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Patients with cancer and atrial fibrillation treated with doacs: A prospective cohort study

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ABSTRACT

Background: Limited data are available on the use of direct oral anticoagulants (DOACs) in patients with cancer and atrial fibrillation (AF).
Methods: Consecutive patients with non-valvular AF treated with DOACs were enrolled in a prospective cohort with the aim of evaluating thromboembolic (ischemic stroke or transient ischemic attack or systemic embolism) and major bleeding (MB) events according to presence and type of cancer. The risk of study outcomes over time was compared using Kaplan-Meier method and log-rank test or Cox proportional hazards regression.
Results: 2304 patients with non-valvular AF receiving DOACs were enrolled and 16 excluded: 2288 analysed of whom 289 (12.6%) had cancer. Gastrointestinal (21%), genitourinary (15%), prostate (15%), haematological (14%), breast (13%), and lung (8%) were the more frequent sites of cancer.
After a mean follow-up of 451 days, thromboembolic events occurred in 2.1% and 0.8% patient-year of cancer and non-cancer patients (adjusted-HR 2.58, 95% CI 1.08–6.16, $p = 0.033$). The rate of MB was 6.6% and 3.0% patient-year in cancer and non-cancer patients (adjusted-HR 2.02, 95% CI 1.25–3.27, $p = 0.004$). The differences in bleeding were mainly accounted for by bleeding at gastrointestinal and genitourinary sites. No significant differences were found concerning the rates of non-cancer-related mortality, fatal bleeding or fatal thrombotic events.
Conclusions: In this study, the higher bleeding risk found in cancer compared to non-cancer patients was mainly due to an excess of bleeding at gastrointestinal and at genitourinary sites. Larger studies on the optimal management of cancer patients with AF are needed.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and an important risk factor for stroke, heart failure and dementia [1–3]. The incidence of AF is known to be related to ageing, cardiovascular conditions (such as hypertension, heart failure, valvular disease) and non-cardiovascular conditions (such as diabetes, thyroid dysfunction, chronic pulmonary or kidney diseases). More recently, a correlation has been reported between AF and cancer [4,5]. The prevalence of a concomitant history of cancer was reported up to 20% of AF patients in recent registries or cohort studies [6,7].

For several decades, vitamin K antagonists (VKAs) have been used in patients with AF to reduce the incidence of stroke or systemic embolism. Direct oral anticoagulants (DOACs) are being increasingly prescribed and are now recommended as the first choice anticoagulant agents in patients with non-valvular AF. In patients affected by both AF and cancer, antithrombotic treatment is challenging. Cancer patients are at high risk of both thromboembolic and bleeding events for the direct interaction of cancer with the coagulation system and for the effect of chemotherapy [5]. Clinically relevant data on antithrombotic treatment in cancer patients with AF are limited and only a position paper examines this topic [8]. Indeed, only a few number of cancer patients (those with presumed long life expectancy) were included in the DOAC phase III trials on AF. Post-hoc analyses from these studies led to inconclusive results concerning the thrombotic and bleeding risks of cancer and non-cancer patients as well as in cancer patients receiving DOACs or VKAs [9,10]. A retrospective analysis of a Danish cohort of AF patients on oral anticoagulant treatment showed a similar rate of

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thromboembolic and bleeding complications in cancer and non-cancer patients [7]. However, among cancer patients thrombotic and bleeding risks also differ according to the status of the neoplastic disease.

The aim of this study was to prospectively evaluate the risk of thromboembolic and bleeding events according to presence and type of cancer in patients with non-valvular AF treated with DOACs.

2. Methods

2.1. Study design, setting and patients

Consecutive in- and out-patients with confirmed non-valvular AF who were prescribed with DOACs in four Italian hospitals from August 2013 to March 2017 were enrolled in a prospective cohort study. These patients could be either anticoagulation naïve or switched from prior treatment with VKAs. The choice of the individual DOACs was in charge of the attending physician. Exclusion criteria were refusal of informed consent and a valvular AF. AF was defined 'valvular' if it was related to rheumatic valvular disease (predominantly moderate or severe mitral stenosis) or associated with prosthetic heart valves [11]. The study period started at the time of the DOAC prescription.

