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EDITORIAL COMMENT

Atrial Fibrillation in Active Cancer

A BLITZ to Expect and Manage

Gerasimos Filippatos, MD, Dimitrios Farmakis, MD, PhD

Atrial fibrillation (AF) and cancer frequently coexist, the one complicating the management and worsening the prognosis of the other.[1-3] Given the growing incidence of both conditions,[4,5] their coexistence is expected to have an increasing impact on clinical practice. In this issue of *JACC: Advances*, Gulizia et al[6] shed some new light on the topic by reporting data from the BLITZ-AF Cancer Registry. The investigators enrolled 1,514 patients from 6 European countries with a cancer diagnosis within 3 years and electrocardiographically-confirmed AF within 1 year.

The first important finding of the study is the high prevalence of cardiovascular (CV) risk factors and disease among patients with cancer and AF. Indeed, 72% of patients had arterial hypertension, 40% had hypercholesterolemia, 22% had diabetes, 11% had active smoking, and 58% had obesity. Similarly, 21% had a history of heart failure, 18% had coronary artery disease, 39% had valvular heart disease, and 10% had peripheral arterial disease. Data from the earlier CardioTox registry also shows that CV risk factors are prevalent and associated with increased all-cause mortality[7]; they also carry a higher risk of cancer therapy-related CV disease, thus interfering with anticancer treatment and jeopardizing its outcomes, which may partly explain the resulting increased mortality.[7] At the same time, the frequent coexistence of cancer with AF and CV disease stresses their interrelated pathophysiology, guided by aging and other common predisposing factors.[8]

Another finding of the BLITZ-AF registry stressed by the authors is the underuse of proper antithrombotic therapy, particularly before cardiology consultation, despite a median CHA_2DS_2VASc score of 3 and a median HAS-BLED score of 1. However, after consultation, 76% of patients were on direct oral anticoagulants (DOAC) or vitamin K antagonists, and some additional patients were receiving low molecular weight heparin (LMWH). Two factors should be considered in order to better understand this finding: the actual thromboembolic and bleeding burden of these patients and the challenges regarding antithrombotic therapy, particularly in patients with an active malignancy.[9]

Starting with the challenges (**Figure 1**), active cancer may carry an increased hemorrhagic risk due to tumors in the gastrointestinal (GI) or genitourinary track, intracranial disease, extensive hepatic disease with coagulation defects, renal function impairment, and thrombocytopenia due to bone marrow infiltration or myelotoxicity of anticancer therapy.[9] Active cancer may also carry an increased thrombotic risk, which is particularly true for certain cancer types such as pancreatic or gastric adenocarcinomas.[9] Anticancer therapies including platinum compounds, anti-angiogenetic agents, immunomodulatory drugs or hormonal therapies may further increase the risk of thromboembolism.[9] Therefore, the general scores used for the prediction of hemorrhagic and thrombotic risks, although they seem to perform rather well,[2] may not be accurate in patients suffering from certain types of active cancer or being treated with specific anticancer therapies.[9] Therefore, decision-making on anticoagulation requires consideration of additional factors in patients with an active malignancy.[10] Another issue that may complicate anticoagulation therapy is the potential interactions between anticancer therapies and anticoagulants. For example, DOAC use is uncertain in combination with

From the Heart Failure and Cardio-Oncology Unit, Department of Cardiology, Athens University Hospital Attikon, National and Kapodistrian University of Athens Medical School, Athens, Greece.
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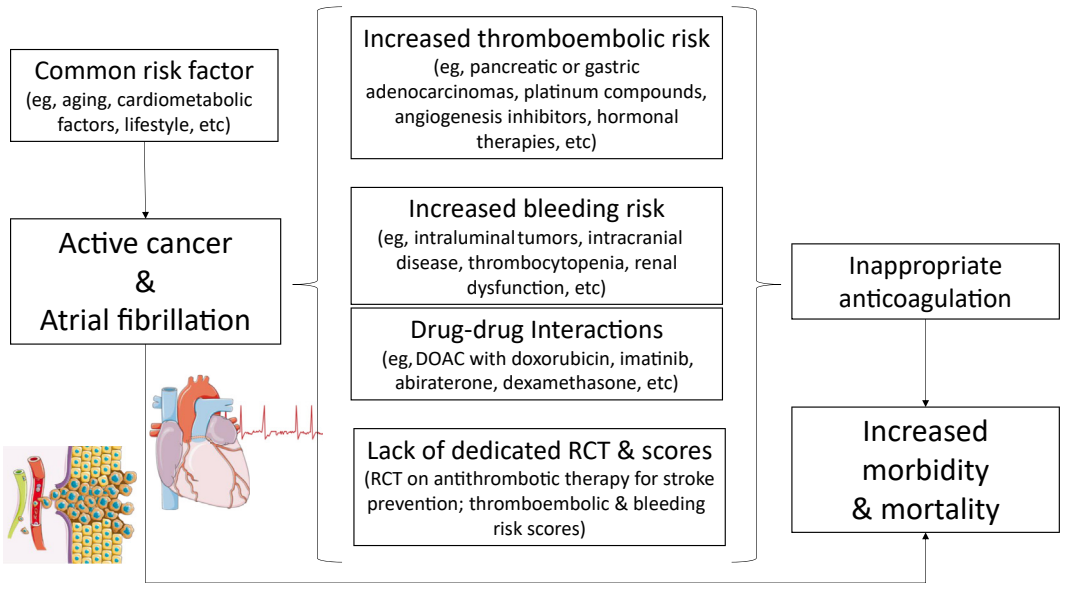
FIGURE 1 Atrial Fibrillation and Active Cancer Frequently Coexist, Partly Because of Common Risk Factors



