

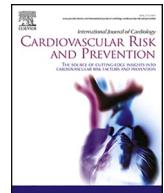


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Effect of current smoking on ischemic events in patients with atrial fibrillation taking vitamin K antagonist



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ABSTRACT

Purpose: We investigated the association between current smoking and clinical outcomes in patients with atrial fibrillation (AF) prescribed vitamin K antagonist (VKA).

Methods: We conducted a retrospective study at 71 centers in Japan. The inclusion criterion was taking a VKA for AF. Exclusion criteria were mechanical heart valves or history of pulmonary thrombosis or deep vein thrombosis. Consecutive patients were registered in February 2013 and followed until February 2017. The primary outcomes included ischemic events and major bleedings. The secondary outcomes were ischemic stroke, hemorrhagic stroke, and all-cause mortality.

Results: A total of 7826 patients were included, with a mean age of 73 years; 5274 (67%) were men. The adjusted hazard ratios (HRs; 95% confidence intervals [CIs]) of current smokers relative to non-current smokers for ischemic events and major bleedings were 1.64 (1.05–2.57) and 1.09 (0.72–1.65), respectively. The adjusted HRs (95% CIs) of current smokers relative to non-current smokers for ischemic stroke, hemorrhagic stroke, and all-cause mortality were 1.65 (1.03–2.64), 0.52 (0.12–2.15), and 1.26 (0.83–1.92), respectively.

Conclusions: There were significant associations between current smoking and ischemic events or ischemic stroke in patients with AF on VKA.

1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia, and approximately 33.5 million individuals worldwide suffer from AF each year [1]. AF is considered a consequence of risk factors such as advanced age, hypertension, heart failure, hyperthyroidism, cigarette smoking, obesity, alcohol abuse, and sleep apnea, however the etiology of AF is not fully understood [1,2]. Smoking has been reported to be a significant prognostic factor in patients with AF [1,3]. In addition, smoking was found to be associated with poor control of the international normalized ratio of prothrombin time (PT-INR) among AF patients receiving vitamin K antagonist (VKA) treatment [4–7]. However, little is known about the effect of smoking on clinical outcomes in patients with AF [8–10].

Therefore, we conducted a retrospective study of patients with AF on VKA. The objectives were to describe the association between smoking

status and clinical outcomes in patients with AF prescribed VKA.

2. Methods

We conducted a subanalysis of a historical registry study from 71 centers in Japan, published in 2021 [11]. Patients with AF taking a VKA on February 26, 2013, were included in this study. Patients with mechanical heart valves or a history of pulmonary thrombosis or deep vein thrombosis were excluded. Participants were followed until February 25, 2017 [11]. We included those with a history of strokes or major bleedings [11]. The index date of February 26, 2013, was determined because apixaban was launched in Japan on February 27, 2013, and physicians could select several oral anticoagulants (OACs) from among three direct oral anticoagulants (DOACs) and VKA [11]. The study protocol was approved by the institutional review boards of all 71

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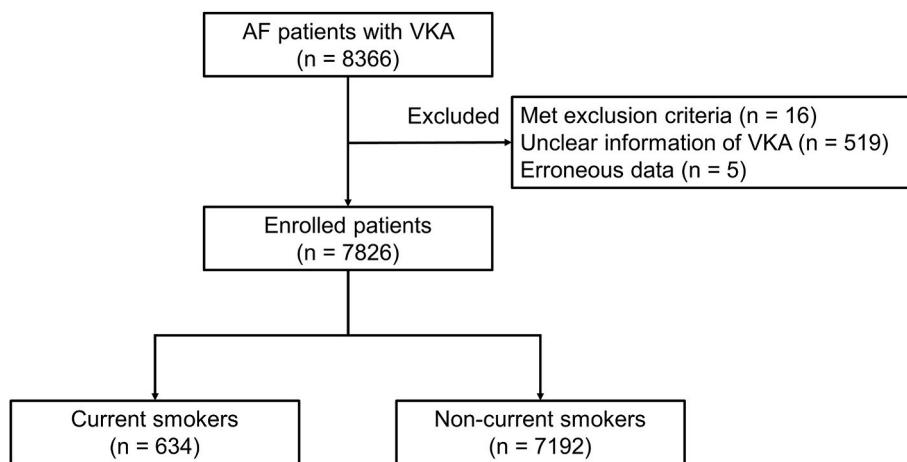


Fig. 1. Study flowchart. AF, atrial fibrillation; VKA, vitamin K antagonist.

participating centers ([Supplemental Table 1](#)) [11]. The institutional review boards approved the study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan [11,12]. In accordance with the guidelines, written informed consent was replaced by the opt-out method.

