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Original article

Rhythm versus rate control strategies regarding anticoagulant use in elderly non-valvular atrial fibrillation patients: Subanalysis of the ANAFIE (All Nippon AF In the Elderly) Registry

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ABSTRACT

Background: Data on real-world antiarrhythmic and anticoagulant therapy use in elderly atrial fibrillation (AF) patients are lacking; thus, we performed a subanalysis of data from the ANAFIE registry to clarify the current management of Japanese patients aged ≥75 years with non-valvular AF.
Methods: The ANAFIE registry was a multicenter, prospective, observational study. Patients were stratified into three groups: rhythm control group, rate control group, and no antiarrhythmic group. The $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were used to estimate embolic and bleeding risk.
Results: Among 32,490 patients, the overall frequencies of AF by type were 42.0 % (paroxysmal), 30.1 % (persistent and long-standing persistent), and 27.9 % (permanent). Significant differences ($p < 0.0001$, each) in age were observed among the three groups; more patients aged 75–79 years received rhythm control (44.2 %) vs rate control (38.8 %). Patients aged ≥85 years received either rate control therapy or no antiarrhythmic agent (~20 %, each). In the overall population, 36.9 % and 19.6 % of patients were receiving rate and rhythm control therapy, respectively; 43.4 % were not receiving antiarrhythmic therapy. The rate control group consisted mainly of patients with persistent (16.3 %) and permanent AF (38.6 %), and the rhythm control group, of patients with paroxysmal AF (79.0 %). Significantly lower embolic and bleeding risk scores and significantly higher embolic risk scores were observed in patients in the rhythm and rate control groups, respectively. In total, 92.1 % of elderly Japanese patients with AF were receiving anticoagulant therapy. The frequency of direct-acting oral anticoagulant (DOAC) use was similar (~66 %)

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among the three groups. Significantly more patients in the rate control group (28.6 %) were being treated with warfarin than in the rhythm control group (21.6 %) ($p < 0.0001$).
Conclusions: Use versus non-use and antiarrhythmic therapy varied significantly by age, stroke risk scores, type of AF, and DOAC use between subgroups.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than 5 % of the population worldwide [1]. AF is more common in older patients (occurring in approximately 23 % of individuals aged ≥85 years) [2] and is associated with increased stroke risk [3], and higher cardiovascular morbidity and mortality [4–6]. Currently, there are two main approaches to AF management [7–10]: rate control and rhythm control. During the application of either approach, the use of anticoagulant drugs, usually in the form of oral anticoagulants (OACs), is recommended for stroke prevention, as it has been demonstrated that this can prevent the majority of ischemic strokes and prolong the life of AF patients [11,12].

Rate control is currently achieved with beta-blockers, digoxin, calcium channel blockers (e.g. diltiazem and verapamil), or combination therapy, and it often improves the AF-related symptoms. Rhythm control aims to restore sinus rhythm, which is the main goal in patients with AF, by means of antiarrhythmic drugs, catheter ablation, or combination therapy. However, several randomized controlled trials [10,13–15] have shown that the rhythm-control strategy using antiarrhythmic drugs offers no survival advantage over the rate-control strategy. Furthermore, several trials [10,12] have emphasized that anticoagulation therapy is important for AF management, even if either of the control strategies is implemented.

With the exception of patients at very low risk, the clinical benefits of OACs are almost universal and were found to be superior to no anticoagulation or aspirin in patients with different levels of risk [16,17]. Notably, it has been reported that stroke risk without OACs often exceeds bleeding risk with OACs, even in elderly patients [18]. Although many AF trials have not had an upper age limit for patient inclusion, the age of clinical study cohorts is about 5–10 years younger than the average age of AF patients (∼75 years) in real-world settings [19–21]. A recently published subanalysis of the SAKURA AF Registry reported that age ≥75 years was one of the main determinants of death among the Japanese AF population. Interestingly, no difference was found for any cause of death among warfarin and direct-acting OAC (DOAC) users [22]. Nonetheless, more information is needed to understand current clinical practices regarding antiarrhythmic use and rate control in elderly patients.

The overall objective of the All Nippon AF In the Elderly (ANAFIE) registry was to collect real-world information about the clinical status of patients with non-valvular AF (NVAF) aged ≥75 years, current anticoagulant therapy, and prognosis [23]. The aim of this analysis of the ANAFIE registry was to determine the use and type of current antiarrhythmic therapies, plus anticoagulant use in subgroups based on antiarrhythmic therapy in a large cohort of elderly Japanese patients with AF.

