Anticoagulation in cancer-associated thrombosis: Evidence from the trials

A recent webinar organized by Pfizer featured renowned hematology expert, Professor John Eikelboom, who shared the latest evidence-based treatment guidelines and developments in the management of cancer-associated thrombosis (CAT) with direct oral anticoagulants (DOACs).

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Venous thromboembolism (VTE) is one of the leading causes of morbidity and mortality in cancer patients, complicating cancer treatment and diminishing patients' quality of life.[1] Beyond the elevated risks of recurrence and major bleeding, cancer patients with VTE also have a higher case fatality rate.[2] Therefore, a comprehensive patient management plan includes both identifying individuals who would most likely benefit from VTE prophylaxis, as well as effectively treating patients to reduce their risk of VTE recurrence and mortality.[3]

Current guidelines on the management of CAT

Historically, low-molecular-weight heparin (LMWH) were the preferred treatment choices for CAT. However, LMWH has several notable limitations such as burdensome administration, high discontinuation rate, as well as limited efficacy data after 6 months.[4,5] Subsequent guidelines recommended DOACs as the first-line treatment of CAT, which offer several advantages over LMWH, including oral mode of administration, fixed-dose regimen, fewer drug-drug interactions, and not needing laboratory monitoring.[6-8]

Current guidelines recommend the use of DOACs or LMWH for the management of CAT depending on patient profile and treatment type (**Table 1**). The Oncologist and CHEST guidelines suggest apixaban, edoxaban or rivaroxaban as the preferred treatment option, followed by LMWHs as an alternative.[2,8] Meanwhile, prior to the publication of the CARAVAGGIO study that assessed the efficacy of apixaban versus LMWH, ASCO guidelines recommended LMWH or rivaroxaban for

Table 1. International guidelines on the management of CAT[2,3,8-11]

ASCO (2020)*	The Oncologist (2021)	ASH (2021)	Chest (2021)	ITAC (2022)	ESMO (2023)
• Initial anticoagulation with LMWH, UFH, fondaparinux or rivaroxaban • Long-term (up to 6 months) treatment with LMWH, edoxaban, or rivaroxaban • Extended (>6 months) treatment with LMWH, edoxaban, rivaroxaban or VKAs in select patients	• Initial therapy with apixaban, edoxaban, or rivaroxaban in patients without GI or GU cancer • LMWH in patients with GI or GU malignancies with luminal lesions	• Initial treatment with apixaban, rivaroxaban or LMWH • Long-term (3-6 months) treatment with apixaban, edoxaban or rivaroxaban preferred over LMWH • Extended (>6 months) treatment with DOACs or LMWH	• Initial treatment with apixaban, edoxaban, rivaroxaban • Apixaban or LMWH preferred in patients with luminal GI malignancies	• Initial anticoagulation with apixaban, rivaroxaban or edoxaban in patients without GI or GU malignancies, or LMWH • Long-term (up to 6 months) treatment with edoxaban, rivaroxaban or apixaban in patients with creatinine clearance ≥30 mL/min	• Initial treatment with apixaban, rivaroxaban, LMWH or UFH • Long-term (up to 6 months) and extended (>6 months) treatment with apixaban, edoxaban, rivaroxaban or LMWH

* Published prior to the approval of apixaban for CAT
ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; ESMO, European Society for Medical Oncology; ISTH, International Society on Thrombosis and Haemostasis; DOAC, direct oral anticoagulant; GI, gastrointestinal; GU, genitourinary; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist

initial treatment, and edoxaban or rivaroxaban for long-term maintenance.[3] The ASH, ITAC and ESMO panels, on the other hand, suggests apixaban, rivaroxaban or LMWH for the initial treatment of CAT, and apixaban, edoxaban or rivaroxaban over LMWH for treatment lasting anywhere between 3 and 6 months.[9-11]

DOACs are preferred over LMWH for the initial treatment for VTE in patients without gastric and gastroesophageal lesions[2]

