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Original Article

Major determinants for the selecting antithrombotic therapies in patients with nonvalvular atrial fibrillation in Japan (JAPAF study)

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ABSTRACT

Background: Oral anticoagulants (OACs) can help prevent stroke in patients with nonvalvular atrial fibrillation (NVAF). The aim of this study was to characterize the use of OACs other than direct thrombin inhibitors (DTIs) for NVAF.

Methods: Patients with NVAF taking antithrombotics other than DTIs were enrolled in this cross-sectional study. Patient demographics and medication history were collected, and the patients were classified as taking antiplatelet monotherapy (AP), anticoagulant monotherapy (AC), or combination therapy (AP+AC). OAC users were also stratified as naïve (N; initiated within 6 months), switcher (S; switched within 6 months), or prevalent user (P; continued for >6 months).

Results: A total of 3053 patients (AP, 216; AC, 2381; AP+AC, 456) from 268 sites were enrolled from 2012 to 2013. Significant differences were observed in $CHADS_2$ scores (AP/AC/AP+AC: 2.0/2.1/2.7, $P<0.0001$), angina complications (20.1/8.6/32.1, $P<0.0001$), myocardial infarction (5.1/2.8/18.1, $P<0.0001$), prothrombin time–international normalized ratio (PT–INR) ($-$/2.00/1.94, $P=0.0350$), and others. There were 2831 OAC users (N, 328; S, 213; P, 2290). Significant differences were observed in history of bleeding (N/S/P: 2.4/9.4/4.5, $P<0.001$), PT–INR (1.83/2.01/2.00, $P<0.0001$), and others.

Conclusions: Patients taking AP+AC had higher $CHADS_2$ scores than those taking an AP or AC alone. Additionally, the combination therapy (AP+AC) was preferred in patients with cardiovascular comorbidity. Changes in AC regimens were not influenced by $CHADS_2$ scores or complications but influenced by history of bleeding. These characteristics were thus identified as major factors affecting the selection of antithrombotic regimens other than DTIs in patients with NVAF.

1. Introduction

The prevalence of atrial fibrillation (AF) increases with aging in Japan [1]. An epidemiological survey conducted by the Japanese Circulation Society indicated that the prevalence of AF was gradually increasing, and estimated a prevalence rate of 0.79% by 2020 [2]. The results of cohort-based [3] and community-based [4] surveys showed that the prevalence of AF in Japan is already $>1\%$.

AF is an important risk factor for stroke. The incidence of stroke in patients with nonvalvular AF (NVAF) was reported to be about 5% per year, and 2- to 7-fold higher than in the population without AF [5,6]. The result of a Japanese study indicated that, among 15,831 patients hospitalized with acute cerebral infarction, AF was observed in 3335 patients, 78.4% of whom were found to have cardiogenic embolism [7]. Medical treatment in patients with AF should thus also be targeted at preventing cerebral thrombosis/embolism, as well as other types of embolisms.

Antithrombotic treatment is important for preventing stroke in patients with NVAF, and warfarin and anticoagulants have been the recommended treatments; additionally, aspirin and antiplatelet preparations have been acceptable. The Japanese Guidelines for Treatment of Stroke 2009 [8] recommended warfarin for managing NVAF patients with more than two risk factors (congestive heart failure, hypertension, age >75 years, or diabetes mellitus), whereas antiplatelet preparations are acceptable in patients with contraindications to warfarin. Additionally, the latest Japanese Guidelines for Pharmacotherapy of Atrial Fibrillation [9] addressed the importance of many risk factors when selecting suitable antithrombotic drug therapies such as warfarin, in accordance with the severity of the risk.

In March 2011, the new oral direct thrombin inhibitor (DTI) dabigatran, with a novel mechanism of action, was introduced on the market [10], and a new drug application for the factor Xa inhibitor rivaroxaban was filed in 2011. These drugs are superior,

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or at least not inferior, to warfarin in terms of efficacy and safety [11,12], and are therefore likely to change the standard of antithrombotic therapy in the near future.

The aim of this cross-sectional study was to investigate the relationships between patient characteristics and antithrombotic therapy prescribed for the prevention of ischemic stroke and systemic embolism in patients with NVAF in clinical practice. Additionally, because the data were to be used to compare with the characteristic data of postmarketing surveillance (PMS) for dabigatran by Nippon Boehringer Ingelheim [13], which was performed in parallel to this study, patients prescribed with dabigatran were excluded from this study.

