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ORIGINAL ARTICLE

Major bleeding and thromboembolism risks of antithrombotic treatment in patients with incident atrial fibrillation/flutter and a history of cancer

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Abstract

Background: Literature shows that atrial fibrillation (AF) patients with a history of cancer have a higher risk of thromboembolism (TE) and major bleeding (MB) compared to patients without. However, cancer type and time between cancer and AF diagnosis is often lacking in such analyses.

Objectives: To examine MB and TE rates of AF patients with a prior cancer diagnosis, stratified by cancer type and interval between cancer and AF diagnosis.

Methods: This Danish population-based cohort study included all patients aged ≥50 years with incident AF between January 1, 1995, and December 31, 2016, and identified those who had cancer before the AF diagnosis. From hospital and drug prescription databases, data on cancer type, time interval between cancer and AF diagnosis (ie, <1, 1-3, or >3 years), outcomes, and antithrombotic exposure were collected. Follow-up started from the AF diagnosis until the occurrence of an outcome or the end of the 2-year follow-up. Incidence rates (IRs) per 100 patient-years and adjusted hazard ratios (aHRs) with corresponding 95% CIs were calculated using Cox regression.

Results: We identified 39,178 patients with incident AF and a prior cancer diagnosis. These patients demonstrated higher MB (IR, 3.35 [3.25-3.45] vs 2.23 [2.29-2.35]) and TE rates (IR, 3.21 [3.11-3.31] vs 2.53 [2.50-2.56]) than those without prior cancer. The higher MB risk in AF patients with a prior cancer diagnosis was observed in all examined time intervals, while a higher TE risk was only observed in those with a cancer diagnosis <1 year prior (aHR, 1.27 [1.16-1.40]). Prior respiratory cancer was associated with increased MB (aHR, 1.37 [1.26-1.48]) and TE risks (aHR, 1.26 [1.15-1.38]).

Conclusion: A prior cancer diagnosis confers additional MB and, to a lesser extent and in certain conditions, thromboembolic risks in patients with AF. The type and timing of the prior cancer diagnosis determines the degree of risk.

Nienke van Rein and Gordon Chu shared first authorship.

KEYWORDS
anticoagulants, atrial fibrillation, hemorrhage, neoplasms, thromboembolism

Essentials

- Whether prior cancer affects antithrombotic treatment in atrial fibrillation is unclear.
- This Danish population-based study presents major bleeding and thromboembolism rates of antithrombotic treatment.
- Prior cancer increases bleeding and, to a lesser extent, thromboembolic risks.
- The degree of additional risks depended on the type and timing of the prior cancer diagnosis.

1 | INTRODUCTION

Routine clinical care data have indicated that a history of cancer is common among patients with atrial fibrillation (AF): as many as 1 in 4 patients have both conditions [1]. Because cancer is associated with an increased risk of arterial and venous thromboembolism (VTE) as well as with bleeding, patients with AF with a history of cancer are likely to have a poorer prognosis than patients with AF without cancer [2–7]. The additional thromboembolic and bleeding risks conferred by cancer have been associated with the type and extent of the cancer, cancer treatment, and other cancer-related factors (eg, cancer-related thrombocytopenia, renal dysfunction, or malnourishment) [7–13].

Whether a history of cancer confers these additional risks in patients with AF, either shortly after cancer diagnosis or persistently, is unclear. Post hoc analyses of direct oral anticoagulant (DOAC) trials and nationwide cohort studies have shown conflicting results and often have lacked data on cancer type and the time interval between the prior cancer diagnosis and the incident AF diagnosis [8,14–16]. Moreover, data on major bleeding (MB) and thromboembolic event rates associated with different antithrombotic strategies are currently lacking but would be essential for creating specific risk profiles for clinical practice, as well as for future implementation of safe and effective antithrombotic management strategies in patients with AF with a history of cancer.

We therefore conducted a nationwide cohort study to examine the thromboembolic and bleeding risks in patients with incident AF with a history of cancer and to compare the rates of thromboembolism and bleeding associated with various antithrombotic management strategies in patients with AF, with or without a history of cancer. Cancer type and the time interval between diagnosis of AF and the cancer diagnosis were considered in these analyses.

2 | METHODS

2.1 | Settings and database

All Danish residents receive tax-funded medical care from the Danish National Health Service and are automatically included in various nationwide healthcare-related registries [17]. A unique identification number (the Civil Personal Register Number) enables linkage of individual patient data among these healthcare-related registries [18]. Data from the Danish National Patient Registry covering all Danish hospitals, the Danish National Prescription Registry, and the Danish Registry of Causes of Death were used in this study [19–23]. The project was approved by the Danish Data Protection Agency by Aarhus University (record number 2016-051-000001, serial number 2679). According to Danish law, no further approvals were required.

The Danish National Patient Registry contains information on all inpatient hospitalizations since 1977 and on all hospital specialist outpatient clinic and emergency department visits since 1995. The dates of visit/admission and discharge, the discharge diagnoses, and selected treatments are recorded. Between 1977 and 1993, the diagnoses were coded in accordance with the International Classification of Diseases (ICD), Eighth Revision. From 1993 onward, the ICD, Tenth Revision, was used [24]. The Danish National Prescription Registry lists all prescriptions dispensed at community pharmacies in Denmark since 1995, with details on the date, quantity, and Anatomic Therapeutic Chemical code of the dispensed drug [23]. Finally, the records of the Danish Registry of Causes of Death contain the dates and causes of death since 1943 and computerized ones since 1970, as classified by ICD-10 code [21].

2.2 | Study population

All inhabitants in Denmark aged 50 years or older with a first primary or secondary inpatient or outpatient clinic discharge diagnosis of atrial fibrillation or atrial flutter (both hereafter abbreviated as AF) between January 1, 1995, and December 31, 2016, registered in the Danish National Patient Registry, were included. Patients with an AF diagnosis in an acute setting (eg, emergency department) were ineligible for inclusion. A diagnosis of AF and flutter has a positive predictive value of 99% in the patient registry [25]. Subsequently, within this group, patients with a prior history of cancer were identified as those with a first ICD code for malignancy before the first AF diagnosis. To ensure that AF was not diagnosed simultaneously with cancer during the same hospitalization, only patients with an AF diagnosis at least 30 days after cancer diagnosis were included. Cancers were stratified as a) gastrointestinal cancer, b) respiratory and intrathoracic cancers, c) breast cancer, d) urogenital cancer, e) intracranial cancer,

f) hematological cancer, g) skin cancer, and h) other cancers. Patients with squamous cell cancer of the skin as their only malignancy or those with insufficient documentation (eg, unknown primary cancer) were excluded from the analyses. The ICD codes for AF and the cancers of interest are listed in the Supplementary Tables S1 and S2. The time interval between the prior cancer diagnosis and the AF diagnosis was further stratified into <1 year, 1 to 3 years, and >3 years.

2.3 | Antithrombotic drug use

Through linkage with the patients' civil personal register numbers, dispensing data for vitamin K antagonists (VKAs; warfarin and phenprocoumon), DOACs (edoxaban, dabigatran, rivaroxaban, and apixaban), and platelet inhibitors (aspirin, clopidogrel, dipyridamole, prasugrel, and ticagrelor) were obtained from the Danish National Prescription Registry. The Anatomic Therapeutic Chemical codes of the antithrombotic drugs of interest are listed in the Supplementary Table S3.

Antithrombotic drug exposure was evaluated through a time-dependent analysis, in which exposure was considered to start on the day when the prescription was filled. For DOACs and antiplatelet drugs, exposure duration was calculated by dividing the number of pills dispensed with the dosing regimen (ie, twice daily for dabigatran, apixaban, ticagrelor, and dipyridamole; once daily for all other antithrombotic drugs). To account for delays in filling prescriptions and the duration of action of individual drugs, a washout period of 14 days was included. For VKAs, we assumed the exposure to be 90 days per prescription because drugs for chronic conditions are rarely provided for more than 3 months at a time in Denmark. Although low-dose aspirin is available as an over-the-counter drug, prescriptions are usually necessary for eligibility for financial reimbursement for long-term treatment [26,27]. Therefore, aspirin use was included and was coded as a prescription. The following antithrombotic exposure categories were identified in this study: no antithrombotic treatment, monotherapy with a VKA, monotherapy with a DOAC, monotherapy with an antiplatelet agent, dual therapy with a VKA or DOAC and 1 antiplatelet drug, dual antiplatelet therapy, and triple therapy with a VKA or DOAC and 2 antiplatelet drugs.

2.4 | Outcomes and comorbidities

The Supplementary Table S1 contains the ICD codes of the outcomes of interest collected from the Danish National Patient Registry and the Danish Registry of Causes of Death. The following outcomes of interest were considered: MB, ischemic stroke, myocardial infarction, systemic embolism (SE), VTE, and all-cause mortality.

MB was defined by admission to a hospital with a primary or secondary diagnosis of bleeding or fatal bleeding. Similarly, the thromboembolic events of interest were defined by hospital admission with a primary or secondary diagnosis of ischemic stroke, myocardial infarction, SE or VTE, or a fatal course of the abovementioned thromboembolic events. The outcomes of fatal thromboembolic and MB events were included only if the event was recorded as the primary cause of death in the Danish Registry of Causes of Death.

