The Challenge of Thromboprophylaxis in Cancer Patients—Balancing the Thrombotic and Bleeding Risks

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Thrombosis is responsible for one in four deaths worldwide,[1] and many of these deaths could have been prevented by timely initiation of anti-thrombotic therapy. Thrombosis is also one of the leading causes of death among cancer patients.[2,3] The association between cancer and thrombosis has been described long ago (in 1823) by Jean Baptiste Bouillaud, but the condition is named Trousseau syndrome in the honour of Armand Trousseau who diagnosed the syndrome to himself in 1865 and died from it in 1867.[2] The pathophysiology of cancer-associated venous thrombosis is intensively studied, owing to its complexity that likely involves both the intrinsic and extrinsic pathway in a cancer type-specific manner.[4]

The incidence of cancer-related venous thromboembolism (VTE) is high, has increased in recent decades (likely owing to better awareness of the syndrome, diagnostic improvements and better treatment strategies with longer survival of cancer patients) and is associated with increased risk of recurrent events and high mortality[2,5,6] (see ►**Table 1**). Biologically aggressive, rapidly metastatic cancers with short survival time are associated with the greatest thrombogenic potential, and the incidence of VTE is the highest in the first months post-cancer diagnosis, possibly owing to anti-cancer treatment initiation (which may be thrombogenic) and high early mortality rates in patients with the highest risk of VTE.[2]

Malignancy is generally associated with a hyper-coagulable state that results from various combinations of factors related to cancer itself, anti-cancer treatments and the patient (see ►**Table 1**), but cancer patients also have increased risk of bleeding owing to cancer-associated alterations in haemostasis (e.g. liver infiltration causing thrombocytopaenia or coagulopathy, haematologic malignancies causing coagulation defects, direct erosion of blood vessels by cancer, highly vascular malignancies prone to bleeding such as gastrointestinal malignancies, intracranial tumours) or anti-cancer treatment-associated side effects (e.g. surgery, tissue damage post-irradiation, platelet alterations caused by chemotherapy or irradiation).[7,8] The currently recommended treatment strategies for cancer-associated VTE are summarized in ►**Table 1**.

With conventional therapy, cancer patients have higher rates of recurrent VTE and two- to sixfold greater risk of anticoagulant-related major bleeding (an absolute incidence of 3–9% in the first 6 months of treatment) compared with non-cancer patients,[7] but available data suggest that the clinical presentation and course of anticoagulant-related major bleedings are not more severe in cancer patients compared with those without cancer.[7] Nevertheless, the physician's reluctance to use anticoagulant therapy in the anticipation of serious bleeding and the limitations (see ►**Table 1**) of the currently recommended first-choice therapy with low molecular weight heparin (LMWH) or, alternatively, vitamin K antagonists (VKAs) often result in significant underuse of thromboprophylaxis in cancer patients.[2,9] Non-VKA oral anticoagulants (NOACs)—direct thrombin inhibitor dabigatran and direct inhibitors of activated factor X rivaroxaban, apixaban and edoxaban—are increasingly investigated as viable options for many unmet needs in the treatment of cancer-associated thrombosis.

However, currently available data on the NOACs use in cancer patients are limited. In the meta-analyses of randomized clinical trials (see ►**Table 1**), NOACs use in cancer patients was associated with lower recurrence of VTE and similar rates of major or clinically relevant non-major (CRNM) bleeding events, compared with dalteparin or warfarin,[10,11] and in a recent systematic review and meta-analysis of six 'real-world' observational studies of patients with active cancer taking rivaroxaban for secondary prevention of VTE, the weighted average rates of recurrent VTE (4.2%; 95% confidence interval [CI], 2.6–6.6%) and major bleeding (2.9%; 95% CI, 1.6–5.0%) among rivaroxaban-managed patients were broadly similar to those seen in recent randomized trials of anticoagulation in cancer-related thrombosis.[12] A pilot, randomized, open-label trial of rivaroxaban

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Table 1 A summary of cancer-associated thrombotic and bleeding risk characteristics[2–6,9,17,18]

