CLINICAL STUDY

Comparative Bleeding Risk in Patients with Atrial Fibrillation with Cancer versus Without Cancer from Nationwide Prospective Cohort

CODE-AF Registry

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Summary

Comparison of the bleeding risk for long-term oral anticoagulation (OAC) in patients with nonvalvular atrial fibrillation (AF) with and without cancers has been inconsistent. This study aimed to clarify the differences in the bleeding risk in patients with AF with cancers and those without cancers during the long-term OAC.

The CODE-AF prospective registry enrolled 5,902 consecutive patients treated for AF at 10 tertiary referral centers in Korea. Of the enrolled patients, 464 (7.8%) were diagnosed with cancers and were followed for all stroke and bleeding events (net composite events).

The age, CHA_2DS_2-VASC, and HAS-BLED scores were similar between AF patients with and without cancers. Male population greatly comprised patients with AF with cancers. They were equally prescribed with direct OAC compared to those without cancers. The incidence rate for clinically relevant nonmajor (CRNM) bleeding events was higher in the patients with AF with cancers than in those without cancers (4.4 per 100 person-years versus 2.8 per 100 person-years, $P = 0.023$), and net composite events were also more frequent in patients with AF with cancers than in those without cancers (6.4 per 100 person-years versus 4.0 per 100 person-years, $P = 0.004$). Patients with AF with cancers showed a significantly higher rate of CRNM bleeding (hazard ratio [HR] 1.54, confidence interval [CI] 1.05-2.25, $P = 0.002$) than those without cancers.

Based on the AF cohort, AF with cancers could face a significantly higher risk for CRNM bleeding events in the long-term OAC than those without cancers.

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Key words: Non-valvular atrial fibrillation, Anti-coagulation, Composite events

Atrial fibrillation (AF) is the most common arrhythmia, which can be complicated by stroke with thromboembolism; however, long-term oral anticoagulation (OAC) is associated with a risk of bleeding events.[1)] In patients with nonvalvular AF (NVAF), CHA_2DS_2-VASc and HAD-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, and Elderly, Drugs/alcohol concomitantly) scores are the most commonly used tools to evaluate the risk of ischemic

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stroke and bleeding events with OAC.[1,2] Recent studies demonstrated that cancers could uncommonly coexist with AF, as a comorbid diagnosis.[3,4] Several types of cancers have been particularly associated with thromboembolism and bleeding events, and previous large cohort studies have demonstrated that patients with AF with cancers were at a higher bleeding risk with similar rates of thromboembolic events than those without cancers.[5,6] Especially, cancers in AF influence bleeding adverse outcomes, and the clinical benefits of OAC in patients with NVAF with cancers are still under debate.[4] Bleeding adverse outcomes have not been proven in patients with AF with cancers in the Asian population.[7] Therefore, in a prospective national cohort of patients with NVAF, we investigated and compared all bleeding and composite events (all stroke and bleeding) during long-term OAC in AF patients with versus without cancers.

Methods

Study population: The CODE-AF is a prospective registry of patients with NVAF of age over 18 years old who are consecutively enrolled from over 10 tertiary referral centers, encompassing all the geographical provinces of South Korea. The study design has been previously described[8] and coordinated by the Korea Heart Rhythm Society, which supports national coordinators and participating centers. Data are entered into a common electronic web-based database that limits inconsistencies and errors and provides online help for all key variables. The study was approved by the ethics committee of each center (4-2016-0105) and all patients provided informed consent and registered at ClinicalTrials.gov (NCT02786095). The collected data were registered and adjusted in the web-based clinical research management system, iCreat (internet-based clinical research and trial management system, http://icreat.nih.go.kr), provided by the Korean government. From June 2016 to Dec 2017, a total of 5902 patients with NVAF were prospectively and consecutively enrolled in all centers.

