Age-Related Differences in the Clinical Characteristics and Treatment of Elderly Patients With Atrial Fibrillation in Japan — Insight From the ANAFIE (All Nippon AF In Elderly) Registry —

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Background: Atrial fibrillation (AF) is increasing as the global population ages. Elderly AF patients (≥75 years) have a worse prognosis than younger patients, and effective management is often difficult due to multiple comorbidities. This analysis examined the age-related differences in clinical characteristics and treatment in real-world elderly Japanese AF patients.

Methods and Results: The ANAFIE Registry is a multicenter, prospective, observational registry of 32,726 non-valvular AF patients aged ≥75 years. The present study assessed the age-related differences in baseline clinical status and anticoagulant therapy between age groups 75–<80, 80–<85, 85–<90, and ≥90 years. The prevalence of persistent or permanent AF increased, and that of paroxysmal AF decreased, with increasing age (trend P<0.0001). The risk of stroke, based on CHADS2 and CHA2DS2-VASc scores, and bleeding, based on HAS-BLED score, increased with age. Both warfarin and apixaban were used more often as age increased (trend P<0.0001, for each), while other anticoagulants were used less. Anticoagulant doses were significantly lower in older patients.

Conclusions: Permanent/persistent AF, comorbidities, and cardiovascular and bleeding risk all increased significantly with age. Furthermore, use of warfarin and apixaban increased with age, accompanied by a decrease in other oral anticoagulant usage.

Key Words: Anticoagulation; Atrial fibrillation; Comorbidity; Elderly; Stroke prophylaxis

Atrial fibrillation (AF) is the most common arrhythmia and an important risk factor for thromboembolic events, including ischemic stroke, acute mesenteric ischemia, and acute limb ischemia. The prevalence is 1–2% in the general adult population and as high as 2–3% according to age. The proportion of individuals with AF is 0.1–0.9% in those aged <60 years, 1.0–4.5% in 60–69-year-olds, 3.4–7.3% in 70–79-year-olds, and 7.2–17% in ≥80-year-olds. In Japan, the prevalence of AF also increases with age and is 4.4% for men and 2.2% for women aged ≥80 years.

In Europe, it is estimated that 14–17 million individuals will have AF in 2030, and in the USA, the number of adults with AF is predicted to at least double by 2050. In 2050, it is projected that 1.034 million people in Japan will have AF. The increasing prevalence of AF is most likely due to global aging and improved survival from other forms of cardiovascular disease. In addition, age-related...
Age-Related Differences in Elderly AF

Japanese patients with AF have involved populations with a mean age well below 75 years. This lack of clinical trial data in older patients makes it difficult to generalize these results to patients aged ≥75 years who may present with multiple comorbidities. Furthermore, available AF treatment guidelines do not provide specific information regarding the management of older patients. Anticoagulants have been reported to be underused in the elderly, and the presence of comorbidities further limited the use of anticoagulants in elderly patients.

The ANAFIE registry was designed to obtain real-world information on patients with NVAF aged ≥75 years, including current status, current anticoagulant therapy, and prognosis. The aim of this analysis of ANAFIE registry data was to compare age-related differences in clinical characteristics and treatment between age groups in a large cohort of elderly Japanese patients with AF.

**Methods**

**Study Design**
In brief, the ANAFIE Registry (UMIN Clinical Trials...
NVAF, were aged ≥75 years, and were able to visit the hospital for specified visits. Those participating in an interventional study, and those with mitral stenosis, artificial heart valves or life expectancy <1 year, and patients with a recent (<1-month) history of cardiovascular events were excluded. Full details of inclusion/exclusion criteria were published previously.

**Data Collection**

Data on the following parameters were collected at baseline, and at the month 12 and month 24 follow-up visits: demographic and clinical data, type of anticoagulant, other medication, and blood coagulation test results in warfarin recipients. Invasive procedures (except those related to AF) and other clinical events were also recorded.

**Patients**

Eligible patients had electrocardiogram (ECG)-confirmed NVAF, were aged ≥75 years, and were able to visit the hospital for specified visits. Those participating in an interventional study, and those with mitral stenosis, artificial heart valves or life expectancy <1 year, and patients with a recent (<1-month) history of cardiovascular events were excluded. Full details of inclusion/exclusion criteria were published previously.

