

[ ORIGINAL ARTICLE ]

## Oral Anticoagulants in Japanese Patients with Atrial Fibrillation and Active Cancer

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### Abstract:

**Objective** Oral anticoagulants (OACs), which include direct oral anticoagulants (DOACs) and warfarin, are widely used for the prevention of thromboembolic events in patients with atrial fibrillation (AF). Cancer is associated with a prothrombotic state as well as an increased bleeding risk. Few data are available on the efficacy and safety of OACs in Japanese cancer patients with AF. We sought to investigate the efficacy and safety of OACs in this population.

**Methods** This retrospective cohort study included active cancer patients in whom AF was recorded by electrocardiography in our hospital from January 2014 to December 2016 and who were treated with DOACs or warfarin. Patients were followed for 1 year. The study outcomes were stroke or systemic embolism and major bleeding.

**Result** A total of 224 patients with AF and active cancer were treated with OACs (DOACs, n=127; warfarin, n=97). Overall, stroke or systemic embolism and major bleeding occurred in seven (3.8%/year) and eight (4.9%/year) patients, respectively. Stroke or systemic embolism occurred in three patients in the DOAC group (2.8%/year) and four patients in the warfarin group (5.4%/year). Major bleeding occurred in four patients in the DOAC group (4.0%/year) and four patients in the warfarin group (6.5%/year).

**Conclusion** The rates of stroke or systemic embolism and major bleeding events were not negligible among Japanese cancer patients with AF receiving OACs. Further investigations on the optimal management of Japanese patients with AF and cancer are needed.

**Key words:** atrial fibrillation, neoplasms, anticoagulants, stroke, thrombosis, hemorrhage

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### Introduction

Thrombosis induced by cancer itself and/or chemotherapy has been defined as cancer-associated thrombosis (CAT) (1). As the prognosis of patients with cancer improves and as chemotherapy advances, the incidence of CAT [mainly consisting venous thromboembolism (VTE)] in cancer patients has increased. It may affect up to 20% of hospitalized patients. CAT has become an emerging critical issue in the clinical setting. Because patients with cancer are both hypercoagulable and have a bleeding diathesis simultaneously, the safety of anticoagulation has always been a topic of interest. Recently, direct oral anticoagulants (DOACs) have emerged

and their effectiveness in the treatment of VTE has been demonstrated. There is increasing evidence of the effectiveness of DOACs as prophylaxis against CAT (2-4).

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, and its most common complication is cerebral infarction. There are many reports on the use of anticoagulant therapy, including warfarin and DOACs, as prophylaxis against cerebral infarction. Clinical trials have shown that DOACs are at least as safe and effective as warfarin in patients with atrial fibrillation (5-8). Although there have been some reports on the efficacy and safety of DOACs in cancer patients with AF (9, 10), few data are available on these patients in Japan. Previous studies have reported that the incidence of major bleeding and intracra-

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nial hemorrhage in Japanese or Asian AF patients treated with warfarin was higher in comparison to Westerners (11, 12). We conducted a retrospective cohort study to evaluate the efficacy and safety of DOACs and warfarin among Japanese patients with AF and cancer.

## Materials and Methods

### Study population

This study was approved by the Osaka International Cancer Institute Ethics Committee. We retrospectively assessed electronic health data of patients treated in our hospital between January 2014 - December 2016 and identified 224 active cancer cases in whom AF was recorded by electrocardiography and who were treated with either DOACs or warfarin. Patients with prosthetic valves or a life expectancy of less than one month were excluded from this study. Active cancer was defined as evidence of neoplasm on imaging, or ongoing cancer therapy. Cancer patients' data were evaluated up to 1 year after the initiation of anticoagulation; the data of anticoagulated subjects newly diagnosed with cancer were evaluated for up to 1 year after the cancer diagnosis.

