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EDITORIAL COMMENT

Caught Between a Rock and a Hard Place

Anticoagulation in Atrial Fibrillation Patients With Cancer*

Pouria Shoureshi, MD,[a,b] Alex Y. Tan, MD[a,b]

Atrial fibrillation (AF) is a significant risk factor for ischemic stroke in the general population, with guidelines recommending the use of the CHA_2DS_2VASc score for risk stratification and anticoagulant therapy.[1,2] However, the utility of this score in predicting ischemic stroke in AF patients with active cancer has not been validated.[3,4] Cancer presents a clinical dilemma as it increases the risk of both thrombosis (ischemic stroke) and bleeding.[5,6] The causes of thrombosis include cancer-related hypercoagulability, noninfectious endocarditis, paradoxical embolization of cancer-related clots, and tumor occlusion.[7,8] On the other hand, coagulopathy, which contributes to bleeding, is attributed to factors such as cytokine secretion (tumor necrosis factor-α), tissue factor expression, liver metastases, tumor cell characteristics (eg, mucin production in adenocarcinoma), and treatment-related aspects like chemotherapy-induced thrombocytopenia. Previous research indicates that bleeding tends to be the predominant issue in individuals with cancer,[5] making it challenging to decide whether anticoagulation is appropriate or not when AF is diagnosed in the setting of active cancer. Striking the right balance between the risk of major bleeding and preventing cancer-related blood clotting events is crucial but remains an area with a significant gap in knowledge.

Ullah et al[9] conducted a large retrospective study of over 4 million patients, utilizing the National Readmission Database data from 2015 to 2019. Their main objective was to assess how well the CHA_2DS_2VASc score predicts the risk of stroke in cancer patients with AF and to compare major outcomes such as stroke vs major bleeding in these patients. They included patients who were admitted with a principal admission diagnosis of AF and determined their 30-day outcomes based on 30-day readmission data. They stratified patients into 2 groups: those with and those without active cancer. Using the CHA_2DS_2VASc score, they categorized patients into low-risk (CHA_2DS_2VASc 0 or 1 for females), moderate-risk,[1,2] and high thromboembolic risk (3 or higher) categories. The primary aim was to assess the association between CHA_2DS_2VASc score and 30-day risk of ischemic stroke, major bleeding, and all-cause readmission in both cancer and noncancer cohorts. Furthermore, subgroup analyses were conducted to investigate the specific risks associated with different types of cancer.

There are several major findings in this study. Firstly, the CHA_2DS_2VASc score was overall modestly predictive (area under the curve between 0.5 and 0.7) of stroke for most cancer types but not predictive for certain types of cancer such as prostate and colorectal cancer. Secondly, cancer patients have an increased risk of bleeding compared to noncancer patients, in spite of the relatively low rate of anticoagulation in the overall cohort of about 1/3, which is equally so in both cancer and noncancer groups. Thirdly, bleeding and stroke risk are not equal among cancer types. Bleeding risk was highest in hematological and lung cancers, irrespective of anticoagulation and CHA_2DS_2VASc category. A fourth and unexpected finding is that cancer patients appear to have a lower 30-day stroke risk compared with noncancer patients. Although this seems counterintuitive, one must caution against overinterpreting this finding given

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From the [a]Cardiology Division, Department of Internal Medicine, Central Virginia VA Health Care System/McGuire Veterans Affairs Medical Center, Richmond, Virginia, USA; and the [b]Department of Internal Medicine, Cardiology Division/Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA.

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the short duration of follow-up, competing cancer-related mortality, and the limitations of data capture imposed by the use of administrative claims database, which lack granular clinical data such as HASBLED (Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage) score, laboratory parameters, burden and type of AF (paroxysmal vs persistent) and anticoagulation therapy as well as cancer severity and treatment regimens. Additionally, there may be a selection bias by virtue of patients being selected from a hospital event and the population skewed toward a higher thrombotic risk with the majority (over 90%) of the cohort falling into the high CHA_2DS_2VASc score category. Despite that, it is interesting that only 1/3 of patients are on anticoagulation. Thus, the generalizability of these results to the larger population may be somewhat limited. Notwithstanding these limitations, the major strengths of the study are the large sample size of over 4 million derived from a nationally representative database that accounts for nearly 60% of all discharges and readmissions in the United States and the stratification of outcomes by cancer types, which reinforces the idea that one size does not fit all in the cancer population as far as hemostasis is concerned.

In conclusion, the study adds valuable evidence to the intricate landscape of anticoagulation therapy in cancer patients with AF. Overall, the observations of Ullah et al align with our understanding that malignancy-induced alterations in hemostasis can lead to both thrombotic and bleeding complications,[5,6] which support the rationale for excluding oncologic patients from the development of legacy $CHADS_2$ and CHA_2DS_2VASc score systems.[10,11] It suggests that the traditional risk factors included in these scores may not fully capture the thrombotic risk posed by cancer. The findings underscore the need for a nuanced approach that considers both thrombotic and bleeding risks, cancer type, and individual patient characteristics. While the CHA_2DS_2VASc score remains a valuable tool, its performance in cancer patients requires further validation and refinement. Clinicians must weigh the benefits and risks of anticoagulation therapy in this vulnerable population, integrating additional criteria and using risk prediction models that account for the unique thrombotic and bleeding tendencies associated with cancer. Ultimately, individualized treatment decisions should be guided by a multidisciplinary approach, incorporating the expertise of cardiologists, oncologists, and hematologists to better optimize patient outcomes.

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ADDRESS FOR CORRESPONDENCE: Prof Alex Y. Tan, Virginia Commonwealth University/Pauley Heart Center, 1201 Broad Rock Blvd, Richmond, Virginia 23249, USA. E-mail: Alex.tan@vcuhealth.org OR Alex.tan@va.gov.

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