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ORIGINAL ARTICLE
Valvular Heart Disease

Bioprosthetic Valve Positions in Patients With Atrial Fibrillation

— Insights From the BPV-AF Registry —

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Background: Data on the impact of valve position on clinical outcomes in patients with atrial fibrillation (AF) and bioprosthetic valves (BPVs) are limited.

Methods and Results: The BPV-AF Registry was a multicenter, prospective, observational study involving 894 patients with BPVs and AF. In this post-hoc substudy, patients were classified according to BPV position: aortic (n=588; 65.8%), mitral (n=195; 21.8%), or both (n=111; 12.4%). The primary outcome was a composite of stroke/systemic embolism, major bleeding, heart failure requiring hospitalization, all-cause death, or BPV reoperation. During a mean follow up of 15.3±4.0 months, the primary outcome occurred in 90 (15.3%) patients (12.7/100 patient-years) in the aortic group, 25 (12.8%; 10.2/100 patient-years) in the mitral group, and 16 (14.4%; 11.8/100 patient-years) in the both-valves group (log-rank P=0.621). The unadjusted and adjusted risks were not significant for the mitral and both-valves groups relative to the aortic group (unadjusted hazard ratio [95% confidence interval] 0.80 [0.52–1.25] and 0.92 [0.54–1.57]; adjusted hazard ratio 0.89 [0.51–1.54] and 1.10 [0.58–2.09], respectively). There was no significant difference in the incidence of stroke/systemic embolism or major bleeding among the 3 groups (log-rank P=0.651 and 0.156, respectively).

Conclusions: In patients with BPVs and AF, the risk for the composite outcome was comparable regardless of the BPV position.

Key Words: Atrial fibrillation; Bioprosthetic valve; Bleeding; Thromboembolism

With the rapid progression of an aging society, the number of patients with atrial fibrillation (AF) is increasing.[1,2] Additionally, there has been a rise in the use of bioprosthetic valves (BPVs) for valve replacement because of significant valvular heart disease, driven by the improved durability of BPVs and the expansion of transcatheter interventions.[3,4] Therefore, the coexistence of AF and BPV implantation is a growing concern, and risk stratification for patients with these overlapping conditions is crucial for the appropriate treatment, includ-

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ing antithrombotic therapy.[5–7]

The position and number of implanted valves significantly influence patient characteristics and outcomes, even after treating the underlying valvular heart disease with valve replacements. In patients with or without AF who have undergone BPV implantation, those with a BPV in the mitral position have a higher thromboembolic risk than those with a BPV in the aortic position.[8] Additionally, patients undergoing double valve replacement have a higher perioperative risk than those undergoing isolated valve replacement.[9] However, data on outcomes after the perioperative period in patients with both aortic and mitral BPVs and AF remain sparse.

We previously reported that the bleeding risk in patients with AF and BPVs in the mitral position was higher than that in the aortic position, while the thromboembolic risk was comparable between the two groups.[10] However, because of the limited number of patients, we could not include patients with AF who had BPVs in both the aortic and mitral positions. Therefore, this study was performed to evaluate the influence of valve position in patients with AF and BPVs, including the mitral, aortic, and both valves, using a large prospective registry in Japan.

Methods

Study Population

The BPV-AF Registry was a multicenter, prospective, and observational study designed to clarify antithrombotic therapy and outcomes in patients with BPV replacement and AF in real-world clinical practice in Japan. Briefly, 894 patients who had undergone BPV replacement at least 3 months before enrollment and had been diagnosed with AF were included from 16 hospitals in Japan between September 2018 and October 2019. The enrolled patients were followed up for a minimum of 1 year (until October 2020). The study design and main results of the BPV-AF Registry have been published elsewhere.[11,12] The study was conducted in compliance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable regulatory and legal requirements. The 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 (UMIN000034485).

In this post-hoc substudy, all enrolled patients were divided into 3 groups according to the position of the BPVs: aortic valve, mitral valve, or both valves. The aortic valve group included patients who underwent both surgical aortic valve replacement and transcatheter aortic valve implantation (TAVI). Baseline characteristics and clinical outcomes were compared across the 3 groups.

