Clinical Characteristics and Outcomes of Very Elderly Patients With Atrial Fibrillation at High Bleeding Risk
— The Fushimi AF Registry —

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Background: The ELDERCARE-AF trial demonstrated that low-dose edoxaban prevented stroke or systemic embolism (SE) in very elderly Japanese patients with non-valvular atrial fibrillation (NVAF) in whom standard oral anticoagulant therapy was inappropriate because of high bleeding risk. The aim of this study was to elucidate the characteristics and outcomes of such patients in routine clinical practice.

Methods and Results: Data were extracted from the Fushimi AF Registry for ELDERCARE-eligible NVAF patients aged ≥80 years, with a CHADS2 score ≥2 and ≥1 bleeding risk factors, as shown in the ELDERCARE-AF trial. ELDERCARE-eligible patients (n=549; 12.8% of the entire cohort, 52.9% of those aged ≥80 years and with CHADS2 score ≥2) were less often male, were older, had more comorbidity and higher risk scores than non-eligible patients from the entire cohort (n=3,734). The crude incidence (% per patient-year) of adverse events was significantly higher in ELDERCARE-eligible than non-eligible patients (stroke/SE, 4.8% vs. 2.0%; major bleeding, 3.6% vs. 1.9%; all-cause mortality, 15.5% vs. 3.9%; cardiovascular death, 2.7% vs. 0.6%; all log-rank P<0.001). Compared with non-eligible patients aged ≥80 years and with a CHADS2 score ≥2 (n=488), the incidence of stroke/SE, all-cause mortality, and cardiovascular death remained significantly higher in ELDERCARE-eligible patients.

Conclusions: Patients with NVAF who met the inclusion criteria of the ELDERCARE-AF trial were common in routine clinical practice, and had poor clinical outcomes.

Key Words: Atrial fibrillation; Bleeding risk; Very elderly

Elderly patients with non-valvular atrial fibrillation (NVAF) have a high risk of thromboembolism, such as stroke and systemic embolism (SE), with increasing age; in these patients, oral anticoagulant (OAC) therapy is beneficial. Current clinical guidelines recommend that these patients receive OAC therapy to prevent stroke, but NVAF patients at high risk of stroke are also at high risk of serious bleeding, and OACs tend to be withheld in such patients because of high bleeding risks. The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial demonstrated that low-dose edoxaban (15 mg, once daily) prevented stroke or SE in very elderly (≥80 years) Japanese patients with NVAF who were considered inappropriate for standard OAC therapy due to bleeding risk (i.e., low creatinine clearance [15–30 mL/min], a history of bleeding from a critical area or organ, low body weight [≤45 kg], continuous use of non-steroidal anti-inflammatory drugs [NSAIDs],...
or current use of an antiplatelet drug), without significantly increasing the risk of major bleeding compared with placebo. Therefore, low-dose edoxaban may be a feasible anticoagulant treatment for elderly NVAF patients at bleeding risk, rather than leaving such patients untreated with no antithrombotic therapy.

In contemporary routine community-based practice, the clinical characteristics and outcomes of such patients, who are eligible for the ELDERCARE-AF trial, are unclear. The objective of the present study was to investigate the characteristics and outcomes of very elderly Japanese NVAF patients with bleeding risk using the data from a large-scale, community-based prospective survey of Japanese AF patients, namely the Fushimi AF Registry.

