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EDITORIAL COMMENT

The Pursuit of "Best" Anticoagulant for Cancer-Associated Thrombosis

Are We There Yet?*

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Cancer is a major risk factor for venous thromboembolism (VTE). Epidemiology studies show that approximately 20% of VTE are related to cancer, and 15% to 20% of patients with cancer would develop VTE during the course of their cancer journey.[1] Historical data suggest that VTE is a leading cause of death in the cancer population (cause of death in 9.2%), second after cancer progression (cause of death in 70.9%).[2] It can cause morbidity and mortality, and lead to hospitalizations, delays in cancer treatment, and an increased risk of complications. In addition to a significantly increased risk of VTE, patients with cancer also have an increased risk of bleeding on anticoagulation compared with those without cancer.[3] In addition, they commonly have many comorbidities, including reduced liver and/or kidney function, advanced age and frailty, polypharmacy, etc. Therefore, anticoagulant treatment for VTE in the cancer population can be challenging given these competing risks.

Historically, low-molecular-weight heparin (LMWH) was shown to be associated with a reduced risk of recurrent VTE with a similar risk of major bleeding events compared with vitamin K antagonist (VKA) in patients with cancer-associated thrombosis.[4] Therefore, LMWH had been the preferred anticoagulant in the cancer population in the past decade until the introduction of direct oral anticoagulants (DOACs). DOACs are oral agents without the need for intense laboratory monitoring, providing an attractive alternative. Since 2018, multiple randomized controlled trials (RCTs) and subsequent meta-analyses have shown that compared with LMWH, DOACs are associated with comparable efficacy in preventing recurrent VTE, but with potentially higher risks of bleeding complications particularly in those with unresected luminal gastrointestinal (GI) or genitourinary (GU) cancers.[5-12] However, it remains unclear whether an individual DOAC would provide the best risk-benefit profile, as no head-to-head comparison among different anticoagulants had been done. Therefore, major international guidelines have not suggested a preference of one DOAC over another.[13,14]

In this issue of *JACC: CardioOncology*, Fujisaki et al[15] attempted to answer the question of whether a specific DOAC is preferred for treatment of VTE in patients with cancer by conducting a systematic review and meta-analysis comparing anticoagulation strategies for cancer-associated thrombosis. They included RCTs comparing different anticoagulants for the treatment of cancer-associated VTE published before November 25, 2022. Studies that were not exclusively in cancer patients were included if they reported outcomes in the subgroup of cancer patients. Active cancer was defined as cancer diagnosis or treatment within 12 months before or after trial enrollment, recurrent or metastatic cancer, or hematological cancer not in complete remission. The primary efficacy outcome was objectively confirmed recurrent VTE, and the primary safety outcome was major bleeding as defined by the International Society

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on Thrombosis and Haemostasis (ISTH) criteria.[16] Secondary outcomes included clinically relevant non-major bleeding (CRNMB) by ISTH criteria and overall mortality.[17] The outcomes associated with different anticoagulant agents were then compared using network meta-analysis. Overall, they included 6,623 patients from 17 RCTs. They found each DOAC to be associated with similar efficacy but different safety profiles. Apixaban seemed to fare the best with lower risks of major bleeding compared with edoxaban, whereas edoxaban was also associated with a reduced risk of CRNMB events compared with rivaroxaban. When compared with LMWH, apixaban had a reduced risk of recurrent VTE without an increased risk of bleeding, whereas edoxaban and rivaroxaban were associated with an increased risk of bleeding.

Clinicians have long desired the "best" anticoagulant that is effective in preventing VTE with low risk of bleeding, especially in vulnerable populations such as those with cancer who are known to have high risks of both recurrent VTE and bleeding events.[3] Therefore, the investigators' efforts to address this question are appreciated. However, the results should be interpreted with caution as they are not direct head-to-head comparisons among different DOACs in the same cohort, and hence the evidence remains indirect. Patients enrolled in individual RCTs could have different baseline characteristics that could introduce bias, especially in a study-level meta-analysis. A previous meta-analysis showed that the annualized risks of recurrent VTE and major bleeding were lower in the subgroup of patients reporting a history of cancer randomized to VKA in studies of the general population (EINSTEIN, HOKUSAI, RE-COVER, AMPLIFY) compared with patients who were randomized to VKA in studies enrolling only those with cancer-associated thrombosis (CLOT, ONCENOX, CANTHANOX, and so on).[4] suggesting distinct differences in the populations, with higher risk of recurrence and bleeding in patients with active cancer enrolled in the cancer-associated thrombosis trials. All of these studies were also included in this systematic review and network meta-analysis by Fukisaki et al.[15] To answer this question definitively, a large RCT is needed comparing different DOACs head-to-head in the same trial; however, we are not aware of any such studies planned for patients with cancer-associated thrombosis at this time. The ongoing COBRRA trial (Comparison of Bleeding Risk Between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism; NCT03266783) comparing rivaroxaban to apixaban head-to-head in patients with acute VTE, but without cancer, might provide additional insights.

Although the use of DOACs represents significant advances in the treatment of cancer-associated thrombosis in recent years, many knowledge gaps persist.[18] The increased risk of bleeding, especially in patients with GI or GU lesions, remains a major concern. Other challenges with the current anticoagulant agents include use in patients with renal and liver dysfunction, drug-drug interactions, and more.[18] Novel anticoagulant therapies such as factor XI inhibitors might provide potential solutions to address these knowledge gaps. Studies are ongoing to investigate the use of abelacimab (a monoclonal antibody against factor XI and XIa) in the treatment of cancer-associated thrombosis: ASTER (A Study Comparing Abelacimab to Apixaban in the Treatment of Cancer-Associated VTE; NCT05171049), comparing abelacimab with apixaban in cancer patients where DOACs are not contraindicated, and MAGNOLIA (A Study Comparing Abelacimab to Dalteparin in the Treatment of Gastrointestinal/Genitourinary Cancer and Associated VTE; NCT05171075) comparing abelacimab with dalteparin in patients with unresected or metastatic GI/GU cancers. The recent report from the AZALEA-TIMI 71 (Safety and Tolerability of Abelacimab [MAA868] vs. Rivaroxaban in Patients With Atrial Fibrillation-Thrombolysis In Myocardial Infarction 71) phase II trial in patients with atrial fibrillation and moderate to high risk for stroke showed promising results with abelacimab.[19] Compared with rivaroxaban 20 mg daily, abelacimab 150 mg subcutaneously monthly showed a 67% risk reduction in composite CRNMB and major bleeding events, a 74% reduction in major bleeding, and a 93% risk reduction in GI bleeding events. Whether similar findings can be seen in large phase III trials in high-risk patients such as those with cancer-associated thrombosis while maintaining efficacy remains to be investigated.

In the meantime, studies such as the one by Fujisaki et al[15] could provide insights to guide clinicians in the anticoagulant management of cancer-associated thrombosis. Additionally, the "one size fits all" approach may not be appropriate, as the best anticoagulant for each individual patient may differ based on his or her unique medical and social considerations. Shared decision-making with patients for individualized treatment plans is needed. The road in search of the optimal anticoagulant for cancer-associated thrombosis continues—we have much to learn from current trials in progress in the near future.

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