Impact of Valvular Heart Disease on Mortality, Thromboembolic and Cardiac Events in Japanese Patients With Atrial Fibrillation
— The Fushimi AF Registry —

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Background: There is a growing burden of valvular heart disease (VHD) and atrial fibrillation (AF) due to population aging, but data regarding the characteristics and outcomes of patients with AF and concomitant VHD are lacking.

Methods and Results: The Fushimi AF Registry is a community-based prospective survey of AF patients in Fushimi-ku, Kyoto. Among 3,566 patients with available echocardiographic data, 20% had VHD, consisting of 131 valvular AF (VAF: 3.7%) and 583 nonvalvular AF with VHD (NVAF-VHD: 16.3%). Here, VAF was defined as AF with mitral stenosis or a prosthetic heart valve. AF patients with VHD were older, had more comorbidities with a higher CHADS2 score, and were prescribed oral anticoagulants more frequently than those without VHD. After adjusting for confounders, VHD was not associated with stroke or systemic embolism, all-cause mortality, or cardiac death. NVAF-VHD was significantly associated with an increased risk of hospitalization for heart failure (adjusted hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.16–1.78), whereas VAF was not (HR, 1.28; 95% CI, 0.86–1.92). Among all types of VHD, aortic valve diseases were associated with a higher risk of cardiac events, whereas mitral valve diseases were not.

Conclusions: Although VHD did not significantly affect thromboembolism or mortality, it affected cardiac events depending on type, with aortic valve diseases having higher risk, in Japanese patients with AF.

Key Words: Atrial fibrillation; Heart failure; Mortality; Thromboembolism; Valvular heart disease

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and confers a substantial risk of thromboembolism (i.e., ischemic stroke or systemic embolism [SE]), heart failure (HF), and death.1,2 Valvular heart disease (VHD) is also common, and associated with increased morbidity and mortality.3,4 VHD, independent of the underlying cardiac rhythm, is associated with a higher risk of thromboembolic events,5 and the effect of VHD on the risk of thromboembolism in AF patients has thus been of concern. AF accompanying mitral rheumatic valve disease (predominantly mitral stenosis [MS]) or mechanical prosthetic valves, so-called “valvular AF” (VAF), has been demonstrated to have a significantly high risk of thromboembolism.6 The incidence rate of stroke in cases of MS with AF is approximately 6-fold that for MS without AF, and the relative risk is approximately 15-fold in patients with both AF and MS.7 Therefore, previous studies of the risk factors for stroke in AF patients have excluded VAF, and randomized clinical trials of non-vitamin K antagonist oral anticoagulants (NOAC) for AF patients also enrolled those with nonvalvular AF (NVAF).8–11 Furthermore, the risk of thromboembolism may differ depending on the type of VHD; mitral regurgitation (MR)
Study Patients

The detailed study design, patient enrollment, the definition of the measurements, and subjects’ baseline clinical characteristics of the Fushimi AF Registry were previously described. The inclusion criterion for the registry was documentation of AF on a 12-lead ECG or Holter monitoring at any time. A total of 81 institutions participated in the registry. Patient enrollment began in March 2011. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the

may protect against thromboembolic events in AF patients because the MR jet may agitate the blood in the left atrium, leading to a decrease in blood stasis. In contemporary clinical settings, there is a paucity of data on thromboembolic and cardiac events in patients with AF and any form of VHD.

In Japan, there is a growing burden of VHD and AF due to population aging. The aim of this study was to analyze the clinical characteristics and incidences of adverse outcomes, including thromboembolism, in patients with AF and VHD from a large community-based prospective survey of Japanese AF patients, the Fushimi AF Registry.