Comorbidities were defined as diagnoses present on or before the index date. The comorbidities of interest were ischemic heart disease, heart failure, valvular heart disease, hypertension, ischemic stroke, SE, diabetes, liver disease, renal failure, and anemia. The ICD codes of the comorbidities of interest are listed in the Supplementary Table S4. The Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, prior Stroke, TIA or thromboembolism, Vascular disease, Age 65-75, female Sex Command VTE: COntemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (CHA_2DS_2-VASc) score was calculated on the basis of these diagnostic codes [28]. Previous studies have demonstrated good validity of the outcomes and comorbidities diagnoses registered in the Danish National Patient Registry [29–32].

2.5 | Statistical analysis

Person-times were calculated from the index date until the occurrence of an outcome of interest or the end of the study period with a follow-up of 2 years, whichever occurred first. The index date was defined as the date of the AF diagnosis. In calculating follow-up time until a major bleed or another outcome, we did not consider the occurrence of other outcomes. For example, if a patient experienced both an ischemic stroke and a MB event, we calculated separate follow-up times for each analysis. Thus, all follow-up from the diagnosis of atrial fibrillation to the first MB event was included in the analysis of MB, and all follow-up until the first ischemic stroke was included in the ischemic stroke analysis. Incidence rates (IRs) per 100 person years with corresponding 95% CIs of the outcomes among the exposure groups were calculated, and subsequent stratification was performed by cancer type and the time interval between the cancer diagnosis and AF diagnosis.

To examine the effect of the presence of a prior cancer diagnosis on the thromboembolic and MB risks in patients with AF, we compared the risk estimates in patients with AF with vs without a history of cancer. Cox regression models were constructed to estimate hazard ratios and corresponding 95% CIs. Patients with AF without cancer (and without antithrombotic treatment) served as the reference group for all comparisons. Hazard ratios were adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure. All analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Baseline characteristics

Between 1995 and 2016, 39,178 patients with an incident AF diagnosis and a prior history of cancer were identified. Of these, 20,404

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TABLE 1 Baseline characteristics of all patients in Denmark ≥50 years of age with a first primary or secondary hospital inpatient or outpatient discharge diagnosis of atrial fibrillation or flutter between January 1, 1995, and December 31, 2016, and a prior cancer diagnosis.

Patient characteristics	Matched AF patients without a prior cancer diagnosis	AF patients with a prior cancer diagnosis	No antithrombotic treatment	Monotherapy			Dual therapy			Triple therapy VKA/ DOAC + dual antiplatelet
				VKA	DOAC	Antiplatelet	Dual antiplatelet	VKA + antiplatelet	DOAC + antiplatelet	
General characteristics										
Patients, n (%)	221,532	39,178	15,094 (38.5)	7453 (19.0)	2887 (7.4)	8215 (21.0)	1308 (3.3)	2831 (7.2)	863 (1.3)	527
Age (y), mean (SD)	74 (11)	77 (9)	76 (10)	75 (9)	77 (9)	79 (9)	80 (9)	77 (8)	79 (8)	77 (8)
Female sex, n (%)	97,739 (44)	20,404 (52.1)	8000 (53.0)	3712 (49.8)	1568 (54.3)	4463 (54.3)	669 (51.1)	1316 (46.5)	448 (51.9)	228 (43.3)
CHA_2DS_2-VASc score, mean (SD)	3.1 (1.8)	3.4 (1.7)	3.0 (1.6)	3.2 (1.6)	3.3 (1.6)	3.8 (1.6)	4.8 (1.6)	3.9 (1.6)	4.2 (1.6)	4.7 (1.5)
Interval between prior cancer diagnosis and AF diagnosis, n (%)										
<1 y	-	5189 (13.2)	2683 (17.8)	718 (9.6)	222 (7.7)	1040 (12.7)	151 (11.5)	275 (9.7)	60 (7.0)	40 (7.6)
1-3 y	-	5152 (13.2)	2091 (13.9)	929 (12.5)	357 (12.4)	1110 (13.75)	163 (12.5)	346 (12.2)	95 (11.0)	61 (11.6)
>3 y	-	28,837 (73.6)	10,320 (68.4)	5806 (77.9)	2308 (79.9)	6065 (73.8)	994 (76.0)	2210 (78.1)	708 (82.0)	426 (80.8)
Type of cancer, n (%)										
Respiratory and intrathoracic cancers	-	5645 (14.4)	2580 (17.1)	865 (11.6)	304 (10.4)	1226 (14.9)	188 (14.4)	338 (11.9)	78 (9.0)	66 (12.5)
Breast cancer	-	8004 (20.4)	2977 (19.7)	1546 (20.7)	689 (23.9)	1701 (20.7)	251 (19.2)	563 (19.9)	172 (19.9)	105 (19.9)
Urogenital cancer	-	12,947 (33.0)	4640 (30.7)	2601 (34.9)	1006 (34.8)	2676 (32.6)	475 (36.3)	1043 (36.8)	317 (39.7)	189 (35.9)
Gastrointestinal cancer	-	8880 (22.7)	3565 (23.6)	1584 (21.3)	581 (20.1)	1985 (24.2)	291 (22.2)	590 (20.8)	176 (20.4)	108 (20.5)
Skin cancer	-	2370 (6.0)	761 (5.0)	499 (6.7)	254 (8.8)	471 (5.7)	95 (7.3)	184 (6.5)	65 (7.5)	41 (7.8)
Intracranial cancer	-	520 (1.3)	212 (1.4)	80 (1.1)	26 (0.9)	126 (1.5)	16 (1.2)	35 (1.2)	19 (2.2)	6 (1.1)
Hematological cancer	-	3912 (10.0)	1726 (11.4)	717 (9.6)	257 (8.9)	731 (8.9)	113 (8.6)	239 (8.4)	80 (9.3)	49 (9.3)
Other cancers	-	1073 (2.7)	453 (3.0)	202 (39.7)	76 (2.6)	219 (2.7)	25 (1.9)	63 (2.2)	26 (3.0)	9 (1.7)
Comorbidities, n (%)										
IHD	62,849 (59)	11,190 (28.6)	3302 (21.9)	1530 (20.5)	472 (16.3)	3264 (39.7)	682 (52.1)	1255 (44.3)	378 (43.8)	307 (58.3)
Valvular heart disease	18,099 (48)	3333 (8.5)	970 (6.4)	805 (10.8)	182 (6.3)	683 (8.3)	135 (10.3)	414 (14.6)	90 (10.3)	54 (10.2)
Hypertension	72,624 (33)	14,546 (37.1)	4547 (30.1)	2633 (35.3)	1295 (44.9)	3215 (39.1)	683 (52.2)	1342 (47.4)	530 (61.4)	301 (57.1)
Diabetes mellitus	24,980 (11)	4764 (12.2)	1575 (10.4)	785 (10.5)	315 (10.9)	1140 (13.9)	224 (17.1)	473 (16.7)	167 (19.4)	85 (16.1)
Liver disease	4171 (1.9)	987 (2.5)	455 (3.0)	137 (1.8)	67 (2.3)	212 (2.6)	28 (2.1)	55 (1.9)	19 (2.2)	14 (2.7)
Renal failure	7545 (3.4)	2108 (5.4)	891 (5.9)	318 (4.3)	80 (2.8)	492 (6.0)	89 (6.8)	174 (6.1)	39 (4.5)	25 (4.7)

(Continues)

TABLE 1 (Continued)

Patient characteristics	Matched AF patients without a prior cancer diagnosis	AF patients with a prior cancer diagnosis	No antithrombotic treatment	Monotherapy			Dual therapy			Triple therapy
				VKA	DOAC	Antiplatelet	Dual antiplatelet	VKA + antiplatelet	DOAC + antiplatelet	VKA/ DOAC + dual antiplatelet
Previous, n (%)										
iCVA	33,928 (15)	6120 (15.6)	1632 (10.8)	866 (11.6)	398 (13.8)	1473 (17.9)	689 (52.7)	570 (20.1)	225 (26.1)	267 (50.7)
MI	29,845 (13)	5038 (12.9)	1290 (8.5)	567 (7.6)	174 (6.0)	1590 (19.4)	440 (33.6)	588 (19.7)	184 (21.3)	205 (38.9)
MB	29,267 (13)	7702 (19.7)	2962 (19.6)	1230 (16.5)	552 (19.1)	1749 (21.3)	333 (25.5)	559 (19.7)	206 (23.9)	111 (21.1)

Data are stratified by the type of therapy.

AF, atrial fibrillation/flutter; DOAC, direct oral anticoagulant; iCVA, ischemic cerebrovascular accident; IHD, ischemic heart disease; MB, major bleeding; MI, myocardial infarction; VKA, vitamin K antagonist.

(52%) were women, and the mean age was 77 years (SD, 9). The mean CHA_2DS_2-VASc score was 3.4 (SD, 1.7). The most common comorbidity was hypertension, which was present in 14,546 patients (37%) and was followed by ischemic heart disease in 29% of patients. A total of 16% and 20% of patients had a prior history of ischemic stroke and MB, respectively. The baseline characteristics are listed in Table 1.

The most frequently observed cancer type was urogenital cancer (33%), which was followed by gastrointestinal (22%), breast (20%), respiratory (14%), hematological (10%), skin (6%), other (3%), and intracranial (1%) cancers. Most patients (74%) had a cancer diagnosis >3 years before the AF diagnosis, whereas 13% had a cancer diagnosis 1 to 3 years before and another 13% had a cancer diagnosis <1 year before the AF diagnosis.

