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Original article

Current status of anticoagulation in patients with breast cancer and atrial fibrillation

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ABSTRACT

Objective: Balance between embolic and bleeding risk is challenging among patients with cancer. There is a lack of specific recommendations for the use of antithrombotic therapy in oncologic patients with atrial fibrillation (AF). We compared the embolic and bleeding risk, the preventive management and the incidence of events between patients with and without cancer. We further evaluated the effectiveness and safety of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) within patients with cancer.

Methods and results: The AMBER-AF registry is an observational multicentre study that analysed patients with non-valvular AF treated in Oncology and Cardiology Departments in Spain. 1,237 female patients with AF were enrolled: 637 with breast cancer and 599 without cancer. Mean follow-up was 3.1 years. Both groups were similar in age, embolic risk and bleeding risk. Lack of guidelines-recommended therapies was more frequent among patients with cancer. Compared with patients without cancer, adjusted rates of stroke (hazard ratio [95% confidence interval]) in cancer patients were higher (1.56 [1.04−2.35]), whereas bleeding rates remained similar (1.25 [0.95−1.64]). Within the group of patients with cancer, the use of DOACs vs VKAs did not entail differences in the adjusted rates of stroke (0.91 [0.42−1.99]) or severe bleedings (1.53 [0.93−2.53]).

Conclusions: Antithrombotic management of AF frequently differs in patients with breast cancer. While breast cancer is associated with a higher risk of incident stroke, bleeding events remained similar. Patients with cancer treated with DOACs experienced similar rates of stroke and bleeding as those with VKAs.

What is already known about this subject?

Prevalence of atrial fibrillation among patients with cancer is

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high and antithrombotic management is usually required for stroke prevention. While cancer causes a prothrombotic state that facilitates embolic events bleeding risk remains an issue due to cancer itself and cancer therapies. International guidelines do not include specific recommendations for antithrombotic management, mainly because of paucity of information in comparison with general population.

What does this study add?

- Antithrombotic management of patients with atrial fibrillation differs from patients without cancer. They are often precluded from anticoagulation therapy regardless of stroke risk.
- Ischemic stroke rates were found to be higher among patients with cancer, while incident major bleeding risk did not differ compared with patients without cancer.
- Direct oral anticoagulants presented similar rates of stroke/systemic embolism and bleeding events as vitamin K antagonists among patients with breast cancer and atrial fibrillation.

How might this impact on clinical practice?

Clinicians should avoid underuse of anticoagulants when clinically indicated guided by current ischemic risk scores, with greater concern about stroke prevention. An effort should be made to stop the use of suboptimal therapies such as antiplatelet drugs for atrial fibrillation. Direct oral anticoagulants can be a reasonable option for anticoagulation among patients with atrial fibrillation and breast cancer.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an estimated prevalence of approximately 3% in adults that increases with age [1]. AF is a common cause of stroke, hospitalization and death, whereas anticoagulation therapy for the prevention of stroke can trigger bleeding events.

Cancer is one of the chronic pathologies whose survival is increasing in recent decades, and it is associated with a higher prevalence of AF. The onset of AF may be related to comorbidities, direct tumour effects, left ventricular dysfunction, surgical procedures or cardiotoxicity induced by cancer therapies [2].

Cancer causes a prothrombotic state, and it has been associated with a higher predisposition to bleeding. European clinical practice guidelines for the management of AF make no distinctions in patients with concomitant oncological pathology. The same criteria apply as in the general population regarding the use of antithrombotic therapies [3]. The European Society of Cardiology Position Paper on Cancer treatments admits that the embolic-haemorrhagic risk balance can be modified in AF and cancer, but recommendations for the use of anticoagulants remain the same as in non-oncological patients [4]. In addition, cancer itself and cancer therapies may increase the risk of thrombosis or haemorrhage, with an unpredictable anticoagulant response. In these patients, none of the risk prediction scales have been tested. We believe that this group of patients deserves a specific analysis before general recommendations can be applied.

