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MALIGNANCY AND ATRIAL FIBRILLATION – HARDSHIPS TO MANAGE BLEEDING AND THROMBOEMBOLIC RISK

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ABSTRACT

Atrial fibrillation (AF) and cancer are conditions that often coexist. Both of them, as well as their treatment, are connected with changes in coagulation processes, increasing the risk of bleeding or thromboembolic events. Despite that, the level of evidence supporting existing recommendations remains low. (Lyon et al., 2022)
In this study, we focused on analyzing the existing literature on the assessment and management of bleeding and thromboembolic risk, with the aim of establishing an evidence-based approach to managing bleeding and thromboembolic risk in oncology patients with AF.
Cancer is widely associated with a hypercoagulability state, but in the case of AF and stroke risk, it does not seem to be higher in general in comparison with non-cancer populations. It changes when individual cancer types are analyzed. As for the bleeding risk, many malignancies seem to increase it. Another challenge is that the existing risk scores often show lower predictive value for patients with recent malignancy. There is a need for individual assessment in every patient, but we lack the tools to make it easier for clinicians. Cardio-oncology guidelines addressing AF do exist, but the level of evidence supporting them remains low; thus, further research in this field is needed.

KEYWORDS

Atrial Fibrillation, Cancer, Anticoagulation, Bleeding Risk, Thromboembolism

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List of abbreviations:
AF – atrial fibrillation
CV – cardiovascular
OACs – oral anticoagulants
NOACs – non-vitamin K oral anticoagulants
VKAs – vitamin K antagonists
TIA – transient ischemic attack

Introduction

In recent years, we have seen great advances in oncology. Patients with malignancy tend to live longer due to earlier diagnosis and more effective treatment. This leads to an increasing population of elderly patients with coexisting cancer and cardiovascular diseases - atrial fibrillation is one of them. These conditions often coexist due to shared risk factors and similar demographics. (Menichelli et al., 2021) Managing them at once is challenging, because of the risk of stroke in AF and thromboembolic and bleeding risk connected to malignancy itself. Assessing these risks is a complex issue, followed by clinicians' concerns about interactions between oral anticoagulants and antineoplastic agents. (Beavers et al., 2022) The CHA_2DS_2–VASc (congestive heart failure, arterial hypertension, age ≥ 75 years, diabetes mellitus, stroke/thromboembolism, vascular disease, age 65–74 years, sex category) score appears to have lower predictive value in oncologic patients, which may further complicate the task.

This review aims to summarize updates and new research on the assessment and management of coexisting cancer and atrial fibrillation.

Methods

A literature review was conducted, analyzing studies from the PubMed database, with particular focus on articles published after the 2022 ESC Cardio-oncology Guidelines (Lyon et al., 2022).

Pathophysiology

Atrial fibrillation is a condition where an unorganized supraventricular electrical activity impairs the contractility of atrial muscle fibers, causing a slowdown in the blood flow. With coexisting endothelial dysfunction (marked by increased levels of von Willebrand and E-selectin), the risk of thrombus formation increases, potentially leading to an ischemic stroke. (Violi et al., 2014)

As far as we know, cancer may increase the risk of developing atrial fibrillation. It is the highest in the first 3 months following cancer diagnosis. (Mauriello et al., 2025; Menichelli et al., 2021) There are several mechanisms linking these conditions, sometimes in a bidirectional way. One of them is inflammation. Active cancer may disturb the body's natural homeostasis by increasing the production of proinflammatory chemokines and cytokines, such as IL-1 and IL-6, as well as C-reactive protein. These agents have been shown to be risk factors for the development of AF. (Leiva et al., 2021) Additionally, many patients with cancer experience pain, which also triggers an inflammatory reaction and causes an autonomic system imbalance, increasing the risk of AF even further. (Farmakis et al., 2014) In addition, oncology patients often have high CHA_2DS_2-VASc scores at baseline (Matetic et al., 2023; Ullah et al., 2023), and cancer and AF share several important risk factors. (Menichelli et al., 2021)

Cancer treatment can also predispose to the onset of AF. Surgeries (especially thoracic ones) increase the risk of AF, possibly due to mechanical stimulation of the pericardium, inflammation, anesthetic medications, and disturbances in electrolyte levels. Also, exposure to ionizing radiation may increase the risk of vascular cell inflammation and tissue fibrosis, including myocardium if irradiated. This can lead to impaired electrical conduction in atria and predispose to AF. (Menichelli et al., 2021) The maximum radiation dose to the pulmonary veins appears strongly associated with AF development. In the study of Butler et al., the highest incidence of AF occurred in non-small cell lung cancer and esophageal cancer patients, those with the highest doses of radiation administered. (Butler et al., 2024)