Methods

Study design

The study design and baseline clinical characteristics of the ANAFIE registry have been reported elsewhere [23,24]. Briefly, the ANAFIE registry was initiated in October 2016 and was a multicenter, prospective, observational study incorporating a minimum 2-year follow-up for each patient [23]. This was a non-interventional study, and patients were not randomized to therapy but instead treated as per routine clinical practice by their physician(s). A specific or recommended target heart rate was not set for patients in the rate control group; rather, the target heart rate was established according to the investigator's judgement. The institutional review boards of the participating institutions approved the study (approval number M16172 in Toho University Omori Medical Center), and all patients provided written informed consent and were free to withdraw from the registry at any time.

Patients

Patients aged ≥75 years with a definitive diagnosis of NVAF who could attend the study visits were eligible for the study. Patients with valvular disease, history of a recent cardiovascular event, history of recent bleeding event leading to hospitalization, and a life expectancy <1 year were excluded [23].

The groups described in this study were defined as follows: the rhythm control group consisted of patients receiving rhythm control therapy, including patients receiving rate control therapy; the rate control group consisted of patients receiving rate control therapy only; and the no antiarrhythmic agent group consisted of patients who were not receiving rhythm control or rate control therapy. Patients with unknown concomitant medications other than anticoagulants at the time of enrollment were not included in the subgroups.

Data collection

Data on patient background characteristics (including demographics, medical history including AF, type of AF, and treatment decisions), type of anticoagulant use, and use of other concomitant drugs were recorded as part of the registry [23]. Follow-up data were collected at 12 and 24 months.

The types of AF were defined as follows: paroxysmal AF was defined AF that returned to sinus rhythm within 7 days after onset; persistent AF was defined as AF that persisted beyond 7 days after onset, excluding AF classified as long-standing persistent; long-standing persistent AF was defined as AF sustained for more than 1 year after onset; and permanent AF was defined as AF that cannot be defibrillated electrically or pharmacologically.

Statistical analysis

Details of the sample size calculation and statistical analysis have been published previously [23]. Frequency tables were created for categorical variables, and summary statistics were calculated for continuous variables. For continuous variables, *p*-values were calculated using a two-sample *t*-test or analysis of variance. For categorical variables, the *p*-values were calculated using the chi-square test. However, unknown data were not included in the analysis. We considered a two-tailed *p*-value of less than 0.05 to indicate significance.

For the present analysis, patients were stratified into three groups: rhythm control agents, rate control agents alone, and no antiarrhythmic agent. The $CHADS_2$ [25] and CHA_2DS_2-VASc scores [26] were used to estimate embolic risk, and the HAS-BLED score [27] was used to evaluate bleeding risk, according to treatment strategy. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Tokyo, Japan).

Results

Patient characteristics

Table 1 summarizes the characteristics of the subanalysis population. The total population analyzed included 32,490 patients. There was a statistically significant difference in the sex distribution, with 57.3 % male patients. Overall, patients had a mean age of 81.5 years, and a mean body mass index (BMI) of 23.3 kg/m^2. The majority (93.4 %) of the patient population was between 75 and 89 years of age, and only 6.6 % were ≥90 years of age. The mean blood pressure of patients in this subanalysis was within the normal range (127.3/70.6 mmHg). Significant differences were noted in age, weight, height, BMI, and blood pressure. Paroxysmal AF was the most common AF type recorded, occurring in 42.0 % of patients. The remaining patients had persistent AF (16.6 %), long-standing persistent AF (13.5 %), or permanent AF (27.9 %). Overall, 43.4 % of patients were not receiving antiarrhythmic therapy, 36.9 % were receiving rate control therapy, and 19.6 % were receiving rhythm control therapy.

When analyzing the patient characteristics by therapy group, we observed significant differences in the distribution of age between the rhythm control and rate control groups, and between the rhythm control and no arrhythmic agent groups. There were significantly more patients (44.2 %) in the 75–79 years age group in the rhythm control group than in the rate control (38.8 %) and no antiarrhythmic agent groups (38.9 %). In the group aged 80–84 years, a similar proportion of patients were receiving rhythm control (34.0 %) and rate control (34.7 %) therapies, while a smaller proportion (33.2 %) was not receiving any antiarrhythmic agents. Slightly fewer patients in the age groups above 85 years received rhythm control therapy. In those age groups, patients generally received either no antiarrhythmic agent or rate control therapy (Table 1).