**Table 1. Patient Demographics and Characteristics at Baseline by Age Category**

| Age (years)          | 75–<80 years (n=13,059) | 80–<85 years (n=11,103) | 85–<90 years (n=6,401) | ≥90 years (n=2,163) | P-value for trend† |
|----------------------|-------------------------|------------------------|------------------------|---------------------|-------------------|
| Mean ± SD            | 7.9±1.4                 | 8.1±1.4                | 8.7±1.4                | 9.0±2.1             | –                 |
| Median (IQR)         | 77.0 (76.0–78.0)        | 82.0 (81.0–83.0)       | 86.0 (85.0–88.0)       | 91.0 (90.0–93.0)    |                   |
| Sex                  |                         |                        |                        |                     |                   |
| Male                 | 8,278 (63.4)            | 6,447 (58.1)           | 3,146 (49.1)           | 862 (39.9)          | <0.0001           |
| Creatinine clearance (mL/min) |                      |                        |                        |                     |                   |
| Mean ± SD            | 56.7±17.1               | 47.7±18.8              | 39.1±28.8              | 31.0±11.6           | <0.0001           |
| Median (IQR)         | 56.1 (45.7–67.1)        | 47.1 (36.9–56.9)       | 38.0 (29.3–46.8)       | 29.9 (22.8–37.9)    |                   |
| <15 mL/min or with dialysis | 96 (0.7)              | 109 (1.0)              | 115 (1.8)              | 108 (5.0)           |                   |
| 15–<30 mL/min         | 461 (3.5)               | 991 (8.9)              | 1,273 (19.9)           | 791 (36.6)          |                   |
| 30–<50 mL/min         | 3,111 (23.8)            | 4,145 (37.3)           | 2,849 (44.5)           | 781 (36.1)          |                   |
| 50–<80 mL/min         | 5,958 (45.6)            | 3,543 (31.9)           | 967 (15.1)             | 109 (5.0)           |                   |
| ≥80 mL/min            | 871 (6.7)               | 224 (2.0)              | 26 (0.4)               | 1 (0.0)             |                   |
| Unknown               | 2,562 (19.6)            | 2,091 (18.8)           | 1,171 (18.3)           | 373 (17.2)          |                   |
| Smoking habit         |                         |                        |                        |                     | <0.0001           |
| Non-smoker            | 5,899 (45.2)            | 5,609 (50.5)           | 3,570 (55.8)           | 1,274 (58.9)        |                   |
| Ex-smoker             | 4,508 (34.5)            | 3,350 (30.2)           | 1,661 (25.9)           | 501 (23.2)          |                   |
| Current smoker        | 736 (5.6)               | 358 (3.2)              | 133 (2.1)              | 23 (1.1)            |                   |
| Unknown               | 1,916 (14.7)            | 1,786 (16.1)           | 1,037 (16.2)           | 365 (16.9)          |                   |
| Alcohol consumption   |                         |                        |                        |                     | <0.0001           |
| Habitual              | 3,014 (23.1)            | 1,894 (17.1)           | 772 (12.1)             | 167 (7.7)           |                   |
| Occasional            | 2,658 (20.4)            | 2,039 (18.4)           | 944 (14.7)             | 284 (13.1)          |                   |
| None                  | 5,280 (40.4)            | 5,264 (47.4)           | 3,574 (55.8)           | 1,336 (61.8)        |                   |
| Unknown               | 2,107 (16.1)            | 1,906 (17.2)           | 1,111 (17.4)           | 376 (17.4)          |                   |
| SBP (mmHg)§           |                         |                        |                        |                     | 0.0340            |
| Mean ± SD            | 127.5±16.5              | 127.3±17.1             | 127.5±17.7             | 126.5±18.1          |                   |
| Median (IQR)         | 128.0 (117.0–138.0)     | 128.0 (116.0–138.0)    | 127.0 (116.0–138.0)    | 126.0 (114.0–138.0) |                   |
| DBP (mmHg)§           |                         |                        |                        |                     | <0.0001           |
| Mean ± SD            | 71.9±11.4               | 70.3±11.4              | 69.5±12.0              | 68.2±12.0           |                   |
| Median (IQR)         | 71.0 (64.0–80.0)        | 70.0 (62.0–78.0)       | 70.0 (61.0–77.0)       | 68.0 (60.0–76.0)    |                   |
| Type of AF            |                         |                        |                        |                     | <0.0001           |
| Paroxysmal            | 5,851 (44.8)            | 4,608 (41.5)           | 2,534 (39.6)           | 758 (35.0)          |                   |
| Persistent            | 2,133 (16.3)            | 1,811 (16.3)           | 1,078 (16.8)           | 401 (18.5)          |                   |
| Long-standing persistent | 1,682 (12.9)          | 1,529 (13.8)           | 898 (14.0)             | 318 (14.7)          |                   |
| Permanent             | 3,393 (26.0)            | 3,155 (28.4)           | 1,891 (29.5)           | 866 (31.7)          |                   |