2.1. Data collection and definitions

Clinical research coordinators collected clinical information through a review of hospital charts [11]. We collected follow-up information at 1, 2, 3, and 4 years for the same procedure [11]. Data on patient characteristics, laboratory data, risk of ischemic stroke ($\text{CHA}_2\text{DS}_2\text{-VASc}$ score), and risk of hemorrhagic stroke (HAS-BLED score) were collected [11]. The $\text{CHA}_2\text{DS}_2\text{-VASc}$ score was developed to predict thrombotic events in patients with AF and consists of congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus (DM), previous stroke, vascular disease, age of 65–74 years, and female sex [13]. The HAS-BLED score was developed to predict major bleeding events in anticoagulation for patients with AF and is composed of hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile PT-INR of anticoagulation, age >65 years, and concomitant use of drugs and alcohol [11,14]. Patients were divided into current smokers and non-current smokers. Current smokers were defined as those who smoked at baseline, and other patients, including those who smoked in the past, were considered non-current smokers.

2.2. Outcomes

The primary outcomes in this study were ischemic events and major bleedings. Ischemic events were defined as ischemic stroke and systemic embolism [15]. Major bleedings was defined by the International Society on Thrombosis and Hemostasis criteria [16]. The secondary outcomes were ischemic stroke including transient ischemic attack, hemorrhagic stroke including intracranial hemorrhage and subarachnoid hemorrhage, and all-cause mortality.

2.3. Statistical analysis

We compared the clinical characteristics and outcomes of current smokers and non-current smokers. Categorical and continuous data are presented as number (%) and mean and standard deviation (SD) for parametric data or as median and interquartile range (IQR) for nonparametric data, respectively. Numbers of missing of observed variables are also presented. We used chi-square test for group comparisons of categorical data and Student *t*-test or Wilcoxon rank-sum test for group comparison of continuous data based on their distribution. Prior

to Student *t*-test, homogeneity of variances was examined using the O'Brien test. The observation started from the index date on February 26, 2013, until the date of death or last visit at the participating centers [11]. Follow-up periods were calculated separately for each outcome taking into consideration censoring due to death, switch from VKA to DOACs, or last visit to calculate the incidences and survival functions [11]. We ignored nonfatal outcomes other than the analyzed outcomes in the survival analyses [11]. The incidence of outcomes was stratified by group and evaluated with cases per 1000 patient-years. Cumulative incidence was assessed using the Kaplan-Meier method. Intergroup differences were evaluated using the log-rank test.

We used Cox proportional hazard models to estimate the effects of outcomes of current smokers relative to non-current smokers. The results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). In addition to the risk stratification scores for ischemic and bleeding events in patients with AF, clinically relevant variables were adjusted to estimate the adjusted HRs in the multivariable Cox proportional hazard models. $\text{CHA}_2\text{DS}_2\text{-VASc}$ score and HAS-BLED score were initially selected as adjusters for ischemic events and bleeding events, respectively [11]. The adjusters for ischemic events and ischemic stroke were then determined as age, CHDS₂-VSc score ($\text{CHA}_2\text{DS}_2\text{-VASc}$ score minus A2 score minus A score to avoid the duplication of age), baseline hemoglobin level, history of major bleeding, hemodialysis (HD) or renal transplant, statin use, and time in therapeutic range (TTR). The adjusters for major bleedings and hemorrhagic stroke were also determined as age, HAS-BD score (HAS-BLED score minus L and E scores to avoid the duplication of PT-INR and age), baseline hemoglobin level, history of coronary artery disease (CAD), statin use, and TTR. The adjustment for all-cause mortality were age, CHDS₂-VSc score, HAS-BD score, baseline hemoglobin level, history of major bleeding, hemodialysis or renal transplant, statin use, and TTR. To cover all potential risk adjusting variables for both current smokers and non-current smokers, we did not conduct the variable selection in the Cox proportional hazard models and presented the results with full adjusters.

To estimate the adjusted HRs for each subgroup and the interaction *P* values, we constructed the same multivariable Cox proportional hazard models for ischemic events and major bleedings in the subgroups. The subgroups of ischemic events and major bleedings included age (≥ 75 or <75 years), sex, AF type (paroxysmal or persistent), history of DM, estimated glomerular filtration rate (eGFR) (≥ 60 , <60 but ≥ 30 , <30 mL/min/1.73 m² or HD), history of stroke, history of CAD, $\text{CHA}_2\text{DS}_2\text{-VASc}$ score (≥ 2 or <2), HAS-BLED score (≥ 3 or <3), and use of a proton-pump inhibitor (PPI) or H₂ blocker.

We performed all statistical analyses using JMP 15 (SAS Institute Inc, Cary, NC, USA). All reported *P* values were two-tailed. The level of statistical significance was set at *P* < 0.05.

Table 1
Patients' characteristics.

