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ORIGINAL ARTICLE
Valvular Heart Disease

R_2-CHA_2DS_2-VASc Score for Cardiovascular Event Prediction After Bioprosthetic Valve Replacement

— Subanalysis From the BPV-AF Registry —

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Background: There are few studies evaluating the prognostic prediction method in atrial fibrillation (AF) patients after bioprosthetic valve (BPV) replacement. The R_2-CHA_2DS_2-VASc score is increasingly used for the prediction of cardiovascular (CV) events in patients with AF, device implantation, and acute coronary syndrome. We aimed to evaluate the predictive value of the R_2-CHA_2DS_2-VASc score for future CV events in AF patients after BPV replacement.

Methods and Results: The BPV-AF, an observational, multicenter, prospective registry, enrolled AF patients who underwent BPV replacement. The primary outcome measure was a composite of stroke, systemic embolism, CV events including heart failure requiring hospitalization, and cardiac death. A total of 766 patients was included in the analysis. The mean R_2-CHA_2DS_2-VASc score was 5.7±1.8. Low (scores 0–1), moderate (scores 2–4), and high (scores 5–11) R_2-CHA_2DS_2-VASc score groups consisted of 12 (1.6%), 178 (23.2%), and 576 (75.2%) patients, respectively. The median follow-up period was 491 (interquartile range 393–561) days. Kaplan-Meier analysis showed a higher incidence of the composite CV events in the high R_2-CHA_2DS_2-VASc score group (log rank test; P<0.001). Multivariate Cox proportional hazards regression analysis revealed that the R_2-CHA_2DS_2-VASc score as a continuous variable was an independent predictor of composite CV outcomes (hazard ratio 1.36; 95% confidence interval 1.18–1.55; P<0.001).

Conclusions: The R_2-CHA_2DS_2-VASc score is useful for CV risk stratification in AF patients after BPV replacement.

Key Words: Atrial fibrillation; Bioprosthetic valve replacement; R_2-CHA_2DS_2-VASc score; Risk stratification

The incidence of valvular heart disease is increasing in the aging society, and surgical valve replacement with bioprosthetic valve (BPV) is widely performed.[1–3] Atrial fibrillation (AF) is also increasing and associated with cardiovascular (CV) events including thromboembolism, heart failure, and death.[4–6] Various clinical features have been identified to stratify the CV risk. The $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used for thromboembolic risk stratification for patients with AF, and also predict mortality and other CV events.[7–9] In addition to the components of the $CHADS_2$ and CHA_2DS_2-VASc scores, chronic kidney disease (CKD) is known as an important CV risk factor in the general population and increases the risk of thromboembolism in AF patients independently of other risk factors.[10,11] Thus, the R_2-CHA_2DS_2-VASc score, which includes renal dysfunction in addition to the components of the CHA_2DS_2-VASc score, is increasingly being used for the prediction of CV events.[12–19] The R_2-CHA_2DS_2-VASc score has been reported to improve the predictive ability for morbidity and mortality risk in patients with AF.[12] However, the predictive performance of the R_2-CHA_2DS_2-VASc score in

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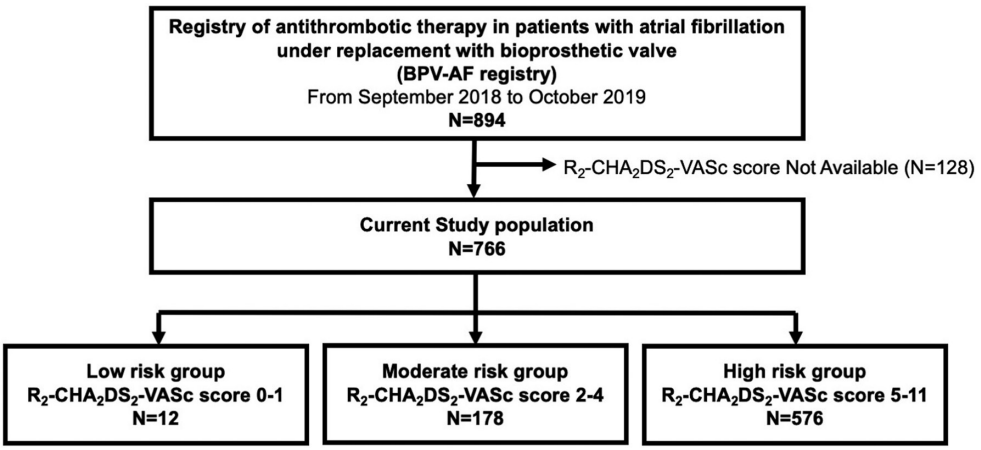

Figure 1. Study population.

