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ORIGINAL ARTICLE

# Atrial fibrillation in cancer: thromboembolism and bleeding in daily practice

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## Abstract

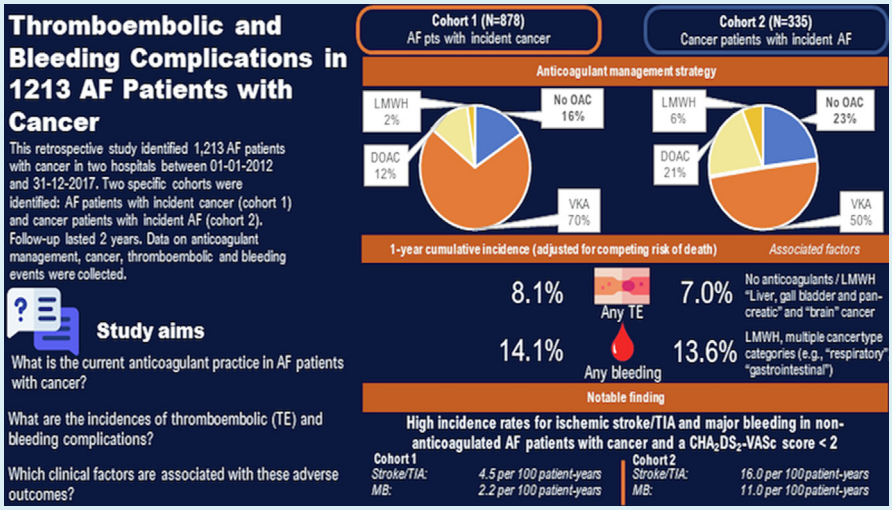
**Background:** Cancer is suggested to confer thromboembolic and bleeding risk in patients with atrial fibrillation (AF).

**Objectives:** We aimed to describe current anticoagulant practice in patients with AF and active cancer, present incidences of thromboembolic and bleeding complications, and evaluate the association between cancer type or anticoagulant management strategy with AF-related complications.

**Methods:** This retrospective study identified patients with AF and active cancer in 2 hospitals between January 1, 2012, and December 31, 2017. Follow-up lasted for 2 years. Data on cancer and anticoagulant treatment were collected. The outcomes of interest included ischemic stroke or transient ischemic attack (TIA) and clinically relevant nonmajor bleeding (CRNMB/MB). Incidence rates (IRs) per 100 patient-years and subdistribution hazard ratios (SHRs) with corresponding 95% Cis were estimated.

**Results:** We identified 878 patients with AF who developed cancer (cohort 1) and 335 patients with cancer who developed AF (cohort 2). IRs for ischemic stroke/TIA and MB/CRNMB were 3.9 (2.8-5.3) and 15.7 (13.3-18.5) for cohort 1 and 4.0 (2.2-6.7) and 16.7 (12.6-21.7) for cohort 2. 14.2% (cohort 1) and 19.1% (cohort 2) of patients with a $CHA_2DS_2$-VASc score of $\geq 2$ did not receive anticoagulant treatment. Withholding anticoagulants was associated with thromboembolic complications (SHR: 5.1 [3.20-8.0]). In nonanticoagulated patients with a $CHA_2DS_2$-VASc score of $<2$, IRs for stroke/TIA were 4.5 (0.75-15.0; cohort 1) and 16.0 (5.1-38.7; cohort 2).

**Conclusion:** Patients with AF and active cancer experience high rates of thromboembolic and bleeding complications, underlying the complexity of anticoagulant management in these patients. Our data suggest that the presence of cancer is an important factor in determining the indication for anticoagulants in patients with a low $CHA_2DS_2$-VASc score.




**KEYWORDS**
anticoagulation, atrial fibrillation, bleeding, cancer, thromboembolism

**Essentials**

- Data on the treatment and complications of patients with atrial fibrillation (AF) and cancer are scarce.
- Anticoagulation, thromboembolisms, and bleedings were assessed in patients with AF and cancer.
- The majority of the patients received anticoagulants, with increasing prescription of direct oral anticoagulants.
- Patients with AF and cancer experienced high rates of thromboembolism and bleeding.

## 1 | INTRODUCTION

An increasing body of evidence has demonstrated the association between cancer and atrial fibrillation (AF). [1–9] Not only can cancer contribute to the development of AF, for instance, via the arrhythmogenicity of certain cancer treatments, but also it is considered to complicate the anticoagulant management of patients with AF as cancer confers additional risks for both bleeding and thrombosis. [2,9,10] The cancer type, stage, treatment, and cancer-related comorbidities (eg, chemotherapy-induced thrombocytopenia) all contribute to its risk-modulating effect.

Notably, current international guidelines do not provide specific recommendations for the anticoagulant treatment in patients with AF and cancer [11–14], and most available risk stratification tools for AF mostly do not take malignancy into account. [15,16] Contributing to this paucity of data, the exclusion of patients with cancer and the lack of cancer-related data in most direct oral anticoagulant (DOAC) trials for AF prevented accurate subgroup analyses. [17–20] Currently, the best available evidence regarding anticoagulant management in patients with AF and cancer is obtained from nationwide cohort studies and meta-analyses. [21–23] Most recommendations are therefore based on expert opinion and extrapolation of data from venous thromboembolism (VTE) studies in patients with cancer. [24–27]

Detailed data on anticoagulant practices and outcomes of daily anticoagulant management in patients with AF and cancer in a practice-based setting are largely unavailable. To address this gap of knowledge, we conducted a retrospective study aiming to assess the incidence of thrombotic and bleeding events, present the anticoagulant management strategies in patients with AF along with cancer, and describe the association between the different cancer types or anticoagulant management strategies and AF-related outcomes.

