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Original article

Atrial fibrillation in patients with active malignancy and use of anticoagulants: Under-prescription but no adverse impact on all-cause mortality

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ABSTRACT

Prescription of anticoagulants (ACs) in patients with cancer and atrial fibrillation (AF) is challenging and the impact on survival is not defined.

In this study data prospectively collected in Oncology Units were retrospectively evaluated. Among 4664 patients admitted for malignancy, 394 patients (8.4%) had documented AF (mean age of 74 ± 9) and AC was prescribed to 155 patients (40%). Neither the type of cancer, the stage of the disease (metastatic or not) nor the ongoing treatments were significantly associated with prescription of AC, which was independently associated with BMI (OR 1.10; CI 95% 1.03–1.17; p = .003), valvular heart disease (OR 3.76; CI95% 1.59–8.87; p = .002), and previous venous thromboembolism (OR 6.67; 95%CI 2.67–16.70; $p < .001$). During a median follow-up of 212 days, survival from all-cause death was 37%, 28% and 18% at 6 months, 1 and 2 years, respectively. Only variables related to neoplastic disease or to patient clinical complexity were independently associated with mortality. A $CHA_2DS_2VASc \geq 4$ was significantly associated with mortality (HR 1.33; 95%CI 1.06–1.67; p = .013). Treatment with ACs was not significantly related to mortality, neither in the whole cohort of patients, nor in patients with metastatic malignancies.

In conclusion the prescription of ACs in patients with AF and active cancer was suboptimal, with one fourth of the patients not treated with ACs and one third using LMWH at prophylactic, non-therapeutic doses. Only few variables (BMI, valvular heart disease and previous venous thromboembolism) predicted prescription of ACs. Prescription of ACs was not associated with all-cause mortality, even in the subgroup with metastasis.

1. Introduction

Cancer and cardiovascular diseases are undoubtedly the main causes of mortality and morbidity in industrialized countries, with an increasing trend, given the aging population and the improvement of sanitary conditions [1].

Atrial fibrillation/flutter (AF) is one of the more common arrhythmias observed in patients with cancer, with a prevalence of 2.4% at the time of cancer diagnosis and an incidence of 1.8% during the course of the disease [2]. In a population study patients with colorectal cancer, as well as patients with other malignancies, showed an increased risk of AF diagnosed in the first 90 days after cancer diagnosis, with a potential role of surgical interventions in explaining this association [3].

In a recent survey conducted by the European Heart Rhythm Association, the main side effects of anticancer therapy in patients treated by cardiologists were thromboembolic complications and left ventricular dysfunction (both reported as ‘frequent’ by 43% of the centres surveyed) [4]. The high risk of AF and associated thromboembolism in cancer patients raise concerns about use of anticoagulants, since in this specific context the risk of bleeding can be significantly higher than in patients without cancer, as clearly shown for patients

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with venous thrombosis [5]. In patients with cancer the risk of bleeding is dependent on several factors. First, there are difficulties in achieving a good anticoagulation control in case of warfarin treatment (time in therapeutic range 46% and 47% respectively in CLOT and CATCH trials) [6,7]. This effect was mainly driven by a supratherapeutic level of INR and cyclic need of chemotherapies, as well as the need of analgesia [8] or the risk of pharmacological interactions can explain its occurrence. Additionally, specific cancer-related factors for an increased risk of bleeding include either a localized bleeding diathesis as a result of local injury by tumor invasion or a generalized hemorrhagic diathesis, due to several factors including thrombocytopenia, platelet dysfunction, acquired von Willebrand syndrome, coagulation factor deficiencies or presence of inhibitors [9]. As a result of the generalized concern on bleeding risk results, registries such as the EORP-AF long-term general registry highlight an underprescription of oral anticoagulants in patients with history of malignancies [10].

The aim of this retrospective analysis of data prospectively collected in an Oncology Unit was to describe the clinical characteristics of patients with AF associated with a diagnosed malignancy, the factors associated with prescription of anticoagulants and patients outcome.

2. Methods

The protocol of this single-centre study was evaluated and approved by the local Institutional Review Board. We retrospectively retrieved the data prospectively collected and stored in an Institutional database collecting the clinical information of patients affected by active cancer and admitted to the units of our Oncology department, for the time period between January 1st 2011 and December 31th 2015.