(Table 1 continued the next page.)
Statistical Analysis
The target sample size of 30,000 patients was based on incidence data for stroke/systemic embolism (the primary registry study outcome). Full details of the sample size calculation have been reported previously; based on this, the significance level was set at 5% (2-sided). 32

All patients meeting the study eligibility criteria who were enrolled in the registry were included in this analysis. Prevalence was assessed as a categorical variable, and summary statistics were calculated for continuous variables. P-values for trends were estimated using a general linear model, and categorical P-values were calculated using the Cochran-Mantel-Haenszel correlation statistic. Patients classified as unknown for a particular variable were excluded from the analysis. All calculations were performed using SAS version 9.4 or higher (SAS Institute, Tokyo, Japan).

Results
Patient Characteristics
A total of 33,278 patients were registered,33 32,726 of whom were included in this analysis. Prior to enrollment, 163 patients were excluded, primarily due to duplicate registrations (n=85) or withdrawal of consent (n=76; Figure 1). A further 389 patients were excluded from the analysis; the most frequent reasons were contract breach (n=232), lack of informed consent (n=71), no definitive diagnosis of NVAF (n=27), and retrospective identification of previous valve replacement (n=17). The analysis population was divided into 4 age groups: 75–<80 years (13,059 patients), 80–<85 years (11,103 patients), 85–<90 years (6,401 patients), and ≥90 years (2,163 patients; Figure 1).

Patient demographic data and clinical characteristics are listed according to age group in Table 1. A number of
Figure 2. Risk scores: (A) CHADS₂; (B) CHA₂DS₂-VASc; and (C) HAS-BLED in elderly patients with atrial fibrillation in Japan. *Positive trend of score against age, P<0.0001 (general linear model). †No patient with score ≥7 was observed. y, years.
variables showed a significant decreasing trend as age increased: the proportion of male patients, current or ex-smokers, alcohol intake, creatinine clearance, systolic and diastolic blood pressure, and patients who had surgery during the previous 3 months (Table 1). Fewer older patients had received previous non-drug therapy for AF (P-value for trend <0.0001). The prevalence of paroxysmal AF decreased and that of persistent or permanent AF increased as age increased (P-value for trend <0.0001; Table 1).

**Comorbidities and Risk**
The prevalence of hypertension, kidney diseases, heart disease, cerebrovascular disease, and dementia significantly

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**Table 2. Anticoagulant Use and Dose at Baseline by Age Category**

| Use of anticoagulants | 75–<80 years (n=13,059) | 80–<85 years (n=11,103) | 85–<90 years (n=6,401) | ≥90 years (n=2,163) | P-value for trend* |
|-----------------------|-------------------------|------------------------|-----------------------|---------------------|-------------------|
| None                  | 978 (7.5)               | 783 (7.1)              | 591 (9.2)             | 293 (13.5)          | <0.0001           |
| Any†                 | 12,081 (92.5)           | 10,320 (92.9)          | 5,810 (90.8)          | 1,870 (86.5)        | <0.0001           |
| Warfarin†             | 3,030 (25.1)            | 2,887 (28.0)           | 1,781 (30.7)          | 656 (35.1)          | <0.0001           |
| Dabigatran†           | 1,250 (10.3)            | 776 (7.5)              | 272 (4.7)             | 55 (2.9)            | <0.0001           |
| Rivaroxaban†          | 2,852 (23.6)            | 2,146 (20.8)           | 1,154 (19.9)          | 311 (16.6)          | <0.0001           |
| Apixaban†             | 2,930 (24.3)            | 2,890 (28.0)           | 1,714 (29.5)          | 551 (29.5)          | <0.0001           |
| Edoxaban†             | 2,013 (16.7)            | 1,618 (15.7)           | 885 (15.2)            | 297 (15.9)          | 0.0265            |
| Non-oral anticoagulant†| 6 (0.0)                 | 3 (0.0)                | 4 (0.1)               | 0 (0.0)             | 0.7834            |

