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EDITORIAL COMMENT

Evolving Treatment Options for Cancer-Related Venous Thromboembolism*

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People with cancer are much more prone to experience venous thromboembolism (VTE) and its consequences, which include increased risk of short- and long-term mortality, need for urgent care and hospitalization, and increased health resource utilization (1,2). For the past decade and a half, low-molecular-weight heparin (LMWH) monotherapy for at least 6 months has been considered the standard of care for cancer-associated VTE (3). However, concerns had been raised about this standard given lack of full confirmation in a subsequent randomized trial (4) as well as demonstrated issues with patient adherence with this injectable option compared with oral anticoagulation (5). The advent of the class of drugs known as direct oral anticoagulants (DOACs) has increased available options to treat and prevent recurrent VTE in cancer patients. Promising data from initial randomized trials suggested a potential reduced risk of recurrent VTE in this setting with DOACs but at the cost of an increased risk of major bleeding as well as clinically relevant non-major bleeding (CRNMB) (6,7). Current guidelines therefore include both LMWHs and DOACs as options but caution against the use of the latter in patients at high risk for bleeding, particularly the subgroup of patients with gastrointestinal malignancies (8–10).

In this issue of *JACC: CardioOncology*, Sabatino et al. (11) provide a new meta-analysis of data of the latest 4 randomized controlled trials (RCTs) comparing the safety and efficacy of DOACs versus LMWH in the treatment of cancer-associated VTE. These 4 included RCTs comprising 2,907 patients evaluated different DOACs: edoxaban in the Hokusai VTE Cancer trial (7), rivaroxaban in the Select-D trial (6), and apixaban in the ADAM-VTE (Apixaban and Dalteparin in Active Malignancy Associated Venous Thromboembolism) and Caravaggio trials (12,13). All 4 RCTs utilized dalteparin, the only approved LMWH for this indication, as the control arm. An important strength of this meta-analysis is the inclusion of the very recently published Caravaggio study, which substantially increases sample size relative to prior such analyses.

The clinical utility of anticoagulation rests on the net benefit to individual patients when evaluating both efficacy and safety. In terms of efficacy, this meta-analysis favored DOACs, finding that dalteparin was associated with higher risk of recurrent VTE (risk ratio [RR]: 1.55; 95% confidence interval [CI]: 1.19 to 2.03; $p = 0.001$). In terms of safety, no significant differences were observed in major bleeding (RR: 0.74; 95% CI: 0.52 to 1.06; $p = 0.11$). However, there was a higher risk of CRNMB with DOACs (RR: 0.68 favoring dalteparin; 95% CI: 0.54 to 0.86; $p = 0.001$), particularly in patients with gastrointestinal malignances with an increased incidence of CRNMB in upper GI cancers ($p = 0.032$) compared with lower GI cancers ($p = 0.052$). Gastrointestinal bleeding was less frequent in the dalteparin group (RR: 0.53; 95% CI: 0.31 to 0.92; $p = 0.020$). Certainly, there are limitations to this meta-analysis. There is heterogeneity in

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the included clinical trials because they differ in their primary outcomes, design, and selection of included patients regarding the cancer type and stage. Moreover, this meta-analysis is not able to address major knowledge gaps in this setting. Which cancer patients are most likely to bleed on anticoagulation? What is the appropriate duration of anticoagulation? Should all incidentally discovered thrombi (e.g., visceral vein thrombi) be treated with full-dose anticoagulation? Many more studies are needed to appropriately answer these questions.

What are the clinical implications of this meta-analysis? First, the findings reaffirm that DOACs are at least as effective (and possibly more effective) than LMWH monotherapy for preventing recurrent VTE. Safety concerns raised by the initial RCTs regarding risk of bleeding, particularly in patients with gastrointestinal malignancies, are reiterated by this meta-analysis. In this context, the findings of the Caravaggio trial are of interest. In this study, there were no significant differences between patients randomized to apixaban or dalteparin either related to major bleeding outcomes (3.8% with apixaban and 4.0% with dalteparin; $p = 0.60$) or CRNMB (9.0% with apixaban and 6.0% with dalteparin). Clinicians may be tempted to draw the conclusion that apixaban is safer than other DOACs in patients with gastrointestinal malignancies. However, it should be noted that the Caravaggio trial (13) included a smaller proportion of patients with upper gastrointestinal cancers (the population most likely to have major bleeding) (4% on apixaban and 5.4% on dalteparin) compared with other included trials (6,12,14). Given this heterogeneity, it is premature to conclude that apixaban is superior to other DOACs until direct comparison studies are conducted.

Overall, however, the findings of this meta-analysis confirm that the introduction of DOACs is a major step forward toward the evolving management of anticoagulant therapy in cancer patients with VTE. It is important to recognize successes in medicine when they occur: the overwhelming majority of patients treated with DOACs for acute cancer-related VTE will not experience either recurrent VTE or major bleeding. This is important for people with cancer who already carry a major burden of illness. Selection of patients for DOAC versus LMWH therapy needs to be individualized, keeping in mind risk of bleeding, drug-drug interactions, financial cost, toxicity, and above all, patient preferences and values.

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REFERENCES

1. Chen H, Tao R, Zhao H, Jiang J, Yang J. Prevention of venous thromboembolism in patients with cancer with direct oral anticoagulants: a systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e19000.

2. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019;380:720–8.

3. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146–53.

4. Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 2015;314:677–86.

5. Khorana AA, McCrae KR, Milentijevic D, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost 2017;1:14–22.

6. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017–23.

7. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2017;378:615–24.

8. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020;38:496–520.

9. Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2019;20:e566–81.

10. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1891–4.

11. Sabatino J, De Rose S, Polimeni A, Sorrentino S, Indolfi C. Direct oral anticoagulants in patients with active cancer: a systematic review and meta-analysis. J Am Coll Cardiol CardioOnc 2020;2:428–40.

12. McBane Ii R, Loprinzi CL, Ashrani A, et al. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE trial. Thromb Haemost 2017;117:1952–61.

13. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382:1599–607.

14. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406–15.

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