Cancer-associated thrombosis	Treatment strategies for cancer-associated thrombosis
• The population-attributable risk of active malignancy underlying a VTE has been reported to be 18% (95% CI, 13.4–22.6), and ~20–30% of all incident VTEs are cancer-associated • Compared with the general population, cancer patients have up to sevenfold greater risk of VTEs, with cumulative incidence of 1–14% depending on the studied cohort	**Primary prevention** • Routine thromboprophylaxis in *all* cancer patients is not recommended by international guidelines—e.g. the European Society for Medical Oncology (ESMO) or American Society for Clinical Oncology (ASCO) • Primary prevention using LMWH or aspirin should be used in most hospitalized patients with active cancer or selected high-risk ambulatory patients (e.g. those with multiple myeloma under active treatment) • Patients undergoing major cancer surgery should receive thromboprophylaxis before and $\geq$ 7–10 d after surgery
• Time trends show a 28% increase in the incidence rates of cancer-associated VTE since late 1980s	**Treatment of acute cancer-associated VTE** • LMWH is currently recommended as the first-choice therapy, owing to lower recurrence rates and comparable bleeding risk with LMWH vs. VKAs
• Different cancer types and stages are associated with different risks of VTE • Pancreas, brain, lung and ovarian cancers portend the highest risk, as well as lymphomas, myeloma and kidney, GI and bone cancers, while breast and prostate cancers bear relatively low risk for VTE • Metastatic disease at the time of cancer diagnosis is among the strongest predictors of VTE	***Limitations of VKA for treatment of cancer-associated VTE*** • Lower efficacy than LMWH • Interactions with food and many drugs including chemotherapy • Narrow therapeutic dosing window • The need for frequent laboratory monitoring of anticoagulation intensity and dose adjustments • Wide INR fluctuations in patients with hepatic metastases
• The incidence of VTE is the highest in the first months of cancer diagnosis, gradually declining thereafter, especially after 1 y	***Limitations of LMWH for treatment of cancer-associated VTE*** • Parenteral administration, associated with local bruising, inconvenient on a long-term basis, still relatively high VTE recurrence rate (7–8% in RCTs)
• Anti-cancer treatments (i.e. surgery, chemotherapy, hormonal therapy, immunomodulatory drugs, angiogenesis suppressants, erythropoiesis stimulants, blood transfusions, central venous catheters) increase the risk of VTE • Patient-related factors such as older age, black ethnicity, co-morbid conditions, a history of prior VTE, prolonged immobilization are also associated with increased risk of VTE	**NOACs in cancer patients—available evidence from trials** • *Meta-analysis* of 6 RCTs in comparing NOACs vs. VKAs in VTE showed significant reduction in recurrent VTE (RR, 0.57; 95% CI, 0.36–0.91) with NOACs and comparable major bleeding rates (OR, 0.77; 95% CI, 0.44–1.33) in the sub-group of cancer patients[10] • *Meta-analysis* of 12 RCTS comparing NOACs vs. LMWH/VKA (a total of 1,388 cancer patients on NOACs) showed similar major bleeding rates with NOACs vs. comparator (3.0% vs. 4.6%, RR, 0.64; 95% CI, 0.37–1.12) and similar CRNM bleeding rates (14% vs. 20%, RR, 0.83; 95% CI, 0.64–1.07)[11] • **The SELECT-D pilot RCT** of rivaroxaban vs. dalteparin in cancer-associated VTE (n = 203) showed the 6-mo cumulative VTE recurrence rate of 11% (95% CI, 7–16%) with dalteparin and 4% (95% CI, 2–9%) with rivaroxaban (HR, 0.43; 95% CI, 0.19–0.99), the 6-mo cumulative rate of major bleeding of 4% (95% CI, 2–8%) for dalteparin and 6% (95% CI, 3–11%) for rivaroxaban (HR, 1.83; 95% CI, 0.68–4.96); corresponding rates of CRNM bleeding were 4% (95% CI, 2–9%) and 13% (95% CI, 9–19%), respectively (HR, 3.76; 95% CI, 1.63–8.69)[13] • **The HOKUSAI VTE Cancer study** of edoxaban vs. dalteparin in cancer-associated VTE (n = 1,050) showed non-inferiority of edoxaban for the composite outcome of recurrent VTE or major bleeding (12.8% vs. 13.5%; HR, 0.97; 95% CI, 0.70–1.36), with an absolute 3.4% reduction in the risk of recurrent VTE and an absolute 2.9% increase in the risk of major bleeding[14]
• Specific clinical presentation, that is, bilateral deep venous thrombosis and upper limb VTE, suggest a greater likelihood of a cancer-associated VTE	**NOACs in cancer patents—ongoing trials** ADAM-VTE (apixaban vs. dalteparin), CARAVAGGIO (apixaban vs. dalteparin), CANVAS (dabigatran, rivaroxaban, apixaban or edoxaban vs. LMWH or warfarin), the CALLISTO clinical research program (the efficacy and safety of rivaroxaban in cancer-associated thrombosis)
• Cancer-associated venous thrombosis is associated with a sixfold greater mortality compared with a VTE in non-cancer patients	**Knowledge gaps to be addressed in on-going/future studies:** optimal prevention and treatment of cancer-associated thrombosis, effectiveness and safety of NOACs for extended treatment ($>$ 6 mo), dosing and continuation of NOACs in patients with chemotherapy-induced side effects, temporary interruptions for invasive procedures, treatment persistence, patient satisfaction and quality of life, etc.