Table 1. Baseline Characteristics of Study Patients

|                     | VAF    | NVAF-VHD | No-VHD  | P value |
|---------------------|--------|----------|---------|---------|
| No. of patients     | 131 (3.7) | 583 (16.3) | 2,852 (80.0) |         |
| Age, years          | 74.3±8.9 | 76.9±10.5 | 72.9±10.7 | <0.01   |
| Female sex          | 74 (56.5) | 296 (51.1) | 1,052 (36.9) | <0.01   |
| Weight, kg          | 54.3±11.5 | 54.7±13.3 | 60.6±13.6 | <0.01   |
| Body mass index, kg/m² | 22.1±3.7 | 22.1±4.1 | 23.3±4.1 | <0.01   |
| Systolic blood pressure, mmHg | 117.3±17.0 | 122.2±20.6 | 124.9±19.0 | <0.01   |
| Pulse rate, beats/min | 74.7±13.8 | 78.7±15.8 | 78.2±16.4 | 0.06    |
| Type of AF          |        |          |         | <0.01   |
| Persistent/permanent | 84 (64.1) | 381 (65.3) | 1,306 (45.8) |         |
| Paroxysmal          | 47 (35.9) | 202 (34.7) | 1,546 (54.2) |         |
| CHADS2 score        | 2.2±1.0 | 2.5±1.3 | 2.0±1.3 | <0.01   |
| CHA2DS2-VASc score  | 3.7±1.3 | 4.0±1.6 | 3.3±1.7 | <0.01   |
| Comorbidities       |        |          |         |         |
| Prior stroke/SE     | 19 (14.5) | 137 (23.5) | 558 (19.6) | 0.03    |
| HF                  | 81 (61.8) | 310 (53.2) | 663 (23.3) | <0.01   |
| Hypertension        | 68 (51.9) | 374 (64.2) | 1,806 (63.3) | 0.03    |
| Diabetes mellitus   | 29 (22.1) | 124 (21.3) | 711 (24.9) | 0.14    |
| Dyslipidemia        | 60 (45.8) | 211 (36.2) | 1,290 (45.2) | <0.01   |
| Coronary artery disease | 24 (18.3) | 93 (16.0) | 424 (14.9) | 0.49    |
| CKD                 | 58 (44.3) | 281 (48.2) | 1,027 (36.0) | <0.01   |
| Major bleeding      | 6 (4.6) | 31 (5.3) | 129 (4.5) | 0.72    |
| COPD                | 9 (6.9) | 35 (6.0) | 155 (5.4) | 0.71    |
| Prescription data   |        |          |         |         |
| OAC                 | 103 (78.6) | 366 (63.0) | 1,577 (55.6) | <0.01   |
| Warfarin            | 102 (77.9) | 309 (53.2) | 1,098 (38.7) | <0.01   |
| PT-INR              | 2.0±0.4 | 1.8±0.5 | 1.8±0.5 | <0.01   |
| NOAC                | 1 (0.7) | 57 (9.8) | 479 (16.9) | <0.01   |
| Antiplatelet drugs  | 38 (29.0) | 184 (31.7) | 754 (26.6) | 0.04    |
| β-blockers          | 56 (42.8) | 242 (41.7) | 868 (30.6) | <0.01   |
| ACEI/ARB            | 58 (44.3) | 322 (55.4) | 1,236 (43.6) | <0.01   |
| Loop diuretics      | 60 (45.8) | 258 (44.4) | 573 (20.2) | <0.01   |
| Mineralocorticoid receptor antagonist | 39 (29.8) | 105 (18.1) | 245 (8.6) | <0.01   |
| Type of VHD         |        |          |         |         |
| MS                  | 63 (48.1) | 0 | 0 |         |
| MR                  | 0 | 409 (70.2) | 0 |         |
| AS                  | 0 | 93 (16.0) | 0 |         |
| AR                  | 0 | 152 (26.1) | 0 |         |
| TR                  | 0 | 186 (31.9) | 0 |         |
| Prosthetic valve    | 68 (51.9) | 0 | 0 |         |

Value are presented as number (%) or mean±SD. AF, atrial fibrillation (valvular [V] or nonvalvular [NV]); ACEI, angiotensin-converting enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; MR, mitral regurgitation; MS, mitral stenosis; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PT-INR, prothrombin time-international normalized ratio; SE, systemic embolism; TR, tricuspid regurgitation; VHD, valvular heart disease.
ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital. Because the study was observational, written informed consent was not obtained from patients according to the ethical guidelines for epidemiological research issued by the Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan.