**Daily anticoagulant dose (mg)**

**Dabigatran**

| No. patients | Mean ± SD | Median (IQR) |
|--------------|-----------|--------------|
| 1,250        | 214.2±43.6| (220.0–220.0) |
| 75 mg        | 3 (0.2)   | 3 (0.4)      |
| 110 mg       | 111 (8.9) | 68 (8.8)     |
| 150 mg       | 48 (3.8)  | 42 (5.4)     |
| 220 mg       | 973 (77.8)| 627 (80.8)   |
| 300 mg       | 113 (9.0) | 32 (4.1)     |
| Others       | 2 (0.2)   | 4 (0.5)      |

**Rivaroxaban**

| No. patients | Mean ± SD | Median (IQR) |
|--------------|-----------|--------------|
| 2,852        | 12.4±2.7  | 10.0 (10.0–10.0) |
| 75 mg        | 3 (0.2)   | 3 (0.4)      |
| 110 mg       | 111 (8.9) | 68 (8.8)     |
| 15 mg        | 1,370 (48.0)| 584 (27.2) |
| Others       | 2 (0.2)   | 4 (0.5)      |

**Apixaban**

| No. patients | Mean ± SD | Median (IQR) |
|--------------|-----------|--------------|
| 2,930        | 7.6±2.7   | 10.0 (10.0–10.0) |
| 10 mg        | 1,468 (51.5)| 1,556 (72.5)|
| Others       | 14 (0.5)  | 6 (0.3)      |

**Edoxaban**

| No. patients | Mean ± SD | Median (IQR) |
|--------------|-----------|--------------|
| 2,013        | 35.7±12.3 | 30.0 (30.0–30.0) |
| 15 mg        | 34 (1.7)  | 74 (4.6)     |
| Others       | 2 (0.1)   | 1 (0.1)      |

Data given as n (%) unless otherwise indicated. †Percentage calculated using the no. patients in the ‘Any’ group as the denominator. IQR, interquartile range (quartile 1 to quartile 3); SD, standard deviation.
increased as age increased. Conversely, dyslipidemia, diabetes mellitus, severe hepatic impairment, and hyperthyroidism were significantly less common with advancing age (Table 1).

CHADS\(_2\), CHA\(_2\)DS\(_{-2}\)-VASc, and HAS-BLED scores increased as age increased, but numerical increases in scores and the proportion of patients in each risk category were relatively small (Figure 2).

### Anti-Thrombotic Agents

Both warfarin and apixaban were used more often and other anticoagulants less often as age increased (P-value for trend <0.0001, each; Table 2). There was a significant trend for the use of lower anticoagulant doses in older patients (Table 2). For all anticoagulants, treatment had been initiated at least 1 month previously in the majority of patients (≥84%), without any significant differences across the different age groups. In the vast majority of patients (≥98%), dabigatran and apixaban were given twice daily, and rivaroxaban and edoxaban were given once daily.

For patients receiving warfarin, mean±SD prothrombin time-international normalized ratio (PT-INR) decreased with age (2.9±0.4, 2.6±0.4, 1.9±0.4, and 1.9±0.4 in patients aged 75–80, 80–85, 85–90, and ≥90 years, respectively; P-value for trend <0.0001). Corresponding values for the proportion of time in the therapeutic range (TTR) also decreased with age (77.7%, 75.7%, 73.3%, and 68.7%, respectively; P-value for trend <0.0001).

There was no significant difference in antiplatelet use between the different age groups. Antiplatelet agents were used in 18.3%, 18.9%, 18.9%, and 18.7% of patients aged 75–80, 80–85, 85–90, and ≥90 years, respectively (P-value for trend =0.4043).

### Discussion

The ANAFIE registry is the first prospective observational registry to include specifically elderly patients with NVAF.

In the present study, the prevalence of permanent/persistent forms of AF, comorbidities, and the cardiovascular and bleeding risks all increased significantly with age. In contrast, use of warfarin and apixaban increased with age, accompanied by a corresponding decrease in the use of DOAC.

The present findings of increased comorbidities and cardiovascular risk in elderly patients with AF are consistent with previous reports. In the Akershus Cardiac Examination (ACE) 1950 study, 87.6% of men with AF and 86.4% of women with AF had comorbidities, compared with 74.4% and 66.3%, respectively, without AF.\(^4\) Data from a Chinese AF registry indicated that older patients (≥75 years) with AF were more likely to have higher mean CHADS\(_2\); score, as well as higher risk of death and higher risk of MACE, compared with younger patients (≥65–<75 years).\(^4\) Similarly, in a US National Health and Wellness Survey, almost all patients with AF (98%) had at least 1 additional comorbidity, and 81% were at high or moderate risk for stroke according to CHADS\(_2\); score.\(^4\)