Guideline-directed oral anticoagulation: CHA_2DS_2-VASc and HAS-BLED scores were calculated for all patients with NVAF enrolled in all the centers. In patients with NVAF, based on the CHA_2DS_2-VASc score, OAC was strongly prescribed according to the 2016 European Society of Cardiology and 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for patients with AF.[1,9]

Study follow-up and clinical outcome: Outpatient follow-up visits were scheduled every 3 or 6 months, and a personal phone interview was performed for those who could not make the follow-up visit. Active cancer was defined as recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer in incomplete remission.[10] Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a decline in hemoglobin levels of 2 g/dL or more, leading to transfusion of two or more units of whole blood or red cells.[11] CRNM was defined as overt bleeding associated with medical intervention, unscheduled visits with healthcare professionals, or discomfort which did not meet the criteria for major bleeding.[12] Finally, net composite events were defined as all stroke and bleeding events.

Statistical analysis: Continuous variables are presented as the means ± standard deviations, and categorical variables are expressed as frequencies or percentages. The predicted probability of clinical outcomes was evaluated using Cox regression hazard model, as shown in the Table. The product limit (Kaplan-Meier) method of survival probability calculated the cumulative incidence and its curve and the 95% confidence interval for bleeding. The survival curves between the AF with and without cancers were compared using the stratified log-rank test. Statistical analyses were performed using SPSS (SPSS Inc., version 20.0, Chicago, IL, USA) and MedCalc (MedCalc software, version 12.3, Acacialaan, Ostend, Belgium). A P value < 0.05 was considered statistically significant.

Result

Baseline characteristics: Of the total enrolled patients, 464 (7.8%) were previously diagnosed with cancer. The age and the CHA_2DS_2-VASC and HAS-BLED scores were similar between the AF groups with and without cancers. However, the AF with cancer group had a larger proportion of males, a lower BMI, and a larger left atrial size than the AF without cancer group. Among the patients with AF with cancers, gastro-intestinal and genitourinary cancers were more frequently found than others (Table I).

Anticoagulation, bleeding, and composite events: Most patients with AF were prescribed with OAC based on the current guideline, and the two groups of patients with AF with and without cancers were similarly prescribed (Table I). The sex and BMI were not significantly associated with risk of all bleeding (Supplemental Table II). Regardless of underlying disease, overall bleeding risk in patients with AF with cancers was significantly higher than in those without cancers (3.2% versus 1.1%, P = 0.001) (Figure 1). The incidence rates for ischemic stroke, CRNM bleeding, all bleeding, and net composite events were more frequent in the AF with cancer group than in those without cancer group (0.9 per 100 person-years versus 0.7 per 100 person-years, P = 0.496, 4.4 per 100 person-years versus 2.8 per 100 person-years, P = 0.023, 5.5 per 100 person-years versus 3.5 per 100 person-years, P = 0.009, 6.4 per 100 person-years versus 4.0 per 100 person-years, P = 0.004) (Table II) (Figure 2). The AF with cancer group showed a significantly higher risk of CRNM bleeding, all bleeding, and net composite events (hazard ratio [HR] 1.54, confidence interval [CI] 1.05-2.25, P = 0.002, HR 1.56, CI 1.11-2.19, P = 0.011, HR 1.56, CI 1.14-2.16, P = 0.002) compared with those without cancer (Table III) (Figure 3). In the AF with cancer group, genitourinary and lung cancers were associated with a significantly high risk of all bleeding (HR 2.10, 95% CI 1.17-3.78, P = 0.013, HR 2.27, 95% CI 1.06-4.87, P = 0.036) (Supplemental Table I). In addition, adenocarcinoma among the AF with cancer was significantly associated with all bleeding (Supplemental Table III).