Clinical Outcomes

The primary outcome of the present study was defined as a composite of stroke/systemic embolism, major bleeding (based on the International Society on Thrombosis and Haemostasis criteria[13]), heart failure requiring hospitalization, all-cause death, or BPV reoperation, consistent with our previous substudy of patients with a BPV in the aortic position.[14] The secondary outcomes were stroke/systemic embolism and major bleeding. Other outcomes for each component of the primary outcome were also presented. Detailed definitions of each event have been published previously.[11,12]

Statistical Analysis

Continuous variables are presented as mean±standard deviation or median and interquartile range, and were compared using analysis of variance or the Kruskal-Wallis test depending on the distribution. Categorical variables are presented as number and percentage and were compared using the chi-squared test. The incidence rates for all outcomes were calculated per 100 person-years (PY). The cumulative incidences of the primary and secondary outcomes were calculated using the Kaplan-Meier method, and differences were assessed with the log-rank test. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcomes, comparing the mitral valve and both-valves groups with the aortic valve group as the reference. In the multivariable Cox proportional hazards regression models, the following risk-adjusting variables were included to estimate HRs and 95% CIs: each component of the CHA_2DS_2-VASc score (heart failure, hypertension, age, diabetes, ischemic stroke, vascular disease, and sex) was incorporated as a separate risk-adjusting variable. Additionally, body mass index, estimated glomerular filtration rate, type of AF, direct oral anticoagulants (DOACs), antiplatelet therapy, and left ventricular ejection fraction were also included, considering clinical relevance in accordance with our previous report.[14] Multivariable models were not constructed for outcomes with fewer than 20 events because they were insufficient for reliable models. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). All reported P values are 2-tailed, and $P<0.05$ was considered statistically significant.

Results

Baseline and Operative Characteristics

Among the 894 patients, 588 (65.8%) had a BPV in the aortic valve position, 195 (21.8%) in the mitral valve position, and 111 (12.4%) in both valve positions. The baseline characteristics of each group based on the valve position are shown in **Table 1**. Patients in the aortic valve group

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Table 1. Baseline Characteristics

	Aortic valve (n=588)	Mitral valve (n=195)	Both valves (n=111)	P value
Male	287 (48.8)	77 (39.5)	46 (41.4)	0.047
Age (years)	81.5±6.7	77.8±7.3	78.6±6.2	<0.001
Weight (kg)	54.7±11.9	52.1±10.5	52.1±9.3	0.012
BMI (kg/m^2)	22.6±3.9	21.3±3.1	21.6±2.8	<0.001
$CHADS_2$ score	2.7±1.2	2.2±1.2	2.3±1.1	<0.001
≥2.0	456 (85.2)	133 (71.1)	84 (76.4)	<0.001
CHA_2DS_2-VASc score	4.3±1.5	3.8±1.3	3.9±1.3	<0.001
≥3.0	484 (89.8)	158 (84.5)	91 (82.7)	0.039
HAS-BLED score	2.6±1.1	2.2±1	2.3±1	<0.001
≥3.0	265 (49.6)	65 (35.1)	44 (40.4)	0.002
eGFR (mL/min/1.73 m^2)	45.1±17.5	48.8±17.6	51.4±17.3	<0.001
Type of AF				
Paroxysmal	261 (44.4)	52 (26.7)	19 (17.1)	<0.001
Persistent	205 (34.9)	67 (34.4)	38 (34.2)	
Permanent	122 (20.8)	76 (39.0)	54 (48.7)	
Previous history of CVD				
Ischemic stroke	88 (15.0)	16 (8.2)	19 (17.1)	0.033
Hemorrhagic stroke	14 (2.4)	4 (2.1)	3 (2.7)	0.933
Intracranial hemorrhage	17 (2.9)	11 (5.6)	2 (1.8)	0.113
Systemic embolism	7 (1.2)	2 (1.0)	2 (1.8)	0.830
Major bleeding	24 (4.1)	16 (8.2)	7 (6.3)	0.071
Comorbidities				
Hypertension	495 (84.2)	111 (56.9)	76 (68.5)	<0.001
Heart failure	328 (55.8)	105 (53.9)	59 (53.2)	0.818
Dyslipidemia	319 (54.3)	79 (40.5)	45 (40.5)	0.001
Diabetes	121 (20.6)	42 (21.5)	26 (23.4)	0.788
Renal dysfunction	60 (10.2)	17 (8.7)	7 (6.3)	0.406
Chronic respiratory disease	58 (9.9)	19 (9.7)	9 (8.1)	0.846
Malignant tumor	52 (8.8)	9 (4.6)	7 (6.3)	0.133
Vascular disease	70 (11.9)	14 (7.2)	4 (3.6)	0.010
Myocardial infarction	31 (5.3)	12 (6.2)	2 (1.8)	0.222
Peripheral arterial disease	29 (4.9)	2 (1.0)	2 (1.8)	0.023
Aortic plaque	16 (2.7)	3 (1.5)	0 (0.0)	0.154
Thrombosis and embolism	17 (2.9)	5 (2.6)	6 (5.4)	0.331
Echocardiography parameters				
LVEF (%)	61.9±10.6	56.3±11.7	56.6±12.8	<0.001
<40	25 (4.6)	18 (10.0)	13 (12.4)	<0.001
40–49	39 (7.1)	24 (13.3)	10 (9.5)	
≥50	484 (88.3)	138 (76.7)	82 (78.1)	
LVEDD	44.7±7.1	47.5±7.9	45.8±6.7	<0.001
LVESD	29.5±7.5	33.0±8.7	31.7±6.8	<0.001
LAD	46.8±8.1	53.2±11.4	53.2±11.9	<0.001
LA volume	103.7±43.5	137.6±90.9	145.8±83.9	<0.001
LA volume index (LA volume/BSA)	69.7±28.3	96.9±65.4	102.8±59.1	<0.001

