タイトル	Impact of Cancer on Bleeding and Ischemic Stroke in Atrial Fibrillation Patients Taking Rivaroxaban, a Direct Oral Anticoagulant
作成者（著者）	Akitsu, Katsuya / Nakanishi, Rine / Kinoshita, Toshio / Yuzawa, Hitomi / Fujino, Tadashi / Ikeda, Takanori
公開者	The Medical Society of Toho University
発行日	2019.06.01
ISSN	21891990
掲載情報	Toho Journal of Medicine. 5(2). p.40-46.
資料種別	学術雑誌論文
内容記述	Original Article
著者版フラグ	publisher
JaLCDOI	info:doi/10.14994/tohojmed.2018-027
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD18050842

Original Article

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

Katsuya Akitsu[1] Rine Nakanishi[1]* Toshio Kinoshita[2]
Hitomi Yuzawa[2] Tadashi Fujino[1] and Takanori Ikeda[1]

[1]Department of Cardiovascular Medicine, Toho University Graduate School of Medicine, Tokyo, Japan
[2]Division of Cardiovascular Medicine, Department of Internal Medicine,
Toho University Faculty of Medicine, Tokyo, Japan

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_2DS_2-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.

Toho J Med 5 (2): 40–46, 2019

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

*Corresponding Author: Katsuya Akitsu, 6-11-1 Omorinishi, Ota, Tokyo 143-8541, Japan, tel: 03–3761–4151
e-mail: Nakanishi.rine@gmail.com
DOI: 10.14994/tohojmed.2018-027

Received Oct. 16, 2018: Accepted Nov. 11, 2018
Toho Journal of Medicine 5 (2), June 1, 2019.
ISSN 2189–1990, CODEN: TJMOA2

Introduction

Atrial fibrillation (AF) is occasionally seen among patients with cancer, and its incidence is increasing.[1] Cancer patients with AF are more likely to experience ischemic stroke, possibly owing to hypercoagulability,[2] 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.[3]

Direct oral anticoagulants (DOACs) constitute an effective treatment strategy for stroke prevention in NVAF patients.[4] 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.[1, 5] 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.[6, 7] 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).[5] The HAS-BLED score was used to assess the bleeding risk.[8, 9]

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 ± 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_2DS_2-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-

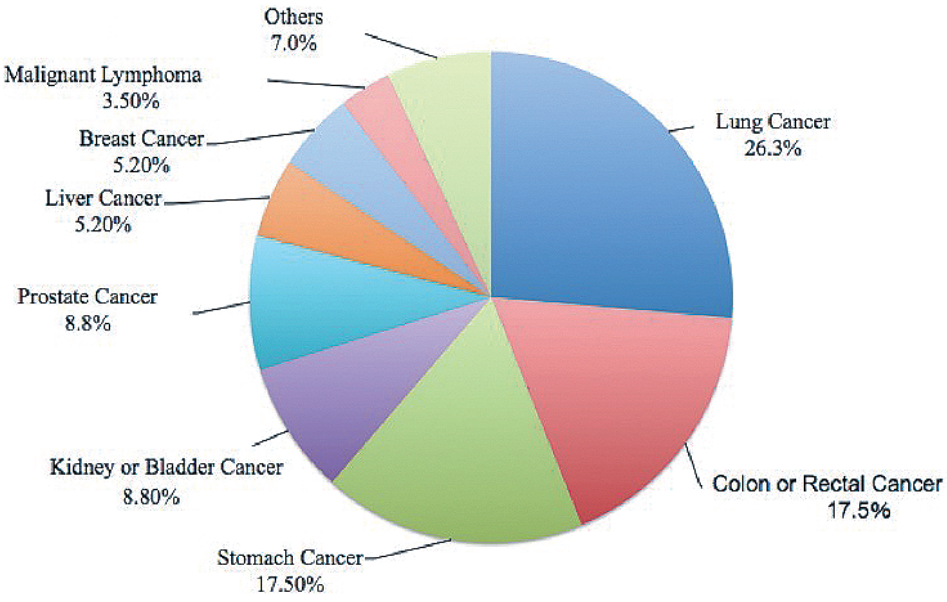

Fig. 1 Types of cancer among study participants.

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 ± 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 $CHADS_2$ score was 1.68 ± 1.25, the CHA_2DS_2-VASc score was 2.88 ± 1.70, and the HAS-BLED score was 1.24 ± 1.0.[10] 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 $CHADS_2$ and CHA_2DS_2-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 cancer patients than in non-cancer patients.

Bleeding events

During the mean follow-up of 19.7 ± 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_2DS_2-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
$CHADS_2$ score	2.14 ± 1.44	1.63 ± 1.21	0.003 *
CHA_2DS_2-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_2DS_2-VASc score) revealed that a significantly higher CHA_2DS_2-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 bleeding 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,[11] and hypoalbuminemia is a significant predictor of bleeding.[11, 12] 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,[11] and the risk for recurrent venous thrombosis is four-fold higher for cancer patients than non-cancer patients.[12] Recent studies reported that cancer patients could be safely and effectively treated with DOACs.[13–15] Although the sample set was small, our group previously reported that in a subanalysis 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
$CHADS_2$ score	1.89 ± 1.41	1.67 ± 1.24	0.445
CHA_2DS_2-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.[16] DOACs are therefore considered a class I indication for preventing venous thrombosis among cancer patients based on current guidelines.[17] 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 previously (0.9%-1.8%).[18] 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.[18] 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.[19] 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_2DS_2-VASc score was associated with an increased incidence of ischemic stroke. The cancer patients were less likely to have a higher CHA_2DS_2-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

