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# Impact of Cancer on Bleeding and Ischemic Stroke in Atrial Fibrillation Patients Taking Rivaroxaban, a Direct Oral Anticoagulant

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## ABSTRACT

**Introduction:** The impact of cancer in atrial fibrillation (AF) patients who are undergoing anticoagulant therapy is not known because patients with cancer have been excluded from recent randomized clinical trials of direct oral anticoagulants (DOACs) for the prevention of stroke in patients with non-valvular AF (NVAf). Therefore, we examined whether cancer is associated with an increased risk of bleeding or ischemic stroke among patients with NVAf taking the DOAC rivaroxaban.

**Methods:** We enrolled 564 patients who were prescribed rivaroxaban to manage NVAf between July 2012 and July 2016 at our institution. We used multivariate Cox proportional hazard models to assess the relationship between cancer and the risk of bleeding or ischemic stroke.

**Results:** Bleeding events occurred in 19 patients (3.4%), including 6 with major bleeding (0.11%). Patients with cancer or cancer history had more bleeding (hazard ratio (HR), 7.23; 95% confidence interval (CI), 2.48-21.09;  $P < 0.001$ ). A lower albumin level ( $< 3.6$  mg/dl) indicated a higher tendency for bleeding (HR, 2.87; 95% CI, 0.96-8.57;  $P = 0.059$ ). Nine patients (1.6%) experienced ischemic stroke during therapy; one of them had cancer. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was significantly associated with the incidence of ischemic stroke, whereas comorbidity with cancer was not.

**Conclusions:** Bleeding events in patients with NVAf treated with rivaroxaban were associated with comorbidity of cancer and a lower albumin level, whereas cancer was not correlated with an increased risk of ischemic stroke. Therefore, caution should be used when prescribing DOACs to patients with cancer or low albumin levels, and we should follow-up for bleeding events closely.

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**KEYWORDS:** DOAC, cancer, atrial fibrillation, bleeding, ischemic stroke

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## Introduction

Atrial fibrillation (AF) is occasionally seen among patients with cancer, and its incidence is increasing.<sup>1)</sup> Cancer patients with AF are more likely to experience ischemic stroke, possibly owing to hypercoagulability,<sup>2)</sup> and the optimal preventive therapy is therefore of clinical importance. The current guidelines, however, have not yet recommended therapeutic management to prevent ischemic stroke among non-valvular AF (NVAF) patients with cancer.<sup>3)</sup>

Direct oral anticoagulants (DOACs) constitute an effective treatment strategy for stroke prevention in NVAF patients.<sup>4)</sup> To date, however, few studies have evaluated the association between cancer and bleeding risk among NVAF patients because cancer patients have been excluded from recent randomized clinical trials of DOACs for the prevention of stroke in NVAF patients.<sup>1,5)</sup> To address this shortcoming in our knowledge, we investigated whether cancer is associated with an increased risk of bleeding or ischemic stroke among NVAF patients taking the DOAC rivaroxaban, which inhibits factor Xa activity.

## Materials and Methods

### Study population

We identified 592 consecutive patients who were prescribed rivaroxaban as anticoagulant therapy to manage NVAF between July 2012 and July 2016 at our institution (Toho University Omori Medical Center, Tokyo, Japan). Among them, 339 had paroxysmal AF, 136 had persistent AF, 102 had permanent AF, and 14 were unknown. We excluded 27 patients who discontinued taking rivaroxaban within 2 weeks because of an economic issue (N = 4), gastric dyspepsia (N = 3), allergy (N = 1), or an unknown reason (N = 19). Thus, we ultimately enrolled 564 patients (95.2%) in the study. Of these, 87 patients (15.4%) had been diagnosed with cancer within 5 years, 57 (10.1%) of whom had been aggressively treated.