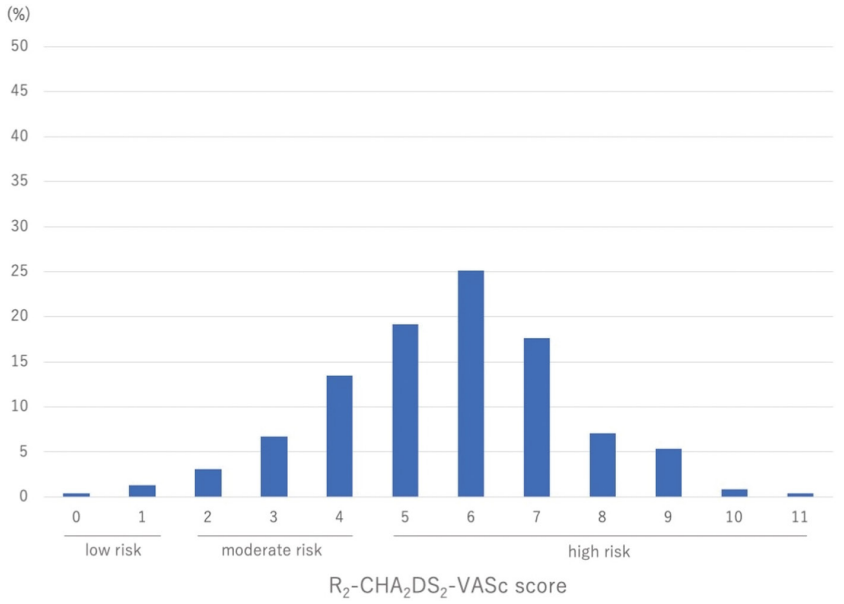

Figure 2. Frequency distribution of the R2-CHA2DS2-VASc score.

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Table 1. Baseline Patient Demographic and Clinical Characteristics

	All (n=766)	R_2-CHA_2DS_2-VASc 0–1 (n=12)	R_2-CHA_2DS_2-VASc 2–4 (n=178)	R_2-CHA_2DS_2-VASc 5–11 (n=576)	P value
Female	419 (54.7)	0 (0.0)	67.0 (37.6)	352 (61.1)	<0.001
Age (years)	80.3±6.8	66.4±5.8	76.4±6.7	81.8±5.9	<0.001
Weight (kg)	53.8±11.3	62.9±8.4	55.8±11.4	53.0±11.2	<0.001
BMI (kg/m^2)	22.2±3.7	22.7±3.4	21.9±3.1	22.3±3.9	0.531
HAS-BLED score					
Mean±SD	2.4±1.0	1.1±0.7	2.0±0.8	2.6±1.0	<0.001
≥3.0	337 (44.5)	0 (0.0)	43 (24.3)	294 (51.8)	<0.001
eGFR (mL/min/1.73 m^2)	47.1±17.5	68.9±5.6	61.5±17.6	42.1±14.7	<0.001
CCr (mL/min)	40.9±18.2	76.0±13.6	55.2±18.5	36.0±14.9	<0.001
Type of AF					0.277
Paroxysmal	288 (37.6)	4 (33.3)	65 (36.5)	219 (38.0)	
Persistent	254 (33.2)	6 (50.0)	68 (38.2)	180 (31.3)	
Permanent	224 (29.2)	2 (16.7)	45 (25.3)	177 (30.7)	
Left atrial plication, LAA occlusion/excision	86 (11.2)	1 (8.3)	22 (12.4)	63 (11)	0.831
Previous history of CVD					
Ischemic stroke	108 (14.1)	0 (0.0)	4 (2.3)	104 (18.1)	<0.001
Hemorrhagic stroke	19 (2.5)	0 (0.0)	2 (1.1)	17 (3)	0.463
Intracranial hemorrhage	26 (3.4)	0 (0.0)	6 (3.4)	20 (3.5)	0.806
Systemic embolism	11 (1.4)	0 (0.0)	1 (0.6)	10 (1.7)	0.558
Major bleeding	45 (5.9)	1 (8.3)	11 (6.2)	33 (5.7)	0.913
Comorbidities					
Hypertension	575 (75.1)	4 (33.3)	104 (58.4)	467 (81.1)	<0.001
Heart failure	434 (56.7)	5 (41.7)	71 (39.9)	358 (62.2)	<0.001
Dyslipidemia	384 (50.1)	2 (16.7)	70 (39.3)	312 (54.2)	<0.001
Diabetes	160 (20.9)	0 (0.0)	22 (12.4)	138 (24.0)	<0.001
Renal dysfunction	70 (9.1)	0 (0.0)	6 (3.4)	64 (11.1)	0.004
Chronic respiratory disease	65 (8.5)	0 (0.0)	16 (9.0)	49 (8.5)	0.557
Malignant tumour	61 (8.0)	1 (8.3)	9 (5.1)	51 (8.9)	0.262
Myocardial infarction	39 (5.1)	0 (0.0)	5 (2.8)	34 (5.9)	0.188
Peripheral arterial disease	28 (3.7)	0 (0.0)	1 (0.6)	27 (4.7)	0.030
Thrombosis and embolism	24 (3.1)	0 (0.0)	1 (0.6)	23 (4.0)	0.059
Liver dysfunction	21 (2.7)	1 (8.3)	5 (2.8)	15 (2.6)	0.371
Dementia	37 (4.8)	0 (0.0)	3 (1.7)	34 (5.9)	0.053
Left ventricular ejection fraction					0.272
<40%	51 (7.1)	1 (8.3)	7 (4.2)	43 (8.0)	
40–49%	67 (9.4)	1 (8.3)	20 (12.0)	46 (8.6)	
≥50%	598 (83.5)	10 (83.3)	140 (83.8)	448 (83.4)	

