

Safety of Apixaban for Cancer-Associated Thrombosis

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Venous thromboembolism (VTE) is a common complication in patients with cancer and is associated with significant morbimortality and adverse outcomes.¹ Management of cancer-associated thrombosis poses challenges for clinicians. Compared with other patients with VTE, patients with cancer-associated VTE who receive anticoagulant therapy have a higher risk both for recurrent VTE and for bleeding complications.² Until recently, subcutaneous low-molecular-weight heparin (LMWH) monotherapy has been the standard of treatment for cancer-associated thrombosis.^{3–5} Compared with vitamin K antagonists, LMWHs may lead to reduction in VTE events though not in bleeding or mortality.⁶

Direct oral anticoagulants (DOACs) have become the anticoagulant treatment of choice for the majority of patients with acute VTE.³ Compared with vitamin K antagonists, in most subgroups, they are similar in efficacy but are associated with lower risk of major bleeding.⁷ In addition, these drugs are given in fixed doses and do not require laboratory monitoring of the anticoagulant effect. Several trials have assessed the efficacy and safety of DOACs for patients with cancer-associated thrombosis.^{8–11} A recent meta-analysis included four randomized trials (2,907 patients with cancer-related VTE) that compared apixaban (two trials), edoxaban (one trial), or rivaroxaban (one trial) with dalteparin.¹² Risk for recurrent VTE was 3.5% absolute points lower in patients treated with a DOAC, but clinically relevant nonmajor bleeding (CRNMB) was 4.7% higher. Though the risk of major bleeding was nonsignificantly higher, DOACs had a 6.6% significant absolute increase in the subgroup who had gastrointestinal cancer.¹² Broadly similar observations have been noted in other meta-analyses

of the DOACs for the treatment of acute VTE associated with cancer.¹³

The study by Ageno et al in this issue of *Thrombosis and Haemostasis* is a welcome addition to the body of evidence.¹⁴ Using data from the multicenter, randomized, open-label, noninferiority Caravaggio trial,¹¹ the authors investigated sites of bleeding, clinical presentation, and course of major bleeding. Among 576 patients randomized to apixaban, major bleeding occurred in 22 (3.8%) patients, compared with 23 of 579 (4.0%) patients randomized to dalteparin. The sites of major bleeding were similar between the two treatment groups. The clinical presentation of major bleeding was severe or fatal in 6 patients on apixaban and in 5 patients on dalteparin, while the clinical course was severe in 5 patients on apixaban and in 7 patients on dalteparin. Major bleeding occurred in 9 patients with gastrointestinal cancer in each treatment group. Finally, there were 52 CRNMBs in the apixaban group and 35 in the dalteparin group. Strengths of the study include high-quality data and thorough reporting. Study limitations comprise lack of competing risk assessment, and a low number of bleeding events that precludes further phenotyping, if a true difference were to exist.

The results reported by Ageno et al come from the largest trial to date evaluating the efficacy and safety of a DOAC for patients with cancer-associated thrombosis and suggest that treatment with apixaban might be associated with a better safety profile than other DOACs. In the Hokusai VTE Cancer Trial, major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.03–3.04)⁸ (→ **Table 1**). There was also more CRNMB in patients receiving edoxaban

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Table 1 Major randomized trials of direct oral anticoagulants for the treatment of cancer-associated thrombosis