2. Material and methods

This was a cross-sectional study carried out to investigate the characteristics, treatments, and pathological backgrounds of patients with NVAF treated for the prevention of ischemic stroke. Surveillance was performed from October 2011 to March 2014 (entry of patients: April 2012 to December 2013) at 268 medical sites that participated in the PMS for dabigatran throughout Japan. Patients with NVAF who received antithrombotic treatments to prevent ischemic stroke were registered. Site investigators collected the patient data from medical records at the first visit after registration.

2.1. Subjects

Adult patients with AF, regardless of sex, complications, hospitalization, or medical history, who received antithrombotic treatment to prevent a cerebrovascular ischemic attack, were enrolled in this study. The exclusion criteria were (i) patients who received artificial valve replacement, (ii) those with valvular disease, (iii) those with DTI preparation (dabigatran) use, and (iv) those without antithrombotic treatment.

2.2. Surveillance method

Patient characteristics, AF history and characteristics, comorbidity, and history of antithrombotic treatment were obtained from medical records and transcribed into an electrical case report by the site investigators. The collected characteristics included sex, date of birth, body weight, height, smoking history, and alcohol consumption. The AF history and characteristics included onset date, symptomatic or asymptomatic status, type of AF, and treatment including surgical intervention. Comorbidity included congestive heart failure, hypertension, diabetes mellitus, stroke, transient ischemic attack (TIA), systemic embolism, pulmonary embolism, peripheral artery diseases (arteriosclerosis obliterans, chronic arterial occlusion), dyslipidemia (hyperlipidemia), angina pectoris, myocardial infarction (MI), valvular disease, renal dysfunction including impaired creatinine clearance calculated by using the Cockcroft–Gault method [14], hepatic diseases, dementia, and bleeding events. Information was collected on current antithrombotic treatments and withdrawn treatments before this study. The start and end dates of administration, dosage of anticoagulant (warfarin, dabigatran, rivaroxaban, heparin, other non-oral anticoagulant [non-OACs]), and antiplatelet preparations (aspirin, ticlopidine, cilostazol, clopidogrel, eicosapentaenoic acid ethylate, beraprost sodium, sarpogrelate hydrochloride, and others) were included. Details on concomitant use of angiotensin II receptor blockers (ARB), angiotensin-converting enzyme inhibitors, beta-blockers, antihypertensives, insulin, oral hypoglycemics, and statins were also collected. The prothrombin time–international normalized ratio (PT–INR) within 3 months before visit was recorded for patients treated with warfarin, if available. The study protocol and provision of information to participants were carried out in line with the ethical guidelines for epidemiological research (established by the Ministry of Health, Labour, and Welfare in Japan) and approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (September 28, 2011; no. E1220). No medical intervention and no biological specimens from human subjects were specified in this study; therefore, verbal and/or anonymized information and consent were acceptable, as well as written informed consent. This study was registered to UMIN Clinical Trial Registry (no. 000009644).

2.3. Statistical analysis

For primary analysis, we classified the patients according to their antithrombotic regimen: antiplatelet monotherapy (AP), anticoagulant monotherapy (AC), and concomitant use of antiplatelet and anticoagulant (AP+AC). Patient characteristics, AF history and characteristics, comorbidity, and history of antithrombotic treatment were tabulated for each group and compared among the three groups. The measured values and order values are shown as means and standard deviations (SDs) in the tables, and P values were calculated by using ANOVA adjusted by sex and age, in 10-year steps. Nominal scale values are shown as frequencies and proportions, and P values were calculated by using the Cochran–Mantel–Haenszel method adjusted by sex and age. The pair-wise test for the factor with a statistical difference among the three groups was performed under a closed testing procedure as adjusted for multiplicity. Multivariate analysis was performed through multiple multinomial logit analysis with the above items as independent variables, and variable selection in the model by using a stepwise method.

Additionally, we further classified patients taking OACs (AC and AP+AC) into the following three groups: naïve (N) patients with an OAC regimen initiated within 6 months before the observation date and not changed; switchers (S), in whom OACs were changed within 6 months before the observation date; and prevalent users (P), who continued the use of the same OAC for >6 months before the observation date. We also classified patients taking OACs into warfarin users and rivaroxaban users, for reference. The patient distribution in the treatment history of OACs was also compared by using the analysis methods. A two-sided P value of ≤ 0.05 was considered significant. The statistical analysis was performed by using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Primary analysis