Patients with cancer may experience an erratic control of the international normalised ratio (INR). Therefore, the use of vitamin K antagonists (VKA) may not be the optimal anticoagulant, especially during active chemotherapy. A higher rate of thrombotic events has been described with VKAs, regardless of the indication for anticoagulation [5].

We do not have specific data on the safety and efficacy of DOACs in patients with AF and cancer. Although this condition did not constitute an absolute contraindication for participation in the pivotal clinical trials that compared DOACs vs VKA for the prevention of stroke and systemic embolism, patients with a short life expectancy were excluded, and the reduced number of patients was insufficient to obtain solid conclusions [6–9].

Breast cancer is one of the most prevalent cancers, and these patients frequently require chronic antitumor treatments. Their high overall survival allows a prolonged clinical follow-up, facilitating the study of embolic and haemorrhagic events that may not be *a priori* attributable to a direct effect of the tumour. The main purpose of our study was 1) to determine the clinical characteristics and risk profile of patients with AF and breast cancer, as compared with patients without malignancies; 2) to assess the general antithrombotic strategies in patients with breast cancer and if they differ from the ones used in patients without cancer and 3) to describe the incidence of ischemic and bleeding events in both populations.

2. Methods

2.1. Study design

The AMBER-AF registry (Antithrombotic Management of patients with Breast cancER and Atrial Fibrillation multicentre registry) was designed as an ambispective observational study with a retrospective review of consecutive patients with non-valvular AF and prospective follow-up.

Female patients attended either in Oncology and Cardiology Departments between January 2011 and January 2018 in 9 tertiary hospitals were studied. Inclusion criteria were age >18 years old and history of AF. For comparison purposes two cohorts were established: the cancer cohort was constituted by consecutive patients with clinical history of breast cancer and atrial fibrillation seen at Oncology Departments, whereas the no-cancer cohort was formed with contemporary patients with AF without malignancy history at enrolment evaluated at Cardiology Departments in the same hospitals. The number of participating patients per centre was decided according to the size of each hospital and the centres were encouraged to include an equal proportion of patients with and without cancer. No explicit exclusion criteria were defined other than valvular AF or mechanic cardiac prostheses to avoid selection bias.

All data were captured using a dedicated electronic case report form. Clinical and therapeutic data were collected. The risk of thromboembolic and bleeding events was assessed by calculating the CHA_2DS_2-VASc and the HAS-BLED scores. Cancer stage, ongoing chemotherapy treatment and type, and prior use of anthracyclines, taxanes, targeted therapy or radiotherapy was noted. Information related to adjuvant endocrine agents (hormonal therapy) was collected, including use of the selective estrogen receptor modulator tamoxifen, aromatase inhibitors or ovarian suppression. Clinical follow-up was performed in both cohorts monitoring the incidence of embolic and bleeding events, and it continued for as long as available regardless of subsequent clinical events. Switches between antithrombotic therapies were collected. A labile INR was considered if time within therapeutic range was below 60%, according to the definition proposed by Pisters et al. [10].

2.2. Outcomes

Our primary endpoints were ischemic stroke/systemic embolism, and major bleeding events. Ischemic stroke was considered in the case of an abrupt onset of a focal neurological deficit non-attributable to an identifiable nonvascular cause and excluding intracranial bleeding. The definition of major bleeding events was consistent with the International Society of Thrombosis and Haemostasis (ISTH) criteria [11]. Systemic embolic event consisted on an abrupt episode of arterial occlusion with clinical or radiologic documentation in the absence of prior instrumentation. The primary safety outcome for our study included fatal bleeding, bleeding into a critical organ (intracranial, intraspinal, pericardial, retroperitoneal or intramuscular with compartment syndrome) or relevant bleeding with a haemoglobin drop $\geq$2 g/dL. The study protocol complied with the Declaration of Helsinki and it was authorized by the Reference Ethic Committee and the Local Ethic Committees of all participant institutions. Access to the medical records was granted for retrospective analysis and all patients provided written informed consent for the prospective follow-up.