Table I. All Patients' Baseline Characteristics

	AF without cancer (n = 1890)	AF with cancer (n = 464)	P
Age	75.0 ± 9.0	74.9 ± 9.2	0.869
Male (%)	1077 (57.0)	310 (66.8)	< 0.001*
BMI, kg/m^2	24.6 ± 3.3	23.9 ± 3.5	< 0.001*
CHA_2DS_2-VASc score	3.4 ± 1.6	3.2 ± 1.6	0.050
HAS-BLED score	2.2 ± 1.0	2.1 ± 1.0	0.052
HTN (%)	1322 (69.9)	316 (68.1)	0.473
DM (%)	496 (26.2)	137 (29.5)	0.171
Stroke/TIA (%)	326 (17.2)	67 (14.4)	0.166
Peripheral artery disease (%)	99 (5.2)	21 (4.5)	0.612
Dyslipidemia (%)	621 (32.9)	142 (30.6)	0.371
Previous MI (%)	75 (4.0)	12 (2.6)	0.202
Previous HF (%)	248 (13.1)	52 (11.2)	0.303
ESRD on dialysis (%)	46 (2.5)	16 (3.5)	0.288
LV EF (%)	47.7 ± 28.2	53.7 ± 20.9	< 0.001*
LA diameter AP (mm)	35.4 ± 22.2	39.4 ± 16.6	< 0.001*
Treatment			
Warfarin (%)	382 (20.2)	59 (12.7)	< 0.001*
Direct OAC (%)	1123 (59.4)	274 (59.1)	0.927
Rivaroxaban (%)	255 (13.5)	59 (12.7)	
Dabigatran (%)	337 (17.8)	59 (12.7)	
Apixaban (%)	381 (20.2)	111 (24.0)	
Edoxaban (%)	150 (7.9)	45 (9.7)	
Antiplatelet therapy (%)	352 (18.6)	100 (21.6)	0.171
Anti-arrhythmic drug (%)	822 (43.5)	194 (41.8)	0.546
Follow-up duration (year)	1.90 ± 1.09	1.90 ± 1.07	0.999
Classification of cancer			
Gastro-intestinal cancer (%)		165 (35.6)	
Genito-urinary cancer (%)		95 (20.5)	
Lung cancer (%)		52 (11.2)	
Thyroid cancer (%)		49 (10.5)	
Breast cancer (%)		39 (8.4)	
Hepato-biliary cancer (%)		28 (6.0)	
Status of cancer			
Chemotherapy (%)		319 (68.8)	
Surgical therapy (%)		403 (86.9)	
Active cancer (%)		266 (57.3)	

Values are presented as mean ± standard deviation for continuous variables or as number (%) for categorical variables. AF indicates atrial fibrillation; BMI, body mass index; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; and OAC, oral anti-coagulant. *Statistically significant.

Discussion

In the national prospective AF cohort, OAC in patients with AF with cancers was associated with a significantly higher risk of all bleeding, particularly CRNM bleeding events, compared with those without cancers in long-term observation. Cancer could be another contributing factor in bleeding risk assessment, and such patients must be monitored with great attention in AF.

Various cancers may be more commonly associated with AF as a complication from a sympatho-vagal imbalance, inflammatory cascades, post-surgery state, paraneoplastic syndrome, metabolic derangement, chemotherapy, and/or other underlying general conditions.[4,13] While AF might be an underlying cancer-related general condition, chemotherapy might also induce or contribute to a thrombotic or bleeding tendency in patients with cancer even though the causal relationship is uncertain.[3,4] Regardless of the cancer status and general conditions, long-term OAC for AF in comorbid cancer remains challenging.[14]

Long-term OAC is the most important treatment strategy to reduce the risk of ischemic stroke in patients with AF, and direct OAC has reduced stroke occurrence more than conventional warfarin has.[15] In the present study, direct OACs were primarily used and prescribed more for AF patients with cancers than for those without cancers. In an Asian population with NVAF, old age and a high CHA_2DS_2-VASC score were considered independent risk factors for stroke and bleeding adverse outcomes.[16] Compared with ORBIT-AF, the incidence risk of stroke seems to be more similar between patients with AF with and without cancers.[5] In the present study, patients with AF with cancers had a similar age and CHA_2DS_2-VASC and HAS-BLED scores with those without cancers (Table I). The risk of CRNM and all bleeding incidence was significantly higher in the AF patients with cancers than in

