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ORIGINAL ARTICLE

Management and outcomes of patients with atrial fibrillation and *a history of* cancer: the ORBIT-AF registry

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Aims The presence of cancer can complicate treatment choices for patients with atrial fibrillation (AF) increasing both the risk of thrombotic and bleeding events.

Methods and results Using data from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation, we aimed to characterize AF patients with cancer, to describe their management and to assess the association between cancer and cardiovascular (CV) outcomes. Among 9749 patients, 23.8% had history of cancer (57% solid malignancy, 1.3% leukaemia, 3.3% lymphoma, 40% other type, and 2.2% metastatic cancer). Patients with history of cancer were older, more likely to have CV disease, CV risk factors, and prior gastrointestinal bleeding. No difference in antiarrhythmic and antithrombotic therapy was observed between those with and without cancer. Patients with history of cancer had a significantly higher risk of death (7.8 vs. 4.9 deaths per 100 patient-years follow-up, $P = 0.0003$) mainly driven by non-CV death (4.2 vs. 2.4 per 100 patient-years follow-up; $P = 0.0004$) and higher risk of major bleeding (5.1 vs. 3.5 per 100 patient-years follow-up; $P = 0.02$) compared with non-cancer patients; no differences were observed in risks of strokes/non-central nervous system embolism (1.96 vs. 1.48, $P = 0.74$) and CV death (2.89 vs. 2.07, $P = 0.35$) between the two groups.

Conclusion A history of cancer is common among AF patients with up to one in four patients having both. Antithrombotic therapy, rates of cerebrovascular accident, other thrombotic events and cardiac death were similar in AF patients with or without a history of cancer. Patients with cancer, however, were at higher risk of major bleeding and non-CV death.

Keywords Cancer • Atrial fibrillation • Anticoagulant therapy

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Introduction

The selection of antithrombotic therapy for stroke prevention in patients with atrial fibrillation (AF) and cancer is challenging. Some malignancies induce a prothrombotic state and may further increase the risk of thrombotic events in patients with AF. However, some malignancies and the therapies used to treat cancer can increase patients' risk of bleeding events on anticoagulation.[1]

Anticoagulant therapy with warfarin has been the mainstay of treatment for stroke prevention in patients with AF, however little is known on how patients with AF and cancer are routinely treated in clinical practice for stroke prevention and whether their risk for embolic events and/or bleeding is increased compared to patients with AF without cancer. In order to maximize the benefits and minimize the risk of warfarin therapy, its dose is typically adjusted by monitoring the prothrombin time, expressed as the international normalized ratio (INR). Both nutritional factors and concomitant medications can influence warfarin activity in patients with cancer and maintaining INR at target is more difficult in these patients.[2,3] Despite these challenges, there are no existing INR monitoring guidelines specifically for patients with AF and concurrent malignancy.[2–5]

The purpose of this analysis was to better characterize AF patients with history of cancer and describe their treatment, thrombotic and bleeding risk, INR control, and the safety of anticoagulation in community clinical practice.

Methods

Study design and patient population

The rationale and study design of Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) have been previously described.[6] ORBIT-AF is a national, community-based registry of outpatients with AF. Eligible patients were enrolled by 174 nationally representative sample primary care, cardiology, and/or electrophysiology sites in the USA. Major inclusion criteria were 18 years or older and electrocardiographically documented AF that was not due to a reversible cause and follow-up was out to a maximum of 3 years. Patients with a life expectancy < 6 months or transient AF because of a reversible condition, such as after cardiac surgery, were excluded. Data collection was mainly obtained from the patient's medical record, and included demographics, medical history, and AF history at baseline. Additionally, at baseline and every 6 months, investigators recorded medical and surgical therapies, vital signs, laboratory measurements, and echocardiographic data. The collection of medication data included use and monitoring of oral anticoagulant therapy (OAC) therapies. Sites were also instructed to enter which OAC treatment was used, as well as values for INR monitoring, and reason for discontinuation.

At each follow-up, investigators recorded the incidence and dates of the outcomes of interest, including death, cause-specific hospitalization (cardiovascular, bleeding, or other, as determined by the investigator), incident heart failure, myocardial infarction (MI), stroke or systemic embolism (adjudicated by the coordinating centre, from primary source documentation), or major bleeding as defined by the International Society of Thrombosis and Haemostasis criteria.[7]

The ORBIT-AF registry was approved by the institutional review board of Duke University, and each site received institutional review board approval pursuant to local requirements. All participants provided informed consent for participation in ORBIT-AF. The study was done in accordance with the Declaration of Helsinki.

