Left Atrial Spontaneous Echo Contrast Occurring in Patients with Low CHADS2 or CHA2DS2-VASc Scores

Kanako Akamatsu
Osaka Medical College
Takahide Ito (in3016@osaka-med.ac.jp)
Osaka Medical College https://orcid.org/0000-0003-4850-9132
Michishige Ozeki
Osaka Medical College
Masatoshi Miyamura
Osaka Medical College
Koichi Sohmiya
Osaka Medical College
Masaaki Hoshiga
Osaka Medical College

Research

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Abstract

Background: Left atrial spontaneous echo contrast (LASEC) is common in patients with atrial fibrillation (AF), although scarce information exists regarding LASEC occurring in AF patients with low thromboembolic risk scores. We investigated prevalence and determinants of LASEC under low CHADS 2 or CHA 2 DS 2 -VASc scores.

Methods: Among 713 patients with nonvalvular AF who underwent transesophageal echocardiography, 361 with a CHADS 2 score <2 (CHADS 2 group) and 227 with a CHA 2 DS 2 -VASc score <2 (CHA 2 DS 2 -VASc group) were separately examined for clinical and echocardiographic findings.

Results: LASEC was found in 80 patients of CHADS 2 group (22%) and in 44 of CHA 2 DS 2 -VASc group (19%). With multivariate logistic regression analysis, adjusted for non-paroxysmal AF, renal dysfunction, LA diameter ≥50 mm, left ventricular (LV) ejection fraction <50%, LV hypertrophy, and B-type natriuretic peptide (BNP) ≥200 pg/mL, it was demonstrated that for CHADS 2 group, “non-paroxysmal AF” (OR 5.86, 95%CI 3.21-10.7, P <0.001), BNP ≥200 pg/mL (Odds ratio 3.22, 95%CI 1.25-8.28, P = 0.015), and LV hypertrophy (Odds ratio 2.16, 95%CI 1.11-4.20, P = 0.024) were significant independent determinants of LASEC, and that for CHA 2 DS 2 -VASc group, “non-paroxysmal AF” (Odds ratio 3.42, 95%CI 1.53-7.65, P = 0.002) was a significant independent determinant of LASEC.

Conclusions: LASEC was present in a considerable proportion of patients who had low CHADS 2 or CHA 2 DS 2 -VASc scores. Information on chronicity of AF, BNP, and LV hypertrophy may help identify patients at risk for thromboembolism.

Introduction

There are numerous reports that left atrial spontaneous echo contrast (LASEC) is one of the strongest predictors of intraatrial thrombosis and subsequent thromboembolism [1–4]. Thromboembolic risk scores typified by $CHADS_2$ and CHA_2DS_2-VASc have been used for the past decade to assess an embolic risk and to guide prophylactic anticoagulation in patients with nonvalvular atrial fibrillation (AF) [5]. Studies on the association of transesophageal echocardiography (TEE) findings with $CHADS_2$ or CHA_2DS_2-VASc scores in nonvalvular AF patients have indicated a trend of which the greater score of $CHADS_2$ or CHA_2DS_2-VASc, the more likely LASEC to be observed [6–8]; however, a certain number of patients are found to have LASEC despite low scores levels [6–10].

Generally, patients with non-paroxysmal AF or those with chronic heart failure tend to have conditions predisposed to left atrial (LA) thrombus formation [11, 12]. Also, those with increased LA size, impaired left ventricular (LV) systolic function, and reduced LA appendage (LAA) velocity are likely to have LASEC and LA thrombus [13–16]. However, scarce information has existed regarding LASEC occurring in AF patients who have low thromboembolic risk scores. [9, 10]. We therefore examined prevalence and

determinants of the presence of LASEC in nonvalvular AF patients with low $CHADS_2$ or CHA_2DS_2-VASc scores.