A population study showed that although elderly AF patients (age ≥75 years) were at higher risk of stroke and of bleeding, the benefits of anticoagulant therapy for stroke prevention persist despite increasing age.\(^35\) Nevertheless, given the greater risks associated with anticoagulation therapy in elderly patients, appropriate treatment is underprescribed and underused in this patient group.\(^36\) Such decisions are not evidence based, given that a recent systematic review, meta-analysis, and cost-effectiveness analysis confirmed that oral anticoagulation is an important therapeutic strategy for stroke prevention in AF.\(^37\)

It is important to note that the ANAFIE registry included a patient population with different patient baseline characteristics compared with previous large-scale analyses of patients with AF, such as the ENGAGE AF-TIMI 48 clinical trial,\(^38,39\) and other Japanese registries including the J-RHYTHM Registry,\(^40\) the Fushimi AF Registry,\(^28\) and the SAKURA AF Registry.\(^41\) In general, patients in ANAFIE were older, included a higher proportion of women, and had impaired kidney function. Despite this, the anticoagulant treatment rate was extremely high (92%), with 66% using DOAC. This is in contrast to a European registry study in elderly AF patients, in which similar CHADS\(_2\), CHA\(_2\)DS\(_{-2}\)-VASc, and HAS-BLED scores were observed, but anticoagulation treatment rates were much lower compared with the ANAFIE population.\(^42\) Use of warfarin therapy was also relatively high in this analysis, particularly for the oldest patients, and PT-INR and TTR data indicated good anticoagulation control. Warfarin has been shown to be of clinical benefit in elderly (age ≥80 years) Chinese patients with AF.\(^43\) Increased warfarin use might be due to prior renal function in older patients. As a result, warfarin might be used in place of DOAC in elderly patients with renal dysfunction. Interestingly, the use of apixaban increased in a similar way and was used more often as age increased compared with other anticoagulants. This is consistent with the ARISTOTLE trial, in which apixaban was effective for stroke prevention, bleeding complications, and mortality consistently across all age groups, including patients aged ≥80 years.\(^44\)

The overall uptake of anticoagulation in patients with AF has been much lower in Asia (57.4%) than in Europe (90.2%).\(^47\) In addition, approximately one-third of patients are not treated in accordance with guideline recommendations.\(^47\) In contrast, anticoagulants were used in a much higher proportion of patients in this analysis (86.5–92.5%).

The large proportion of patients using anticoagulants in the ANAFIE registry may be partially attributable to the recommendation for anticoagulant therapy in elderly patients in the 2013 Japanese AF guidelines;\(^47\) since their publication, physicians likely prescribed the treatment to older patients more frequently and gained experience and confidence in doing so. In addition, it is possible that selection bias in the present analysis, based on the inclusion of patients able to complete the 24-month observation period, may have contributed to the high rates of anticoagulation therapy observed. Thus, the present study shows the current status of treatment in elderly patients who were considered by the treating physician to be relatively healthy as to be able to obtain long-term benefit from an anticoagulant treatment regimen. It should be noted that the physicians who participated in the ANAFIE study consisted of many general practitioners who were eager to treat AF, rather than of specialists. Those practitioners might have considered anticoagulant therapy to provide clinical benefit for patients; this, in turn, may explain the increased rate of anticoagulant therapy observed in this study. Data from another registry in Japan, J-RHYTHM, also showed relatively high rates of anticoagulant use: J-RHYTHM enrolled 7,937 patients across a wider age range, of whom 34% were ≥75 years old.\(^42\) The overall rate of oral anticoagulant use in that population was relatively high (87.3%).
and 53% achieved target INR. In contrast, in the present study, patients had an INR within the therapeutic range 68.7–77.7% of the time.

Of note, some elderly patients in this study received lower daily doses of DOAC than those recommended in the package inserts for these agents (e.g., dabigatran 75 mg range 68.7–77.7% of the time. Furthermore, the dose reductions increased with age. We speculate that physicians decided to reduce the dosage for their older patients in an attempt to mitigate these bleeding risks. Further studies are needed to ascertain whether this strategy is widespread, both in Japan and in other countries, and how it may affect patient outcomes.

The present study had several potential limitations, including the observational registry-based design. Despite this, however, the patients included are representative of routine clinical settings and therefore the findings are likely to have good external validity, at least in Japan. The study is based on 1 ethnicity (Japanese) and extrapolation of these findings to different populations should be done with caution. Finally, this study reports only baseline data from the ANAFIE registry, and the identification of prognostic information (for stroke/systemic embolism and bleeding) must await future data collection and evaluation.