This study included all patients in ORBIT-AF with baseline cancer history data and with at least one follow-up, enrolled in 174 sites from 29 June 2010 to 9 August 2011. History of cancer was collected at baseline as part of the patient's medical history; if cancer was selected sites had to specify if (i) solid malignancy, (ii) leukaemia, (iii) lymphoma, (iv) other, and (v) metastatic. Skin cancers, except for malignant melanoma, were excluded. Additional information on cancer status (remote or active), stage of disease, site of disease, and treatment details were not part of baseline medical history collection.

The objectives of the present analysis were (i) to characterize ORBIT-AF population with history of cancer and describe antiplatelet/anticoagulant use in this 'real-world' population, (ii) to describe INR control among cancer patients treated with warfarin compared with patients without a history of cancer, and (iii) to assess the association between cancer and bleeding and thrombotic outcomes.

Statistical analysis

Baseline characteristics were compared according to cancer history. Continuous variables were presented as medians [interquartile range (IQR)] and compared using the Wilcoxon rank-sum test. Categorical variables were presented as frequency (percentage) and compared using the Chi-square test. The five-factor numerical ORBIT bleeding risk was calculated as follows: 1 point each for age > 75 years, insufficient kidney function (estimated glomerular filtration rate < 60 mL/min/1.73 m2), and treatment with any antiplatelet; 2 points were assigned to a positive clinical history for bleeding and the presence of anaemia or abnormal haemoglobin (<13 mg/dL for men and < 12 mg/dL for women). An ORBIT score of 0 to 2 defines 'low risk', a score of 3 'intermediate risk', and a score >3 'high risk'.[8] In order to assess the association between cancer and outcome unadjusted and adjusted Cox frailty models were performed. Frailty models accounted for the variability in outcomes between sites. In adjusted models, previously constructed multivariable models were used. Covariates for multivariable modelling were obtained using backward selection, with an alpha for exclusion of 0.05. Multiple imputation was used to account for missing covariate data, combining the final model estimates over five imputed data sets. (Appendix) Finally, the number of INR checks and time in therapeutic range (TTR) were presented, both overall and stratified by history of cancer. For both measures, the median (IQR) was presented and those with and without a history of cancer were compared using the Wilcoxon-rank sum test. Analyses of the aggregate, deidentified data were performed by the Duke Clinical Research Institute using SAS software (version 9.3, SAS Institute, Cary, NC, USA).

Results

Of the 9749 patients included in this analysis, 2318 (23.8%) had a documented history of cancer. Among those with a history of cancer, 57% had solid malignancy, 1.3% leukaemia, 3.3% lymphoma, 40% other type, and 2.2% had metastatic cancer. Patients with history of cancer were older (median age 79 vs. 73 years) and more likely to have cardiovascular (CV) risk factors, CV disease, and prior gastrointestinal (GI) bleeding compared with non-cancer patients. New onset AF was less common in cancer patients who more frequently tended to have permanent/persistent AF compared with those without cancer. Patients with history of cancer were less likely to have received prior cardioversion; catheter ablation of AF and rate control was more common than rhythm control. No major difference in antiarrhythmic therapy and antiplatelet/antithrombotic therapy was observed between those with and without cancer, in particular use of antiplatelet therapy only was 18% vs. 18%,

Table 1 Baseline characteristics in AF patients with and without history of cancer