2.3. Statistics analysis

Variables are presented as number (percentage) or mean ±SD, as appropriate. Event rates per 100 patient-years are presented as proportions of patients per year. Baseline characteristics between the cancer and no-cancer cohorts were compared with the Chi-square test for discrete variables and the Student *t*-test for continuous variables provided that populations were normally distributed. Hazard ratios (HRs) between the occurrence of events during follow-up were calculated for each group with the use of Cox proportional-hazards models. The following adjustment factors were included in the model: for the analysis of ischemic events CHA_2DS_2-VASc score and use of anticoagulation, whereas for the analysis of bleeding events HAS-BLED score and use of anticoagulation were considered. Kaplan-Meier curves for both ischemic and bleeding events in both populations are provided. Observations with missing data were excluded from the analysis (<1% from total). Analysis were conducted using SPSS software V.22.0 and R V.3.5.1, with a two-tailed significance value of 0.05.

3. Results

3.1. Patient characteristics

A total of 1,237 consecutive patients were enrolled, 637 in the cancer cohort and 599 in the no-cancer cohort from the Oncology and Cardiology Departments respectively. While mean age was similar between patients with cancer and no-cancer (75.4 ± 9.6 vs 75.1 ± 10.1 years), available follow up in years was shorter for patients with cancer (2.8 ± 2.4 vs 3.4 ± 2.7, $p < 0.001$).

The main demographic and clinical characteristics of the two groups are shown in Table 1. Patients included in the cancer group, compared with those without cancer, had less frequently a previous myocardial infarction (10% vs 18%), reflecting the cardiology setting for selection of the latter. The prevalence of other comorbidities, risk factors and type of AF presentation was similar between groups.

Overall, stroke risk was high (CHA_2DS_2-VASc score of 4.4 ± 1.4). Only 18 patients (2.8%) in the cancer group and 9 patients (1.5%) in the no-cancer group had CHA_2DS_2-VASc score 1. According to the ESC guidelines, the remaining 97.2% and 98.5%, respectively, had class IA indication for the use of anticoagulation based on a CHA_2DS_2-VASc $\geq$ 2.

Baseline bleeding risk, as assessed by HAS-BLED, did not show significant differences between groups (2.2 ± 1.3 vs 2.3 ± 1.3, for cancer and no-cancer respectively). The prevalence of patients considered to be of high bleeding risk, defined as HAS-BLED score $\geq$3 was similar (35% vs 38%). No significant differences were detected in labile INR (32% vs 37%). However, the proportion of patients with abnormal liver function was higher among those with cancer (9% vs 4%).

The specific characteristics of the cancer group are also shown in Table 1. The proportion of the patients with metastatic disease at baseline was 22%, and 56 patients (8.8%) were diagnosed during follow-up. 55% of the sample had received radiotherapy in the past or at the initial period of observation. A 14% of the sample were receiving active chemotherapy at the time of inclusion, while 31% had received chemotherapy at any time at the end of follow-up.

3.2. Antithrombotic strategies

At baseline, anticoagulation therapy was prescribed in 85% of patients with cancer and 86% of those without (Fig. 1). The majority of patients received VKAs (65% vs 66%, respectively), while DOACs remained as a secondary option. Remarkably, almost 9% of patients in both groups were receiving an antiplatelet therapy regimen. An almost twofold higher percentage of patients with cancer were prescribed low molecular weight heparins (5.0% vs 2.8%) or had no antithrombotic treatment (6.4% vs 3.3%).

Throughout the duration of the study, 75.3% of the patients continued with the same antithrombotic treatment, while the remaining underwent at least one treatment switch. Substitution of AVK for DOAC was the most common switch in both populations (Fig. 1).