A total of 15,094 (39%) patients did not receive any antithrombotic treatment at baseline. The most common management strategies for the ones who did were antiplatelet (21%) or VKA (19%) monotherapy. DOAC monotherapy was prescribed in 7% of patients. Dual antiplatelet therapy was prescribed to 3% of patients. Dual and triple therapy with an anticoagulant were prescribed in 9% and 1% of patients, respectively.

3.2 | MB risks in patients with AF with or without a history of cancer, by antithrombotic treatment strategy

The IRs (per 100 patient-years) of MB in patients with or without prior cancer were 3.35 (95% CI, 3.25-3.45) and 2.32 (95% CI, 2.29-2.35), respectively, with an adjusted hazard ratio (aHR) of 1.24 (95% CI, 1.20-1.28; Table 2 and Supplementary Table S5). The IRs for MB of the various antithrombotic management strategies ranged between 1.74 and 9.95 in patients with AF without cancer and between 2.80 and 11.32 in those with a history of cancer (Figure 1 and Supplementary Table S5). Bleeding risk increased with intensifying combinations of antithrombotic therapy. In general, higher bleeding rates were observed across all antithrombotic treatment strategies in patients with AF as compared with patients without prior cancer. Similarly, untreated patients with AF with prior cancer experienced higher MB rates (IR, 2.80; 95% CI, 2.65-2.96) than untreated patients with AF without prior cancer (IR, 1.74; 95% CI, 1.70-1.78), resulting in an aHR of 1.33 (95% CI, 1.24-1.44). Although DOAC use was associated with fewer MB events than VKA and antiplatelet monotherapy in patients with AF without cancer, the bleeding risk of DOACs approached that of antiplatelet and VKA monotherapy in patients with AF with prior cancer (Figure 1).

3.3 | MB risks, stratified by the time interval between diagnosis of cancer and AF

The higher bleeding risk seen in patients with AF with prior cancer was observed across all tested time intervals (Table 2). The extent of

TABLE 2 Hazard ratios for major bleeding and thromboembolism in patients with atrial fibrillation/atrial flutter with prior cancer, stratified by time interval between cancer and atrial fibrillation/atrial flutter diagnosis and the cancer type.

Outcome and patient characteristics	Hazard ratio (95% CI)	Hazard ratio[a] (95% CI)	Hazard ratio[b] (95% CI)
Major bleeding			
No cancer vs prior cancer	1.39 (1.35-1.44)	1.28 (1.24-1.32)	1.24 (1.20-1.28)
<1 y interval	1.40 (1.28-1.54)	1.35 (1.23-1.48)	1.34 (1.22-1.47)
1-3 y interval	1.55 (1.43-1.68)	1.40 (1.29-1.52)	1.37 (1.26-1.48)
>3 y interval	1.37 (1.32-1.42)	1.25 (1.21-1.30)	1.21 (1.16-1.25)
Respiratory cancer	1.68 (1.55-1.83)	1.57 (1.44-1.70)	1.54 (1.41-1.67)
Breast cancer	0.94 (0.87-1.01)	1.04 (0.96-1.12)	1.02 (0.94-1.10)
Urogenital cancer	1.70 (1.62-1.79)	1.45 (1.38-1.53)	1.39 (1.32-1.46)
Gastrointestinal cancer	1.49 (1.39-1.58)	1.21 (1.14-1.29)	1.17 (1.10-1.25)
Skin cancer	1.21 (1.07-1.37)	1.10 (0.97-1.24)	1.05 (0.93-1.20)
Intracranial cancer	1.52 (1.18-1.97)	1.51 (1.17-1.95)	1.39 (1.07-1.80)
Hematological cancer	1.38 (1.24-1.52)	1.33 (1.20-1.47)	1.27 (1.15-1.40)
Other cancer	1.27 (1.06-1.53)	1.23 (1.02-1.48)	1.20 (0.99-1.44)
Thromboembolism			
No cancer vs prior cancer	1.21 (1.17-1.25)	1.07 (1.04-1.11)	1.05 (1.02-1.09)
<1 y interval	1.28 (1.16-1.40)	1.27 (1.16-1.40)	1.27 (1.16-1.40)
1-3 y interval	1.21 (1.11-1.32)	1.11 (1.02-1.22)	1.09 (1.00-1.20)
>3 y interval	1.20 (1.16-1.25)	1.04 (1.01-1.08)	1.02 (0.98-1.06)
Respiratory cancer	1.32 (1.21-1.45)	1.28 (1.17-1.40)	1.26 (1.15-1.38)
Breast cancer	1.13 (1.06-1.21)	1.01 (0.94-1.08)	1.00 (0.93-1.07)
Urogenital cancer	1.26 (1.20-1.33)	1.10 (1.04-1.16)	1.06 (1.01-1.12)
Gastrointestinal cancer	1.26 (1.18-1.35)	1.03 (0.97-1.10)	1.00 (0.94-1.07)
Skin cancer	1.04 (0.92-1.19)	0.94 (0.82-1.06)	0.92 (0.81-1.05)
Intracranial cancer	0.98 (0.72-1.33)	0.97 (0.71-1.31)	0.90 (0.66-1.21)
Hematological cancer	1.15 (1.03-1.28)	1.13 (1.01-1.25)	1.10 (0.99-1.23)
Other cancers	1.21 (1.01-1.46)	1.14 (0.94-1.37)	1.14 (0.94-1.36)

Patients with atrial fibrillation/atrial flutter without prior cancer served as reference.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure.

this additional risk was associated with the time interval between the prior cancer diagnosis and AF diagnosis. The highest MB risks were observed in those with a cancer diagnosis 1 to 3 years and <1 year prior, with aHRs of 1.37 (95% CI, 1.26-1.48) and 1.34 (95% CI, 1.22-1.47), respectively (Table 2). Similarly, although to a lesser extent, patients with AF in whom cancer was diagnosed >3 years prior had a higher bleeding risk than patients with AF without a history of cancer (aHR, 1.21; 95% CI, 1.16-1.25).

Remarkably high MB IRs (per 100 patient-years) were observed for triple therapy in patients with AF with a cancer diagnosis <1 year (IR, 16.9; 95% CI, 6.05-36.27; Table 3) and 1 to 3 years prior (IR, 19.1; 95% CI, 8.7-35.6); this rate was lower but still considerable in patients without cancer (IR, 10.0; 95% CI, 8.9-11.0).

3.4 | MB risks, stratified by cancer type

Most cancer types, except for breast and skin cancer, were associated with an increased MB rate (Table 2). The IRs per 100 patient-years for MB were, in descending order, 4.15 (95% CI, 3.81-4.50) for respiratory tract cancer, 4.11 (95% CI, 3.92-4.31) for urogenital cancer, 3.66 (95% CI, 2.80-4.68) for intracranial cancer, 3.57 (95% CI, 3.36-3.80) for gastrointestinal cancer, and 3.34 (95% CI, 3.02-3.69) for hematological cancer (Table 4).

The highest bleeding rate was observed in patients with AF with prior urogenital cancer treated with triple therapy (IR, 19.6; 95% CI, 12.7-28.3; Table 4). Notably, DOACs were associated with higher MB rates than VKAs in respiratory, gastrointestinal, and hematological cancers.