Methods

Study population

We reviewed echocardiography reports and clinical charts on 713 patients with nonvalvular AF who underwent TEE between 2012 and 2018 in Osaka Medical College Hospital. TEE was performed in order to screen intracardiac thrombosis prior to pulmonary vein isolation procedure and/or direct cardioversion. There were 493 men and 220 women with a mean age of 67 years. Patients with rheumatic/degenerative mitral valve disease, congenital heart disease, and those in whom echocardiography and/or laboratory data considered to be important for the current analysis, particularly the serum B-type natriuretic peptide (BNP) level and left ventricular (LV) ejection fraction, were lacking were excluded. This study was approved by the Ethics Committee of Osaka Medical College with notification for guaranteed withdrawal of participants on the website providing means of “opt-out” (No. 2194-01).

Echocardiography

Ultrasound machines used were Vivid 7 Dimension and Vivid E9 with the phased array probes for both transthoracic echocardiography and TEE (GE-Vingmed, Horten, Norway). The LA diameter, and LV dimensions and wall thickness were measured under 2-dimensional image guidance. The LV ejection fraction was obtained with the modified Simpson’s rule in the 2- and 4-chamber views. LV mass was calculated using the Devereux formula, indexed by the body surface area to draw LV mass index. An LV mass index ≥ 115 g/m^2 in men and ≥ 95 g/m^2 in women were considered as the presence of LV hypertrophy [17]. The severity of mitral regurgitation was determined semi-quantitatively using color-flow mapping.

Standard multiplane TEE was performed using the same ultrasound machines with 6Tc and 6VT-D probes, respectively. The entire LA cavity was thoroughly examined for LASEC and LA thrombus with the gain setting being adjusted for optimal analysis. Attention was paid to differentiate the LAA thrombus from pectinate muscles [18]. The TEE images, on a routine basis, were stored as cine-loops for the subsequent analysis. LASEC severity was qualitatively assessed as none, mild, and severe as described previously [19, 20]. The LAA velocity was also obtained with the pulsed Doppler sample volume 1 to 2 cm positioned inside the LAA orifice, averaged over 3 and 5 consecutive cardiac cycles in case of patients in sinus rhythm and of those in AF, respectively.

Thromboembolic risk scores

$CHADS_2$ score was calculated by giving 1 point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes, and 2 points for prior stroke or transient ischemic attack [21], and patients with a $CHADS_2$ score < 2 were classified into the “low risk” category ($CHADS_2$ group) [9, 22]. CHA_2DS_2-VASc

score was calculated by giving 1 point each for congestive heart failure or LV systolic dysfunction (ejection fraction < 40%), hypertension, diabetes, vascular disease, age 65 to 74 years, and female gender, and 2 points for prior stroke or transient ischemic attack and for age ≥ 75 years [5], and patients with a CHA_2DS_2-VASc score < 2 were classified as "low risk" (CHA_2DS_2-VASc group) [9, 22].

Clinical definitions

Abnormalities of some clinical variables were determined in the followings. Based on K/DOQI clinical practice guidelines [23], renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. An elevation of the serum B-type natriuretic peptide (BNP) level ≥ 200 pg/mL was considered clinically significant in accordance with the statement guideline by the Japanese Heart Failure Society (www.asas.or.jp/jhfs/english/outline/guidelines_20180822.html). An LA diameter ≥ 50 mm and an LAA velocity < 20 cm/s were defined as LA enlargement and significant LAA dysfunction, respectively [2, 24].

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables as percentages. Comparisons of categorical variables were performed using the chi-square test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression analyses were introduced to predict determinants of LASEC for $CHADS_2$ and CHA_2DS_2-VASc groups for each. All analyses were performed using JMP Pro ver. 13.0 (SAS Institute, Cary, NC). A P values < 0.05 was considered significant.

Results

Figure 1 shows percentages of the presence of LASEC classified by $CHADS_2$ and CHA_2DS_2-VASc scores in a total of 713 patients. Overall, the incidence of LASEC was found to increase accordingly with increases in $CHADS_2$ and CHA_2DS_2-VASc scores. There were 361 patients with a $CHADS_2$ score < 2 ($CHADS_2$ group) and 227 with a CHA_2DS_2-VASc score < 2 (CHA_2DS_2-VASc group), and the following analyses were performed separately for these two groups.