The medical history of each patient, including the prevalence of cancer, was reviewed to evaluate the relationship between cancer and bleeding due to rivaroxaban. A history of cancer was monitored before starting rivaroxaban therapy. Thirty patients who had been diagnosed with cancer but had no recurrence for > 5 years after cancer treatment (regarding breast cancer, those whose cancers had not recurred for > 10 years were defined as cured) were excluded from the study.

### Administration of rivaroxaban

Rivaroxaban was administered continuously as a therapy to prevent undue coagulation. According to the guidelines, the administration of rivaroxaban was commonly started at 10 or 15 mg once a day, and the dosage was determined based on the creatinine clearance (CCr (ml/min)), which was calculated using the Cockcroft-Gault equation.<sup>6,7)</sup> The patients were followed at 1- to 3-month intervals at our outpatient clinic. The presence of symptoms, physical examinations, medication adherence, and blood tests were also evaluated during the follow-up.

### Outcome measures

We defined the primary end point of this study as the occurrence of bleeding. Major bleeding was defined as fatal bleeding, a decrease of the hemoglobin level of 2 g/dl and more, the need for a transfusion of > 2 units of blood, or symptomatic hemorrhage in critical organs, in accordance with the criteria of the ROCKET Trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).<sup>5)</sup> The HAS-BLED score was used to assess the bleeding risk.<sup>8,9)</sup>

We also investigated the incidence of ischemic stroke that developed during anticoagulation therapy by rivaroxaban. We defined the incidence of ischemic stroke as a newly developed ischemic stroke with symptoms that were documented by MRI or angiography.

### Statistical analysis

All continuous data are expressed as the mean  $\pm$  standard deviation, median (quartile: 25-75%), or number (%). Comparisons of variables between cancer and non-cancer groups were analyzed using univariate analysis (unpaired *t*-test or Fisher's exact test). The multivariate Cox proportional hazards model was used to identify the relationship between cancer and bleeding risk after adjusting for body mass index (BMI), HAS-BLED score, CHA<sub>2</sub>DS<sub>2</sub>-VASc score (Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack), and albumin. The cutoff value of albumin was determined using an area under the curve by a receiver-operating characteristic analysis based on bleeding occurrences. The area under the curve was 3.60 mg/dl. The relationship between cancer and major bleeding events was analyzed using the Kaplan-Meier method, and the curves were compared using a log-rank test. A *P*-value of < 0.05 was considered to reflect a statistically significant difference in values. Statistical analyses were performed using R com-

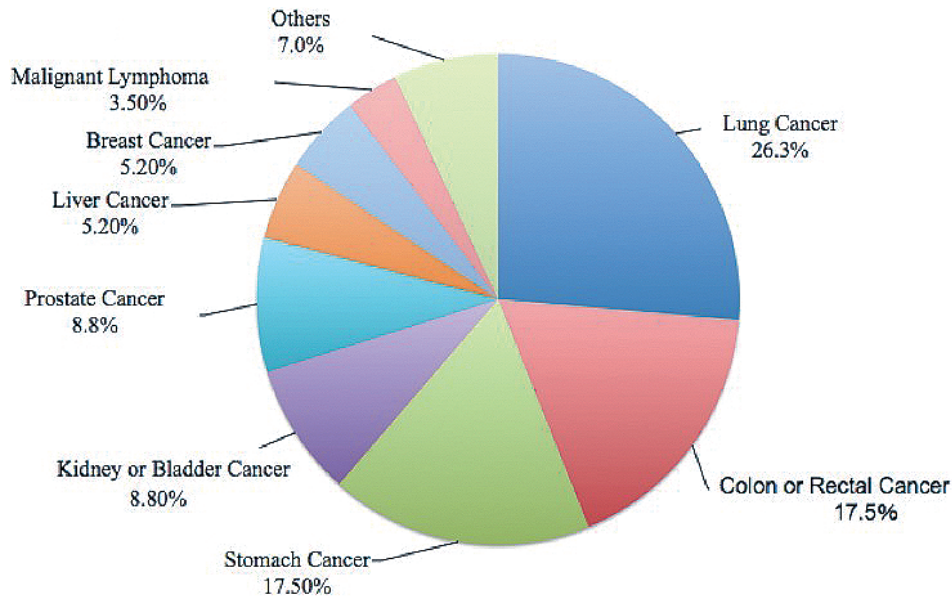


Fig. 1 Types of cancer among study participants.

mander (EZR Version 1.70 El Capitan software, Jichi Medical University, Saitama, Japan).