A total of 3138 patients from 274 medical sites were initially registered to this study. Eighty-five patients were ineligible because of not meeting the inclusion or exclusion criteria: patients with no antithrombotic treatment ($n=17$), with dabigatran treatment ($n=4$), with mitral valve stenosis ($n=21$) and those who underwent mitral valve replacement ($n=46$; 10 patients with mitral valve stenosis), with no detailed information on OACs ($n=1$), with input error ($n=5$), and with duplicated case registration ($n=1$). The remaining 3053 patients included 216 (7.1%) in the AP group, 2381 (78.0%) in the AC group, and 456 (14.9%) in the AP+AC group. The main antithrombotic regimens were warfarin ($n=2523$; mean $\pm$ SD daily dose: 2.70 ± 1.10 mg), aspirin ($n=479$, 99.5 ± 13.9 mg), rivaroxaban ($n=311$, 12.2 ± 2.5 mg), clopidogrel ($n=122$, 71.9 ± 8.2 mg), and cilostazol ($n=59$, 152.6 ± 56.8 mg).

ARBs ($n=1391$), beta-blockers ($n=1145$), statins ($n=873$), or antiarrhythmic drugs ($n=794$) were administered concomitantly

Table 1
Antithrombotic and other drugs at the observation point.

	Antithrombotic drugs						Total	
	AP		AC		AP+AC			
	n[a]	Dose[b]	*n*[a]	Dose[b]	*n*[a]	Dose[b]	*n*[a]	Dose[b]
Total	216		2381		456		3053	
Antithrombotic drugs								
Warfarin	–		2095 (88.0)	2.71 ± 1.11	428 (93.9)	2.64 ± 1.07	2523 (82.6)	2.70 ± 1.10
Rivaroxaban	–		283 (11.9)	12.3 ± 2.5	28(6.1)	11.4 ± 2.3	311 (10.2)	12.2 ± 2.5
Heparin	–		2 (0.1)				2 (0.1)	
Other non-oral anticoagulant	–		6 (0.3)				6(0.2)	
Aspirin	150 (69.4)	99.8 ± 10.8	–		329 (72.2)	99.3 ± 13.9	479 (15.7)	99.5 ± 13.0
Ticlopidine	6 (2.8)	150.0 ± 54.8	–		23 (5.0)	173.9 ± 44.9	29 (0.9)	169.0 ± 47.1
Cilostazol	12 (5.6)	154.2 ± 58.2	–		47 (10.3)	152.2 ± 57.0	59 (1.9)	152.6 ± 56.8
Clopidogrel	43 (19.9)	70.4 ± 9.8	–		79 (17.3)	72.8 ± 7.2	122 (4.0)	71.9 ± 8.2
Antihypertensive drugs	160 (74.1)		1759 (73.9)		365 (80.0)		2284 (74.8)	
ARBs	89 (41.2)		1078 (45.3)		224 (49.1)		1391 (45.6)	
ACEIs	16 (7.4)		204 (8.6)		41 (9.0)		261 (8.5)	
Beta-blockers	66 (30.6)		901 (37.8)		178 (39.0)		1145 (37.5)	
Antiarrhythmic drugs	53 (24.5)		628 (26.4)		113 (24.8)		794 (26.0)	
Oral hypoglycemia	24 (11.1)		322 (13.5)		88 (19.3)		434 (14.2)	
Statin	69 (31.9)		618 (26.0)		186 (40.8)		873 (28.6)	

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy; ARBs, angiotensin II receptor blockers; ACEIs, angiotensin-converting enzyme inhibitors.

[a] Data are *n* (%).

[b] Doses are in mg/day; mean ± SD.

Table 2
Characteristics of patients according to regimen.

	AP		AC		AP+AC		*P*-value[a]	Total	
	n	%	n	%	n	%		n	%
Total	216		2381		456			3053	
Sex									
Male	150	69.4	1540	64.7	327	71.7	0.0005	2017	66.1
Female	66	30.6	841	35.3	129	28.3		1036	33.9
Age (years)									
Mean (SD)	74.1 (9.9)		73.7 (9.7)		75.9 (7.9)		< 0.0001	74.1 (9.5)	
< 65	34	15.7	404	17.0	37	8.1	< 0.0001	475	15.6
65– < 75	78	36.1	874	36.7	181	39.7		1133	37.1
75–	104	48.1	1103	46.3	238	52.2		1445	47.3
Body weight (kg)									
Mean (SD)	60.9 (12.1)		61.1 (12.4)		61.7 (11.7)		0.5751	61.2 (12.3)	
BMI (kg/m^2)									
Mean (SD)	23.6 (3.7)		23.7 (3.6)		23.9 (3.4)		0.3358	23.7 (3.6)	
Prevalence periods of AF (years)									
Mean (SD)	4.10 (3.36)		4.40 (3.12)		5.09 (3.29)		0.0054	4.48 (3.17)	
Type of AF									
Paroxysmal	80	37.0	788	33.6	132	30.0	0.0058	1000	33.3
Persistent	59	27.3	455	19.4	97	22.0		611	20.4
Permanent	77	35.6	1100	46.9	211	48.0		1388	46.3
Smoking history									
Nonsmoker	98	52.1	1323	62.5	215	55.4	0.0430	1636	60.8
Ex-smoker	76	40.4	610	28.8	137	35.3		823	30.6
Smoker	14	7.4	184	8.7	36	9.3		234	8.7
Alcohol consumption (g/week)									
None	90	49.5	1149	55.4	215	56.0	0.5478	1454	55.1
< 14	30	16.5	244	11.8	39	10.2		313	11.9
14– < 112	37	20.3	373	18.0	74	19.3		484	18.3
> 112	25	13.7	307	14.8	56	14.6		388	14.7