Variable	All patients (N = 7826)	Current smokers (N = 634)	Non-current smokers (N = 7192)	P value
Age, years, mean (SD)	73 (10)	66 (11)	73 (10)	<0.0001
Men, n (%)	5274 (67)	570 (90)	4704 (65)	<0.0001
Type of atrial fibrillation, n (%)				
Paroxysmal	2643 (34)	197 (31)	2446 (34)	0.24
Persistent	4185 (53)	359 (57)	3826 (53)	
Unknown	998 (13)	78 (12)	920 (13)	
Medical history, n (%)				
Alcohol abuse	43 (0.55)	15 (2.37)	28 (0.39)	<0.0001
Hypertension	6119 (78)	489 (77)	5630 (78)	0.5
Diabetes mellitus	2444 (31)	212 (33)	2232 (31)	0.21
Dyslipidemia	3912 (50)	338 (53)	3574 (50)	0.08
Peripheral arterial disease	647 (8)	42 (7)	605 (8)	0.12
Coronary artery disease	2075 (27)	156 (25)	1919 (27)	0.26
Acute coronary syndrome	819 (10)	65 (10)	754 (10)	0.86
Percutaneous coronary intervention	684 (9)	58 (9)	626 (9)	0.7
Coronary artery bypass graft				
Stroke	1903 (24)	131 (21)	1772 (25)	0.03
Chronic obstructive pulmonary disease	330 (4)	38 (6)	292 (4)	0.02
Chronic liver disease				
Malignancy	606 (8)	66 (10)	540 (8)	0.01
Heart failure	875 (11)	65 (10)	810 (11)	0.44
Major bleeding	3291 (42)	277 (44)	3014 (42)	0.38
Baseline laboratory data				
BMI, kg/m ² , mean (SD) ^a	24.4 (4.1)	24.6 (4.0)	24.3 (4.1)	0.22
LVEF <40%, n (%) ^a	387 (6)	50 (9)	337 (6)	0.001
eGFR <60 mL/min/1.73 m ² [2] or HD, n (%) ^a	4052 (52)	249 (40)	3803 (54)	<0.0001
eGFR <30 mL/min/1.73 m ² [2] or HD, n (%) ^a	512 (7)	37 (6)	475 (7)	0.44
Hemoglobin <11 g/dL, n (%) ^a	726 (10)	26 (4)	700 (10)	<0.0001
Platelet <10 × 10 ⁹ /μL, n (%) ^a	234 (3)	13 (2)	221 (3)	0.16
TTR, %, median (IQR)	84 (39–100)	75 (37–100)	85 (40–100)	0.002
Medication, n (%)				
Aspirin	1684 (22)	135 (21)	1549 (22)	0.89
Clopidogrel or Prasugrel	347 (4)	24 (4)	323 (4)	0.41
Ticlopidine	124 (1.6)	8 (1)	116 (2)	0.5
Statins	2599 (33)	206 (32)	2393 (33)	0.69
Beta-blockers	3316 (42)	298 (47)	3018 (42)	0.01
ACEI or ARB	4081 (52)	369 (58)	3712 (52)	0.002
NSAIDs	313 (4)	19 (3)	294 (4)	0.18
PPIs or H ₂ blockers	3476 (44)	285 (45)	3191 (44)	0.78
Switch from VKA to DOACs	1893 (24)	162 (26)	1731 (24)	0.4
CHA ₂ DS ₂ -VASC score, median (IQR)	4 (3–5)	3 (2–4)	4 (3–5)	<0.0001
HAS-BLED score, median (IQR)	2 (1–3)	2 (1–2)	1 (1–3)	<0.0001
Follow-up period, years, median (IQR)	2.94 (1.14–3.93)	2.73 (0.99–3.92)	2.95 (1.16–3.93)	0.096

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; DOACs, direct oral anticoagulants; eGFR,

estimated glomerular filtration rate; HD, hemodialysis; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors; SD, standard deviation; TTR, time in therapeutic range; VKA, vitamin K antagonist.

^a Variables with missing data: BMI (51 in Current smokers and 848 in Non-current smokers); LVEF (77 in Current smokers and 1124 in Non-current smokers); eGFR (14 in Current smokers and 184 in Non-current smokers); Hemoglobin (24 in Current smokers and 244 in Non-current smokers); Platelet (25 in Current smokers and 229 in Non-current smokers).

3. Results

3.1. Patient characteristics

We initially registered 8366 patients in this study. Of those, 540 (7%) were excluded from the final analyses due to the conflicting eligibility criteria (n = 16), unclear information of VKA use in medical records (n = 519), and erroneous data (n = 5), leaving a study population of 7826 cases (Fig. 1).

Of the 7826 eligible patients, the mean (SD) age was 73 (10) years; 5274 (67%) were men. The numbers of patients with paroxysmal AF and persistent AF were 2643 (34%) and 4185 (53%), respectively. The median (IQR) TTR was 84% (39%–100%) at baseline (Table 1).