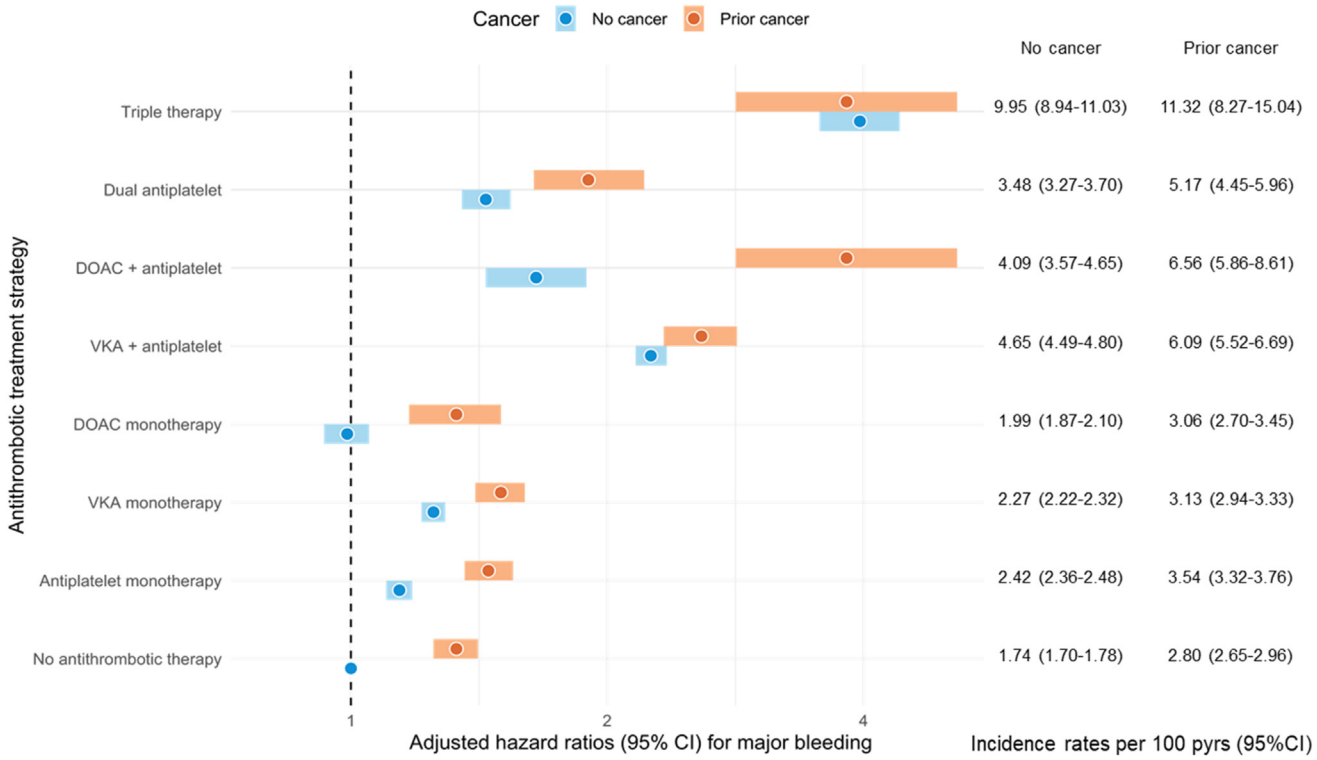

FIGURE 1 Incidence rates per 100 patient-years and adjusted hazard ratios for major bleeding, by antithrombotic management strategy. Patients with atrial fibrillation/flutter without antithrombotic treatment and no history of cancer served as a reference. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

3.5 | Thromboembolic risks by antithrombotic treatment, time interval, and cancer type

The IRs of thromboembolism per 100 patient-years were 3.21 (95% CI, 3.11-3.31) in patients with AF with prior cancer and 2.53 (95% CI, 2.50-2.56) in patients without prior cancer, thus resulting in an aHR of 1.05 (95% CI, 1.02-1.09; Table 2 and Supplementary Table S6). In general, the thromboembolic IRs were higher in patients with than in those without prior cancer across nearly all antithrombotic treatment strategies, including patients who did not receive any antithrombotic treatment. As expected, patients with AF treated with VKA or DOAC monotherapy displayed the lowest IRs of thromboembolism, whereas those treated with (dual) antiplatelet and triple therapy demonstrated the highest IRs (Figure 2 and Supplementary Table S6).

The additional thromboembolic risk of a prior cancer diagnosis was observed predominantly in patients with AF with a cancer diagnosis <1 year prior and to a lesser degree in those with cancer 1 to 3 years prior or >3 years prior, with aHRs of 1.27 (95% CI, 1.20-1.28), 1.09 (95% CI, 1.00-1.20), and 1.02 (95% CI, 0.98-1.06), respectively (Table 2). Across nearly all treatment options and in nearly all tested time intervals, the IRs of thromboembolisms were higher in patients with than in patients without a prior cancer diagnosis (Table 5). Notably, an exceptionally high IR of 19.94 (95% CI, 6.19-46.32) was found for thromboembolism in patients with AF with a <1-year-old cancer diagnosis who were treated with triple therapy.

Thromboembolic risks differed by cancer type, with IRs ranging from 2.60 in intracranial cancer to 3.61 in respiratory cancer (Table 6). Patients with a history of respiratory and urogenital cancer had greater thromboembolic risk than patients without prior cancer, with aHRs of 1.26 (95% CI, 1.15-1.38) and 1.06 (95% CI, 1.01-1.12), respectively (Table 2). The IR of thromboembolism using triple therapy in patients with respiratory and breast cancer was nearly twice that in patients without cancer using triple therapy.

4 | DISCUSSION

In this study, using nationwide routine clinical care data, we presented data on the MB and thromboembolic event rates in patients with AF with or without prior cancer according to their antithrombotic management strategy. Compared with patients with AF without cancer, patients with AF with prior cancer generally had greater risks of MB and thromboembolic complications. The extent of the additional risks conferred by a prior cancer diagnosis depended on the type of cancer and the time interval between diagnosis of prior cancer and AF.

4.1 | MB risk in patients with AF with prior cancer

The elevated bleeding risk in patients with AF with prior cancer has been well established in previous studies [1,6–9,15,33,34]. In our study, we

TABLE 3 Incidence rates and hazard ratios for major bleeding associated with antithrombotic therapy in patients with atrial fibrillation/atrial flutter with or without prior cancer, stratified by interval between prior cancer diagnosis and atrial fibrillation/atrial flutter diagnosis and treatment.

	No cancer			Prior cancer			No cancer			Prior cancer
Period between cancer and AF and treatment	MB	Person years	Incidence rate (95% CI)	MB	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
<1 y between prior cancer diagnosis and AF diagnosis										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	447	12,922	3.44 (3.13-3.77)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	160	5687	2.81 (2.40-3.27)	Reference	Reference	1.51 (1.29-1.76)	1.43 (1.22-1.68)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	287	7305	3.93 (3.49-4.40)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.14 (1.90-2.41)	1.76 (1.56-1.98)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	102	2704	3.77 (3.09-4.55)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.05 (1.68-2.49)	1.62 (1.33-1.97)
VKA	7142	314,735	2.27 (2.22-2.32)	89	2900	3.07 (2.47-3.75)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.71 (1.39-2.11)	1.54 (1.25-1.90)
DOAC	1144	57,576	1.99 (1.87-2.10)	25	682	3.67 (2.41-5.30)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.97 (1.33-2.92)	1.63 (1.10-2.42)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	20	294	6.80 (4.24-10.23)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	3.58 (2.31-5.56)	2.52 (1.62-3.90)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	46	696	6.61 (4.88-8.71)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.55 (2.66-4.75)	2.78 (2.09-3.73)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	5	30	16.88 (6.05-36.27)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	7.61 (3.17-18.29)	5.62 (2.34-13.51)
1-3 y between prior cancer diagnosis and AF diagnosis										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	570	15,201	3.75 (3.45-4.07)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	192	5737	3.35 (2.90-3.84)	Reference	Reference	1.83 (1.59-2.12)	1.60 (1.39-1.85)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	378	9464	3.99 (3.60-4.41)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.18 (1.97-2.42)	1.69 (1.52-1.87)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	125	3342	3.74 (3.12-4.44)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.06 (1.73-2.46)	1.51 (1.27-1.81)
VKA	7142	314,735	2.27 (2.22-2.32)	123	3823	3.22 (2.68-3.82)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.80 (1.50-2.15)	1.49 (1.25-1.78)
DOAC	1144	57,576	1.99 (1.87-2.10)	37	951	3.89 (2.77-5.28)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	2.05 (1.49-2.84)	1.68 (1.21-2.32)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	23	408	5.63 (3.63-8.26)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	3.04 (2.02-4.58)	2.08 (1.38-3.14)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	62	898	6.90 (5.32-8.76)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.68 (2.86-4.72)	2.80 (2.18-3.59)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	8	42	19.11 (8.73-35.57)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	8.72 (4.36-17.45)	5.83 (2.91-11.67)
>3 y between prior cancer diagnosis and AF diagnosis										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	3256	99,332	3.28 (3.17-3.39)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	984	36,250	2.71 (2.55-2.89)	Reference	Reference	1.51 (1.41-1.61)	1.27 (1.19-1.36)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	2272	63,082	3.60 (3.46-3.75)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	1.98 (1.89-2.08)	1.56 (1.48-1.64)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	774	22,250	3.48 (3.24-3.73)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	1.94 (1.80-2.09)	1.42 (1.32-1.53)
VKA	7142	314,735	2.27 (2.22-2.32)	781	25,031	3.12 (2.91-3.34)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.75 (1.62-1.88)	1.50 (1.39-1.61)
DOAC	1144	57,576	1.99 (1.87-2.10)	194	6731	2.88 (2.50-3.31)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.53 (1.32-1.76)	1.25 (1.08-1.44)

(Continues)

TABLE 3 (Continued)

Period between cancer and AF and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	MB	Person years	Incidence rate (95% CI)	MB	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	139	2818	4.93 (4.16-5.80)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	2.70 (2.28-3.19)	1.81 (1.53-2.14)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	354	5943	5.96 (5.36-6.60)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.18 (2.86-3.54)	2.47 (2.22-2.75)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	30	308	9.73 (6.65-13.63)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	4.44 (3.10-6.35)	3.37 (2.35-4.82)

Patients with atrial fibrillation/atrial flutter without cancer and without any antithrombotic therapy served as a reference.

AF, atrial fibrillation/flutter; DOAC, direct oral anticoagulant; MB, major bleeding; VKA, vitamin K antagonist.

[a]Adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure.

found an elevated bleeding risk in nearly all tested cancer types, except skin and breast cancer. Moreover, untreated patients with AF with cancer bled more than untreated patients with AF without cancer, thus indicating that the elevated bleeding tendency was associated with a prior cancer diagnosis independently of antithrombotic treatment. Besides, these patients could have been left untreated by the treating physician due to an estimated high bleeding risk.

