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Exploring Clinical and Echocardiographic Factors in EHRA Type 2 Atrial Fibrillation for Predicting Ischaemic Stroke: A Search for Unrevealed Insights

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Abstract

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults. Valvular heart diseases (VHD), regardless of the arrhythmic problems, increase the risk of thromboembolism, which is even higher in those with associated atrial fibrillation. The EHRA (Evaluated Heart valves, Rheumatic or Artificial) classification categorized AF patients with significant VHD into type 1 and type 2. Unfortunately, there is currently very limited data on risk prediction in stroke-related valvular AF, particularly in the Asian population.

Aims: To investigate the clinical and echocardiographic risk factors for ischaemic stroke prediction in patients with EHRA type 2 VHD.

Methods: This retrospective study enrolled 695 AF patients with EHRA type 2 VHD. The data were collected from patients' medical records who met the inclusion and exclusion criteria from 2015 until 2020. The primary outcome was ischaemic strokes within the observation period.

Results: There were 67 ischaemic stroke events (9,6%) of the total sample. Our analysis found that none of the analyzed variables proved to be statistically significant risk factors in predicting the occurrence of ischaemic stroke. The median CHA2DS2-VASc risk prediction in the sample was 3, with an accuracy of AUC 0.502 (CI 95%; 0.429 – 0.576), sensitivity of 56.7%, and specificity of 44.7%.

Conclusion: Based on the parameters analyzed in this study, no factor was statistically well-predictive to predict the ischaemic stroke incidence in EHRA type 2 VHD AF. In addition, the CHA2DS2-VAS accuracy was low in this population. Further exploration is needed to build an accurate ischaemic stroke risk prediction for EHRA type 2 VHD.

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Keywords: Atrial fibrillation, ischaemic stroke, valvular heart disease.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults affecting approximately 2 - 4% of the population worldwide.[1-3] Patients with AF have an increased risk for thromboembolism. CHA2DS2-VASc (congestive heart failure or left ventricular disease, hypertension, age > 75 years old, diabetes, stroke (doubled), vascular disease, age > 65 years old, female sex) score has been widely used to predict thromboembolism in patients with non-valvular AF. However, the latest consensus from the European Heart Rhythm Association and the European Society of Cardiology (ESC) no longer used the terminology of non-valvular AF as it was deemed outdated. The consensus then divided AF into two classifications, which are the EHRA (Evaluated Heart valves, Rheumatic or Artificial) type 1 and type 2, which only consisted of patients with valvular AF.[4] Study by Lip et al. (2018) discovered that the predictive value of thromboembolism of CHA2DS2-VASc score in the EHRA type 1 VHD group was modest, c-indexes 0,62 (0,55-0,7) within one year and 0,66 (0,61-0,72) within 2.5 years follow up.[5] While the predictive value in the EHRA type 2 VHD group was modest, c-indexes 0,63 (0,60-0,65) within one year and 0,62 (0,60-0,64) within 2.5 years follow up. These findings implied that the CHA2DS2-VASc scoring system was inappropriate for predicting thromboembolism in valvular AF.[6-8] VHD, with or without AF, is already a high risk for thromboembolism, which increases even more in patients with AF. Therefore, a different scoring system is needed to provide a more accurate prediction of ischaemic stroke in patients with valvular AF.[9-10] Previous study showed that hypertension and glomerular filtration rate (GFR) were associated with ischaemic stroke in EHRA type 1 VHD.[11] Unfortunately, there is still insufficient information regarding the correlation between these parameters and the incidence of ischaemic stroke in EHRA type 2 VHD. Therefore, this study aims to investigate the clinical and echocardiographic risk factors for ischaemic stroke prediction in patients with EHRA type 2 VHD.