## 2 | METHODS

### 2.1 | Study design, definition, and population

This retrospective study included patients aged ≥18 years with both active cancer and AF between January 1, 2012, and December 31, 2017. In line with the International Society of Thrombosis and Hemostasis (ISTH) guidelines, active cancer was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment has been administered within 6 months; or hematological cancer that is not in complete remission. [28] AF was documented on electrocardiography.

From a university hospital (Leiden University Medical Center, Leiden) and a nonuniversity teaching hospital (Rijnstate, Arnhem) in the Netherlands, patients with cancer diagnosed during the study period were identified by consulting the Netherlands Cancer Registry.

This is a nationwide population-based cancer database that records all cancer diagnoses since 1989, and its completeness is estimated at ~95%. [29]

The identified patients with cancer were subsequently screened for AF using the Diagnosis Treatment Combination coding system (DBC 401 for AF). This system was introduced in the Netherlands in 2005 for the registration and reimbursement of care provided by medical specialists and hospitals. [30] After primary screening for both cancer and AF diagnoses, the electronic health records of potentially suitable patients were reviewed to assess their eligibility for this study: the abovementioned criteria for both AF and active cancer diagnoses had to be confirmed. Exclusion criteria for this study were as follows: (i) patients with nonmelanoma skin cancer; (ii) patients with cancer and AF with both diagnosed and found to be active prior to January 1, 2012; (iii) patients in whom both diagnoses did not overlap (eg, active cancer period between 2012 and 2014, a novel AF diagnosis in 2016); and (iv) patients who had a follow-up of <1 month (eg, due to immediate discharge upon cancer diagnosis to a hospice for palliative care or who were referred to another hospital for further treatment).

## 2.2 | Index date and follow-up

Follow-up started at the moment the patient had active cancer and AF simultaneously (index date). Two specific cohorts were identified – cohort 1: patients with AF who subsequently developed cancer between January 1, 2012, and December 31, 2017, and cohort 2: patients with active cancer who subsequently developed AF between January 1, 2012, and December 31, 2017. Patients were followed for 2 years or until (i) death, (ii) one of the diagnoses was considered to be in remission (eg, for AF, successful catheter ablation with no signs of recurrence; and for cancer, 6 months after last treatment with no signs of recurrence), or (iii) the patient was lost to follow-up (eg, continuing treatment in another hospital).

## 2.3 | Data collection

All data were collected in an electronic case report form. At baseline, data on patient characteristics, laboratory findings, cancer status (eg, type and staging), cancer treatment prior and after the index date, and AF-related risk factors (eg, $CHA_2DS_2$-VASc score and AF-BLEED) were collected. [15,31] The course of anticoagulant treatment (ie, type and dosage) during follow-up was collected on a day-to-day basis.

## 2.4 | Aims and outcomes

The aims of this study were to (i) describe the anticoagulant management strategies in patients with AF who subsequently developed cancer between January 1, 2012, and December 31, 2017 (cohort 1), and in patients with active cancer who subsequently developed AF between January 1, 2012, and December 31, 2017 (cohort 2); (ii) present incidences of thromboembolic and bleeding complications during follow-up; and (iii) describe the association between the applied anticoagulant management strategy and the risk of thromboembolic and bleeding complications.

Outcomes of interest were any clinically relevant bleeding, venous thromboembolism (VTE), systemic embolism (SE), myocardial infarction (MI), ischemic stroke, transient ischemic attack (TIA), and all-cause mortality. Nonsurgical bleeding was scored according to the ISTH criteria for nonsurgical major bleeding (MB) and clinically relevant nonmajor bleeding (CRNMB). [32,33] Postsurgical bleedings were scored according to the ISTH criteria for surgical MB and nonsurgical CRNMB bleeding. [34] These outcomes were identified by reviewing the electronic health records of the included patients. An overview of the data collected and the definitions of the outcomes of interest are compiled in the Supplementary Material (Supplementary Tables 1 and 2). Outcomes were evaluated by 2 investigators (G.C. and J.S.) while a third author (FAK) provided the final decision in case of uncertainty.

## 2.5 | Statistical analysis

Continuous baseline variables were presented as means (SD) or medians (IQR), and categorical variables were presented as proportions (n/N) and percentages (%). The primary anticoagulant management strategies (ie, ignoring short interruptions or bridging with LMWH) after inclusion were tabulated per cohort and per year. Incidence rates per 100 patient-years with 95% CIs were calculated for the outcomes of interest. To assess the cumulative incidences of thromboembolic and bleeding complications while accounting for the competing risk of death, cumulative incidence competing risk analyses were performed for 1- and 2-year periods.

To assess the association between the anticoagulant management strategy and the outcomes of interest, while accounting for the competing risk of death, competitive risk regression models with anticoagulant treatment as a time-dependent variable were constructed. Patients from both cohorts were pooled together for this analysis for reasons of power. We utilized the cmprsk crr() package from R to perform these analyses. Subdistribution hazard ratios (SHR) with 95% CIs were reported. The results of the regression models applied to cohorts 1 and 2 separately are shown in the Supplementary Material. Non–time-dependent covariates include the cancer type category, presence of lymph nodal and/or distant metastases, and the AF-BLEED or $CHA_2DS_2$-VASc score. The following cancer categories were constructed: (1) breast cancer (as reference); (2) respiratory tract, intrathoracic, and ENT cancer; (3) gastrointestinal cancer; (4) liver/gall bladder/pancreatic cancer; (5) urogenital cancer; (6) hematological cancer; (7) brain cancer; and (8) other cancer (including melanoma and soft tissue/bone cancer). SPSS v26.0.0.0 and R v.3.6.2 (R Foundation for Statistical Computing, 2019) were used for the analyses.