Clinical characteristics of the patient groups

Clinical characteristics of $CHADS_2$ and CHA_2DS_2-VASc groups are presented in Table 1. With the exception of gender distribution, similar clinical features were found in both groups. About 10% of patients were shown to have significant LA enlargement and about 5% to have reduced LV ejection fraction. LASEC was detected in 80 of $CHADS_2$ group (22%) and in 44 of CHA_2DS_2-VASc group (19%). A very small number of patients had significant LAA dysfunction (LAA velocity < 20 cm/s) and dense LASEC, and LAA thrombus was noted in only one patient, belonging to $CHADS_2$ group.

Table 1
Clinical characteristics of the study groups.

Variable	$CHADS_2$ group (n = 361)	CHA_2DS_2-VASc group (n = 227)
Age (years)	65 ± 11	63 ± 12
Female, n (%)	98 (27)	40 (18)
Paroxysmal AF, n (%)	258 (71)	173 (76)
$CHADS_2$ score	0.14 ± 0.36	1.32 ± 1.08
CHA_2DS_2-VASc score	0.74 ± 0.87	2.14 ± 1.59
Congestive heart failure, n (%)	58 (16)	30 (13)
Hypertension, n (%)	141 (39)	73 (32)
Age ≥ 75 years, n (%)	23 (6)	0 (0)
Diabetes mellitus, n (%)	15 (4)	6 (3)
Dyslipidemia, n (%)	67 (19)	45 (20)
Stroke/TIA, n (%)	0 (0)	0 (0)
Vascular disease, n (%)	9 (2)	0 (0)
eGFR (mL/min/1.73 m^2)	68 ± 16	69 ± 15
eGFR < 60 mL/min/1.73 m^2, n (%)	90 (25)	54 (24)
BNP (pg/mL)	93 ± 253	82 ± 200
BNP ≥ 200 pg/mL, n (%)	31 (9)	19 (8)
Anticoagulation		
Warfarin	98 (27)	67 (30)
DOACs	252 (70)	154 (68)
Echocardiography		
LA diameter (mm)	42 ± 7	41 ± 7
LA diameter ≥ 50 mm, n (%)	48 (13)	22 (10)
LV end-diastolic dimension (mm)	48 ± 6	48 ± 6

BNP, B-type natriuretic peptide; DOACs; direct oral anticoagulants; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; LAA, left atrial appendage; LVEF, left ventricular ejection fraction,; MR, mitral regurgitation; TIA, transient ischemic attack.

Variable	$CHADS_2$ group (n = 361)	CHA_2DS_2-VASc group (n = 227)
LV end-systolic dimension (mm)	31 ± 7	31 ± 6
LVEF (%)	62 ± 8	62 ± 75
LVEF < 40%, n (%)	20 (6)	12 (5)
Thickness of IVS (mm)	9 ± 2	9 ± 2
Thickness of LV posterior wall (mm)	9 ± 1	9 ± 1
LV mass (g)	159 ± 46	161 ± 48
LV mass index (g/m^2)	93 ± 24	93 ± 25
LV hypertrophy, n (%)	89 (25)	49 (22)
More-than-mild MR, n (%)	17 (5)	9 (4)
LAA velocity (cm/s)	58 ± 28	60 ± 29
LAA velocity < 20 cm/s, n (%)	20 (6)	11 (5)
No LASEC, n (%)	281 (78)	183 (81)
Mild LASEC, n (%)	66 (18)	39 (17)
Severe LASEC, n (%)	14 (4)	5 (2)
LA thrombus, n (%)	1 (0)	0 (0)

BNP, B-type natriuretic peptide; DOACs; direct oral anticoagulants; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; LAA, left atrial appendage; LVEF, left ventricular ejection fraction,; MR, mitral regurgitation; TIA, transient ischemic attack.

Determinants of LASEC

Table 2 shows the results of univariate logistic regression analysis for assessing determinants of the presence of LASEC for each group. Variables incorporated into the model were female gender, non-paroxysmal AF, eGFR < 60 mL/min/1.73 m^2, BNP ≥ 200 pg/mL, LA diameter ≥ 50 mm, LV ejection fraction < 50%, and LV hypertrophy. For $CHADS_2$ group, those except female gender were significantly related to the presence of LASEC whereas for the CHA_2DS_2-VASc score group, those except female gender and renal dysfunction were significantly related to the presence of LASEC.

Table 2

Univariate logistic regression analysis for assessing determinants of LASEC.