Chemotherapy agents influence the heart as well and can be the cause of AF onset. The most well-known for their toxicity to the myocardium are anthracyclines, followed by tyrosine kinase inhibitors, alkylating agents, and others. (Mauriello et al., 2025)

Risk of thromboembolism vs bleeding

Malignancy is widely associated with hypercoagulability, being an important part of Geneva and Wells scores for venous thrombosis and pulmonary embolism. (Khan et al., 2021) However, oncology patients are a wide and nonhomogeneous group, and the risk of stroke in AF in this population is a separate issue. Different types of cancer vary in risk of bleeding and thromboembolic events (D'Souza et al., 2018). El-Rayes et al. showed that a higher risk of bleeding is common among oncologic patients, although those with breast cancer and lymphoma had a similar risk of bleeding as cancer-free control subjects. (El-Rayes et al., 2025) They concluded that their findings support the current European Society of Cardiology cardio-oncology guidelines (Lyon et al., 2022) approach to stroke prophylaxis in AF that more factors than just CHA_2DS_2-VASc and solely the presence of malignancy should be considered. The 2023 study of Ajabnoor et al. showed that a history of hematological, lung, prostate, or colorectal cancers was associated with increased risk of major bleeding events. (Ajabnoor et al., 2023) The paper published by Ullah et al. in 2023 seems to support the evidence that hematological and lung cancer increase bleeding risk irrespective of anticoagulation. (Ullah et al., 2023)

There even has been a study that focused on bleeding after starting anticoagulation for atrial fibrillation and asked whether it can be associated with new diagnoses of malignancy. They found out that in anticoagulated patients with AF, bleeding was strongly associated with new cancer diagnoses. Patients with antecedent bleeding were diagnosed at earlier stages of the disease. (Grewal et al., 2025)

2022 ESC cardio-oncology guidelines proposed a structured approach to anticoagulation for AF in patients with cancer called **TBIP** (**T**hrombotic risk, **B**leeding risk, **I**nteractions between the drugs, **P**atient access and preferences). (Lyon et al., 2022) It still includes using CHA_2DS_2-VASc score but puts emphasis on individual assessment of thromboembolic and bleeding risk considering cancer type, stage and prognosis. It also reminds of the need for regular reassessment of the risks due to possible changes in the patient's characteristics. Including a summary of the most important factors influencing the above risks in the recommendations would serve as an advisory tool for clinicians in deciding whether to initiate thromboembolism prophylaxis with oral anticoagulants (OACs).

Also, malignancies differ by age and comorbidities in the population. This has an impact on the frequency of prescribing OACs to patients with AF and coexisting cancer. Ajabnoor et al. showed that patients with lung cancer, followed by hematological malignancies, and AF were the least likely to get OACs prescribed among the groups analyzed in their study – and patients with breast or prostate cancer – the most. (Ajabnoor et al., 2024) This might be due to increased risk of bleeding in the first two (Ajabnoor et al., 2023). Besides that, they have shown that oncology patients with non-valvular AF tend to receive OACs less frequently. It was more obvious in lung cancer and hematologic malignancies, as well as in elderly patients (Ajabnoor et al., 2024). Although they noticed a progressive increase in NOACs prescription since 2012, in comparison to VKAs or aspirin-only treatment, both in cancer and cancer-free patients.

Overall, a picture appears – in general oncologic patients with AF seem to have similar stroke risk as non-cancer AF patients, which suggests not starting anticoagulation earlier based only on the presence of malignancy. Rather than that, we should weigh the decision individually, considering each patient's characteristics and type of malignancy. (Ajabnoor et al., 2023; El-Rayes et al., 2025; Raposeiras-Roubín et al., 2023; Ullah et al., 2023).

Scores and assessment

As we have previously mentioned, balancing between thromboembolic and bleeding risk in cancer patients with coexisting AF might pose a challenge, especially when commonly used risk scores are not properly validated in this group.