A total of 634 (8%) patients were current smokers. Compared with non-current smokers, current smokers were younger (mean 66 years vs. 73 years, P < 0.0001), populated with a higher proportion of men (90% vs. 65%, P < 0.0001), and were more likely to have alcohol abuse (2.37% vs. 0.39%, P < 0.0001), chronic obstructive pulmonary disease (6% vs. 4%, P = 0.02), and chronic liver disease (10% vs. 8%, P = 0.01). A higher proportion of patients in the current smokers group had reduced left ventricular ejection fraction (9% vs. 6%, P = 0.001). Current smokers also included a smaller number of patients with reduced eGFR (<60 mL/min/1.73 m²) or HD (40% vs. 54%, P < 0.0001) and reduced hemoglobin level (<11 g/dL; 4% vs. 10%, P < 0.0001). TTR was significantly lower in current smokers than in non-current smokers (75% vs. 85%, P = 0.002). Current smokers were prescribed more beta-blockers (47% vs. 42%, P = 0.01) and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (58% vs. 52%, P = 0.002) than were non-current smokers. Switch from VKA to DOACs was not significantly higher in current smokers than in non-current smokers (26% vs. 24%, P = 0.4). CHA₂DS₂-VASC score was significantly lower in current smokers than in non-current smokers (median 3 vs. 4, P < 0.0001). HAS-BLED score was significantly higher in current smokers than in non-current smokers (median 2 vs. 1, P < 0.0001; Table 1).

3.2. Outcomes

The cumulative incidences of primary outcomes at 4 years, including ischemic events and major bleedings, were 5.24% and 6.93% in current smokers and 4.78% and 7.8% in non-current smokers, respectively (Fig. 2). The incidences of ischemic events and major bleedings with cases per 1000 patient-years in current smokers and non-current smokers were 13.61 vs. 12.21 and 15.57 vs. 20.64, respectively. The adjusted HRs (95% CIs) of current smokers relative to non-current smokers for ischemic events and major bleedings were 1.64 (1.05–2.57) and 1.09 (0.72–1.65), respectively (Table 2).

The cumulative incidences of secondary outcomes at 4 years, including ischemic stroke, hemorrhagic stroke, and all-cause mortalities, were 4.72%, 0.39%, and 5.59% in current smokers and 4.29%, 1.12%, and 8.6% in non-current smokers, respectively (Fig. 2). The incidences of ischemic stroke, hemorrhagic stroke, and all-cause mortality with cases per 1000 patient-years in current smokers and non-current smokers were 12.37 vs. 10.96, 1.23 vs. 2.86, and 14.69 vs. 21.36, respectively. The adjusted HRs (95% CIs) of current smokers relative to non-current smokers for ischemic stroke, hemorrhagic stroke, and all-cause mortality were 1.65 (1.03–2.64), 0.52 (0.12–2.15),