### Study outcomes

The outcomes of the study were thromboembolic events (stroke or systemic embolism) and major bleeding. Stroke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery, lasting for at least 24 hours, that is not due to a non-vascular cause (i.e., trauma, brain tumor). Systemic embolism was defined as an acute vascular occlusion of an extremity or organ. Using the International Society of Thrombosis and Haemostasis (ISTH) criteria (13), major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, reduction in the hemoglobin level of at least 20 g/L, or transfusion of at least 2 units of blood.

### Statistical analysis

Continuous variables are presented as the mean  $\pm$  standard deviation and were analyzed using the unpaired Student's *t*-test. Categorical variables are presented as percentages (%) and were compared using chi-squared tests. Cumulative event rates were evaluated with the Kaplan-Meier method, and the difference between the DOAC and warfarin groups was analyzed using a log-rank test. All statistical analyses were performed using the JMP<sup>®</sup> software program (version 13.2 SAS Institute, Cary, USA). P values of <0.05 were considered to indicate statistical significance.

## Results

### Characteristics of the study patients

A total of 224 patients with AF and cancer and who received oral anticoagulants were identified. The baseline

characteristics are listed in Table 1. Of 224 patients with AF and cancer, 127 patients were treated with DOACs (apixaban, n=46; rivaroxaban, n=44; dabigatran, n=25; edoxaban, n=12) and 97 patients were treated with warfarin. There were no significant differences in age, gender, CHADS<sub>2</sub> score, CHA<sub>2</sub>DS<sub>2</sub>-VAsc score, HAS-BLED score [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (not included), Elderly (>65 years), Drugs/alcohol concomitantly] (14), serum creatinine, cancer type, or cancer stage between the DOAC and warfarin groups (Table 1). Cancer was diagnosed during oral anticoagulant treatment in 144 patients (64.3%). The rate of patients in whom cancer was diagnosed during anticoagulation was significantly lower in the DOAC group than in the warfarin group (48.8% vs. 84.5%, *p*<0.0001).

### Outcome events

Thromboembolic events occurred during treatment with OACs in seven patients (Table 2). The incidence of thromboembolic events was 3.8%/year [95% confidence interval (CI) 1.8-7.8] (Figure A). In the DOAC group, three patients experienced a thromboembolic event (2.8%/year, 95% CI 0.9 to 8.3) and one of three patients died of stroke. In the warfarin group, four patients experienced a thromboembolic event (5.4%/year, 95% CI 2.0 to 13.4) and no patients died of stroke or systemic embolism. The rates of stroke or systemic embolism in the DOAC and warfarin groups did not differ to a statistically significant extent (*p*=0.35). Table 2 showed individual components of the outcome data.

Major bleeding occurred in eight patients during treatment with OACs (Table 2); no patients died of major bleeding. The incidence of major bleeding was 4.9%/year (95% CI 2.5 to 9.6) (Figure B). Gastrointestinal bleeding occurred in six of eight patients in patients with gastrointestinal (n=4), hematological (n=1), and head and neck cancer (n=1). In the DOAC group, four patients experienced major bleeding (4.0%/year, 95% CI 1.5 to 10.4). In the warfarin group, four patients experienced a major bleeding (6.5%/year, 95% CI 2.4 to 16.2). The rates of major bleeding in the DOAC and warfarin groups did not differ to a statistically significant extent (*p*=0.50).

## Discussion

This single-center retrospective cohort study investigated the efficacy and safety of OACs in patients with AF and active cancer in Japan. The incidence rates of thromboembolic events and major bleeding were 3.8%/year (95% CI 1.8 to 7.8) and 4.9%/year (95% CI 2.5 to 9.6), respectively.