At the end of follow-up, anticoagulation use remained stable within patients with cancer, while a mild increase was noted in patients without cancer (85% vs 90%, respectively). VKAs remained as the first option in both groups (52.6% vs 51.4%). An almost twofold increase in the use of DOACs was demonstrated in both groups, from 15.4% at baseline to 26.7% at the end of follow-up for patients with cancer and from 18.7% to 35.7% for patients without cancer. A progressive decrease in the use of antiplatelet drugs, low molecular weight heparins or lack of any preventive treatment was noted for patients without cancer, in contrast with those with cancer that remained stable.

3.3. Incidence of major outcomes

Patients with cancer had higher incidence stroke or systemic embolism after adjustment for CHA_2DS_2-VASc and anticoagulation use (HR 1.56, 95% CI (1.04–2.35)). During follow-up, 67 patients in the cancer group (10.5%) and 50 patients in the group without cancer (8.3%) suffered an ischemic stroke or a systemic embolism (Log Rank $p = 0.027$).

Cancer was not associated with higher incidence of bleeding events in the Cox model after adjustment for HAS-BLED and use of anticoagulation (HR 1.25, 95% CI (0.95–1.64). 110 patients with cancer (17.3%) presented bleeding event vs 99 patients (16.5%) without cancer (Log Rank $p = 0.09$). Kaplan Meier curves for embolic and bleeding events are shown in Fig. 2.

Overall mortality was higher among patients with cancer (157 deaths, 24.6%) than in patients without cancer (105 deaths, 17.5%). Of note, embolic or bleeding events that led to death accounted for 34% of mortality in the cancer group (53 deaths) and 25% in the no cancer group (26 deaths).

3.4. Incidence of events between AVK and DOACs in patients with cancer

Incidence of thromboembolic and major bleeding events according to the antithrombotic strategy with VKAs or DOACs was further evaluated in the cohort of 637 patients with cancer. There was no evidence that the incidence of ischemic stroke/systemic embolism differed between patients with cancer treated with AVK and DOAC after CHA_2DS_2-VASc adjustment: HR 0.91 (95% CI,

Table 1
Baseline demographics and patient characteristics.

	Cancer group N = 637	No-cancer group N = 599	*p* value
Age (years), mean ± SD	75.4 ± 9.6	75.1 ± 10.1	0.605
Follow-up (years), mean ± SD	2.8 ± 2.4	3.4 ± 2.7	0.000
CHA_2DS_2-VASc score, mean ± SD	4.4 ± 1.6	4.4 ± 1.5	0.586
CHA_2DS_2-VASc ≥ 2	619 (97.2%)	590 (98.5%)	0.112
HAS-BLED score, mean ± SD	2.2 ± 1.3	2.3 ± 1.3	0.299
HAS-BLED ≥ 3	221 (34.7%)	230 (38.4%)	0.176
Type of AF			0.053
Paroxysmal	317 (49.8%)	331 (55.3%)	
Persistent/permanent	320 (50.2%)	268 (44.7%)	
Aterial hypertension	549 (86.2%)	528 (88.1%)	0.303
Diabetes mellitus	184 (28.9%)	182 (30.4%)	0.564
Previous MI	58 (10.4%)	106 (17.7%)	0.000
Congestive heart failure	254 (39.9%)	248 (41.4%)	0.585
Previous stroke/systemic embolism	99 (15.5%)	92 (15.4%)	0.929
Chronic obstructive pulmonary disease	67 (12.0%)	79 (13.2%)	0.553
Vascular disease	59 (9.3%)	57 (9.5%)	0.879
Previous bleeding*	64 (10.0%)	61 (10.2%)	0.937
Labile INR	188 (32%)	204 (36.6%)	0.101
Anticoagulation therapy (initial)	541 (84.9%)	526 (87.8%)	0.140
Type of antithrombotic therapy (initial)			0.018
VKA	411 (64.5%)	397 (66.3%)	
DOAC	98 (15.4%)	112 (18.7%)	
Low molecular weight heparin	32 (5.0%)	17 (2.8%)	
Antiplatelet	55 (8.6%)	53 (8.8%)	
No treatment	41 (6.4%)	20 (3.3%)	
Anticoagulation therapy (end of FU)	540 (84.8%)	536 (89.5%)	0.014
Type of antithrombotic therapy (end of FU)			0.000
VKA	335 (52.6%)	308 (51.4%)	
DOAC	170 (26.7%)	214 (35.7%)	
Low molecular weight heparin	35 (5.5%)	14 (2.3%)	
Antiplatelet	54 (8.5%)	47 (7.8%)	
No treatment	43 (6.8%)	16 (2.7%)	
Abnormal liver function**	57 (9.0%)	24 (4.0%)	0.000
Metastatic disease		–	NA
- Baseline	140 (22%)		
- End of follow-up	196 (31%)		
Previous/concurrent radiotherapy	353 (55%)	–	NA
Active chemotherapy	87 (14%)	–	NA
Therapy agents used			
Anthracyclines	148 (23%)	–	NA
Endocrine/hormonal therapy		–	NA
- Tamoxifen	83 (13%)	–	NA
- Aromatase inhibitors	369 (58%)	–	NA
Antimicrotubule agents (taxanes)	137 (22%)		
HER2 inhibitors	76 (12%)		