Definitions
We defined VAF as AF with MS or a prosthetic heart valve (either mechanical or biological) according to the guidelines for pharmacotherapy of atrial fibrillation published in 2013 by the Japanese Circulation Society. NVAF was defined as AF without MS or a prosthetic heart valve. Among the NVAF patients, we defined the NVAF-VHD group as patients with other VHD and the No-VHD group as those without VHD. The diagnosis of VHD was made at the discretion of treating physicians and detailed echocardiographic information on VHD severity was not collected. The classification of valvular lesions and severity relied on clinical data collected in the case report forms.

The primary endpoint in the analysis was the incidence of stroke or SE during the follow-up period. Other clinical endpoints included the incidence of all-cause death, cardiac death, and hospitalization for HF during the follow-up period. Stroke was defined as the sudden onset of focal neurological symptoms in a location consistent with the territory of a major cerebral artery, and the finding of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. SE was defined as acute arterial thromboembolism in an extremity or organ other than the brain. Cardiac death was defined as death following HF, acute coronary syndrome, or dysrhythmia. Oral anticoagulants (OAC) included warfarin and NOAC (dabigatran, rivaroxaban, apixaban, and edoxaban). Antiplatelet drugs (APD) included aspirin, clopidogrel,prasugrel, ticlopidine, and cilostazol.

Statistical Analysis
Continuous variables are presented as the mean and standard deviation (SD). Categorical variables are presented as counts and proportions (percentages). We compared categorical variables using the chi-square test and continuous variables using the independent samples t-test for normally distributed data or the Mann-Whitney U-test for non-normal distribution. The Kaplan-Meier method was used to estimate the cumulative incidences by groups. Univariate and multivariate analyses were performed to clarify whether VHD was associated with clinical outcomes. We used a multivariate Cox proportional hazards model to assess the effect of VHD on the clinical outcomes of AF patients. The covariates included were sex, age ≥75 years, body weight ≤50 kg, type of AF, prior stroke/SE, history of HF, hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, history of major bleeding, prescription of OAC, and prescription of APD at baseline. Significance was set at a 2-sided P-value of <0.05. These analyses were performed using JMP version 14.1.0 (SAS Institute, Cary, NC, USA) and survival package for R version 3.4.1 for Windows.

Results
Of 4,875 patients who were enrolled 1 year before (by the end of November 2017), follow-up data (collected annually) were available for 4,454 (follow-up rate 91.4%) as of November 2018. In the entire cohort, 3,566 patients had available echocardiographic data at baseline. We compared the clinical characteristics and outcomes among 131 VAF patients (3.7%), 583 NVAF-VHD patients (16.3%), and 2,852 No-VHD patients (80.0%). Baseline clinical characteristics of the 3 groups are shown in Table 1. Compared with the No-VHD group, patients in the VAF and NVAF-VHD groups were older, more often female, had a lower body weight, and more often had a persistent/permanent type of AF. They were likely to have major comorbidities: prior stroke/SE 14.5% in VAF, 23.5% in NVAF-VHD, 19.6% in No-VHD (P=0.03); pre-existing HF 61.8%, 53.2%, and 23.3% (P<0.01); and chronic kidney disease 44.3%, 48.2%, and 36.0% (P<0.01), respectively. The mean CHADS2 score was 2.18 in VAF, 2.49 in NVAF-VHD, and 1.96 in No-VHD (P<0.01). The proportion of patients receiving OAC was 78.6% in VAF, 63.0% in NVAF-VHD, and 55.6% in No-VHD. All the VAF patients taking OAC received warfarin, except for 1 patient who received NOAC. In the NVAF-VHD group, 409 (70.2%) had MR, 93 (16.0%) had aortic stenosis (AS), 152 (26.1%) had aortic regurgitation (AR), and 186 (31.9%) had tricuspid regurgitation (TR).