Methods

Study Population

The detailed study design, patient enrollment, definitions of measurements, and baseline clinical characteristics of patients in the Fushimi AF Registry (University Hospital Medical Information Network [UMIN] Clinical Trials Registry ID: UMIN000005834; http://www.umin.ac.jp/ctr/index.htm) have been described elsewhere. The inclusion criterion for the Registry is documentation of atrial fibrillation (AF) on a 12-lead electrocardiogram or Holter mon-
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| Table 1. Baseline Characteristics |
|----------------------------------|
|                                | ELDERCARE eligible (n=549) | Non-eligible (entire cohort; n=3,734) | P value* | Non-eligible (≥80 years, CHADS2 ≥2; n=488) | P value* |
| Age (years)                    | 86.2±4.8                    | 71.4±10.2                          | <0.001   | 84.1±3.7                                  | <0.001  |
| Male sex                       | 176 (32.1)                  | 2,417 (64.7)                       | <0.001   | 279 (57.2)                                 | <0.001  |
| Type of AF                     |                            |                                   | 0.063    | 0.362                                      |          |
| Paroxysmal                     | 254 (46.3)                  | 1,886 (50.5)                       | 212 (43.4) | 463 (47.1)                                 |          |
| Sustained                      | 295 (53.7)                  | 1,848 (49.5)                       | 368 (56.6) | 521 (52.9)                                 |          |
| Body weight (kg)               | 46.8±10.3                   | 61.6±12.8                          | <0.001   | 58.6±8.7                                  | <0.001  |
| BMI (kg/m²)                    | 20.4±3.5                    | 23.6±4.0                           | <0.001   | 23.8±3.3                                  | <0.001  |
| History of stroke/SE           | 188 (34.2)                  | 661 (17.7)                         | <0.001   | 120 (24.6)                                 | <0.001  |
| History of stroke              | 175 (31.9)                  | 585 (15.7)                         | <0.001   | 112 (23.0)                                 | 0.001   |
| History of SE                  | 11 (2.0)                    | 41 (1.1)                           | 0.091    | 5 (1.0)                                    | 0.219   |
| Pre-existing heart failure     | 291 (53.0)                  | 855 (22.9)                         | <0.001   | 193 (39.6)                                 | <0.001  |
| Hypertension                   | 408 (74.3)                  | 2,293 (61.4)                       | <0.001   | 384 (78.7)                                 | 0.008   |
| Diabetes                       | 119 (21.7)                  | 894 (23.9)                         | 0.243    | 137 (28.1)                                 | 0.017   |
| Dyslipidemia                   | 234 (42.6)                  | 1,670 (44.7)                       | 0.355    | 213 (43.7)                                 | 0.734   |
| Coronary artery disease        | 177 (32.2)                  | 453 (12.1)                         | <0.001   | 41 (8.4)                                   | <0.001  |
| Peripheral artery disease      | 44 (8.0)                    | 132 (3.5)                          | <0.001   | 14 (2.9)                                   | <0.001  |
| Chronic kidney disease         | 346 (63.0)                  | 1,188 (31.8)                       | <0.001   | 235 (48.2)                                 | <0.001  |
| Calculated CrCl (mL/min)       | 33.0±16.0                   | 59.7±33.3                          | <0.001   | 48.0±15.7                                  | <0.001  |
| COPD                           | 34 (6.2)                    | 197 (5.3)                          | 0.374    | 28 (5.7)                                   | 0.758   |
| CHADS2 score                   | 3.2±1.1                     | 1.8±1.3                            | <0.001   | 2.9±1.0                                    | 0.003   |
| CHA2DS2-VASc score             | 5.1±1.2                     | 3.1±1.6                            | <0.001   | 4.4±1.1                                    | <0.001  |
| HAS-BLED score                 | 2.4±1.0                     | 1.6±1.0                            | <0.001   | 1.9±0.9                                    | <0.001  |
| Prescription at baseline       |                            |                                   |          |                                           |
| Oral anticoagulant             | 268 (48.8)                  | 2,084 (55.8)                       | 0.002    | 301 (61.7)                                 | <0.001  |
| Warfarin                       | 219 (39.9)                  | 1,506 (40.3)                       | 0.853    | 213 (43.7)                                 | 0.25    |
| DOAC                           | 49 (8.9)                    | 578 (15.5)                         | <0.001   | 88 (18.0)                                  | <0.001  |
| Antiplatelet drug              | 249 (45.3)                  | 902 (24.2)                         | <0.001   | 109 (22.3)                                 | <0.001  |
| Anti-arrhythmic drug           | 48 (8.7)                    | 803 (21.5)                         | <0.001   | 62 (12.7)                                  | 0.042   |
| ACEI/ARB                       | 285 (51.9)                  | 1,611 (43.4)                       | <0.001   | 245 (50.2)                                 | 0.522   |
| Calcium channel blocker        | 166 (30.2)                  | 1,182 (31.7)                       | 0.51     | 180 (36.9)                                 | 0.027   |
| Diuretics                      | 281 (51.2)                  | 2,783 (74.5)                       | <0.001   | 299 (61.3)                                 | 0.002   |
| Statins                        | 155 (28.2)                  | 900 (24.1)                         | 0.035    | 120 (24.6)                                 | 0.168   |
| Low body weight                | 302 (55.0)                  | 265 (7.1)                          | <0.001   | 374 (38.0)                                 |          |
| Low CrCl                       | 198 (36.1)                  | 96 (2.6)                           | <0.001   | 403 (41.0)                                 |          |
| Use of antiplatelet drugs      | 173 (31.5)                  | 335 (9.0)                          | <0.001   | 529 (53.8)                                 |          |
| History of bleeding            | 66 (12.0)                   | 131 (3.5)                          | <0.001   | 222 (22.8)                                 |          |