Table 1
Patient characteristics for the overall study population and by type of therapy.

	Rhythm control	Rate control only	No antiarrhythmic agent	Total	*p*-value*
Patients	6369 (19.6)	12,005 (36.9)	14,116 (43.4)	32,490 (100)	
Male	3358 (52.7)	6620 (55.1)	8623 (61.1)	18,601 (57.3)	<0.0001
Age, years	80.8 ± 4.6	81.5 ± 4.8	81.7 ± 4.9	81.5 ± 4.8	<0.0001
Age					
75–79 years	2818 (44.2)	4657 (38.8)	5492 (38.9)	12,967 (39.9)	<0.0001
80–84 years	2167 (34.0)	4170 (34.7)	4685 (33.2)	11,022 (33.9)	
85–89 years	1091 (17.1)	2413 (20.1)	2848 (20.2)	6352 (19.6)	
90–94 years	261 (4.1)	667 (5.6)	936 (6.6)	1864 (5.7)	
95–99 years	32 (0.5)	91 (0.8)	151 (1.1)	274 (0.8)	
≥100 years	0 (0.0)	7 (0.1)	4 (0.0)	11 (0.0)	
Height, cm	157.0 ± 9.4	156.8 ± 9.6	157.7 ± 9.5	157.2 ± 9.5	<0.0001
Weight, kg	57.4 ± 10.7	57.4 ± 11.3	58.3 ± 11.2	57.8 ± 11.2	<0.0001
Weight					<0.0001
<60 kg	3418 (53.7)	6552 (54.6)	7035 (49.8)	17,005 (52.3)	
≥60 kg	2408 (37.8)	4548 (37.9)	5682 (40.3)	12,638 (38.9)	
Unknown	543 (8.5)	905 (7.5)	1399 (9.9)	2847 (8.8)	
Body mass index, kg/m^2	23.2 ± 3.4	23.3 ± 3.6	23.4 ± 3.6	23.3 ± 3.6	0.0018
Creatinine clearance, mL/min	49.3 ± 17.5	47.3 ± 26.4	49.1 ± 18.6	48.4 ± 21.8	
Systolic blood pressure, mmHg	128.2 ± 16.6	125.8 ± 17.1	128.2 ± 17.1	127.3 ± 17.0	<0.0001
Diastolic blood pressure, mmHg	69.6 ± 11.0	70.6 ± 11.9	71.2 ± 11.6	70.6 ± 11.6	<0.0001
Type of atrial fibrillation					
Paroxysmal	5034 (79.0)	3355 (27.9)	5250 (37.2)	13,639 (42.0)	<0.0001
Persistent	624 (9.8)	1951 (16.3)	2806 (19.9)	5381 (16.6)	
Long-standing persistent	285 (4.5)	2065 (17.2)	2049 (14.5)	4399 (13.5)	
Permanent	426 (6.7)	4634 (38.6)	4011 (28.4)	9071 (27.9)	
Comorbidities/medical history	6195 (97.3)	11,727 (97.7)	13,684 (96.9)	31,606 (97.3)	0.0011
Hypertension	4775 (75.0)	8953 (74.6)	10,747 (76.1)	24,475 (75.3)	0.0111
Diabetes mellitus	1443 (22.7)	3493 (29.1)	3814 (27.0)	8750 (26.9)	<0.0001
Dyslipidemia	2938 (46.1)	5177 (43.1)	5700 (40.4)	13,815 (42.5)	<0.0001
Hyperuricemia	1126 (17.7)	3168 (26.4)	3084 (21.8)	7378 (22.7)	<0.0001
Kidney disease	1332 (20.9)	3266 (27.2)	3009 (21.3)	7607 (23.4)	<0.0001
Severe hepatic dysfunction	46 (0.7)	107 (0.9)	146 (1.0)	299 (0.9)	0.0879
Respiratory disease	808 (12.7)	1589 (13.2)	1767 (12.5)	4164 (12.8)	0.2105
Cardiac disorders	3430 (53.9)	7994 (66.6)	7687 (54.5)	19,111 (58.8)	<0.0001
Cerebrovascular disorders	1191 (18.7)	2665 (22.2)	3501 (24.8)	7357 (22.6)	<0.0001
Other vascular disorders	327 (5.1)	693 (5.8)	710 (5.0)	1730 (5.3)	0.0216
Thromboembolic disorders	495 (7.8)	1002 (8.3)	1284 (9.1)	2781 (8.6)	0.0042
Hyperthyroidism	88 (1.4)	196 (1.6)	197 (1.4)	481 (1.5)	0.2198
Gastrointestinal disease	1955 (30.7)	3468 (28.9)	4101 (29.1)	9524 (29.3)	0.0249
Primary malignancy	689 (10.8)	1270 (10.6)	1600 (11.3)	3559 (11.0)	0.1388
Dementia	345 (5.4)	950 (7.9)	1258 (8.9)	2553 (7.9)	<0.0001