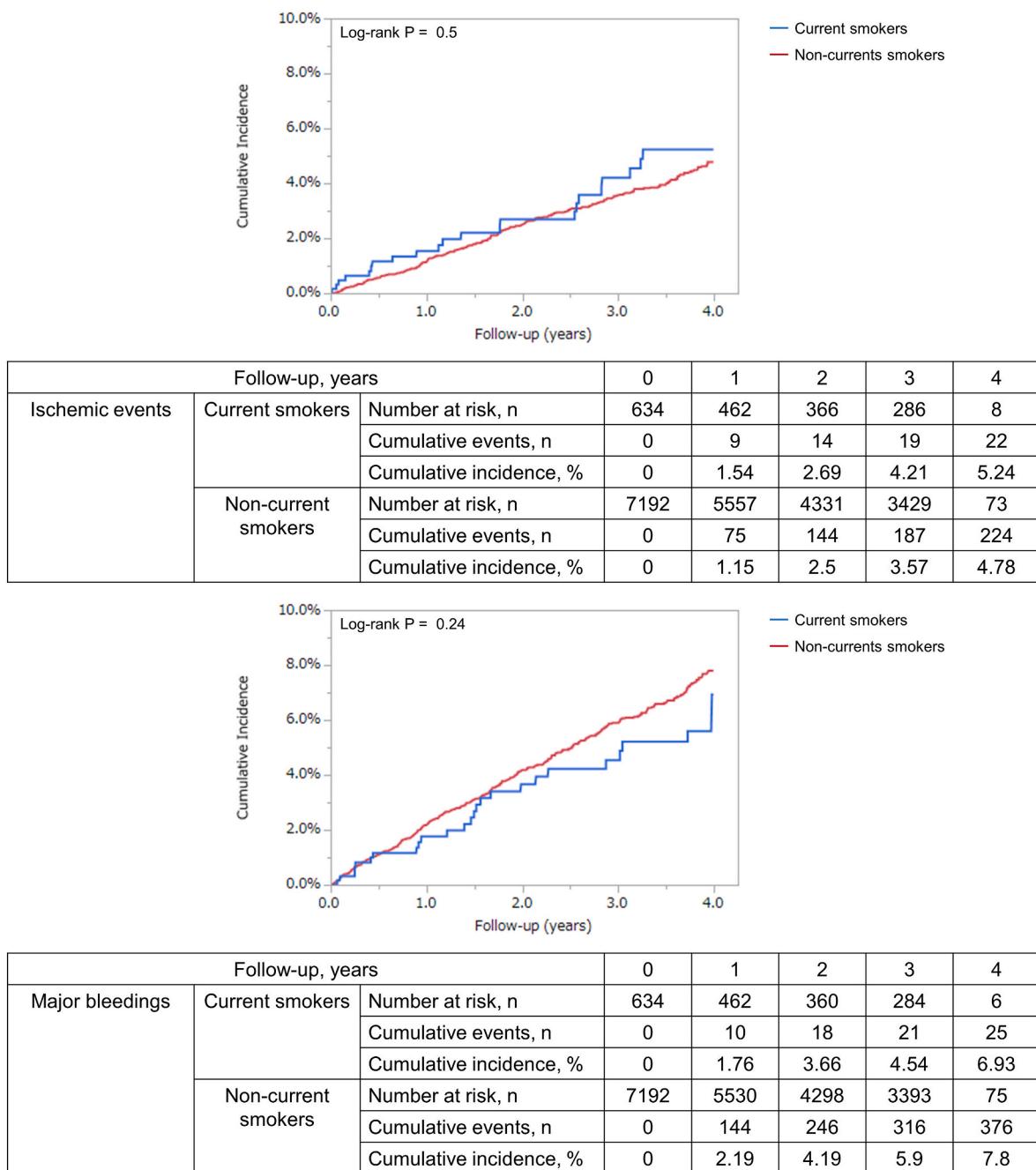


Fig. 2. Cumulative incidence of outcomes. A: Ischemic events. B: Major bleedings. C: Ischemic stroke. D: Hemorrhagic stroke. E: All-cause mortality.

and 1.26 (0.83–1.92), respectively (Table 2).

In the subgroup analyses, current smokers had consistently higher HRs in the most subgroups for ischemic events; in particular, those with numerically higher HRs were patient with age <75 years, paroxysmal AF, CHA₂DS₂-VASc score ≥2, and without the use of PPI or H₂ blocker. The interaction P values were not significant for any of the subgroups (Fig. 3A). The subgroup analyses did not identify any pertinent subgroup with a significant effect of current smokers on major bleeding, and none of the interaction P values were significant (Fig. 3B).

4. Discussion

Our investigation presented that current smokers had significantly more ischemic events and ischemic stroke than the non-current

smokers, but we found no significant difference in hemorrhagic events or mortality between the two groups.

Smoking is well-known risk factor for both stroke and cardiovascular death in the general population [10]. However, reports of smoking-related adverse events including stroke, thromboembolism, major bleeding, and death in patients with AF varied and there were no consensus [10]. These varied findings could be due to differences in patient characteristics and research methods. The present results from a large-scale registry of consecutive patients were consistent with previous studies reporting an association between smoking status and ischemic events [8,17–19]. Although general control of TTR was satisfactory, TTR was significantly lower in the current smokers than in non-current smokers in this study. Smoking is known to affect VKA metabolism, and a strong predictor of poor anticoagulation control in

