Direct Oral Anticoagulants in Patients Cancer

BY LISA LOHR, PHARMD, BCPS, BCOP

In the treatment of cancer-associated thrombosis (CAT), injectable low molecular weight heparins (LMWHs) have been shown to be more effective than oral warfarin. However, LMWHs are expensive and many patients object to giving themselves injections for a prolonged period of time. Direct oral anticoagulants (DOACs), which inhibit factor Xa or thrombin, have in general been shown to be effective and safe. The original registration trials of these agents did not exclude patients with cancer and post hoc subgroup analyses did not show any serious safety or efficacy signals. Prospective clinical trials for CAT have recently been published or data presented for three factor Xa inhibitors—apixaban, rivaroxaban, and edoxaban. Trials with dabigatran, a direct thrombin inhibitor, are underway.

Rivaroxaban

Rivaroxaban is a factor Xa inhibitor that is FDA-approved in the treatment of non-valvular atrial fibrillation (NVAF), treatment and secondary prophylaxis in venous thromboembolism (VTE), prevention of cerebrovascular accident (CVA)/transient ischemic attack (TIA) in those with coronary or peripheral artery disease, and primary VTE prophylaxis after hip or knee surgery. In addition, rivaroxaban has been studied in acute coronary syndrome, heparin-induced thrombocytopenia (HIT), and superficial vein thrombosis (SVT). Rivaroxaban is not recommended in those with moderate-severe renal impairment (depending on indication) or moderate/severe hepatic impairment, especially with coagulopathy. **Table 1** summarizes some key information about rivaroxaban.

CME/CNE Article

Rivaroxaban has been prospectively studied in two trials with patients with cancer. Rivaroxaban was studied in a prospective, randomized, open-label trial in patients with active cancer and VTE (*N Engl J Med* 2019;380:720-728). See the Select-D trial diagram for a summary of this trial. Rivaroxaban was given as 15 mg PO BID for 3 weeks, then 20 mg daily for the rest of the 6-month treatment. It was compared to dalteparin 200 IU/kg SQ daily for 1 month, then 150 IU/kg daily for 5 more months. The exclusion criteria included previous history of VTE, significant liver disease, active bleeding, or high risk of bleeding and uncontrolled hypertension. To avoid drug-drug interactions, patients receiving concomitant P-glycoprotein inducers/inhibitors or strong CYP3A4 inhibitors/inducers were excluded. Primary outcome of VTE recurrence in 6 months was worse with dalteparin at 11 percent (95% CI, 7-9%) than that seen with rivaroxaban at 4 percent (95% CI, 2-9%) [HR 0.43 (95% CI, 0.19-0.99)]. There was no real difference in the rate of major bleeding between dalteparin (4%) and rivaroxaban (6%). There were less clinically relevant non-major bleeding (CRNMB) episodes with dalteparin at 4 percent (95% CI, 2-9%) than with rivaroxaban at 13 percent (95% CI, 9-19%) [HR 3.76 (95% CI, 1.63-8.69)]. The authors concluded that rivaroxaban treatment resulted in fewer VTE recurrences, and a similar rate of major bleeding, but more cases of CRNMB.

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Rivaroxaban was also studied for thromboprophylaxis in those beginning a new systemic treatment for cancer (*N Engl J Med* 2019;380(8):711-719). Patients starting systemic cancer treatment were randomized to either rivaroxaban 10 mg PO daily or placebo for 6 months. Inclusion criteria included a fairly good performance status and Khorana risk score of 2 or more, indicating that they were at higher risk of VTE. Exclusion criteria included those with primary brain cancer, brain metastases, VTE diagnosed within 30 days of

Continued on page 8

Table 1: Rivaroxaban

MOA	Factor Xa inhibitor
FDA-approved uses	NVAF, CAD/PAD, primary PX in hip/knee surgeries, VTE TX and secondary PX
Off-label uses	ACS, HIT, SVT
Dose/Administration	NVAF: 20 mg daily VTE/PE: 15 mg BID x 21 days, then 20mg daily CAT PX: 10 mg daily (*N Engl J Med* 2019;380:720-728) CAT TX: 15 mg BID x 3 weeks, then 20 mg daily (*J Clin Oncol* 2018;36:2017-2023) Dose ≥15 mg: take with food Dose 2.5 mg and 10 mg: take without regard to meals
PK	Bioavailability of 10 mg 80-100% (66% with 20 mg), half-life 5-9 hrs (11-13 hrs in elderly), time to peak=2-4hrs, hepatic metabolism through CYP3A4 (major)/CYP2J2, renal excretion: 36% as unchanged drug, 33% as metabolites. Substrate of Pgp.
Important drug interactions	Pgp/CYP3A4 strong inducers and inhibitors
Dosage adjustments	Depending on indication: avoid use in patients with CrCl <15 or < 30mL/min. Avoid use in those with moderate-severe hepatic impairment with coagulopathy. Dosage adjustment needed for renal impairment.
Tests to detect presence of drug	PT, Antifactor Xa assay (calibrated to rivaroxaban)
Reversal agent	Andexanet alfa, otherwise PCC, activated PCC, or recombinant Factor VIIa.