Both clinical diagnosis of AF and administrative codes (ICD-9-CM codes 427.3×) were used for identifying the patients with a diagnosis of AF associated with cancer, taking into account all the cases with documented AF. The number of cases with a diagnosis of cancer admitted in the same period was considered for calculating AF prevalence. Patients were eligible for the study if: (i) AF was reported and an ECG with AF was present on clinical records; (ii) age higher than or equal to 18 years. Multiple admissions of the same patient for AF were censored considering only the first admission for the index period.

According to the common practice in use at the Oncology Department all the patient at admission underwent a physical examination, a 12-lead electrocardiogram, an echocardiogram and blood sampling analysis. The institutional protocol provided a cardiology evaluation with echocardiogram for all patients with active cancer prior to start the therapy. Moreover, on call, a further cardiac evaluation took place when a patient described symptoms for suspected cardiac disease or in any case of need for specific decision making. For the purpose of this analysis we collected information about demographic, clinical and laboratory data, as well as prescribed treatments.

Information about patient outcome were obtained from clinical records, administrative databases and, whenever possible, by phone calls. Comparisons were made between anticoagulated and not anticoagulated patients, as the result of cardiology consultation for the AF diagnosis.

2.1. Definitions

AF was defined according to European Society of Cardiology guidelines [11].

We stratified the thromboembolic risk according to CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes, stroke [doubled], vascular disease, age 65–74, and sex category [female]). Based on a point system, 2 points are assigned for a history of stroke or TIA, or age ≥ 75; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease [myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.], and female sex. We assessed the bleeding risk according to HASBLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, each item leads to 1 point) [12].

Valvular disease was considered present if a patient had at least moderate stenosis or regurgitation of heart valves or if a prosthetic valve or surgical repair of one or more heart valves had been performed at medical history. Heart failure was considered present if the typical presentation was detected at the clinical evaluation or if ejection fraction (EF) was less than or equal to 40%.

Chronic kidney disease (CKD) was considered as present if a patients had a known history of reduction in renal function, defined as a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for > 3 months [13].

History of bleeding was systematically collected, according to what reported in the clinical records.

Treatment with anticoagulants was evaluated by considering treatment with vitamin-K-antagonists (VKA), direct oral anticoagulants (DOACs) or low-molecular weight heparin (LMWH), the latter administered at anticoagulant dose.

Venous thromboembolism (VTE) was defined as present if pulmonary embolism (PE) or deep vein thrombosis (DVT) were objectively diagnosed, including also asymptomatic VTE incidentally diagnosed during the clinical work-out [14].

Major bleeding was defined according to International Society on Thrombosis and Haemostasis criteria [15,16].

2.2. Study end-points

The primary endpoint of the study was the evaluation of the variables related to the prescription of anticoagulants in this specific set of patients. Secondary endpoint was all-cause mortality, with an the analysis of the variables associated with this outcome, with special focus on anticoagulation.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (m ± ds) when normally distributed or as median (interquartile range [IQ range] if not normally distributed according to Kolmogorov-Smirnov test, while categorical variables were reported as absolute numbers and percentage.

For statistical analysis, *t*-test for unpaired data or the Mann-Whitney-*U* test were used according to the distribution of the continuous variables, while for the categorical variables the $\chi 2$ or the Fisher exact test was used when appropriate.

For the evaluation of independent predictors of prescription of anticoagulants, an univariate and stepwise multivariate logistic regression analysis was performed. Variables with a value of $p < .10$ at univariate logistic analysis were entered in the multivariable model.

With regard to multivariable logistic regression analysis, two models were considered in order to avoid collinearity, by introducing CHA_2DS_2-VASc and HASBLED scores or, alternatively, the single variables contributing to these scores (if eligible).

Results are presented by the odds ratio (OR), the 95% confidence interval (95%CI), and the *p*-value.

For the evaluation of survival, we calculated univariate and multivariate hazard ratio (HR) and 95% confidence intervals (CI 95%) by means of Cox proportional hazard regression models. Variables with a $p < .10$ at univariate analysis were entered in the multivariate model. As in the case of the multivariable logistic regression, two models were considered in order to avoid collinearity, by introducing CHA_2DS_2-VASc and HASBLED scores or, alternatively, the single variables contributing to these scores (if eligible). A further survival analysis was conducted, splitting the CHA_2DS_2-VASc score a first time at a level usually considered an indication for anticoagulation [11], i.e. CHA_2DS_2-VASc > 1 (> 2 if female), and in a second analysis considering CHA_2DS_2-VASc score ≥ 4, expression of a very high risk of thromboembolism (when also in presence of some risk of bleeding, anticoagulation should be always taken in consideration).

