Bleeding and New-Onset Cancers in Patients With Atrial Fibrillation Receiving Nonvitamin K Antagonist Oral Anticoagulants

Yu-Feng Hu, MD, PhD[a,b,*], Shih-Lin Chang, MD, PhD[a,b], Chang-Ming Chern, MD[c], Cheng-Hsueh Wu, MD[b,d], Yenn-Jiang Lin, MD, PhD[a,b], Li-Wei Lo, MD, PhD[a,b], Tze-Fan Chao, MD[a,b], Fa-Po Chung, MD[a,b], Jo-Nan Liao, MD[a,b], Ting-Yung Chang, MD[a,b], Ting-Chun Huang, MD[a], Cheng-I Wu, MD[a,b], Chih-Min Liu, MD[a,b], Simon Salim, MD[a], Jennifer Jeanne Vicera, MD[a], Le Phat Tai, MD[a], and Shih-Ann Chen, MD[a,b]

Whether bleeding should be considered a sufficient sign to justify thorough cancer surveillance in atrial fibrillation (AF) patients receiving nonvitamin K antagonist oral anticoagulants (NOACs) remains unclear. We investigated the relationships between bleeding events and new-onset cancers in AF patients receiving NOACs in a prospective cohort (n = 395, mean follow-up duration of 2.8 years). There were 18 patients who were diagnosed with new-onset cancers 584 ± 372 days after the initiation of NOACs. The patients with new-onset cancers had higher HAS-BLED scores (no, preexisting and new-onset cancer: 1.51 ± 0.81, 1.69 ± 0.87, and 2.11 ± 0.96, respectively; p = 0.006) and a higher incidence of bleeding events (22%, 33%, 67%, respectively; p < 0.001) than did patients without new-onset cancers. Bleeding events that preceded the diagnosis of new-onset cancers were independently correlated with new-onset cancers (odds ratio: 7.89, p = 0.001) in the multivariate logistic regression. More than half of the patients (61%) with new-onset cancers had either a significant period of drug interruption for at least 2 months or discontinued NOACs. In conclusions, bleeding in AF patients receiving NOACs could be an alerting sign of new-onset cancers and should prompt the initiation of thorough surveillance to detect early cancers. **(Am J Cardiol 2019;123:782−786)**

There is an increased risk of malignant cancer in the patients with atrial fibrillation (AF), which contributes to the majority of noncardiovascular death.[1−3] Routine screening is not suggested.[2,4] Bleeding has been considered an alerting sign to reveal preexisting gastrointestinal (GI) cancers.[5−7] However, in patients receiving nonvitamin K antagonist oral anticoagulants (NOACs), bleeding is not an uncommon complication,[8] and it can generally be attributed to coagulopathy or a variety of benign pathology.[9,10] Whether bleeding should be considered a sufficient sign to justify thorough cancer surveillance as in those without NOACs remains unclear. We, therefore, investigated the relations between bleeding events and new-onset cancers in AF patients receiving NOACs in a prospective cohort. The aim was to determine whether bleeding would be a predictor of new-onset cancers after NOACs use.

Methods

Nonvalvular AF patients who received NOACs (dabigatran etexilate, rivaroxaban, apixaban, and edoxaban) treatment were enrolled at the cardiology and neurology clinics of Taipei Veterans General Hospital, Taipei, Taiwan from April 2013 to July 2017. All patients had approved indications for NOACs according to the guidelines.[11,12] The clinical characteristics, concomitant medications, laboratory measurements, and history of cancer and treatment were recorded during enrollment. The time to initiate NOACs was recorded during the enrollment by the interview of the patient and medical record of drug prescription. The patients were prospectively followed every 3 to 6 months through their medical records, clinic visits, or phone interviews to determine the incidence of bleeding, stroke, and new-onset cancers. The bleeding sites and severity were evaluated by reviewing laboratory data or medical records.[13,14] Ethical approval was granted by the Institutional Review Board of the Veterans General Hospital, Taipei, Taiwan. All subjects gave written informed consent.

New-onset cancer was defined as the diagnosis after the initiation of NOACs. Preexisting cancer was defined as

[a]Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [b]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan; [c]Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan; and [d]Department of Critical Care Medicine, Taipei Veterans General Hospital, Taipei, Taiwan. Manuscript received August 31, 2018; revised manuscript received and accepted November 28, 2018.