The local consensus provided by the Hong Kong Society for Thrombosis and Haemostasis recommends a three-step approach for evaluating patients, wherein DOACs are a valid alternative in patients with a lower risk of bleeding, and those who do not have gastrointestinal mucosal abnormalities, renal and hepatic function impairment, as well as drug-drug interaction (**Figure 1**).[12]

Three pivotal randomized clinical trials demonstrated the efficacy of DOACs for CAT

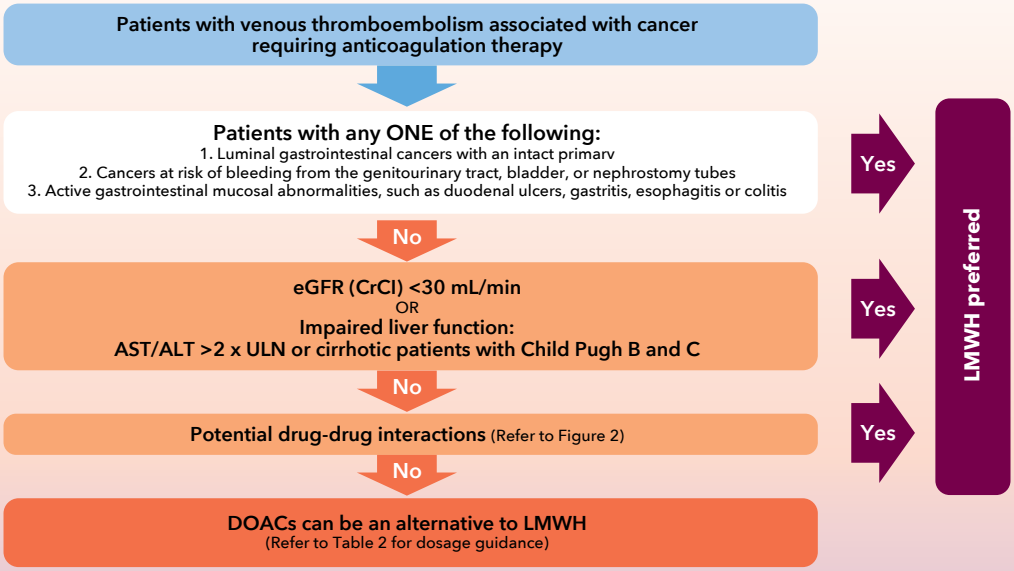
The use of DOACs in patients with CAT were assessed in three important trials that directly compared DOACs with LMWH. Hokusai VTE Cancer was an open-label, non-inferiority trial that assessed LMWH, followed by oral edoxaban or subcutaneous dalteparin in cancer patients who had acute symptomatic or incidental VTE. The primary outcome was a composite of recurrent VTE or major bleeding in 12 months. The study showed that edoxaban was noninferior to dalteparin in reducing the risk of recurrent VTE or major bleeding (12.8 vs 13.5%; hazard ratio [HR] 0.97; 95% confidence interval [CI], 0.70–1.36). In comparison to dalteparin, edoxaban had a lower rate of recurrent VTE (7.9 vs 11.3%; HR, 0.71; 95% CI, 0.48–1.06) but a higher rate of major bleeding (6.9 vs 4.0%; HR, 1.77, 95% CI, 1.03–3.04).[13]

Separately, SELECT-D was a prospective, randomized, open-label, multicenter pilot trial that compared rivaroxaban to dalteparin in patients with active cancer who had symptomatic pulmonary embolism (PE). The primary outcome was VTE recurrence over 6 months. Rivaroxaban was associated with relatively low VTE recurrence (4% vs 11%; HR, 0.43; 95% CI, 0.19–0.99) versus dalteparin, but higher rates of clinically relevant nonmajor bleeding (13% vs 4%; HR, 3.76; 95% CI, 1.63–8.69).[14]