Patients included in the study were categorized as it follows: i) non-cancer patients those without clinical evidence of cancer; ii) cancer patients. Cancer patients were categorized as iii) patients with active cancer, at time of inclusion in the study, in presence of a diagnosis of cancer or any anti-cancer treatment within 6 months before the study inclusion, or recurrent locally advanced or metastatic cancer; iv) patients with history of cancer, at time of inclusion in the study, those with a cancer not satisfying the criteria for active disease. Patients with a cancer diagnosed during the study period, i.e. v) incidental cancer, were subsequently included in the group of active cancer patients.

The study was approved by the Ethical Committee and/or Institutional Review Boards of the participating centres.

2.2. Study outcomes

The primary outcomes of the study were thromboembolic events (ischemic stroke, transient ischemic attack [TIA] or systemic embolism) and major bleeding all occurring while on treatment with DOACs.

Major bleeding was defined according to the ISTH criteria [12].

Ischemic stroke was defined as a new, focal neurological deficit of sudden onset, lasting at least 24 h, that is not due to a readily identifiable non-vascular cause (i.e., brain tumor, trauma). All strokes during the study had to be assessed by imaging or autopsy and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology (ACC) [13].

Additional outcomes were: 1) clinically relevant non-major bleeding (CRNMB), defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of DOAC; 2) clinically relevant bleeding, defined as the composite of major and of clinically relevant non-major bleedings; 3) acute myocardial infarction (AMI) defined as an appropriate clinical situation suggestive of a myocardial infarction (e.g., abnormal history, physical examination) and/or or new ECG changes and/or elevation of Troponin T or $I \geq 2 \times$ ULN; 4) all cause mortality; 5) non-cancer related mortality; 6) the composite of fatal bleeding and fatal thrombotic events.

2.3. Data collection

For all included patients the following data were collected: age, gender, comorbidities (hypertension, congestive heart failure, diabetes, previous stroke, vascular diseases, renal or liver failure, previous major bleeding), type and dose of DOACs, date of DOAC prescription, concomitant medications (non-steroidal anti-inflammatory and antiplatelet agents) and creatinine clearance (estimated by Cockcroft–Gault formula) [14]. Risks for stroke and bleeding were assessed according to $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores, respectively [11]. In patients with cancer, data on cancer site, date of diagnosis, anti-cancer therapy, the presence of metastases, locally advanced disease and cancer recurrence were also collected.

All patients entered a scheduled follow-up program with medical visit or, if not possible, by phone calls every 6 months or whenever clinical issues occurred. At each follow-up visit, data on clinical outcomes as thromboembolic and bleeding events were collected as well as any adverse events, occurrence of cancer and treatment adherence. Thrombotic and bleeding risks were reassessed at each contact. All the events were locally adjudicated.

2.4. Statistical analysis

Main basal characteristics and outcome events of patients with cancer and of those with non-cancer were compared. Categorical data were reported as frequencies and continuous data as mean ± standard deviation (SD). Categorical data were compared with the use of χ^2 test and continuous data with the use of *t*-test. The reported *p*-values were based on two sided tests.

Outcome event rates were reported as proportions of patient-year. Patients remained in the analysis until death, or the first between withdrawal of anticoagulant treatment or occurrence of a study outcome event (thromboembolic event or major bleeding). The risk of study outcomes over time in cancer and non-cancer patients was compared using survival analysis (Kaplan-Meier method and log-rank test or Cox proportional hazards regression). Analyses were adjusted for significant differences among the two population.

