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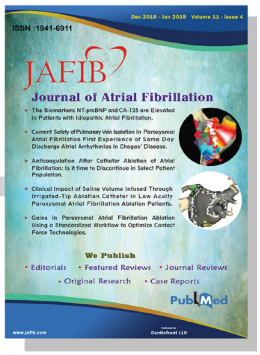

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The Impact of Cancer on Major Bleeding and Stroke/Systemic Emboli in Patients Using Direct Oral Anticoagulants:From the Database of a Single-Center Registry

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Abstract

Background: Few data are available on direct oral anticoagulant (DOAC) use in patients with cancer and atrial fibrillation (AF).

Methods: We retrospectively analyzed prospectively collected data from a single-center registryon 2,272 patients who took DOACs for AF (apixaban:1,014; edoxaban:267; rivaroxaban:498; dabigatran:493). Patients were monitored for 2 years and classified into non-cancer (n=2009) and cancer group (n=263) (cancer onset during DOAC treatment, active cancerat DOAC administration, and cancer history). Major bleeding (MB) and thromboembolic events (TEEs) were evaluated.

Results: The mean age was 73±10 years. $CHADS_2$ and HAS-BLED scores were 1.95 ± 1.32 and 1.89 ± 0.96, respectively. In the present study, the prevalence of gastrointestinal and genitourinary cancer was 61% and 8%, respectively. The MB and TEEs incidences were 2.4 and 2.2 per 100-patient years, respectively. The appropriate dosing rate, body weight, and Ccr value in cancer patients were significantly lower than those in non-cancer patients. Cancer patients were significantly older than non-cancer patients. In MB patients diagnosed with gastrointestinal or genitourinary cancer during follow-up, the clinically relevant bleeding such as melena or hematuria occurred. Additionally, there was a significantly higher MB incidence in cancer patients than in non-cancer patients ($p<0.01$).

Conclusions: AF patients with cancer was associated with a higher risk of MB compared with those without cancer despite higher rate of inappropriate low dose. Bleeding such as melena and hematuria after DOAC administration might suggest that the symptoms are associated with cancer of the site.

Introduction

Atrial fibrillation (AF) is the most frequent sustained type of arrhythmia; it affects 1.5% to 2% of the general population, and this prevalence increases to 10% at 80 years of age and to 18% at 85 years of age[1-3]. In addition to aging, several cardiovascular conditions such as hypertension, heart failure, and valvular disease, as well as noncardiovascular conditions such as chronic pulmonary disease, diabetes, electrolyte abnormalities, thyroid dysfunction, and chronic kidney disease predispose patients to developing AF[2]. Cancer is a risk factor of AF[4] that predisposes patients to serious complications such as a five fold increased risk of stroke, a three fold increased risk of heart failure, and nearly a doubled risk of death[1,5,6]. While oral anticoagulants are effective in reducing the risk of stroke[1,7], they increase the risk of bleeding[8].

Although some studies have described the relationship between AF and venous thromboembolism (VTE)[9], few data are available on the adverse effects of anticoagulation in cancer patients with AF. Although direct oral anticoagulant (DOAC) trials in AF patients included only a few cancer patients (in particular, those with a life expectancy that was assumed to be long)[10-13], DOACs are prescribed increasingly to AF patients with cancer[14].

Given the increasing occurrence of malignancies in elderly people and the coexistence of other conditions that predispose cancer patients to developing AF, an association between these two conditions would be expected[14]. Therefore, considering that both AF and cancer occur frequently, any increased risk of thromboembolic events and bleeding may have major public health implications. Hence, we examined the risks of thromboembolic events and bleeding complications in AF patients with and without cancer who were prescribed DOACs.

Key Words

Direct Oral Anticoagulant, Atrial Fibrillation, Major Bleeding, Stroke, Systemic Embolism, Cancer

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Methods

Ethical considerations

The institutional database that was used in this study was approved by our local ethics committee, and informed consent was obtained from all patients.