Categorical variables are presented as n (%). Continuous variables are presented as mean±SD. AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LA, left atrium; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

were more often male, older, and had a higher body weight. They also had higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. The prevalence of paroxysmal AF was higher in the aortic valve group than in the other groups. Regarding medical histories and comorbidities, patients in the mitral valve group had ischemic stroke less often, while patients in the aortic valve group had hypertension, dyslipidemia, and peripheral arterial disease more often. Patients in the aortic valve group had a higher left ventricular ejection fraction but smaller left atrial diameter, left atrial volume, and left atrial volume index.

Regarding operative characteristics, patients in the aortic group underwent BPV replacement mainly for treatment of aortic stenosis, with 40.1% of patients undergoing TAVI. Patients in the aortic group underwent surgery with concurrent left atrial plication or left atrial appendage

Table 2. Operative Characteristics

	Aortic valve (n=588)	Mitral valve (n=195)	Both valves (n=111)	
			Aortic valve	Mitral valve
VHD subtype				
Stenosis	445 (75.7)	81 (41.5)	69 (62.2)	56 (50.5)
Regurgitation	114 (19.4)	95 (48.7)	33 (29.7)	43 (38.7)
Other	29 (4.9)	19 (9.7)	9 (8.1)	12 (10.8)
Operation type				
Surgery	352 (59.9)	195 (100.0)	111 (100.0)	111 (100.0)
TAVI	236 (40.1)	–	0 (0.0)	–
History of replacement				
First replacement	561 (95.4)	171 (87.7)	100 (90.1)	
Re-replacement	25 (4.3)	24 (12.3)	11 (9.9)	
Left atrial plication, LAA occlusion/excision	49 (8.4)	34 (17.5)	20 (18)	

Categorical variables are presented as n (%). LAA, left atrial appendage; TAVI, transcatheter aortic valve implantation; VHD, valvular heart disease.

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

	Aortic valve (n=588)	Mitral valve (n=195)	Both valves (n=111)	P value
No antithrombotic drug	40 (6.8)	11 (5.6)	5 (4.5)	0.605
Warfarin-based therapy	n=258	n=144	n=87	
No antiplatelet drug	175 (67.8)	114 (79.2)	63 (72.4)	0.052
With antiplatelet drug	83 (32.2)	30 (20.8)	24 (27.6)	
With aspirin (monotherapy)	70 (27.1)	27 (18.8)	23 (26.4)	0.156
With P2Y12 (monotherapy)	11 (4.3)	1 (0.7)	0 (0.0)	0.023
Prasgrel	2	0	0	
Clopidogrel	8	1	0	
Ticlopidine	1	0	0	
With DAPT	0 (0.0)	0 (0.0)	0 (0.0)	–
With others	2 (0.8)	2 (1.4)	1 (1.2)	0.835
DOAC-based therapy	n=221	n=31	n=11	
No antiplatelet drug	157 (71.0)	25 (80.7)	7 (63.6)	0.444
With antiplatelet drug	64 (29.0)	6 (19.4)	4 (36.4)	
With aspirin (monotherapy)	46 (20.8)	5 (16.1)	4 (36.4)	0.365
With P2Y12 (monotherapy)	16 (7.2)	0 (0.0)	0 (0.0)	0.198
Prasgrel	2	0	0	
Clopidogrel	14	0	0	
Ticlopidine	0	0	0	
With DAPT	0 (0.0)	0 (0.0)	0 (0.0)	
With others	2 (0.9)	1 (3.2)	0 (0.0)	0.489
Antiplatelet therapy (without warfarin/DOAC)	n=69	n=9	n=8	
Aspirin (monotherapy)	53 (76.8)	8 (88.9)	6 (75.0)	0.698
P2Y12 (monotherapy)	10 (14.5)	1 (11.1)	0 (0.0)	0.503
Prasgrel	0	0	0	
Clopidogrel	10	1	0	
Ticlopidine	0	0	0	
DAPT	4 (5.8)	0 (0.0)	0 (0.0)	0.596
Prasgrel	0	0	0	
Clopidogrel	4	0	0	
Ticlopidine	0	0	0	
With others	2 (2.9)	0 (0.0)	2 (25.0)	0.015