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*Corresponding author: Tel: +886 2 2875 7156; fax: +886 2 2873 5656.

E-mail address: huhuhu0609@gmail.com (Y.-F. Hu).

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cancer that had been diagnosed before the initiation of NOACs. The clinical course after bleeding; the surveillance of cancer diagnosis, stage, and therapy (surgery, radiation, chemotherapy, hormone, target therapy); the interruption and reinitiation of NOACs; and the chronological order of bleeding and cancer diagnosis were explored in detail through medical records. The interval from the time point of first bleeding event after NOACs initiation to the diagnosis of new-onset cancer was also explored.

We calculated the CHA2DS2-VASc and HAS-BLED scores at enrollment. The CHA2DS2-VASc risk score assigned 1 point for congestive heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female gender and 2 points for either age (75 years and older) or stroke.[12] The HAS-BLED score is calculated by adding 1 point for hypertension, abnormal renal function, liver disease, stroke, bleeding history, age (65 years and older), and either concomitant antiplatelet or nonsteroidal anti-inflammatory drugs or excess alcohol consumption (>8 drinks per week). For previous warfarin users, a history of labile INRs (i.e., less than 60% of time in a therapeutic range) was scored as 1 point.[12]

Major bleeding episodes were defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a reduced hemoglobin level of 20 g/L according to the statement by the International Society on Thrombosis and Haemostasis.[15]

All continuous variables are expressed as the means ± SDs. The 2-sample independent *t* test, 1-way ANOVA, and a chi-square test were used, as appropriate. Multivariate binary logistic regression analysis was used to compare the patients with and without new-onset cancer. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off point of the CHA2DS2-VASc score to predict new-onset cancers in patients with bleeding. Statistical significance was established at $p < 0.05$. PSAW SPSS 22.0 was used for the statistical analysis.

Results

We prospectively followed 395 patients who received NOACs for a mean duration of 2.8 ± 1.5 years (0.5 to 4.7 years). There were 248 patients receiving dabigatran etexilate, 104 receiving rivaroxaban, 41 receiving apixaban, and 2 receiving edoxaban. A total of 18 (4.5%) patients were diagnosed with new-onset cancers after receiving NOACs (7 GI cancers, 6 urinary tract cancers, 4 lung cancers, and 1 blood cancer). The mean duration from the initiation of NOACs to the diagnosis of new-onset cancer was 584 ± 372 days (17 to 1314 days). There were 42 (10.6%) patients who had preexisting cancers before receiving NOACs. The patients with new-onset cancers tended to be older than those without new-onset cancers (Table 1). There were no differences in gender, body weight, co-morbidities, history of gastrointestinal bleeding, alcohol, or concomitant medications between the patients with and without cancers. Liver and cardiac function did not differ between the groups. The patients with cancers (either preexisting or new-onset) had higher levels of creatinine. The levels of PT and APTT did not differ between the 3 groups. The patients with new-onset cancers had higher HAS-BLED scores than those without new-onset cancers (Figure 1). There was a marginal trend of increased CHA2DS2-VASc scores in the patients with new-onset cancers (Figure 1).

Table 1
The baseline characteristics of the patients with and without cancer

	No cancer (n = 335)	Preexisting cancer (n = 42)	New-onset cancer (n = 18)	p value
Variable				
Age (years)	74.02 ± 10.13	75.26 ± 11.14	79.39 ± 8.75	0.08
Male	216 (64.5%)	27 (64.3%)	14 (77.8%)	0.51
Body weight (kg)	67.17 ± 12.15	65.26 ± 11.14	68.82 ± 10.06	0.51
History of stroke	96 (28.7%)	15 (35.7%)	7 (38.9%)	0.45
Diabetes mellitus	77 (23.0%)	13 (31.0%)	7 (38.9%)	0.19
Congestive heart failure	72 (21.5%)	8 (19.0%)	2 (11.1%)	0.55
Hypertension	253 (75.5%)	30 (71.4%)	17 (94.4%)	0.14
Coronary artery disease	39 (11.6%)	6 (14.3%)	4 (22.2%)	0.38
Hyperlipidemia	127 (37.8%)	10 (23.8%)	6 (33.3%)	0.19
History of gastrointestinal bleeding	47 (14.0%)	7 (16.7%)	5 (27.8%)	0.27
Alcohol consumption	35 (10.4%)	5 (11.9%)	0 (0%)	0.33
Predisposing medication*	30 (9.0%)	4 (9.5%)	3 (16.7%)	0.55
CHA2DS2-VASc score	3.49 ± 1.49	3.74 ± 1.65	4.17 ± 1.69	0.13
HAS-BLED score	1.51 ± 0.81	1.69 ± 0.87	2.11 ± 0.96	0.006
Creatinine (mg/dl)	1.03 ± 0.29	1.15 ± 0.58	1.11 ± 0.22	0.047
Estimated glomerular filtration rate (ml/min)	68.34 ± 17.95	64.76 ± 24.83	61.61 ± 11.24	0.19
ALT (U/L)	22.66 ± 12.27	19.62 ± 10.86	18.00 ± 8.66	0.13
PT	13.12 ± 9.78	12.90 ± 2.89	11.92 ± 1.74	0.88
APTT	34.94 ± 8.33	36.05 ± 8.35	33.91 ± 8.11	0.68
Left atrial diameter	45.27 ± 8.28	45.42 ± 9.13	43.70 ± 8.19	0.77
Left ventricular ejection fraction	55.53 ± 8.22	54.61 ± 10.03	58.81 ± 9.00	0.27