**TABLE 1** Baseline characteristics of AF with cancer between January 1, 2012, and December 31, 2017.

| Characteristics | Cohort 1 Patients with AF who developed cancer | Cohort 2 Patients with cancer who developed AF |
|---|---|---|
| **N** | 878 | 335 |
| **Age, mean (SD)** | 74.6 (8.6) | 71.9 (9.3) |
| **Male, n (%)** | 548 (62.4) | 201 (60.0) |
| **Cancer type** | | |
| Lower GI cancer, n (%) | 150 (17.1) | 38 (11.3) |
| Lung/pleural cancer, n (%) | 127 (14.5) | 71 (21.2) |
| Hematological, n (%) | 120 (13.7) | 78 (23.3) |
| Renal/urological cancer, n (%) | 98 (11.2) | 25 (7.5) |
| Male reproductive, n (%) | 83 (9.5) | 29 (8.7) |
| Breast cancer, n (%) | 79 (9.0) | 24 (7.2) |
| Upper GI cancer, n (%) | 49 (5.6) | 15 (4.5) |
| Melanoma, n (%) | 36 (4.1) | 6 (1.8) |
| Female reproductive, n (%) | 34 (3.9) | 13 (3.9) |
| Head and neck cancer, n (%) | 27 (3.1) | 10 (3.0) |
| Pancreatic cancer, n (%) | 33 (2.5) | 5 (1.5) |
| Sarcoma, n (%) | 16 (1.8) | 5 (1.5) |
| Brain cancer, n (%) | 9 (1.0) | 3 (0.9) |
| Other, n (%) | 13 (1.5) | 9 (2.7) |
| **Cancer staging** | | |
| Metastasis to lymph nodes (N+) | 170 (19.4) | 83 (24.8) |
| Distant metastasis (M+) | 161 (18.3) | 92 (27.5) |
| Both lymph nodal and distant metastases (N+ and M+) | 50 (5.7) | 31 (9.3) |
| Prior history of a different cancer, n (%) | 152 (17.3) | 63 (18.8) |
| **Cancer treatment** | | |
| No therapy at all | 139 (15.8) | 63 (18.8) |
| Surgery | 430 (49.0) | 134 (40.0) |
| Chemotherapy | 249 (28.4) | 112 (33.4) |
| Targeted or immunotherapy | 53 (6.0) | 34 (10.1) |
| Radiation therapy | 254 (28.9) | 77 (23.0) |
| Hormonal therapy | 87 (9.9) | 25 (7.5) |
| Stem cell therapy | 8 (0.9) | 8 (2.4) |
| **Medical history** | | |
| Hypertension, n (%) | 558 (63.6) | 177 (52.8) |
| Diabetes mellitus, n (%) | 167 (19.0) | 57 (17.0) |
| Ischemic heart disease, n (%) | 196 (22.3) | 49 (14.6) |
| Heart failure, n (%) | 67 (7.6) | 15 (4.5) |
| Peripheral arterial disease, n (%) | 74 (8.4) | 32 (9.6) |
| Transient ischemic attack, n (%) | 74 (8.4) | 21 (6.3) |
| Ischemic stroke, n (%) | 72 (8.2) | 22 (6.6) |
| Intracranial bleeding, n (%) | 18 (2.1) | 5 (1.5) |
| History of bleeding, n (%) | 156 (17.8) | 38 (11.3) |
| $CHA_2DS_2$-VASc score, mean (SD) | 2.7 (1.6) | 2.3 (1.6) |
| $CHA_2DS_2$-VASc score $\geq$ 2, n (%) | 705 (80.3) | 236 (70.4) |
| AF-BLEED score, mean (SD) | 4.3 (1.6) | 4.2 (1.4) |
| AF-BLEED score > 3, n (%) | 682 (77.7) | 271 (80.9) |

$CHA_2DS_2$-VASc score: congestive heart failure (points = 1), hypertension (1), age $\geq$ 75 years (2), diabetes mellitus (1), prior stroke or transient ischemic attack (2), vascular disease (1), age range of 65 to 74 years (1), and female sex (1).

AF-BLEED: active cancer (points = 2), male with uncontrolled hypertension (1), anemia (1.5), history of bleeding (1.5), age $\geq$ 75 years (1.5), and renal dysfunction (1.5).

AF, atrial fibrillation; GI, gastrointestinal.

## 3 | RESULTS

### 3.1 | Baseline characteristics

Between January 1, 2012, and December 31, 2017, 1213 patients with cancer and AF were identified and included in this study. Cohort 1, which included patients with prevalent AF who developed cancer after January 1, 2012, consisted of 878 patients. Cohort 2, which included patients with active cancer who developed new AF, comprised 335 patients. The baseline characteristics for cohorts 1 and 2 are listed in Table 1. The median follow-up durations were 316 and 265 days for cohorts 1 and 2, respectively. Less than 5% of the included patients were lost to follow-up (Table 2).

In cohort 1, the most frequently observed cancer type was lower gastrointestinal tract cancer, followed by lung, hematological, and renal cancer. Nodal and distant metastases (hematological cancers excluded) were present in 19.4% and 18.3% of the cases, respectively, with 5.7% of the cases having both. Anticancer treatment was withheld in 15.8%. In cohort 2, hematological cancer was the most prevalent, followed by lung, lower gastrointestinal tract, and male reproductive cancer. Nodal and distant metastases were present in 24.8% and 27.5% of the cases, respectively, with 9.3% of the cases having both.