Unadjusted and adjusted HRs for death, according to anticoagulation, were calculated using proportional hazard Cox regression, with adjustments done for age, heart failure, major bleedings, type and stage of neoplastic disease, main risk scores for thrombosis and bleeding, VTE, type and pattern of AF. Survival analysis was assessed using Kaplan-Meier method. Values of $p < .05$ are considered statistically significant. For the statistical analysis SPSS version 18 (SPSS inc. Chicago Illinois) was used.

3. Results

3.1. Prevalence of AF in patients with active cancer

Between 2011 and 2015, 4664 patients were admitted for diagnosed active cancer and 394 were found to present a diagnosis of AF (prevalence 8.4%).

Information about anticoagulation treatment was incomplete in 14 patients and these were excluded from the subsequent analysis.

3.2. Characteristics of cancer patients with AF and use of anticoagulants

The group of 380 patients with AF had a mean age of 74 ± 9 years (median 76; IQ range 69–81) and 233 were male (61.3%). The CHA_2DS_2VASc score indicated a low risk of stroke only in few patients, since it was > 1 in males and > 2 in females in 97.1% of the patients. Mean CHA_2DS_2VASc score was 4.1 ± 1.8. Mean HAS-BLED score was 2.16 ± 1.05.

At the time of AF diagnosis and after cardiology consultation, 225 patients (59.2%) did not receive a prescription of anticoagulants. In detail, 91 (23,9%) had no prescription of anticoagulants while 134 (35.3%) were prescribed a prophylactic dose, and non-treatment dose, of LMWH. In case of treatment with anticoagulants (155 patients, 40.8% of the analysed group), 31 patients (20%%) had prescription of a VKA, 3 (1,9%) of a DOAC and 121 (78,1%) had LMWH at a full anticoagulant dose. Clinical characteristics of AF patients are shown in Table 1, according to prescription or not of anticoagulants, following cardiology consultation.

The main type of neoplastic disease was hemolymphopoietic system cancers ($n = 126$; 33.2%), followed by pulmonary ($n = 90$; 23.7%) and gastrointestinal ($n = 69$; 18.2%) cancers. Other forms of cancer accounted for 25% of the cases (95 patients). Neither the kind of cancer nor the stage of the disease or oncological treatments were significantly associated with prescription of anticoagulants, as shown in Table 2. Details about chemotherapy are shown in Web Table 1.

Prescription of anticoagulants was not influenced by hematological laboratory parameters, that is, hemoglobin (11 [9.4–12.7] g/dl in the non anticoagulated patients [AC-] vs 10.9 [9.7–12.5] g/dl in anticoagulated patients [AC+]; $p = .545$], or platelet count (215 [129–296] x 10^3 in AC- vs 234 × 10^3 [152–303] in AC+; $p = .271$).

Stepwise logistic regression showed that body mass index as a continuous variable (OR 1.10; CI 95% 1.03–1.17; $p = .003$), valvular heart disease (OR 3.76; 95%CI 1.59–8.87; $p = .002$) and history of VTE (OR 6.67; 95%CI 2.67–16.67; $p < .001$) were the only variables independently associated with prescription of anticoagulant therapy.

Heart failure, peripheral artery disease, antiarrhythmic treatment, antiplatelet drugs and CKD-EPI < 50 ml/min/1.73 m^2 were not significantly associated with prescription of anticoagulants, neither in a first model including separate clinical variables (Web Table 2). Similar results were found in a second model that considered CHA_2DS_2-VASc > 1 (> 2 if female) (see Web Table 3).

3.3. Survival of cancer patients with AF and associated variables

During a median follow-up of 212 days (IQ range 92–731), survival from all-cause death using Kaplan Meier analysis was 37% at 6 months, 28% at 1 year and 18% at 2 years (Fig. 1). Median survival time was 242 days (IQR 92–731). Eight patients (2.1%) were lost to follow-up.

Variables that were associated with the risk of death in patients with AF and cancer according to Cox proportional hazard univariate regression are listed in Web Table 4. The risks associated with different clinical variables, according to Cox proportional multivariable regression analysis are summarised in Fig. 2.

On Cox proportional multivariable regression analysis, only variables related to the specific type of neoplastic disease (i.e. hemolymphopoietic system cancer associated with lower risk of death, gastrointestinal cancer associated with increased risk of death) or to patient complexity were independently associated with mortality (Table 3).