Data are shown as mean ± standard deviation or n (%).
* Two-tailed tests were used. "Unknown" was excluded from the calculation.

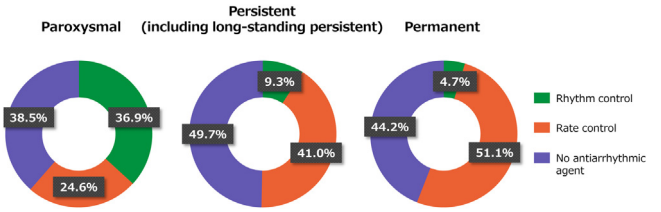

Fig. 1. Distribution of antiarrhythmic therapy by type of atrial fibrillation (AF): (**A**) Paroxysmal AF; (**B**) Persistent AF (including long-standing persistent); (**C**) Permanent AF.

When analyzing the clinical characteristics by type of AF, we also noted significant differences between the type of antiarrhythmic therapy groups. In patients who received rhythm control therapy, paroxysmal AF was the most common type, while permanent and persistent AF were the most common types of AF among patients who received rate control therapy. Among patients in the rhythm control, rate control, and no antiarrhythmic therapy groups, there were significant differences in positive medical history or comorbidities ($p = 0.0011$), the most common comorbidities being hypertension, cardiac disorders, and dyslipidemia, followed by diabetes mellitus, kidney disease, and hyperuricemia. Overall, between 7.8 % and 9.1 % of patients had thromboembolic disorders.

Antiarrhythmic therapy

In patients with paroxysmal AF, treatment was broadly split between the rhythm control (36.9 %), rate control (24.6 %), and no antiarrhythmic therapies (38.5 %; Fig. 1). In patients with persistent or permanent AF, few patients (<10 % in either group) received the rhythm control strategy; rate control treatment was received by slightly fewer than half (41.0 %) of patients with persistent AF, and slightly more than half of the patients (51.1 %) with permanent AF, with the remainder receiving no antiarrhythmic therapy.

In general, the most frequently prescribed antiarrhythmic drugs for rhythm control therapy were pilsicainide, cibenzoline, and propafenone, among others, and the most frequently prescribed drugs for rate control therapy were β-blockers, such as bisoprolol and carvedilol. These antiarrhythmic drugs were generally prescribed at the standard doses according to the current treatment guidelines [7–9].

Fig. 2 summarizes the results showing the type of antiarrhythmic therapy by risk score ($CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED). The distributions significantly differed among the three therapy groups ($p < 0.0001$). For embolic risk scores ($CHADS_2$ and CHA_2DS_2-VASc), more patients in the rhythm control therapy group had lower scores (1, 2, or 3) ($p < 0.0001$, each). In contrast, more patients in the rate control group had higher scores (>4) ($p < 0.0001$). Regarding HAS-BLED, the rhythm control therapy group had lower bleeding risk scores (e.g. a score of 1) ($p < 0.0001$).

Anticoagulant therapy

The proportion of patients receiving anticoagulant therapy was 94.8 % in the rate control group, 89.2 % in the rhythm control group, and 91.0 % in the no antiarrhythmic therapy group (Fig. 3). In total, 92.1 % of elderly Japanese AF patients were receiving anticoagulant therapy.

The frequency of DOAC use was similar (~66 %) among the three groups (i.e. rate control, rhythm control, and no antiarrhythmic therapy groups) (Fig. 3). In terms of DOAC use, the type of AF did not seem to affect the physician's decision. The rate of off-label underdosage ranged from 0.0 % to 28.9% (each DOAC) and that for off-label overdosage was 2.3% to 7.6% (each DOAC) (data not shown). Regarding the use of warfarin, more patients in the rate control group (28.6 %) were being treated with warfarin than those in the rhythm control group (21.6 %) ($p < 0.0001$).