After stratification by cancer type, DOACs, compared with VKAs, showed similar or lower MB rates in patients with AF with prior cancer, except in those with prior respiratory or hematological cancer. No clear explanation could be provided on the basis of the available data, but potential reasons may include drug–drug interactions between DOACs and anticancer treatments specific to these cancer types and differences in the extent of cancer (eg, metastasis or irresectability) or in different patient characteristics [6,35–37]. Current guidelines recommend for the use of DOACs rather than VKAs in patients with AF [38,39]. However, no specific recommendations regarding anticoagulation therapy have been provided for patients with AF with active cancer or a history of cancer because most DOAC randomized controlled trials have excluded patients with active cancer [40–43]. Subsequent nationwide cohort studies or post hoc analyses have suggested that DOACs have similar or superior safety profiles to those of VKAs in patients with AF with prior cancer [9,14,44–49]. However, given the observational nature of these studies and our study, no definitive inferences on the preferred anticoagulant can be drawn from the numerical comparison of bleeding rates of DOACs and VKAs, also considering that confounding by indication will always play a role in these studies.

Furthermore, in line with findings from a previous nationwide cohort study, we observed an association between the time interval between prior cancer and AF, and bleeding outcomes [8]. For all periods, greater risks of MB were found in patients with AF with than in patients without prior cancer, and higher bleeding risks were observed in patients with a relative recent cancer diagnosis (ie, <3 years before AF) than in those with cancer diagnosed >3 years before AF. We hypothesized that patients with cancer diagnosed >3 years prior were likely to have "stable" cancer or to be in remission and thus more similar to AF patients without cancer. Interestingly, a milder increase in MB risk also persisted in patients with a cancer diagnosis >3 years prior. Possible explanations for the persisting and residual susceptibility for MB are late complications or persisting damage due to anticancer treatments and again differences in patient characteristics. Interestingly, whereas DOACs were associated with lower IRs of MB than VKAs in patients with AF without cancer, higher IRs of MB were observed in patients treated with DOACs rather than VKAs in patients with AF with a cancer diagnosis <3 years prior.

4.2 | Thromboembolic risk in patients with AF with prior cancer

Most prior studies have demonstrated no association between cancer and ischemic stroke/thromboembolism incidence in patients with

TABLE 4 Incidence rates and hazard ratios for major bleeding associated with antithrombotic therapy in patients with atrial fibrillation/atrial flutter with or without prior cancer, stratified by cancer type.

	No cancer			Prior cancer			No cancer		Prior cancer	
Type cancer and treatment	MB	Person years	Incidence rate (95% CI)	MB	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Respiratory and intrathoracic cancers										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	555	13,379	4.15 (3.81-4.50)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	171	5222	3.27 (2.81-3.79)	Reference	Reference	1.75 (1.50-2.04)	1.60 (1.37-1.86)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	384	8157	4.71 (4.25-5.19)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.55 (2.30-2.82)	2.02 (1.83-2.24)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	144	3172	4.54 (3.84-5.32)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.48 (2.10-2.92)	1.90 (1.61-2.24)
VKA	7142	314,735	2.27 (2.22-2.32)	115	2950	3.90 (3.23-4.66)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	2.15 (1.79-2.59)	1.85 (1.54-2.23)
DOAC	1144	575,76	1.99 (1.87-2.10)	37	723	5.12 (3.64-6.94)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	2.68 (1.94-3.70)	2.25 (1.63-3.10)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	20	388	5.15 (3.21-7.75)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	2.74 (1.76-4.25)	1.98 (1.27-3.07)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	66	881	7.49 (5.82-9.44)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	4.01 (3.15-5.11)	3.14 (2.46-4.00)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	[b]	[b]	4.62 (0.77-14.25)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	2.12 (0.53-8.47)	1.56 (0.39-6.25)
Breast cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	686	30,952	2.22 (2.05-2.39)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	215	12,019	1.79 (1.56-2.04)	Reference	Reference	1.01 (0.88-1.15)	1.04 (0.91-1.19)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	471	18,994	2.49 (2.27-2.72)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	1.38 (1.26-1.52)	1.33 (1.21-1.46)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	175	6816	2.57 (2.21-2.97)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	1.44 (1.24-1.67)	1.26 (1.08-1.46)
VKA	7142	314,735	2.27 (2.22-2.32)	159	7408	2.15 (1.83-2.50)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.21 (1.04-1.42)	1.26 (1.08-1.48)
DOAC	1144	57,576	1.99 (1.87-2.10)	47	2209	2.13 (1.58-2.79)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.14 (0.86-1.53)	1.09 (0.82-1.45)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	23	790	2.91 (1.88-4.27)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	1.61 (1.07-2.42)	1.29 (0.86-1.95)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	61	1624	3.76 (2.89-4.78)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	2.03 (1.58-2.61)	1.95 (1.51-2.51)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	6	85	7.03 (2.80-14.25)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	3.32 (1.49-7.40)	3.01 (1.35-6.70)
Urogenital cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	1664	40,485	4.11 (3.92-4.31)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	530	14,025	3.78 (3.47-4.11)	Reference	Reference	2.08 (1.90-2.27)	1.62 (1.48-1.77)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	1134	26,460	4.29 (4.04-4.54)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.34 (2.20-2.49)	1.72 (1.62-1.83)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	377	8980	4.20 (3.79-4.64)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.33 (2.10-2.58)	1.59 (1.43-1.76)
VKA	7142	314,735	2.27 (2.22-2.32)	384	10,834	3.54 (3.20-3.91)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.98 (1.79-2.19)	1.60 (1.44-1.77)
DOAC	1144	57,576	1.99 (1.87-2.10)	90	2870	3.14 (2.53-3.83)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.66 (1.35-2.04)	1.27 (1.03-1.56)

(Continues)

TABLE 4 (Continued)

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	MB	Person years	Incidence rate (95% CI)	MB	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	77	1178	6.53 (5.18-8.10)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	3.52 (2.81-4.41)	2.29 (1.83-2.86)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	181	2471	7.33 (6.31-8.45)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.86 (3.33-4.48)	2.74 (2.37-3.18)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	25	128	19.56 (12.86-28.26)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	8.68 (5.86-12.86)	5.81 (3.92-8.62)
Gastrointestinal cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	1001	28,000	3.57 (3.36-3.80)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	319	10,902	2.93 (2.62-3.26)	Reference	Reference	1.61 (1.44-1.80)	1.22 (1.09-1.37)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	682	17,098	3.99 (3.70-4.30)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.19 (2.02-2.37)	1.54 (1.42-1.67)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	246	6496	3.79 (3.33-4.28)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.10 (1.85-2.38)	1.40 (1.24-1.60)
VKA	7142	314,735	2.27 (2.22-2.32)	225	6495	3.46 (3.03-3.94)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.94 (1.70-2.21)	1.48 (1.30-1.69)
DOAC	1144	57,576	1.99 (1.87-2.10)	56	1594	3.51 (2.67-4.52)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.86 (1.43-2.52)	1.35 (1.03-1.75)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	48	890	5.40 (4.01-7.07)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	2.98 (2.24-3.96)	1.75 (1.32-2.33)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	101	1558	6.48 (5.30-7.83)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.47 (2.85-4.22)	2.43 (2.00-2.96)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	6	66	9.13 (3.63-18.50)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	4.01 (1.80-8.93)	2.53 (1.14-5.65)
Skin cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	247	8584	2.88 (2.53-3.25)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	66	2946	2.24 (1.74-2.83)	Reference	Reference	1.26 (0.99-1.60)	1.07 (0.84-1.36)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	181	5638	3.21 (2.77-3.70)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	1.77 (1.53-2.06)	1.38 (1.19-1.60)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	43	1785	2.41 (1.76-3.20)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	1.35 (1.00-1.82)	0.97 (0.72-1.31)
VKA	7142	314,735	2.27 (2.22-2.32)	65	2361	2.75 (2.14-3.48)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.55 (1.22-1.98)	1.31 (1.03-1.67)
DOAC	1144	57,576	1.99 (1.87-2.10)	17	698	2.44 (1.45-3.78)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.29 (0.80-2.08)	1.03 (0.64-1.67)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	13	224	5.81 (3.19-9.56)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	3.16 (1.73-5.44)	2.01 (1.17-3.46)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	40	540	7.40 (5.34-9.94)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.97 (2.91-5.42)	3.05 (2.24-4.17)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	[b]	[b]	9.99 (2.48-25.90)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	4.66 (1.50-14.47)	4.20 (1.36-13.04)
Intracranial cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	58	1585	3.66 (2.80-4.68)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	20	602	3.32 (2.07-5.00)	Reference	Reference	1.83 (1.18-2.84)	1.72 (1.11-2.67)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	38	983	3.86 (2.76-5.23)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	2.13 (1.55-2.93)	1.67 (1.22-2.31)

(Continues)

TABLE 4 (Continued)