Of note, a CHA_2DS_2VASc ≥ 4 was significantly associated with all-cause death in this cohort. Treatment with anticoagulants was not significantly related to mortality, neither in the whole cohort of patients (HR 1.11; CI 95% 0.89–1.37; $p = .360$. Fig. 1) nor in the subgroup of patients with metastatic malignancies (HR 0.94; CI95% 0.71–1.26; $p = .688$. Fig. 2).

4. Discussion

The prevalence of AF in cancer patients varies according to therapies performed and the site of malignancy. Do to the mixed characteristics of our population we can consider a prevalence of 8.4% of AF in line with previous reports [17–19].

Our study shows that in patients with AF associated with active cancer, admitted to an Oncology Unit, management of AF with regard to prescription of anticoagulation substantially differs from current management of AF in patients without active cancer. First, we found that anticoagulant usage (predominantly LMWH) was low, and independently associated with body mass index, valvular heart disease and history of venous thromboembolism. Second, a CHA_2DS_2VASc ≥ 4 was significantly associated with all-cause death. Third, anticoagulant use was not associated with lower mortality.

While recent data from registries showed that in unselected populations with non-valvular AF, oral anticoagulants are prescribed to around 85% of patients, in line with guidelines [20], the present study indicates that anticoagulants are currently prescribed to around 59% of cancer patients with AF and more than one third received LMWH at the doses used for prophylaxis of VTE, and not for stroke prevention in AF, while in around 25% no anticoagulants are prescribed. The low rate of prescription of anticoagulants in AF is even more evident by considering that in our local Institutional AF program approximately 90% of patients were discharged with prescription of oral anticoagulants [21].

This unusual picture may reflects the influence of the studies evaluating LMWH in prevention of VTE in cancer [6] and the lack of studies focused on the outcome of AF patients who present in the context of an active cancer. The relatively wide use of LMWH is paralleled by a limited use of DOACs, although a wider utilization of DOACs is expected [22,23]. With regard to a wider use of NOACs in the setting of cancer patients with AF, similar to the setting of VTE [24], the risk of interactions has to be carefully evaluated for appropriate dosing [25].

There is a growing interest in the management of arterial thromboembolism and stroke in the setting of cancer [26], even independently of AF, but the nature of the disease and the many factors involved, including the type of cancer and its invasiveness, the type of medical and surgical treatments applied as well as use of the specific antineoplastic agents make the approach to this topic extremely complex [27,28].

AF is the most common arrhythmia observed during chemotherapy [29], with an associated two-fold risk of thromboembolic complications

Table 1
Clinical characteristics of patients, AF patterns and antiplatelet and antiarrhythmic drug treatment according to prescription of anticoagulation. Values are in form of number (%) when not otherwise indicated.