The CARAVAGGIO study was a multinational, randomized, investigator-initiated, open-label, noninferiority trial wherein patients with symptomatic or incidental acute proximal deep-vein thrombosis or PE received oral apixaban or subcutaneous dalteparin for 6 months. The primary outcome was recurrent VTE during the trial period, and the principal safety outcome was major bleeding. In this study, apixaban was non-inferior to dalteparin in reducing the incidence of recurrent VTEs in patients with cancer-associated VTE (5.6 vs 7.9%; HR, 0.63; 95% CI, 0.37–1.07). No differences in the incidence of major bleeding were observed between patients receiving apixaban and dalteparin (3.8 vs 4.0%; HR, 0.82; 95% CI, 0.40–1.69).[15]

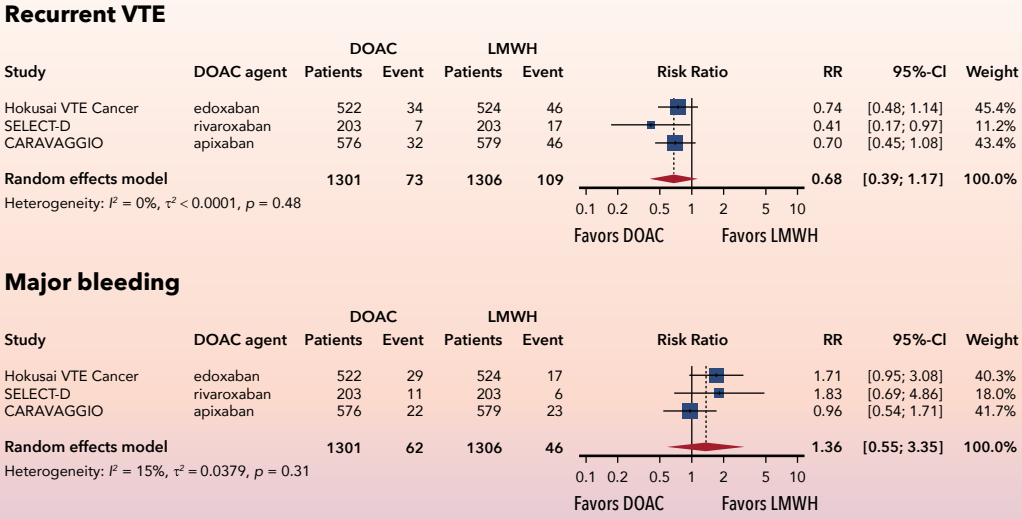
Both the Hokusai VTE Cancer and SELECT-D studies observed an increased risk of major bleeding, particularly in patients

Figure 1. HKSTH treatment decision pathway for CAT[12]



ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HKSTH, Hong Kong Society for Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; ULN, upper limit of normal
Adapted from Wong R, et al. 2020

Figure 2. Relative risk of recurrent VTE and major bleeding between the Hokusai VTE, SELECT-D and CARAVAGGIO trial[16]



CI, confidence interval; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; RR, relative risk; VTE venous thromboembolism.
Adapted from Mulder FI, et al. 2020

with gastrointestinal (GI) cancer (**Figure 2**).[16] In the Hokusai VTE Cancer trial, major bleeding events were significantly more frequent among patients with GI cancer treated with edoxaban than dalteparin (22 of 522; 4.2% vs 5 of 524; 1%).[17] In the SELECT-D study, patients with esophageal or gastroesophageal cancer receiving rivaroxaban experienced more major bleeding events than those receiving dalteparin (4 of 11; 36% vs 1 of 19; 5%).[14]

In contrast, the frequency of major bleeding in patients with GI cancer was low and similar between the apixaban and dalteparin groups (11 of 576; 1.9% vs 10 of 579; 1.7%). No major bleeding events occurred in patients with resected upper GI or colorectal cancer, thus supporting the safety of apixaban as an alternative to LMWH in patients with CAT, including those with GI cancer.[15,18] Following the publication of the CARAVAGGIO trial, apixaban has become the preferred DOAC to treat VTE in patients with cancer and luminal GI malignancies.[8]

The CARAVAGGIO study showed that apixaban was noninferior to dalteparin, without an increased risk of major bleeding.[15]