Outcomes
The annual incidence rates of major clinical events in each group are shown in Table 2. The incidence rates of stroke/SE were 1.67, 1.96, and 1.28 per 100 person-years in the VAF, NVAF-VHD, and No-VHD groups, respectively. The rates of all-cause death were 4.62, 5.74, and 3.21 per 100 person-years, those of cardiac death were 1.07, 1.01, and 0.44 per 100 person-years, and those of hospitalization for HF were 3.59, 4.41, and 1.80 per 100 person-years, respectively. Kaplan-Meier curves for the incidences of stroke/SE, all-cause death, cardiac death, and hospitalization for HF in each group are shown in Figure 1. The

| Events          | VAF (n=131) | NVAF-VHD (n=583) | No-VHD (n=2,852) |
|-----------------|-------------|------------------|------------------|
| No. of events   | Incidence rate | No. of events   | Incidence rate | No. of events   | Incidence rate |
| Stroke/SE       | 12 1.67     | 63 1.96          | 238 1.28         |
| Ischemic stroke/SE | 9 1.23   | 47 1.42          | 176 0.94         |
| All-cause death | 33 4.62     | 170 5.74         | 541 3.21         |
| Cardiac death   | 5 1.07      | 36 1.01          | 86 0.44          |
| Hospitalization for HF | 27 3.59 | 140 4.41        | 323 1.8          |

Incidence rates are presented as per 100 person-years. Abbreviations as in Table 1.
After adjusting for potential confounders by multivariate Cox regression analysis, neither VAF nor NVAF-VHD was significantly associated with an increased risk of stroke/SE compared with No-VHD (VAF: adjusted HR 0.98, 95% CI 0.54–1.78, P=0.95; NVAF-VHD: adjusted HR 1.05, 95% CI 0.77–1.43, P=0.75) (Figure 3). Regarding all-cause death and cardiac death, neither VAF nor NVAF-VHD was significantly associated with an increased risk compared with No-VHD. NVAF-VHD was significantly associated with an increased risk of hospitalization for HF compared with No-VHD (adjusted HR 1.44, 95% CI 1.16–1.78, P<0.01), whereas VAF was not (adjusted HR 1.28, 95% CI 0.86–1.92, P=0.22).

Figure 1. Kaplan-Meier curves for stroke/systemic embolism (SE), all-cause death, cardiac death, and hospitalization for heart failure (HF). CI, confidence interval; HR, hazard ratio; NVAF, nonvalvular atrial fibrillation; VAF, valvular atrial fibrillation; VHD, valvular heart disease.
We further analyzed clinical outcomes according to each type of VHD (MS, MR, AS, AR, and TR). Baseline characteristics of each VHD are shown in Table 3. AF patients with aortic valve disease (AS and AR) were older and more likely to have paroxysmal AF, hypertension and chronic kidney disease. On multivariate Cox regression analysis, no VHD type was significantly associated with an increased risk of stroke/SE compared with No-VHD (Figure 4). The adjusted HR of stroke/SE for MS was 1.06 (95% CI 0.44–2.15, P=0.89), for MR was 0.80 (95% CI 0.52–1.21, P=0.28), for AS was 1.34 (95% CI 0.66–2.74, P=0.42), for AR was 1.21 (95% CI 0.65–2.23, P=0.55), and for TR was 0.99 (95% CI 0.56–1.73, P=0.96) compared with No-VHD. AS was significantly associated with an increased risk of cardiac death (HR 2.95, 95% CI 1.54–5.66, P<0.01) and hospitalization for HF (HR 1.78, 95% CI 1.10–2.88, P=0.02) compared with No-VHD. AR was also significantly associated with an increased risk of hospitalization for HF.
Table 3. Baseline Characteristics of Each Type of VHD