	$CHADS_2$ group			CHA_2DS_2-VASc group		
Variable	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Female gender	1.51	0.88–2.57	0.13	1.78	0.80–3.90	0.16
Non-paroxysmal AF	7.17	4.17–12.3	< 0.001	4.72	2.34–9.53	< 0.001
eGFR < 60 mL/min/1.73 m^2	2.05	1.20–3.51	0.009	1.67	0.81–3.44	0.17
BNP ≥ 200 pg/mL	6.00	2.79–12.9	< 0.001	4.45	1.68–11.7	0.003
LA diameter ≥ 50 mm	3.72	1.97–7.02	< 0.001	4.19	1.68–10.4	0.002
LVEF < 40%	7.59	2.92–19.8	< 0.001	6.74	2.03–22.4	0.002
LV hypertrophy	3.52	2.07–5.99	< 0.001	3.39	1.66–6.93	< 0.001
All abbreviations are as in Table 1.						

Multivariate logistic regression analysis (Table 3), adjusted for variables used in the univariate analysis, demonstrated that for $CHADS_2$ score group, non-paroxysmal AF, BNP ≥ 200 pg/mL, and LV hypertrophy were significant independent determinants of LASEC, and that for CHA_2DS_2-VASc score group, only non-paroxysmal AF was a significant independent determinant of LASEC.

Table 3
Multivariate logistic regression analysis for assessing determinants of LASEC.

	$CHADS_2$ group			CHA_2DS_2-VASc group		
Variable	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Female	1.29	0.67–2.50	0.44	1.31	0.41–3.17	0.59
Non-paroxysmal AF	5.86	3.21–10.7	< 0.001	3.42	1.53–7.65	0.002
eGFR < 60 mL/min/1.73 m^2	1.66	0.88–3.14	0.12	1.38	0.58–3.29	0.76
BNP ≥ 200 pg/mL	3.22	1.25–8.28	0.015	1.85	1.25–8.28	0.22
LA diameter ≥ 50 mm	1.37	0.64–2.94	0.42	1.66	0.55–4.97	0.35
LVEF < 40%	2.58	0.79–8.49	0.12	3.19	0.68–15.0	0.19
LV hypertrophy	2.16	1.11–4.20	0.024	2.65	1.07–6.58	0.058
All abbreviations are as in Table 1..						

Figure 2 compares contribution of selected clinical and echocardiographic variables to LASEC detection, which is based on the multivariate analysis as in Table 3, with an additional covariate of “LAA velocity < 20 cm/s” being included. It was found that for both groups, “LAA velocity < 20 cm/s” and “non-paroxysmal AF” were exceeding a LogWorth value of 2, which is identical to P < 0.01.

Discussion

The present study indicated that a considerable number of nonvalvular AF patients had LASEC even with low thromboembolic risk scores, and that in our population, the presence of LASEC was related to non-paroxysmal AF, elevated BNP level, or presence of LV hypertrophy.

Previous studies on LASEC and thromboembolic risk scores

Several reports exist regarding relationship between TEE findings and thromboembolic risk scores, and in most cases, the prevalence of LASEC and LAA dysfunction is shown to increase as $CHADS_2$ and CHA_2DS_2-VASc scores increased [6–8]. A possible explanation for this association is that elevated thromboembolic risk scores are more likely to be associated with cardiac conditions predisposed to thrombus formation such as LA enlargement and LV systolic dysfunction [14–16]. Increased $CHADS_2$

and CHA_2DS_2-VASc scores may also enhance production of various inflammatory cytokines that exert as prothrombotic substrates [25, 26].

LASEC appearance under low thromboembolic risk scores

There are a few reports on LASEC observed under low thromboembolic risk scores [6, 9, 10, 15]. Our finding that about 20% of the low-risk score patients had LASEC was similar to that reported previously [6, 15]. The pathogenesis of SEC is quite complex, with multiple interrelated factors that are contributing [27]; in fact, some investigators failed to find relationship between thromboembolic risk scores, LASEC, and LAA velocity [22].

