5/48)**	**2–4 (n = 29/163)**	**≥ 5 (n = 8/41)**	**≤ 1 (n = 2/48)**	**2–4 (n = 15/163)**	**≥ 5 (n = 5/41)**
LVEDVi [mL/m^2]	1.00 (0.96–1.05)	**1.02 (1.00–1.04)¶**	1.03 (0.98–1.08)	1.03 (0.95–1.13)	**1.03 (1.01–1.05)¶**	1.02 (0.94–1.09)	1.01 (0.93–1.07)	1.03 (0.99–1.06)	1.00 (0.91–1.08)
LVESVi [mL/m^2]	1.00 (0.93–1.06)	1.02 (0.99–1.04)	1.04 (0.97–1.09)	1.00 (0.86–1.16)	**1.03 (1.00–1.05)§**	1.06 (0.97–1.13)	1.01 (0.90–1.07)	1.02 (0.98–1.06)	0.97 (0.80–1.08)
LVMi [g/m^2]	1.02 (0.99–1.04)	**1.01 (1.00–1.02)¶**	1.00 (0.98–1.02)	1.03 (0.98–1.08)	**1.01 (1.00–1.02)¶**	0.99 (0.95–1.02)	1.01 (0.96–1.06)	1.01 (0.99–1.02)	1.01 (0.98–1.04)
LVEF [%]	0.99 (0.91–1.07)	0.99 (0.97–1.01)	0.98 (0.94–1.03)	1.05 (0.91–1.21)	0.98 (0.96–1.01)	0.95 (0.90–1.01)	0.95 (0.86–1.09)	0.99 (0.95–1.04)	1.01 (0.94–1.12)
LV GLS [%]	0.97 (0.76–1.23)	1.01 (0.95–1.07)	0.97 (0.82–1.18)	0.81 (0.58–1.13)	1.00 (0.92–1.08)	1.15 (0.88–1.53)	4.42 (0.09–200.39)	1.08 (0.97–1.17)	0.81 (0.63–1.04)
E [cm/s]	**1.03 (1.00–1.07)§**	**1.01 (1.00–1.02)§**	1.01 (0.98–1.03)	**1.08 (1.01–1.15)¶**	1.01 (0.99–1.02)	0.98 (0.94–1.02)	1.03 (0.97–1.09)	1.01 (0.99–1.02)	1.02 (0.98–1.05)
DT [ms]	0.99 (0.97–1.01)	0.99 (0.98–1.00)	0.99 (0.98–1.00)	0.99 (0.97–1.01)	0.99 (0.98–1.00)	0.99 (0.97–1.01)	0.99 (0.95–1.02)	1.00 (0.98–1.01)	1.00 (0.98–1.02)
E/e'	**1.40 (1.08–1.80)¶**	**1.08 (1.03–1.13)¶**	1.09 (0.92–1.25)	1.34 (0.87–2.04)	**1.10 (1.04–1.16)¶**	1.00 (0.76–1.24)	**3.35 (1.31–694.88)¶**	1.09 (0.99–1.18)	1.05 (0.79–1.30)
LAVi [mL/m^2]	1.00 (0.97–1.03)	**1.01 (1.00–1.03)§**	1.00 (0.97–1.03)	1.00 (0.96–1.03)	1.01 (0.99–1.03)	1.03 (0.98–1.07)	1.00 (0.92–1.04)	**1.03 (1.00–1.05)§**	0.97 (0.91–1.03)
LAEi	0.00 (0.00–7.32)	0.44 (0.06–2.89)	0.35 (0.01–13.32)	0.00 (0.00–711.93)	0.49 (0.03–5.67)	3.65 (0.02–903.62)	0.00 (0.00–116.62)	1.12 (0.03–29.07)	2.68 (0.00–3724.5)
LAEF [%]	1.04 (0.98–1.09)	1.00 (0.97–1.03)	1.01 (0.97–1.06)	1.03 (0.96–1.10)	1.01 (0.97–1.04)	1.02 (0.96–1.08)	1.08 (097–1.24)	1.00 (0.94–1.05)	0.98 (0.90–1.05)
$LA\varepsilon_R$ [%]	0.91 (0.78–1.06)	0.97 (0.92–1.01)	1.05 (0.96–1.15)	0.98 (0.81–1.19)	1.00 (0.94–1.04)	1.00 (0.88–1.13)	**0.65 (0.31–0.98)§**	0.92 (0.83–1.01)	1.14 (0.98–1.32)
$LASR_R$ [1/s]	0.44 (0.08–2.41)	0.77 (0.36–1.47)	1.32 (0.30–5.53)	0.18 (0.01–2.16)	1.13 (0.46–2.34)	0.27 (0.02–2.23)	2.44 (0.10–96.10)	0.4 (0.07–1.58)	5.30 (0.46–67.71)
$LASR_{CD}$ [1/s]	1.37 (0.36–5.21)	1.40 (0.89–2.36)	1.92 (0.55–6.57)	1.44 (0.25–8.24)	1.13 (0.67–2.15)	4.92 (0.93–28.84)	0.80 (0.08–12.28)	2.57 (0.95–8.63)	0.98 (0.09–9.48)