**TABLE 2** Mean follow-up duration per cohort and reasons for the end of follow-up

| Follow-up | Cohort 1 (n = 878) | Cohort 2 (n = 335) |
|---|---|---|
| Median follow-up in days (IQR) | 315 (521) | 265 (568) |
| Completed 2-year follow-up, n (%) | 235 (26.8) | 85 (25.4) |
| Reasons for shorter follow-up, n (%) | | |
| Remission cancer | 322 (50.1) | 100 (40.0) |
| Remission AF | 4 (0.6) | 1 (0.4) |
| Lost to follow-up | 27 (4.2) | 12 (4.8) |
| Deceased | 290 (45.1) | 137 (54.8) |

AF, atrial fibrillation.

## 3.2 | Primary anticoagulant management strategy in patients with atrial fibrillation and cancer

In cohort 1, anticoagulant treatment was prescribed in 739/878 (84.2%) patients after cancer diagnosis, of whom 728 were already on anticoagulant treatment (Table 3). The majority of the patients were treated with vitamin K antagonist (VKA) (69.8%), followed by DOAC (12.1%); 2.3% were primarily treated with a LMWH. Switching or discontinuation of prevalent anticoagulant treatment occurred only in 19/728 (2.6%) and in 20/728 (2.7%) patients upon cancer diagnosis. When solely considering patients with a $CHA_2DS_2$-VASc score of ≥2, 605/705 (86%) patients with AF who developed cancer were treated with anticoagulants.

In cohort 2, 27/335 (8.1%) patients were already treated with anticoagulation therapy for another reason than the novel AF diagnosis (Table 3). Upon diagnosing AF, anticoagulation therapy was prescribed or continued in 258/335 (77.0%) patients. The majority of the patients were treated with VKA (49.6%), followed by DOAC (21%) and LMWH (6.3%). One hundred ninety-one out of 236 (81.0%) patients with a $CHA_2DS_2$-VASc score of ≥2 were treated with anticoagulants.

Although most patients with AF and cancer were primarily treated with VKA, DOACs were increasingly prescribed: the use of DOACs in both cohorts combined increased from 2.4% (3/126) during 2012 to 2013 to 31% (82/262 patients) during 2017 to 2018 (Figure 1).

## 3.3 | Thromboembolic and bleeding complications in patients with atrial fibrillation who developed cancer (cohort 1)

In cohort 1, the incidence rates per 100 patient-years (95% CI) of ischemic stroke, ischemic stroke/TIA, myocardial infarction/systemic embolism, and VTE were 2.7 (1.8-3.9), 3.9 (2.8-5.3), 2.2 (1.4-3.3), and 2.5 (1.6-3.7), respectively (Table 4). For MB and any clinically relevant bleeding, IRs were 8.1 (6.4-10.1) and 15.7 (13.3-18.5). When considering an intention-to-treat analysis of patients with a $CHA_2DS_2$-VASc score of <2 in whom anticoagulants were withheld at the index date (n = 39), the IRs for stroke/TIA and MB were 4.5 (0.76-15) and 2.16 (0.11-10.7), respectively. The IRs of the different thromboembolic and bleeding complications in nonanticoagulated patients with AF who had a $CHA_2DS_2$-VASc score of <2 are listed in Supplementary Table 3.

The 1-year cumulative incidence of stroke/TIA/systemic embolism was 4.0% (2.6-5.4). The 1- and 2-year cumulative incidences of other thromboembolic and bleeding outcomes, adjusted for the competing risk of death, are listed in Table 5. Figure 2 demonstrates the Kaplan-Meier curves for all-cause death.

## 3.4 | Thromboembolic and bleeding complications in patients with cancer who developed atrial fibrillation (cohort 2)

In cohort 2, the IRs of ischemic stroke and ischemic stroke/TIA were 3.1 (1.5-5.4) and 4.0 (2.2-6.7), respectively; for myocardial infarction/systemic embolism and VTE, the IRs were 2.7 (1.3-5.0) and 2.1 (0.9-4.1), respectively (Table 4). For bleeding, the IR of MB was 7.0 (4.6-10.4), and for any clinically relevant bleeding, it was 16.7 (12.6-21.7). In nonanticoagulated patients with AF who had a $CHA_2DS_2$-VASc score of <2 (n = 32), the IRs for stroke/TIA and MB were 16.0 (5.1-38.7) and 11.1 (2.8-30.1), respectively (Supplementary Table 3).

The 1-year cumulative incidence of stroke, TIA, or systemic embolism (95% CI) was 3.9% (1.6-6.3) in cohort 2. The 1- and 2-year cumulative incidences of other thromboembolic and bleeding outcomes for cohort 2, adjusted for the competing risk of death, are listed in Table 5.

## 3.5 | Risk of outcomes associated with daily anticoagulation strategy

Withholding anticoagulant treatment (ie, no antithrombotic therapy or treatment with platelet aggregation inhibitors solely) was associated with an increased risk of any thromboembolic complication for a subdistribution HR (SHR) of 5.06 (23.20-7.99; Table 6). This was similarly the case for the composite endpoint arterial thromboembolism and stroke, TIA, or SE. The $CHA_2DS_2$-VASc score (per point increase), the cancer categories "liver, gall bladder, and pancreatic cancer" and "brain cancer" and management with LMWH were independently associated with an increased risk of any thromboembolic complications.