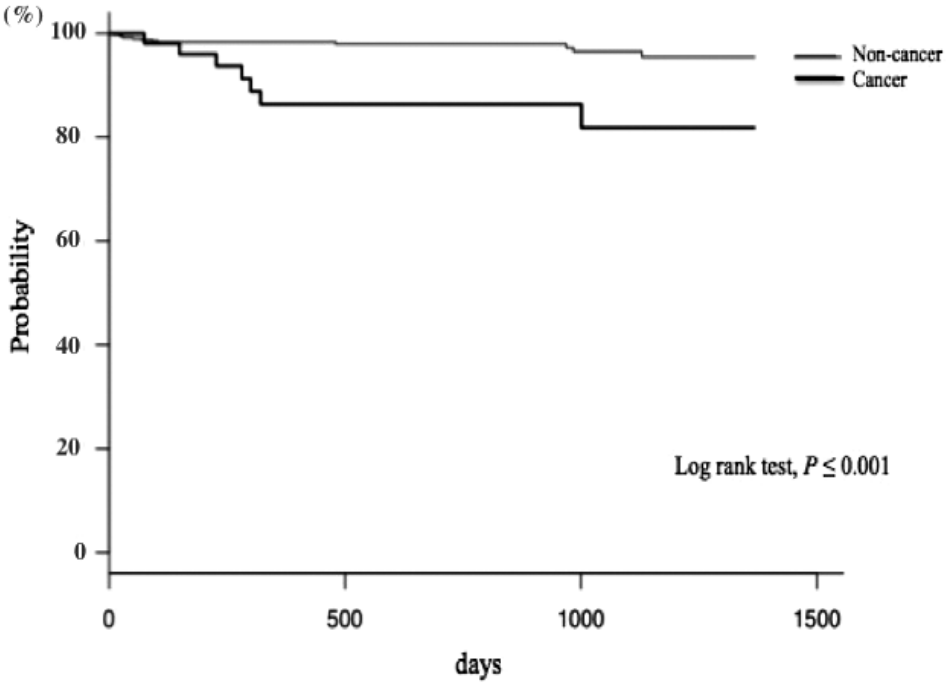

Fig. 2 Kaplan-Meier curve showing the bleeding risk between NVAF patients with or without cancer.
Abbreviation: NVAF = non-valvular atrial fibrillation.

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

No.	Age (years)	Gender	Weight (kg)	BMI	$CHADS_2$-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_2DS_2-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_2DS_2-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.[20] 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.

Disclaimer: Takanori Ikeda is one of the Editors of Toho Journal of Medicine. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Funding and Disclosures: TI received scholarship funds from Daiichi Sankyo, Bristol-Myers Squibb, Medtronic Japan, St. Jude Medical, and Bayer Yakuhin Ltd., and remuneration (e.g., lecture fees) from Daiichi Sankyo, Ono Pharma, Bayer Yakuhin Ltd., Bristol-Myers Squibb, and Pfizer.

Conflicts of interest: Dr. Takanori Ikeda receives grant support from Bayer Pharmaceuticals. The other authors have no conflict of interest.

References

1) Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. J Am Coll Cardiol. 2014; 63: 945-53.
2) Lee MJ, Chung JW, Ahn MJ, Kim S, Seok JM, Jang HM, et al. Hypercoagulability and mortality of patients with stroke and active cancer: the OASIS-CANCER study. J Stroke. 2017; 19: 77-87.
3) Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College Of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017; 70: 3042-67.
4) Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Kardiol Pol. 2016; 74: 1359-469.
5) Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-91.
6) Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace. 2012; 14: 1385-413.
7) January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014; 64: e1-e76.
8) Owada S, Tomita H, Kinjo T, Ishida Y, Itoh T, Sasaki K, et al. CHA_2DS_2-VASc and HAS-BLED scores and activated partial thromboplastin time for prediction of high plasma concentration of dabigatran at trough. Thromb Res. 2015; 135: 62-7.
9) Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol. 2011; 57: 173-80.
10) Developed with the special contribution of the European Heart Rhythm Association (EHRA), Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), Authors/Task Force Members, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31: 2369-429.
11) Posch F, Königsbrügge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: a network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res. 2015; 136: 582-9.
12) Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res. 2014; 134: 1214-9.
13) DiMarco JP, Flaker G, Waldo AL, Corley SD, Greene HL, Safford RE, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J. 2005; 149: 650-6.
14) Ñamendys-Silva SA, González-Herrera MO, Texcocano-Becerra J, Herrera-Gómez A. Hypoalbuminemia in critically ill patients with cancer: incidence and mortality. Am J Hosp Palliat Care. 2011; 28: 253-7.
15) Rojas-Hernandez CM. The role of direct oral anticoagulants in cancer-related venous thromboembolism: a perspective beyond the guidelines. Support Care Cancer. 2018; 26: 711-20.
16) Kabuki T, Nakanishi R, Hisatake S, Fujii T, Dobashi S, Wakakura S, et al. A treatment strategy using subcutaneous fondaparinux followed by oral rivaroxaban is effective for treating acute venous thromboembolism. J Cardiol. 2017; 70: 163-8.
17) Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016; 149: 315-52.
18) Ogawa S, Minematsu K, Ikeda T, Kitazono T, Nakagawara J, Miyamoto S, et al. Design and baseline characteristics of the Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with Atrial Fibrillation (XAPASS). J Arrhythm. 2018; 34: 167-75.
19) Stefan O, Vera N, Otto B, Heinz L, Wolfgang G. Stroke in cancer patients: a risk factor analysis. J Neurooncol. 2009; 94: 221-6.
20) Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol. 2017; 69: 2779-90.