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	MB	Person years	Incidence rate (95% CI)	MB	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	16	411	3.89 (2.28-6.12)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.17 (1.33-3.54)	1.70 (1.04-2.77)
VKA	7142	314,735	2.27 (2.22-2.32)	13	359	3.62 (1.99-5.96)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	2.05 (1.19-3.54)	1.74 (1.01-3.00)
DOAC	1144	57,576	1.99 (1.87-2.10)	[b]	[b]	2.73 (0.45-8.53)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.44 (0.36-5.76)	1.14 (0.28-4.56)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	[b]	[b]	8.35 (2.08-21.65)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	4.48 (1.44-13.88)	3.18 (1.02-9.84)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	4	102	3.94 (1.22-9.15)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	2.08 (0.78-5.55)	1.47 (0.55-3.92)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	[b]	[b]	NP	4.78 (4.29-5.33)	3.98 (3.57-4.44)	NP	NP
Hematological cancer										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	376	11,241	3.34 (3.02-3.69)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	131	4534	2.89 (2.42-3.41)	Reference	Reference	1.57 (1.32-1.87)	1.42 (1.20-1.69)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68s)	245	6707	3.65 (3.21-4.13)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	1.99 (1.75-2.26)	1.61 (1.41-1.82)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	76	2250	3.38 (2.67-4.20)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	1.86 (1.49-2.33)	1.43 (1.14-1.79)
VKA	7142	314,735	2.27 (2.22-2.32)	89	2772	3.21 (2.59-3.92)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.78 (1.45-2.20)	1.53 (1.24-1.89)
DOAC	1144	57,576	1.99 (1.87-2.10)	26	694	3.75 (2.49-5.38)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.96 (1.34-2.89)	1.64 (1.12-2.42)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	12	285	4.21 (2.25-7.06)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	2.27 (1.29-4.01)	1.61 (0.92-2.85)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	39	666	5.85 (4.20-7.89)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	3.13 (2.29-4.29)	2.58 (1.88-3.53)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	[b]	[b]	7.44 (1.85-19.29)	4.78 (4.29-5.33)	3.98 (3.57-4.44)	3.48 (1.12-10.78)	2.76 (0.89-8.57)
Other cancers										
All patients	26,209	1,131,207	2.32 (2.29-2.35)	111	3654	3.04 (2.51-3.64)				
No antithrombotic therapy	7053	405,277	1.74 (1.70-1.78)	34	1490	2.28 (1.60-3.14)	Reference	Reference	1.27 (0.90-1.77)	1.21 (0.84-1.69)
Antithrombotic therapy	19,156	725,930	2.64 (2.60-2.68)	77	2164	3.56 (2.82-4.41)	1.50 (1.46-1.54)	1.31 (1.28-1.35)	1.97 (1.57-2.47)	1.59 (1.27-1.99)
Antiplatelet	5842	241,466	2.42 (2.36-2.48)	31	822	3.77 (2.59-5.26)	1.39 (1.34-1.44)	1.13 (1.09-1.17)	2.11 (1.48-3.01)	1.61 (1.13-2.30)
VKA	7142	314,735	2.27 (2.22-2.32)	27	848	3.18 (2.13-4.54)	1.30 (1.26-1.35)	1.25 (1.21-1.30)	1.79 (1.23-2.61)	1.51 (1.03-2.20)
DOAC	1144	57,576	1.99 (1.87-2.10)	5	222	2.26 (0.81-4.85)	1.09 (1.02-1.16)	0.99 (0.93-1.05)	1.20 (4.98-2.88)	1.09 (0.45-2.61)
Dual antiplatelet	1012	29,075	3.48 (3.27-3.70)	5	70	7.14 (2.56-15.34)	1.96 (1.83-2.09)	1.43 (1.34-1.53)	3.94 (1.64-9.46)	2.99 (1.25-7.19)
VKA/DOAC + antiplatelet	3668	79,581	4.61 (4.46-4.76)	9	192	4.70 (2.26-8.47)	2.57 (2.46-2.67)	2.20 (2.11-2.30)	2.54 (1.32-4.88)	2.02 (1.05-3.89)
VKA/DOAC triple therapy	348	3497	9.95 (8.94-11.03)	[b]	[b]	NP	4.78 (4.29-5.33)	3.98 (3.57-4.44)	NP	NP

Patients with atrial fibrillation/atrial flutter without cancer and without any antithrombotic therapy served as a reference.

DOAC, direct oral anticoagulant; MB, major bleeding; NP, not possible; VKA, vitamin K antagonist.

[a]Adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure.

[b]Because of Danish privacy regulations, censoring occurred when the number of people or events was below 4.

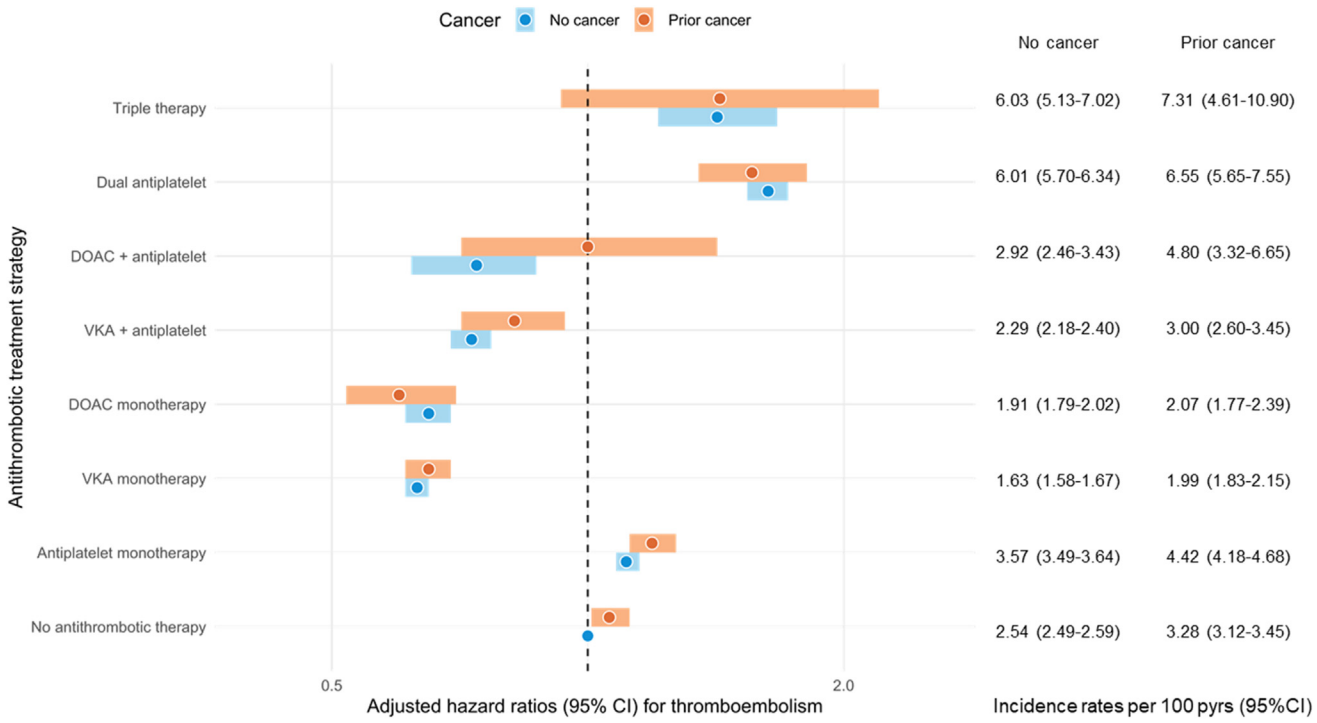

FIGURE 2 Incidence rates per 100 patient-years and adjusted hazard ratios for thromboembolisms, by antithrombotic management strategy. Patients with atrial fibrillation/flutter without antithrombotic treatment and no history of cancer served as a reference. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

AF [1,7–9,14,34,49], except for certain cancer types such as pancreatic and uterine cancer, although the association has not been found consistently [7,8,10,50]. We found that patients with AF with prior cancer are at elevated risk of developing thromboembolism, particularly those with a cancer diagnosis <1 year before AF diagnosis. We hypothesized that this time period is characterized by active cancer with ongoing treatment and frequent interventions, which contribute to an increased thromboembolic risk. In contrast, the increased risk was not observed in patients with a cancer diagnosis >3 years prior, thus probably reflecting stable cancer or cancer in remission. A similar difference in thrombogenicity has been observed in patients with VTE in the COMMAND VTE registry, in which patients with active cancer were found to have elevated risk of VTE recurrence, whereas patients with a prior history of cancer were not [51]. Furthermore, patients with AF with prior respiratory and urogenital cancer were at elevated risk of developing thromboembolic complications, in line with findings from prior publications on cancer sites at high risk of developing VTE [2,52].

These findings prompt the question of whether certain cancer characteristics, such as respiratory cancer or recent diagnosed cancer, should be incorporated in the formal assessment performed before starting anticoagulant treatment in patients with AF. The CHA_2DS_2-VASc score, which has been implemented in contemporary guidelines to guide the initiation of anticoagulants in AF, does not include active or prior cancer in the risk. However, inferences regarding whether patients with recent cancer and a CHA_2DS_2-VASc score of 0 or 1 should be anticoagulated cannot be drawn, given the observational nature of this study where unknown considerations by the treating physicians would have played a role in the decision to prescribe anticoagulation or not, particularly in the case of cancer patients.

Prior observational studies have demonstrated comparable or lower thromboembolic risks for DOACs than VKAs in AF patients with cancer [45,46,48,49]. Although we did not directly compare VKAs with DOACs, we observed numerically higher thromboembolic rates among patients with prior respiratory or urogenital cancer, or in those with a cancer diagnosis 1 to 3 years prior, who received DOACs rather than VKAs. Differences in the event rates for ischemic stroke between rivaroxaban/dabigatran and VKAs have been observed in lung and colon cancer [53]. Given the observational nature of this study, no inferences can be made regarding the comparison of bleeding and thromboembolic risks between DOACs and VKAs. However, our results do provide a rationale for performing future randomized trials between DOACs and VKAs in patients with AF with cancer because certain anticoagulants might be preferred in certain conditions.