Study	Hokusai Cancer VTE ⁸	SELECT-D ⁹	Caravaggio ¹¹
Inclusion criteria	<p>Male or female subjects with age ≥ 18 years</p> <p>Confirmed symptomatic or unsuspected VTE</p> <p>Cancer (other than basal-cell or squamous-cell carcinoma of the skin), either active or diagnosed within 2 years prior to randomization</p> <p>Intention for long-term treatment with parenteral LMWH</p> <p>Able to provide written informed consent</p>	<p>Active cancer (other than basal-cell or squamous-cell carcinoma of the skin) and confirmed VTE</p> <p>Age ≥ 18 years</p> <p>Weight ≥ 40 kg</p> <p>ECOG ≤ 2</p> <p>Adequate hematologic, hepatic, and renal function</p>	<p>Active cancer (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor or known intracerebral metastases and acute leukemia) and confirmed VTE</p>
Exclusion criteria	<p>Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of VTE</p> <p>More than 72 hours pretreatment with anticoagulant treatment prior to randomization to treat the current episode</p> <p>Treatment with therapeutic doses of an anticoagulant other than that used for pretreatment of the current VTE episode prior to randomization</p> <p>Active bleeding or any contraindication for treatment with dalteparin or edoxaban</p> <p>Indication for dalteparin other than VTE</p> <p>ECOG of 3 or 4</p> <p>Calculated CrCl < 30 mL/min</p> <p>History of HIT</p> <p>Acute hepatitis, chronic active hepatitis, liver cirrhosis</p> <p>Life expectancy < 3 months</p> <p>Platelet count $< 50,000$/mL</p> <p>Uncontrolled hypertension</p> <p>Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding</p> <p>Chronic treatment with nonaspirin NSAIDs</p> <p>Treatment with aspirin or dual antiplatelet therapy</p> <p>Treatment with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or</p>	<p>Previous treatment dose of anticoagulant or > 75 mg aspirin per day</p> <p>History of VTE, clinically significant liver disease, bacterial endocarditis, active bleeding or high risk of bleeding, or uncontrolled hypertension</p> <p>Inadequate contraceptive measures if of childbearing potential</p> <p>Concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers or P-gp inhibitors or inducers</p>	<p>Age < 18 years</p> <p>ECOG of 3 or 4</p> <p>Life expectancy of less than 6 months</p> <p>Administration of therapeutic doses of LMWH, fondaparinux, or UFH for more than 72 hours before randomization</p> <p>3 or more doses of a VKA before randomization</p> <p>Thrombectomy, vena cava filter insertion, or thrombolysis used to manage the index episode</p> <p>Indication for anticoagulant treatment for a disease other than the index VTE episode</p> <p>Concomitant use of strong inhibitors or inducers of both cytochrome P-450 3A4 and P-gp</p> <p>Concomitant thienopyridine, aspirin, or dual antiplatelet therapy</p> <p>Active bleeding or high risk of bleeding contraindicating anticoagulant treatment</p> <p>Recent brain, spinal, or ophthalmic surgery</p> <p>Hemoglobin level < 8 g/dL or platelet count $< 75,000$/mL or history of HIT</p> <p>CrCl < 30 mL/min</p> <p>Acute hepatitis, chronic active hepatitis, liver cirrhosis</p> <p>Uncontrolled hypertension</p> <p>Bacterial endocarditis</p> <p>Hypersensitivity to the study drugs</p> <p>Women of childbearing</p>

Table 1 (Continued)

Study	Hokusai Cancer VTE ⁸		SELECT-D ⁹		Caravaggio ¹¹	
	saquinavir, ketoconazole, itraconazole, erythromycin, azithromycin, or clarithromycin at the time of randomization				potential without proper contraceptive measures, and women who are pregnant or breast feeding	
Definition of major bleeding	Overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death		Clinically overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death		Clinically overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to a transfusion of 2 or more units of blood, occurred in a critical site, necessitated surgical intervention or contributed to death	
Definition of CRNMB	Overt not meeting the criteria for major bleeding, that requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life		Overt bleeding with medical intervention Unscheduled contact with a physician Interruption or discontinuation of a study drug Discomfort or impairment of activities of daily life		Acute clinically overt bleeding that does not meet the criteria for major and consists of: Any bleeding compromising hemodynamics Spontaneous hematoma larger than 25 cm ² , or 100 cm ² if there was a traumatic cause Intramuscular hematoma documented by ultrasonography Epistaxis or gingival bleeding requiring tamponade or other medical intervention or bleeding from venipuncture for > 5 minutes Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after invasive procedures Hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention Any other bleeding considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.	
Anticoagulant	Edoxaban	Dalteparin	Rivaroxaban	Dalteparin	Apixaban	Dalteparin
Mean age, years	64.3	63.7	67 ^a	67 ^a	67.2	67.2
Weight, kg	78.8	79.1	–	–	75.7	76.1

(Continued)

Table 1 (Continued)

Study	Hokusai Cancer VTE ⁸		SELECT-D ⁹		Caravaggio ¹¹	
CrCl < 50 mL/min, %	7.3	6.5	–	–	8.9	10.5
Metastatic disease, %	52.2	53.4	58	58	67.5	68.4
Anticancer treatment, %	71.6	73.1	69	70	60.8	63.4
Major bleeding, %	6.9	4.0	5.4	3.0	3.8	4.0
CRNMB, %	14.6	11.1	12.3	3.4	9.0	6.0
Major or CRNMB, %	18.6	13.9	–	–	12.2	9.7
Major GI bleeding, %	3.8	1.1	3.9	2.0	1.9	1.7

Abbreviations: CrCl, creatinine clearance; CRNMB, clinically relevant nonmajor bleeding; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
^aMedian values.

(HR, 1.38; 95% CI, 0.98–1.94). In a subgroup analysis of patients with gastrointestinal cancer, major bleeding rates favored dalteparin therapy (edoxaban 13.2% vs. dalteparin 2.4%; *p* = 0.02). Bleeding rates were similar in the patients with nongastrointestinal cancer. There were no fatal bleeding events in the edoxaban arm and one fatal bleed in the dalteparin arm. In the SELECT-D trial, major bleeding rates were 6% for rivaroxaban and 4% for dalteparin (HR, 1.83; 95% CI, 0.68–4.96).⁹ Most major bleeding events involved the gastrointestinal tract. Patients with upper gastrointestinal cancer were more likely to experience a major bleed with rivaroxaban compared with dalteparin. CRNMB was also more frequent with rivaroxaban (13% vs. 4%; HR, 3.76; 95% CI, 1.63–8.69) and primarily involved gastrointestinal or genitourinary sources.