Methods

Our study conducted a retrospective cohort study and recruited patients with AF EHRA type 2 VHD at the National Cardiovascular Center Harapan Kita (NCCHK) hospital, Jakarta, Indonesia, from January 1, 2015, to July 31, 2020. Data were collected from patients' medical records. Ethical clearance was received from the Research Ethics Committee / Institutional Review Board of National Cardiovascular Center Harapan Kita with the number LB.02.01/VII/541/KEP030/2021. Inclusion criteria were adult patients (age > 18 years old) with AF EHRA type 2 VHD who were on direct anticoagulants or vitamin K antagonists. Exclusion criteria were patients with patent foramen ovale (PFO) based on echocardiography, patients with ischaemic stroke who did not have echocardiography and clinical data within one year prior to the stroke event, and patients with periprocedural stroke. Incidence of ischaemic stroke was defined as a stroke that occurred after the patient was diagnosed with AF. The clinical and echocardiographic parameters were age, sex, body mass index, atrial fibrillation type, CHA2DS2-VASc score, hypertension, diabetes mellitus, history of stroke, history of an acute coronary syndrome, history of coronary artery disease, smoking, heart failure, consumption of statin, anti-platelet, warfarin, direct anticoagulant, left ventricular ejection fraction, TAPSE, left atrial diameter, hemoglobin, hematocrit, creatinine, GFR, and time-in-therapeutic range (TTR).

After data collection, we analyzed the association between clinical and echocardiographic parameters with the incidence of ischaemic stroke in patients with AF EHRA type 2 by performing bivariate analysis using Chi-square. Based on the bivariate analysis, variables with a p-value of < 0.25 were further included in the multivariate analysis. Logistic regression using backward selection was employed in multivariate analysis. The final model formulation included variables with $p<0.05$ from the multivariate analysis. In the final model, good calibration was defined as a p-value of > 0.05 in the Hosmer and Leeshawn calibration test. Good discrimination was described as an area under the curve (AUC) greater than or equal to the expected AUC (>0.65).

Table 1. Baseline characteristic.

Variables	Ischaemic Stroke	Non-Ischaemic Stroke
Sex		
Male [n(%)]	37 (55.2)	328 (52.2)
Female [n(%)]	30 (44.8)	300 (47.8)
Body Mass Indexa		
BMI ≥ 25 kg/m^2 [n(%)]	13 (25)	157 (32.7)
BMI < 25 kg/m2 [n(%)]	39 (75)	323 (67.3)
AF Type	52	491
Non-paroxysmal [n(%)]	(77.6)	(78.2)
Paroxysmal [n(%)]	15 (22,4)	137 (21.8)
Hypertension [n(%)]	48 (71.6)	392 (62.4)
Diabetes mellitus [n(%)]	17 (25.4)	167 (26.6)
History of stroke [n(%)]	0 (0)	33 (5.3)
History of coronary heart disease [n(%)]	8 (11.9)	96 (15.3)
History of acute coronary syndrome [n(%)]	8 (11.9)	88 (14)
History of Peripheral artery disease [n(%)]	1 (1.5)	6 (1)
smoking [n(%)]	13 (19.4)	140 (22.3)
CHA2DS2-VASc score[median (min-max)]	3 (1-7)	3 (0-9)
Heart Failure [n(%)]	61 (91)	593 (94,4)
Statin [n(%)]	21 (31.3)	210 (33.4)
Antiplatelet [n(%)]	21 (31.3)	162 (25.8)
Warfarin[n(%)]	54(80.6)	521 (83)
Direct antikoagulant [n(%)]	0 (0)	28 (4.5)
Left ventricular ejection fraction (LVEF) b (%) [median (min-max)]	56 (18-87)	55 (12-89)
TAPSEc (mm) [median (min-max)]	15 (6-30)	15 (4-35)
Left atrial diameter d (mm) [median (min-max)]	46,5 (25-83.3)	47 (17-106)
Hemoglobin (g/dL) [median (min-max)]	13 (8.7-17)	13 (4.5-21.5)
Hematocrite (%) [median (min-max)]	38.3 (25-50,1)	38,9 (13.3-63.1)
Serum Creatinine (mg/dL) [median (min-max)]	1.07 (0.54 – 6.41)	1,09 (0,14 – 24,8)
GFR (mL/min/1,73 m2) [median (min-max)]	71 (7-188)	66 (0.78-329)
TTRe (%) [median (min-max)]	3.5 (0-60.7)	5.8 (0-100)

a: missing data 23.5%; b: missing data 0.6%; c: missing data 0.9%; d: missing data 7.2%; e: missing data: 33.4%. AF = atrial fibrillation, TAPSE= Tricuspid Annular Plane Systolic Excursion, GFR = glomerular filtration rate, TTR = Time in Therapeutic Range.

Table 2. Chi-square analysis on clinical history variables.