#### Ethical considerations and IRB

The study protocol was approved by the Institutional Review Board (IRB) of the Toho University Omori Medical Center, with number M18104, on October 10, 2018. We disclosed the research by posting it in the hospital, on the website of the hospital, or verbally to patients themselves.

### Results

#### Baseline characteristics

Overall, the mean age of study patients was  $69.1 \pm 12.2$  years, and 372 (66.0%) were male. The majority of patients were older, with 70.3% > 65 years old and 35.5% > 77 years old. The mean CHADS<sub>2</sub> score was  $1.68 \pm 1.25$ , the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was  $2.88 \pm 1.70$ , and the HAS-BLED score was  $1.24 \pm 1.0$ .<sup>10</sup> Of the 57 patients undergoing treatment for aggressive cancer, one-fourth suffered from lung cancer, followed by colon, stomach, kidney, prostate, liver, breast, malignant lymphoma, and other cancers (Fig. 1). According to Fig. 1, lung cancer was the most commonly occurring cancer.

Table 1 presents the baseline characteristics among cancer and non-cancer patients. Compared with non-cancer patients, those with cancer were older, had lower BMI, and higher CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. As we observed, the HAS-BLED score was expected to be higher in cancer patients. Regarding lab data, CCr, albumin, and hemoglobin levels were significantly lower in can-

cer patients than in non-cancer patients.

#### Bleeding events

During the mean follow-up of  $19.7 \pm 14.3$  months, 19 patients (3.4%) experienced a bleeding event; six (1.1%) of those patients experienced major bleeding, including intracerebral hemorrhage ( $n = 3$ ) and gastrointestinal bleeding ( $n = 3$ ). No patients died because of major bleeding. Table 2 is a summary of the patients with or without bleeding. Bleeding events were more frequent among cancer patients and those with a lower serum albumin level. Other baseline clinical factors did not differ significantly between the two groups.

Applying the Cox proportional hazards model after adjusting for BMI, the HAS-BLED score, and serum albumin level, cancer was an independent, significant predictor of bleeding (hazard ratio (HR), 7.23; 95% confidence interval (CI), 2.48-21.09;  $P < 0.001$ ). Lower serum albumin trended toward significance of bleeding risk (Table 3). Fig. 2 shows the Kaplan-Meier curves regarding bleeding events between the cancer and non-cancer groups. The incidence of cancer was significantly associated with an increase in bleeding compared with the non-cancer group (log-rank test,  $P < 0.001$ ).

#### Ischemic stroke events

Table 4 lists nine patients who experienced ischemic stroke during the follow-up period. In the majority of patients, the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were increased. Only one patient taking the optimal dose of rivaroxaban was being treated for cancer. Two non-cancer patients had a

Table 1 Baseline characteristics among patients with cancer and without.