LASEC occurring under low $CHADS_2$ or CHA_2DS_2-VASc scores may result from the difference in individual risk components (hypertension, diabetes, etc.), rather than the difference in the scores themselves. As shown in Table 4, for example, congestive heart failure was more common in patients with LASEC than those without, whereas other risk components such as hypertension did not show such differences. Congestive heart failure is a syndrome commonly associated with cardiac changes that may result in development of LASEC [11–15].

Table 4
Prevalence of thromboembolic risk factors in patients with LASEC and those without.

	$CHADS_2$ group			**CHA_2DS_2-VASc group**		
Variable	LASEC absent (n = 281)	LASEC present (n = 80)	P	LASEC absent (n = 183)	LASEC present (n = 44)	P
Congestive heart failure, n (%)	28 (10)	30 (38)	< 0.001	14 (8)	16 (36)	< 0.001
Hypertension, n (%)	111 (40)	30 (38)	0.75	62 (34)	11 (25)	0.25
Age ≥ 75 years, n (%)	21 (8)	2 (3)	0.08	0 (0)	0 (0)	-
Diabetes mellitus, n (%)	14 (5)	1 (1)	0.09	6 (3)	0 (0)	0.11
Stroke/TIA, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Vascular disease, n (%)	5 (2)	4 (5)	0.13	0 (0)	0 (0)	-
Female, n (%)	71 (25)	27 (34)	0.14	29 (16)	11 (25)	0.17
All abbreviations are as in Table 1.						

There are two studies that focus on the condition of low thromboembolic risk scores. An elevated plasma homocysteine could be a risk of LA thrombus in nonvalvular AF patients [9]. Homocysteine seems to accelerate arterial and venous thrombosis through biological damage to vascular endothelium by

generating oxidative stress, reducing NO-production, and inducing inflammatory response [9]. Another study, using computed tomography to assess relationship between LAA morphologies (cactus, cauliflower, chicken-wing, and windsock) and a risk of stroke, demonstrated that the cauliflower type was mostly related to prior stroke especially in those with low $CHADS_2$ scores [28].

Clinical implications

One message in the present study was to determine what clinical variables, except TEE variables, would be a risk of LASEC under low $CHADS_2$ or CHA_2DS_2-VASc scores. The exception of TEE variables was intended based on the fact that TEE is a semi-invasive procedure with its application as a screening tool being limited. As shown in Fig. 2, “LAA velocity < 20 cm/s” and “non-paroxysmal AF” are comparable in both groups for contributing to LASEC detection. This finding may indicate that AF chronicity, even without support from TEE, becomes a simple marker of LASEC, and particularly sustain the recommendation by Puwanant et al. that a screening TEE should be performed in patients with a $CHADS_2$ score of 0 whose AF is persistent [6]. Among patients with non-paroxysmal AF, there may be a degree of atrial remodeling that may accelerate thrombus formation.

Limitations

The present study is subject to the limitations inherent to a single center study. All clinical and echocardiographic data were obtained retrospectively and thus a certain kind of misclassification might be inevitable. Another limitation was that the duration of AF and the adequacy of anticoagulation could not be reliably extracted from the patient records, which might result in overestimation of the number of non-paroxysmal AF patients. However, both LASEC represents not only a history of AF but also condition of the atrial tissue [29, 30]. Also, almost all patients were on anticoagulation that was religiously monitored. Finally, there were a small number of patients and thus our findings may not be generalized to other population.

Conclusions

We investigated clinical and echocardiographic variables that would determine LASEC formation on nonvalvular AF patients with low $CHADS_2$ or CHA_2DS_2-VASc scores. There were a considerable number of patients (about 20%) who had LASEC. With the results of the multivariate analysis taken into account, information on chronicity of AF, BNP, and LV hypertrophy may help identify patients at risk for thromboembolism. A large-scale study should be needed to confirm our observations.

Abbreviations

AF
atrial fibrillation
BNP
B-type natriuretic peptide

eGFR
estimated glomerular filtration rate
LA
left atrial
LAA
left atrial appendage
LASEC
left atrial spontaneous echo contrast
LV
left ventricular
TEE
transesophageal echocardiography

Declarations

Ethics approval and consent to participate

This study was approved by the ethics review board of Osaka Medical College with notification for guaranteed withdrawal of participants on the website providing means of “opt-out” (No. 2194-01).