The AF-BLEED score was associated with a higher incidence of bleeding complications per point increase, with SHRs of 1.34 (1.22-1.47) and 1.23 (1.09-1.40) for any clinical relevant bleeding and MB, respectively. The cancer categories "respiratory, intrathoracic, and ENT cancer," "gastrointestinal cancer," "brain cancer," "other cancer," and "liver, gall bladder, and pancreatic cancer" were associated with any clinical relevant bleeding, with the latter also being associated with MB (SHR = 5.40 [1.73-16.9], Table 6). The results per cohort are reported in Supplementary Table 4.

**TABLE 3** Primary antithrombotic management strategy in patients with AF and cancer.

| Cohort 1; n = 878 | | | Antithrombotic strategy after cancer diagnosis | | | | |
|---|---|---|---|---|---|---|---|
| **Antithrombotic strategy** | | **N** | **None** | **PAI (+DAPT)** | **VKA (+PAI)** | **DOAC (+PAI)** | **LMWH (+PAI)** |
| Antithrombotic strategy prior to cancer diagnosis | None | 71 | 47 | 1 | 14 | 7 | 2 |
| | PAI (+/−DAPT) | 79 | 0 | 71 | 6 | 0 | 2 |
| | VKA (+/−PAI) | 615 | 15 | 2 | 586 | 0 | 12 |
| | DOAC (+/−PAI) | 102 | 2 | 0 | 1 | 99 | 0 |
| | LMWH (+/−PAI) | 11 | 0 | 1 | 6 | 0 | 4 |
| **Cohort 2; n = 335** | | | **Antithrombotic strategy after AF diagnosis** | | | | |
| | | **N** | **None** | **PAI (+DAPT)** | **VKA (+PI)** | **DOAC (+PAI)** | **LMWH (+PAI)** |
| Antithrombotic strategy prior to AF diagnosis | None | 249 | 54 | 7 | 117 | 55 | 16 |
| | PAI (+/-DAPT) | 59 | 3 | 13 | 31 | 11 | 1 |
| | VKA (+/-PAI) | 19 | 0 | 0 | 17 | 1 | 1 |
| | DOAC (+/-PAI) | 3 | 0 | 0 | 0 | 3 | 0 |
| | LMWH (+/-PAI) | 5 | 0 | 0 | 1 | 1 | 3 |

AF, atrial fibrillation; DAPT, dual antiplatelet inhibitor; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PAI, platelet aggregation inhibitor; VKA, vitamin K antagonist.

## 4 | DISCUSSION

In this practice-based study, we described the anticoagulant management strategies of patients with AF and active cancer, observed considerable incidences of both thromboembolic and bleeding complications, and demonstrated an association between certain cancer types and a higher risk of thrombotic complications and/or bleeding. Patients with a CHA2DS2-VASc score of <2 who remained untreated faced an unexpected high incidence of thromboembolic outcomes (Graphical Abstract/Supplementary Table 3).

Prior studies in patients with cancer and AF have reported anticoagulant prescription ranging from 40% to 92% and LMWH usage ranging from 5% to 78%. [35–38] In our cohort, anticoagulant treatment was withheld in 14% to 19% of the patients with a $CHA_2DS_2$-VASc score of ≥2, comparable to the anticoagulant coverage found in the general population with AF. For instance, 22% of all patients with

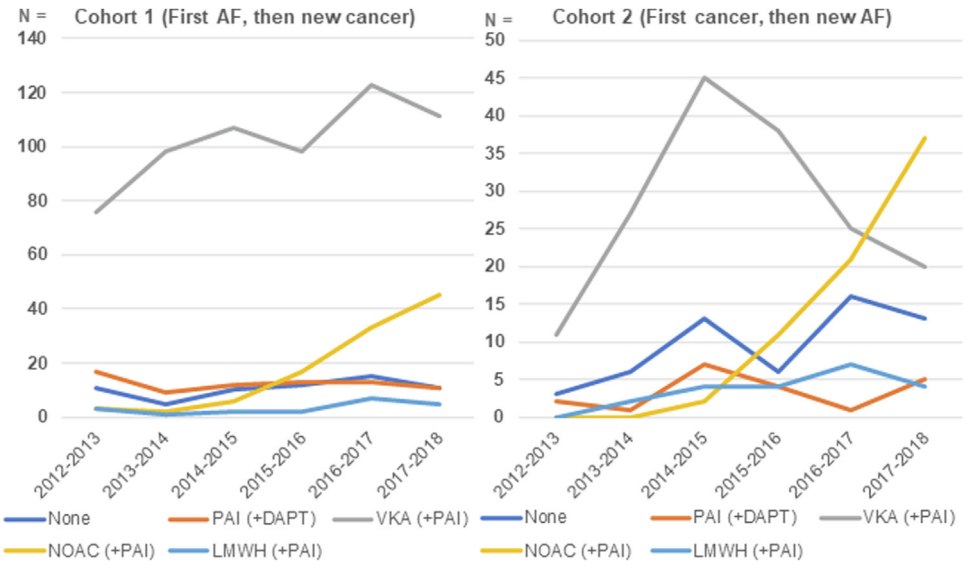



**FIGURE 1** The anticoagulant management strategies between 2012 and 2017 in patients with AF and incident cancer (cohort 1) and patients with cancer and incident AF (cohort 2). AF, atrial fibrillation; DAPT, dual antiplatelet inhibitors; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PAI, platelet aggregation inhibitor; VKA, vitamin K antagonist.