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy; AF, atrial fibrillation; BMI, body mass index.

[a] *P*-values were calculated by using the Cochran–Mantel–Haenszel test adjusted by sex and age for classification (sex, type of AF, smoking history, and alcohol history) and order (age) values, and ANOVA adjusted by sex and age for measured values (age, body weight, BMI, and prevalence periods of AF).

with antithrombotic drugs. The pharmacological regimens in each group are shown in Table 1.

3.1.1. *Patient characteristics*

The patient characteristics are shown in Table 2. There were significant differences in sex, age, smoking history, prevalence periods of AF, and type of AF among the three groups. According to the results of multiple multinomial logit analysis, the proportion of men was lower in the AC group than in the AP+AC group. The mean age was also lower in the AC group than in the AP+AC group (73.7 and 75.9 years, respectively). The mean prevalence period of AF was longer in the AP+AC group than in the AP or AC group (5.09, 4.10, and 4.40 years, respectively). The proportion of

permanent type of AF was higher in the AP+AC group than in the AP group. There were no significant differences in characteristics between the AP group and the AC group (Supplementary Table S1).

3.1.2. $CHADS_2$ and comorbidity

The mean $CHADS_2$ score in the AP+AC group (2.7 ± 1.4) was significantly higher than that in the AP group (2.0 ± 1.3) or AC group (2.1 ± 1.3) (Table 3). A total of 32.5% of patients had scores of 0 or 1, although only 20.8% of the patients in the AP+AC group had low scores. In contrast, a higher proportion of patients in the AP+AC group (27.1%) had scores ≥ 4 compared with the other two groups (12.1% in AP, 13.8% in AC). The results of multiple multinomial logit analysis excluded the six composite factors of the $CHADS_2$ score (age, heart failure, hypertension, diabetes, stroke, and TIA). The $CHADS_2$ score in the AP+AC group was statistically higher than that in the AP group or AC group (Supplementary Table S2).

The main comorbidity is also shown in Table 3. There were significant differences in comorbidity among the three groups, except in terms of pulmonary thromboembolism, hepatic insufficiency, and bleeding history. The prevalence rate of heart failure was significantly higher in the AP+AC group than in the AP group and the AC group, and higher in the AC group than in the AP group.

Table 3
$CHADS_2$ scores, comorbidity, creatinine clearance, and PT–INR according to regimen.

	AP		AC		AP+AC		*P*-value[a]	Total	
	n	%	*n*	%	*n*	%		*n*	%
Total	216		2381		456			3053	
$CHADS_2$ score									
Mean (SD)	2.0 (1.3)		2.1 (1.3)		2.7 (1.4)		<0.0001	2.2 (1.3)	
0	22	10.3	212	9.0	23	5.1	<0.0001	257	8.5
1	58	27.1	596	25.3	71	15.7		725	24.0
2	65	30.4	739	31.3	104	23.1		908	30.0
3	43	20.1	486	20.6	131	29.0		660	21.8
4	16	7.5	230	9.7	81	18.0		327	10.8
5	10	4.7	77	3.3	28	6.2		115	3.8
6	0	0.0	19	0.8	13	2.9		32	1.1
Comorbidity									
Heart failure	51	23.7	766	32.3	190	41.9	<0.0001	1007	33.1
Hypertension	160	74.1	1605	67.6	329	72.5	0.0328	2094	68.8
Diabetes	47	21.9	520	21.9	139	30.6	0.0007	706	23.2
Stroke	34	15.7	441	18.5	153	33.6	<0.0001	628	20.6
TIA	5	2.3	49	2.1	19	4.3	0.0127	73	2.4
Systematic thromboembolism	3	1.4	23	1.0	19	4.2	<0.0001	45	1.5
Pulmonary thromboembolism	1	0.5	5	0.2	4	0.9	0.0695	10	0.3
Deep vein thrombosis	0	0.0	17	0.7	11	2.4	0.0002	28	0.9
Peripheral artery diseases	16	7.5	64	2.7	63	14.1	<0.0001	143	4.7
Dyslipidemia	85	39.7	893	37.6	232	51.2	<0.0001	1210	39.8
Angina pectoris	43	20.1	204	8.6	146	32.1	<0.0001	393	12.9
Myocardial infarction	11	5.1	67	2.8	82	18.1	<0.0001	160	5.3
Hepatic insufficiency	13	6.0	200	8.4	37	8.1	0.4639	250	8.2
Renal insufficiency	25	11.8	429	18.8	112	25.7	0.0002	566	19.3
Bleeding history	8	3.7	103	4.3	28	6.2	0.3625	139	4.6
Creatinine clearance (mL/min)									
Mean (SD)	63.5 (27.6)		63.4 (25.9)		58.1 (23.7)		0.1080	62.7 (25.8)	
PT–INR									
Mean (SD)	–		2.00 (0.44)		1.94 (0.44)		0.0350	1.99 (0.44)	