Baseline characteristics (%)	No cancer (*N* = 7431)	History of cancer (*N* = 2318)	*P*-value
Age (year) median (IQR)	73 (65–81)	79 (72–84)	<0.0001
Male	56.9	59.1	0.06
Weight (Kg) median (IQR)	87.1 (72.7–104.1)	83.0 (70.5–97.5)	<0.0001
Race			<0.0001
White	88.0	94.8	
Black	5.7	2.4	
Hispanic	4.8	1.9	
Other	1.6	0.9	
CV risk factors			
Hyperlipidaemia	71.3	75.3	0.0001
Hypertension	82.3	85.9	<0.0001
Diabetes	30.0	27.9	0.06
Smoking	46.7	53.9	<0.0001
Chronic kidney disease	35.9	41.3	<0.0001
Medical history			
Peripheral vascular disease	12.6	16.0	<0.0001
Congestive heart failure	32.4	34.4	0.07
Prior myocardial infarction	15.4	18.1	0.002
Stroke/transient ischaemic attack	14.4	17.6	0.0001
Prior gastrointestinal bleed	8.1	12.7	<0.0001
CHADS2 risk score ≥ 2	69.6	80.1	<0.0001
CHADS VASC score ≥ 2	89.5	96.2	<0.0001
ORBIT risk score			<0.0001
0–2	54.8	45.3	
3	16.1	17.6	
≥3	21.2	32.1	
AF type			<0.0001
New onset	5.0	2.7	
Paroxysmal	51.2	49.0	
Persistent/ permanent AF	43.7	48.3	
Current AF management			<.0001
Rate control	67.2	71.7	
Rhythm control	32.8	28.3	
Prior cardioversions	31.1	27.1	0.0003
Prior catheter ablation	6.1	4.0	0.0001
Prior antiarrhythmic drugs	46.1	44.5	0.18
EHRA score			0.004
No symptoms	37.6	40.1	
Mild	44.9	45.6	
Severe	15.3	12.6	
Disabling	1.9	1.6	
Cardiac medications			
Beta blockers	64.1	64.9	0.47
ACE-I	36.0	34.2	0.11
Statin	55.2	56.1	0.42
Digoxin	23.4	24.0	0.57
Current antiarrhythmic drugs	29.5	26.3	0.002
Current antithrombotic therapy	51.4	49.8	0.18
Aspirin	44.7	43.1	0.20
Clopidogrel	7.2	6.9	0.61
Dabigatran	5.1	4.6	0.33
Current warfarin	71.3	72.0	0.53
Triple therapy	1.8	1.4	0.27
Contraindications to OAC			
High bleeding risk	16.8	21.6	0.05
Comorbid illness	4.1	8.4	0.003
Prior Bleeding	27.0	33.5	0.02

CV, cardiovascular; IQR, interquartile range; ORBIT, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; AF, atrial fibrillation; EHRA, European Heart Rhythm Association; ACE-I, angiotensin converting enzyme inhibitors; OAC, oral anticoagulant therapy. Triple Therapy [OAC plus Aspirin plus Thienopiridine (clopidogrel, prasugrel, or ticagrelor)].

oral anticoagulant only was 49% vs. 47%, and both was 28% vs. 29%, respectively, in those with and without history of cancer.Also, the rate of warfarin discontinuation (22.2% vs. 21.5%) and reasons for discontinuations were similar between the two groups. ORBIT risk score was significantly higher in patients with history of cancer compared with those without [median (IQR) 3.0 (1.0–4.0) and 2.0 (1.0–3.0), respectively, $P \leq 0.0001$]. High risk of bleeding, presence of comorbidities, and prior bleed were more common contraindication to OAC in patients with history of cancer (*Table 1*).

International normalized ratio control

Of the 9749 patients included in the analysis, 6325 were on warfarin at baseline and had time in TTR available. Patients with AF and cancer were more likely to visit a warfarin clinic and had a higher number of INR checks (median of 28 vs. 24, $P < 0.0001$). (*Figure 1*) compared with AF patients without cancer. Time in TTR appeared to be similar between the two groups (*Table 3*).

Cancer and cardiovascular outcomes

At a median follow-up of 2.5 years, patients with history of cancer had a significantly higher risk of all-cause death (7.8 vs. 4.9 per 100

patient-years follow-up) that was mainly driven by non-CV death (4.2 vs. 2.4) and experienced higher rate of major bleeding (5.1 vs. 3.5) compared with non-cancer patients. No differences were observed in risks of strokes/non-central nervous system (CNS) embolism, CV death and heart failure events between the two groups (*Table 2*). Even after multivariable adjustment, all-cause death [hazard ratio (HR) = 1.26, 95% confidence interval (CI) 1.11–1.42; $P = 0.0003$], non-CV death (HR = 1.35, 95% CI 1.14–1.60; $P = 0.0004$), and major bleeding (HR = 1.21, 95% CI 1.04–1.40; $P = 0.0155$) remained significantly associated with a history of cancer.

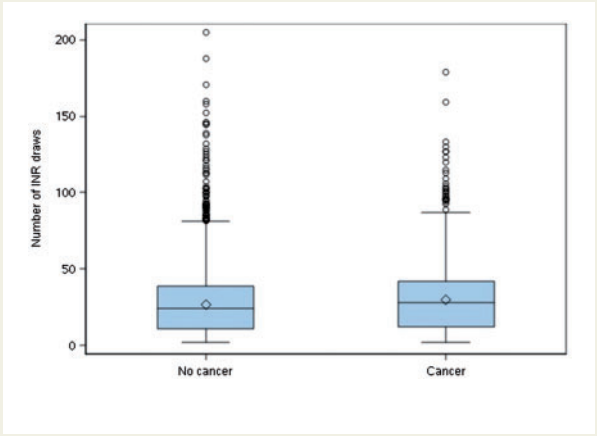

Figure 1 Number of INR checks in AF patients with and without history of cancer. INR, International Normalized Ratio; AF, atrial fibrillation.