Unless indicated otherwise, data are given as the mean±SD or n (%). *ELDERCARE eligible vs. non-eligible (entire cohort). #ELDERCARE eligible vs. non-eligible (aged 80 years, CHADS2 score ≥2). †Data from are from Okumura et al. Patients receiving antiplatelet drugs for any reason. Among the bleeding risk factors, low body weight was defined as body weight ≤45 kg, low creatinine clearance (CrCl) was defined as 15 mL/min/CrCl<30 mL/min, the use of anticoagulant was for the treatment of concomitant coronary artery disease or peripheral artery disease, and a history of bleeding was for bleeding from a critical area or organ. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; N/A, not available; SE, systemic embolism.

Monitoring at any time. There were no exclusion criteria. In all, 81 institutions in the Fushimi district in Kyoto, Japan, participated in the Registry. Patient enrollment in the Registry started from March 2011. Follow-up data were primarily collected by reviewing inpatient and outpatient medical records, with additional follow-up information collected by contacting patients, their relatives, and/or referring physicians by mail or telephone. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital. Because the present research is part of an observational study not using human biological specimens, written informed consent was not obtained from each patient according to the ethical guidelines for epidemiological research issued by Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan.

The present study enrolled “ELDERCARE-eligible”
patients from the Fushimi AF Registry, using the same criteria as the ELDERCARE-AF trial, namely patients with NVAF who were aged ≥80 years, had a CHADS score ≥2, and had ≥1 risk factors for bleeding on OAC therapy, including low creatinine clearance (15–30 mL/min), a history of bleeding from a critical area or organ, low body weight (≤45 kg), current use of antiplatelet drugs (for a purpose other than prophylaxis of cardioembolic stroke), or continuous use of NSAIDs. The Fushimi AF Registry does not collect data about the continuous use of NSAIDs; thus, we evaluated the bleeding risks other than the continuous use of NSAIDs. With regard to the “current use of antiplatelet drugs”, patients receiving antiplatelet drugs who had concomitant coronary artery disease or peripheral artery disease were included in the present study.

Figure 2. Kaplan-Meier curves for the incidences of stroke/systemic embolism (SE), major bleeding, all-cause mortality, cardiovascular death, and oral anticoagulant (OAC) discontinuation in the entire cohort: comparisons between ELDERCARE-eligible and non-eligible patients. Values in parentheses after hazard ratios (HRs) are 95% confidence intervals.
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Endpoints and Definitions
The endpoints in this study were the incidences of stroke or SE, major bleeding, all-cause mortality, and cardiovascular death. We also evaluated the discontinuation rates of OAC therapy in patients receiving OAC at baseline. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, and the diagnosis of ischemic or hemorrhagic stroke was confirmed by computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organ. Major bleeding was defined based on the criteria of the International Society on Thrombosis and Haemostasis as a reduction in the hemoglobin level by at least 2 g/dL, the transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Causes of death were adjudicated after consideration of all available information, as reported previously.