Variables	Ischaemic stroke				P	OR	Confidence Interval 95%	
	Yes		No					
	N	%	N	%			Min	Max
Age								
≥ 54 years	35	52.2	330	52.5	0.962	0.988	0.596	1.635
< 54 years	32	47.8	298	475				
Sex								
Male	37	55.2	328	52.2	0.641	1.128	0.680	1.872
Female	30	44.8	300	47.8				
Body mass index								
≥ 25 kg/m2	13	25	157	32.7	0.258	0.686	0.356	1.322
< 25 kg/m2	39	75	323	67.3				
AF type								
Non-paroxysmal	52	77.6	491	78.2	0.914	1.034	0565	1.893
Paroxysmal	15	22.4	137	21.8				
Hypertension								
Yes	48	71.6	392	62.4	0.137	1.521	0.873	2.650
No	19	28.4	236	37.6				
Diabetes mellitus								
Yes	17	25.4	167	26.6	0.830	0.939	0.527	1.673
No	50	74.6	461	73.4				
History of coronary heart disease								
Yes	8	11.9	96	15.3	0.465	0.751	0.348	1.622
No	59	88.1	532	84.7				
History of acute coronary syndrome								
Yes	8	11.9	88	14	0.640	0.832	0.384	1.801
No	59	88.1	540	86				
History of Peripheral artery disease								
Yes	1	1.5	6	1	0.676	1.571	0.186	13.246
No	66	98.5	622	99				
Smoking								
Yes	13	19.4	140	22.3	0.587	0.839	0.445	1.582
No	54	80.6	488	77.7				
CHA2DS2-VASc								
≥ 3	38	56.7	347	55.3	0.819	1.061	0.638	1.764
< 3	29	43.3	281	44.7				
Heart Failure								
Yes	61	91	593	94.4	0.264	0.6	0.243	1.484
No	6	9	35	5.6				
Statin								
Yes	46	68.7	418	66.6	0.729	1.1	0.640	1.892
No	21	31.3	210	33.4				
Antiplatelet								
Yes	46	68.7	466	74.2				
No	21	31.3	162	25.8	0.327	0.761	0.441	1.315
Warfarin								
Yes	13	19.4	107	17				
No	54	80.6	521	83	0.626	1.172	0.618	2.224
Direct Anticoagulant								
Yes	67	100	600	95.5				
No	0	0	28	4.5	0.099	1.112	1.084	1.140

Table 3. Chi-square analysis on echocardiographic and laboratory variables.

Variables	Ischaemic stroke				P	OR	Confidence Interval 95%	
	Yes		No					
	N	%	N	%			Min	Max
Left ventricular ejection fraction								
< 30%	17	25.4	110	17.6	0.120	1.589	0.883	2.859
≥ 30%	50	74.6	514	82.4				
TAPSE								
< 17 mm	41	61.2	385	61.9	0.910	0.971	0.579	1.628
≥17 mm	26	38.8	237	38.1				
Left atrial diameter								
≥ 46 mm	34	53.1	330	56.8	0.574	0.862	0.514	1.447
< 46 mm	30	46.9	251	43.2				
Haemoglobin								
≥ 12 g/dL	44	65.7	439	69.9	0.474	0.824	0.484	1.403
< 12 g/dL	23	34.3	189	30.1				
Hematocrit								
≥ 38%	36	53.7	355	56.5	0.661	0.893	0.539	1.480
< 38%	31	46.3	273	43.5				
Creatinine Serum								
≥ 1.35 mg/dL	20	29.9	187	29.8	0.990	1.004	0.579	1.740
< 1.35 mg/dL	47	70.1	441	70.2				
GFR								
<15 mL/min/1.73m2	2	3	5	0.8	0.088	0.834	0.729	20.155
≥15 mL/min/1.73m2	65	97	623	99.2				
TTR								
<50%	42	93.3	370	88.9	0.364	1.741	0.519	5.841
>50%	3	6.7	46	11.1				

Notes: Data was analysed with multiple logistic regression with backward method. (*) Variable was significant if P value <0,05. Nagelkerke R2 = 0.318

Table 4. Chi-square analysis on echocardiographic and laboratory variables.

Variables	P	OR	Confidence Interval 95%	
			Minimum	Maximum
Hypertension	0.136	1.526	0.876	2.659
LVEF <30%	0.213	1.463	0.804	2.663
GFR < 15 mL/min/1.73m2	0.123	3.584	0.672	19.105

LVEF = left ventricular ejection fraction, GFR = glomerular filtration rate.