4.3 | Strengths and limitations

This study is the first to provide thromboembolic and bleeding rates observed for different antithrombotic treatment strategies in patients with incident AF with a prior cancer diagnosis. The large number of patients obtained from the Danish nationwide cohort enabled

TABLE 5 Incidence rates and hazard ratios for thromboembolisms, by antithrombotic therapy, in patients with atrial fibrillation/atrial flutter with prior cancer and patients with atrial fibrillation/atrial flutter without cancer.

	No cancer			Prior cancer						
Period between cancer and AF and treatment	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
<1 y between prior cancer diagnosis and AF diagnosis										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	443	12,728	3.48 (3.17-3.81)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	196	5745	3.41 (2.96-3.91)	Reference	Reference	1.23 (1.07-1.41)	1.22 (1.06-1.41)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	247	6982	3.54 (3.11-4.00)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.29 (1.14-1.47)	1.10 (0.97-1.25)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	123	2667	4.61 (3.84-5.47)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.68 (1.41-2.01)	1.35 (1.13-1.61)
VKA	5061	310,823	1.63 (1.58-1.67)	65	2807	2.32 (1.80-2.92)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.87 (0.69-1.12)	0.83 (0.65-1.06)
DOAC	1051	55,105	1.91 (1.79-2.02)	11	649	1.69 (0.88-2.90)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.61 (0.34-1.10)	0.53 (0.30-0.96)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	16	214	7.47 (4.38-11.74)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.53 (1.55-4.13)	1.82 (1.12-2.98)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	28	624	4.49 (3.02-6.36)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.29 (1.10-2.31)	1.26 (0.87-1.83)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	4	20	19.94 (6.19-46.32)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	5.17 (1.94-13.79)	3.96 (1.49-10.56)
1-3 y between prior cancer diagnosis and AF diagnosis										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	491	15,186	3.23 (2.96-3.53)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	202	5930	3.41 (2.96-3.90)	Reference	Reference	1.26 (1.10-1.45)	1.14 (0.99-1.31)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	289	9256	3.12 (2.78-3.50)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.15 (1.02-1.29)	0.91 (0.81-1.03)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	149	3372	4.42 (3.75-5.17)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.65 (1.40-1.93)	1.21 (1.03-1.42)
VKA	5061	310,823	1.63 (1.58-1.67)	62	3771	1.64 (1.27-2.09)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.62 (0.48-0.80)	0.55 (0.42-0.70)
DOAC	1051	55,105	1.91 (1.79-2.02)	24	918	2.61 (1.70-3.80)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.92 (0.62-1.38)	0.80 (0.53-1.19)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	23	318	7.24 (4.67-10.62)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.57 (1.70-3.86)	1.83 (1.21-2.75)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	30	843	3.56 (2.43-4.99)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.26 (0.88-1.80)	0.96 (0.67-1.38)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	[b]	[b]	2.87 (0.16-12.63)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	0.82 (0.11-5.79)	0.56 (0.08-3.97)
>3 y between prior cancer diagnosis and AF diagnosis										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	3118	98,362	3.17 (3.06-3.28)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	1205	37,151	3.24 (3.06-3.43)	Reference	Reference	1.23 (1.16-1.30)	1.02 (0.96-1.09)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	1913	61,211	3.13 (2.99-3.27)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.16 (1.11-1.22)	0.88 (0.84-0.92)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	958	21,759	4.40 (4.13-4.69)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.67 (1.56-1.78)	1.17 (1.09-1.25)
VKA	5061	310,823	1.63 (1.58-1.67)	497	24,831	2.00 (1.83-2.18)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.76 (0.70-0.83)	0.65 (0.59-0.71)
DOAC	1051	55,105	1.91 (1.79-2.02)	132	6518	2.03 (1.70-2.39)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.72 (0.51-0.85)	0.58 (0.49-0.69)

(Continues)

TABLE 5 (Continued)

Period between cancer and AF and treatment	No cancer			Prior cancer						
	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	143	2245	6.37 (5.38-7.47)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.32 (1.96-2.73)	1.50 (1.27-1.77)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	167	5627	2.97 (2.54-3.44)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.06 (0.91-1.23)	0.78 (0.67-0.90)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	16	232	6.89 (4.04-10.84)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	1.90 (1.16-3.10)	1.35 (0.83-2.20)

Data are stratified by the interval between prior cancer and atrial fibrillation/atrial flutter.

AF, atrial fibrillation/flutter; DOAC, direct oral anticoagulant; TE, thromboembolism; VKA, vitamin K antagonist.

[a]Adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure.

[b]Because of Danish privacy regulations, censoring occurred when the number of people or events was below 4.

TABLE 6 Incidence rates and hazard ratio of thromboembolism, by antithrombotic therapy, in patients with atrial fibrillation/atrial flutter with prior history of cancer and patients with atrial fibrillation/atrial flutter without cancer, stratified by cancer type.

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Respiratory and intrathoracic cancers										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	480	13,302	3.61 (3.30-3.94)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	180	5370	3.35 (2.89-3.87)	Reference	Reference	1.20 (1.04-1.40)	1.16 (1.00-1.34)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	300	7932	3.78 (3.37-4.23)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.38 (1.23-1.54)	1.13 (1.01-1.27)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	148	3158	4.68 (3.97-5.48)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.72 (1.46-2.03)	1.34 (1.14-1.58)
VKA	5061	310,823	1.63 (1.58-1.67)	68	2904	2.34 (1.83-2.94)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.87 (0.69-1.11)	0.79 (0.63-1.01)
DOAC	1051	55,105	1.91 (1.79-2.02)	23	703	3.27 (2.11-4.80)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	1.14 (0.76-1.72)	0.98 (0.65-1.48)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	26	301	8.64 (5.73-12.40)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.99 (2.03-4.39)	2.16 (1.47-3.18)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	31	832	3.73 (2.56-5.20)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.33 (0.93-1.89)	1.05 (0.74-1.50)

(Continues)

TABLE 6 (Continued)

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	4	34	11.66 (3.62-27.08)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	3.33 (1.25-8.87)	2.31 (0.87-6.15)
Breast cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	889	30,128	2.95 (2.76-3.15)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	360	12,026	2.99 (2.69-3.31)	Reference	Reference	1.15 (1.03-1.27)	1.01 (0.91-1.13)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	529	18,102	2.92 (2.68-3.18)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.10 (1.01-1.20)	0.86 (0.78-0.94)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	286	6563	4.36 (3.87-4.88)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.66 (1.48-1.87)	1.21 (1.08-1.37)
VKA	5061	310,823	1.63 (1.58-1.67)	117	7229	1.62 (1.34-1.93)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.62 (0.52-0.75)	0.55 (0.46-0.66)
DOAC	1051	55,105	1.91 (1.79-2.02)	39	2085	1.87 (1.34-2.52)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.67 (0.49-0.92)	0.55 (0.40-0.76)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	34	645	5.27 (3.69-7.24)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	1.95 (1.39-2.72)	1.37 (0.98-1.92)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	46	1527	3.01 (2.22-3.97)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.09 (0.81-1.45)	0.83 (0.62-1.11)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	7	52	13.38 (5.75-25.87)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	3.56 (1.69-7.46)	2.52 (1.20-5.29)
Urogenital cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	1367	40,576	3.37 (3.19-3.55)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	534	14,582	3.66 (3.36-3.98)	Reference	Reference	1.37 (1.25-1.49)	1.12 (1.02-1.22)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	833	25,994	3.20 (2.99-3.43)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.18 (1.10-1.27)	0.90 (0.83-0.96)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	401	8921	4.49 (4.07-4.95)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.69 (1.53-1.86)	1.17 (1.06-1.30)
VKA	5061	310,823	1.63 (1.58-1.67)	216	10,883	1.98 (1.73-2.26)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.75 (0.66-0.86)	0.64 (0.56-0.73)
DOAC	1051	55,105	1.91 (1.79-2.02)	69	2813	2.45 (1.92-3.08)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.87 (0.69-1.10)	0.71 (0.56-0.90)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	67	911	7.36 (5.73-9.26)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.61 (2.05-3.32)	1.68 (1.32-2.14)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	74	2360	3.14 (2.47-3.91)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.10 (0.87-1.38)	0.79 (0.63-0.99)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	6	106	5.67 (2.25-11.49)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	1.54 (0.69-3.43)	1.06 (0.48-2.37)
Gastrointestinal cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	930	27,695	3.36 (3.15-3.58)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	389	11,242	3.46 (3.13-3.82)	Reference	Reference	1.29 (1.17-1.43)	1.02 (0.92-1.13)

(Continues)

TABLE 6 (Continued)