Statistical Analysis
Continuous variables are expressed as the mean ± SD and categorical variables are presented as numbers and percentages. Continuous variables were compared using Student’s t-test for normally distributed variables or the Wilcoxon rank-sum test for non-normally distributed variables. Categorical variables were compared using the Chi-squared test when appropriate; otherwise, Fisher’s exact test was used. The cumulative incidence of clinical outcomes was estimated by the Kaplan-Meier method, and the significance of differences was assessed using the log-rank test. In addition, multivariable Cox proportional hazard models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) to evaluate which of the 4 bleeding risk factors were clinically relevant.

All analyses were performed using JMP version 14 (SAS Institute, Cary, NC, USA). Two-sided P<0.05 was considered significant.

Results
Follow-up data were available for 4,375 patients with NVAF, and 92 patients were excluded because of incomplete data entry. Therefore, 4,283 patients with NVAF were analyzed in the present study. The median follow-up period was 1,517 days (interquartile range 740–2,550 days). Of the 4,283 patients with NVAF, 1,233 were aged ≥80 years (28.8% of the entire cohort; Figure 1A). The number of patients with a CHADS 2 score ≥2 was 1,037, accounting for 84.1% of patients aged ≥80 years (Figure 1B). The distribution of bleeding risk factors among patients aged ≥80 years with a CHADS 2 score ≥2 is shown in Figure 1C: 29.1% had low body weight (≤45 kg), 19.1% had low creatinine clearance, and 31.6% had a CHADS 2 score ≥2.

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The baseline characteristics of ELDERCARE-eligible and non-eligible patients are presented in Table 1. Compared with non-eligible patients in the entire cohort (n=3,734), ELDERCARE-eligible patients were less often male (32.1% vs. 64.7%; P<0.001), older (mean age 86.2 vs. 71.4 years; P<0.001), and had more comorbidities and higher risk scores (CHADS 2, 3.2 vs. 1.8; CHA 2DS 2-VASc, 5.1 vs. 3.1; HAS-BLED 2.4 vs. 1.6; all P<0.001). Compared with non-eligible patients aged ≥80 years with a CHADS 2 score ≥2 (Figure 1D), 16.7% were receiving antiplatelet drugs for the treatment of concomitant coronary artery disease or peripheral artery disease, and 6.4% had a history of bleeding in a critical area or organ. Consequently, ELDERCARE-eligible patients (n=549) accounted for 12.8% of patients in the entire cohort and for 52.9% of patients aged ≥80 years with a CHADS 2 score ≥2 (Figure 1D).

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Clinical Outcomes

As indicated in Figure 2 and Table 2, ELDERCARE-eligible patients had a significantly higher (all log-rank P<0.001) incidence of stroke/SE (4.8% vs. 2.0% per patient-year), major bleeding (3.6% vs. 1.9% per patient-year), all-cause mortality (15.5% vs. 3.9% per patient-year), and cardiovascular death (2.7% vs. 0.6% per patient-year) than non-eligible patients in the entire cohort. Discontinuation rates of OAC therapy were significantly higher in ELDERCARE-eligible than non-eligible patients (15.5% vs. 10.3% [P=0.007]; Table 2; Figure 3). However, the incidence of major bleeding was not significantly different between ELDERCARE-eligible and non-eligible patients (15.8% vs. 8.5% per patient-year; log-rank P<0.001).

Compared with non-eligible patients aged ≥80 years with a CHADS score ≥2, the incidence of stroke/SE, all-cause mortality, and cardiovascular death, and the discontinuation rates of OAC therapy, remained significantly higher in ELDERCARE-eligible patients (stroke/SE, 4.8% vs. 2.9% [log-rank P=0.009]; all-cause mortality, 15.5% vs. 8.4% [P<0.001]; cardiovascular death, 2.7% vs. 1.4% [P=0.011]; discontinuation of OAC therapy, 15.5% vs. 10.3% [P=0.007]; Table 2; Figure 3). However, the incidence of major bleeding was not significantly different between ELDERCARE-eligible and non-eligible patients (3.6% vs. 3.1%, respectively; P=0.340).