|                         | MS            | MR            | AS            | AR            | TR            |
|-------------------------|---------------|---------------|---------------|---------------|---------------|
| No. of patients         | 63 (1.8)      | 409 (11.5)    | 93 (2.6)      | 152 (4.3)     | 186 (5.2)     |
| Age, years              | 73.6±9.2      | 75.3±10.4     | 82.1±8.8      | 79.5±7.9      | 78.2±10.2     |
| Female sex              | 41 (65.1)     | 206 (50.4)    | 60 (64.5)     | 69 (45.4)     | 95 (51.1)     |
| Weight, kg              | 51.4±9.9      | 54.8±13.8     | 54.5±12.6     | 54.3±12.8     | 53.4±11.6     |
| Body mass index, kg/m²  | 21.6±3.3      | 22.0±4.1      | 22.8±4.2      | 21.8±4.1      | 21.6±3.8      |
| Systolic blood pressure, mmHg | 117.9±17.7   | 120.9±18.6    | 124.0±22.0    | 122.3±18.7    | 121.3±22.0    |
| Pulse rate, beats/min   | 75.7±14.1     | 78.6±15.7     | 77.3±16.1     | 78.4±16.8     | 77.1±14.5     |
| Type of AF              |               |               |               |               |               |
| Persistent/permanent    | 47 (74.6)     | 289 (70.7)    | 42 (45.2)     | 91 (59.9)     | 136 (73.1)    |
| Paroxysmal              | 16 (25.4)     | 120 (29.3)    | 51 (54.8)     | 61 (40.1)     | 50 (26.9)     |
| CHADS2 score            | 2.3±1.1       | 2.5±1.3       | 2.7±1.1       | 2.6±1.1       | 2.4±1.2       |
| CHA2DS2-VASc score      | 3.9±1.4       | 3.9±1.7       | 4.5±1.3       | 4.2±1.5       | 4.0±1.5       |
| Comorbidities           |               |               |               |               |               |
| Prior stroke/SE         | 13 (20.6)     | 102 (24.9)    | 17 (18.3)     | 39 (25.7)     | 41 (22.0)     |
| Heart failure           | 46 (73.0)     | 229 (56.0)    | 57 (61.3)     | 74 (48.7)     | 95 (51.1)     |
| Hypertension            | 28 (44.4)     | 255 (62.4)    | 66 (71.0)     | 101 (66.5)    | 114 (61.3)    |
| Diabetes mellitus       | 13 (20.6)     | 78 (19.1)     | 21 (22.6)     | 29 (19.1)     | 40 (21.5)     |
| Dyslipidemia            | 28 (44.4)     | 142 (34.7)    | 42 (45.2)     | 59 (38.8)     | 51 (27.4)     |
| Coronary artery disease | 8 (12.7)      | 68 (16.6)     | 12 (12.9)     | 28 (18.4)     | 27 (14.5)     |
| CKD                     | 26 (41.3)     | 187 (45.7)    | 54 (58.1)     | 78 (51.3)     | 85 (45.7)     |
| Major bleeding          | 2 (3.2)       | 18 (4.4)      | 10 (10.8)     | 5 (3.3)       | 8 (4.3)       |
| COPD                    | 4 (6.4)       | 23 (5.6)      | 4 (4.3)       | 14 (9.2)      | 13 (7.0)      |
| Prescription data       |               |               |               |               |               |
| OAC                     | 52 (82.5)     | 271 (66.4)    | 53 (57.6)     | 99 (65.6)     | 119 (64.3)    |
| Warfarin                | 52 (82.5)     | 233 (57.1)    | 43 (46.7)     | 91 (60.3)     | 107 (57.8)    |
| PT-INR                  | 1.9±0.4       | 1.9±0.5       | 1.8±0.5       | 1.8±0.5       | 1.8±0.5       |
| NOAC                    | 0 (0)         | 39 (9.3)      | 10 (10.9)     | 8 (5.3)       | 12 (6.5)      |
| Antiplatelet drugs      | 13 (20.6)     | 125 (30.6)    | 33 (35.9)     | 47 (31.1)     | 66 (35.7)     |
| β-blockers              | 23 (36.5)     | 179 (43.9)    | 41 (44.6)     | 48 (31.8)     | 66 (35.7)     |
| ACEI/ARB                | 27 (42.9)     | 239 (58.6)    | 47 (51.1)     | 96 (63.6)     | 96 (51.9)     |
| Loop diuretics          | 30 (47.6)     | 186 (45.6)    | 44 (47.8)     | 59 (39.1)     | 78 (42.2)     |
| Mineralocorticoid receptor antagonist | 20 (31.8) | 82 (20.1) | 18 (19.6) | 26 (17.2) | 32 (17.3) |

Value are presented as number (%) or mean±SD. Abbreviations as in Table 1.

