Reducing complexity and burden of anticoagulant management in patients with cancer-associated venous thromboembolism

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TITLE	Apixaban for the treatment of venous thromboembolism associated with cancer.
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Venous thromboembolism (VTE) is the second leading cause of mortality and a major cause of morbidity in patients with cancer. Over the past two decades, VTE management in such patients involved daily subcutaneous injections of low-molecular-weight heparin, typically administered for as long as the malignancy was active. Despite the reduction in VTE recurrence associated with low-molecular-weight heparin compared to vitamin K antagonists, the continuous risk of bleeding and the burden of long-term injections affected decision-making by treating oncologists and compromised patients' compliance. Direct oral anticoagulants (DOAC) have been designed to improve the management of patients with thrombosis in terms of safety (major bleeding), drug and food interactions, and the administration mode. Since their introduction in the early 2000s, DOAC have dramatically advanced the treatment of patients with arterial and venous thrombosis in the general population; however, concerns regarding increased bleeding risk and interactions with anticancer therapies have significantly limited the inclusion of patients with cancer in major clinical trials. Nevertheless, studies evaluating the use of the direct anti-Xa agents edoxaban and rivaroxaban in oncology patients have shown benefits in reducing VTE recurrence, which have been somewhat offset by elevated bleeding risk, particularly in the gastrointestinal tract.

Given the improved safety profile of apixaban in non-cancer settings, the multinational, randomized, investigator-initiated, non-inferiority Caravaggio trial was designed to evaluate the efficacy and safety of this agent in managing cancer-associated VTE. Oncology patients (N=1,170) with symptomatic or incidental acute proximal deep vein thrombosis or pulmonary embolism from 119 medical centers were randomized to receive therapeutic doses of oral apixaban or subcutaneous dalteparin for 6 months. Results of this landmark study, published in *The New England Journal of Medicine* in 2020, demonstrated a VTE recurrence rate of 5.6% (32/576 patients) in the apixaban group and of 7.9% (46/579 patients) in the dalteparin group (hazard ratio=0.63; 95% confidence interval: 0.37-1.07; $P<0.001$ for non-inferiority) (Figure 1).[1] Major bleeding rates were similar in both groups (3.8% and 4.0%, respectively; hazard ratio=0.82; 95% confidence interval: 0.40-1.69; $P=0.60$). Importantly, no interaction between apixaban and anticancer therapies was observed.[2] These findings prompted broad implementation of DOAC in the treatment of cancer-associated VTE. Notably, this trial included only a minority of patients with hematologic malignancies, mainly those with lymphoma and myeloma, whereas patients with acute leukemia were considered ineligible for enrollment.

Since the balance between bleeding and thrombosis shifts toward bleeding during long-term anticoagulation, maintaining treatment safety is of paramount importance. Recently published results of the Apixaban Cancer Associated Thrombosis (API-CAT) trial demonstrated that extended anticoagulation with reduced-dose apixaban (2.5 mg twice daily) was associated with a lower incidence of clinically relevant bleeding, while preserving an efficacy comparable to that of full-dose apixaban (5 mg twice daily).[3]

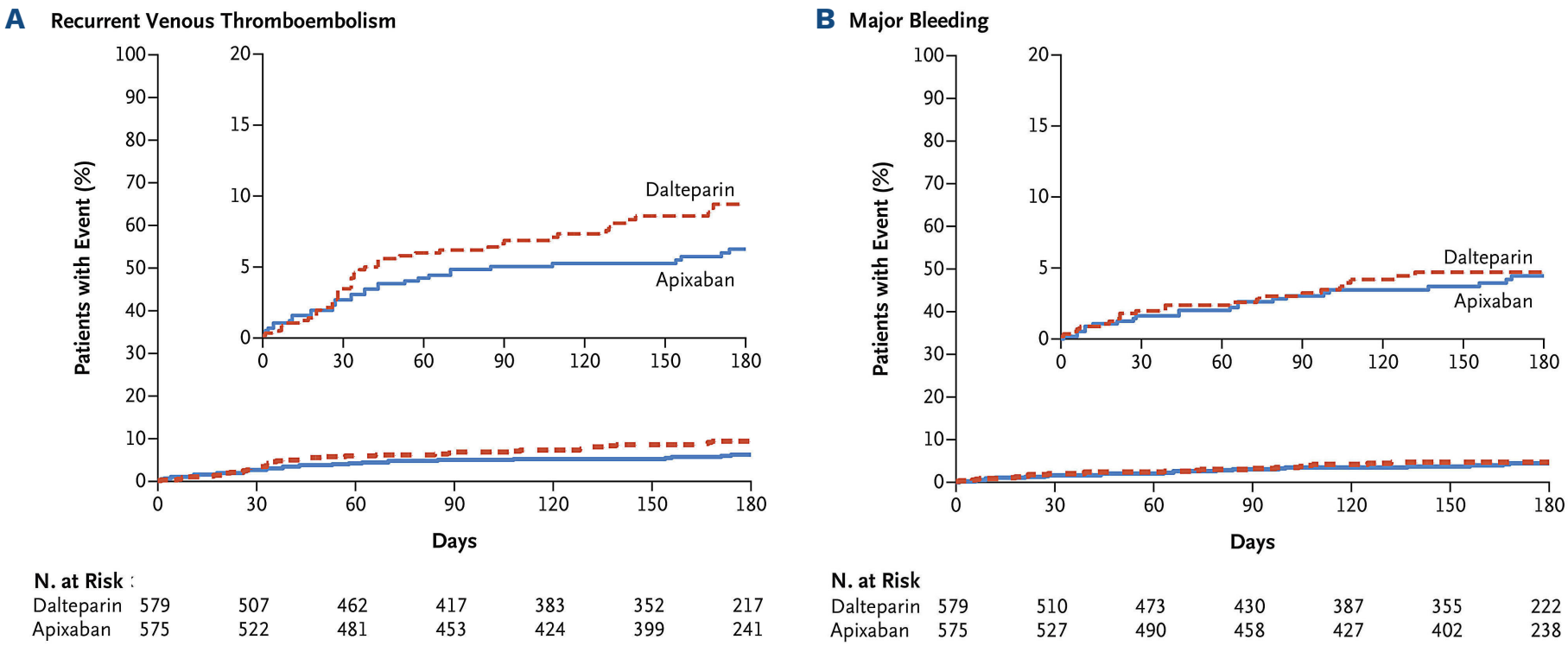

Figure 1. Recurrent venous thromboembolism and major bleeding in cancer patients treated with apixaban or dalteparin. (A, B) Cumulative percentages of patients with recurrent venous thromboembolism (A) and major bleeding (B) who received either oral apixaban or subcutaneous dalteparin. The insets show the same data on an expanded y axis. Figure reproduced, with permission, from Agnelli *et al.*[1]

The therapeutic modality, investigated in Caravaggio, API-CAT, and other trials of anti-Xa agents, has proven to be effective and safe for VTE treatment across a broad spectrum of patients with cancer. This simplified approach, endorsed by major clinical guidelines and widely adopted by clinicians, represents a paradigm shift, introducing meaningful advances in the standard of care for cancer-associated thrombosis.

Disclosures

BB served as a member of the Steering Committee of the Caravaggio study.

References

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