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy; TIA, transient ischemic attack; PT–INR, prothrombin time–international normalized ratio.

[a] *P*-values were calculated by using the Cochran–Mantel–Haenszel test adjusted by sex and age for classification values, and ANOVA adjusted by sex and age for order ($CHADS_2$ score) and measured (creatinine clearance and PT–INR) values.

Table 4
Antiplatelet regimen at the point of a bleeding event and at the observational point.

Antithrombotic regimens on bleeding events	**Antithrombotic regimen at the observational point**						**Total**		Bowker's test
	AP		AC		AP+AC				
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
AP	0		5	(4.6)	3	(2.8)	8	(7.3)	*P*=0.2643
AC	3	(2.8)	68	(62.4)	8	(7.3)	79	(72.5)	
AP+AC	0		11	(10.1)	11	(10.1)	22	(20.2)	
Subtotal	3	(2.8)	84	(77.1)	22	(20.2)	109	(100.0)	
No antithrombotics	5	(3.6)	19	(13.7)	6	(4.3)	30	(21.6)	

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy.

The prevalence rates of stroke and MI were higher in the AP+AC group than in the AP group and the AC group. The prevalences of peripheral artery diseases and angina were lower in the AC group than in the AP+AC group or the AP group. The prevalence of renal sufficiency was lower in the AC group than in the AP+AC group or the AC group.

The prevalences of TIA and dyslipidemia were lower in the AC group than in the AP+AC group (Supplementary Table S2).

3.1.3. Bleeding events

A total of 139 bleeding events were reported, for which 109 patients were prescribed an antithrombotic regimen (Table 4). The regimens for bleeding events were AP monotherapy in 9 (7.3%), AC monotherapy in 79 (72.5%), and AP+AC therapy in 22 (20.2%) patients. AP monotherapy was changed to AC monotherapy in 5 patients and AP+AC in 3 patients at the observation point, whereas AC monotherapy was changed to AP monotherapy in 3 patients and AP+AC in 8 patients, and was continued in the remaining 68 patients. Among the 22 AP+AC patients, 11 continued and 11 discontinued the AP regimen. This switching of antithrombotic drugs was not significant in Bowker's test.

3.2. Subanalysis for OAC regimens

Among the 2837 patients in the AC and AP+AC groups, six were excluded from analysis because of monotherapy with non-OACs at the observation point. Among the remaining 2831 patients, there were 328 in the N group, 213 in the S group, and 2290 in the P group (Table 5). In the N group, 216 patients received warfarin and 112 received rivaroxaban (Table 7). In the P group, warfarin was administered in 2252 patients, rivaroxaban in 36 patients, and warfarin and rivaroxaban concomitantly in 3 patients. The regimens in the S group were rivaroxaban switched to warfarin in 4 patients, dabigatran to warfarin in 48 patients, warfarin to rivaroxaban in 91 patients, and dabigatran to rivaroxaban in 70 patients.

The patient characteristics, $CHADS_2$ scores, comorbidity, creatinine clearance, and PT–INR stratified to warfarin users ($n=2520$) and rivaroxaban users ($n=308$) are shown in Supplementary Table S3. There were significant differences in sex, body weight, smoking history, alcohol history, $CHADS_2$ score, prevalence periods, comorbidity (heart failure, hypertension, diabetes, peripheral artery diseases, and angina), and creatinine clearance.