	Overall	AC -	AC +	OR	CI95%	p
N	380	225	155			
Female gender	147 (38,7)	85 (37,8)	62 (40)	1,10	0,72-1,67	0,662
Age ≥ 75 yrs	206 (55,2)	120 (53,3)	86 (55,5)	1,09	0,72-1,64	0,679
BMI median (IQ range)	26 (23–28)	25 (22–27)	27 (24–30)	1,09	1,03-1,15	0,002
Hypertension	244 (64,2)	139 (62,1)	105 (67,7)	1,29	0,83-1,96	0,256
Diabetes	68 (17,9)	44 (19,6)	24 (15,6)	0,75	0,44-1,30	0,313
Previous stroke/SE	48 (12,6)	27 (12,1)	21 (13.5)	1,14	0,62-2,11	0,667
CAD	87 (22,9)	53 (23,7)	34 (21,9)	0,91	0,56-1,48	0,695
PAD	126 (33,2)	67 (29,9)	59 (38,1)	1,44	0,93-2,22	0,098
HF (NYHA > 1 or LV EF ≤40%)	199 (52.4%)	108 (48)	91 (58,7)	1,54	1,02-2,33	0,040
LV EF ≤40%	28 (7,4)	15 (6,7)	13 (8,4)	1,28	0,59-2,77	0,528
Valvular disease	48 (12,6)	19 (8,5)	29 (18,7)	2,48	1,34-4,61	0,003
Previous VTE	61 (16.1)	20 (8.9)	41 (26.5)	3.67	2.05–6.56	< 0.001
Previous pulmonary embolism	31 (8,2)	10 (4,5)	21 (13,5)	3,35	1,53-7,34	0,002
Previous DVT	40 (10.6)	14 (6.3)	26 (16.8)	3.02	1.52–6.01	0.001
CKD	86 (22,7)	55 (24,6)	31 (20)	0,77	0,47-1,26	0,298
CKD-EPI < 50 ml/min/1.73 m^2	123 (32,4)	82 (36,4)	41 (26,5)	0,63	0,40-0,98	0,041
COPD	74 (19,5)	43 (19,2)	31 (20)	1,05	0,63-1,76	0,846
Liver disease	95 (25)	54 (24,1)	41 (26,5)	1,13	0,71-1,81	0,605
Thyroid disease	67 (17,6)	35 (15,6)	22 (20,6)	1,41	0,83-2,40	0,201
History of any bleeding	80 (21,1)	58 (25,9)	22 (14,2)	0,47	0,27-0,81	0,006
History of major bleeding	22 (5,8)	18 (8)	4 (2,6)	0,30	0,10-0,91	0,026
CHA_2DS_2-VASc score > 1 (> 2 if female)	369 (97,1)	196 (87.1)	148 (95.5)	3,13	1,33-7,34	0,006
HASBLED score > 2	128 (33,7)	74 (32,9)	54 (34,8)	1,09	0,71-1,68	0,693
Symptomatic AF (EHRA score > 1)	206 (55,2)	118 (53,6)	88 (57,5)	1,17	0,77-1,77	0,459
AF features						
Paroxysmal AF (vs other patterns)	84 (22,1)	52 (23,1)	32 (20,6)	0,87	0,53-1,42	0,569
First detected AF (vs previously known)	159 (41,8)	99 (44)	60 (38,7)	0,80	0,53-1,22	0,304
Rhythm control	101 (26,6)	67 (29,9)	34 (21,9)	0,66	0,41-1,07	0,091
Cardioversion (ECV + PhCV)	71 (18,7)	47 (21)	24 (15,5)	0,69	0,40-1,18	0,177
Antiarrhythmic and antiplatelet drugs						
Antiplatelet drugs	71 (18,7)	53 (23,6)	18 (12)	0,44	0,25-0,79	0,005
AAD	46 (12,1)	34 (15,1)	12 (7,7)	0,47	0,24-0,94	0,031

List of abbreviations; AC: anticoagulation; AF: atrial fibrillation; OR: odds ratio; CI 95%: 95% confidence interval; BMI: body mass index; SE: systemic embolism; CAD: coronary artery disease; PAD peripheral artery disease; ECV: electrical cardioversion; PhCV: pharmacological cardioversion; HF: heart failure; NYHA: New York Heart Association; EF: ejection fraction; VTE: venous thromboembolism; DVT: deep vein thrombosis; CKD: chronic kidney disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration group formula; COPD: chronic obstructive pulmonary disease; AAD: antiarrhythmic drug.

[2]. Also, the association between AF and surgery is well known [30]. Some observational studies based on administrative data [2,31,32] or market scans [22] have been published, but in these studies detailed data on metastatic involvement were missing and no analysis of anticoagulated vs. non anticoagulated patients were presented.

The first finding of the study was that anticoagulation was prescribed in patients at high risk of thromboembolic complications and with a higher BMI, suggesting lack of cachexia and a better clinical status. In effect, our data show that BMI, valvular heart disease and history of VTE are independent predictors of anticoagulation prescription. In the literature focused on outcome of cancer patients, BMI is an important variable, since it was recognized as associated with better of survival in lung cancer [33,34]. In our study prevention of thromboembolic complications by anticoagulation therapy was instituted in patients with a greater likelihood of survival free of cancer progression [35]. Moreover, the data show that lack of high risk features (valvular heart disease and no VTE) and worse clinical status (i.e. cachexia) did not lead to prescription of anticoagulation.

Our data have to be interpreted taking into account that the appropriate decision making on anticoagulation for preventing AF-associated stroke was not currently defined. Cancer per se is not an absolute contraindication to oral anticoagulants, although the issue of relative

Table 2
Characterization of cancer disease, stage and treatment according to prescription of anticoagulation.