**TABLE 4** Incidence rates per 100 patient-years of thromboembolic and bleeding events and death in patients with AF and cancer.

| | Cohort 1, n = 878 | | Cohort 2, n = 335 | |
|---|---|---|---|---|
| **Outcomes** | **Number** | **IR per 100 py (95% CI)** | **Number** | **IR per 100 py (95% CI)** |
| All bleeding events (MB + CRNMB) | 140 | 15.7 (13.3-18.5) | 52 | 16.7 (12.6-21.7) |
| • MB only | 76 | 8.1 (6.4-10.1) | 23 | 7.0 (4.6-10.4) |
| Arterial thromboembolism | 58 | 6.2 (4.7-7.9) | 21 | 6.5 (4.1-9.8) |
| • Ischemic stroke | 26 | 2.7 (1.8-3.9) | 10 | 3.1 (1.5-5.4) |
| • Ischemic stroke/TIA | 37 | 3.9 (2.8-5.3) | 13 | 4.0 (2.2-6.7) |
| • Ischemic stroke/TIA/SE | 42 | 4.4 (3.2-5.9) | 15 | 4.6 (2.7-7.5) |
| • AMI/SE | 21 | 2.2 (1.4-3.3) | 9 | 2.7 (1.3-5.0) |
| Venous thromboembolism | 24 | 2.5 (1.6-3.7) | 7 | 2.1 (0.9-4.1) |
| Death | 286 | 29.3 (26.0-32.8) | 126 | 37.4 (31.3-44.4) |

AF, atrial fibrillation; AMI, acute myocardial infarction; CRNMB, clinically relevant nonmajor bleeding; IR, incidence rate; MB, major bleeding; py, patient-years; SE, systemic embolism; TIA, transient ischemic attack.

AF who had a $CHA_2DS_2$-VASc score of ≥2 were not prescribed anticoagulants in the ORBIT-AF I Registry. [39] Reassuringly, only 3.4% of the patients in our study were treated primarily with LMWH, which has been the primary choice for patients with cancer-associated VTE, but is not indicated for long-term stroke prophylaxis in patients with AF. [14,24] Of note, a recent international survey examining the current practices of anticoagulant management in patients with AF and cancer demonstrated that nearly 25% of the physicians consider LMWH to be indicated for stroke prevention. [40]

**TABLE 5** One- and 2-year cumulative incidences of outcomes of interest in patients with AF and cancer after adjusting for the competing risk of death.

| Outcomes | 1-year cumulative incidence (95% CI) | 2-year cumulative incidence (95% CI) |
|---|---|---|
| **Cohort 1: patients with AF who developed cancer (n = 878)** | | |
| Any thromboembolic complication | 8.1% (6.2-10.0) | 11.7% (9.2-14.3) |
| Arterial thromboembolism | 5.6% (3.9-7.2%) | 8.6% (6.4-10.8) |
| Stroke/TIA/systemic embolism | 4.0% (2.6-5.4) | 6.4% (4.4-8.3) |
| Venous thromboembolism | 2.7% (1.5-3.8) | 3.3% (1.9-4.6) |
| Any clinically relevant bleeding | 14.1% (11.6-16.6) | 20.2% (17.1-23.3) |
| Major bleeding | 7.5% (5.6-9.4) | 11.3% (8.8-13.8) |
| **Cohort 2: patients with cancer who developed AF (n = 335)** | | |
| Any thromboembolic complication | 7.0% (4.0-10.0) | 11.3% (7.2-15.4) |
| Arterial thromboembolism | 5.3% (2.6-7.9) | 8.5% (4.9-12.1) |
| Stroke/TIA/systemic embolism | 3.9% (1.6-6.3) | 6.1% (3.0-9.3) |
| Venous thromboembolism | 1.7% (0.2-3.2) | 2.8% (0.6-5.0) |
| Any clinically relevant bleeding | 13.6% (9.7-17.6) | 19.5% (14.5-24.5) |
| Major bleeding | 6.5% (3.7-9.3) | 8.1% (4.8-11.4) |

AF, atrial fibrillation; TIA, transient ischemic attack.

The thromboembolic and bleeding burden in patients with cancer has been demonstrated in various cancer-associated thrombosis studies. VTEs occur frequently in patients with cancer and mark a poorer prognosis. [41] For example, patients with VTE and cancer are more likely to experience MB during anticoagulant treatment than patients with VTE but without cancer. [42] Incidences of both thromboembolic and bleeding complications in our study indeed were high. Venous thromboembolism, often occurring despite anticoagulant treatment, accounted for 20% to 25% of thromboembolic complications observed in our study and therefore contributed considerably to the burden of thrombotic complications.

Compared to the general anticoagulated population with AF, with event rates for stroke, TIA, or SE of 0.78 and 1.16 in patients who had $CHA_2DS_2$-VASc scores of 2 and 3, respectively, the risk for stroke, TIA, or SE in our study appeared to be higher (IR per 100 py of 4.4 and 4.6 for cohorts 1 and 2, respectively). [43] These findings are in contrast to various nationwide cohort studies and post-hoc analyses, which did not demonstrate an increased risk of any thromboembolic complication or ischemic stroke in patients with AF and cancer. [2,4,10,44] Importantly, most of these nationwide cohort or registry studies assessed in patients with AF a history of cancer or recent cancer and not necessarily patients with AF and active cancer. [2,10,44]

Our findings support the suggestion to evaluate the inclusion of active cancer in stroke risk assessment scores, preferably limited to specific high-risk cancer types such as pancreatic cancer. [45–47] Current guidelines have adopted the $CHA_2DS_2$-VASc score to identify (very) low-risk patients (ie, $CHA_2DS_2$-VASc score < 2) in whom anticoagulants could be withheld. However, the thromboembolic risks in our nonanticoagulated patients with a $CHA_2DS_2$-VASc score of 0 or 1