Data are presented as n (%) or mean±SD. AF, atrial fibrillation; BMI, body mass index; CCr, creatinine clearance; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LAA, left atrial appendage.

AF patients undergoing BPV replacement has not been assessed. The aim of the present study was to investigate the value of the R_2-CHA_2DS_2-VASc score to the prognosis and risk stratification of AF patients after BPV replacement.

Methods

Study Population

The present study was a subgroup analysis of the registry investigating antithrombotic therapy in patients with AF after BPV replacement (BPV-AF Registry). Details of the main study design and primary results have been published previously.[20,21] In brief, it was a multicenter, prospective, observational registry that enrolled 894 AF patients who had undergone BPV replacement in Japan between September 2018 and October 2019. The key inclusion criteria were as follows: BPV replacement at least 3 months prior to enrollment; definitive diagnosis of AF; availability of at least 1-year follow-up data during the observation period; and ability to provide written informed consent. The key exclusion criteria were as follows: transient postoperative AF; participation in interventional studies during the data collection period; moderate or severe mitral stenosis; and mechanical valve replacement.

From the 894 patients enrolled into the BPV-AF registry, 766 patients whose R_2-CHA_2DS_2-VASc score had been obtained were included in the present subanalysis (**Figure 1**). The R_2-CHA_2DS_2-VASc score was modified from the CHA_2DS_2-VASc score (congestive heart failure, hyperten-

Table 2. Operative Characteristics Describing the Prosthesis Position, and Full Details of the Aortic and Mitral Valves

	All (n=766)	R_2-CHA_2DS_2-VASc 0–1 (n=12)	R_2-CHA_2DS_2-VASc 2–4 (n=178)	R_2-CHA_2DS_2-VASc 5–11 (n=576)	P value
Prosthesis position					<0.001
Aortic valve	491 (64.1)	8 (66.7)	86 (48.3)	397 (68.9)	
Mitral valve	176 (23)	3 (25.0)	61 (34.3)	112 (19.4)	
Both valves	99 (12.9)	1 (8.3)	31 (17.4)	67 (11.6)	
Aortic valve	(n=491)	(n=8)	(n=86)	(n=397)	
VHD subtype					<0.001
Stenosis	364 (74.1)	3 (37.5)	50 (58.1)	311 (78.3)	
Regurgitation	101 (20.6)	3 (37.5)	32 (37.2)	66 (16.6)	
Other	26 (5.3)	2 (25)	4 (4.7)	20 (5)	
Operation type					<0.001
Surgery	291 (59.3)	8 (100)	71 (82.6)	212 (53.4)	
TAVI	200 (40.7)	0 (0)	15 (17.4)	185 (46.6)	
History of replacement					0.147
First replacement	465 (94.7)	6 (75.0)	83 (96.5)	376 (94.7)	
Re-replacement	24 (4.9)	2 (25.0)	3 (3.5)	19 (4.8)	
Mitral valve	(n=176)	(n=3)	(n=61)	(n=112)	
VHD subtype					0.051
Stenosis	72 (40.9)	0 (0.0)	29 (47.5)	43 (38.4)	
Regurgitation	88 (50.0)	2 (66.7)	24 (39.3)	62 (55.4)	
Other	16 (9.1)	1 (33.3)	8 (13.1)	7 (6.3)	
History of replacement					0.311
First replacement	155 (88.1)	2 (66.7)	53 (86.9)	100 (89.3)	
Re-replacement	21 (11.9)	1 (33.3)	8 (13.1)	12 (10.7)	

Data are presented as n (%). TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease.

sion, age >75 years, diabetes, stroke, vascular disease, age 65–74 years, female sex) by adding reduced estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m^2). Patients were stratified into three risk groups according to their R_2-CHA_2DS_2-VASc score as follows: low (scores 0–1); moderate (scores 2–4); and high (scores 5–11).[13] Baseline characteristics and clinical outcomes were compared.

The main study was conducted in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare of Japan, and all other applicable regulatory and legal requirements. The study protocol and informed consent document were reviewed and approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (M30-068; September 26, 2018) and each participating hospital. The main study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000034485).