Discussion

In this nationwide cohort of patients with AF and a prior history of cancer, we were able to achieve our first objective to characterize this population. First, we found that approximately one in four AF patients had a history of cancer. Second, patients with AF and history of cancer had a higher burden of cardiovascular risk factors and concomitant cardiovascular disease. Third, AF patients with cancer appeared to have persistent forms of AF and were more likely to be managed with rate control. Surprisingly, beside a higher bleeding risk in patients with history of cancer, patterns of antithrombotic and antiplatelet therapy were similar to those without history of cancer. Fourth, AF patients with history of cancer treated with OAC attended warfarin clinic more frequently and required a higher number of INR checks to obtain the target INR. Regarding our other objectives, no differences were observed in risks of strokes/non-CNS embolism, CV death and heart failure between AF patients with and without history of cancer, although the former were characterized by a higher risk of major bleeding and non-CV death.

Both the incidence of AF and cancer increase with aging; thus the two conditions often coexist later in life as confirmed in this nationwide cohort. Approximately a quarter of AF patients had history of cancer and they tended to be older compared with those without cancer. AF can result as complication of cancer treatment or be triggered by paraneoplastic conditions.[9,10]

Prior studies have also shown that cardiovascular comorbidities are frequent in cancer patients. Using data from the ORBIT-AF, we were able to confirm that patients with AF and history of cancer carry overall a higher burden of cardiovascular risk factors and more frequently have concomitant CV conditions such as prior MI, prior stroke, and peripheral vascular disease compared with AF patients without cancer.[11]

Currently there are neither guidelines for AF therapy and antithrombotic therapy nor scoring systems (e.g. CHADS2VASC; HAS-BLED) specifically for patients with AF and concomitant cancer, therefore it is expected that clinical practice would vary. In this study, AF patients with history of cancer were more likely to be managed with a rate control strategy; however, patterns of antiplatelet and antithrombotic treatment were similar in those with and without a history of cancer. The ORBIT bleeding risk score resulted significantly higher among those with history of cancer.[8] Prior bleeding, in particular GI bleeding and absence of anticoagulant therapy due to perceived bleeding risk were more common in patients with a history of cancer.The small number of patients treated with dabigatran most likely reflects the fact that this novel oral anticoagulant was approved at the end of 2010 and enrolment in the registry ended months later in August 2011.

For decades anticoagulant therapy with warfarin has been the mainstay of treatment for stroke and systemic thromboembolism prevention in patients with AF. In order to maximize the benefits and minimize the risk of warfarin therapy, its dose is adjusted by monitoring the INR. In cancer patients, many factors can interfere with the anticoagulant regimen and frequent INR checks may be required due to drug–drug interaction between warfarin and cancer treatment, changes in renal and hepatic function, dietary/nutritional status, chemotherapeutic toxicity, and disease state.[4] Maintaining INR at target is generally more difficult in these patients. Also there are no current INR monitoring guidelines for patients with AF and concurrent malignancy.[2–5] In this study, we found that INR checks were performed more frequently in patients with a history of cancer but overall time in TTR was similar. Yet, since anticipated life expectancy ≤ 6 months was one of the exclusion criteria of the ORBIT-AF registry, it is likely that terminal cancer patients were not included in this analysis. These patients may be the most difficult to keep in therapeutic INR range, and their exclusion may have underestimated the challenges with warfarin therapy in cancer patients in general.

Although the presence of cardiovascular disease in cancer patients has recently emerged to rival cancer as the predominant cause of mortality,[12] data obtained from this cohort over the long-term follow-up of 2.5 years, showed that patients with cancer had a significantly higher risk of all-cause death that was primarily driven by non-CV death compared with patients without history of cancer.

Cancer is also a prothrombotic state and may further increase the risk of thrombotic events in patients with AF. Some anticancer therapies have been associated with both thromboembolic complications and increased risk of bleeding events.[1,13–15] In this analysis, we found that the risk of other CV outcomes such as stroke, non-CNS embolism, heart failure and risk of CV death was also similar between those with and without history of cancer, yet patients with history of cancer were at higher risk of major bleeding. Incidence of each CV event remained similar after excluding all patients on dabigatran (data not shown).