Discussion

This was a subanalysis of a large observational study, the ANAFIE registry, which aimed to assess the status of anticoagulant therapy in a population of elderly patients (≥75 years of age) and to analyze the patterns of anticoagulant use in subgroups based on the type of antiarrhythmic therapy received. To our knowledge, the ANAFIE registry is the first observational study targeting elderly NVAF patients – a population for which better data are required to inform evidence-based care.

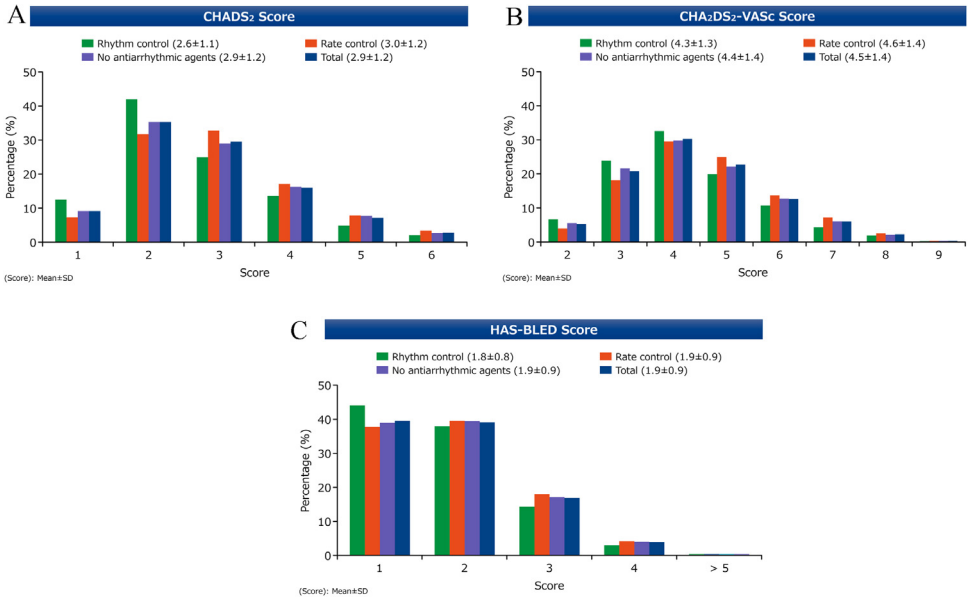

Fig. 2. Type of antiarrhythmic therapy by risk score: (**A**) $CHADS_2$; (**B**) CHA_2DS_2-VASc; (**C**) HAS-BLED.
SD, standard deviation