* Antiplatelet or NSAID.

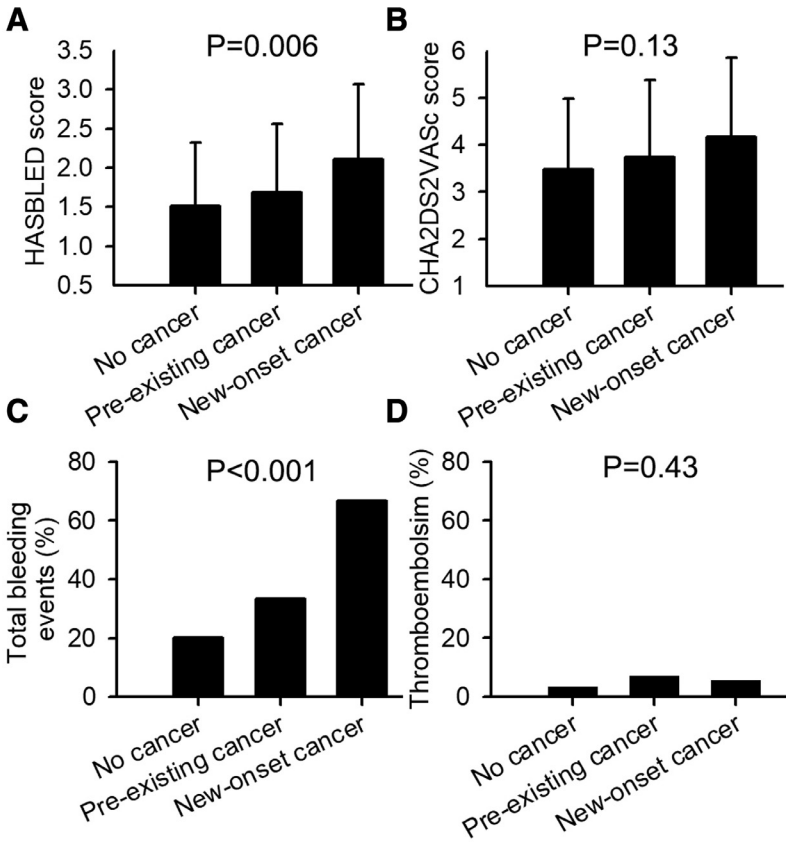

Figure 1. The risk and incidence of bleeding and thromboembolism in AF patients with and without cancers.(*A*) The HAS-BLED score increased from the patients with no cancer, to those with preexisting cancer to those with new-onset cancer (1.51 ± 0.81, 1.69 ± 0.87, and 2.11 ± 0.96, p = 0.006). (*B*) There was a marginal trend of increased CHA2DS2-VASc scores in the patients with new-onset cancers (3.49 ± 1.49, 3.74 ± 1.65, and 4.17 ± 1.69, p = 0.13). (*C*) The total bleeding events increased in patients with preexisting and new-onset cancers (68 [20.2%], 14 [33.3%], and 12 [66.7%], p < 0.001). There were 54.3% GI bleeding, 18.1% hematuria, 6.4% hemoptysis, and 21.3% other miscellaneous bleeding. (*D*) The incidence of thromboembolism did not differ (3.3 %, 7.1%, and 5.6%, p = 0.43).