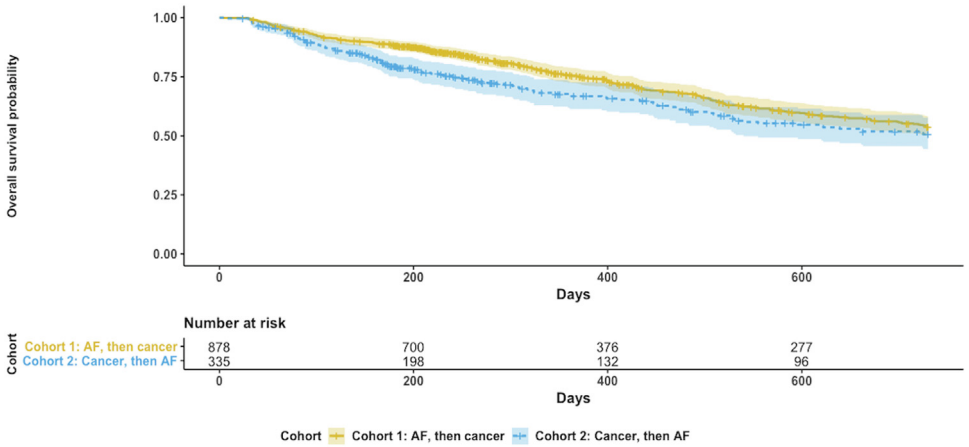



**FIGURE 2** Kaplan-Meier curve for survival in patients with AF and cancer. AF, atrial fibrillation.

**TABLE 6** Competing risk regression analyses with subdistribution hazard ratios and 95% CIs for outcomes with daily anticoagulant management strategies as time-dependent covariates in patients with cancer and atrial fibrillation.

| Variables | Any thromboembolic complications | Any ATE | Stroke/TIA/SE | Any bleeding complications | Major bleeding |
|---|---|---|---|---|---|
| Subdistribution HR (95% CI) | | | | | |
| VKA | Reference | Reference | Reference | Reference | Reference |
| No anticoagulant[a] | 5.06 (3.20-7.99) | 4.88 (3.10-7.67) | 4.95 (3.14-7.79) | 1.10 (0.74-1.65) | 1.33 (0.78-2.26) |
| DOAC | 1.11 (0.54-2.26) | 1.15 (0.58-2.28) | 1.28 (0.65-2.49) | 1.07 (0.68-1.67) | 1.07 (0.58-1.98) |
| LMWH | 4.89 (1.93-12.4) | 3.69 (1.57-8.68) | 3.80 (1.62-8.92) | 2.14 (1.09-4.17) | 3.06 (1.41-6.63) |
| $CHA_2DS_2$-VASc (per point increase) | 1.23 (1.09-1.40) | 1.22 (1.08-1.38) | 1.22 (1.08-1.38) | N/A | N/A |
| AF-BLEED (per point increase) | N/A | N/A | N/A | 1.34 (1.22-1.47) | 1.23 (1.09-1.40) |
| Cancer type | | | | | |
| Breast | Reference | Reference | Reference | Reference | Reference |
| Respiratory, intrathoracic, and ENT cancer | 1.38 (0.54-3.54) | 1.63 (0.65-4.08) | 1.57 (0.63-3.92) | 2.35 (1.12-4.93) | 1.28 (0.47-3.48) |
| Gastrointestinal cancer | 2.04 (0.83-4.97) | 1.95 (0.80-4.75) | 1.94 (0.79-4.72) | 2.98 (1.45-6.12) | 2.39 (0.97-5.91) |
| Liver, gall bladder, and pancreatic cancer | 4.23 (1.42-12.6) | 4.48 (1.56-12.9) | 4.51 (1.57-12.9) | 3.20 (1.11-9.19) | 5.40 (1.73-16.9) |
| Urogenital cancer | 0.95 (0.39-2.34) | 0.91 (0.37-2.24) | 0.95 (0.39-2.34) | 1.33 (0.64-2.74) | 1.04 (0.42-2.62) |
| Hematological cancer | 1.09 (0.43-2.75) | 1.10 (0.44-2.75) | 1.10 (0.44-2.76) | 1.35 (0.63-2.87) | 1.27 (0.50-3.25) |
| Brain cancer | 2.84 (0.57-14.3) | 2.87 (0.57-14.4) | 2.89 (0.58-14.5) | 5.60 (1.47-21.3) | N/A |
| Other cancer (including melanoma and soft tissue/bone cancer) | 0.65 (0.17-2.56) | 0.64 (0.16-2.52) | 0.65 (0.17-2.54) | 3.58 (1.54-8.31) | 2.42 (0.83-7.08) |
| Cancer staging | | | | | |
| Localized cancer | Reference | Reference | Reference | Reference | Reference |
| Lymph nodal metastasis | 0.82 (0.48-1.41) | 0.78 (0.46-1.32) | 0.84 (0.50-1.41) | 1.02 (0.71-1.47) | 1.07 (0.64-1.80) |
| Distant metastasis | 1.42 (0.85-2.38) | 1.55 (0.96-2.51) | 1.52 (0.94-2.46) | 1.14 (0.77-1.68) | 1.10 (0.67-1.82) |

$CHA_2DS_2$-VASc score: congestive heart failure (points = 1), hypertension (1), age ≥ 75 y (2), diabetes mellitus (1), prior stroke or transient ischemic attack (2), vascular disease (1), age range of 65 to 74 y (1), and female sex (1).