	Overall	AC -	AC +	OR	CI95%	p
Cancer						
Digestive system cancer	69 (18,2)	40(17,8)	29 (19,7)	1,06	0,63-1,81	0,817
Respiratory system cancer	90 (23,7)	53 (23,6)	37 (23,9)	1,02	0,63-1,65	0,943
Hemolinphopoietic system cancer	126 (33,2)	71 (31,6)	55 (35,5)	1,19	0,77-1,84	0,424
Other cancer	95 (25)	61 (27,1)	34 (21,9)	0,76	0,47-1,22	0,252
Stage						
Metastasis	219 (57,6)	136 (60,4)	83 (53,5)	0,75	0,50-1,14	0,181
Treatment						
Radiotherapy	108 (28,4)	70 (31,1)	38 (24,5)	0,72	0,45-1,14	0,161
Surgery	195 (51,3)	117 (52)	78 (50,3)	0,94	0,62-1,41	0,748
Chemotherapy	256 (67,4)	148 (65,8)	108 (69,7)	1,19	0,77-1,86	0,426

List of abbreviations; AC: anticoagulation; OR: odds ratio; CI 95%: 95% confidence interval.

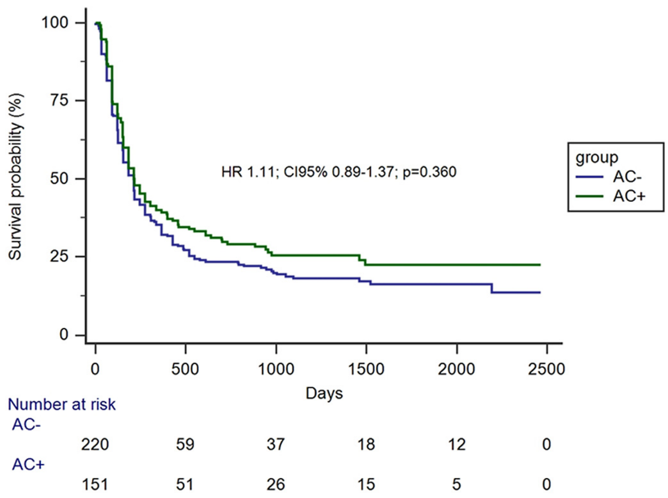

Fig. 1. Cumulative survival according to prescription of anticoagulants (AC+) or no prescription of anticoagulants (AC-). The survival curves did not significantly differ (HR 1.11; CI 95% 0.89–1.37; p = .360).

contraindications is well debated and has been subject to variable interpretation [36,37].

Decision making on anticoagulation in cancer patients with AF is particularly challenging, given the risk of complications, mainly major bleeding, related to the effects of anticoagulants in the presence of active malignancy with metastasis [38]. Moreover, the value of CHA_2DS_2VASc score in prediction AF-associated stroke in patients with cancer is unknown, and according to a study based on administrative data, that did not take into account prophylactic treatment with anticoagulants, predictive value may be low [32]. However, the rate of stroke in patients with malignancies appears to be higher when compared with the general population [30] and both cancer and AF are independent risk factors for ischemic stroke, thus making reasonable to consider anticoagulant therapy.

Our study shows a reasonable pattern of anticoagulant prescription, since VTE shares common risks with AF and prognostic significance [39] and therefore potentiates the need for anticoagulants.

The second finding of our study relates to the association between anticoagulation and mortality in the specific setting of cancer patients with active malignancies. Our data show that anticoagulation per se is not associated with increased mortality in cancer patients. The factors that in our analysis that emerged as independently associated with mortality were the specific type of malignancy (hemolymphopoietic cancer associated with lower risk of death, gastrointestinal system cancer associated with increased risk of death) and the burden of comorbidities, as described to CHA_2DS_2-VASc score. This finding was observed in the whole population, as well as in analysis of subgroups.

Our results are of clinical interest, even with the limitations of their observational nature, since according to published literature, patients with cancer taking warfarin have an increased risk (up to twofold) of major and fatal bleeding, as compared to non-cancer patients taking warfarin [40]. Therefore a potential impact of anticoagulation on the risk of bleeding and death is often assumed. An increased risk of bleeding in cancer patients vs. non cancer patients with AF was not confirmed in a recent analysis from the Danish national registry [41].