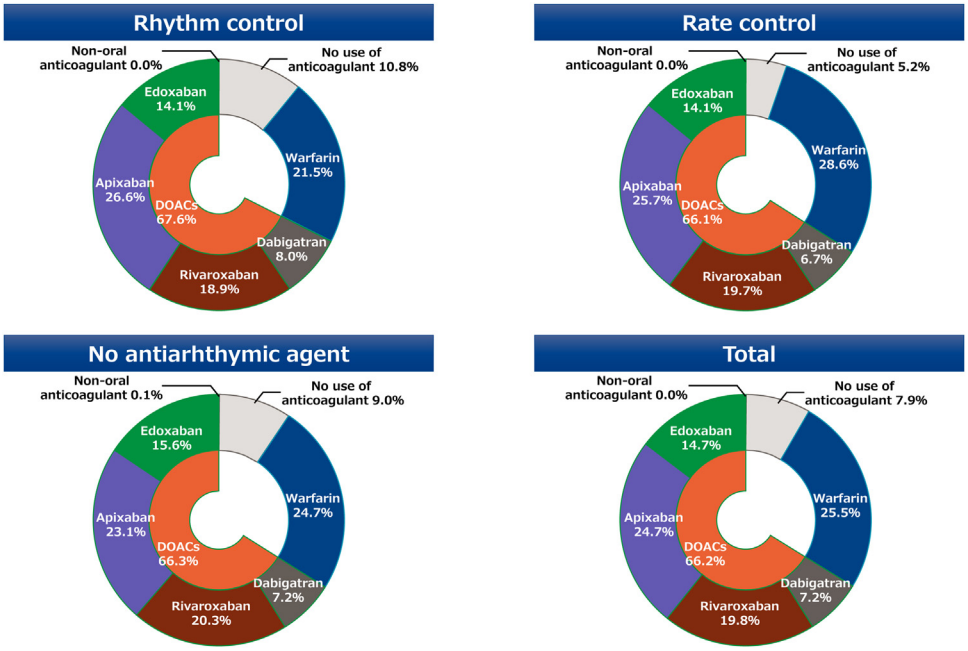

Fig. 3. Distribution of anticoagulant therapy by treatment type.
DOAC, direct-acting oral anticoagulant.

Overall frequencies of AF by type were 42.0 % (paroxysmal), 30.1 % (persistent and long-standing persistent), and 27.9 % (permanent) in the present study. The RealiseAF international registry [28] is a large-scale, international, cross-sectional survey that analyzed 9816 patients with AF. The relative frequencies by AF type in the RealiseAF international registry were 26.5 %, 23.8 %, and 49.6 %, respectively [28]. In this analysis, statistically significant differences were obtained among the three groups for various factors, but these differences were likely attributable to the large number of patients analyzed; thus, most differences noted were not clinically remarkable. However, clinically relevant differences were found in the three management strategy groups for age and type of AF ($p < 0.0001$, each). We observed that the rate control group consisted mainly of patients with persistent (16.3 %) and permanent AF (38.6 %). In contrast, the rhythm control group consisted mainly of patients with paroxysmal AF (79.0 %).

Regarding management strategies, it is notable that over 40 % of patients in the studied population were not receiving antiarrhythmic therapy, while ~37 % and ~20 % were receiving rate control and rhythm control therapy, respectively. When analyzing the treatment strategy by type of AF, among patients with paroxysmal AF, nearly 40 % were not receiving antiarrhythmic therapy, while ~37 % of patients with this type of AF were receiving rhythm control treatment, and ~25 %, were receiving rate control treatment. It is noteworthy that among patients with persistent or permanent AF, between 40 % and 51 % were receiving rate control. In contrast, the RealiseAF international registry reported that >80 % of patients received at least one antiarrhythmic drug. Another relevant difference with the RealiseAF registry is that more than 50 % of patients in that registry had undergone rhythm control [28].

In the present analysis, patients in the rhythm control therapy group had significantly lower embolic risk scores (CHADS2 and CHA2DS2-VASc) and bleeding scores (HAS-BLED) compared with the other groups, while patients in the rate control group had higher embolic risk scores ($p < 0.0001$). Regarding the risk of embolism, generally, persistent and permanent AF are associated with a higher risk of stroke or systemic embolism compared with those with paroxysmal AF [29]. This is likely the reason why the rate control group had the highest proportion of patients receiving anticoagulant therapy. In the rate control group, compared with the other treatment groups, a significantly greater proportion of patients (28.6 %) was receiving warfarin ($p < 0.0001$). This is likely attributable to the patients with permanent AF in this group, as they probably started receiving anticoagulation therapy much earlier than other patients. These findings are in line with those reported in the RealiseAF registry study, in which patients with persistent and permanent AF also had the highest percentages of anticoagulant use (54.4 % and 59.0 %, respectively, vs 37.7 % for paroxysmal AF) [28].

In recent years, there has been a shift in management strategies, with rate control strategies in AF being used more commonly than rhythm control strategies [30]. Although pooled data suggest that the rate and rhythm control strategies result in similar clinical outcomes [31], there is currently a lack of evidence to support the choice between rate or rhythm control strategies in elderly AF patients. Patient-specific factors, such as comorbidities, drug tolerance, and cost issues, should be considered when choosing one strategy over another [31–33]. In the present subanalysis, a larger proportion of elderly Japanese patients (aged ≥85 years) were receiving rate control (37.4 %) than rhythm control therapy (16.3 %), suggesting that age should be another factor to consider when choosing between rhythm and rate strategies to treat AF. In the AFFIRM study [10] and a recent meta-analysis of 12 studies [33] comparing rate vs rhythm strategies, it was reported that rhythm control was associated with a higher hospitalization rate. Further, in the AFFIRM study [10], there were also more adverse events associated with rhythm control.