Categorical variables are presented as n (%). DAPT, dual-antiplatelet therapy; DOAC, direct oral anticoagulants.

Table 4. Clinical Outcomes

Outcome / Valve position	No. patients with event (%)	Per 100 PY	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Composite outcome						
Aortic	90 (15.3)	12.7	Ref.	–	Ref.	–
Mitral	25 (12.8)	10.2	0.80 (0.52–1.25)	0.333	0.89 (0.51–1.54)	0.669
Both	16 (14.4)	11.8	0.92 (0.54–1.57)	0.768	1.10 (0.58–2.09)	0.773
Stroke/systemic embolism						
Aortic	14 (2.4)	1.90	Ref.	–	Ref.	–
Mitral	4 (2.1)	1.59	0.84 (0.28–2.56)	0.761	0.54 (0.13–2.13)	0.375
Both	4 (3.6)	2.90	1.55 (0.51–4.72)	0.437	0.50 (0.09–2.72)	0.424
Stroke						
Aortic	12 (2.0)	1.62	Ref.	–	–	–
Mitral	3 (1.5)	1.19	0.74 (0.21–2.61)	0.637	–	–
Both	3 (2.7)	2.16	1.36 (0.38–4.80)	0.638	–	–
Systemic embolism						
Aortic	2 (0.3)	0.27	Ref.	–	–	–
Mitral	1 (0.5)	0.40	1.49 (0.14–16.38)	0.747	–	–
Both	1 (0.9)	0.72	2.73 (0.25–30.06)	0.413	–	–
Major bleeding						
Aortic	17 (2.9)	2.31	Ref.	–	Ref.	–
Mitral	1 (0.5)	0.40	0.17 (0.02–1.30)	0.088	0.14 (0.02–1.22)	0.075
Both	3 (2.7)	2.15	0.94 (0.28–3.21)	0.922	0.44 (0.09–2.32)	0.335
HF requiring hospitalization						
Aortic	42 (7.1)	5.79	Ref.	–	Ref.	–
Mitral	18 (9.2)	7.32	1.26 (0.72–2.19)	0.415	1.73 (0.85–3.53)	0.131
Both	4 (3.6)	2.90	0.49 (0.18–1.37)	0.176	1.00 (0.34–2.96)	1.000
All-cause death						
Aortic	33 (5.6)	4.42	Ref.	–	Ref.	–
Mitral	8 (4.1)	3.17	0.71 (0.33–1.54)	0.387	0.73 (0.29–1.83)	0.504
Both	6 (5.4)	4.30	0.97 (0.41–2.31)	0.938	1.19 (0.42–3.35)	0.749
BPV reoperation						
Aortic	5 (0.9)	0.67	Ref.	–	–	–
Mitral	1 (0.5)	0.40	0.60 (0.07–5.13)	0.640	–	–
Both	1 (0.9)	0.72	1.08 (0.13–9.24)	0.945	–	–

BPV, bioprosthetic valve; CI, confidence interval; HF, heart failure; HR, hazard ratio; PY, patient-years.

occlusion/excision less often (**Table 2**).