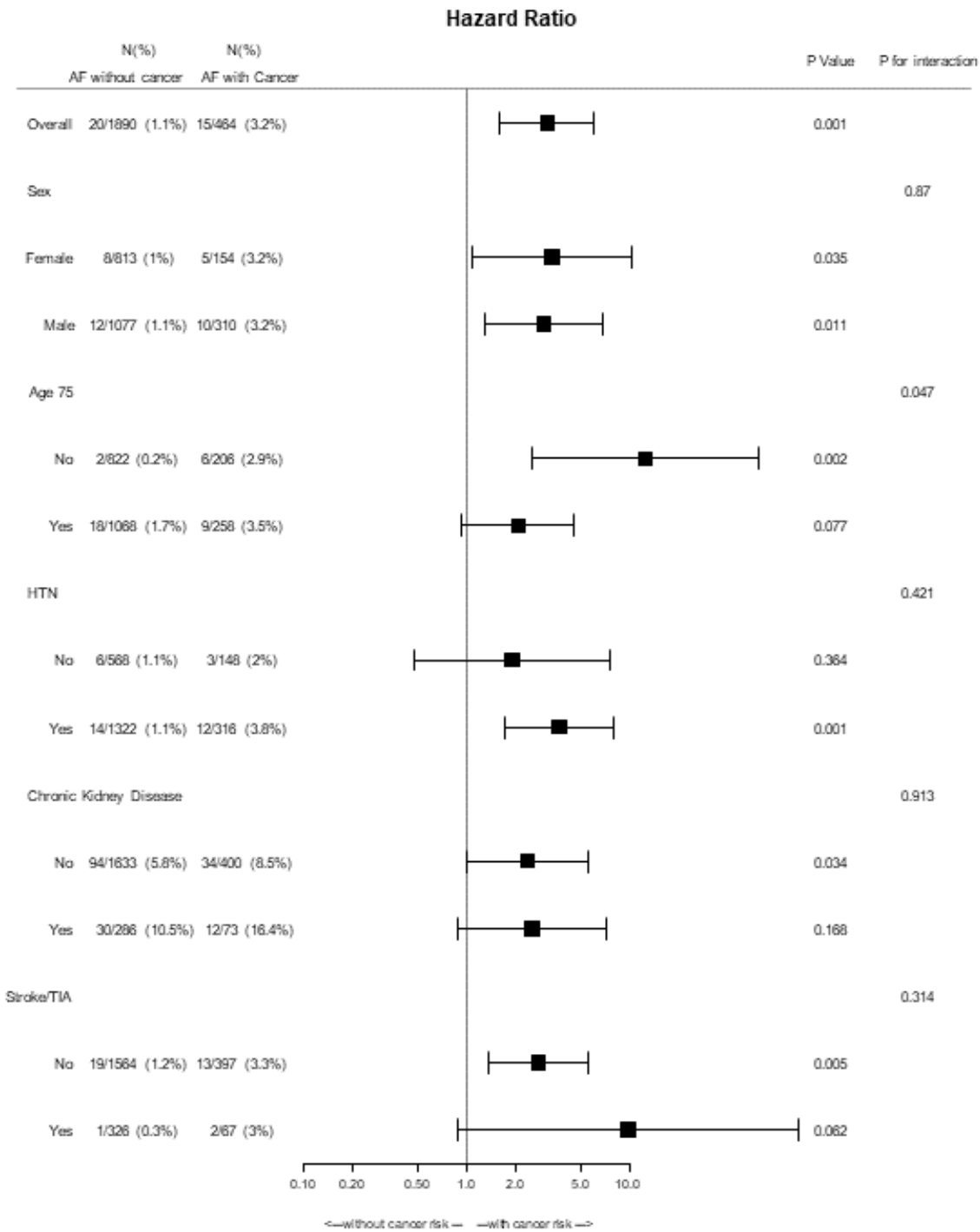

Figure 1. Forrest plot of all bleeding in patients with AF with cancer and those without cancer based on the underlying disease.

those without cancers in the adjusted model (Figures 1-3).