Our findings extend to a wider range of cancer patients the prior

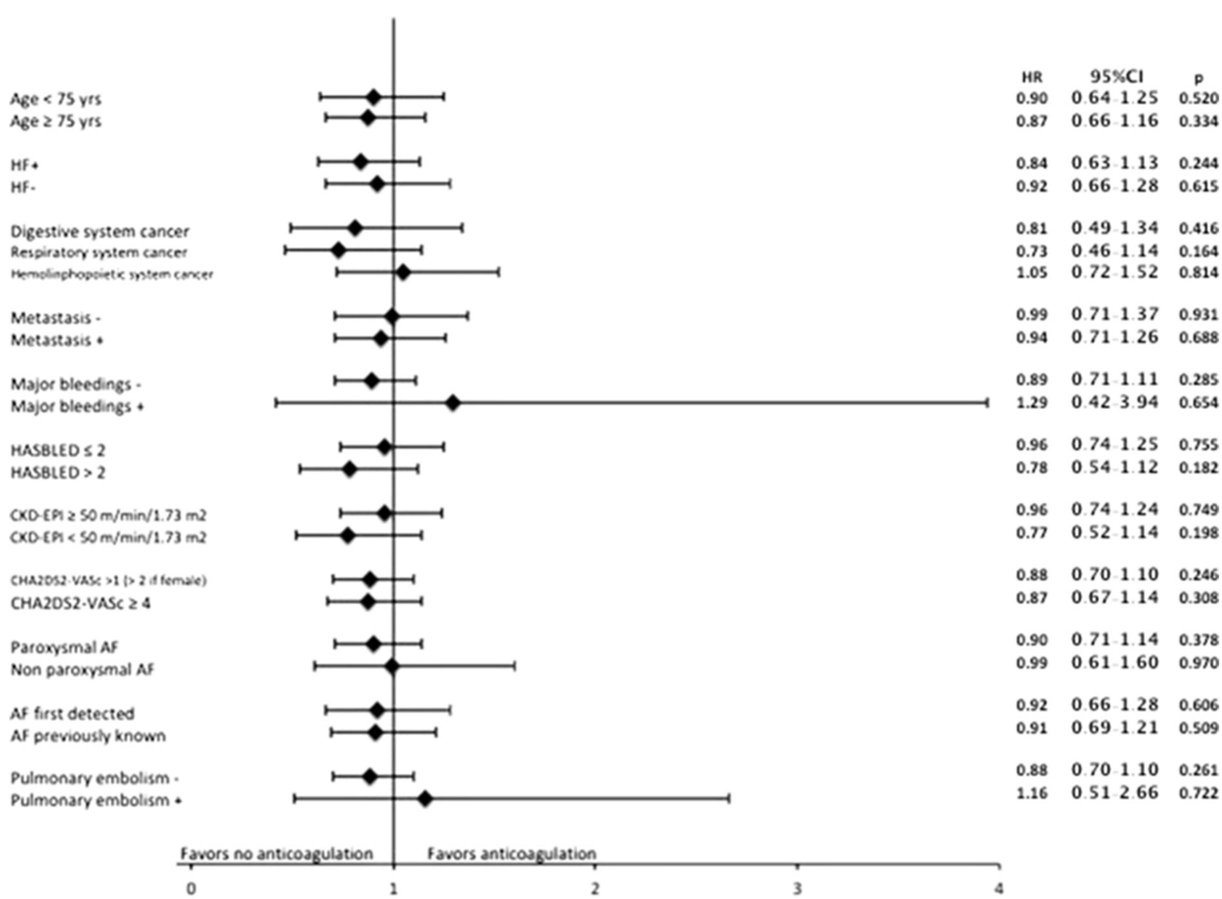

Fig. 2. Forest plot of the survival analysis according to anticoagulation. The table to the right side shows hazard ratio (HR) 95% confidence interval (95%CI) a statistical significance, meaning thereby the absence of significant differences in the various subgroups. Of note, p for interaction is always not statistically significant. List of abbreviations: HF: heart failure; AF: atrial fibrillation.

Table 3
Independent predictors of mortality according to multivariate Cox regression.