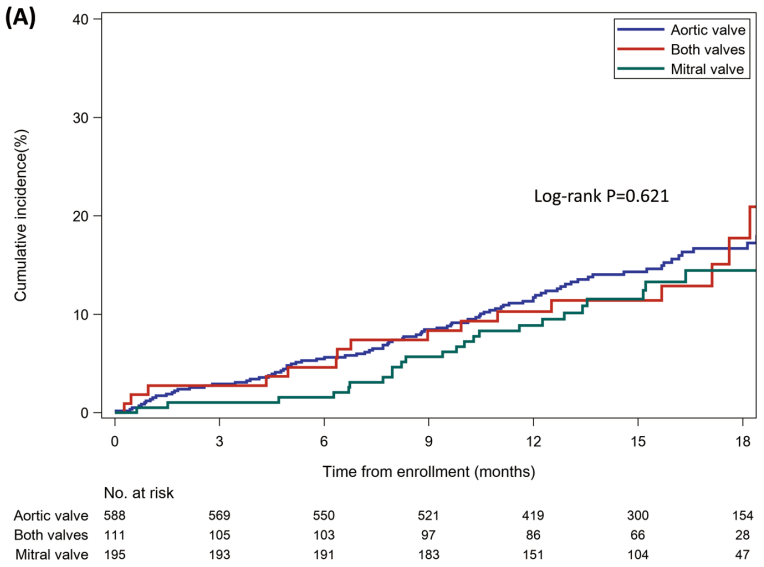
The administration status of antithrombotic agents is presented in **Table 3**. DOAC-based therapy was received more frequently in the aortic valve group (221 [37.6%] patients) than in the mitral valve and both-valves groups (31 [15.9%] and 11 [9.9%], respectively).

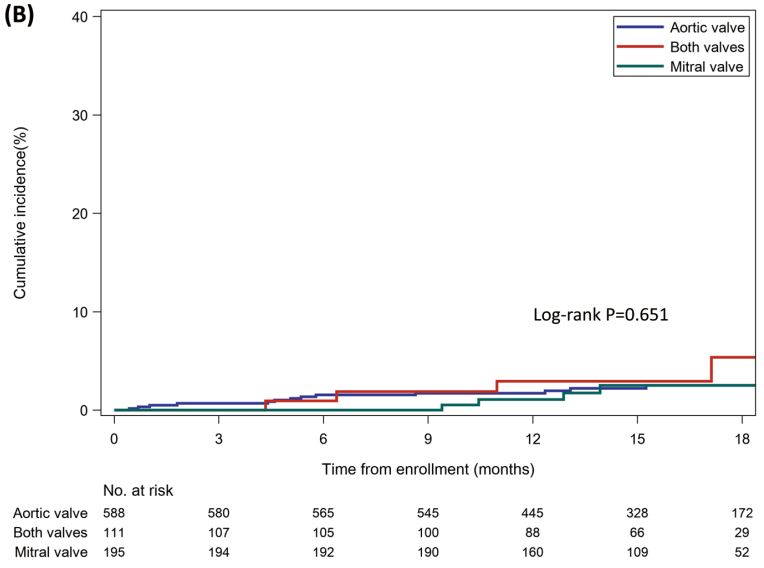
Clinical Outcomes

During the mean follow-up period of 15.3±4.0 months, the primary outcome was observed in 90 (15.3%) patients (12.7/100 PY) in the aortic valve group, 25 (12.8%) patients (10.2/100 PY) in the mitral valve group, and 16 (14.4%) patients (11.8/100 PY) in the both-valves group (**Table 4**). The cumulative incidence of the primary outcome was not significantly different among the 3 groups (log-rank P=0.621; **Figure A**). The Cox proportional hazards regression models for the primary outcome showed no significant difference in the mitral valve and both-valves groups relative to the aortic valve group (unadjusted HR 0.80, 95% CI 0.52–1.25, P=0.333, and adjusted HR 0.89, 95% CI 0.51–1.54, P=0.669 in the mitral valve group; unadjusted HR 0.92, 95% CI 0.54–1.57, P=0.768, and adjusted HR 1.10, 95% CI 0.58–2.09, P=0.773 in the both-valves group; **Table 4**).