Values are expressed as n (%) unless otherwise indicated. SD: standard deviation; AF: atrial fibrillation; MI: myocardial infarction; CHA_2DS_2-VASc**:** Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol; INR: international normalised ratio; FU: follow-up; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; HER2: human epidermal growth receptor factor 2. * Major bleeding event according to ISTH criteria. ** Chronic hepatic disease (eg. cirrhosis) or biochemical evidence of significant hepatic derangement.

0.42–1.99).

In addition, no significant differences in the incidence of major bleeding events were found between DOACs and VKA after adjustment for HAS-BLED score: HR 1.53 (95% CI, 0.93–2.53) (Fig. 3). Gastrointestinal bleeding was the main source of haemorrhages in both groups, accounting for 45% of bleedings among patients treated with DOACs and, 37% in patients treated with VKAs.

4. Discussion

4.1. Main findings

In this analysis of individual patients' data from the real-world AMBER-AF registry, we have found that in patients with breast cancer: (1) the choice of antithrombotic therapy differs from patients without cancer, with a higher prevalence anticoagulant underuse; (2) while the risk of developing a stroke or systemic embolism was largely increased among patients with cancer, no significant differences were noted in major bleeding events; and (3) among our population of patients with cancer, DOACs proved to be as effective as VKA in preventing stroke and systemic embolism, whereas no significant differences were found in the incidence of bleeding events.

4.2. Patient characteristics & antithrombotic strategies

Both embolic and bleeding risk was similar at baseline for both groups. However, management of stroke prophylaxis was different in patients with and without cancer (Fig. 1). Patients with cancer received treatment with DOAC less frequently than those without cancer, and a higher use of low molecular weight heparins was observed in the former. A frequent and possibly inappropriate use of antiplatelet agents for stroke prevention was noted for both groups. We consider this last observation remarkable;