Patients were analysed according to presence of cancer or absence of cancer. Patients were also analysed according to cancer type: history of cancer and active cancer. Patients with active cancer were further categorized according to: active cancer at baseline or incidental cancer.

Statistical analysis was performed with SPSS software (version 20) and values < 0.05 were considered statistically significant.

3. Results

Overall, 2304 patients were considered for the analysis, of whom 16 were excluded and 2288 were finally included in the analysis of baseline features (eFigure 1). Nine-hundred and fifty-two patients (41.6%) were switched from prior treatment with VKAs to DOACs. Dabigatran, rivaroxaban and apixaban were prescribed in 30, 35 and 35% of patients, respectively.

Overall, 289 patients had cancer (12.6%): active cancer in 104 (4.5%) and history of cancer in 185 (8.1%). An active cancer was present at time of DOAC prescription in 68 patients (2.9%): 13 had the diagnosis made in the 6 months before DOAC was started, 33 were on anti-cancer therapy, 18 had a metastatic disease and 8 had a recurrence of cancer. Four out of these patients had more than one criteria for active cancer. In 36 patients (1.6%), cancer was diagnosed during the study period (12 patients with metastatic disease). The mean time from study inclusion to cancer diagnosis was 238 ± 141 days. Thirty-three patients (92%) received the cancer diagnosis in the first year from inclusion (16 patients in the first 6 months). The occurrence of major gastrointestinal bleeding led to cancer diagnosis in 6 patients.

In the cancer group, sites of cancer were gastrointestinal (20.8%), genitourinary (15.2%), prostatic (15.2%), haematological (13.8%), breast (13.1%), lung (8.0%), skin (3.5%), pancreas (2.4%), brain (1.7%), thyroid (1.4%), liver (1.4%) and other (3.5%). Cancer site among patients with incidental cancer was as it follow: gastrointestinal in 33.3%, genitourinary in 16.7%, lung in 16.7%, haematological in 11.1%, pancreas in 8.3%, liver in 5.5% and prostatic, skin and brain in 2.8% each (eFigure 2).

Male gender and age ≥ 75 years were more frequent in cancer compared to non-cancer patients. No other significant difference was observed. Baseline features of cancer and non-cancer patients are detailed in Table 1. Baseline features among different cancer groups are reported in eTable 1.

3.1. Outcome events

Complete outcome data were available in 2200 patients of whom 280 with cancer (eFigure 1). The mean follow-up was 451.2 days: 441.3 ± 267.6 in cancer and 452.6 ± 254.8 in non-cancer patients ($p = 0.49$).

The incidence of thromboembolic events during treatment with DOACs was 2.1% patient-year (95% CI 1.0 to 4.2) in cancer and 0.8% patient-year (95% CI 0.5 to 1.3) in non-cancer patients (adjusted-HR 2.58, 95% CI 1.08 to 6.16) Fig. 1a. Individual components of the outcome data according to cancer and non-cancer are reported in Table 2.

The incidence of major bleeding was 6.6% patient-year (95% CI 4.4 to 9.8) in cancer and 3.0% patient-year (95% CI 2.4 to 3.8) in non-cancer patients (adjusted-HR 2.02, 95% CI 1.25 to 3.27) Fig. 1b. The rate of clinically relevant bleeding was significantly higher in cancer (18.2% patient-year, 95% CI 14.4 to 22.9) compared to non-cancer patients (10.6% patient-year, 95% CI 9.5 to 12.0): adjusted-HR 1.65, 95% CI 1.23 to 2.19.

In the non-cancer group, 16 patients experienced an AMI (0.7% patient-year, 95% CI 0.4 to 1.1), one patient in the cancer cohort experienced a venous thromboembolic event (0.3% patient-year, 95% CI 0.1 to 1.7).

As expected, overall mortality was higher in cancer compared to non-cancer patients (10.9 vs 4.5% patient-year, adjusted-HR 2.25, 95% CI 1.55 to 3.28). Non-cancer-related mortality was non-significantly

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