The incidence of stroke/systemic embolism was numerically higher in the both-valves group (3.6%; 2.90/100 PY) than in the aortic valve group (2.4%; 1.90/100 PY) and the mitral valve group (2.1%; 1.59/100 PY; **Table 4**). However, there was no significant difference in the cumulative incidence of stroke/systemic embolism among the 3 groups (log-rank P=0.651; **Figure B**). The unadjusted and adjusted HRs in the mitral valve group and the both-valves group relative to the aortic valve group were also not significantly different (unadjusted HR 0.84, 95% CI 0.28–2.56, P=0.761, and adjusted HR 0.54, 95% CI 0.13–2.13, P=0.375 in the mitral valve group; unadjusted HR 1.55, 95% CI 0.51–4.72, P=0.437, and adjusted HR 0.50, 95% CI 0.09–2.72, P=0.424 in the both-valves group; **Table 4**).

Major bleeding was observed in 17 (2.9%) patients (2.31/100 PY) in the aortic valve group, 1 (0.5%) patient (0.40/100 PY) in the mitral valve group, and 3 (2.7%) patients (2.15/100 PY) in the both-valves group (**Table 4**). Although the incidence of major bleeding was numerically lower in the mitral valve group, the cumulative incidence of major bleeding was not significantly different among the





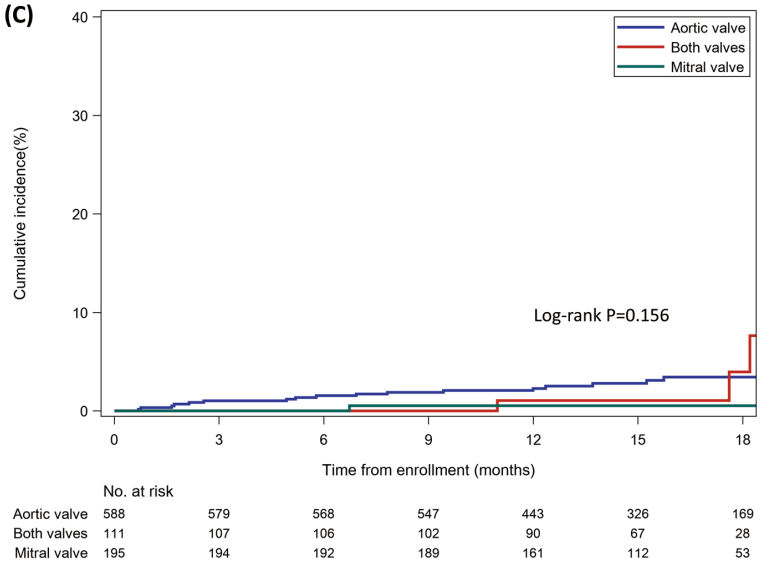


Figure. Kaplan-Meier curves for clinical outcomes according to bioprosthetic valve (BPV) positions. (**A**) Composite outcome (stroke, systemic embolism, major bleeding, heart failure requiring hospitalization, all-cause death, or BPV reoperation). (**B**) Stroke or systemic embolism. (**C**) Major bleeding.

3 groups with the limited number of events (log-rank P=0.156; **Figure C**). Both the unadjusted and adjusted HRs in the mitral valve group were not significantly lower than those in the aortic valve group (unadjusted HR 0.17, 95% CI 0.02–1.30, P=0.088, and adjusted HR 0.14, 95% CI 0.02–1.22, P=0.075; **Table 4**).

Discussion

The 2 main findings of the present study involving patients with BPVs and AF are as follows. First, the risk for the composite endpoint was comparable regardless of whether patients had BPVs in the aortic valve, mitral valve, or both valve positions. Second, the thromboembolic and bleeding risks did not significantly differ based on the valve position.

Generally, patients who undergo surgical valve replacement in the mitral position are considered to have a higher risk of thromboembolic events than those who undergo surgical valve replacement in the aortic position. For example, the recommended prothrombin time-international normalized ratio for patients with a mechanical valve is higher in the mitral position than in the aortic position.[5–7] Additionally, a previous study suggested that the thromboembolic risk of patients with a BPV in the mitral position was higher than in the aortic position, partly because of the higher prevalence of AF.[8] Furthermore, patients who underwent double valve replacement have an increased thromboembolic risk, especially in the perioperative period.[9] However, in the present study, no significant difference in the cumulative incidence of stroke/systemic embolism was observed based on valve position, and the valve position itself was not independently associated with the thromboembolic risk (although the incidence of stroke/systemic embolism was numerically higher in the both-valves group). In patients with BPVs and AF, AF may have a greater influence on thromboembolic events than BPVs. In fact, in the Fushimi AF Registry, a community-based AF population, the 1-year incidence of stroke or systemic embolism was 2.7%;[15] this was even higher than in our registry. This may suggest that regardless of the BPV position, we can utilize risk stratification parameters similar to those used in the general AF population, such as the CHA_2DS_2-VASc score, for patients with BPVs and AF.[6]