Study design and population

For this retrospective analysis, we identified 2,272 consecutive pa-

tients who were prescribed a DOAC for AF, including paroxysmal AF, between September 2011 and January 2016 at the Tachikawa General Hospital, Nagaoka, Japan. Data on the patients' baseline characteristics; history, including comorbidities (coronary artery disease and peripheral artery disease); and clinical outcomes, including those at the 2-year follow-up interval, were collected. Patients with valvular disease requiring surgery, those with a prosthetic mechanical heart valve, and those with mitral stenosis were excluded.

Baseline characteristics such as age;sex; body weight; renal function (creatinine clearance[Ccr] and creatinine); coronary artery disease and peripheral artery disease; Congestive Heart Failure, Hypertension, Age ≥ 75Years, Diabetes Mellitus ($CHADS_2$) score; and Hypertension, Renal Disease and Liver Disease, Stroke History, Prior Major Bleeding or Predisposition to Bleeding, Age >65 years, Medication Usage Predisposing to Bleeding (HAS-BLED) score were compared among patients receiving each type of DOAC therapy. All patients in the DOAC database were included in the analysis.

The prescription of DOAC

Four DOACs (apixaban [N=1,014], rivaroxaban [N=498], edoxaban [N=267], and dabigatran [N=493]) were prescribed for AF per the doctor's discretion. The prescription dose was decided according to the regimen for each DOAC in Japan. In Japan, lower doses of dabigatran should be considered for elderly patients (age ≥70 years), patients with moderate renal impairment (Ccr 30–49mL/min), those with concomitant use of interacting drugs (e.g., verapamil), or those with a high risk of bleeding. Lower doses of rivaroxaban should be considered for patients with moderate renal impairment (Ccr 30–49mL/min).

Lower doses of edoxaban is recommended in patients with moderate or severe renal impairment (Ccr 15–49mL/min), those with weight ≤60kg or those with concomitant use of interacting drugs (e.g., verapamil), while low-dose apixaban is recommended in patients with at least two of the following: age ≥80 years, weight ≤ 60kg, or serum creatinine ≥1.5mg/dL. However, an over- or under-dose was also prescribed per the doctor's discretion. The baseline characteristics of the patients who were administered one of these four DOACs are presented in Supplementary [Table 1].

The definition of cancer

A history of cancer was checked before starting DOAC therapy. When gastrointestinal disorder or hematuria developed, the presence of malignancies was checked. According to a previous paper[15], the patients with cancer were classified into three groups: those in whom cancer was diagnosed during DOAC treatment (n=64), those who had active cancer at the time a DOAC was prescribed (n=63), and those with a history of cured cancer at the time a DOAC was prescribed (n=136). "Active cancer at the time a DOAC was prescribed" was defined as cancer that was diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment was administered within 6 months before a DOAC was prescribed; or hematologic cancer that was not in complete remission[16].

Clinical outcome

The primary outcome was stroke, systemic embolism orVTE the main safety outcome was major bleeding, defined using the Randomized Evaluation of Long-Term Anticoagulant Therapy criteria[10,17].

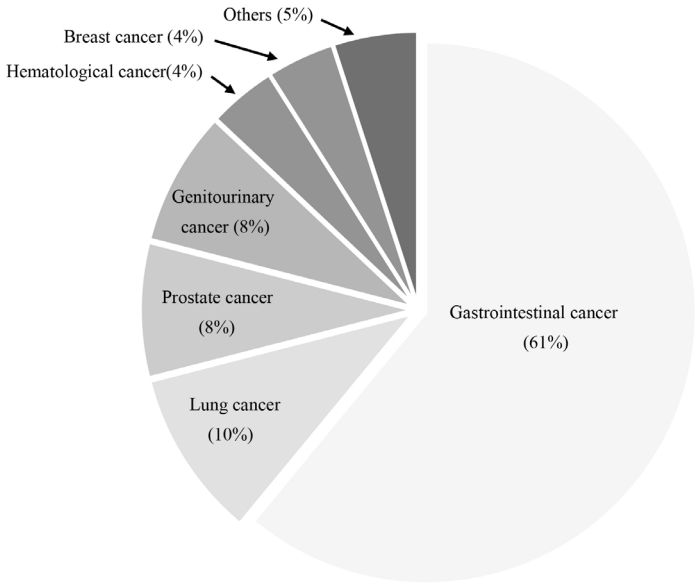

Table 1: The category of cancer (N=263)