According to the recent AHA/ESC AF guideline,[1,2] cancer has not been considered a contributing factor in assessing bleeding risk in patients with AF. In the ORBIT-AF cohort, the proportion of CHA_2DS_2-VASc score ≥ 2 in the AF with cancer was higher than in those without cancer (96.2% versus 89.5%). The risk of stroke was similar to those without cancer. However, major bleeding was significantly associated with patients with AF with cancer who were at higher risk of bleeding, particularly CNRM bleeding events, than those without cancer.[5] In the present study, we observed a similar CHA_2DS_2-VASc score (3.4 versus 3.2) and a relatively lower proportion of CHA_2DS_2-VASc score ≥ 2 (88.1% versus 87.1%) between the two groups. However, the incidence of major bleeding in the AF with cancer was slightly higher than in those without

Table II. The Comparison of Incidence Rate for All Events Between AF with and Without Cancer

	All	AF without cancer	AF with cancer	*P*
All caused death	35 (0.7)	20 (0.50)	15 (1.7)	< 0.001*
Cardiac death	12 (0.2)	7 (0.1)	5 (0.5)	0.052
Ischemic stroke	33 (0.7)	25 (0.7)	8 (0.9)	0.496
Hemorrhagic stroke	5 (0.1)	4 (0.1)	1 (0.1)	0.982
Major bleeding	32 (0.7)	23 (0.6)	9 (1.0)	0.228
CRNM bleeding	138 (3.1)	101 (2.8)	37 (4.4)	0.023*
All bleeding	170 (3.9)	124 (3.5)	46 (5.5)	0.009*
Net composite event[#]	195 (4.5)	142 (4.0)	53 (6.4)	0.004*

Incidence rate (events 100 patient-years of follow-up). CRNM indicates clinically relevant nonmajor.
[#]Net composite events: all stroke and bleeding event, *statistically significant.

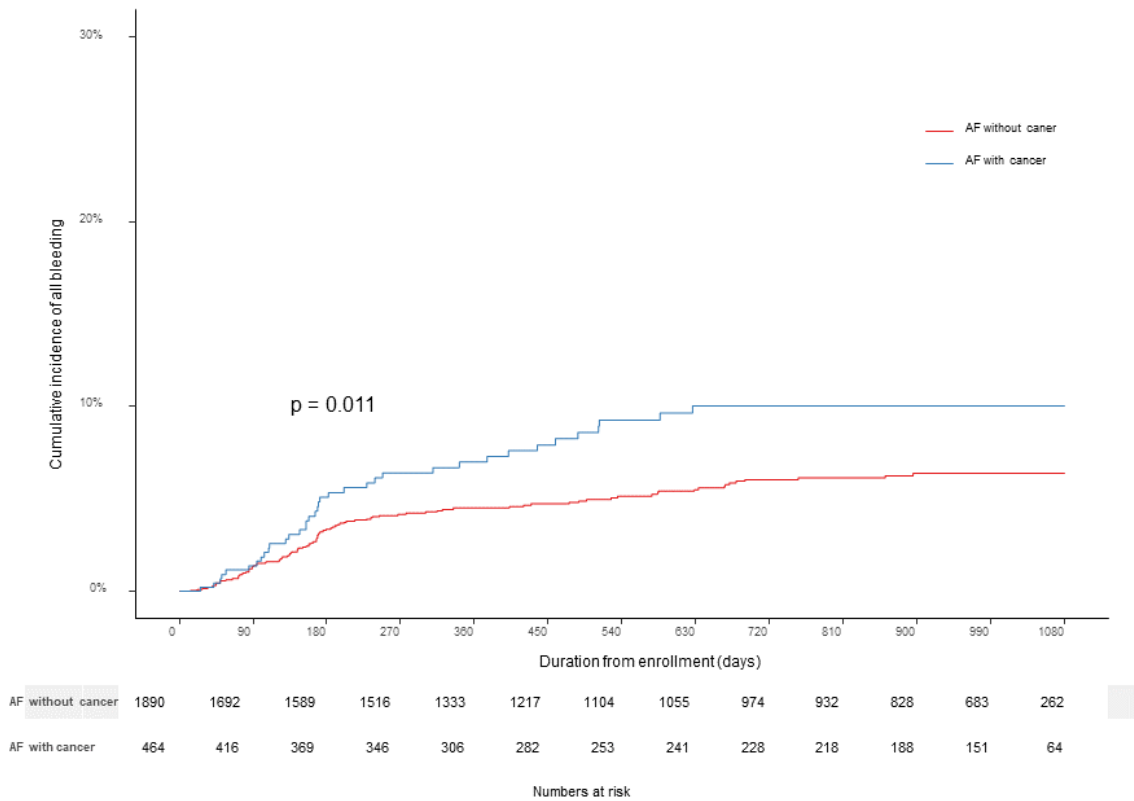

Figure 2. The comparison of cumulative incidence of all bleeding between AF with and without cancer.

