Direct Oral Anticoagulants for the Treatment of Cancer-Associated Venous Thromboembolism in Real-World Clinical Practice
— Caution Regarding Substantial Frequency of Bleeding Complications —

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Venous thromboembolism (VTE) is one of the most frequently encountered complications in patients with cancer, affecting morbidity and mortality in these specific cohorts. In cancer patients, the risk of developing VTE is 4–7-fold higher than in the general population. Various factors influence this increased risk of VTE, including patient-related factors, cancer-related factors, and treatment-related factors (Figure). The management of cancer-associated VTE is challenging because of the greater risk of recurrent VTE despite anticoagulant therapy (3-fold), as well as major bleeding complication (2-fold), compared with the corresponding risks in non-cancer patients. As for anticoagulant agents, for over a decade most clinical practice guidelines have recommended the use of low-molecular-weight heparin (LMWH) as the standard of care for treatment of cancer-associated VTE. This recommendation is based on pivotal randomized controlled trials (RCTs) comparing LMWH with warfarin in cancer-patient populations that demonstrated a lower incidence of recurrent VTE in LMWH groups than in warfarin groups with similar or superior safety profile. However, despite consensus guidelines recommending the use of LMWH as a first-line anticoagulant for cancer-associated VTE, suboptimal adherence to guidelines in daily practice has been reported, mainly due to the pain, bruising, and induration that accompany the injections inherent to LMWH therapy, which affect patient compliance and...
adherence to treatment.

Direct oral anticoagulants (DOACs) are promising therapeutic options for the treatment of cancer-associated VTE, given the great convenience of oral administration and the lack of any need for routine coagulation monitoring, compared with LMWH and warfarin, respectively. Recently, 3 RCTs with head-to-head comparisons of DOACs (edoxaban, rivaroxaban, and apixaban) and LMWH for the treatment of cancer-associated VTE have been published (Table). Unlike previous RCTs comparing DOACs with warfarin in the general population, these trials set strict inclusion criteria for patients with active cancer to reflect real-world oncology practice. The populations of these trials had rates of metastatic disease, systemic anti-cancer therapy, and mortality comparable to those of landmark trials comparing LMWH and warfarin for cancer-associated VTE, signifying the use of representative cancer populations. Although the Hokusai VTE Cancer trial\(^7\) and the SELECT-D trial\(^8\) showed similar trends towards a lower incidence of recurrent VTE with DOACs (edoxaban and rivaroxaban) compared with dalteparin, a higher risk of major bleeding in the DOACs arm was also revealed, particularly among patients with gastrointestinal cancer. In the latest Caravaggio trial,\(^9\) the non-inferiority of apixaban to dalteparin in terms of the efficacy outcome of recurrent VTE was observed, consistent with the findings of 2 other trials.\(^7,8\) In addition, an equivalent safety outcome of major bleeding in the apixaban group, compared with the dalteparin group, was also obtained, suggesting a favorable risk-benefit ratio for apixaban in patients with acute VTE and cancer. The disparity of the findings with reference to bleeding events between the former 2 trials and the last 1 may be related to the intrinsic bleeding profiles with different DOACs.\(^10\) However, the interpretation of these findings requires caution, because several differences in the primary outcomes, duration of treatment, and patient selection exist among the studies.

In this issue of the Journal, Ogino and coworkers\(^11\) investigate the current status of treatment for cancer-associated VTE using DOACs in real-world clinical settings. This retrospective observational study enrolled 303 patients with cancer-associated VTE treated with DOACs, and evaluated the incidence of recurrent VTE, major bleeding, and all-cause death with a relatively longer mean follow-up period of 665 days. During the follow-up period, recurrent VTE occurred in 26 of the 303 patients (8.6%), and major bleeding occurred in 54 patients (17.8%), indicating a more than 2-fold higher incidence of major bleeding in their cohort than in previously reported trials (Table). Using a multivariate Cox regression analysis, they reported that a major bleeding event was an independent risk factor correlated with all-cause death.