Statistical Analysis

Continuous data with a normal distribution are presented as means ± standard deviations, and categorical data are presented ascounts with percentages. The cancer andnon-cancer groups were compared using a Student t-test test for continuous data and Fisher's exact test for categorical data. Cancer that was diagnosed during DOAC treatment, active cancer at the time a DOAC was prescribed, and cancer history at the time a DOAC was prescribed were compared using analysis of variance for parametric data, followed by multiple comparisons using Dunn's method, and using a chi-squared testfor categorical data. In addition, using Kaplan-Meier event rate curves, we compared the outcomes of major bleeding and stroke/systemic emboli/VTE of patients in the cancer group with the outcomes of those in the non-cancer group. A two-sided p-value <0.05 was considered statistically significant for all analyses.

Results

Patient characteristics

Overall, the mean age of the patients in this study was 73 ± 10 years. The CHADS2 and HAS-BLED scores were 1.95±1.32 and 1.89±0.96, respectively. Among the 263 patients with cancer (11.5%), the category of cancer is shown in Table1. Overall, the incidences of major bleeding and thromboembolic events were2.4 and 2.2 per 100-patient years, respectively.

Comparison of baseline characteristics between patients in the cancer group and those in the non-cancer group [Table 2]

A comparison of the cancer group (n=263) and the non-cancer group (n=2,009) revealed that the $CHADS_2$ and HAS-BLED

scores in the cancer group were significantly higher than those in the non-cancer group (2.14 ± 1.23 vs. 1.92 ± 1.33, p=0.038; 2.02 ± 0.87 vs. 1.86 ± 0.96, p<0.01, respectively). Furthermore, the rate of

Table 2: Baseline characteristics of the non-cancer and the cancer groups in this study

	Non-cancer group	Cancer group	P value
N	2009	263	-
Age (years)	72±10	76±7	<0.01
Male (%)	62	71	<0.01
Body weight (kg)	60.5±10.3	56.7±11.7	<0.01
Ccr (ml/min)	62.5±18.5	55.9±12.5	<0.01
Cr (mg/dl)	0.91±0.24	0.92±0.25	0.53
CAD	194(9.6)	29(11.2)	0.31
PAD	65(3.2)	10(3.8)	0.26
Stroke or TIA	286(14.2)	52(19.3)	0.03
Carotid stenosis	25(1.2)	4(1.4)	0.80
Intracranial bleeding	39(2.0)	4(1.4)	0.59
GI bleeding	25(1.3)	15(5.5)	0.01
Anti-platelet therapy	266(16.6)	38(15.0)	0.53
Appropriate dose (%)	78	72	0.08
$CHADS_2$ score	1.92±1.33	2.14±1.23	<0.01
HAS-BLED score	1.86±0.96	2.02±0.87	<0.01
All-cause death (100-patient years)	3.2	9.8	<0.01
Cancer-associated death	0	6.8	
Major bleeding (100-patient years)	2.1	6.3	<0.01
Intracranial bleeding	0.7	0.3	
Gastrointestinal bleeding	1.1	4.8	
Stroke/emboli/VTE (100-patient years)	1.9	3.4	0.08
Ischemic strokes	1.5	2.0	
VTE	0	0.8	