AF-BLEED: active cancer (points = 2), male with uncontrolled hypertension (1), anemia (1.5), history of bleeding (1.5), age ≥ 75 y (1.5), and renal dysfunction (1.5).

ATE, arterial thromboembolic event; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct anticoagulants; GI, gastrointestinal; HR, hazard ratio; LMWH, low-molecular-weight heparin; MB, major bleeding; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

[a]No anticoagulant treatment; monoantiplatelet and dual antiplatelet therapy are counted as no anticoagulant.

were considerable and exceeded the incidence expected in noncancer patients with a $CHA_2DS_2$-VASc of 2 or 3 (Supplementary Table 3). In line with these results, one nationwide cohort study demonstrated that the thromboembolic risks in nonanticoagulated patients with cancer and AF who had a $CHA_2DS_2$-VASc score of 1 were higher than those without cancer, with incidence rates warranting consideration of anticoagulant treatment according to current guidelines. [1]

Remarkably, in the subgroup of patients with a $CHA_2DS_2$-VASc score of <2 who were not anticoagulated, the incidence of thromboembolic and/or bleeding events was numerically higher in patients of cohort 2 (ie, cancer patients who subsequently developed AF) than those in cohort 1 (ie, patients with AF who subsequently developed cancer). One possible explanation, although speculative, is that the development of incident atrial fibrillation during cancer could reflect a more severe disease state. Although atrial fibrillation is known to be a chronic disease, it can be triggered by the presence of concomitant comorbidities. Several of these comorbidities such as pulmonary embolism, anticancer-related cardiovascular toxicity, and surgery are associated with an increased risk of bleeding and/or stroke. [48]

The incidences of bleeding complications found in this study (IR per 100 py of 8.1 and 7.0 for cohort 1 and 2, respectively) were also higher in comparison to the general noncancer AF population. Two nationwide cohort studies demonstrated incidence rates of MB of 1.9 and 2.3 per 100 patient-years. [49,50] Our findings were in line with the bleeding rates and risks reported in other AF and cancer studies. [2–4,10,44] One study found 6.6/100 patient-years for MB and 18.2/100 patient-years for any clinically relevant bleeding. [3] Our findings support the notion that active cancer is an important bleeding risk factor and including cancer in bleeding risk assessment scores, such as in the AF-BLEED score, seems to be appropriate. [31] Certain notorious cancer types that have been demonstrated to cause high incidence of bleeding during the treatment of VTE were also associated with an increased bleeding risk in our population with AF (eg, pancreatic cancer and upper GI cancer). Available risk stratification scores such as AF-BLEED could be used to identify and target modifiable risk factors (eg, hypertension and renal dysfunction) for bleeding, as is recommended for patients with AF or VTE in general. [14,51]

DOAC prescription gradually increased over time to nearly a third of all patients with AF and cancer, with DOACs overtaking VKA as the preferred anticoagulant in patients with cancer who develop AF. Similarly, this increase in DOAC adoption was observed in a study with patients with AF and breast cancer and in a recent international survey examining contemporary practices and anticoagulant preferences. [37,40] Patients with AF who were already treated with a DOAC continued their DOAC treatment after cancer diagnosis: a switch to VKA occurred only once. A recent expert opinion guideline by the ISTH recommends continuing the existing anticoagulant treatment, unless, for example, interfering drug-drug interactions occur. [24] Other guidelines do not cover this topic.

The major strength of this study lies in the high number of patients with active cancer included in this study. In contrast to other studies, we have taken the remission of cancer and/or AF into account when considering follow-up duration, resulting in a more accurate assessment of thromboembolic and bleeding complications in patients with AF and cancer. Moreover, data on cancer type, stage, and treatment and full details of antithrombotic management of patients with AF and cancer, with low rates of loss to follow-up, were available. Finally and importantly, we focused on a practice-based cohort of all-comers rather than on patients from a trial setting. In addition, we studied patients from an academic and teaching hospital, who were followed for a considerable time period. All these factors contribute to high external validity and a representative reflection of contemporary practice.

## 5 | LIMITATIONS

We consider the retrospective nature of this study and the lack of a control group of patients with AF without cancer as its main limitations. Furthermore, there is no crosstalk between hospitals regarding the registration and reimbursement code that we used to identify patients with AF. Therefore, a patient with cancer and AF diagnosed in a different hospital than the 2 participating hospitals could have been missed. Moreover, depending on the clinical situation, it is also likely that not all patients with cancer, with a suspicion of AF, would pursue a definitive diagnosis, especially in the terminal stages of the disease. The number of patients in some subgroups (eg, cancer types such as sarcoma or pancreatic cancer) was small.

Data regarding race, ethnicity, and sociocultural characteristics of the participants were not obtained as these were not readily available or were not available in the electronic health records; 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, due to the observational nature of this study, no definitive conclusions can be drawn regarding the optimal anticoagulant management strategy in patients with AF and active cancer.

## 6 | CONCLUSION

Patients with AF and active cancer experience high rates of thromboembolic and bleeding complications. The majority of such patients receive anticoagulant treatment, with DOACs being increasingly more commonly prescribed. Our findings highlight the complexity of anticoagulant treatment in patients with cancer and call for dedicated studies to guide optimal management of individual patients in specific settings.

### AUTHOR CONTRIBUTIONS

The authors have reviewed and approved the submission of this manuscript. F.A.K., M.V.H. and G.C. were responsible for the conception and/or design of the research. G.C. and J.S. collected the data. G.C. performed the data analysis. G.C. and F.A.K. drafted the

manuscript. All authors provided critical feedback and critically revised the manuscript.

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## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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## SUPPLEMENTARY MATERIAL

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