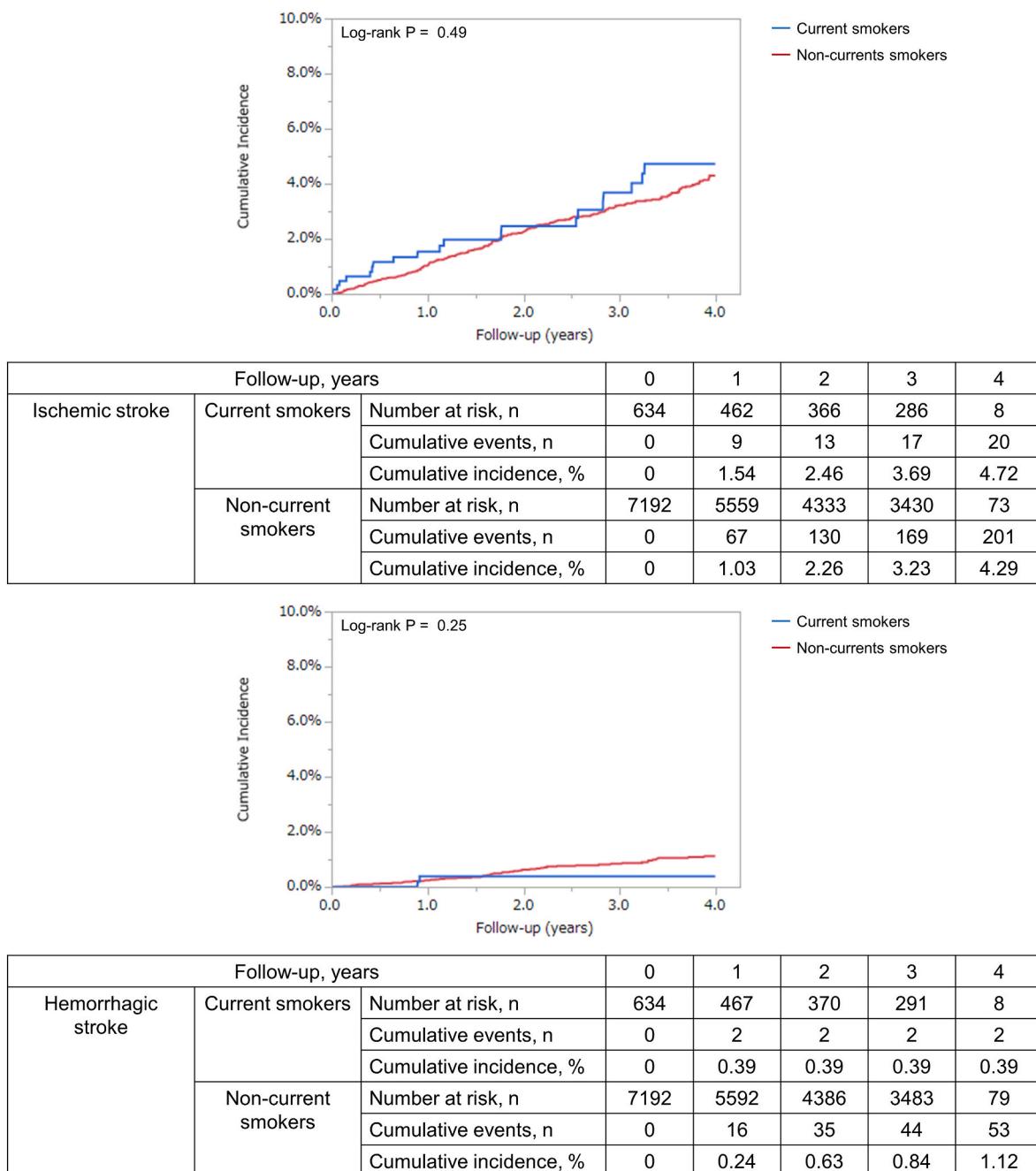


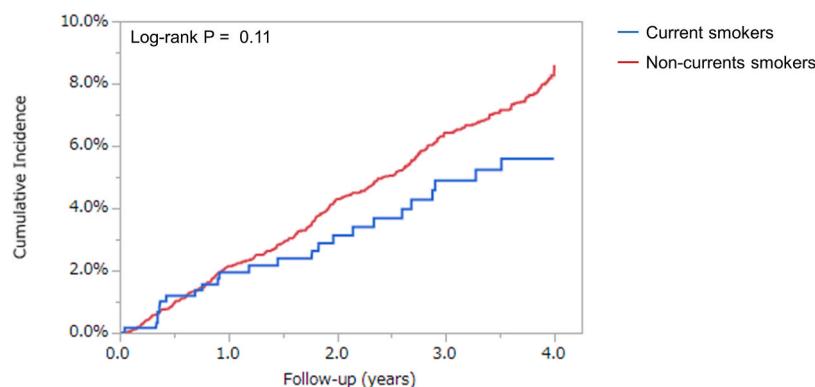
Fig. 2. (continued).

patients with AF [6,7], such interference of VKA might be associated with the elevated risk of ischemic events. In addition, smokers have been reported to have a 2-fold increased risk of strokes [1]. Cigarette smoking is a well-known vascular risk factor [8]. Although the mechanisms for smoking-related vascular diseases are complex and have not been fully elucidated [1], inflammation, oxidative stress including lipid peroxidation, endothelial dysfunction, and hemostatic and coagulation disturbances could contribute to smoking-induced arterial tissue damage, such as atherosclerosis and structural wall damage/vulnerability [8,10]. Furthermore, nicotine readily crosses the blood-brain barrier and is distributed throughout the brain, resulting in causing ischemic stroke due to the higher levels of plasma catecholamine [1].

Although most guidelines recommend the use of DOACs as the first-line OAC, VKA is still used to prevent and treat arterial and venous thromboembolism [20,21]. To date, VKA has been recommended for

patients with a mechanical prosthetic heart valve replacement or those with moderate-to-severe mitral stenosis of the rheumatic origin, as well as in cases where the use of DOACs is limited by social conditions (such as financial constraints) or comorbidities (extreme weight and severe renal or liver disease) [21]. Therefore, further studies are warranted on the association of current smoking with clinical outcomes in patients with AF on VKA.

Quitting smoking is generally recommended to reduce the cardiovascular risks [1]. The benefits of smoking cessation are time-dependent and showed a dose-response relationship [1]. Smoking cessation for more than ten years reduced by approximately 50% the risk of suffering from cardiogenic stroke [1]. Even former smokers have been found to fully recover within fifteen years or more after smoking cessation [1]. In addition to the beneficial effect of smoking cessation on ischemic events, the adjusted HR of current smokers relative to non-current smokers for



Follow-up, years			0	1	2	3	4
All-cause mortality	Current smokers	Number at risk, n	634	467	370	291	8
		Cumulative events, n	0	11	16	22	24
		Cumulative incidence, %	0	1.94	3.13	4.89	5.59
	Non-current smokers	Number at risk, n	7192	5597	4394	3492	81
		Cumulative events, n	0	140	250	338	396
		Cumulative incidence, %	0	2.14	4.29	6.42	8.6

Fig. 2. (continued).