§p < 0.05; ¶p < 0.01. Abbreviations are the same as Table 1. Data were were expressed as hazard ratio (95% confidence interval).

Table 5. Utility of echocardiographic parameters versus CHA_2DS_2-VASc score in multivariate analysis in left ventricular ejection fraction (LVEF) ≥ 50% (n = 187).

Composite end-points	
Model 1	
E	**CHA_2DS_2-VASc score**
5.018 (1.800–13.989) P = 0.002	1.118 (0.940–1.329) P = 0.207
Model 2	
E/e'	**CHA_2DS_2-VASc score**
1.085 (1.026–1.147) P = 0.004	1.079 (0.905–1.288) P = 0.395
Model 3	
LVMi	**CHA_2DS_2-VASc score**
1.007 (1.007–1.025) P < 0.001	1.064 (0.886–1.278) P = 0.505
Model 4	
LAVi	**CHA_2DS_2-VASc score**
1.020 (1.005–1.034) P = 0.008	1.119 (0.934–1.339) P = 0.223

Abbreviations are the same as described in Table 1. Expressed as hazard ratio (95% confidence interval)

events. Besides, the subgroup analysis performed in patients with preserved LVEF (EF ≥ 50%) showed that LVMi, E, and E/e' remained superior over the CHA_2DS_2-VASc score in terms of overall prognosis (Table 5). Fifth, samples had a relatively rapid heart rate. Yet the range of heart rate was in line with the lenient rate control strategy. The relationship between heart rate and HF in AF also remains controversial [5, 17]. Finally, stroke was evaluated by the computed tomography imaging and not by magnetic resonance imaging.

Conclusions

In permanent NVAF, echocardiographic parameters provide better discrimination over CHA_2DS_2--VASc score in overall prognosis and HF. For stroke prediction, E/e' adds value to CHA_2DS_2-VASc score. These findings may assist in refining risk stratification in NVAF.

Conflict of interest: None declared

References

1. Camm AJ, Lip GY, De Ca, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace. 2012; 14(10): 1385–413.
2. Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation. 2013; 128(20): 2192–2201, doi: 10.1161/CIRCULATIONAHA.112.000491, indexed in Pubmed: 24016454.
3. Crandall MA, Horne BD, Day JD, et al. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol. 2009; 32(8): 981–986, doi: 10.1111/j.1540-8159.2009.02427.x, indexed in Pubmed: 19659615.
4. Jover E, Roldán V, Gallego P, et al. Predictive value of the CHA2DS2-VASc score in atrial fibrillation patients at high risk for stroke despite oral anticoagulation. Rev Esp Cardiol (Engl Ed). 2012; 65(7): 627–633, doi: 10.1016/j.recesp.2012.02.017, indexed in Pubmed: 22609214.
5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014; 130(23): 2071–2104, doi: 10.1161/CIR.0000000000000040, indexed in Pubmed: 24682348.
6. Osranek M, Bursi F, Bailey KR, et al. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. Eur Heart J. 2005; 26(23): 2556–2561, doi: 10.1093/eurheartj/ehi483, indexed in Pubmed: 16141257.
7. Handke M, Harloff A, Hetzel A, et al. Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation--a transesophageal echocardiographic study in 500 patients with cerebral ischemia. J Am Soc Echocardiogr. 2005; 18(12): 1366–1372, doi: 10.1016/j.echo.2005.05.006, indexed in Pubmed: 16376768.
8. Vieira MJ, Teixeira R, Gonçalves L, et al. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr. 2014; 27(5): 463–478, doi: 10.1016/j.echo.2014.01.021, indexed in Pubmed: 24656882.
9. Lee SH, Choi S, Chung WJ, et al. Tissue Doppler index, E/E', and ischemic stroke in patients with atrial fibrillation and preserved left ventricular ejection fraction. J Neurol Sci. 2008; 271(1-2): 148–152, doi: 10.1016/j.jns.2008.04.006, indexed in Pubmed: 18501379.
10. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18(12): 1440–1463, doi: 10.1016/j.echo.2005.10.005, indexed in Pubmed: 16376782.
11. Maiello M, Sharma RK, Matteo CM, et al. Differential left atrial remodeling in LV diastolic dysfunction and mitral regurgitation. Echocardiography. 2009; 26(7): 772–778, doi: 10.1111/j.1540-8175.2008.00889.x, indexed in Pubmed: 20003018.
12. Nagueh S, Appleton C, Gillebert T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. J Am Soc Echocardiogr. 2009; 22(2): 107–133, doi: 10.1016/j.echo.2008.11.023.
13. Tsai WC, Liu YW, Huang YY, et al. Diagnostic value of segmental longitudinal strain by automated function imaging in coronary artery disease without left ventricular dysfunction.