Several studies have suggested that the widely used CHA_2DS_2-VASc score shows lower predictive value for people with coexisting cancer and AF in comparison to general AF population without a recent history of malignancy. (D'Souza et al., 2018; Matetic et al., 2023; Raposeiras-Roubín et al., 2023) In a 2023 study of Raposeiras-Roubín et al. not only CHA_2DS_2-VASc, but also HAS-BLED score, showed suboptimal performance in oncology patients. (Raposeiras-Roubín et al., 2023)

Ullah et al. researched the discriminative accuracy of the CHA_2DS_2VASc score for ischemic stroke in patients primarily hospitalized for AF, and found out that the CHA_2DS_2VASc category (low/moderate/high-risk) failed to distinguish between the risk for 30-day ischemic stroke among patients with prostate and colorectal cancer (but was discriminatory in other types of malignancy). (Ullah et al., 2023) Although, one of the study's conclusions was that in the analyzed group cancer was associated with relatively lower 30-day risk of ischemic stroke compared with the noncancer cohort regardless of CHA_2DS_2VASc risk category. This could be due to lack of information about post discharge mortality and thus, not accounting for death as a competing risk in these cases.

In their meta-analysis, Balomenakis et al., 2023 found no significant association between cancer and thromboembolic risk in AF patients, but they admit that the quality of the evidence their study provides is low due to its limitations. They mention other studies that, as they declare, are consistent with their results. However, this data may be influenced by survivorship bias.

Taking the above into consideration, a question arises: what factors influence thromboembolic and bleeding risk in oncologic patients with AF? While many factors are already well-established, they are scattered among many papers and studies, thus compiling them in one place could help in the diagnostic and therapeutic process.

We know that different types of malignancy are associated with different levels of thromboembolic and bleeding risk, especially during anticoagulation. Examples, based on Ajabnoor et al., 2023; Ullah et al., 2023 are shown in **Table 1.** However, the connection is not always clear-cut – for example, the risk of bleeding seems higher in patients with more recent diagnosis of cancer. (Ajabnoor et al., 2023) Therefore, there is still a great need for further research on how different types of malignancy and/or cancer treatment influence the thromboembolic and bleeding risk.

Table 1.

High bleeding risk	High stroke risk
Lung cancer	Breast cancer
Hematological malignancies Prostate cancer Colorectal cancer	Prostate cancer

A study published in 2025 (Celik et al., 2025) focused on identifying clusters of patients with AF and malignancy based on the comorbidities and concomitant drug use these patients shared or differed in. They followed 633 patients in Italy treated with **direct oral anticoagulants** (based on 2021 EHR guidelines (Steffel et al., 2021)). They identified four profiles of patients/comorbidities:

- Unspecific pattern (n = 246),
- Diabetes and Liver pattern (n = 94),
- Neurocognitive and Psychiatric Pattern (n = 90),
- Musculoskeletal, Immunological, and Dermatological pattern (n = 203),

and found out that **the neurocognitive and psychiatric pattern** was associated with a higher risk of the composite outcome, thromboembolism, and bleeding than the non-specific pattern. Respectively, 42,7% and 24,4% of patients in neurocognitive/psychiatric and non-specific patterns had a previous history of stroke/TIA.

Discussion

The existing studies on AF and malignancy are often observational and retrospective. There are also many variables that make comparison of the data more difficult – such as differences in anticoagulation status, AF subtype, baseline patient characteristics, handling of competing risks, and follow-up time. Even the definitions of active/recent cancer differ - e.g., in Raposeiras-Roubín et al., 2023 and D'Souza et al., 2018.

Managing thromboembolic and bleeding risk in patients with coexisting cancer and AF still presents a challenge, especially when the widely used risk score, such as CHA_2DS_2-VASc (or now CHA_2DS_2-VA), does not seem to be discriminatory enough in this case. Thus, considering cancer's type, stage, treatment status, and the patient's comorbidities in deciding whether to include anticoagulant prophylaxis is crucial. Yet, we still lack high-quality evidence in this field, as malignancy is often an exclusion criterion in many studies.

Conclusions

Atrial fibrillation and malignancy often coexist because of the changing demographics of oncology patients and shared risk factors. Management of thromboembolic and bleeding risk in this group poses a challenge due to numerous nuances and the need for individual assessment. The commonly used CHA_2DS_2VASc score appears to have limited discriminatory ability in the context of malignancy. Although studies suggest that the risk of stroke in AF in cancer patients is similar to that of cancer-free controls, bleeding risk is often increased, especially in active malignancy and in certain cancer types. Current cardio-oncology guidelines (Lyon et al., 2022) for AF management are based primarily on expert consensus and/or small/retrospective studies and registries. Therefore, prospective, large-scale studies are needed.

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