Outcomes

The primary outcome of the present subgroup analysis was a composite of stroke, systemic embolism, CV events (including myocardial infarction, stroke, systemic embolism, and death from bleeding), heart failure requiring hospitalization, and CV death. The detailed definitions of each event have been published previously.[20,21]

The secondary outcomes were stroke, systemic embolism, major bleeding, CV events, heart failure requiring hospitalization, CV death, all-cause mortality, reoperation of the BPV, and bleeding events (including clinically relevant bleeding and minor bleeding).

Statistical Analysis

Categorical variables were expressed as numbers and percentages and compared with the Chi-square test or Fisher's exact test variables, as appropriate. Continuous variables were expressed as median with interquartile range (IQR) or mean and standard deviation and were compared using the Wilcoxon rank-sum test or Student t test based on their distribution. For the primary outcome, incidence rates in percent and per 100 person-years and 95% confidence intervals (CIs) were calculated using a Poisson distribution. The cumulative incidences were estimated using the Kaplan-Meier method, and differences among each group were assessed using a log-rank test. We used the Cox proportional hazards regression model to estimate hazard ratios (HRs) and their 95% CIs for the primary outcome measure. The multivariable Cox proportional hazards assumptions were conducted for the primary outcome measure using the following covariates: antiplatelet use, type of AF, transcatheter aortic valve implantation (TAVI), malignancy, and valve position (mitral, aortic, or both) as potential confounders. All P values reported are 2-tailed, and P<0.05 was considered statistically significant. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Among the 766 patients with BPV replacement and AF, low, moderate, and high R_2-CHA_2DS_2-VASc score groups consisted of 12 (1.6%), 178 (23.2%), and 576 (75.2%) patients, respectively (**Figure 1**). The distribution of the

Table 3. Administration Status of Antithrombotic Agents (Anticoagulant and Antiplatelet Drugs)

	All (n=766)	R_2-CHA_2DS_2-VASc 0–1 (n=12)	R_2-CHA_2DS_2-VASc 2–4 (n=178)	R_2-CHA_2DS_2-VASc 5–11 (n=576)	P value
No antithrombotic drug	38 (5.0)	2 (16.7)	12 (6.7)	24 (4.2)	
Warfarin-based therapy	419 (54.7)	5 (41.7)	107 (60.1)	307 (53.3)	
No antiplatelet drug	306 (73.0)	5 (100.0)	80 (74.8)	221 (72.0)	0.420
With antiplatelet drug	113 (27.0)	0 (0.0)	27 (25.2)	86 (28.0)	
With aspirin (monotherapy)	97 (23.2)	0 (0.0)	26 (24.3)	71 (23.1)	0.682
With P2Y12 (monotherapy)	11 (2.6)	0 (0.0)	0 (0.0)	11 (3.6)	0.156
With DAPT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
With others	5 (1.2)	0 (0.0)	1 (0.9)	4 (1.3)	1.000
Warfarin monitoring					
Time in therapeutic range (%)					0.056
Mean±SD	70.4±35.0	68.1±47.2	78.1±31.1	67.8±35.8	
Median (IQR)	85.2 (45.6–100.0)	86.1 (36.1–100.0)	99.1 (64.3–100.0)	81.3 (39.2–100.0)	
PT-INR					
Age <70 years					1.000
<2.0	13 (54.2)	1 (50.0)	9 (56.3)	3 (50.0)	
2.0–3.0	11 (45.8)	1 (50.0)	7 (43.8)	3 (50.0)	
>3.0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Age ≥70 years					0.021
<1.6	80 (21.0)	1 (33.3)	10 (11.5)	69 (23.7)	
1.6–2.6	264 (69.3)	2 (66.7)	72 (82.8)	190 (65.3)	
>2.6	37 (9.7)	0 (0.0)	5 (5.8)	32 (11)	
DOAC-based therapy	241 (31.5)	3 (25.0)	37 (20.8)	201 (34.9)	
No antiplatelet drug	173 (71.8)	2 (66.7)	25 (67.6)	146 (72.6)	0.691
With antiplatelet drug	68 (28.2)	1 (33.3)	12 (32.4)	55 (27.4)	
With aspirin (monotherapy)	50 (20.8)	1 (33.3)	10 (27.0)	39 (19.4)	0.312
With P2Y12 (monotherapy)	15 (6.2)	0 (0.0)	1 (2.7)	14 (7.0)	0.570
With DAPT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
With others	3 (1.2)	0 (0.0)	1 (2.7)	2 (1.0)	0.421
Antiplatelet therapy (without warfarin/DOAC)	68 (8.9)	2 (16.7)	22 (12.4)	44 (7.6)	
Aspirin (monotherapy)	54 (79.4)	2 (100)	19 (86.4)	33 (75.0)	0.594
P2Y12 (monotherapy)	9 (13.2)	0 (0.0)	3 (13.6)	6 (13.6)	1.000
DAPT	3 (4.4)	0 (0.0)	0 (0.0)	3 (6.8)	0.585
With others	2 (2.9)	0 (0.0)	0 (0.0)	2 (4.6)	0.575

Data are presented as n (%), unless indicated otherwise. DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, international normalized ratio; PT, prothrombin time.