cancer without reaching statistical significance (1.0% versus 0.6%), as in Table II. CNRM bleeding might also be more important in the AF with cancer than in those without cancer, but discontinuing OAC due to CNRM bleeding could be debated in the limited clinical evidence during long-term OAC.

Patients with AF with cancers represent a large proportion of cardiovascular diseases with a high risk of bleeding,[6] but collaboration with cardiologists showed a favorable outcome in patients with AF with cancers in reducing the net composite events.[14] However, the strategy for long-term OAC in patients with AF with cancer, based on the collaboration, is yet to be defined. Little is known about how AF with cancer is optimally treated with long-term OAC. In the present study, AF with cancer was also shown to be associated with a significantly higher risk of CNRM bleeding but with a similar risk of stroke for a similar age and CHA_2DS_2-VASC and HAS-BLED scores (Table II, Figures 2, 3). Particularly, the enrolled population comprised a lower proportion of pre-existing cardiovascular and renal diseases, and the incidence of CRNM bleeding appeared relatively lower than the data from Aristotle trial[17] (6.4 per 100 patient-years), ROCKET-AF trial[18] (11.8 per 100 patient-years), and ENGAGE AF-TIMI 48 trial[19] (6.6 per 100 patent-years). Consistent with previous results,[6] most AF with active cancer was associated with an increased risk of all bleeding, owing to invasive growth or the side effects of chemotherapy or cancer-associated hemostasis. In the present study, the higher incidence rates for CRNM bleeding might be correlated

Table III. The Comparison of Cox Proportional Hazard for All Events in the AF with Cancer

	Unadjusted Hazard Ratio (95% CI)	*P*	Adjusted Hazard Ratio (95% CI)	*P*
All death	3.12 (1.69–6.98)	< 0.001*	3.08 (1.57–6.04)	0.001*
Cardiac death	2.97 (0.94–9.35)	0.064	3.00 (0.95–9.49)	0.062
Major bleeding	1.62 (0.75–3.50)	0.221	1.63 (0.75–3.54)	0.215
CRNM bleeding	1.53 (1.05–2.33)	0.002*	1.54 (1.05–2.25)	0.002*
All bleeding	1.55 (1.11–2.18)	0.011*	1.56 (1.11–2.19)	0.011*
Net composite event[#]	1.56 (1.14–2.14)	0.006*	1.56 (1.14–2.16)	0.002*

Incidence rate (events 100 patient-years of follow-up). CRNM indicates clinically relevant nonmajor; and CI, confidence interval. [#]Net composite events: all stroke and bleeding event, *statistically significant.