3.2.1. Patient characteristics

There were significant differences in terms of sex, body weight, body mass index (BMI), prevalence period of AF, and type of AF among the three groups (Table 5). The results of multiple multinomial logit analysis showed that the proportion of female patients was higher in the N group than in the P group, BMI was higher in the P group than in the N or S group, and the proportion

Table 5
Characteristics of patients in the AC and AP+AC groups.

	N group		S group		P group		*P*-value[a]	Total	
	n	%	n	%	n	%		n	%
Total	328		213		2290			2831	
Sex									
Male	185	56.4	129	60.6	1549	67.6	< 0.0001	1863	65.8
Female	143	43.6	84	39.4	741	32.4		968	34.2
Age (years)									
Mean (SD)	74.0 (11.0)		74.0 (9.2)		74.1 (9.2)		0.3968	74.1 (9.4)	
< 65	66	20.1	31	14.6	343	15.0	0.7153	440	15.5
65– < 75	97	29.6	79	37.1	878	38.3		1054	37.2
> 75	165	50.3	103	48.4	1069	46.7		1337	47.2
Body weight (kg)									
Mean (SD)	58.5 (12.9)		59.7 (11.1)		61.8 (12.3)		0.0018	61.2 (12.3)	
BMI (kg/m^2)									
Mean (SD)	23.0 (3.7)		23.2 (3.4)		23.9 (3.6)		0.0008	23.7 (3.6)	
Prevalence period of AF (years)									
Mean (SD)	1.77 (2.78)		4.62 (3.11)		4.89 (3.01)		< 0.0001	4.50 (3.15)	
Type of AF									
Paroxysmal	119	36.7	65	30.8	733	32.7	< 0.0001	917	33.0
Persistent	98	30.2	30	14.2	424	18.9		552	19.9
Permanent	107	33.0	116	55.0	1085	48.4		1308	47.1
Smoking history									
Nonsmoker	182	63.4	117	63.6	1236	60.9	0.1077	1535	61.4
Ex-smoker	72	25.1	55	29.9	617	30.4		744	29.8
Smoker	33	11.5	12	6.5	175	8.6		220	8.8
Alcohol consumption (g/week)									
None	174	62.1	108	60.3	1079	54.2	0.2907	1361	55.5
< 14	30	10.7	23	12.8	229	11.5		282	11.5
14– < 112	45	16.1	31	17.3	371	18.6		447	18.2
> 112	31	11.1	17	9.5	313	15.7		361	14.7

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy; N, naïve (initiated within 6 months); S, switcher (switched within 6 months); P, prevalent user (continued for > 6 months); BMI, body mass index; AF, atrial fibrillation.

[a] *P* values were calculated by using the Cochran–Mantel–Haenszel test adjusted by sex and age for classification (sex, type of AF, smoking history, and alcohol history) and order (age) values, and ANOVA adjusted by sex and age for measured (age, body weight, BMI, and prevalence periods of AF) and order (age) values.

Table 6
$CHADS_2$ score, comorbidity, and creatinine clearance in the AC and AP+AC groups.

	N group		S group		P group		*P*-value[a]	Total	
	n	%	n	%	n	%		n	%
Total	328		213		2290			2831	
Risk classification ($CHADS_2$)									
Mean (SD)	2.1 (1.3)		2.2 (1.4)		2.2 (1.3)		0.4314	2.2 (1.3)	
0	24	7.3	24	11.3	187	8.3	0.3049	235	8.4
1	92	28.1	42	19.7	531	23.5		665	23.7
2	105	32.1	60	28.2	676	29.9		841	30.0
3	52	15.9	48	22.5	516	22.8		616	22.0
4	35	10.7	30	14.1	246	10.9		311	11.1
5	18	5.5	8	3.8	78	3.4		104	3.7
6	1	0.3	1	0.5	30	1.3		32	1.1
Comorbidity									
Heart failure	98	30.0	65	30.5	792	34.8	0.0539	955	33.9
Hypertension	224	68.3	150	70.4	1555	68.1	0.8048	1929	68.3
Diabetes	65	19.8	44	20.7	549	24.0	0.2425	658	23.3
Stroke	68	20.7	51	23.9	474	20.7	0.4406	593	21.0
TIA	8	2.5	5	2.3	55	2.4	0.9962	68	2.4
Systematic thromboembolism	3	0.9	5	2.3	34	1.5	0.4283	42	1.5
Pulmonary thromboembolism	0	0.0	0	0.0	9	0.4	0.3326	9	0.3
Deep vein thrombosis	3	0.9	1	0.5	24	1.1	0.5669	28	1.0
Peripheral artery diseases	20	6.2	4	1.9	103	4.6	0.0601	127	4.5
Dyslipidemia	107	32.8	92	43.8	922	40.4	0.0088	1121	39.8
Angina pectoris	29	8.9	20	9.4	301	13.2	0.0558	350	12.4
Myocardial infarction	12	3.7	5	2.4	132	5.8	0.0714	149	5.3
Hepatic insufficient	24	7.3	17	8.0	194	8.5	0.8300	235	8.3
Renal insufficient	51	16.4	36	17.1	453	20.7	0.0833	540	19.9
Dementia	30	9.1	9	4.2	129	5.6	0.0432	168	5.9
History of hemorrhage	8	2.4	20	9.4	103	4.5	0.0007	131	4.6
Creatinine clearance (mL/min)									
Mean (SD)	62.7 (26.7)		66.8 (20.6)		62.1 (26.0)		0.0694	62.7 (25.8)	