R_2-CHA_2DS_2-VASc score is shown in **Figure 2**. The mean R_2-CHA_2DS_2-VASc score was 5.7±1.8. More than half of the patients were classified into the high-risk group. The baseline clinical characteristics of each group are summarized in **Table 1**. The mean age of patients was 80.3 years, and 54.7% were female. The median follow-up period was 491 (IQR 393–561) days. Operative characteristics are described in **Table 2**. Aortic stenosis and TAVI were more frequent in the high R_2-CHA_2DS_2-VASc score group. Administration status of antithrombotic agents is shown in **Table 3** and it was not significantly different among the three groups.

Association of R_2-CHA_2DS_2-VASc Score and Clinical Outcome

During the follow-up period, the primary endpoint was recorded in 8.74%/years (95% CI 7.06–10.83) in total study population and 10.99%/years (95% CI 8.8–13.72) in the high R_2-CHA_2DS_2-VASc score group (**Table 4**). The incidence of secondary outcomes is also shown in **Table 4**. The incidence of stroke or systemic embolism was 1.82%/years (95% CI 1.15–2.89).

Kaplan-Meier analysis showed a higher incidence of the composite CV outcome in the high R_2-CHA_2DS_2-VASc score group (log rank test; P<0.001; **Figure 3**). Multivariate Cox proportional hazards regression analysis revealed that the R_2-CHA_2DS_2-VASc score as a continuous variable was an independent predictor of composite CV outcome (HR 1.36; 95% CI 1.18–1.55; P<0.001), stroke and systemic embolism (HR 1.53; 95% CI 1.12–2.08; P=0.007), CV events (HR 1.47; 95% CI 1.10–1.98; P=0.010), heart failure requiring hospitalization (HR 1.29; 95% CI 1.10–1.52; P=0.002), and CV death (HR 1.67; 95% CI 1.10–2.53; P=0.016; **Table 5**).

Discussion

This is the first prospective analysis to evaluate the prognostic estimation value of the R_2-CHA_2DS_2-VASc score in AF patients after BPV replacement. The major findings of

Table 4. Summary of Clinical Outcomes

	All (n=766)		R_2-CHA_2DS_2-VASc 0–1 (n=12)		R_2-CHA_2DS_2-VASc 2–4 (n=178)		R_2-CHA_2DS_2-VASc 5–11 (n=576)	
	n (%)	%/years (95% CI)	n (%)	%/years (95% CI)	n (%)	%/years (95% CI)	n (%)	%/years (95% CI)
Primary outcome								
Composite of stroke, SE, cardiovascular events*, HF requiring hospitalization, and cardiac death	84 (11.0)	8.74 (7.06–10.83)	1 (8.3)	6.47 (0.91–45.97)	5 (2.8)	2.12 (0.88–5.09)	78 (13.5)	10.99 (8.8–13.72)
Secondary outcomes								
Stroke/SE	18 (2.4)	1.82 (1.15–2.89)	1 (8.3)	6.47 (0.91–45.97)	0 (0.0)	–	17 (3.0)	2.31 (1.44–3.72)
Major bleeding	16 (2.1)	1.62 (0.99–2.64)	1 (8.3)	6.78 (0.95–48.12)	1 (0.6)	0.42 (0.06–2.99)	14 (2.4)	1.90 (1.12–3.20)
Cardiovascular events*	19 (2.5)	1.92 (1.23–3.01)	1 (8.3)	6.47 (0.91–45.97)	0 (0.0)	–	18 (3.1)	2.45 (1.54–3.88)
HF requiring hospitalization	58 (7.6)	5.96 (4.61–7.71)	0 (0.0)	–	5 (2.8)	2.12 (0.88–5.09)	53 (9.2)	7.35 (5.61–9.61)
Cardiovascular death	10 (1.3)	1.00 (0.54–1.86)	0 (0.0)	–	0 (0.0)	–	10 (1.7)	1.34 (0.72–2.49)
All-cause death	39 (5.1)	3.90 (2.85–5.33)	0 (0.0)	–	5 (2.8)	2.11 (0.88–5.06)	34 (5.9)	4.55 (3.25–6.36)
Reoperation of the BPV	6 (0.8)	0.60 (0.27–1.34)	1 (8.3)	6.46 (0.91–45.86)	1 (0.6)	0.42 (0.06–2.99)	4 (0.7)	0.54 (0.2–1.43)
Major bleeding, clinically relevant bleeding, minor bleeding	54 (7.1)	5.62 (4.30–7.33)	1 (8.3)	6.78 (0.95–48.12)	9 (5.1)	3.88 (2.02–7.45)	44 (7.6)	6.16 (4.58–8.28)

*Cardiovascular events included myocardial infarction, stroke, SE, and death from bleeding. BPV, bioprosthetic valve; HF, heart failure; SE, systemic embolism.

