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EDITORIAL COMMENT

Cancer and Clot

A Deadly Dance*

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The association between cancer and venous thromboembolism (VTE) is well established, and the American Society of Clinical Oncology and the International Initiative on Thrombosis and Cancer have issued Clinical Practice Guidelines for VTE prophylaxis and treatment that have been widely adopted (1–3). However, less is known about risks that predispose cancer patients to arterial thromboembolism (ATE).

In this issue of the *JACC: CardioOncology*, Mulder et al. (4) reported an increased short-term risk of ATE before and after a recent diagnosis of cancer. The authors define ATE as a composite endpoint including myocardial infarction, ischemic or unspecified stroke, and peripheral arterial occlusion. Nearly half a million patients with first-time diagnosis of cancer from 1997 to 2017 were identified from the Danish population-based health registries and were matched with non-cancer control subjects. The authors found that the incidence of ATE was more than double for cases versus control subjects through the first 6 months post-diagnosis (6-month cumulative incidence of ATE was 1.50% in cancer patients and only 0.76% in matched control subjects [hazard ratio: 2.36]). Factors identified to be associated with increased ATE risk in cancer patients were age, prior ATE, presence of metastatic disease, and whether the patient received chemotherapy as initial treatment within the first 4 months since cancer diagnosis. Additionally, the authors separately reported on rates of myocardial infarction and ischemic or unspecified stroke and found that the 2-fold risk as compared with non-cancer control subjects was associated with each of these outcomes. The increased risks diminish over a 2-year time period, and it is not clear whether the cancer, initial oncologic treatments, or both drive the increased risk. However, the increased risk seen during the 6 months preceding the cancer diagnosis must be related to the underlying malignancy.

The strengths of this epidemiologic analysis include a comprehensive population-based registry of all patients from Denmark. The data cover a 20-year period and include heterogeneous cancer diagnoses as well as all types of ATE. Furthermore, Mulder et al. applied rigorous analytic methods that accounted for the competing risk of death and treated ATE as a time-dependent covariate. Although these data are retrospective, rely on administrative diagnosis codes, and lack granular patient-specific information including laboratory and imaging results, they can inform improvement of care for the newly diagnosed cancer patient. These findings, along with other recent reports, raise the question whether a patient diagnosed with cancer should be considered for primary prevention of cardiovascular disease (5). Although cancer patients have a higher risk of thromboembolic events and primary prophylaxis may be effective, prophylactic measures are not routinely implemented in practice primarily due to modest absolute risk reductions and a known increased risk of major bleeding. This is especially concerning for the cancer patient population, already predisposed to bleeding due to frequent coagulopathy, invasive procedures, or antineoplastic agents.

Compared with the published literature, although similar time trends in short-term risks were identified, the absolute risks of ATE reported by Mulder

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et al. (4) are lower than those reported by Navi et al. (5) in a U.S. population-based study that utilized claims data from the SEER (Surveillance, Epidemiology, and End Results)-Medicare linkage. Lower absolute risks are likely due to the age of Medicare enrollees, at 65+ years of age as opposed to those 18 years of age and older in the Danish cohort. Mulder et al. (4) also observed an early ATE risk, with the highest rates of ATE among patients with cancers associated with smoking (bladder, lung, and colon cancers); the association of ATE with lung cancer has been described previously.

Given the significant increased risk of death reported among cancer patients who had an ATE versus those who did not (hazard ratio: 3.28), these results may inform clinical trials for the evaluation of therapeutic strategies including antithrombotic and statin medications for ATE. Admittedly, conducting ATE prevention trials in this setting is challenging because there is a short window post-cancer diagnosis to enroll patients and no agreed-upon optimal antithrombotic strategy to evaluate. Furthermore, any approach that compromises clotting could interfere with the necessary treatment for the newly diagnosed cancer. Risk prediction models that identify patients most likely to benefit from prophylaxis to reduce risk of ATE and mortality are not as widely developed as for VTE (6,7). Elevated levels of absolute neutrophil count and soluble P-selectin have been identified as potential biomarkers for cancer-associated ATE but have not been validated in prospective studies (8,9). However, well-known risk factors for ATE include age, hypertension, hypercholesteremia, smoking, obesity, diabetes, and distant metastases. These are easily identified at cancer diagnosis and should be addressed to try to reduce the heightened ATE risk (5). Clinicians can inform patients, particularly those who smoke, of the increased risk of ATE and help them to identify symptoms and signs of heart disease or stroke and to differentiate those from the effects of the cancer or its treatment. The other potential opportunity to improve outcomes may be in those patients newly diagnosed with an ATE; clinicians can be alerted to the possibility of an underlying malignancy that might be amenable to an early diagnosis when treatment can be most effective.

Although the data presented by Mulder et al. (4) do not yet clarify a path to intervention, either therapeutic or prophylactic, their study does add to the growing body of evidence that cancer enhances the risk of arterial as well as venous thrombosis. ATE and VTE can occur either before or after the diagnosis of cancer, and both can contribute to the morbidity and mortality associated with cancer. Tackling these challenges will help improve the quality of life for many patients with cancer.

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