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EDITORIAL COMMENT

Direct Oral Anticoagulants in Patients With Cancer and Nonvalvular Atrial Fibrillation*

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Numerous randomized clinical trials and more than a decade of experience have clearly established direct oral anticoagulants (DOACs), also known as non-vitamin K antagonist oral anticoagulants (NOACs), as the therapy of choice for the prevention of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF). Collectively, DOACs are associated with a statistically significant reduction in the risk of stroke, SE, intracranial hemorrhage, and all-cause mortality, and a trend toward less major bleeding, compared with warfarin and other vitamin K antagonists (VKAs) (1).

Although cancer is emerging as an important risk factor for NVAF (2), the efficacy and safety of DOACs compared with VKAs in NVAF have been studied less rigorously among patients with comorbid malignancies. Decision making around anticoagulation in this population is complicated by an increased risk of bleeding, the prothrombotic state associated with cancer and anticancer therapies, potential drug-drug interactions, and altered pharmacokinetics. Post hoc analyses of several DOAC trials have demonstrated similar efficacy of these agents among NVAF patients with cancer compared with other NVAF patients (3,4), but the exclusion of patients with higher risk of bleeding and/or thromboembolism from clinical trials limit generalizability.

In this issue of *JACC: CardioOncology*, Deitelzweig et al (5) present real-world evidence supporting the use of DOACs for the prevention of stroke and SE in NVAF patients with cancer. In this substudy of ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients), a large retrospective study using administrative claims data to compare outcomes among NVAF patients receiving DOACs and those receiving warfarin (6), some 40,000 patients were identified as having active cancer: prostate cancer was the most common malignancy (29%), followed by breast (17%), genitourinary (14%), lung (13%), and gastrointestinal (GI) (13%) cancers. Of note, upper GI cancers alone accounted for only ~1%-2% of patients. Thirty-eight percent of patients were on warfarin, with the remainder receiving apixaban, dabigatran, or rivaroxaban. Because of the study period (2013-2015), edoxaban was not represented. The patients included were at high risk for both stroke and major bleeding: ~60% of patients had a CHA_2DS_2-VASc score of ≥4, and ~75% had a HAS-BLED score of ≥3. Propensity score matching was used to balance stroke risk, bleeding risk, and other baseline characteristics between treatment groups.

In the comparisons with warfarin, the authors found that apixaban was associated with lower rates of stroke, SE, and major bleeding, while similar rates of both stroke, SE and major bleeding were seen with rivaroxaban and dabigatran compared with warfarin. In the comparisons between DOACs, apixaban had a lower risk of stroke and SE compared with dabigatran, but there were no differences in stroke and SE in other DOAC-DOAC comparisons. Both apixaban and dabigatran were associated with lower risks of major bleeding compared with rivaroxaban. Consistent treatment effects were seen across different cancer types.

Similar findings have been reported in smaller observational studies, but they are subject to residual confounding (7-9). With the largest cohort of patients

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studied to date, Deitelzweig et al (5) were able to include a large number of clinically important variables in propensity score matching to minimize the bias related to prescribing decisions.

Although the overall findings of this study and the parent ARISTOPHANES study are consistent, it is important to note how different this cancer subgroup is from the larger ARISTOPHANES population. Not only were the cancer patients more likely to be older and male, they also had numerically higher rates of nearly every comorbid condition examined, including renal disease, heart failure, and coronary disease. Notably, the proportions of cancer patients in each study group with a CHA_2DS_2-VASc score of ≥4 was 58%-64% (vs 48%-58% overall in ARISTOPHANES) and the proportion of cancer patients with a HAS-BLED score of ≥3 was 72%-78% (vs 54%-63% overall in ARISTOPHANES). These differences are reflected in the unadjusted rates of stroke and SE and major bleeding in the 2 studies. For example, the rate of major bleeding with warfarin was 6.3% per 100 person-years in ARISTOPHANES overall and 10.6% in this cancer substudy.

Important questions remain regarding other patients with NVAF and cancer who were not well represented in this analysis because it only included patients who received an oral anticoagulant. The sizable proportion of patients with high stroke and bleeding risk scores in this study suggests that low-risk patients were not prescribed anticoagulation (10). Also, patients with a history of bleeding or at risk of thrombocytopenia (a common complication with chemotherapy) were likely not placed on anticoagulant therapy. For example, patients with upper GI cancers composed only 1%-2% of the study population, even though they made up ∼10% of cancer patients with NVAF in a Korean nationwide population-based registry (2). This type of selection bias might also be more art than science and can importantly affect results in observational studies.

Furthermore, much has changed in oncology since the 2013-2015 study period. Reflecting this evolving landscape, only 27 of more than 40,000 patients in the analysis by Deitelzweig et al (5) received immunotherapy. According to one estimate, the proportion of cancer patients in the United States who were eligible for immune checkpoint inhibitors increased from 1.5% in 2011 to 43.6% in 2018 (11). The role of DOACs in these patients, who may experience bleeding related to immune-mediated adverse effects such as enterocolitis and thrombocytopenia, or who may have altered drug clearance due to hepatitis, thyroiditis, or glomerulonephritis, remains unclear.

Finally, there are practical issues that need to be considered when making complicated decisions around anticoagulation in patients with NVAF and cancer. As in the general population, DOACs have a number of advantages over VKAs beyond safety and efficacy. These include more predictable anticoagulant responses, fewer drug-drug and drug-food interactions, and less need for laboratory monitoring. On the other hand, DOACs may be unaffordable for many patients, particularly the elderly and those who are unable to work because of illness. Where drug-drug interactions do exist, the ability to measure the anticoagulant effect has value. Serum DOAC levels might be increased by CYP3A4 or permeability glycoprotein inhibitors such as tamoxifen, abiraterone, sunitinib, imatinib, and others, whereas DOAC levels might be decreased by inducers such as paclitaxel, enzalutamide, or dexamethasone (12). The ability to measure anticoagulant activity may also be useful in patients with unpredictable or impaired drug absorption (due to nausea, vomiting, diarrhea, or surgery such as gastrectomy or colectomy) or altered drug distribution (due to inflammation, hypoalbuminemia, and changing tissue volumes).

The study by Deitelzweig et al (5) has advanced our understanding of best practices for patients who can receive anticoagulation for NVAF in the context of cancer, but it leaves a host of questions unanswered, most notably: Which patients with NVAF and cancer should be anticoagulated at all? There clearly remains a large group of patients who are not receiving OACs; in many cases this may be appropriate. Notably, the high rates of discontinuation—35%-60% of patients in each group discontinued anticoagulant therapy over median follow-up intervals of <150 days—in this study tell us that adherence and compliance might be problematic, and that anticoagulation might not be appropriate at palliative or other stages of the malignancy. Further research is needed to better define, within the modern oncology landscape, how to best calculate the complex arithmetic of balancing risks and benefits in this challenging population.

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