	Cancer (N = 57)	Non-cancer (N = 507)	P-value
Baseline			
Age (years)	73.72 ± 7.65	68.55 ± 12.53	0.002 *
Male gender (n, %)	32 (56.1)	340 (67.3)	0.105
BMI	21.51 ± 4.40	23.25 ± 4.11	0.003 *
Hypertension (n, %)	34 (59.6)	277 (54.7)	0.574
Diabetes (n, %)	21 (36.8)	132 (26.1)	0.086
Congestive heart failure (n, %)	22 (38.6)	144 (28.4)	0.125
Vascular disease (n, %)	9 (15.8)	78 (15.4)	0.998
History of bleeding (n, %)	4 (7.0)	22 (4.3)	0.322
Alcohol (n, %)	3 (5.3)	22 (4.3)	0.732
Antiplatelet drug therapy (n, %)	3 (5.3)	62 (12.2)	0.185
CHADS <sub>2</sub> score	2.14 ± 1.44	1.63 ± 1.21	0.003 *
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.65 ± 1.65	2.79 ± 1.69	<0.001 *
HAS-BLED score	1.47 ± 0.93	1.22 ± 1.05	0.078
Laboratory data			
BNP (pg/ml)	283.80 ± 251.28	216.22 ± 327.25	0.17
CCr (ml/min)	61.05 ± 24.24	70.49 ± 29.28	0.020 *
HbA1c	5.95 ± 0.59	5.98 ± 0.74	0.807
ALB (g/dl)	3.66 ± 0.63	3.90 ± 0.62	0.009 *
AST (IU)	30.81 ± 17.39	30.04 ± 34.4	0.869
ALT (IU)	21.95 ± 15.74	25.93 ± 31.28	0.344
ALP (IU)	243.60 ± 76.72	226.15 ± 94.56	0.197
Hb (g/dl)	12.95 ± 2.17	13.83 ± 2.06	0.003 *
Plt (× 10,000)	199.68 ± 65.40	202.66 ± 80.57	0.788
PT-INR	2.00 ± 4.36	1.58 ± 1.68	0.189

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; CCr = creatinine clearance; HbA1c = hemoglobin A1c; ALB = albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; Hb = hemoglobin; Plt = platelet; PT-INR = international normalized ratio of prothrombin time.

lower rivaroxaban dose than the optimal dose. The Cox proportional hazards model (after adjusting for BMI and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score) revealed that a significantly higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score was associated with the incidence of ischemic stroke, whereas the presence of cancer was not (Table 5).

## Discussion

### Main findings

We noted several important findings in the current study. First, the presence of cancer was a significant predictor of bleeding among NVAf patients taking rivaroxaban, independent of other clinical risk factors. Second, no significant association between a specific type of cancer and bleeding was observed. Finally, cancer was not an independent risk of the incidence of ischemic stroke.

### Bleeding risk

Among cancer patients, hypercoagulability and bleed-

ing risk can co-exist. We demonstrated that cancer may be associated with an increased bleeding risk. Interestingly, a lower serum albumin level was also associated with a higher risk of bleeding. It is well known that the progression of cancer is inversely associated with albumin level,<sup>11</sup> and hypoalbuminemia is a significant predictor of bleeding.<sup>11,12</sup> We observed similar results, suggesting that cancer patients with lower albumin levels should be cautious about treatment with DOACs. They should be followed up for bleeding in detail during treatment with DOACs.

### Ischemic stroke

Cancer patients tend to have thrombosis,<sup>11</sup> and the risk for recurrent venous thrombosis is four-fold higher for cancer patients than non-cancer patients.<sup>12</sup> Recent studies reported that cancer patients could be safely and effectively treated with DOACs.<sup>13-15</sup> Although the sample set was small, our group previously reported that in a sub-analysis of 23 patients with cancer, rivaroxaban was safely

Table 2 Comparison of patient characteristics regarding bleeding events.

