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COMMENTARY

Revisiting important issues in cancer and atrial fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrythmia in adults, affecting 1.5% to 2% of the general population [1]. Its prevalence continues to increase, and as many as 1 in 3 individuals can develop AF in their lifetime [1]. AF is associated with a 2-fold increased risk of thromboembolism and a 6-fold increased risk of congestive heart failure and other cardiovascular complications [2]. Patients with cancer have an ~50% increased risk of AF compared to those without cancer [3–5]. Many anticancer therapies and/or cancer surgery can heighten the risks of AF. Similarly, a new diagnosis of AF is associated with an increased risk of cancer [3]. The mutual association is thought to be at least in part due to their shared risk factors, such as age, obesity, and smoking [6].

In the general population, risk assessment tools such as the CHA_2DS_2-VASc score (variables including age, sex, history of congestive heart failure, hypertension, stroke/transient ischemic attacks (TIAs)/thromboembolism, vascular disease, and diabetes) or CHADS-65 score are used to predict the risk of stroke and systemic embolism to guide the decision of anticoagulation. Guidelines recommend anticoagulation in men with a CHA_2DS_2-VASc score of $\geq$2 and in women with a score of $\geq$3 or a CHADS-65 score of $\geq$1 [7–9]. However, the applicability of these scores in the cancer population remains unclear as these scores were neither derived nor sufficiently validated in the cancer population. Recent data also revealed concerns that the CHA_2DS_2-VASc score may underestimate the thrombotic risks in those with cancer [10,11]. Patients with cancer-associated thrombosis are known to have an increased risk of recurrent thrombosis and bleeding complications on anticoagulation compared to those without cancer [12,13], but it is less clear whether patients with active cancer and AF had similar outcomes.

In this issue of the journal, Chu et al. aimed to tackle these important questions by conducting a retrospective study to evaluate anticoagulation strategies and associated outcomes in 1213 patients with concurrent AF and active cancer from 2 Dutch hospitals [14]. Two cohorts of patients were included: 1) patients with AF first who then developed cancer (AF → cancer; N = 878) and 2) those with cancer first who then developed AF (cancer → AF; N = 335). Interestingly, the 2 cohorts differed in baseline characteristics, with the most common cancer types being lower gastrointestinal (GI) cancer in the first cohort (AF → cancer) and hematologic malignancy being the predominant type in the second cohort (cancer → AF). Previous large population studies in Denmark and Korea also showed that hematologic and GI malignancies were among the cancer types associated with the highest risks of developing AF after cancer diagnosis [4,5]. The risk of new onset of AF was the highest within the first 90 days after cancer diagnosis and remained elevated even at 5 years, although they did decline over time [4,5].

Regarding the risks of thromboembolic events in patients with AF and cancer, some studies showed similar risks compared to those in patients without cancer [15,16], while others showed increased risks in patients with cancer [11]. In this study, patients with AF and active cancer were found to experience high rates of both thrombotic and bleeding complications. Regardless of whether cancer or AF occurred first, the 1-year cumulative incidences were largely consistent: all thromboembolic events, 7% to 8%; stroke/TIA/systemic embolism, ~4%; major bleeding events, 6.5% to 7.5%, and clinically relevant bleeding, ~14%. These high rates could be due to more stringent definitions of active malignancy (cancer diagnosed or treated within 6 months or recurrent, regionally advanced, or metastatic cancer) and associated hypercoagulable state, while previous studies included cancer diagnosed and/or treated more remotely. It is interesting that despite guideline recommendation of anticoagulation in those with a CHA_2DS_2-VASc score of $\geq$2 in the general population, anticoagulation was not prescribed in 15% to 20% of these patients with cancer with a CHA_2DS_2-VASc score of $\geq$2, similar to that in the noncancer population [17]. The reasons for withholding anticoagulation were not reported. The complexity of vitamin K antagonist (VKA) use and the fact

that 11% to 18% of patients had a history of bleeding could be potential reasons. Previous studies also revealed similar concerns of under–anticoagulation in patients with cancer and AF, with factors contributing to reduced anticoagulation use, including current chemotherapy, history of bleeding, renal disease, and thrombocytopenia [18]. Future studies to further investigate the reasons for withholding anticoagulation and ways to overcome them will be valuable. It is especially important as this study showed that withholding anticoagulation was associated with a 5-fold increased hazard of thromboembolic complications.