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	541	16,453	3.29 (3.02-3.57)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.22 (1.12-1.33)	0.86 (0.79-0.94)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	285	6350	4.49 (3.99-5.03)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.68 (1.49-1.89)	1.12 (0.99-1.26)
VKA	5061	310,823	1.63 (1.58-1.67)	136	6400	2.13 (1.79-2.50)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.81 (0.68-0.95)	0.64 (0.54-0.76)
DOAC	1051	55,105	1.91 (1.79-2.02)	26	1518	1.71 (1.14-2.46)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.60 (0.41-0.89)	0.46 (0.31-0.67)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	44	665	6.62 (4.85-8.77)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.41 (1.79-3.23)	1.42 (1.06-1.91)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	46	1475	3.12 (2.30-4.11)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.11 (0.83-1.48)	0.77 (0.57-1.03)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	4	45	8.81 (2.74-20.47)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	2.25 (0.84-5.99)	1.41 (0.53-3.76)
Skin cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	232	8486	2.73 (2.40-3.10)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	71	3005	2.36 (1.85-2.96)	Reference	Reference	0.90 (0.72-1.14)	0.80 (0.64-1.02)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	161	5481	2.94 (2.51-3.41)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.10 (0.94-1.28)	0.85 (0.73-0.99)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	74	1760	4.20 (3.32-5.24)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.60 (1.27-2.01)	1.12 (0.89-1.41)
VKA	5061	310,823	1.63 (1.58-1.67)	56	2313	2.42 (1.84-3.11)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.93 (0.71-1.21)	0.80 (0.62-1.04)
DOAC	1051	55,105	1.91 (1.79-2.02)	9	680	1.32 (0.64-2.39)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.47 (0.25-0.91)	0.39 (0.20-0.75)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	5	185	2.71 (0.97-5.81)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	0.97 (0.40-2.33)	0.61 (0.25-1.47)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	16	514	3.11 (1.82-4.89)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.11 (0.68-1.82)	0.83 (0.51-1.36)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	[b]	[b]	3.57 (0.20-15.70)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	1.08 (0.15-7.65)	0.88 (0.12-6.24)
Intracranial cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	42	1617	2.60 (1.89-3.46)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	22	648	3.40 (2.17-5.02)	Reference	Reference	1.27 (0.84-1.93)	1.19 (0.78-1.81)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	20	969	2.06 (1.29-3.10)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	0.77 (0.50-1.19)	0.61 (0.39-0.94)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	10	403	2.48 (1.24-4.36)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	0.93 (0.50-1.74)	0.70 (0.38-1.30)
VKA	5061	310,823	1.63 (1.58-1.67)	8	372	2.15 (0.98-4.00)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.83 (0.42-1.66)	0.77 (0.38-1.53)
DOAC	1051	55,105	1.91 (1.79-2.02)	[b]	[b]	NP	0.70 (0.66-0.75)	0.65 (0.61-0.69)	NP	NP
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	[b]	[b]	6.93 (1.15-21.38)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.40 (0.60-9.60)	1.64 (0.41-6.56)

(Continues)

TABLE 6 (Continued)

Type cancer and treatment	No cancer			Prior cancer			No cancer		Prior cancer	
	TE	Person years	Incidence rate (95% CI)	TE	Person years	Incidence rate (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]	Hazard ratio (95% CI)	Hazard ratio (95% CI)[a]
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	[b]	[b]	NP	0.87 (0.83-0.92)	0.73 (0.69-0.77)	NP	NP
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	[b]	[b]	NP	1.78 (1.52-2.08)	1.42 (1.21-1.66)	NP	NP
Hematological cancer										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	343	11,060	3.10 (2.78-3.44)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	135	4602	2.93 (2.47-3.46)	Reference	Reference	1.08 (0.91-1.28)	1.03 (0.87-1.22)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	208	6458	3.22 (2.80-3.68)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.18 (1.03-1.35)	0.99 (0.86-1.13)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	116	2192	5.29 (4.39-6.31)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.97 (1.64-2.36)	1.51 (1.26-1.82)
VKA	5061	310,823	1.63 (1.58-1.67)	50	2717	1.84 (1.38-2.40)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.69 (0.52-0.91)	0.64 (0.48-0.84)
DOAC	1051	55,105	1.91 (1.79-2.02)	11	681	1.62 (0.94-2.77)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.56 (0.31-1.02)	0.50 (0.27-0.90)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	14	233	6.01 (3.39-9.72)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	2.14 (1.27-3.62)	1.52 (0.90-2.57)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	16	603	2.65 (1.56-4.17)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	0.94 (0.57-1.53)	0.77 (0.47-1.26)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	[b]	[b]	3.11 (0.18-13.67)	1.78 (1.52-2.08)	1.42 (1.21-1.66)	0.90 (0.13-6.42)	0.74 (0.10-5.23)
Other cancers										
All patients combined	28,132	1,110,422	2.53 (2.50-2.56)	114	3563	3.20 (2.65-3.82)				
No antithrombotic therapy	10,423	410,820	2.54 (2.49-2.59)	51	1497	3.41 (2.56-4.30)	Reference	Reference	1.28 (0.97-1.69)	1.20 (0.91-1.58)
Antithrombotic therapy	17,709	699,602	2.53 (2.49-2.57)	63	2066	3.05 (2.36-3.86)	0.98 (0.96-1.00)	0.89 (0.84-0.88)	1.14 (0.89-1.46)	0.93 (0.73-1.19)
Antiplatelet	8380	234,945	3.57 (3.49-3.64)	32	789	4.05 (2.81-5.63)	1.40 (1.36-1.44)	1.11 (1.08-1.14)	1.53 (1.08-2.17)	1.15 (0.81-1.63)
VKA	5061	310,823	1.63 (1.58-1.67)	18	824	2.19 (1.32-3.36)	0.64 (0.62-0.66)	0.63 (0.61-0.65)	0.83 (0.52-1.32)	0.75 (0.47-1.19)
DOAC	1051	55,105	1.91 (1.79-2.02)	[b]	[b]	0.46 (0.03-2.02)	0.70 (0.66-0.75)	0.65 (0.61-0.69)	0.16 (0.02-1.17)	0.15 (0.02-1.05)
Dual antiplatelet	1341	22,300	6.01 (5.70-6.34)	6	57	10.53 (4.18-21.33)	2.26 (2.14-2.39)	1.62 (1.53-1.72)	3.85 (1.73-8.58)	2.82 (1.27-6.29)
VKA/DOAC + antiplatelet	1720	73,842	2.33 (2.22-2.44)	6	171	3.50 (1.39-7.10)	0.87 (0.83-0.92)	0.73 (0.69-0.77)	1.25 (0.56-2.77)	0.99 (0.44-2.20)
VKA/DOAC triple therapy	156	2588	6.03 (5.13-7.02)	[b]	[b]	NP	1.78 (1.52-2.08)	1.42 (1.21-1.66)	NP	NP

DOAC, direct oral anticoagulant; NP, not possible; TE, thromboembolism; VKA, vitamin K antagonist.

[a]Adjusted for age, sex, ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, and kidney failure.

[b]Because of Danish privacy regulations, censoring occurred when the number of people or events was below 4.

accurate risk estimation. Moreover, the linkage between the various health care registries allowed for uniform data collection, large numbers of outcome events, and complete follow-up.

The main limitations of this study are the lack of granular data regarding the AF (ie, type, burden, recurrences, and ablation) and cancer diagnosis (ie, cancer activity, treatment, and metastatic status) as well as the observational nature of this study. Cancer activity and metastatic status are suggested to substantially modulate the additional bleeding risk of cancer [7].

Furthermore, granular data on the motivation and justification of physicians for prescribing certain antithrombotic treatments are lacking. Although we attempted to correct for comorbidities, confounding by indication remains an important bias because anticoagulant treatment could be withheld or prescribed with lower intensity in patients with a perceived increased bleeding risk. Therefore, the observational nature of these data does not allow for direct comparisons of effectiveness and safety outcomes of the various antithrombotic treatment strategies. Although we included large numbers of patients, the multiple stratifications performed in this study and the resulting small numbers per subgroup did not allow exploration of all possible associations.

Moreover, data regarding race, ethnicity, and sociocultural characteristics of the participants were not obtained; this is a limitation to the understanding of the impact of the sociocultural background of the studied population on anticoagulant management in patients with AF and cancer. Future studies should consider these characteristics.

Finally, the dispensing data do not include the time in therapeutic range for VKA treatment, the adherence or lack thereof to antithrombotic treatment, and temporary (justified) interruptions of antithrombotic treatment during follow-up, all of which might have affected our results yet also reflect daily practice.

5 | CONCLUSIONS

This study demonstrated that patients with AF and a prior history of cancer experience higher rates of MB than those without cancer and, to a lesser extent and under certain conditions, thromboembolic complications. The degree of additional risk conferred by a prior history of cancer depended on the type and timing of the prior cancer diagnosis.

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AUTHOR CONTRIBUTIONS

G.C. and F.A.K. conceived the study. G.C., N.v.R., F.A.K., H.T.S., and S.C.C. designed the statistical analysis plan. L.P. and H.T.S. established the data platform for the research, and H.T.S. obtained all permissions. N.v.R. retrieved the data and performed the analyses. G.C., N.v.R., F.A.K., H.T.S., and S.C.C. contributed to the interpretation of the results. G.C. wrote the manuscript with support from all authors. All authors reviewed the results, contributed to the refinement of the manuscript, and approved the final version of the manuscript. H.T.S. edited the manuscript extensively and is legally responsible for the study.

RELATIONSHIP DISCLOSURE

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SUPPLEMENTARY MATERIAL

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