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EDITORIAL COMMENT

To Anticoagulate or Not to Anticoagulate to Prevent Arterial Thrombosis During Systemic Cancer Therapy*

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Cancer increases the risk of venous thromboembolism (VTE), arterial thrombosis, and thromboembolic ischemic stroke in patients with atrial fibrillation (AF). Traditionally, the association between thrombosis and malignancy has focused on the occurrence of VTE, the second leading cause of death in cancer, which occurs in about 5% of patients.[1] The epidemiology of arterial thromboembolism (ATE) in cancer patients has received much less attention. However, ATE has long been recognized in cancer patients.[2] Cancer is associated with a 2-fold risk of ATE including myocardial infarction (MI) and stroke.[3] The risk of ATE is higher in older men and in patients with lung or kidney cancer. Conditions related to ATE in cancer include embolization by tumor cells or nonbacterial thrombotic endocarditis, disseminated intravascular coagulation-related peripheral microcirculatory thromboembolism, and paradoxical cerebral embolism.

The prevention of ATE in patients with cancer requires several key considerations. First, patients with cancer often have an increased risk of bleeding along with increased thrombotic risk. Certain cancers such as gastrointestinal or intracranial, coagulation defects, comorbidities such as renal or liver disease, and drug interactions between anticancer drugs and anticoagulants make anticoagulant therapy for ATE prevention very challenging.

Anticoagulant therapy has been shown to be effective in VTE prevention in cancer,[4] and anticoagulation is strongly recommended for stroke prevention in AF patients with CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74, and female sex) scores ≥2 (males) or ≥3 (females) unless there is a prohibitive bleeding risk.[5] Related to this, a recent study demonstrated that AF patients with CHA_2DS_2-VASc scores ≤2 not receiving anticoagulation at time of cancer diagnosis have an increased ATE risk compared with AF patients without cancer, supporting the use of anticoagulation in AF patients with newly diagnosed cancer.[6]

However, the effect of anticoagulation in preventing ATE and MI in cancer patients without concomitant AF is unknown. Therefore, we congratulate Xu et al[7] for their work in examining the efficacy and safety of anticoagulants in the prevention of ATE in ambulatory cancer patients. They performed the first systematic review and meta-analysis of 14 randomized controlled trials with over 10,000 participants, which included studies comparing oral or parenteral anticoagulation to no anticoagulation among ambulatory patients receiving systemic anticancer therapy with no other indication for anticoagulation. Fourteen randomized trials of low molecular weight heparins, direct oral anticoagulants, and warfarin were included. In this study, anticoagulant use was not associated with a reduction in MI, ischemic stroke, intra-abdominal arterial embolism, or peripheral artery occlusion compared with placebo or standard treatment (relative risk: 0.73; 95% CI: 0.50-1.04; $P = 0.08$, $I^2 = 0\%$),[7] whereas an

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increased risk of major and minor bleeding with anticoagulant use was reported. All-cause mortality was not reduced with anticoagulants.

This study evaluated the impact of anticoagulants on ATE prevention among ambulatory cancer patients receiving systemic anticancer therapy using a meta-analysis approach. Their findings support previous results of a single randomized trial showing no benefits of low molecular weight heparin routine use.[8] However, there are important limitations in drawing therapeutic indications for individual cancer patients using pooled data from a meta-analysis.

First and foremost, cancer is a complex disease with different phenotypes related to different types of cancer, patients, and therapies that may have a major impact on anticoagulation's cost/benefit balance. The different therapies used in patients with cancer may also influence ATE differently. For example, accelerated atherosclerosis and plaque rupture have been associated with androgen deprivation therapy (gonadotropin-releasing hormone agonists), immune checkpoint inhibitor therapy, nilotinib, ponatinib, radiation therapy, and vascular endothelial growth factor inhibitors, whereas coronary thrombosis has been associated with alkylating agents (cisplatin and cyclophosphamide), erlotinib, immune checkpoint inhibitor therapy, immunomodulatory imide drugs (lenalidomide and thalidomide), monoclonal antibodies (vascular endothelial growth factor inhibitors and anti-CD20), nilotinib, and platinum agents.[9]

In addition, the type and clinical stage of cancer and comorbidities such as diabetes, previous or recurrent MI, previous coronary revascularization, dyslipidemia, smoking, peripheral arterial disease, or chronic renal failure necessitate ATE risk stratification and subsequent tailored therapy in the individual patient.