The total number of bleeding events was significantly higher in the patients with preexisting and new-onset cancers than in those without cancer (Figure 1). However, the incidence of thromboembolism did not differ between the 3 groups (Figure 1). The incidences of major and minor bleeding both increased in patients with cancer (no cancer, preexisting, and new-onset cancer; major bleeding: 2.4%, 7.1%, and 11.1%, p = 0.04; minor bleeding: 19.1%, 28.6%, and 61.1%, p = 0.001). Some patients developed recurrent episodes of bleeding (n = 25, 22.6%). The number of recurrent bleeding episodes did not differ between groups (1.29 ± 0.55, 1.43 ± 0.65, 1.42 ± 0.79, p = 0.65).

In all patients with bleeding events and new-onset cancer, the bleeding events always preceded the diagnosis of cancer (Table 2, mean duration from bleeding events to cancer diagnosis: 128 ± 206 days). Bleeding events were independently correlated with new-onset cancers (new-onset cancer vs without cancer; odds ratio 7.89, 95% confidence interval 2.53 to 24.61, p = 0.001) after multivariate binary logistic regression including age, history of stroke, diabetes mellitus, hypertension, heart failure, coronary artery disease, history of GI bleeding, hyperlipidemia, alcohol consumption, medication usage predisposing patient to bleeding, HAS-BLED score, and CHA2DS2-VASc score. Eight patients underwent active surveillance of the relevant bleeding source after bleeding events, and cancers were diagnosed within 2 months at the relevant bleeding sites (1 lung cancer, 3 GI cancers, 4 urinary tract cancers). One patient developed recurrent extremity ecchymosis, which was not relevant to the cancer origin (lung cancer). There were 2 patients with low gastrointestinal tract bleeding without active surveillance, and GI cancer was diagnosed one year later. Similarly, 1 patient ignored recurrent hemoptysis for more than 3 months. Lung cancer with bone metastasis was identified accidentally during the follow-up of an aortic aneurysm by computed tomography scan.

There were 14 (77.8%) patients with new-onset cancers diagnosed in the early stage (less than stage III). Seven (38.9%) patients with new-onset cancer had a significant period of drug interruption after the diagnosis of cancer with a duration longer than 2 to 3 months, which was attributed to cancer surveillance and surgery. In these patients, 1 patient developed a stroke after the resumption of NOACs. Four (22.2%) patients refused to receive NOACs after the

Table 2
The clinical information about cancer and bleeding in the patients with new-onset cancers

	Age (y/o)	Gender	Cancer type	Stage	Duration of NOAC use to cancer diagnosis (days)	Time elapsed between first bleeding event and cancer diagnosis (days)	Bleeding events	NOAC use after cancer diagnosis
1	80	Female	Colorectal CA	IIb	787	649	Major/minor	Interrupted, 2 months
2	82	Male	Gastric CA	IV	220	9	Minor	Continued
3	86	Male	Esophageal CA	Ia	319	–	No	Continued
4	84	Male	Colorectal CA	IIa	421	16	Major	Discontinued
5	82	Male	Colorectal CA	I	462	464	Minor	Interrupted, 3 months
6	77	Female	Colorectal CA	I	442	9	Minor	Interrupted, 2 months
7	66	Male	Colorectal CA	I	592	36	Minor	Interrupted, 4 months
8	70	Female	Bladder CA	II	1110	60	Minor	Interrupted, 2 months
9	87	Male	Prostate CA	IIb	573	29	Minor	Continued
10	71	Male	Prostate CA	IIa	54	–	No	Interrupted, 2 months
11	92	Male	Bladder CA	I	456	62	Minor	Discontinued
12	92	Male	Prostate CA	I	17	17	Minor	Discontinued
13	84	Male	Prostate CA	IV	714	–	No	Continued
14	69	Male	Lung CA	IV	1057	97	Minor	Continued
15	70	Female	Lung CA	IIIa	946	90	Minor	Discontinued
16	75	Male	Lung CA	IIa	1314	–	No	Continued
17	69	Male	Lung CA	I	155	–	No	Continued
18	91	Male	Polycythemia vera	–	863		No	Interrupted, 2 months

"-": no applicable.

diagnosis of new-onset cancer due to recurrent minor bleeding (n = 3) and major bleeding (n = 1).