In terms of bleeding risk, patients with a BPV in the aortic position reportedly have a higher cumulative incidence of bleeding events than those in the mitral position, reflecting the older population of patients undergoing surgical aortic valve implantation.[8] In addition, the mean age of patients undergoing aortic valve replacement has been increasing with the widespread use of TAVI.[16] In this study, patients with a BPV in the aortic valve position were older and had a higher HAS-BLED score than those with a BPV in the mitral and both valve positions, partly because patients who underwent TAVI comprised approximately 40% of the aortic valve group. Nevertheless, there was no significant difference in the cumulative incidence of major bleeding among the 3 groups. This may be attributed to comparable baseline risk factors for bleeding among the 3 groups, such as body weight and a history of major bleeding, although our previous report indicated that patients with a BPV and AF in the mitral position had a higher rate of major bleeding due to differences in these factors.[10]

The lack of a significant difference in the composite outcome as well as each component among the 3 groups suggests that the impact of valve position was mitigated by the presence of AF. The exclusion of patients who underwent BPV replacement within 3 months may have also contributed to the similar cumulative incidences in the both-valves group compared with those in the aortic and mitral valve groups. Therefore, valve position alone may be insufficient for risk stratification in patients with BPVs and AF in the chronic phase, and a similar anticoagulation strategy may be considered regardless of valve position. Several randomized trials involving patients with AF and BPVs stratified by each valve position have shown that DOACs were non-inferior to warfarin. In the RIVER trial, which included patients with AF and a BPV in the mitral position, rivaroxaban was found to be non-inferior to warfarin for the composite outcome.[17] In patients with AF who underwent TAVI, edoxaban was also non-inferior to warfarin for a composite of adverse events.[18] Additionally, our previous study, which included patients with AF and a BPV in the aortic position, suggested that the effect of DOACs vs. warfarin did not significantly differ between surgical aortic valve replacement and TAVI.[14] However, no definitive evidence is currently available for patients with AF and BPVs in both valve positions. To establish an appropriate antithrombotic strategy in patients with AF and BPVs in both valve positions, further research is warranted to identify the risk factors for these patients.

Study Limitations

This study has several limitations. First, despite the increased number of enrolled patients compared with our previous study, the follow-up period was relatively short (median of 15.3 months). Additionally, the low event rate for each endpoint resulted in a limited number of events overall. Thus, this study might be too underpowered to precisely evaluate the impact of valve position in this population. Second, we excluded patients who had undergone BPV replacement within 3 months to evaluate antithrombotic therapy in a stable phase. Therefore, the high-risk features in patients with double valve replacement, especially in the early phase, were not reflected. Furthermore, unlike in the main study, we were unable to compare DOAC-based and warfarin-based antithrombotic therapy for each valve position.[12] Third, both the presence of BPVs and the presence of AF were influential factors for thromboembolic events. Although the mechanisms and etiology of thromboembolism may differ, we cannot clearly differentiate whether stroke/systemic embolism originated from BPVs or AF. Fourth, considering the observational nature of this study and the substantial differences in the baseline characteristics among the 3 groups, the possibility of unmeasured confounders in estimating the risk of clinical events cannot be ruled out, despite the intensive multivariable adjustments.

Conclusions

In patients with AF who had undergone BPV replacement at least 3 months prior, the risk for the composite outcome was similar regardless of whether the BPV was positioned in the aortic valve, mitral valve, or both valves. Appropriate risk stratification and management would be necessary for patients with AF and BPVs, irrespective of the valve position.

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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). The main study was registered in the UMIN Clinical Trials Registry under Identifier No. UMIN000034485.

Data Availability

The deidentified participant data that underlie the results reported in the present study will be shared on request immediately after publication until 36 months post-publication. The study protocol will also be available. Researchers requesting data should provide a methodologically sound proposal detailing how the data will be used; this proposal may be reviewed by responsible personnel at Daiichi Sankyo Co., Ltd. Data will be provided to achieve the aims of the approved proposal. Please contact the corresponding author directly to request data sharing. Data requestors will need to sign a data access agreement.

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