Discussion

The main findings of this study are as follows: (1) 20% of AF patients in our cohort had VHD, consisting of VAF (3.7%) and NVAF-VHD (16.7%); (2) AF patients with VHD had distinct clinical characteristics, being older, having more comorbidities, and more frequent OAC prescription; (3) after adjusting for confounders, VHD (VAF or NVAF-VHD) was not associated with stroke/SE, all-cause death, or cardiac death compared with No-VHD; (4) NVAF-VHD was associated with a higher incidence of hospitalization for HF; and (5) among all types of VHD, aortic valve diseases were associated with higher risk of cardiac events, whereas mitral valve diseases were not.

VHD, independent of the underlying cardiac rhythm, is associated with a higher risk of thromboembolic events and the risk is greatly increased by the presence of AF. In particular, AF accompanying rheumatic MS and mechanical prosthetic valves is known to lead to a high risk of thromboembolism. The stroke rate in MS with AF patients is approximately 6-fold that in patients with MS without AF, and the relative risk is approximately 15-fold in patients who have AF and MS. Retrospective studies demonstrated a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation in these patients, and current recommendations of anticoagulation therapy for MS patients are only based on these observational studies. On the other hand, the risk of thromboembolism in patients with a mechanical heart valve is estimated to be 4.0/100 patient-years with no anticoagulation, and AF increases this risk. Embolic events are reduced to a frequency of 0.7–1.0/100 patient-years in patients with mechanical valves who receive warfarin.

According to those studies, AF accompanying mitral rheumatic valve disease (predominantly MS) or with mechanical prosthetic valves is catego-

compared with No-VHD (HR 1.51, 95% CI 1.02–2.24, P=0.04).

Lastly, we investigated the clinical characteristics and outcomes of combined and single VHD. In comparison with patients with single VHD (n=488), those with combined VHD (n=158) were older, weighed less, and had more often persistent/permanent type (Supplementary Table). Incidences of adverse events were almost comparable between combined and single VHD (Supplementary Figure).
warfarin control. However, the event rates of VAF were relatively low in both J-RHYTHM and Fushimi, demonstrating that VAF patients are well-managed in current clinical practice.

In Japanese patients, subanalysis of the J-RHYTHM Registry for VAF revealed that 5.3% of the entire cohort had VAF, and the cumulative incidence rate of thromboembolism during the 2-year follow-up period was significantly higher in VAF than in NVAF (3.2% vs. 1.7%, P=0.046). In the Fushimi AF Registry, 3.7% of the entire cohort had VAF, and the incidence rate of stroke/SE was comparable between VAF and NVAF-VHD (1.67 vs. 1.96 per 100 person-years). In addition, VAF patients receiving warfarin had a lower incidence rate of thromboembolism than those without warfarin (2.8% vs. 14.3% during 2-year follow-up) in the J-RHYTHM Registry, whereas the incidence rates of stroke/SE in VAF patients with and without OAC were not significantly different in the Fushimi AF Registry. The reasons for these discrepancies are unknown, but they may be related to differences in the clinical background between these registries, including age, comorbidities, proportions of patients receiving warfarin (J-RHYTHM vs. Fushimi: 99.3% vs. 78.6% in VAF), and quality of warfarin control. However, the event rates of VAF were relatively low in both J-RHYTHM and Fushimi, demonstrating that VAF patients are well-managed in current clinical practice.

The ORBIT-AF (Outcomes Registry for Better Informed Treatment for Atrial Fibrillation) investigators previously published the prevalence, clinical characteristics, and outcomes of VHD in AF patients in the USA. In the ORBIT-AF, 2,705 patients (27.7%) had a history of significant VHD (moderate-to-severe VHD or prior valve surgery) and 403 patients (4.1%) had moderate-to-severe MS or a mechanical valve. The risk of stroke/SE/transient ischemic attack (TIA) in patients with AS/AR, MR, or TR (i.e., VAF) was not significantly higher (unadjusted HR 1.39, 95% CI 0.86–2.26) by univariate analyses. However, after multivariate analyses, the risk of stroke/SE/TIA was not significantly different in NVAF with VHD and VAF when compared with no/mild VHD (NVAF with