The previous report from the Fushimi AF Registry documented that the incidence rates of stroke or systemic embolism and major bleeding in patients with AF were 2.3%/year and 1.8%/year, respectively (14). In the SAKURA AF Registry, the incidence rates of stroke or systemic embolism and major bleeding in AF patients treated with OACs during the

**Table 1. Patient Characteristics.**

	Overall (n=224)	DOACs (n=127)	Warfarin (n=97)	p
Age, yr	72.7±7.1	72.7±7.1	72.7±7.2	0.99
Female sex, no. (%)	28 (12.5)	19 (15.0)	9 (9.3)	0.20
CHADS <sub>2</sub> score <sup>a</sup>	1.9±1.2	1.9±1.1	2.0±1.3	0.78
CHA <sub>2</sub> DS <sub>2</sub> -VASc score <sup>b</sup>	3.1±1.4	3.1±1.4	3.0±1.5	0.84
HAS-BLED score <sup>c</sup>	2.0±0.9	2.0±0.9	2.1±0.9	0.71
Creatinine, mg/dL	1.0±0.3	1.0±0.3	1.0±0.4	0.94
Anticoagulation prior to cancer diagnosis, no. (%)	144 (64.3)	62 (48.8)	82 (84.5)	<0.0001
Cancer type, no. (%) <sup>d</sup>				
Gastrointestinal	99 (44.2)	54 (42.5)	45 (46.4)	
Lung	54 (24.1)	27 (21.3)	27 (27.8)	
Genitourinary	25 (11.2)	17 (13.4)	8 (8.2)	0.35
Head and neck	22 (9.8)	12 (9.4)	10 (10.3)	
Breast	9 (4.0)	7 (5.5)	2 (2.1)	
Hematological	7 (3.1)	6 (4.7)	1 (1.0)	
Other	8 (3.6)	4 (3.1)	4 (4.1)	
Cancer stage, no. (%) <sup>d,e</sup>				
0	8 (3.7)	3 (2.5)	5 (5.3)	
I	70 (32.4)	37 (30.6)	33 (34.7)	
II	28 (13.0)	14 (11.6)	14 (14.7)	0.23
III	33 (15.3)	16 (13.2)	17 (17.9)	
IV	48 (22.2)	34 (28.1)	14 (14.7)	
Recurrent	29 (13.4)	17 (14.1)	12 (12.6)	
DOAC, no. (%)				
Apixaban		46 (36.2)		
Rivaroxaban		44 (34.6)		
Dabigatran		25 (19.7)		
Edoxaban		12 (9.4)		

<sup>a</sup>1 point each for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus; 2 points for previous stroke/transient ischemic attack

<sup>b</sup>1 point each for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65–74 y, female

<sup>c</sup>1 point for hypertension, 1 point each for abnormal renal function/liver function, 1 point for stroke, 1 point for bleeding history or predisposition, 1 point for labile international normalized ratio (not included), 1 point for elderly (>65 years), 1 point each for drugs/alcohol concomitantly

<sup>d</sup>Cancer type and Cancer staging were analyzed using chi-square test.

<sup>e</sup>Cancer staging was not applied to hematological malignancies.