Data are presented as the mean ± standard deviation or n (%). DOAC: direct oral anticoagulant; Ccr, creatinine clearance; CAD, coronary artery disease; PAD, peripheral artery disease; TIA, transient ischemia attack; CHADS2 score, Congestive Heart Failure, Hypertension, Age ≥ 75 Years, Diabetes Mellitus, Stroke; HAS-BLED score, Hypertension, Renal Disease and Liver Disease, Stroke History, Prior Major Bleeding or Predisposition to Bleeding, Age >65, Medication Usage Predisposing to Bleeding score

the appropriate dose, body weight, and Ccr value in patients in the cancer group were significantly lower than those in patients in the non-cancer group (72% vs.78%,p<0.01; 56.7±11.7 vs. 60.5 ± 10.3kg, p<0.01; 55.9 ± 12.5 vs. 62.5 ± 18.5mL/min, p<0.01, respectively), and the patients in the cancer group were significantly older than those in the non-cancer group (76 ± 7 vs. 72±10 years, p<0.01).

Comparison of baseline characteristics among the three sub-groups ofthe cancer group

There were no significant differences in age, Ccr value, body weight, the rate of the appropriate dose, $CHADS_2$ score, and HAS-BLED score among the three sub-groups of the group of patients with cancer [Table 3]. Furthermore, in the cancer group, 39 patients received some form of chemotherapy, including hormone therapy.

Detailed comparison ofmajor bleedingand stroke between the cancer and non-cancer groups

As shown in [Table 2], the incidences of major bleeding and stroke/systemic emboli/VTE in the non-cancer group were 2.1 per 100-patient years and 1.9 per 100-patient years, respectively. In contrast, in the cancer group, the incidences of major bleeding and stroke/systemic emboli/VTE were 6.3 per 100-patient years and 3.4per 100-patient years, respectively. There was a significant difference in the incidence of major bleeding between the non-cancer and cancer groups (p<0.01). In the cancer group, the incidences of major bleeding and stroke/systemic emboli/VTE in those with cancer that was diagnosed during DOAC treatment, those with active cancer at the time a DOAC was prescribed, and those with a history of cancer at the time a DOAC was prescribed were 12.2 per 100-patient years, 5.7 per 100-patient years, and 3.0 per 100-patient years, and 4.3 per 100-patient years, 6.9 per 100-patient years, and 1.5 per 100-patient years, respectively (p<0.01 and p=0.24) (Table 3). There were no significant differences in the incidences of major bleeding and stroke/systemic emboli/VTE between non-cancer group and those with a history of cancer at the time a DOAC was prescribed. Furthermore, to evaluate the incidence of major bleeding and stroke/systemic emboli/VTE in patients with chemotherapy, the cancer patients (39 patients) receiving chemotherapy weres elected. The chemotherapy regimen is shown in [Table 4A]. The incidences of major bleeding and stroke/systemic emboli/VTE in patients receiving chemotherapy were 3.7per 100-patient years and 7.5per 100-patient years, respectively [Table 4B]). Moreover, of 41 patients

Table 3: The comparison among the cancer history, active cancer, and cancer diagnosed during DOAC administration groups

	Cancer history	Active cancer	Cancer during DOAC	P value
N	136	63	64	-
Age (years)	76±7	76±8	76±8	0.97
Male (%)	70	77	70	<0.01
Body weight (kg)	56.8±11.7	56.5±11.1	57.3±13.3	0.82
Ccr (ml/min)	54.2±19.9	58.1±21.1	57.3±23.8	0.43
Cr (mg/dl)	0.95±0.23	0.89±0.28	0.90±0.25	0.51
CAD	12 (8.8)	7 (11.1)	10 (15.6)	0.52
PAD	6 (4.4)	2 (3.1)	2 (3.1)	0.76
Stroke or TIA	23 (16.9)	14 (22.2)	15 (23.4)	0.49
Carotid stenosis	2 (1.4)	1 (1.5)	1 (1.5)	0.98
Intracranial bleeding	4 (2.9)	0 (0)	0 (0)	0.20
GI bleeding	4(2.9)	6 (9.5)	5 (7.8)	0.18
Anti-platelet therapy	16 (11.7)	13 (20.6)	9 (14.0)	0.26
Appropriate dose (%)	76	60	75	<0.01
$CHADS_2$ score	2.13±1.22	2.00±1.26	2.29±1.21	0.40
HAS-BLED score	1.95±0.87	2.16±0.89	2.00±0.83	0.34
Any cause death (100-patient years)	2	16	8	<0.01
Cancer-associated death	0	12	6	0.08
Major bleeding (100-patient years)	3.0	5.7	12.2	<0.01
Stroke/emboli/VTE (100-patient years)	1.5	6.9	4.3	0.14