Moreover, the conversion from a stable atherosclerotic disease into an acute coronary syndrome is linked in many cases to the rupture/erosion of vulnerable plaque with consequent exposure of the lipid core to the blood. This causes platelet aggregation with a subsequent intra-arterial thrombus, which can be partially (unstable angina or non-ST-segment elevation MI) or totally occlusive (ST-segment elevation MI). In these circumstances, the greatest therapeutic effect is obtained with antiplatelet therapy rather than with anticoagulant therapy. It should be pointed out that in the study by Xu et al,[7] the frequency of antiplatelet use at enrollment was not reported, resulting in an inability to draw firm recommendations. For instance, in the RIETE (Computerized Registry of Patients With Venous Thromboembolism) cohort of cancer patients who have had a VTE event, 86% of the subsequent ATE events occurred during heparin treatment and only 6.3% during antiplatelet treatment.[10] Antiplatelet therapy[11] alone or in combination with low-dose oral anticoagulation[12] reduces the risk of adverse limb events and overall CVD risk in patients with lower extremity arterial disease. The European Society of Cardiology guidelines suggest low-dose rivaroxaban plus aspirin for long-term secondary prevention in patients with a high risk of ischemic events and without high bleeding risk (Class II, Level of Evidence: A).[13]

Improvement in cardiovascular outcomes with combination therapy compared to anticoagulation alone is obtained at the price of more major bleeding events,[12] which could occur more frequently in patients with active cancer therapy. The multicenter COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) study, which was published in 2017, compared rivaroxaban (2.5 mg twice daily) in combination with aspirin 100 mg daily or rivaroxaban 5 mg twice daily alone vs aspirin 100 mg daily alone in stable coronary artery disease or peripheral arterial disease without cancer. This study demonstrated a reduction in all-cause mortality (3.4% vs 4.1%; $P = 0.01$) and cardiovascular mortality (1.7% vs 2.2%; $P = 0.02$). Unfortunately, in the COMPASS study, rivaroxaban 2.5 mg twice daily plus aspirin increased the risk of major bleeding (3.1% vs 1.9%; $P < 0.001$), but with no difference in fatal bleeding or in symptomatic bleeding in critical organs. The hypothesis that a COMPASS approach in cancer patients is beneficial would require further randomized clinical trials considering the increased baseline bleeding risk in cancer.

Current guideline recommendations for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in the general population include low-dose aspirin (75-100 mg daily) among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (Class IIb)[14] and in all patients for secondary prevention (Class I-A). Antiplatelet therapy is not recommended for individuals with low/moderate cardiovascular risk because of the increased risk of major bleeding (Class III).[12] Moreover, in patients with AF, which in cancer patients occurs with a frequency of 2% to 16%, anticoagulation is recommended for stroke prevention in AF patients with CHA_2DS_2-VASc scores ≥2 (males) or ≥3 (females) unless there is a prohibitive bleeding risk[5] and should be considered in ≥1 (males) or ≥2 (females).

In conclusion, patients with cancer have a higher risk of ASCVD, coronary heart disease, and ATE because of common risk factors between the 2 - diseases, the cardiovascular toxicity of cancer therapies,[15] and the cancer-induced proinflammatory and prothrombotic state.[16] However, whether anticoagulation alone or in association with antiplatelet agents (perhaps clopidogrel given fewer gastrointestinal side effects compared to aspirin) has a net clinical benefit to prevent ATE, in which cancer patients, at what stage of the disease, and with which comorbid risk factors, remains to be determined and requires further clinical studies.

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