Termination of anticoagulant therapy after restoration of sinus rhythm in patients treated with a rhythm control strategy could contribute to increased risk of thromboembolic events [10,13]. In this study, we did not observe any differences in anticoagulant use between patients managed using rate or rhythm control. Further, there was no difference among the three therapies regarding the frequency of DOAC use, and the type of AF did not seem to affect the physician's decision regarding DOAC use. Effective anticoagulant

therapy in AF is strongly recommended in the current guidelines [7,8,34–36] as it has been shown to reduce stroke risk and mortality [37–41]. Notably, only a small proportion of patients (<10 %) in this analysis was not receiving any anticoagulant therapy, and it is encouraging to observe high levels of anticoagulant use in elderly Japanese patients with AF. Despite the high costs associated with DOACs, we consider that DOAC use will continue to increase in the future, particularly in elderly AF patients, as it has fewer usage restrictions than warfarin.

This study had several limitations, which mainly relate to the observational, registry-based design, with no randomization to treatment or patient groups. Additionally, cardiac rhythm data, including ablation, at the time of enrollment, were not collected. For persistent AF, there were cases with sinus rhythm and cases of sustained AF, but the treatment in each case was not considered. However, the population studied is representative of routine clinical practice; therefore, the current findings are likely to have good external validity. Extrapolation of results to different populations should be done with caution because the healthcare setting in which patients were treated in Japan may differ from that in other countries. Furthermore, there is the potential for underreporting of data and outcomes if a patient leaves the registry or is not adequately followed up.

Conclusions

Use versus non-use and type of antiarrhythmic therapy varied significantly between the patient subgroups based on age, stroke risk scores, type of AF, and DOAC use. Overall, we observed high levels of anticoagulant use among elderly Japanese patients with AF. The highest proportion of patients on anticoagulant therapy was in the subgroup receiving rate control therapy.

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Disclosure of interest

HY has no conflicts of interest to declare; HI 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, and remuneration from Daiichi Sankyo, Bayer, Pfizer Japan, Bristol-Myers Squibb, and Ono Pharmaceutical; MA received research funding from Bayer, and Daiichi Sankyo, and remuneration from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer, and Daiichi Sankyo; HA received remuneration from Daiichi Sankyo; YK received remuneration from Daiichi Sankyo, Bayer, and Nippon Boehringer Ingelheim; KO received remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and Medtronic; WS received research funding from Bristol-Myers Squibb, Daiichi Sankyo, and Nippon Boehringer Ingelheim, and patent royalties/licensing fees from Daiichi Sankyo, Pfizer Japan, Bristol-Myers Squibb, Bayer, and Nippon Boehringer Ingelheim; HT received research funding from Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, and IQVA services Japan, remuneration from Daiichi Sankyo, Bayer, Nippon Boehringer Ingelheim, Pfizer Japan, Otsuka Pharmaceutical, and Mitsubishi Tanabe Pharma, scholarship funding from Daiichi Sankyo, Mitsubishi Tanabe Pharma, and Teijin Pharma, and consultancy fee from Novartis Pharma, Pfizer Japan, Bayer, Nippon Boehringer Ingelheim, and Ono Pharmaceutical; KT received remuneration from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim; AH participated in a course endowed by Boston Scientific Japan, and has received research funding from Daiichi Sankyo and Bayer, and remuneration from Bayer, Daiichi Sankyo, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Sanofi, Astellas Pharma, Sumitomo Dainippon Pharma, Amgen Astellas BioPharma, and AstraZeneca, and patent royalties/licensing fees from Toa Eiyo M; MY received research funding from Nippon Boehringer Ingelheim, and remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Bayer, Bristol-Myers Squibb, Pfizer Japan, and CSL Behring; T Yamaguchi acted as an advisory board member of Daiichi Sankyo, and received remuneration from Daiichi Sankyo, and Bristol-Myers Squibb; ST received research funding from Nippon Boehringer Ingelheim and remuneration from Daiichi Sankyo; TK has stock and is an employee of Daiichi Sankyo; JK and AT are employees of Daiichi Sankyo; and TI has received research grants from Daiichi Sankyo, Medtronic Japan, and Japan Lifeline and honoraria from Ono Pharma, Bayer Yakuhin, Daiichi Sankyo, Bristol-Myers Squibb, and Pfizer. Additionally, TI was a member of the advisory board for Bayer Yakuhin, Bristol-Myers Squibb, and Daiichi Sankyo.

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