Data are presented as the mean ± standard deviation or n (%). Event rate was described as event per 100-patient years. DOAC, direct oral anticoagulant; Ccr, creatinine clearance; Cr, creatinine; CAD, coronary artery disease; PAD, peripheral artery disease; TIA, transient ischemia attack; CHADS2 score, Congestive Heart Failure, Hypertension, Age ≥ 75 Years, Diabetes Mellitus, Stroke; HAS-BLED score, Hypertension, Renal Disease and Liver Disease, Stroke History, Prior Major Bleeding or Predisposition to Bleeding, Age >65, Medication Usage Predisposing to Bleeding score; VTE, venous thromboembolism

who were diagnosed with gastrointestinal or genitourinary cancer during the follow-up period after a DOAC was prescribed, 32(78%) had clinical events such as melena, hematuria, and cause unknown anemia that was associated with the cancer site as the prodrome.

The Kaplan-Meier analysis revealed that the incidence of major bleeding in the cancer group was significantly higher than that in the non-cancer group (Logrank:p<0.01), and in addition the incidence of stroke/systemic emboli/VTE in the cancer group tended to be higher than that of the non-cancer group (Logrank: p=0.08) [Figure 1].

Predictors for bleeding in patients using DOAC [Table 5]

Multiple logistic regression analyses were performed to determine the independent predictors for major bleeding. As a result, multiple logistic analyses revealed that cancer and lower body weight were independent predictors for major bleeding in patients using DOAC. In addition, there was no difference in the impact of the type of DOAC on major bleeding.

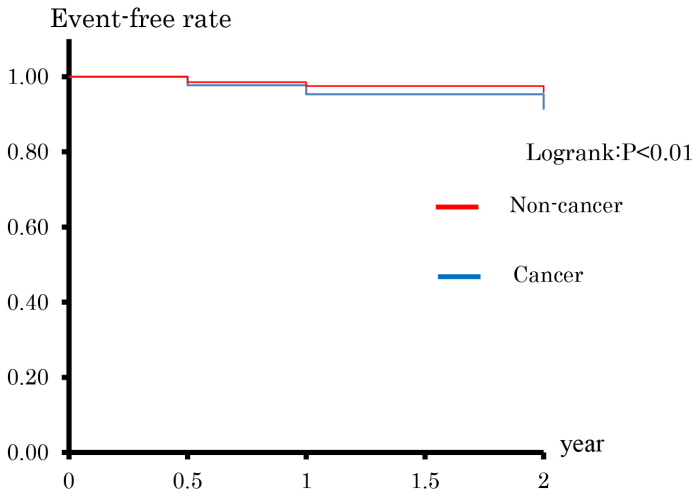

Figure 1A: The Kaplan-Meyer for major bleeding between cancer group and non-cancer group