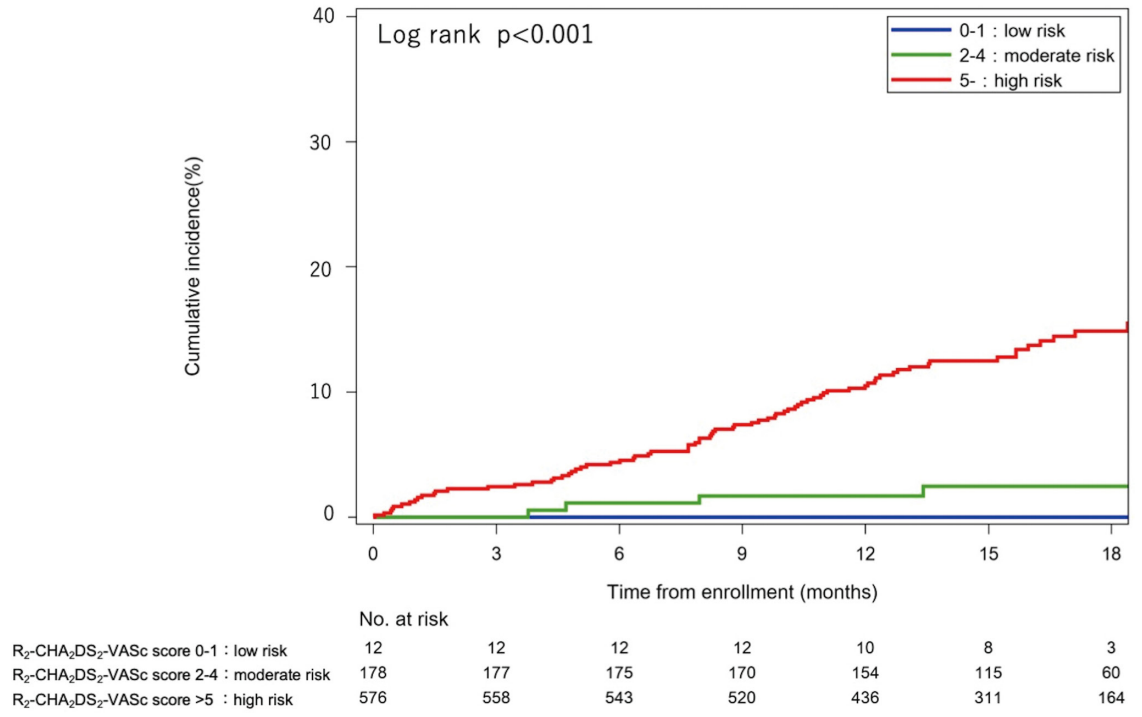

Figure 3. Cumulative incidence for composite cardiovascular events.

Table 5. Cox Proportional Hazards Regression Models for Each Event

Variable	R_2-CHA_2DS_2-VASc score			
	Univariate model		Multivariate model*	
	HR (95% CI)	P value	HR (95% CI)	P value
Composite outcome	1.33 (1.18–1.51)	<0.001	1.36 (1.18–1.55)	<0.001
Stroke/systemic embolism	1.48 (1.13–1.94)	0.005	1.53 (1.12–2.08)	0.007
Major bleeding	1.16 (0.88–1.54)	0.282	1.16 (0.84–1.58)	0.368
Cardiovascular events†	1.43 (1.10–1.86)	0.008	1.47 (1.10–1.98)	0.010
Heart failure requiring hospitalization	1.24 (1.07–1.44)	0.004	1.29 (1.10–1.52)	0.002
Cardiovascular death	1.73 (1.19–2.53)	0.005	1.67 (1.10–2.53)	0.016
All-cause death	1.14 (0.95–1.36)	0.156	1.07 (0.88–1.30)	0.484
Reoperation of the BPV	0.79 (0.52–1.22)	0.290	0.78 (0.49–1.25)	0.302
Major bleeding, clinically relevant bleeding, minor bleeding	1.07 (0.92–1.25)	0.352	1.08 (0.92–1.28)	0.340

*Adjusted for antiplatelet use, type of atrial fibrillation, transcatheter aortic valve implantation, malignancy, and valve position (mitral, aortic, or both). †Cardiovascular events included myocardial infarction, stroke, systemic embolism, and death from bleeding. BPV, bioprosthetic valve; CI, confidence interval; HR, hazard ratio.

the present study are as follows: (1) the R_2-CHA_2DS_2-VASc score could stratify the CV risk of AF patients undergoing BPV replacement; and (2) more than half of the patients were at high risk of CV events as defined by the R_2-CHA_2DS_2-VASc score ≥5.