Table 2
Clinical outcomes among entire cohort.

Outcomes	Current smokers (/1000 PY)	Non-current smokers (/1000 PY)	Crude HR	95% CIs	Adjusted HR	95% CIs
Ischemic events	22 (13.61)	224 (12.21)	1.16	0.75–1.8	1.64	1.05–2.57
Ischemic stroke	20 (12.37)	201 (10.96)	1.18	0.74–1.86	1.65	1.03–2.64
Major bleedings	25 (15.57)	376 (20.64)	0.79	0.52–1.18	1.09	0.72–1.65
Hemorrhagic stroke	2 (1.23)	53 (2.86)	0.45	0.11–1.83	0.52	0.12–2.15
All-cause mortality	24 (14.69)	396 (21.36)	0.72	0.47–1.08	1.26	0.83–1.92

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; PY, patient-years; TTR, time in therapeutic range.

Adjusters for ischemic events and ischemic stroke: age, CHDS₂-VSc score (CHA₂DS₂-VASc score minus A₂ score minus A score), baseline hemoglobin level, history of major bleeding, hemodialysis or renal transplant, statin use, and TTR.

Adjusters for major bleedings and hemorrhagic stroke: age, HAS-BD score (HAS-BLED score minus L score minus E score), baseline hemoglobin level, history of CAD, statin use, and TTR.

Adjusters for all-cause mortality: age, CHDS₂-VSc score, HAS-BD score, baseline hemoglobin level, history of major bleeding, hemodialysis or renal transplant, statin use, and TTR.

all-cause mortality was 1.26 although there were no statistical significance in this study. If this observation was validated in other large studies, quitting smoking could be also considered in terms of mortality. Therefore, we should encourage current smokers to quit and never smokers to maintain their abstinence in patients with AF as well [1].

4.1. Limitations

This study had several limitations. First, we categorized the entire cohort into current smokers and non-current smokers, which included past smoking. In addition, we did not consider details of smoking status, including smoking duration or number of cigarettes smoked per day. Therefore, other assessments of causality such as a dose-dependent relationship could not be conducted. However, because former smokers have been found to have a better prognosis than current smokers [22], it makes sense to separate former smokers and current smokers. Second, since the sample size of current smokers was considerably smaller than that of non-current smokers, statistical power may have been reduced. Therefore, the effects of current smoking in patients with AF may have been underestimated in our study. Third, two-third of the participants were men, and the female patients were not well represented in this study. Therefore, our findings should be interpreted in the context that most participants were men and attested in more

representative population. Fourth, although the SAME-TT2R2 score is a simple score based on clinical risk factors (sex, age, medical history, treatment [interacting drugs, e.g., amiodarone for rhythm control], tobacco and race), to distinguish patients according to low or high probability of poor INR control (TTR <65%) [23], we were unable to calculate SAME-TT2R2 score in this study because details of treatments were lacking. Fifth, we did not incorporate the change in OACs during the follow-up. Because the change in OACs should reflect the risk assessment by physician, we considered such judgment would overwrite the effects of risk factor for events and lose the purpose of this study. Sixth, the sample size was insufficient to assess low-incidence events such as hemorrhagic stroke [11]. Therefore, the effects of current smoking on hemorrhagic events in patients with AF on VKA should be investigated in the further studies. Finally, the registry did not include data on neck procedures such as carotid artery stenting or carotid artery endarterectomy for prevention of ischemic strokes, types of ischemic or hemorrhagic strokes, or reasons for death [11]. In particular, because smoking causes atherosclerosis of the carotid artery [24,25], these factors should be considered in future studies.