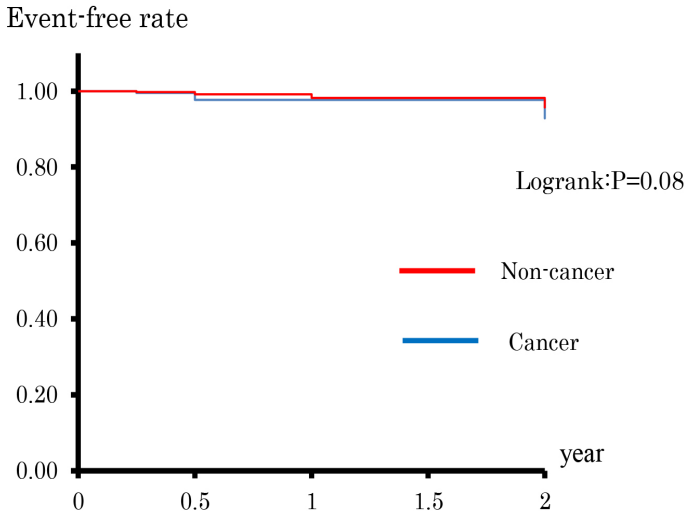

Figure 1B: The Kaplan-Meyer for stroke/systemic emboli/VTE between cancer group and non-cancer group

Discussion

The main findings of the present study are as follows: 1) patients with AF who had cancer under the administration of a DOAC had a higher incidence of major bleeding than those without cancer. Especially, patients who were diagnosed with cancer during the administration of a DOAC, had a higher incidence of major bleeding than those in the other cancer groups, 2) the incidence of stroke/systemic emboli/VTE in the cancer group tended to be higher than that of the non-cancer group. 3) Bleeding such as melena and hematuria after the administration of DOACs might indicate the presence of any type of cancer at the same site.To the best of our knowledge, this is first report to describe the impact of cancer on major bleeding and stroke/systemic emboli/VTE in patients using a DOAC, as well as to evaluate the influence of chemotherapy in single center registry.

Cancer and AF

The bulk of epidemiological evidence on the association between AF and cancer is generally limited, with the exception of AF after surgery for cancer. Several studies reported that the prevalence of AF in patients with cancer was significantly greater than that of those without AF[18-20]. AF in cancer patients may be a comorbid state because these patients share several factors that predispose them to AF, such as advanced age, electrolyte abnormalities, hypoxia, and metabolic disorders[21-23]. Thus far, the potential pathogenetic links between cancer and AF are supposed to be due to the following mechanisms: 1) a direct effect, 2) paraneoplastic manifestations, 3)an autonomicnervous system due to pain and physical stress, 4) medical therapy for cancer, 5) surgical therapy, 6) cancer-related morbidity, and 7) inflammation[14]. Therefore, AF has been found to occur with an increased frequency in patients with malignancies.

Table 4A: Chemotherapy regimen, including hormone therapy in the cancer group

	(N=39)
CBDCA + PTX	3
CBDCA + VP-16	4
CBDCA+PEM	1
CDDP + GEM	2
FOLFOX, UFT/UZEL	1
Gefitinib	1
R-CHOP	6
Regorafenib	1
5-FU+LLV	1
GEM+ PTX	1
TS-1	3
UFT	3
LH-RH	12

CBDCA, carboplatin; PTX, paclitaxel; VP-16; Etoposide; PEM, pemetrexed; GEM, Gemcitabine; 5-FU, 5- fluorouracil; FOLFOX, fluorouracil, folinic acid and oxaliplatin; UFT/UZEL, tegafur/uracil, folinate; R-CHOP, rituximab, cyclophosphamide hydroxydaunorubicin, oncovin and prednisone; LLV, l-leucovorin; TS-1 ,Tegafur/Gimeracil/Oteracil; LH-RH, luteinizing hormone-releasing hormone

Table 4B: The incidence of major bleeding and stroke/systemic emboli in the chemotherapy group of the cancer group

	Chemotherapy
Major bleeding	3.7
Stroke/systemic emboli	7.5
Appropriate dose (%)	52

Event rate was described as event per 100-patient years.