Their coexistence complicates, on the one hand, the prognosis of each other, leading to worse outcomes; on the other, it poses important challenges in clinical practice that may, in turn, lead to inappropriate anticoagulation strategies, thus increasing further morbidity and mortality. DOAC = direct oral anticoagulants; RCT = randomized controlled trials.

commonly used agents such as anthracyclines, vinorelbine, imatinib, sunitinib, vandetanib, abiraterone, or dexamethasone, as the latter drugs are strong P-glycoprotein inducers or inhibitors.[9] A further challenge is the lack of compelling evidence on the efficacy and safety of anticoagulants for the prevention of stroke or systemic embolism in patients with active cancer. Although observational studies have provided evidence supporting the general use of DOAC in patients with cancer and AF,[11] randomized trials are missing. The seminal DOAC trials in AF largely excluded patients with malignancies, and their post-hoc analyses focusing on cancer hardly included any challenging cases with active malignancies.[9] Therefore, guideline recommendations are mainly based on experts' opinions.[12]

Regarding the thrombotic and bleeding burden in patients with active cancer, in BLITZ-AF, previous thromboembolic and hemorrhagic events occurred in 14% and 10% of patients, respectively.[6] This is roughly consistent with the fact that the CHA_2DS_2-VASc score was 4 or higher in 42% of patients and the Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol was 3 or higher in 11% of patients. However, as the risks of thrombosis and bleeding differ between patients with "active cancer" and those with a "history of cancer,"[13] the definition of active cancer is particularly important. Cancer is considered active when recently diagnosed, currently or recently treated, recurrent, locally advanced, or metastatic.[14] In BLITZ-AF, patients with a malignancy diagnosis of up to 3 years before recruitment were considered as having "recent" and therefore "active" cancer.[6] In many patients with a malignant disease, however, treatment may have been successfully completed, and the disease may achieve long-term remission within <1 year after diagnosis. Therefore, it has been proposed to define as "recent" a malignant disease that has been diagnosed or treated up to 6 months before.[14] As a result, the magnitude of the problem may be even greater than what is depicted in the BLITZ-AF registry.

In the report of BLITZ-AF, antiplatelet therapy and LMWH are grouped together, while the proportion of patients receiving LMWH and the dose of LMWH (prophylactic or therapeutic) are not reported.[6] However, in active cancer, it is a common practice to temporarily replace DOAC with LMWH at therapeutic dose over a period during which DOAC use remains uncertain, as in the case of drug-drug interactions, not resected GI or genitourinary track tumors, GI toxicity, or thrombocytopenia between 25,000 and 50,000 $\times$ 10^9/L, an approach also

supported by guideline recommendations.[12] In general, in patients with an active malignancy, the anticoagulation strategy may need to be adjusted according to the risks of thrombosis and bleeding, drug-drug interactions, and patient preferences, as indicated by the acronym TBIP (T for thrombosis, B for bleeding, I for interactions, and P for patients), which was introduced earlier and adopted by the 2022 European Society of Cardiology guidelines.[10,12]

In conclusion, AF is prevalent among patients with cancer, affecting their outcomes and complicating their management, while its burden is expected to grow. Therefore, screening for AF and the proper management of anticoagulation are crucial. On the other hand, making a distinction between active and nonactive cancer is also important in terms of antithrombotic therapy, both in clinical practice and in clinical trials.

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ADDRESS FOR CORRESPONDENCE: Dr Gerasimos Filippatos, Department of Cardiology, Athens University Hospital Attikon, 1 Rimini St, Athens, Greece. E-mail: gfilippatos@gmail.com.

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