The potential explanations for the differences in the risks of major bleeding events remain debatable, including the

differences in patient characteristics, protocol designs, distinct prespecified bleeding definitions, the anticoagulant dose or frequency (once vs. twice daily dosing), or other factors (►Table 1). The baseline characteristics of the patients randomized in Caravaggio were comparable with those of the previous studies.^{8,9} There were similar percentages of enrolled patients with gastrointestinal cancers as well as with active and metastatic cancers in these trials. The proportion of patients who were receiving anticancer treatment or had moderate renal insufficiency were also comparable. However, the presence of active luminal tumors (i.e., luminal gastrointestinal or genitourinary tumors) was not reported in either study. In addition, there were minor differences in the definition of major bleeding across these four trials (►Table 1). Nevertheless, similar rates of major bleeding event rates in the dalteparin arm of these trials

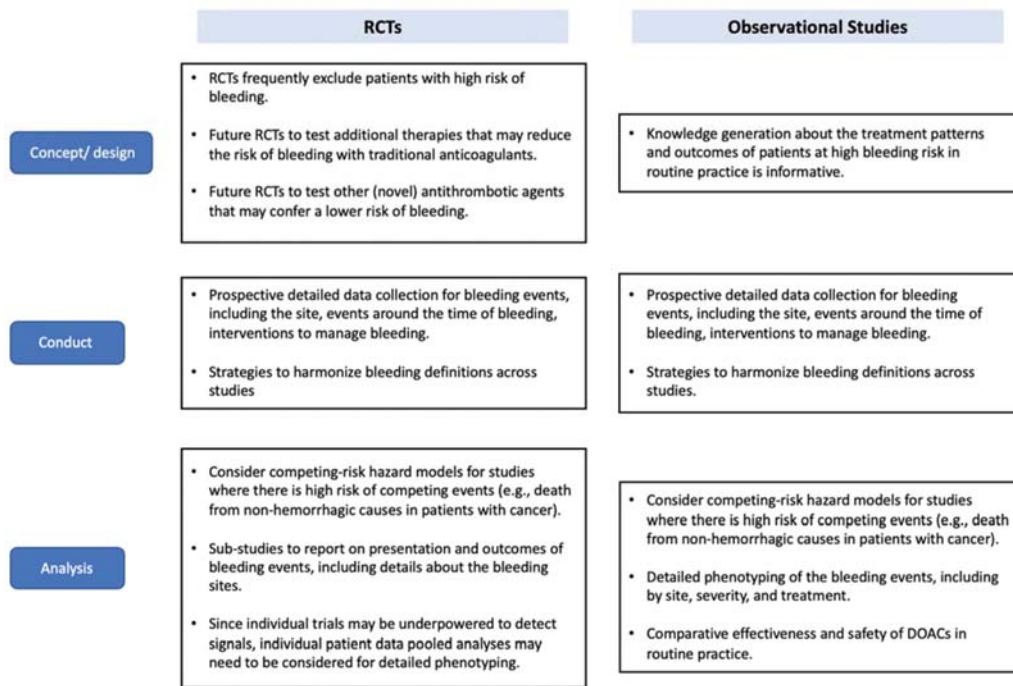


Fig. 1 Considerations for improved knowledge generation for bleeding events in patients receiving anticoagulant therapy. DOACs, direct oral anticoagulants; RCTs, randomized controlled trials.

make it unlikely that a large difference in case mix existed between them. Importantly, dabigatran, has not been specifically studied in this subgroup of patients.

What do we learn from this study for our clinical practice? DOACs provide an attractive alternative to LMWH in the treatment of VTE in cancer patients.¹⁵ At present, due to conflicting data, the use of DOAC for patients with gastrointestinal or urological malignancies would appear risky. If they have to be used for these patients, indirect comparisons suggest that apixaban might be the safest of the DOAC medications. Since it is unlikely that different DOACs will be compared in randomized controlled trials in near future, evidence derived from routine practice can provide key insights regarding how each anticoagulant is used under routine care conditions in diverse patient populations (► **Fig. 1**). For that purpose, data from large registries will complement the perspective from randomized studies.^{16–18}

Conflict of Interest

B.B. reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to a specific type of IVC filters. D.J. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI, and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, ROVI, and Sanofi; received grants for clinical research from Daiichi Sankyo, Sanofi, and ROVI.

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