	HF and Age			CHA_2DS_2-VASc > 1 (> 2 if female)			CHA_2DS_2-VASc ≥ 4		
	HR	CI 95%	p	HR	CI 95%	p	HR	CI 95%	p
Respiratory system cancer	**1,56**	**1.14–2.14**	**0,005**	**1,56**	**1.14–2.13**	**0,005**	**1,62**	**1.18–2.21**	**0,003**
HF	**1,36**	**1.09–1.70**	**0,006**	na	na	na	na	na	na
Age ≥ 75 yrs	**1,34**	**1.08–1.67**	**0,008**	na	na	na	na	na	na
CHA_2DS_2-VASc > 1 (> 2 if female)	na	na	na	1,45	0.98–2.15	0,067	na	na	na
CHA_2DS_2-VASc ≥ 4	na	na	na	na	na	na	**1,33**	**1.06–1.67**	**0,013**
Hemolinphopoietic system cancer	**0,68**	**0.48–0.97**	**0,032**	**0,67**	**0.48–0.95**	**0,026**	**0,70**	**0.50–0.99**	**0,049**
Digestive system cancer	**1,41**	**1.02–1.96**	**0,038**	1,35	0.97–1.86	0,074	**1,43**	**1.03–1.98**	**0,032**
Paroxysmal AF	1,21	0.93–1.57	0,161	1,24	0.95–1.61	0,115	1,21	0.93–1.58	0,147
Presence of metastasis	1,11	0.82–1.49	0,512	1,05	0.78–1.41	0,762	1,10	0.82–1.47	0,548
Radiotherapy	1,07	0.84–1.37	0,595	1,07	0.84–1.37	0,593	1,08	0.85–1.38	0,529

List of abbreviations; AF: atrial fibrillation; HR: hazard ratio; CI 95%: 95% confidence interval; HF: heart failure.
In the first model we introduced among the variables age and heart failure but not the CHA_2DS_2-VASc score. In the second model we considered a CHA_2DS_2-VASc score suggestive of patients at risk of stroke, according to guidelines [11]. In the third model we considered a very high CHA_2DS_2-VASc score. The statistically significant variables in the different scenarios are highlighted in bold style.

observations of Ianotto et al., who found no differences in mortality in patients with myeloproliferative diseases when treated with DOACs or low-dose aspirin [42]. In their series, a lower mortality when compared to our patients was found, maybe reflecting a population with a better prognosis. Our mortality data were consistent with other large randomized series of patients treated with anticoagulation [6].

In our study we did not focus on the specific causes of death (cardiovascular or non-cardiovascular) and we did not investigate the rate of non-fatal stroke or bleedings in our cohort. Therefore, we cannot directly evaluate the real impact of anticoagulants on clinical events and quality of life. Despite the limitations of the sample size and the consequent limited statistical power, the survival curves for all-cause mortality suggest that use of anticoagulants according to physicians' evaluation was not associated with an increase in all-cause mortality in our population of AF patients with active cancer, even in the subgroup with metastatic malignancies. Prevention of the risk of stroke is a major goal in AF patients but fatal strokes accounts for only 7% of the deaths occurring in a general population of patients with AF [43] so our findings of no association between anticoagulation and increased mortality is reassuring that current practice of anticoagulants prescription is reasonably safe, at least taking into account a robust end point such as all-cause mortality, even in a population with increased risk of bleeding such as patients with active cancer [9]. Accordingly, the results of our study may be helpful for physicians taking into consideration prescription of anticoagulants in the difficult and complex setting of patients with active malignancy.

Our survival analysis is based on a retrospective analysis of prospectively collected data and this constitute a limitation, but on the other hand the underlying (cancer-related) pathology and the severity of the outcome, with a median survival of 8 months, indicate a high competing risk for death, making it challenging the planning of long term prospective controlled trials evaluating anticoagulants in AF associated with active cancer.

5. Limitations

Our study has a series of limitations related to its retrospective nature, including potential bias in data collection, recoding process, and effect of confounding. However, data were retrieved from clinical records, and the quality of the Institutional dataset is confirmed by the small percentage of patients lost to follow-up. Our data on follow up are limited to survival, with no details on complications after discharge. In view of these characteristics our findings, related to a complex field such as clinical oncology, have to be considered as exploratory.

As in any epidemiological study on AF not including continuous monitoring of the atrial rhythm through an implanted device [44–46], asymptomatic AF, which is common, particularly in the elderly [47], could have passed unnoticed, especially if in paroxysmal form.

6. Conclusions

The prescription of anticoagulants in patients with AF and active cancer was suboptimal, with one fourth of the patients not treated with anticoagulants and one third using LMWH at prophylactic, non-therapeutic doses. Only few variables, corresponding to BMI, valvular heart disease and previous venous thromboembolism, predicted prescription of ACs in a “real world” cohort of cancer patients. Prescription of ACs was not associated with all-cause mortality, even in the subgroup with metastasis.

Conflict of interest statement

For all the authors none declared with regard to this specific article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.10.012.

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