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EDITORIAL COMMENT

Evaluating Anticoagulant Strategies for Atrial Fibrillation in Patients With Cancer

Challenges and Opportunities*

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Atrial fibrillation is commonly encountered among patients with cancer with a prevalence of about 2% to 5% at cancer diagnosis.[1-4] After cancer diagnosis, the incidence of new-onset atrial fibrillation is higher compared with individuals without cancer due, at least in part, to the presence of shared risk factors, complications of cancer itself and cancer treatments.[1,3,4] Up to 25% of individuals with atrial fibrillation have concurrent cancer, and this proportion is expected to grow due to advances in early detection and treatment of cancer; and aging and growth of the population have resulted in increasing numbers of cancer survivors.[5]

The optimal oral anticoagulation strategy for patients with cancer and atrial fibrillation who are eligible (based on conventional risk prediction tools) is uncertain. Although randomized trial data support the use of direct oral anticoagulants (DOAC) over vitamin K antagonists for prevention of stroke and systemic embolism in atrial fibrillation in the general population, few patients with cancer were included in the landmark trials, leaving a paucity of high-quality data in this population.[6-9] It is well known that cancer and its treatments confer a hypercoagulable state, which increases the risk of both arterial and venous thrombosis, but they also increase the risk of bleeding, thereby creating uncertainty about the overall benefit of anticoagulation. Because of differences in baseline rates of thrombosis and bleeding, and the presence of tumor- and treatment-related factors that may affect the safe provision of anticoagulation (eg, drug interactions, thrombocytopenia, gastrointestinal effects, altered oral intake, surgery, and invasive procedures), efficacy and safety data may not be directly extrapolated from the general population, leaving a substantial knowledge gap.

In this issue of *JACC: CardioOncology*, Potter et al[10] add to the growing body of literature regarding anticoagulation for atrial fibrillation in patients with active cancer. In this nonrandomized, single-center retrospective study, the investigators report on the outcomes of 390 propensity score-matched patients with various types of cancer receiving DOACs (n = 195) or warfarin (n = 195) for atrial fibrillation. The median duration of follow-up was 1,500 days. Fifty-eight patients (20%) died during follow-up. Ischemic stroke/transient ischemic attack occurred in 25 patients in the overall cohort (8.8%), whereas gastrointestinal bleeding occurred in 23 patients (7.8%), and intracranial bleeding occurred in 4 patients (1.6%). Using a competing risk regression model (with death as a competing risk and the DOAC group as the reference group), the risks of ischemic stroke/transient ischemic attack (HR: 0.738; 95% CI: 0.334-1.629), gastrointestinal bleeding (1.819; 95% CI: 0.774-4.277) and intracranial bleeding (HR: 0.295; 95% CI: 0.032-2.709) were not statistically different between the warfarin and DOAC groups. Although these results are somewhat reassuring, uncertainty remains because clinically important differences between groups may not have been excluded, and the direction of treatment effect seen in this study is opposite to what was previously reported in cancer

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and noncancer patients.[11-13] However, with high rates of ischemic stroke and bleeding, these results are consistent with prior observations that patients with atrial fibrillation and active cancer who are receiving anticoagulation are at higher risk of death, thrombosis, and bleeding compared with those without cancer and that conventional approaches to assessing benefit and harm may not apply in this setting.

Observational studies provide important data about the relative effectiveness and safety of treatments and can inform future randomized trials. However, methodological considerations often preclude firm conclusions. For example, treatment decisions by clinicians in routine practice are influenced by prognostically important baseline characteristics that may be different between treatment groups and that are not completely accounted for with a nonrandomized design. An unanswered question is whether oral anticoagulation provides overall net benefit compared with no anticoagulation (or other strategies such as parenteral anticoagulation) in this population. In fact, only a proportion of eligible patients with cancer and atrial fibrillation (30% to 70%) receive anticoagulation.[14,15] Patients with higher CHA_2DS_2VASc scores and lower HAS-BLED scores are almost 2 times more likely to receive anticoagulant agents. Although propensity score matching allows comparison of similar patients, it is based on selected baseline characteristics, and only a subset of eligible patients are analyzed, which affects the generalizability of results. Different cancer types and stages confer variable baseline prognoses that could affect decisions to provide or withhold anticoagulation, as increasing cancer stage has been associated with DOAC discontinuation.[15] It is not currently known how changes in disease status affect stroke and bleeding risks over time. Socioeconomic status is an important baseline characteristic to consider, given the cost differential between warfarin and DOACs and its impact on anticoagulant choice.

Another methodological challenge is the measurement of anticoagulant exposure over time. Unlike prospective studies in which adherence to treatment can be monitored, retrospective studies rely on surrogates of adherence such as drug dispensation (in administrative health database cohort studies) or documentation in medical records during routine care. By including anticoagulant exposure as a time-varying covariate, interruption and switching can be incorporated into analysis (as opposed to censoring at these events) and provide more robust data about the effect of treatments. Unfortunately, many retrospective observational studies do not reliably capture anticoagulant exposure (including time-in-therapeutic range for warfarin), which further limits inferences about treatment effects.

Given the challenges of applying existing data to individual patients, and the high frequency of adverse outcomes, shared decision-making is a key component of management. Shared decision-making relies on identifying patient values for the potential benefits and harms of treatments and incorporating their preferences into decisions. An important knowledge gap is the limited understanding of how thrombotic and bleeding events affect patients and their caregivers, including the impact of these events on patient-reported outcomes such as quality of life and functional status in this population. Studies conducted in patients with atrial fibrillation (without cancer) show that patient health state valuations (ie, how patients perceive the consequences of thrombotic and bleeding events) are highly variable. Patients with atrial fibrillation appear willing to accept bleeding complications to avoid stroke.[16] However, prior studies have been limited by heterogeneous descriptions of health states, including omission of death as an outcome of bleeding.

Over the next 50 years, the number of patients with atrial fibrillation is expected to increase 2.5-fold, and many will also be diagnosed with cancer.[17] Although randomized trials are the ideal way to establish the optimal management of atrial fibrillation in cancer patients, these studies require substantial investment and are challenging to design and execute in a heterogeneous, medically complex patient population. To avoid future uncertainty about the role new anticoagulant drugs in cancer populations, sponsors, investigators, funding agencies, and health regulators need to take steps to ensure that: 1) study populations are diverse, reflecting patients managed in clinical practice (including those historically excluded from research); and 2) study protocols are informed by individuals with lived experience and include outcomes that reflect patient experiences.

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