5. Conclusions

This retrospective study of consecutive patients with AF on VKA

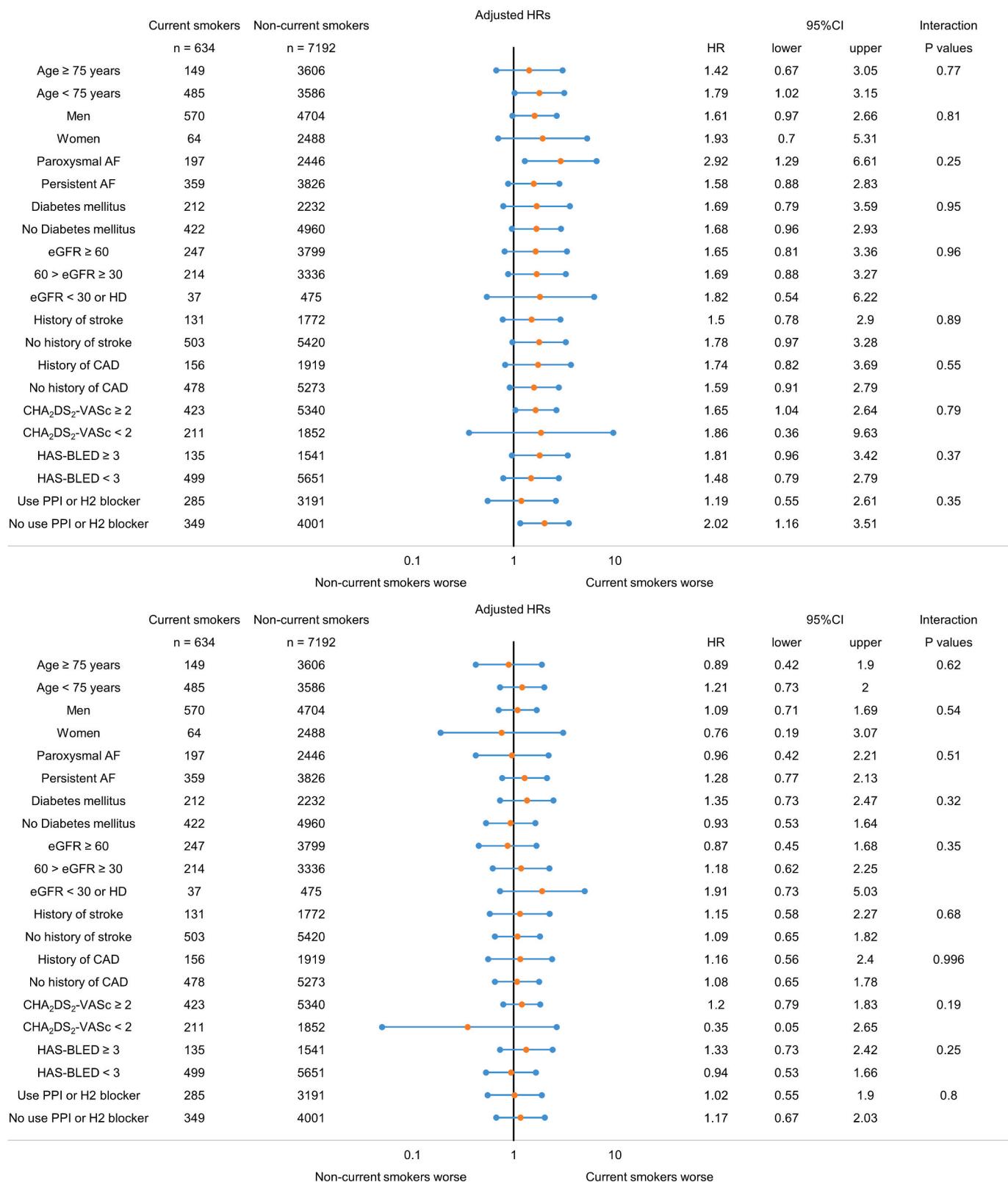


Fig. 3. Subgroup analyses on outcomes. A: Ischemic events. B: Major bleedings. AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; PPI, proton-pump inhibitor.

showed a significant association between current smoking status and ischemic events or ischemic stroke. Further clinical studies are needed to explore the effect of smoking status on clinical outcomes in patients with AF.

Credit author statement

Hideki Arai: Conceptualization, Software, Formal analysis, Investigation, Writing – original draft, Visualization.; **Shinichiro Ueda:**

Conceptualization, Investigation, Data curation, Writing – review & editing, Supervision, Funding acquisition.; **Kazutaka Uchida**: Resources, Writing – review & editing.; **Fumihiro Sakakibara**: Validation, Writing – review & editing.; **Norito Kinjo**: Validation, Writing – review & editing.; **Mari Nezu**: Validation, Writing – review & editing.; **Takeshi Morimoto**: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Supervision, Project administration.

Ethics statement

The institutional review boards of University of the Ryukyus (No. 597) and all 71 participating centers approved the study protocol (Supplemental Table). The institutional review boards waived the need for written informed consent and approved the study in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Funding information

Bristol-Myers Squibb.

Declaration of competing interest

Dr. Morimoto reports lecturer's fees from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Kowa, Toray and Tsumura; manuscript fees from Bristol-Myers Squibb and Kowa; advisory board for Novartis and Teijin. Dr. Uchida reports lecturer's fees from Daiichi Sankyo. Dr. Arai, Dr. Sakakibara, Dr. Kinjo, and Dr. Nezu have no disclosures to report. Dr. Ueda reports receiving a research grant from Bristol-Myers Squibb, Chugai, Kowa, MSD, Pfizer, and Takeda, lecturer's fee from Boehringer Ingelheim, MSD, and Taiho, and manuscript fees from Kowa. He served on an advisory board for Otsuka.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcp.2022.200135>.

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