	Bleeding (N = 19)	Non-bleeding (N = 545)	P-value
Baseline			
Age (years)	72.42 ± 9.09	68.96 ± 12.30	0.225
Male gender (n, %)	13 (68.4)	359 (65.9)	0.998
BMI	23.69 ± 3.70	23.05 ± 4.18	0.534
Hypertension (n, %)	14 (73.7)	297 (54.6)	0.157
Diabetes (n, %)	3 (15.8)	150 (27.6)	0.307
Congestive heart failure (n, %)	4 (21.1)	162 (29.7)	0.609
Vascular disease (n, %)	3 (15.8)	84 (15.4)	0.999
Cancer (n, %)	7 (36.8)	50 (9.2)	0.001 *
History of bleeding (n, %)	1 (5.3)	25 (4.6)	0.599
Alcohol (n, %)	1 (5.3)	24 (4.4)	0.583
Antiplatelet drug therapy (n, %)	3 (5.8)	62 (11.4)	0.472
CHADS <sub>2</sub> score	1.89 ± 1.41	1.67 ± 1.24	0.445
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	3.21 ± 1.55	2.87 ± 1.71	0.386
HAS-BLED score	1.53 ± 0.96	1.23 ± 1.04	0.228
Laboratory data			
BNP (pg/ml)	168.52 ± 138.98	224.51 ± 325.73	0.481
CCr (ml/min)	64.79 ± 22.41	69.68 ± 29.13	0.469
HbA1c	5.91 ± 0.59	5.98 ± 0.73	0.706
ALB (g/dl)	3.52 ± 0.72	3.88 ± 0.62	0.027 *
AST (IU)	32.21 ± 15.00	30.04 ± 33.60	0.780
ALT (IU)	23.05 ± 11.52	25.61 ± 30.53	0.716
ALP (IU)	245.69 ± 68.76	227.44 ± 93.59	0.440
Hb (g/dl)	13.29 ± 2.38	13.75 ± 2.08	0.348
Plt (× 10,000)	206.42 ± 79.25	202.21 ± 79.18	0.820
PT-INR	1.39 ± 0.73	1.63 ± 2.15	0.645

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; CCr = creatinine clearance; HbA1c = hemoglobin A1c; ALB = albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; Hb = hemoglobin; Plt = platelet; PT-INR = international normalized ratio of prothrombin time.

Table 3 The Cox proportional hazards model of bleeding risk after adjusting for BMI, HAS-BLED score, albumin, and the presence of cancer.

Factor	Hazard ratio (95% CI)	P-value
Cancer	7.23 (2.48-21.09)	<0.001 *
BMI	1.06 (0.97-1.16)	0.184
HAS-BLED score	0.85 (0.46-1.55)	0.589
ALB < 3.6 g/dl	2.87 (0.96-8.57)	0.059

Abbreviations: BMI = body mass index; ALB = albumin.

used to treat venous thrombosis.<sup>16)</sup> DOACs are therefore considered a class I indication for preventing venous thrombosis among cancer patients based on current guidelines.<sup>17)</sup> However, there is no treatment strategy for the prevention of ischemic stroke among NVAF patients with cancer. In the current study, we observed that the incidence of ischemic stroke was 1.6% of patients, which is almost equal or even lower than percentages reported pre-

viously (0.9%-1.8%).<sup>18)</sup> We demonstrated that rivaroxaban was effective for preventing ischemic stroke among NVAF patients, regardless of the comorbidity of cancer. A similar risk of ischemic stroke between cancer and non-cancer patients was also observed in a prior study.<sup>18)</sup> The most frequent causes of ischemic stroke in cancer patients are cerebrovascular risk factors, such as hypertension, dyslipidemia, diabetes, AF, and smoking, and vascular risk profiles of cancer patients are similar when compared with patients without cancer.<sup>19)</sup> In our study, there were no significant differences in the frequency of ischemic stroke between cancer and non-cancer patients. We observed that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was associated with an increased incidence of ischemic stroke. The cancer patients were less likely to have a higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score, resulting in a similar risk of ischemic stroke between cancer and non-cancer patients. A prior study reported that optimal dosing was associated with a reasonable risk for major