Prevalences of AF and valvular heart disease are increasing and frequently coexist among aging populations. BPV replacement is a common, increasingly utilized treatment for valvular heart disease. Various adverse events after BPV replacement are associated with increased mortality and disability. The incidence of stroke varied between 1.4% and 2.4% of patients during the in-hospital stay, and between 6.1% and 13.8% during long-term follow-up.[22] The short-term incidence of stroke and systemic embolism in the present study (1.82%/years; 95% CI 1.15–2.89) was comparable with previous reports. Marc et al reported that age >75 years, female gender, past and present cigarette smoking, coronary artery disease, AF, and advanced left ventricular dysfunction were risk factors for embolic stroke after surgical valve replacement.[23] However, data regarding the prediction of prognosis after BPV replacement in AF patients remains limited.

The $CHADS_2$ and CHA_2DS_2-VASc scores have been developed mainly for the assessment of thromboembolic risk in patients with nonvalvular AF.[7,8] A growing body of evidence showed an association between the $CHADS_2$ or CHA_2DS_2-VASc score and CV events regardless of the presence of AF.[9] The CHA_2DS_2-VASc score has also been reported to be a predictor of mechanical prosthetic valve thrombosis.[24] Piccini et al found that CKD is a strong and independent predictor of stroke in the AF population, and validated R_2-CHA_2DS_2-VASc score in the risk stratification.[11] It has been reported that the R_2-CHA_2DS_2-VASc score is a better predictive method for CV morbidity and mortality than the $CHADS_2$ and CHA_2DS_2-VASc scores.[12] The R_2-CHA_2DS_2-VASc score has been proposed as a tool for prediction of CV adverse events and prognosis in several different clinical settings, which include mortality in the high CV risk population,[14] acute coronary syndrome (ACS) in patients with chest pain,[15] no-reflow phenomenon in patients with ST-segment elevation myocardial infarction,[16,17] prognosis of ACS,[18,19] and atrial high-rate episodes in pacemaker patients.[13] In these studies, every 1-point increase in the R_2-CHA_2DS_2-VASc score was associated with a 31–53% increase in the risk of CV events. In the present study, every 1-point increase in the R_2-CHA_2DS_2-VASc score was associated with a 36% increase in the risk of composite CV outcome. Although the optimal cut-off value has not been definitively set yet, most studies defined a R_2-CHA_2DS_2-VASc score of ≥4–5 as a high risk of adverse events. In the present study, an R_2-CHA_2DS_2-VASc score ≥5 was defined as high risk in AF patients after BPV replacement, based on a previous report.[13] The R_2-CHA_2DS_2-VASc score is easily calculated by adding renal impairment to the CHA_2DS_2-VASc score, and will be useful in daily practice.

Study Limitations

Several limitations of this study should be acknowledged. First, this was an observational cohort study and the number of CV events were relatively small. A low incidence of each adverse clinical outcome measure might cause relatively low statistical power in this study. The clinical value of the R_2-CHA_2DS_2-VASc score may need to be validated by future studies with a larger number of patients. Second, this study showed only mid-term outcomes. Therefore, studies with longer follow-up periods are needed.

Conclusions

The R_2-CHA_2DS_2-VASc score is useful for CV risk stratification in AF patients after BPV replacement.

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IRB Information

The protocol and the informed consent document were reviewed and approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (M30-068; September 26, 2018) and institutional review boards at each participating center.

Data Availability

The deidentified participant data and the study protocol will be shared on a request basis for up to 36 months after the publication of this article. Researchers who make the request should include a methodologically sound proposal on how the data will be used; the proposal may be reviewed by the responsible personnel at Daiichi Sankyo Co., Ltd, and the data requestors will need to sign a data access agreement. Please contact the corresponding author directly to request data sharing.