Conclusions

The prevalence of persistent or permanent AF, comorbidities, and the stroke and bleeding risk increased in parallel with increasing age in elderly patients with AF. Despite a higher bleeding risk, the use of oral anticoagulants in this elderly population was relatively high, with high levels of warfarin use. This might be due to poor renal function, commonly observed in older patients, and which can lead to limited use of DOAC.

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Author Contributions

H.I., T. Yamashita, M.A., H.A., Y.K., K.O., W.S., T.I., K.T., A.H., M.Y., T. Yamaguchi, and H.T. designed and conducted the study; K.H., T. Yamashita, M.A., H.A., Y.K., K.O., W.S., T.I., K.T., A.H., M.Y., T. Yamaguchi, and H.T. interpreted the data; K.H., T. Yamashita, M.A., H.A., Y.K., K.O., W.S., T.I., K.T., A.H., M.Y., T. Yamaguchi, and H.T. carried out statistical analysis; K.I., T. Yamashita, M.A., H.A., Y.K., K.O., W.S., T.I., K.T., A.H., M.Y., T. Yamaguchi, and H.T. wrote and reviewed the manuscript; all authors revised and commented on the manuscript, and approved the final version.

Disclosures

K.H. received remuneration from Daiichi Sankyo, Nippon Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Bayer, and Otsuka Pharmaceutical. H.I. received remuneration from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. T. Yamashita received research funding from Bristol-Myers Squibb, Bayer, and Daiichi Sankyo; manuscript fees from Daiichi Sankyo, and Bristol-Myers Squibb; donations from Daiichi Sankyo, and remuneration from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Toa Eiyo, and Ono Pharmaceutical. M.A. received research funding from Bayer; donations from Bayer and Daiichi Sankyo; and remuneration from Pfizer, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer, and Daiichi Sankyo. H.A. received remuneration from Daiichi Sankyo. Y.K. received remuneration from Daiichi Sankyo. K.O. received remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and AstraZeneca. W.S. received research funding from Daiichi Sankyo and Nippon Boehringer Ingelheim; donations from Daiichi Sankyo, Nippon Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Mitsubishi-Tanabe Pharma, Otsuka Pharmaceutical, and Ono Pharmaceutical; and remuneration from Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, Bayer, Otsuka Pharmaceutical, and Nippon Boehringer Ingelheim. A.H. received research funding from Daiichi Sankyo, Medtronic, and Japan Lifeline, and remuneration from Daiichi Sankyo, Bayer, Nippon Boehringer Ingelheim, Ono Pharmaceutical, and Bristol-Myers Squibb. K.T. received remuneration from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. A.H. participated in a course endowed by Boston Scientific Japan, Otsuka Pharmaceutical, Fukuda Denshi, St. Jude Medical, Medtronic, and Japan Lifeline; and has received remuneration from Bayer, Daiichi Sankyo, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Sanofi, Astellas Pharma, Sumitomo Dainippon Pharma, Agena Astellas BioPharma, Toa Eiyo, and AstraZeneca. M.Y. received research funding from Nippon Boehringer Ingelheim, and remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and CSL Behring. T. Yamaguchi received remuneration from Daiichi Sankyo, and manuscript fees from Bristol-Myers Squibb, and others from Otsuka Pharmaceutical. S.T. received research funding from Nippon Boehringer Ingelheim and remuneration from Daiichi Sankyo and Solasia Pharma. T.K., J.K., and A.T. are employees of Daiichi Sankyo. H.T. received remuneration from Otsuka Pharmaceutical, Takeda Pharmaceutical, Mitsubishi-Tanabe Pharma, Kowa Pharmaceutical, and Nippon Boehringer Ingelheim. Bayer, Pfizer, Novartis Pharma, MSD, Teijin Pharma, Bristol-Myers Squibb, Kowa Pharmaceutical, and Astellas Pharma; research funding from Nippon Boehringer Ingelheim, Mitsubishi-Tanabe Pharma, Japan Tobacco, Daiichi Sankyo, IQVIA Services Japan, Acteon Pharmaceuticals Japan, and Omron Healthcare; donations from Astellas Pharma, Novartis Pharma, Daiichi Sankyo, Takeda Pharmaceutical, Mitsubishi-Tanabe Pharma, Teijin Pharma, and MSD; and consultancy from Nippon Boehringer Ingelheim, Bayer, Novartis Pharma, and Ono Pharmaceutical. H.K. declares no conflict of interest.

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