Cancer and DOAC

Treating AF in patients with malignancies is challenging, especially in terms of antithrombotic therapy, because cancer is itself a prothrombotic state, thus further increasing the risk of thromboembolic events in patients with AF[24-27]. However, the increased risk of bleeding in patients with an active malignancy also raises concerns about the safety of DOACs in this population. Cancer patients were reported to be at a two- to six- fold higher risk

of experiencing bleeding events while on anticoagulant therapy[26-27]. In cancer patients, VTE was reported as the second leading cause of death in patients with cancer[28]. The incidence of clinically important bleeding during anticoagulant therapy, even in VTE patients with cancer, was significantly higher than in those without cancer[27]. In addition, a large cohort study of 24,125 patients with newly diagnosed cancer found that although the $CHADS_2$ score predicted the risk of thromboembolism in patients with AF at baseline, it did not predict thromboembolic events in those with new-onset AF (i.e., AF that occurred after cancer was diagnosed)[29].Therefore, thromboembolic and hemorrhagic risk prediction scores such as the $CHADS_2$ and HAS-BLED scores might not be applicable in patients with a malignancy.

There is a paucity of data regarding the choice of anticoagulant, including DOACs, in cancer patients with AF. In a recent study, apixaban was found to have a greater benefit for major bleeding and the composite of stroke/systemic embolism than vitamin K antagonist[30]. In the present study, the incidence of stroke/systemic emboli/VTE in the cancer group was comparable to that in the non-cancer group, which was compatible with this finding. In addition, many studies on the relationship between anticoagulation therapy and cancer in patients with VTE have reported that DOAC therapy was not inferior to low-molecular-weight heparin or a vitamin K antagonist[16,31,32]. Although these reports were concerned with the safety and efficacy of DOACs in patients with VTE and cancer, these reports might indicate that the administration of DOACs does work in cancer-associated cases. Several studies have reported that cancer patients with DOAC tend to suffer from major bleeding more frequently than patients without cancer[16,32,33]. These findings are similar to the present results. While, several previous reports has also described that safety of DOACs might be superior to low-molecular-weight heparin or a vitamin K antagonist in patients with cancer[30,34]. In addition, although the background of patients may be different, the safety of DOAC in the present study was not at least inferior to that of another anticoagulation therapy in patients with AF and cancer[35]. Furthermore, in VTE trials, patients with an active malignancy were either excluded or the number of enrolled patients was small, ranging from 2.6% to 6%[36,38]. In addition, the type and stage of malignancy and the concomitant use of chemotherapy were also not reported. Therefore, these results should be interpreted with caution.

In the present study, 78% of the patients who were diagnosed with gastrointestinalor genitourinary cancer during the follow-up period after a DOAC was administered had clinical eventssuch asmelena, hematuria, and cause unknown anemia that was associated with the cancer site as the prodrome. This finding might be associated with a report that found that gastrointestinal bleeding is often caused by an occult malignancy in patients receiving anticoagulation therapy; as a result, gastrointestinal cancer could be detected earlier[39]. However, 9patients (22%) of the remaining who were diagnosed with cancer during the follow-up period after a DOAC was administered were found to have cancer during a routine medical check-up incidentally. Thus, it might be difficult to create a model for predicting cancer during DOAC administration in the present study. However, the present study might imply that in cases where patients develop melena, hematuria, and cause unknown anemia during DOAC administration, the possibility of gastrointestinal or genitourinary cancer must be explored.

In addition, the present study included patients with a previous operation such as gastrectomyorcolectomy. However, the incidences of major bleeding and stroke/systemic emboli/VTE in those with a history of cancer at the time a DOAC was prescribed was comparable to those in the non-cancer group. In other words, this finding might indicate that DOACs are safe for patients with a past operation such as gastrectomyorcolectomy. Furthermore, compared to a previous report[40], the incidence of VTE in cancer group was obviously low. This finding might be because the patients in the present study received the administration of DOAC.