Possible explanations for the inconsistency in the incidence of major bleeding are the much higher rate of gastric cancer patients (14.5%) and the inclusion of cases of liver dysfunction (9.2%) in the current study, because Ogino et al demonstrated that both of these factors (gastric cancer and liver dysfunction) were independently correlated with major bleeding using a multivariate Cox analysis. Indeed, substantially low rates of patients with gastric cancer were seen (1.9% in the Hokusai VTE Cancer trial, 3% in the SELECT-D trial, and 4.0% for upper gastrointestinal cancer in the Caravaggio trial), and all 3 of these trials excluded patients with liver dysfunction. Although the distribution among DOACs used in the current study was unfortunately not described, the results clearly demonstrated a considerable risk of major bleeding in patients receiving DOAC therapy for cancer-associated VTE in real-world clinical practice.

To prevent serious bleeding complications, clinicians should consider several factors relevant to the risk of bleeding, such as renal and hepatic impairment, drug–drug interactions,\(^12\) cancer type,\(^13\) and damage to endothelial tissues induced by chemotherapy or the use of nonsteroidal anti-inflammatory drugs. Ongoing studies will further elucidate the optimal role of DOACs in such diverse

### Table. Randomized Controlled Trials Comparing Direct Oral Anticoagulants and Low-Molecular-Weight Heparin in Patients With Cancer-Associated VTE

| Study              | Hokusai Cancer VTE | SELECT-D | Caravaggio |
|--------------------|--------------------|----------|------------|
| Study period       | 12 months          | 6 months | 6 months   |
| Treatment arm      | Edoxaban           | Dalteparin | Rivaroxaban | Dalteparin | Apixaban | Dalteparin |
| n                  | 522                | 524      | 203        | 203        | 576      | 579        |
| Age, years (mean)  | 64.3               | 63.7     | 67         | 67         | 67.2     | 67.2       |
| Incidental VTE (%) | 32.0               | 33.0     | 52         | 53         | 20.1     | 19.7       |
| Metastatic disease (%) | 52.5             | 53.4     | 58         | 58         | 67.5*  | 68.4*      |
| Anticancer therapy (%) | 71.6             | 73.1     | 70         | 69         | 60.8    | 63.4       |
| Recurrent VTE (%)  | 7.9                | 11.3     | 4          | 11         | 5.6     | 7.9        |
| Major bleeding (%) | 6.9                | 4.0      | 6          | 4          | 3.8     | 4.0        |
| CRNMB (%)          | 14.6               | 11.1     | 13         | 4          | 9.0     | 6.0        |
| Mortality (%)      | 39.5               | 36.6     | 25         | 30         | 23.4    | 26.4       |

*Includes cases of recurrent locally advanced cancer in addition to those with metastatic disease. CI, confidence interval; CRNMB, clinical relevant non-major bleeding; HR, hazard ratio; NR, not reported; SD, standard deviation; VTE, venous thromboembolism.
subpopulations of cancer patients. In addition, future studies should aim at stratifying patients according to a low or high risk of major bleeding as well as VTE recurrence to provide informative guidance on how to better tailor individual treatment regimens.

Disclosure

None.

References

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013; 122: 1712–1723.
2. Pandoni, P, Lensing AWA, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002; 100: 3484–3488.
3. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, 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: 146–153.
4. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer. Arch Intern Med 2002; 162: 1729–1735.
5. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 2006; 119: 1062–1072.
6. Khorana AA, McCrae KR, Milentijevic D, Fortier J, Nelson WW, Laliberté F, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost 2017; 1: 14–22.
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 2018; 378: 615–624.
8. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, 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: 2017–2023.
9. Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020; 382: 1599–1607.
10. Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonists versus vitamin-K antagonists for stroke prevention in atrial fibrillation: A systematic review and meta-analysis. Stroke 2017; 48: 2494–2503.
11. Ogino Y, Ishigami T, Minamimoto Y, Kimura Y, Akiyama, E, Okada K, et al. Direct oral anticoagulant therapy for cancer-associated venous thromboembolism in routine clinical practice. Circ J 2020; 84: 1330–1338.
12. Riess H, Pandoni P, Harder S, Kreher S, Bauersachs R. Direct oral anticoagulants for the treatment of venous thromboembolism in cancer patients: Potential for drug-drug interactions. Crit Rev Oncol Hematol 2018; 132: 169–179.
13. Zakai NA, Walker RF, MacLehose RF, Adam TJ, Alonso A, Lutsey PL. Impact of anticoagulant choice on hospitalized bleeding risk when treating cancer-associated venous thromboembolism. J Thromb Haemost 2018; 16: 2403–2412.