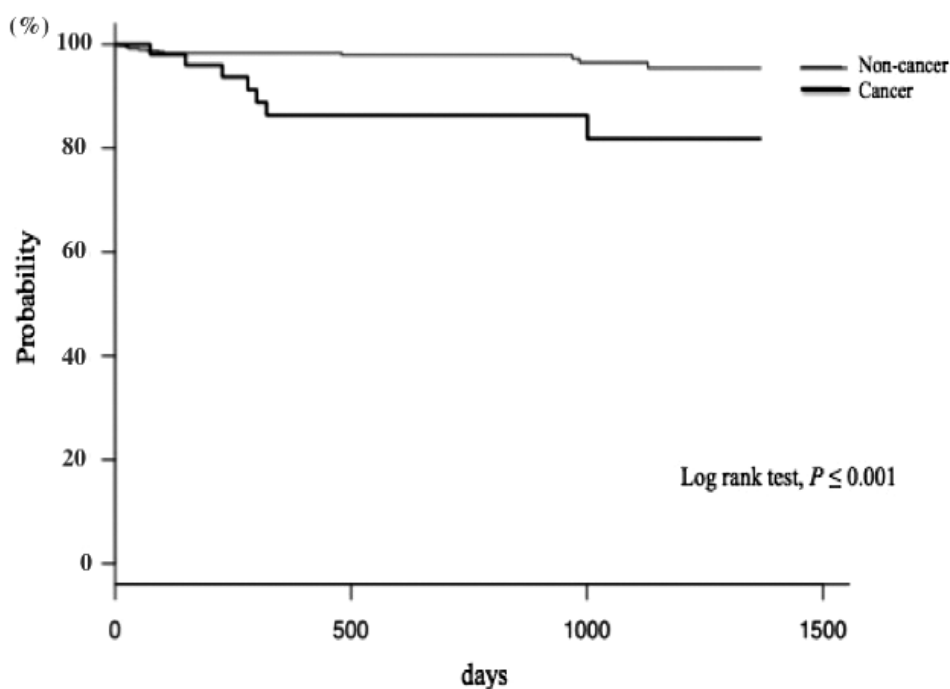


Fig. 2 Kaplan-Meier curve showing the bleeding risk between NVAF patients with or without cancer.

Abbreviation: NVAF = non-valvular atrial fibrillation.

Table 4 Details of patients who had an ischemic stroke during anticoagulant therapy.

No.	Age (years)	Gender	Weight (kg)	BMI	CHA <sub>2</sub> DS <sub>2</sub> -VASc score	HAS-BLED score	Dosage (mg)	Optimal dose (mg)	Cancer
1	74	F	54.3	23.7	6	2	15	15	-
2	75	M	61.6	24.6	4	1	10	15	-
3	80	F	47	20.2	6	2	10	10	+
4	83	M	55.2	19.6	3	1	10	10	-
5	58	M	75.5	26.8	1	0	10	15	-
6	67	F	71.6	26.6	8	4	10	10	-
7	81	F	56.2	25.7	5	4	10	10	-
8	71	F	46.0	19.8	3	1	15	15	-
9	72	F	44.2	20.5	5	2	10	10	-

Abbreviations: BMI = body mass index.

Table 5 The Cox proportional hazards model of ischemic stroke risk after adjusting for BMI, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and the presence of cancer.

Factor	Hazard ratio (95% CI)	P-value
Cancer	0.81 (0.09-7.20)	0.853
BMI	1.02 (0.87-1.18)	0.822
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	1.50 (1.03-2.19)	0.036 *

Abbreviations: BMI = body mass index.

bleeding, but was not associated with an increased risk of ischemic stroke.<sup>20</sup> In this study, even a lower dose than the

optimal dose was not associated with a higher risk of ischemic stroke or bleeding.

#### Study limitations

This study had potential limitations. It was a retrospective and observational study at a single institute. We had a small number of patients with major bleeding, which might have caused a statistical bias. Further research is needed with more patients.

#### Conclusions

Bleeding events in NVAF patients treated with rivaroxaban were associated with the comorbidity of cancer and a

lower albumin level, whereas the presence of cancer was not associated with an increased risk of ischemic stroke. Our results suggest that cancer patients with lower albumin levels should be cautious regarding treatment with DOACs.

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