Consent for publication

Our manuscript does not contain any individual person’s data in any form (including individual details, images or videos).

Availability of data and material

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TI and KA designed the study, analyzed the data, and wrote the initial draft of the manuscript. MO, KS, and MM contributed to the interpretation of data. MH gave their final approval to the manuscript.

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Figures

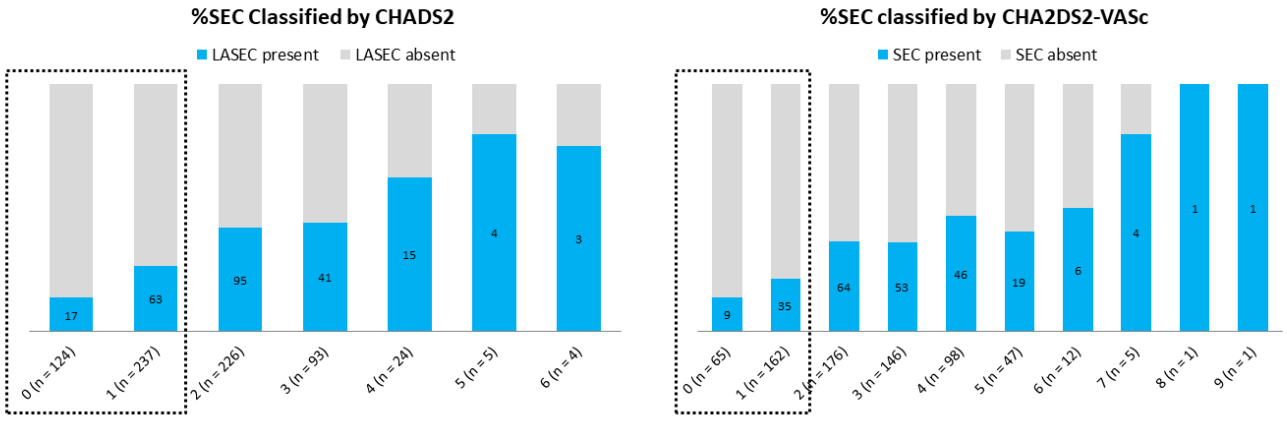

Figure 1

Percentages of the presence of LASEC classified by either CHADS2 (left) or CHA2DS2-VASc (right) score. Subgroups in the rectangles for each graph are those analyzed in the present study.

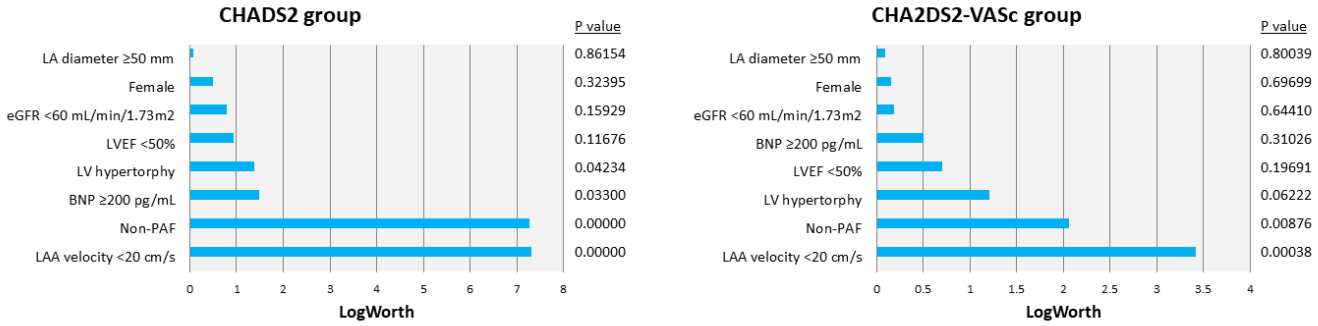

Figure 2

Effect summary on the comparisons of contribution of selected variables to the positivity of LASEC for CHADS2 (left) and CHA2DS2-VASc (right) groups. The larger LogWorth value, the smaller P value with the greater significance of the relationship. A LogWorth of 2 is identical to “P = 0.01”. All abbreviations are as in Table 1.