AP, antiplatelet monotherapy; AC, anticoagulant monotherapy; N, naïve (initiated within 6 months); S, switcher (switched within 6 months); P, prevalent user (continued for > 6 months); TIA, transient ischemic attack.

[a] *P*-values were calculated by using the Cochran–Mantel–Haenszel test adjusted by sex and age for classification values, and ANOVA adjusted by sex and age for order ($CHADS_2$ score) and measured (creatinine clearance) values.

Table 7
Daily doses of AC and PT–INR.

		N group	S group	P group	Total	*P*-value[a]
Daily dose of warfarin (mg)	*n*	216	53	2254	2523	0.0020
	Mean	2.44	2.47	2.73	2.70	
	SD	1.09	1.03	1.10	1.10	
PT–INR	*n*	198	52	2205	2455	< 0.0001
	Mean	1.83	2.01	2.00	1.99	
	SD	0.47	0.44	0.43	0.44	
Daily dose of rivaroxaban (mg)	*n*	112	161	38	311	0.2652
	Mean	12.50	11.96	12.50	12.22	
	SD	2.51	2.45	2.53	2.49	

AC, anticoagulant monotherapy; N, naïve (initiated within 6 months); S, switcher (switched within 6 months); P, prevalent user (continued for > 6 months); PT–INR, prothrombin time–international normalized ratio.

[a] *P* values were calculated by using ANOVA adjusted by sex and age for measured values.

of persistent/paroxysmal AF types was higher in the N group than in the P group.

3.2.2. $CHADS_2$ and comorbidity

The $CHADS_2$ scores were similar in all three groups (Table 6). In terms of comorbidity, the rate of dyslipidemia, dementia, and bleeding history were significant among the three groups. In the results of multiple multinomial logit analysis, the prevalences of heart failure and angina were significantly lower in the N group than in the P group, peripheral artery diseases were significantly higher in the N group than in the P or S group, and bleeding history was higher in the S group than in the P or N group (Supplementary Table S4).

3.2.3. Daily dose of anticoagulants and PT–INR

The mean (± SD) daily doses of warfarin were 2.44 ± 1.09 mg in the N group, 2.47 ± 1.03 mg in the S group, and 2.73 ± 1.10 mg in the P group ($P=0.002$), whereas the daily doses of rivaroxaban were 12.50 ± 2.51, 11.96 ± 2.45, and 12.50 ± 2.53 mg, respectively ($P=0.2652$). The mean (± SD) PT–INR values were only measured in patients receiving warfarin, and were 1.83 ± 0.47 in the N group, 2.01 ± 0.44 in the S group, and 2.00 ± 0.43 in the P group ($P<0.0001$) (Table 7).

4. Discussion

The patient characteristics, $CHADS_2$, and comorbidity in the current study population were similar to those in other Japanese reports [4,15], suggesting that the sample well reflected the Japanese AF population. We investigated the differences in characteristics, $CHADS_2$, and comorbidity among patients prescribed the AP, AC, and AP+AC regimens, to identify the factors determining the choice of regimen. Antithrombotic treatment for patients with NVAF is generally based on anticoagulant preparations, especially warfarin. In this study, there were significant differences in sex, age, smoking history, prevalence period of AF, type of AF, $CHADS_2$