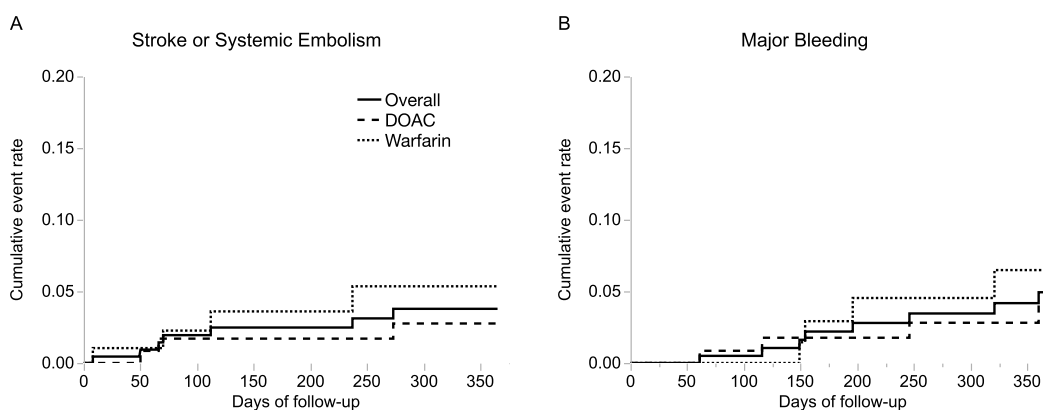
**Table 2. Outcome Events.**

	Overall (n=224)		DOAC (n=127)		Warfarin (n=97)	
	no.	%/year (95% CI)	no.	%/year (95% CI)	no.	%/year (95% CI)
Stroke or systemic embolism	7	3.8 (1.8-7.8)	3	2.8 (0.9-8.3)	4	5.4 (2.0-13.4)
Ischemic stroke	5	2.8 (1.2-6.7)	3	2.8 (0.9-8.3)	2	3.0 (0.7-11.6)
Systemic embolism	2	1.0 (0.2-3.9)	0	0	2	2.4 (0.6-9.3)
Major bleeding	8	4.9 (2.5-9.6)	4	4.0 (1.5-10.4)	4	6.5 (2.4-16.2)
Intracranial bleeding	1	0.7 (0.1-5.1)	0	0	1	2.0 (0.3-13.1)
Gastrointestinal bleeding	6	3.6 (1.6-7.8)	3	3.0 (1.0-9.1)	3	4.5 (1.5-13.2)
Alveolar hemorrhage	1	0.7 (0.1-4.7)	1	1.1 (0.1-7.2)	0	0

follow-up period (median: 39.3 months) were 4.1% and 3.8%, respectively (15). Although our cohort cannot be directly compared to the Fushimi AF Registry and SAKURA AF Registry, the rates of thromboembolic events and major bleeding events in patients with AF and active cancer receiving

OACs are probably higher than in those without active cancer.

A recent retrospective cohort study of patients with AF and active cancer showed that DOAC and warfarin users had similar rates of ischemic stroke, and that the rates of major



**Figure.** The Kaplan-Meier curves for stroke or systemic embolism (A) and major bleeding (B). DOAC: direct oral anticoagulant (apixaban, rivaroxaban, dabigatran, and edoxaban)

bleeding in apixaban users were significantly lower than those in rivaroxaban and warfarin users (10). Although the rates of major bleeding in patients treated with different anticoagulants did not differ to a statistically significant extent in our study, the sample size may have been too small to show a significant difference. Previous studies reported that the rates of major bleeding events were 0.8-1.2% per year in patients with AF and active cancer treated with DOACs (9, 10). In patients with AF and VTE treated with edoxaban, the rate of major bleeding was 6.9% over 12 months (3). Our study showed that the rate of major bleeding events in the DOAC group was 4.0% per year. The patient population might have affected the rate of major bleeding events.

The management of warfarin treatment in cancer patients is challenging because of pharmacokinetic interaction between warfarin and chemotherapy (e.g., 5-fluorouracil and capecitabine) (16, 17), chemotherapy-induced thrombocytopenia, and appetite loss due to cancer itself and/or chemotherapy. Although DOACs may be an available alternative to warfarin for cancer patients with AF, further investigation is needed to address this issue.

The present study is associated with several limitations. First, because our study was a single-center retrospective cohort study, a selection bias was unavoidable. Second, because AF patients were identified using electrocardiography in our hospital, some patients with paroxysmal AF may not have been included. Thus, our study population may not be representative of the general patients with AF and cancer. Third, the small sample size may have limited the analytical power. Finally, the dosage of OACs and coagulation data (e.g., prothrombin time-international normalized ratio) were not collected.

## Conclusion

In summary, we performed a retrospective cohort study of Japanese patients with AF and cancer to investigate the efficacy and safety outcomes of OACs. Our study suggests that the rates of thromboembolic events and major bleeding are

not negligible in patients with AF and active cancer who are receiving OACs.

**The authors state that they have no Conflict of Interest (COI).**

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