Real-world evidence of DOACs in Asia

The risk of recurrent VTE and bleeding between Asian patients receiving DOAC and LMWH was assessed in two retrospective studies conducted in Taiwan and South Korea. Both studies found that the use of a DOAC was associated with a similar risk for recurrent VTE or major bleeding when compared with LMWH. Nonetheless, in the Taiwanese study, DOAC was associated with a significantly lower rate of GI bleeding. These results highlight the importance of choosing the most appropriate initial VTE treatment choice for cancer patients to prevent VTE recurrence and bleeding in at-risk patients.[19,20]

Primary prevention of CAT and management of thrombocytopenia

The primary prevention of VTE in cancer patients varies depending on patient profile. The Khorana score is a validated risk assessment tool used to identify patients with an increased risk of VTE (range, 0 to 6, with higher scores indicating a higher risk of VTE). Two major studies evaluated the efficacy of DOAC thromboprophylaxis in high-risk ambulatory cancer patients with a Khorana score ≥2.[21,22]

The CASSINI study compared rivaroxaban against placebo in patients with a solid tumor or lymphoma, and found that the former did not result in a significantly lower incidence of VTE or death in the 180-day trial period.[21] Meanwhile, the AVERT study, which compared apixaban thromboprophylaxis with placebo, found that apixaban therapy resulted in a significantly lower rate of VTE, without any significant difference in mortality. However, there was an increased incidence of major bleeding in the treatment arm.[22] Although effective for VTE prevention, guidelines do not recommend routine use of thromboprophylaxis, except in those at highest risk.[3,9]

Thrombocytopenia is a common complication in cancer patients, and the treatment of CAT in the context of thrombocytopenia is challenging since patients remain at high risk of both recurrent VTE and bleeding. In patients with severe thrombocytopenia (platelet count <50,000/μL), the therapeutic strategy needs to take into account the risks of bleeding and recurrent VTE, as well as the severity and estimated duration of thrombocytopenia.[23]

Unanswered questions and future directions in the management of CAT

Despite the promising developments in improving the outcomes of CAT, many issues remain. Among them, the optimal approach to primary prophylaxis in hospitalized and ambulatory patients, the appropriate duration of therapy, and the management of high-risk bleeding populations (e.g., patients with thrombocytopenia or central nervous system metastases) are still unclear.[24] Many ongoing trials, such as the EVE trial that assesses the appropriate dose of apixaban in preventing secondary CAT, and the ONCO PE trial that investigates the optimal duration of DOAC in cancer-associated, low-risk PE patients may help address these unanswered questions.[25,26]

Conclusion

Patients with cancer-associated VTE have a considerable risk of recurrence and bleeding, which usually require complex and comprehensive management strategies. Many guidelines now support the first-line use of DOACs over LMWH for the treatment of VTE in patients with cancer based on latest clinical trial results.[2,8] However, with many unanswered questions remaining, ongoing and future studies are an important endeavor to help improve patient outcomes.[24-26]

Insights from the expert

Q. How do you manage patients who experience worsened VTE while on a DOAC?

Owing to the lack of evidence to guide decision-making, several options can be considered. Taking into account possible issues with GI absorption, patients could switch to LMWH given once daily or in divided doses twice daily; if they are deemed to be at very high risk or if they experience recurrent events on LMWH they could be switched to a higher dose of LMWH (e.g., from 100 units/kg to 120–150 units/kg twice daily). Once the thrombosis is controlled, consideration could be given to switching back to apixaban with the addition of aspirin.

Q. What recommendations would you have for treating a cancer patient with myocardial infarction post-percutaneous coronary intervention?

While it may be unclear whether the arterial thrombosis is caused primarily by cancer-related hypercoagulability, or by plaque rupture with superimposed thrombus formation in a cancer patient, patients are generally treated the same way after the first event. If the patient has recurrent events or there are other reasons to consider the event to be cancer-related, a DOAC can be combined with anti-platelet therapy.

Q. In your experience, what is the optimal duration of management in cancer patients who develop VTE?

In cancer patients who develop VTE, indefinite treatment is usually recommended. Anticoagulation treatment is usually only stopped once the patient is no longer receiving treatment for cancer and is thought to be cancer-free.

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