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; LMWH, low molecular weight heparin; NMCR, non-major clinically relevant; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.

(15 mg twice daily for 3 weeks and then 20 mg once daily) versus dalteparin for secondary prevention of VTE in patients with active cancer ($n = 203$) reported lower rates of recurrent VTE, comparable rates of major bleeding and higher rates of CRNM bleeds with rivaroxaban in comparison to dalteparin (see ►**Table 1**).[13] In the recently completed randomized Hokusai VTE Cancer study[14] that compared edoxaban versus dalteparin in 1,050 patients with cancer-associated VTE, edoxaban was non-inferior for the combined primary outcome (see ►**Table 1**), with an absolute 3.4% risk reduction in recurrent VTE, however at the cost of an absolute 2.9% risk increase in major bleeding.

Major bleeds in patients with VTE have heterogeneous severity and clinical impact.[7,15] In this issue of *Thrombosis and Haemostasis*, Kraaijpoel et al presented a descriptive analysis of the major bleeding sites, associated cancer types, clinical presentation, course and management in the Hokusai VTE Cancer study.[16] In the safety population ($n = 1,046$), major bleeding events with edoxaban (6.1% vs. 3.1% with dalteparin) occurred at a median of 2 months of treatment (a month earlier than with dalteparin). There were no fatal bleeds on edoxaban (2 on dalteparin). In general, edoxaban-related bleeding events were slightly less severe, less often required hospitalization or admission to the intensive care unit but were more frequently treated with red blood cell transfusion. Cancer treatment was interrupted or withdrawn in 28.1% of patients with edoxaban-related bleeding and 25% of those with dalteparin-related bleeding. The excess in major bleeding in the edoxaban arm was driven by increased rate of upper gastrointestinal bleeding that was more severe with edoxaban versus dalteparin, and most frequently occurred in patients with all types of gastrointestinal cancers (mostly non-resected), thus suggesting that edoxaban could exacerbate bleeding from the tumour itself. Overall, the clinical impact of major bleeding was comparable with both edoxaban and dalteparin treatment, suggesting that oral edoxaban 60 mg once daily (or 30 mg once daily if the pre-specified dose-reduction criteria are met) is an appropriate alternative to subcutaneous dalteparin in most patients with cancer-associated VTE, whereas the use of edoxaban in patients with a gastrointestinal cancer would require a case-by-case consideration of risks and benefits of such treatment.

These findings are broadly in line with previous reports suggesting no profound difference in the clinical course and outcomes of NOACs-associated major bleedings in comparison to the bleeding events associated with LMWH or VKAs,[7,11] which may be reassuring for physician who treat cancer patients with VTE. Overall, available data generally favour NOACs use in cancer patients but there are many unmet needs currently investigated in the on-going studies (see ►**Table 1**), including possible interactions of NOACs with various anticancer therapies[8] and persistence to treatment on a long-term basis. Until more data are available, a detailed individual assessment of patient's risk profile and consideration of patient's personal values and preferences would, as always, provide the best results in balancing and optimal management of the thrombotic and bleeding risk in a cancer patient.

Conflict of Interest
None.

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