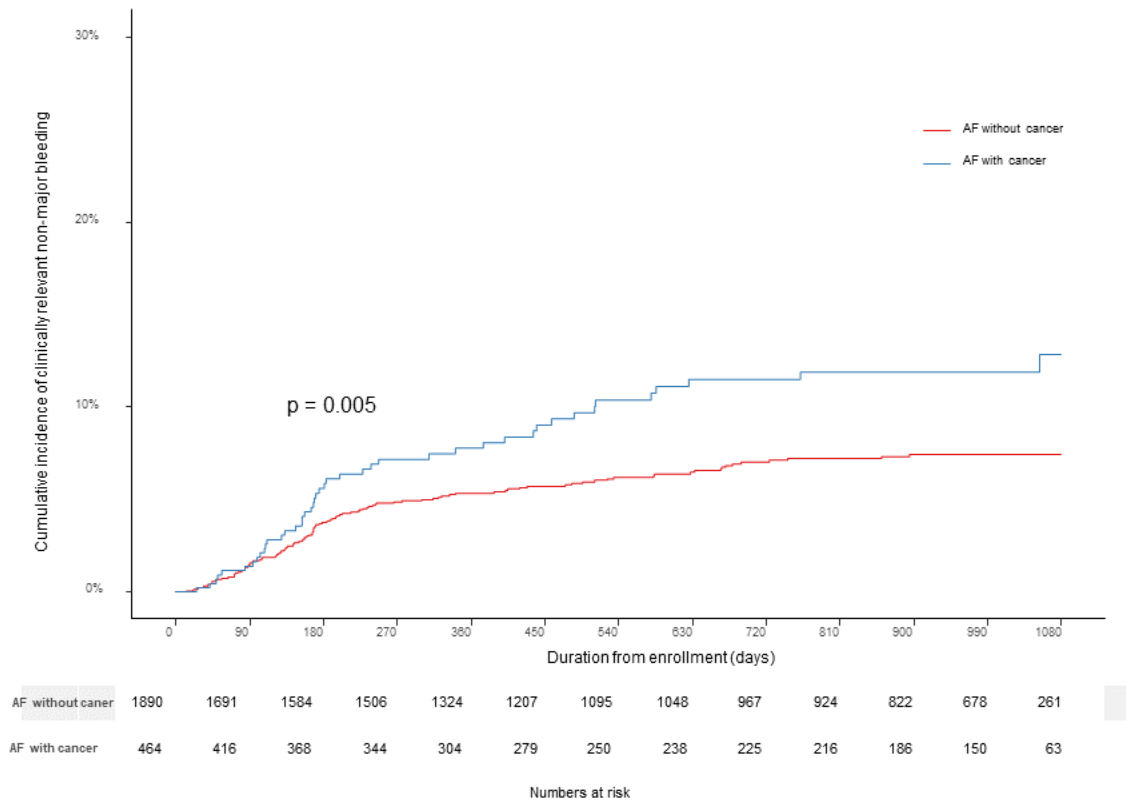

Figure 3. The comparison of cumulative incidence of clinically relevant nonmajor bleeding between AF with and without cancer.

with a more advanced cancer stage and intensive chemotherapy in genitourinary and lung cancer. There could be many differences between AF with versus without cancer, and not all cancers are similar in bleeding risk. However, this is a clinically relevant investigation as tissue alterations and blood cell abnormalities can be hypothesized to promote bleeding in AF patients with cancers.

The limitations of this prospective cohort study are that the present registry was based on hospital diagnoses, and only hospitalized patients or those followed in the outpatient clinic could be included. The information on the cancer stage, specific chemotherapy, and peri-operative and remission statuses were not fully documented because the data were based only on electronic medical records. However, clinical guidelines lack evidence-based consensus for patients with AF with cancers, and previous data provide limited information for the risk of all bleeding events in patients with AF with cancers during long-term OAC. This study involved only a single race of Korean patients, and the risk of bleeding related to coagulability and the types of cancer might be specific to race. Despite some limitations, the present data may provide real-world data for a careful risk-benefit assessment on long-term OAC to prevent all adverse bleeding outcomes in patients with AF with cancer.

Conclusion

AF with cancer was associated with a significantly higher risk of CRNM bleeding events for long-term OAC than those without cancer in this prospective national AF cohort. This study may provide additional information on

assessing bleeding risk in patients with cancer with AF for long-term OAC.

Disclosure

Conflicts of interest: The authors declare no conflict of interest.

Author contributions: Conceptualization: Ki-Woon Kang; Data curation: Ki-Woon Kang and David Shin; Formal analysis: Ki-Woon Kang, David Shin, and Seung Young Shin; Methodology: Ki-Woon Kang, Eue-Keun Choi, Myung-Jin Cha, Jung-Myung Lee, Jin-Bae Kim, Junbeom Park, Jin-Kyu Park, Tae-Hoon Kim, Jaemin Shim, Young Soo Lee, HyungWook Park and Changsoo Kim; Writing-original draft: Ki-Woon Kang, David Shin, Jae-Sun Uhm and Jun Kim; Writing-review and editing: Ki-Woon Kang and Boyoung Joung.

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Supplemental Files

Supplemental Tables I-III

Please see supplemental files; https://doi.org/10.1536/ihj.22-507