Among the ELDERCARE-eligible patients, the baseline
were significantly associated with the incidence of all-cause mortality (adjusted HR 1.85 [95% CI 1.49–2.28; P=0.011] and 1.49 [95% CI 1.18–1.89; P=0.001], respectively) and cardiovascular death (adjusted HR 1.93 [95% CI 1.17–3.19; P<0.001] and 1.80 [95% CI 1.05–3.09; P=0.034], respectively). On univariate analysis, low body weight was associated with the incidence of stroke/SE, but none of the 4 bleeding risk factors was significantly associated with stroke/SE after multivariate adjustment.

**Discussion**

The major findings of the present analysis of a large community-based cohort are that: (1) patients who met the inclusion criteria of the ELDERCARE trial were comparable between patients with and without OACs (stroke/SE, 5.3% vs. 4.3% [P=0.396]; major bleeding, 3.4% vs. 3.6% [P=0.849]; Figure 4; Table 2). We examined the association of each of the 4 bleeding risk factors with the incidence of stroke/SE, major bleeding, all-cause mortality, and cardiovascular death (Figure 5). The incidence of major bleeding was associated with history of bleeding (adjusted HR 2.46; 95% CI 1.28–4.74; P=0.017). Low body weight and low creatinine clearance were significantly associated with the incidence of all-cause mortality (adjusted HR 1.85 [95% CI 1.49–2.28; P=0.011] and 1.49 [95% CI 1.18–1.89; P=0.001], respectively) and cardiovascular death (adjusted HR 1.93 [95% CI 1.17–3.19; P<0.001] and 1.80 [95% CI 1.05–3.09; P=0.034], respectively). On univariate analysis, low body weight was associated with the incidence of stroke/SE, but none of the 4 bleeding risk factors was significantly associated with stroke/SE after multivariate adjustment.

**Figure 5.** Hazard ratios (HRs) and 95% confidence intervals (CIs) for adverse events: (A) stroke/systemic embolism (SE), (B) major bleeding, (C) all-cause mortality, and (D) cardiovascular death. *P<0.05, **P<0.01, ***P<0.001. Low body weight was defined as body weight ≤45kg and low creatinine clearance (CrCl) was defined as 15mL/minsCrCl<30mL/min.
mon, accounting for 12.8% of the entire cohort and for 52.8% of patients aged ≥80 years with a CHADS$_2$ score ≥2; (2) at baseline, ELDERCARE-eligible patients had a higher incidence than non-eligible patients of stroke/SE, major bleeding, and all-cause and cardiovascular mortality, with the subgroup of elderly patients aged ≥80 years with a CHADS$_2$ score ≥2 having a higher incidence of stroke/SE and all-cause and cardiovascular mortality than non-eligible patients, but a comparable incidence of major bleeding; and (3) of the 4 bleeding risk factors, low body weight and low creatinine clearance were associated with all-cause and cardiovascular mortality, and history of bleeding was associated with major bleeding.

The ELDERCARE-AF trial demonstrated that low-dose edoxaban (15 mg, once daily) prevented stroke or SE in very elderly Japanese patients with NVAF in whom standard OAC therapy was considered not appropriate because of bleeding risks. Our present analysis shows that patients who would have been considered eligible for the ELDERCARE-AF trial are common in contemporary community-based clinical practice, accounting for nearly half the NVAF patients aged ≥80 years. Due to high bleeding risks with OAC therapy, these patients were less often prescribed OAC therapy at baseline, and discontinuation rates of OAC therapy were significantly higher. These data clearly demonstrate that OAC therapy was likely to be withheld in these patients and support the potential usefulness of even prescribing low-dose edoxaban for such patients, rather than leaving them patients untreated, on the basis of evidence from the ELDERCARE-AF trial.

Because there is a significant overlap between the risk of thromboembolism and that of bleeding, the ELDERCARE-eligible patients defined on the basis of high bleeding risks had a higher incidence of stroke/SE and higher mortality than non-eligible patients. However, compared with non-eligible patients aged ≥80 years with a CHADS$_2$ score ≥2, the incidence of major bleeding was comparable between eligible and non-eligible patients. The lack of difference in bleeding between eligible and non-eligible patients may suggest the possibility that the higher rate of prescription of OACs to non-eligible patients may have abolished any potential difference.