| Subgroup | Adjusted HR (95% CI) | P value |
|----------|----------------------|---------|
| Stroke/SE |                      |         |
| No-VHD   | reference            | -       |
| MS       | 1.06 (0.44-2.15)     | 0.89    |
| MR       | 0.80 (0.52-1.21)     | 0.28    |
| AS       | 1.34 (0.66-2.74)     | 0.42    |
| AR       | 1.21 (0.65-2.23)     | 0.55    |
| TR       | 0.99 (0.56-1.73)     | 0.96    |
| All-cause death |            |         |
| No-VHD   | reference            | -       |
| MS       | 0.90 (0.51-1.47)     | 0.68    |
| MR       | 0.87 (0.68-1.11)     | 0.27    |
| AS       | 1.33 (0.88-1.99)     | 0.18    |
| AR       | 1.11 (0.78-1.59)     | 0.55    |
| TR       | 1.11 (0.81-1.53)     | 0.50    |
| Cardiac death |               |         |
| No-VHD   | reference            | -       |
| MS       | 0.94 (0.22-2.67)     | 0.92    |
| MR       | 0.95 (0.55-1.64)     | 0.86    |
| AS       | 2.95 (1.54-5.66)     | 0.001   |
| AR       | 1.56 (0.75-3.27)     | 0.24    |
| TR       | 0.86 (0.40-1.87)     | 0.71    |
| Hospitalization for HF |    |         |
| No-VHD   | reference            | -       |
| MS       | 1.65 (0.96-2.67)     | 0.07    |
| MR       | 1.23 (0.95-1.61)     | 0.12    |
| AS       | 1.78 (1.10-2.88)     | 0.02    |
| AR       | 1.51 (1.02-2.24)     | 0.04    |
| TR       | 1.21 (0.85-1.73)     | 0.29    |
VHD: adjusted HR 0.97, 95% CI 0.74–1.27; VAF: adjusted HR 0.93, 95% CI 0.58–1.49), which is consistent with our results. Regarding other outcomes, the risk of all-cause death in the NVAF with VHD group was modestly higher than that in the no/mild VHD group in the multivariate analyses (adjusted HR 1.23, 95% CI 1.07–1.42), but that in the VAF group was comparable (adjusted HR 1.10, 95% CI 0.85–1.42). Therefore, ORBIT-AF demonstrated that VHD does not strongly affect thromboembolism or mortality. In good agreement with our result as well as those from J-RHYTHM and ORBIT-AF, a recent study from France also demonstrated that VAF patients were not at particularly high risk for stroke/SE compared with non-VHD (adjusted HR 1.33, 95% CI 0.93–1.90).\(^1\)

Lastly, we demonstrated the clinical effect of each individual type of VHD. MR may protect against thromboembolic events in AF patients because the MR jet may agitate the blood in the left atrium, leading to less blood stasis,\(^2\) but our study revealed this to not be the case. Although AS is one of the most common valvular disorders and often accompanies AF, there are few data on whether AS is an independent risk factor for thromboembolism. Data regarding AR and TR with AF are also lacking. The ORBIT-AF investigators demonstrated that MS, MR, AS, AR, and TR were not independent risk factors for stroke/SE, and that only AS was associated with all-cause death.\(^3\) Our current results were overall consistent with those of ORBIT-AF, and further confirmed that AS and AR are independent risk factors for hospitalization for HF, highlighting the importance of aortic valve diseases in adverse cardiac outcomes in AF patients.

**Study Limitations**

First, this was an observational study and provided only associative evidence, not causative. Second, the use of OAC was too small to draw definite conclusions.\(^1\)

**Conclusions**

Although VHD did not have a significant effect on thromboembolism or mortality, it affected cardiac events in Japanese patients with AF depending on the type of VHD. Aortic valve diseases, especially AS, had a significant effect on adverse cardiac outcomes in Japanese AF patients.

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**Disclosures**

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**Data Availability**

The deidentified participant data will not be shared.

**IRB Information**

The study protocol was approved by the institutional review boards of the National Hospital Organization Kyoto Medical Center and Iinkai Takeda General Hospital. Reference numbers are 10-058, and 14-033.

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**Supplementary Files**

Please find supplementary file(s);
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