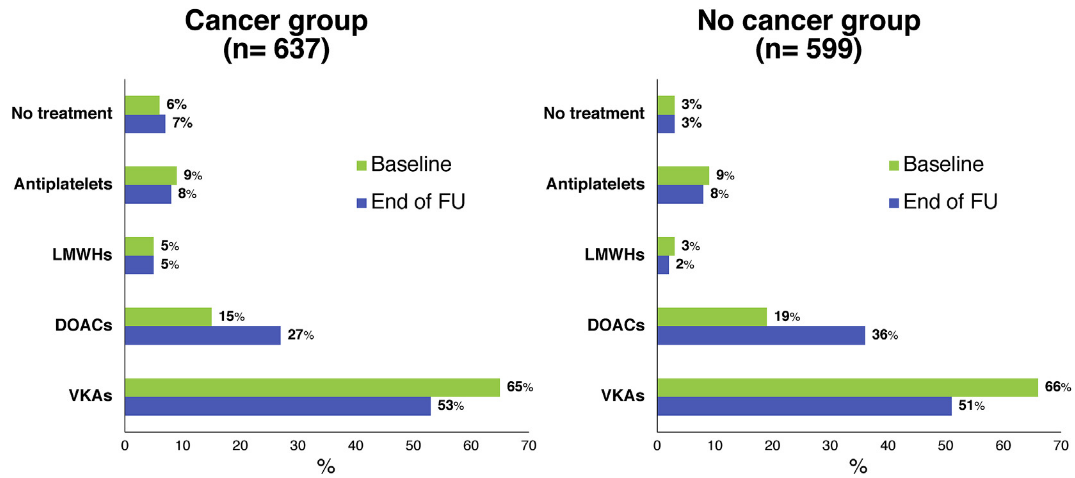
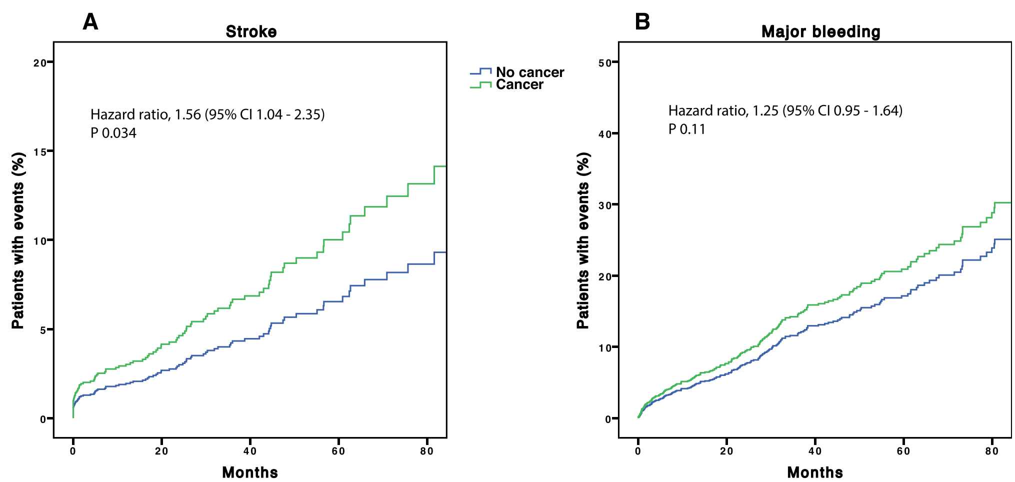


Fig. 1. Prevalence of antithrombotic therapies in patients with atrial fibrillation at baseline and at the end of follow-up by group. VKAs: Vitamin K Antagonists; DOACs: Direct Oral Anticoagulants; LMWHs: low molecular weight heparins; FU: follow up. Total number: cancer group 637; no cancer group 599.



No. at risk						No. at risk					
No cancer	599	398	247	145	76	No cancer	599	397	238	142	70
Cancer	637	356	218	105	40	Cancer	637	358	210	100	36

Fig. 2. Primary endpoint. Kaplan-Meier analysis for the incidence of the primary outcomes in patients with cancer vs without cancer: (Panel A) shows ischemic stroke. (Panel B) shows major bleeding, as defined according to the criteria of the International Society on Thrombosis and Haemostasis. Hazard ratio calculated by Cox proportional hazards model adjusted for baseline characteristics: CHA_2DS_2-VASc score and use of anticoagulation for the analysis of stroke; HAS-BLED score and use of anticoagulation for major bleeding. Referent is the no cancer group. Number of patients: cancer group 637; no cancer group 599. CI: confidence interval.

notwithstanding, current registries in AF note similar findings [12].