Another alarming signal identified by this study was the high risk of thromboembolic events in patients with a CHA_2DS_2-VASc score of <2 without anticoagulation. In these patients, anticoagulation is not typically recommended in the general population [7], but in this cohort of patients with active cancer, there was an unacceptably high risk of stroke/TIA without anticoagulation: 4.5 per 100 patient-years in those with AF → cancer and 16 per 100 patient-years in those with cancer → AF. The striking difference in the risks was speculated to be related to increasing comorbidities in patients with active cancer who developed AF later due to anticancer therapies or related complications such as pulmonary embolism. To further complicate the picture, the risk of major bleeding events in the cancer → AF cohort despite the lack of anticoagulation was also quite high (11.1 per 100 patient-years). It is worth noting that the numbers of patients with a CHA_2DS_2-VASc score of <2 not on anticoagulation were small in both cohorts (N = 39 and 32), which might have affected the event rates. However, these results did challenge the recommendation that a CHA_2DS_2-VASc score of <2 is "safe" to withhold anticoagulation, especially in those who develop AF after cancer diagnosis. This study was not alone in this finding as increased thrombotic risks in those with cancer and a CHA_2DS_2-VASc score of <2 not on anticoagulation had been reported [10,19]. More recently, the 2022 European Society of Cardiology guidelines on cardio-oncology suggested to consider anticoagulation in those with cancer, AF, and a CHA_2DS_2-VASc score of <2 [20]. To improve risk assessment in the cancer population, a Surveillance, Epidemiology, and End Results (SEER) database analysis of patients with lung, colon, breast, and prostate cancer revealed that cancer contributed similarly as age, sex, and diabetes to the hazard of stroke [11]. Investigators added "cancer" as a variable to form the new "$CCHA_2DS_2$-VASc" score, which showed superior predictability than the original CHA_2DS_2-VASc score [11]. Further risk prediction models specific to patients with active cancer as such would be preferred for more accurate risk stratification.

If anticoagulants were to be initiated, the preferred type of anticoagulants has evolved over time. While the majority of this cohort were prescribed VKA, given the time frame of the study conducted (2012-2017), the authors showed that direct oral anticoagulants (DOACs) had surpassed VKA to be the predominant anticoagulant after July 2016, accounting for >30% of anticoagulant prescriptions in 2017. In this cohort, DOACs were associated with comparable risks of thrombosis or bleeding events as VKA. Previous systematic reviews and meta-analyses showed that compared to VKA, DOACs were associated with a reduced risk of stroke/systemic embolism and venous thromboembolism as well as a reduced risk of intracranial and gastrointestinal bleeding events [21,22]. These results support the suggestions from the International Society on Thrombosis and Haemostasis guidance of DOACs over VKA in patients with cancer with new onset of AF in whom anticoagulation is initiated, in the absence of other factors associated with an increased risk of bleeding, such as unresected GI intraluminal tumor or significant drug-drug interactions [23]. Figure summarizes the main issues discussed in the article.

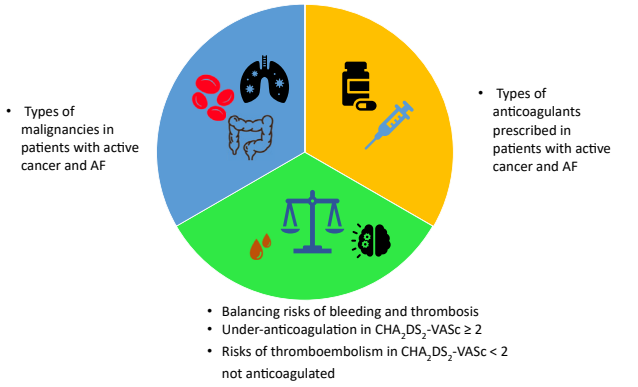

FIGURE Issues to consider in atrial fibrillation and cancer. AF, atrial fibrillation.

How can the results of this study help clinicians in practice? It is important to recognize that patients with cancer are at an increased risk of AF as well as AF-related thromboembolic and bleeding complications. As highlighted by this study, we have a long way to go to define optimal management strategies for these patients, and the commonly used CHA_2DS_2-VASc score might not be ideal. We need an effective risk assessment tool to identify patients with active cancer truly with low risk of thromboembolism, for whom anticoagulation can be safely withheld. On the other hand, accurate and timely diagnosis and treatment of patients with active cancer and AF who can benefit from anticoagulation are also of crucial importance. Factors such as type of malignancy or selected cancer therapies may be important factors to consider.

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