In the 94 bleeding events during follow-up, there were 12 patients (12.8%) diagnosed with new-onset cancer. The CHA2DS2-VASc scores of the patients with bleeding were higher in the patients with new-onset cancers than in those without new-onset cancers (3.75 ± 1.29 vs 4.67 ± 1.61, respectively; p = 0.03). A ROC curve was used to identify the cut-off point of the CHA2DS2-VASc score, and the score >5 predicted new-onset cancer (ROC curve, area under curve: 0.67, p = 0.078, sensitivity: 33.3%, specificity: 89.7%).

Discussion

The patients with new-onset cancers had higher HAS-BLED scores and experienced bleeding events preceding cancer diagnosis. The bleeding events in AF patients receiving NOACs indicated a 7.89-fold higher probability of having new-onset cancers. More than half of the patients (61%) with new-onset cancer either had a significant period of drug interruption for at least 2 months after the diagnosis of cancer or discontinued NOACs.

The present study suggested that bleeding could a potential alerting sign for new-onset cancer. Although the results remain exploratory due to the limited number of patients, the findings implied that thorough cancer surveillance might be needed for the early diagnosis of new-onset cancer in AF patients. Few studies have addressed the potential clinical link between bleeding after anticoagulants and new-onset cancer.[7,16] Clemens A. et al observed a similar incidence of GI cancer and bleeding from phase III trials of AF patients with NOACs, leading to the hypothesis that anticoagulant-related GI bleeding might reveal and increase the detection of GI cancers.[7] Yu HT et al demonstrated that 40 of 3,570 AF patients with hematuria (1.1%) were diagnosed with urinary tract cancer.[16] The patients receiving oral anticoagulants had a higher incidence of urinary tract cancers than did those who did not receive oral anticoagulants.[16] These studies first observed the potential link between bleeding and cancer in patients with AF receiving anticoagulants but did not inspect the direct link between bleeding and new-onset cancers. Limited by retrospective or cross-section designs, both studies also derived their data from an electronic recorded database in which crucial clinical information and details might be lacking. The present study prospectively followed up patients with bleeding events and their cancer surveillance in order to identify the important link between new-onset cancer and bleeding. We also observed that bleeding as a risk factor for new-onset cancer is probably not confined to GI or urinary tract cancers. Two patients with hemoptysis in the present study were diagnosed with lung cancers. Bleeding is not uncommon in the patients receiving NOACs.[10] The HAS-BLED score in AF patients with new-onset cancer was significantly higher than in those without. The clinicians may attribute the cause of bleeding to the concomitant use of NOACs-related coagulopathy and ignore the underlying pathology, such as occult cancer. Clinical predictors, such as CHA2DS2-VASc score, could not adequately detect the presence of new-onset cancers. Addressing the important link between new-onset cancers and bleeding will help in the diagnosis and treatment of cancer at an early stage for AF patients, as there were 78% patients identified with cancer in early stages in the present study.

Temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular AF imposed a significant risk for stroke, as demonstrated in the ROCKET-AF trial.[17] More than half of the patients with new-onset cancer had a significant period of drug interruption or discontinuation that exposed the patients to the risk of stroke. The temporary interruption could be attributed to surgery or cancer surveillance. For the patients with new-onset cancer, surgery is usually needed to eliminate the tumor. The bleeding events preceding the diagnosis of new-onset cancer complicates the use of NOACs, and a multidisciplinary AF team might be needed.[10,12,18] In the present study, the interruption of NOACs, especially in those with minor bleeding or no bleeding, was significantly longer than the current recommendation.[10,12,18] It remains unclear whether the recommended NOACs use in the current guideline for temporary drug interruption due to surgery or bleeding in AF patients could simply be applied to those with active or new-onset cancers.[10] However, the risk of stroke or embolism should not be underestimated, as the patients with new-onset cancers also had a high stroke risk according to the CHA2DS2-VASc score, and 1 patient with recurrent stroke was also observed. If bleeding risk is high, the bridge of low molecular heparin might be probably considered due to lower bleeding rate in the cancer patients, compared with NOACs.[19] NOACs with available antidotes could also be an alternative due to an increased risk of future bleeding. In conclusions, the bleeding in AF patients receiving NOACs could be an alerting sign of new-onset cancer and might prompt the initiation of thorough cancer surveillance.

Disclosures

The investigators have no conflicts of interest to disclose.

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