4.3. Incidence of major outcomes

A significantly higher risk of stroke and systemic embolism was observed during follow-up in patients with cancer (10.5 vs. 8.3%), assessed by both univariate and multivariate Cox analysis adjusted by the use of anticoagulation and CHA_2DS_2-VASc. The relationship between stroke and cancer is complex, with a different pattern of risk factors, stroke-related biomarkers and underlying aetiology compared with non-cancer patients [13,14]. In a sub-analysis of the ROCKET AF study the estimated 1-year cumulative incidence of ischemic stroke in patients with cancer and AF was 1.4%, lower than our data [15]. This could be explained by our older and female-only population. By contrast, in a sub-analysis of the ENGAGE AF-TIMI 48 patients with active malignancy had increased death and major bleeding but not stroke or systemic embolism [16].

Interestingly, no significant differences were noted in the number of bleeding events for patients with cancer. In the subgroup analysis of the ROCKET [8] and RE-LY [6] studies, the risk of bleeding in cancer patients was two-to-six times higher, probably related to the high proportion of colorectal aetiology among cancer patients.

Ning Y et al. [17] followed 1807 oncological patients and detected that the cause of death in 51% of them was cancer, but up to 33% it was cardiovascular disease. This goes in line with our results (34% of mortality related with embolic or bleeding events attributable to AF or its antithrombotic therapy, respectively) and it shows the importance of cardiovascular disease in oncologic patients. It is essential to adopt an optimal management of both pathologies, being especially relevant the embolic and bleeding risk when talking about AF.

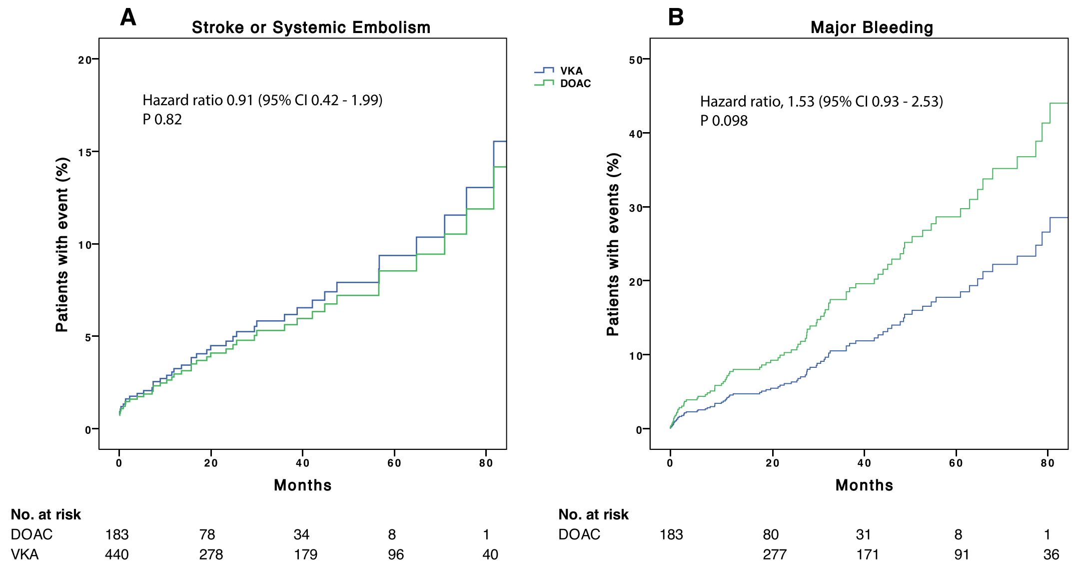


Fig. 3. Key secondary endpoints. Kaplan-Meier analysis for the incidence of stroke or systemic embolism (A) and major bleeding (B) in patients with cancer based on anticoagulation therapy. Hazard ratio calculated by Cox proportional hazards model adjusted for baseline characteristics between patients receiving DOACs and VKA (CHA_2DS_2-VASc score and use of anticoagulation for the analysis of stroke; HAS-BLED score and use of anticoagulation for major bleeding); referent is VKA. Total number of patient-treatment observations: VKA group 440; DOAC group 183. CI: confidence interval; VKA: vitamin K antagonists; DOAC: direct oral anticoagulants.