Table 5. ROC curve of CHA2DS2-VASc in this population.

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0,502	0,037	0,948	0,429	0,576

Results:

At the beginning of the study, 1507 patients with valvular AF in NCCHK hospital were recruited between 1 January 2015 and 31 July 2020. Of these, 765 patients had EHRA type 1, four had PFO, three had periprocedural ischaemic strokes, and 40 had non-complete medical records. Thus, a total of 695 patients were included. The baseline characteristic of the study is described in **Table 1.** Ischaemic stroke was reported in

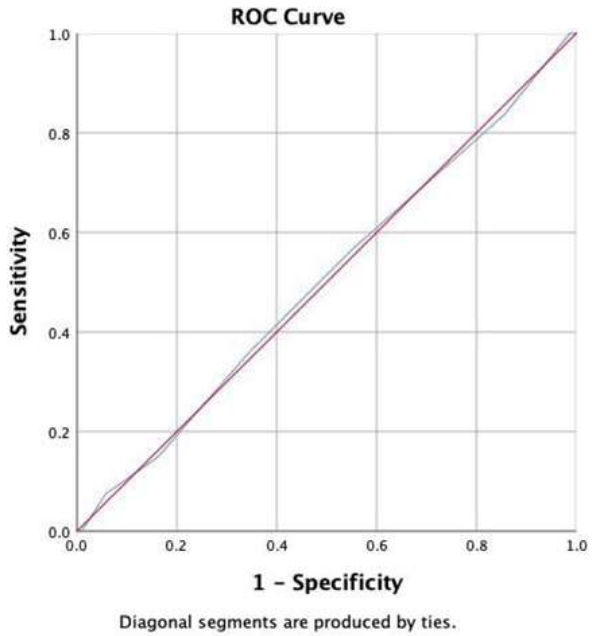

Figure 1. ROC curve of CHA2DS2-VASc in this population.

67 (9.6%) patients during the follow-up period.

For the statistical analysis, we performed a Chi-square analysis for categorical variables. To ensure accuracy and consistency, we converted any numerical variables into categorical ones before conducting the analysis. Cut-off value determination used ROC analysis to divide patients into two groups of categorical variables. From the bivariate Chi-square analysis, we found that several variables were statistically associated with the incidence of ischaemic stroke, in which they had a p-value of < 0.25. These were hypertension (p=0.137), history of stroke (p=0.055), no consumption of direct anticoagulant (p=0.099), LVEF (p=0.120), GFR < 15 mL/minute/1.73 m^2 (p = 0.088), and TTR < 50% (p=0.364), as shown in **Table 2.** and **Table 3.** Then, we performed a multivariate analysis with these variables and found that there was no variable associated with ischaemic stroke as none variable had a p-value of <0.05, as shown in **Table 4.** Therefore, the model formulation was not performed.

We evaluated the sensitivity and specificity of CHA2DS2-VASc in this demographic by utilizing the ROC curve, and it revealed the scoring system had 56.7% sensitivity and 44.7% specificity, as shown in **Figure 1** and **Table 5.**

Limitation

The study has several limitations. Firstly, the study had incomplete medical record data due to retrospective sampling. The analysis did not include dyslipidemia because of incomplete data. The second limitation of this study is that we did not analyze the type of VHD as a predictor factor of ischaemic stroke. This is due to the fact that most of the patients in the study had mixed valvular involvement. Third, the definition of 'stroke incidence' in this study referred to the cases of stroke that had been recorded and reported in NCCHK hospital. It should be noted that any incidents of stroke that occurred outside of NCCHK hospital were not included in this definition.

Conclusion:

After a thorough analysis of risk factors, encompassing clinical, echocardiographic, and laboratory data, we found that none of these factors exhibits a statistically high degree of predictivity with respect to ischaemic stroke incidence in EHRA type 2 VHD AF. Further investigations, particularly prospective cohort studies, are needed to confirm the results of this study.

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Conflicts Of Interest:

The author declares no conflict of interest.

Declarations:

- **Approval of the research protocol**: The study protocol was approved by the Institutional Review Board of Harapan Kita National Cardiac Center in accordance with the Nuremberg Code and Helsinki Declaration (No. LB.02.01/VII/541/KEP030/2021).
- **Informed Consent**: N/A
- **Registry and the Registration No. of the study/trial**: ClinicalTrials.gov ID NCT04222868
- **Animal Studies**: N/A

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