scores, and most comorbidities among the three regimens. Specifically, the proportion of male patients, age, and the prevalence periods of AF were higher in the AP+AC group than in the AC group in multiple analysis. Additionally, the prevalence periods of AF and the ratio of permanent/paroxysmal AF types were higher in the AP+AF group than in the AP group. In contrast, there were no differences between the two monotherapy groups. These results suggest that patient characteristics are not the factors for selecting AP or AC monotherapy, but are the factors for adding a combination drug. The average and the classification of the $CHADS_2$ scores are also significant among the three groups. In the AP+AC group, the $CHADS_2$ score was higher than that in the AP group or the AC group; nevertheless, there were no differences between the AP group and the AC group. The comorbidity of cardiovascular risk factors (heart failure, hypertension, stroke, TIA, systematic thromboembolism, pulmonary thromboembolism, deep vein thrombosis, peripheral artery diseases, angina, and MI) were significant among the three groups. The prevalence rates of heart failure and MI were higher in the AP+AC group than in the AP group, and heart failure, stroke, TIA, peripheral artery diseases, dyslipidemia, angina, and MI were higher in the AP+AC group than in the AC group. On the other hand, AP monotherapy was higher in the treatment of peripheral artery diseases and angina than AC monotherapy. These findings suggest that combination therapy is preferentially adopted in AF complicated by other diseases with thrombotic risk. AP monotherapy was adopted in comorbidities caused by atherosclerosis such as angina. These results show that practitioners prescribe antithrombotic agents in line with the recommendations in the cardiovascular guidelines for stroke, MI, AF, and antithrombotic treatment for cardiovascular diseases [8,9,16,17].

We performed a secondary analysis to investigate the common use of OACs. Warfarin (n=2520) and rivaroxaban (n=308) were administered. There were significant differences in factors such as sex, $CHADS_2$ score, heart failure, hypertension, diabetes, and angina and creatinine clearance. These results show that rivaroxaban is prescribed in AF patients with lower risks rather than warfarin. We stratified all patients with anticoagulant treatment into the N, S, and P groups. These results showed a high proportion of women (43.6%) among the naïve patients compared with those in other reports [7,15], suggesting a recent increase in the incidence of female patients with AF. BMI was higher in the P group than in the N and S groups; however, the clinical relevance of this is unclear. There was no statistical difference among the three groups in the $CHADS_2$ score. With regard to the comorbidity, the prevalence rates of heart failure and angina were lower in the N group than in the P group. Conversely, the prevalence rate of peripheral artery diseases was higher in the N group than in the P or S group. Only bleeding history was higher in the S group than in the other two groups. These findings suggest that the switching of anticoagulant agents was unaffected by patient characteristics, $CHADS_2$ score, and comorbidity, but was influenced by bleeding history.

AC regimens have also demonstrated better preventive effects in terms of stroke than AP regimens [18–20], whereas major or minor bleeding events in Japanese patients with cardiovascular diseases were reported to be more frequent in patients taking AC than in those taking AP regimens [21]. To understand the risk/benefit balance on antithrombotic therapy in actual treatment, we investigated the change of antithrombotic regimens in cases in which bleeding events occurred. After experiencing bleeding events, 62.5% of patients with AP monotherapy changed to AC and 37.5% to AP+AC, whereas among AP+AC patients, 50% changed to AC monotherapy. Conversely, among patients with AC monotherapy, only 13.9% patients changed to AP or AP+AC regimens. AC monotherapy was continued for 86.1% of patients.

These changes of antithrombotic regimens were not significant; therefore, unfortunately, we cannot conclude the relation of the change of regimens with bleeding events.

The PT–INR was lower in N patients than in S or P patients (1.83, 2.01, and 2.00, respectively). These values are included in the recommended lowest relative risk value for ischemic stroke and intracranial hemorrhage for Japanese patients [15].

In conclusion, the presence of atherosclerotic diseases such as angina and peripheral artery diseases is a major factor determining the selection of antithrombotic monotherapy, and the $CHADS_2$ score and comorbidity are major factors determining the combination regimen with AP and AC. Bleeding history was not a factor determining antithrombotic therapy. Conversely, bleeding history is the major factor determining the selection of OACs in Japan.

This study was limited by the lack of information on the economic background and treatment preference of patients. In addition, it was limited by the exclusion of dabigatran users. The patient characteristics in European and US studies [22,23] showed differences between patients using warfarin and dabigatran regimens, such as in terms of $CHADS_2$ scores and comorbidities. We therefore intend to compare our results with the PMS background data for dabigatran.

Conflict of interest

This study was supported financially by Nippon Boehringer Ingelheim Co. Ltd. (Project number 10011060003) on the basis of a consignment contract. KK was an employee of Nippon Boehringer Ingelheim until January 2013. TK was an employee of Nippon Boehringer Ingelheim until August 2013. There are no other conflicts of interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.joa.2016.06.006.

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