Table 2 CV outcomes in AF patients with and without history of cancer

Outcomes	No cancer[a]	History of cancer[a]	Adjusted HR (95% CI)	*P*-values
All-cause death	4.92	7.75	1.26 (1.11–1.42)	0.0003
CV death	2.07	2.89	1.10 (0.90–1.34)	0.35
Non-CV death	2.42	4.24	1.35 (1.14–1.60)	0.0004
First stroke, non-CNS embolism, or TIA	1.48	1.96	1.04 (0.82–1.32)	0.74
First major bleed	3.45	5.13	1.21 (1.04–1.40)	0.02
New onset HF diagnosis (*N* = 6545)	1.53	1.73	0.90 (0.66–1.21)	0.47

CV, cardiovascular; CNS, central nervous system; TIA, transient ischaemic attack; HF, heart failure; HR, hazard ratio; CI, confidence interval.
[a]Event rate per 100 patient-years follow-up.

Table 3 INR checks and TTR by history of cancer

	Overall (*n* = 6965)	No cancer (*n* = 5297)	History of cancer (*n* = 1668)	*P*-value
Home monitoring	2.8	2.9	2.5	0.39
Warfarin clinic	43.9	42.6	48.4	<0.0001
Number of INR checks	24 (11, 40)	24 (11, 39)	28 (12, 42)	<0.0001
TTR (%)	67 (51, 80)	67 (51, 79)	68 (53, 80)	0.10

INR, international normalized ratio; TTR, time in therapeutic range.

Limitations

These findings have to be interpreted in view of the following limitation. First, data were obtained from a prospective, national registry; therefore, the data are observational in nature and are subject to the limitations inherent in such methods, including site participation, patient selection, and reporting biases. Second, we were not able to discern if cancer was remote, active or recently treated since these details were not collected. Likewise, the stage, site of disease, and treatment details were not available. Third, we were not able to separate patients whose cancers have a higher rate of thrombosis and or bleeding risk, i.e. renal cell or pancreatic cancer in the solid tumour group and multiple myeloma in the haematologic malignancy group: in the case of solid malignancy (i.e. not lymphoma or leukaemia), we did not have information on the organ-specific tumour. Fourth, patients' data and outcomes are obtained through via chart review, and their accuracy is thus dependent on completeness of initial documentation and thoroughness of subsequent abstraction. Finally, residual measured and unmeasured confounding may have impacted some of these findings.

Conclusions

Patients with AF and a history of cancer carry a high burden of CV risk factors and frequently have cardiovascular disease. They appear to be similarly treated with antithrombotic and anticoagulant therapy but experience higher risk of major bleeding. This data should be investigated in other larger scale registries and optimal management of cancer patients with AF should be prospectively studied in randomized clinical trials focusing on patients with cancer.

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Conflict of interest: C.M's disclosure can be viewed at https://www.dcri.org/wp-content/uploads/2016/10/COI-Melloni_2016.pdf. B.G. reports Mount Sinai St. Lukes—Data Safety Monitoring Board Boston Scientific Corporation—Data Safety Monitoring Board Teva Pharmaceutical. Industries—Data Safety Monitoring Board Janssen Scientific Affairs—General Consulting St. Jude Medical Inc.—Data Safety Monitoring Board. Janssen Research & Development—Data Safety Monitoring Board Baxter. Healthcare Corporation—Data Safety Monitoring Board Cardiovascular. Research Foundation—Data Safety Monitoring Board Medtronic Inc.—Advisory Board Xenon Pharmaceuticals—General Consulting Cipla Limited—General Consulting Thrombosis Research Institute—Data Safety. Monitoring Board Armetheon Inc.—General Consulting. A.S.G. reports receiving a research grant through his Institution from iRhythm Technologies, Inc. J.A. reports consultant/advisory board support from Bristol Myers Squibb, Pfizer, Janssen, Daiichi, Boehringer Ingelheim, and Alere. E.H. reports advisory board participation from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Daiichi Sankyo, Medtronic and Janssen and honorarium from Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo. K.W.M.'s disclosure can be viewed at http://med.stanford.edu/profiles/kenneth-mahaffey. G.C.F. discloses consulting for Janssen. J.P.P. reports significant research support from ARCA biopharma, Boston Scientific, GE Healthcare, and Johnson & Johnson/Janssen Scientific Affairs and consultancies to Forest Laboratories, Janssen Scientific Affairs, Pfizer/BMS, Spectranetics, and Medtronic. E.D.P. has received consultant fees or honoraria from Astra Zenecca, Boehringer Ingelheim, and Janssen and research grants from Astra Zenecca, Eli Lilly, Janssen, Genentech, and Sanofi. A.F.Y. reports consultant/advisory board support from Bristol-Myers Squibb. All authors have approved the final version of the manuscript. PRK reports consultant for Johnson and Johnson, Clovis, Novartis, and GSK.

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