Comparing the present study with the ELDERCARE-AF trial, the ELDERCARE-eligible patients in the present study had a broadly similar clinical background to patients in the ELDERCARE-AF trial, including age, sex, creatinine clearance, and CHADS$_2$, CHA$_2$:DS$_2$-VASc, and HAS-BLED scores. However, mortality was lower among the trial patients than among eligible patients in the present study, and the incidence of major bleeding in the placebo group in the trial was lower than that among eligible patients without OACs in the present study. Because there were no exclusion criteria in our registry and the trial was a randomized clinical trial with a highly selected population, this may have led to differences between the real-world, community-based population in the present study and the ELDERCARE-AF trial population, which may have contributed to differences in results: patients with a poorer condition or those with social problems, such as the solitary aged person and “elder care by the elderly”, may have been excluded from the trial. In addition, the baseline characteristics and the incidence of stroke/SE and major bleeding were comparable between patients with and without OAC among the ELDERCARE-eligible patients in our Registry. Because warfarin was the predominant OAC in the present study, underdosing, poor adherence, or low time in the therapeutic range of warfarin may have contributed to the results. Some of the ELDERCARE-eligible patients may not have received OAC therapy due to a high bleeding risk, frailty, or social reasons, which could have also affected the results.

The 4 bleeding risk factors may have differential effects on outcomes. As we reported previously, both low body weight and renal impairment were associated with stroke/SE and all-cause mortality among Japanese AF patients enrolled in the Fushimi AF Registry. In the present study, we further demonstrated that low body weight and renal impairment were associated with all-cause mortality and cardiovascular death in the ELDERCARE-eligible population of the same Registry; however, none of the 4 bleeding risk factors was significantly associated with stroke/SE after multivariate adjustment. In addition, the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial demonstrated that anticoagulant monotherapy was non-inferior for efficacy and superior for safety to combination therapy with an anticoagulant and antiplatelet drug in patients with AF and stable coronary artery disease. Therefore, the number of AF patients requiring the continuous long-term use of antiplatelet drugs will hopefully decrease over time, especially because such combination therapy over 1 year is not recommended in current clinical guidelines.

**Study Limitations**

This study has several limitations. First, the results were derived from a prospective observational study. Therefore, we can only show associations and not causality, with limitations inherent to this design, such as selection bias and unmeasured confounders. Second, no data were available regarding the continuous use of NSAIDs, and we were not able to evaluate the association between this bleeding risk factor and outcomes. Third, we selected ELDERCARE-eligible or non-eligible patients based on clinical characteristics at the time of enrollment. So, changes in the characteristics during follow-up were not considered. Fourth, in this study warfarin was the predominant OAC therapy, because direct OACs (DOACs) were unavailable when the Registry was started in 2011. The statistical analysis was based only on OAC usage at the time of enrollment. This did not take into account the initiation, adherence, and switching of OACs, or the quality of the adjustment, such as time spent in the therapeutic range for patients taking warfarin, through the follow-up period. In addition, we have no data regarding reasons for discontinuing OAC therapy. Given the overall superiority of DOAC over warfarin, the results of the study may differ now that DOACs are increasingly used in clinical practice.

**Conclusions**

We showed that patients with NVAF who met the inclusion criteria of the ELDERCARE-AF trial are common in the contemporary, community-based, routine practice and had high risks of stroke/SE, major bleeding, and all-cause and cardiovascular mortality.

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Contributors

Y.I. analyzed the data and wrote the paper. H.O., K.I., S.I., K.D., Y.H., A.F., Y.A., M. Ishii, M. Iguchi, N.M., M.E., H.T., H.W., K.H., M. Abe contributed to the acquisition of data, and helped data analysis and interpretation. M. Akao is a principal investigator of the Fushimi AF Registry, and the corresponding author of this paper. G.Y.H.L. and M. Akao are joint senior authors of this paper.

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IRB Information

The study protocol was approved by the ethics committees of the Takeda General Hospital (Reference no. 10-058 and 14-033, respectively). The study protocol was approved by the ethics committees of the hospitals relevant to the contents of this paper to disclose.

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s):
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