J Am Soc Echocardiogr. 2010; 23(11): 1183–1189, doi: 10.1016/j.echo.2010.08.011, indexed in Pubmed: 20833507.
14. Shih JY, Tsai WC, Huang YY, et al. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. J Am Soc Echocardiogr. 2011; 24(5): 513–519, doi: 10.1016/j.echo.2011.01.016, indexed in Pubmed: 21353469.
15. Tsai WC, Huang YY, Liu YW, et al. Changes of Left Atrial Phasic Function Assessed by Speckle Tracking Echocardiography in Untreated Hypertension. J Med Ultrasound. 2012; 20(4): 220–227, doi: 10.1016/j.jmu.2012.10.010.
16. Lin LJ, Cheng MH, Lee CH, et al. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation — a nationwide descriptive study in Taiwan. Clin Ther. 2008; 30(9): 1726–1736, doi: 10.1016/j.clinthera.2008.09.010, indexed in Pubmed: 18840379.
17. Imai K, Okura H, Tamada T, et al. Prediction of congestive heart failure in patients with non valvular atrial fibrillation. Intern Med. 2014; 53(1): 7–12, indexed in Pubmed: 24390521.
18. van Diepen S, Youngson E, Ezekowitz JA, et al. Which risk score best predicts perioperative outcomes in nonvalvular atrial fibrillation patients undergoing noncardiac surgery? Am Heart J. 2014; 168(1): 60–7.e5, doi: 10.1016/j.ahj.2014.03.015, indexed in Pubmed: 24952861.
19. Henriksson KM, Farahmand B, Johansson S, et al. Survival after stroke--the impact of CHADS2 score and atrial fibrillation. Int J Cardiol. 2010; 141(1): 18–23, doi: 10.1016/j.ijcard.2008.11.122, indexed in Pubmed: 19144430.
20. Naccarelli GV, Panaccio MP, Cummins G, et al. CHADS2 and CHA2DS2-VASc risk factors to predict first cardiovascular hospitalization among atrial fibrillation/atrial flutter patients. Am J Cardiol. 2012; 109(10): 1526–1533, doi: 10.1016/j.amjcard.2012.01.371, indexed in Pubmed: 22360819.
21. Camm AJ, Kirchhof P, Lip GYH, et al. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31(19): 2369–2429, doi: 10.1093/eurheartj/ehq278, indexed in Pubmed: 20802247.
22. Apostolakis S, Sullivan RM, Olshansky B, et al. Left ventricular geometry and outcomes in patients with atrial fibrillation: the AFFIRM Trial. Int J Cardiol. 2014; 170(3): 303–308, doi: 10.1016/j.ijcard.2013.11.002, indexed in Pubmed: 24315343.
23. Barbieri A, Bursi F, Mantovani F, et al. Prognostic impact of left ventricular mass severity according to the classification proposed by the American Society of Echocardiography/European Association of Echocardiography. J Am Soc Echocardiogr. 2011; 24(12): 1383–1391, doi: 10.1016/j.echo.2011.08.012, indexed in Pubmed: 21975437.
24. Okura H, Takada Y, Kubo T, et al. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. Heart. 2006; 92(9): 1248–1252, doi: 10.1136/hrt.2005.082594, indexed in Pubmed: 16449507.
25. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014; 63(6): 493–505, doi: 10.1016/j.jacc.2013.10.055, indexed in Pubmed: 24291276.
26. Vieira MJ, Teixeira R, Gonçalves L, et al. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr. 2014; 27(5): 463–478, doi: 10.1016/j.echo.2014.01.021, indexed in Pubmed: 24656882.