In the present study, cancer patients who underwent chemotherapy were also included. It is not clear if the doses of DOACs that are used to treat AF or VTE in the general population will provide the same protection against stroke/systemic emboli/VTE in patients with an active malignancy because many chemotherapeutic agents have been reported to have significant interactions with the CYP3A4 enzyme and/or P-glycoprotein transporter, which can alter a DOAC's level of anticoagulation and predispose patients to bleeding or thrombotic complications[41-43]. In fact, data on the combined use of any DOACs and specific chemotherapy agents do not exist[41]. Strong and moderate modulators of the CYP3A4 enzyme especially those that also interact with the P-glycoprotein transporter have especially been reported to carry the highest relative risk for significant drug interactions with DOACs[42]. Furthermore, some chemotherapies may also cause thrombocytopenia.

Table 5: Multivariate logistic regression analysis

	Odds Ratio	95% confidence interval	P value
Cancer	2.78	1.59-4.84	<0.01
Ccr (ml/min)	0.99	0.98-1.01	0.79
Appropriate dose	0.57	0.32-1.01	0.055
Age (years)	1.01	0.97-1.05	0.63
Male	1.25	0.70-2.22	0.43
Body weight (kg)	0.96	0.93-0.99	0.03
CHADS2 score	1.28	0.99-1.65	0.058
HAS-BLED score	1.02	0.71-1.45	0.91
Apixaban	1.52	0.75-3.08	0.24
Edoxaban	1.27	0.49-3.29	0.61
Rivaroxaban	0.65	0.25-1.65	0.36
Dabigatran	1.18	0.64-2.43	0.41

Ccr, creatinine clearance; CHADS2 score, Congestive Heart Failure, Hypertension, Age ≥ 75 Years, Diabetes Mellitus, Stroke; HAS-BLED score, Hypertension, Renal Disease and Liver Disease, Stroke History, Prior Major Bleeding or Predisposition to Bleeding, Age >65, Medication Usage Predisposing to Bleeding score.

DOACs should be used with caution in these cases. In fact, in the present study, approximately 50% of the patients receiving chemotherapy were prescribed inappropriate low dose of DOACs. This might result from the fact that the incidence of the stroke/systemic emboli/VTE in chemotherapy group (7.5 per 100-patient years) was high. Therefore, in the real world, clinicians should not only pay attention to the cancer site but also the chemotherapy regimen when administering DOACs to patients with a malignancy and AF.

Limitations

The limitations of this study are as follows. First, although this study was retrospective in design, data on the clinical outcomes, including those at the 2-year follow-up interval, of all patients were collected prospectively. However, a propensity score was not adopted because the variation in the number of patients in the four DOAC groups was large. In addition, at the entry, screening for cancer and the marker such as the initial d-dimer value was not performed. Second, in addition, in the present study, data of AF patients treated by another anticoagulation therapy were not included. Therefore, vitamin K antagonists or heparin data should have also be added. Third, because the present study was retrospective, clinical events such as minor bleeding might not have been detected completely. Fourth, patients with a malignancy were included. However, the stage of malignancy was not evaluated. Fifth, in the present study, because baseline characteristics were quite different between patients with and without cancer, patients with cancer were speculated to be at high risk state for major bleeding, stroke, or VTE in advance. In addition, because the present study was retrospective, we could not create a model to predict major bleeding in patients with cancer DOAC administration. Therefore, further detailed study regarding patients with cancer should be performed. Consequently, no definite conclusion can be drawn from the results of this study. These limitations warrant future studies involving larger populations in long term.

It is possible that due to a small clinical affect we do not see a significant increase in fluid overload read missions when using HSVIAC in the number of patients that we have studied. However with a larger number or higher acuity (systolic heart failure or chronic renal disease) patients this may become clinically significant. Further studies are needed to confirm this potential outcome.

Conclusion

AF patients with cancer was associated with a higher risk of major bleeding compared with those without cancer despite higher rate of inappropriate low dose. Therefore, further detailed study regarding DOACs prescription in patients suffering from any type of cancer and require chemotherapy may be needed. In addition, bleeding such as melena and hematuria after DOAC administration might suggest that the symptoms are associated with cancer of the site.

Disclosure

None.

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