References

1. Ray S. Changing epidemiology and natural history of valvular heart disease. *Clin Med (Lond)* 2010; **10:** 168–171.
2. Hollenberg SM. Valvular heart disease in adults: Etiologies, classification, and diagnosis. *FP Essent* 2017; **457:** 11–16.
3. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery; Yoshimura N, Sato Y, Takeuchi H, Abe T, Enco S, Hirata Y, et al. Thoracic and cardiovascular surgeries in Japan during 2021: Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg* 2024; **72:** 254–291.
4. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA* 2001; **285:** 2370–2375.
5. Doi K, Ogawa H, Ishigami K, Ikeda S, Aono Y, Hamatani Y, et al. Impact of valvular heart disease on mortality, thromboembolic and cardiac events in Japanese patients with atrial fibrillation: The Fushimi AF Registry. *Circ J* 2020; **84:** 714–722.
6. Ogawa H, Akao M. Is progression from paroxysmal to sustained atrial fibrillation bad news? *Circ J* 2022; **86:** 176–181.
7. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285:** 2864–2870.
8. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The EURO Heart Survey on Atrial Fibrillation. *Chest* 2010; **137:** 263–272.
9. Horikoshi T, Nakamura T, Yoshizaki T, Nakamura J, Uematsu M, Kobayashi T, et al. Predictive value of $CHADS_2$, CHA_2DS_2-VASc and R_2-$CHADS_2$ scores for short- and long-term major adverse cardiac events in non-ST-segment elevation myocardial infarction. *Circ J* 2024; **88:** 1246–1253.
10. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation* 2009; **119:** 1363–1369.
11. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: Validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013; **127:** 224–232.
12. Fu S, Zhou S, Luo L, Ye P. $R_{2(GFR)}CHADS_2$ and $R_{2(GFR)}CHA_2DS_2VASc$ schemes improved the performance of $CHADS_2$ and CHA_2DS_2VASc scores in death risk stratification of Chinese older patients with atrial fibrillation. *Clin Interv Aging* 2017; **12:** 1233–1238.
13. Li YP, Chen JY, Chen TW, Lu WD. Atrial high-rate episodes intensify $R_2CHA_2DS_2$-VASc score for prognostic stratification in pacemaker patients. *Sci Rep* 2023; **13:** 7640.
14. D'Errico M, Piscitelli P, Mirijello A, Santoliquido M, Salvatori M, Vigna C, et al. CHA_2DS_2-VASc and $R_2CHA_2DS_2$-VASc scores predict mortality in high cardiovascular risk population. *Eur J Clin Invest* 2022; **52:** e13830.
15. Topaz G, Ben-Zvi E, Pereg D, Kitay-Cohen Y, Benchetrit S, Zitman-Gal T, et al. Prediction of acute-coronary-syndrome using newly-defined R_2-CHA_2DS_2-VASc score among patients with chest pain. *J Cardiol* 2021; **77:** 370–374.
16. Zhang Q, Hu M, Ma S, Niu T. New R_2-CHA_2DS_2-VASc score predicts no-reflow phenomenon and long-term prognosis in patients with ST-segment elevation myocardial infarction after primary percutaneous coronary intervention. *Front Cardiovasc Med* 2022; **9:** 899739.
17. Zorlu Ç, Köseoğlu C. Comparison of $RCHA_2DS_2$-VASc score and CHA_2DS_2-VASc score prediction of no-reflow phenomenon in patients with ST-segment elevation myocardial infarction. *Turk Kardiyol Dern Ars* 2020; **48:** 664–672.
18. Węgiel M, Rakowski T, Dziewierz A, Wojtasik-Bakalarz J, Sorysz D, Bartuś S, et al. CHA_2DS_2-VASc and R_2-CHA_2DS_2-VASc scores predict in-hospital and post-discharge outcome in patients with myocardial infarction. *Postepy Kardiol Interwencyjnej* 2018; **14:** 391–398.
19. Kiliszek M, Szpakowicz A, Filipiak KJ, Kołtowski Ł, Południewska D, Szymański F, et al. CHA_2DS_2-VASc and $R_2CHA_2DS_2$-VASc scores have predictive value in patients with acute coronary syndromes. *Pol Arch Med Wewn* 2015; **125:** 545–552.
20. Furukawa Y, Miyake M, Fujita T, Koyama T, Takegami M, Kimura T, et al. Rationale, design, and baseline characteristics of the bioprosthetic valves with atrial fibrillation (BPV-AF) Study. *Cardiovasc Drugs Ther* 2020; **34:** 689–696.
21. Izumi C, Miyake M, Fujita T, Koyama T, Tanaka H, Ando K, et al. Antithrombotic therapy for patients with atrial fibrillation and bioprosthetic valves: Real-world data from the multicenter, prospective, observational BPV-AF Registry. *Circ J* 2022; **86:** 440–448.
22. Lehto J, Malmberg M, Biancari F, Hartikainen J, Ihlberg L, Yannopoulos F, et al. Occurrence and classification of cerebrovascular events after isolated bioprosthetic surgical aortic valve replacement: A competing risk analysis of the CAREAVR study. *Structural Heart* 2018; **2:** 157–163.
23. Ruel M, Masters RG, Rubens FD, Bédard PJ, Pipe AL, Goldstein WG, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. *Ann Thorac Surg* 2004; **78:** 77–84.
24. Çınar T, Hayıroğlu MI, Tanık VO, Arugaslan E, Keskin M, Uluganyan M, et al. The predictive value of the CHA_2DS_2-VASc score in patients with mechanical mitral valve thrombosis. *J Thromb Thrombolysis* 2018; **45:** 571–577.