4.4. Incidence of events between AVK and DOACs in patients with cancer

In our study patients with cancer treated with DOACs did not differ versus those treated with VKAs with regards to stroke or systemic embolism in a model adjusted for CHA_2DS_2-VASc. Neither significant differences were found for bleeding events between DOACs and VKAs in a model adjusted for baseline HAS-BLED score. Metastatic disease or active chemotherapy were studied as potential covariates but none of them posed any relevant change in the result of the comparison. Gastrointestinal bleeding remained as the main source of haemorrhages for both groups but given the relatively small number of bleeding events (87 major bleedings in both groups), the unrandomized nature of the study and different follow-up times no comparisons were performed for individual sources of bleeding.

Up to date, no specific clinical trials have been conducted comparing the use of DOAC versus VKA in patients with cancer, and the clinical evidence relies on observational studies. In a subanalysis of the ARISTOTLE Trial [18] the safety and efficacy of apixaban versus warfarin were preserved among patients with cancer, but validity of these results is uncertain, given that cancer was considered as “remote” in 87% of cases, only 16% were of breast origin, and no additional information on cancer stage or treatment was available. In the study by Shah et al. [19], it was observed that the risk of major bleeding was significantly lower in patients with apixaban than in patients with VKA, rivaroxaban, or dabigatran. With the available data, the lack of direct evidence for the use of DOAC in cancer patients means that its use must be discussed in each patient. Dynamic fluctuations in hepatic and renal function may affect the levels of these drugs, and dose adjustments may be required. P glycoprotein is an important factor for the elimination of DOAC, and its function can be affected by numerous cancer therapies. Therefore, when considering the use of DOACs in patients with active chemotherapy, the pharmacokinetic properties of cancer therapies should be taken into account.

4.5. Limitations

Limitations of our study include its observational nature, with the accompanying issues of confounding, selection bias, misclassification of the exposure and outcome and possible unmeasured confounders such as frailty. The group of patients with AF without cancer was selected from cardiology consultations, and probably in these the use of DOAC could be higher. Given the design of the study, those patients with cancer in more advanced stages and lower survival have inherently lower representation. The appropriate statistical methods for comparative effectiveness were applied, addressing for confounding variables. Another issue is the more limited duration of follow-up data of patients treated with DOACs, but this is expected given the relatively recent approval compared with VKA.

In spite of the limitations, our study presents several strengths that are worth highlighting. Our study, although observational, detects a differential management of antithrombotic strategies and characterizes practice-based outcomes in a population of patients with cancer in direct comparison with contemporary patients without cancer; in the light of our findings a frequently seen restrain for the use of anticoagulation is not justified.

In addition, landmark studies in AF that showed noninferiority of DOACs compared with VKA did not specifically address patients with cancer. Until randomized clinical trials are conducted in oncological patients, the clinician should rely on robust observational studies. Our data suggest that for patients with breast cancer who need anticoagulation, DOACs can be a reasonable option as an alternative to VKAs or low-molecular-weight heparins. Their pharmacokinetic properties may offer a better profile in certain situations.

5. Conclusions

Patients with breast cancer and atrial fibrillation showed an increased risk of stroke with similar bleeding rates than patients without cancer. An unjustified differential management of anticoagulation with underuse of antithrombotic therapies is frequent among patients with cancer, depriving them from optimal treatment. Based on our findings, DOACs appear to be safe compared with VKA in patients with breast cancer from the standpoint of stroke/systemic embolism and major bleeding.

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Conflicts of interest

JLZ reports honoraria for lectures from Abbott and Daiichi Sankyo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.05.017.

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