Definitions: DOAC=direct (non-vitamin K) oral anticoagulant; NVAF=non-valvular atrial fibrillation; VTE=venous thromboembolism; CAT=cancer-associated thrombosis; CAD/PAD=coronary or peripheral artery disease; ACS=acute coronary syndrome; PX=prophylaxis; TX=treatment; HIT=heparin-induced thrombocytopenia; SVT=superficial vein thrombosis; PE=pulmonary embolism; PK=pharmacokinetics, Pgp=P-glycoprotein; PCC=prothrombin complex concentrate

continued from page 7

enrollment, and bleeding conditions. There was no mention of excluding those with significant drug-drug interactions. Unfortunately, about half of participants stopped the treatment before the end of the 6-month trial period and so statistical significance could not be reached with the primary outcome measure (VTE or death related to VTE at 6 months). A sub-analysis did show that during the period that each participant actually took the treatment, rivaroxaban did show a lower rate of VTE. There were similar rates of major bleeding in the two groups. A summary of this trial is shown in the CASSINI diagram.

Apixaban

Apixaban is another factor Xa inhibitor. It is FDA-approved for treatment of DVT/PE, NVAF, and primary prophylaxis after hip or knee surgery. Also, it has been studied in HIT and secondary prophylaxis for CVA/TIA. Hepatic elimination, renal elimination of unchanged drug, and renal elimination of inactive metabolites each accounts for about one-third of the total. For any of the FDA-approved indications, apixaban is not recommended for those with CrCl <25mL/min. Also in NVAF, the dose should be reduced for those < 60 kg or >80 years old. It is not recommended for use in those with severe hepatic or renal impairment. **Table 2** shows some basic information about apixaban.

Apixaban has been studied in patients with cancer for VTE prophylaxis (*N Engl J Med* 2019;380(8):711-719). A total of 563 outpatients with cancer were enrolled in this randomized, placebo-controlled trial. Apixaban, at a dose of 2.5 mg BID, or placebo were given for 6 months. These patients had newly diagnosed or progressive cancer and were starting a new chemotherapy course. These patients were at elevated risk of CAT, all with a Khorana score of 2 or higher. Patients had high risk of bleeding, acute leukemia, myeloproliferative neoplasm, GFR of <30 mL/min/1.73m^2, a platelet count of under 50K, or weight < 40 kg. VTE occurred in 4.2 percent of apixaban group, compared to 10.2 percent of the placebo group (HR 0.41 (95%CI, 0.26-0.65; p< 0.001). Major bleeding was seen in 3.5 percent of the apixaban patients and 1.8 percent in the placebo group (HR 2.00; 95% CI, 1.01-3.95; p<0.046).

Continued on page 36

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Learning Objectives for This Month's CME Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Summarize findings from recent trials on the use of oral Factor Xa inhibitors in the prevention or treatment of cancer-associated thromboembolism.

Disclosure: The author has disclosed that the U.S. Food and Drug Administration has not approved the use of apixaban, rivaroxaban and edoxaban for the treatment of cancer-associated VTE as discussed in this article. Please consult the product's labeling for approved information.

The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Table 2: Apixaban

MOA	Factor Xa inhibitor
FDA-approved uses	DVT/PE, NVAF, primary PX in hip/knee surgeries
Off-label uses	HIT, secondary prophylaxis for CVA/TIA, CAT
Dose/Administration	DVT/PE: 10 mg BID x 7 days then 5 mg BID NVAF: 5 mg BID Primary PX in hip/knee surgeries: 2.5 mg BID x 10-35 days CAT PX: 2.5 mg BID (*N Engl J Med* 2019;380(8):711-719) CAT TX: 10 mg BID x 7 days, then 5 mg BID (2018 ASH Annual Meeting, Abstract 421) Administer without regard to meals.
PK	Onset 3-4 hours, bioavailability ~50%, half-life=12 (8-15) hrs. Renal elimination: 66% (33% unchanged, 33% inactive metabolites). Hepatic elimination: 34%, substrate of CYP3A4, Pgp
Important drug interactions	Pgp/CYP3A4 strong inducers and inhibitors
Dosage adjustments	NVAF: if sCr≥1.5 mg/dL and either age>80 or weight < 60 kg: 2.5 mg BID. Avoid use with CrCl<25 mL/min. DVT/PE: sCr>2.5 or CrCl<25 mL/min: not studied Not recommended in severe hepatic impairment. Has not been studied in severe renal impairment.
Tests to detect presence of drug	PT, Antifactor Xa assay
Reversal agent	Andexanet alfa, otherwise PCC, activated PCC, or recombinant Factor VIIa

Definitions: DOAC=direct (non-vitamin K) oral anticoagulant; NVAF=non-valvular atrial fibrillation; VTE=venous thromboembolism; CVA=cerebrovascular accident; TIA=transient ischemic attack, CAT=cancer associated thrombosis; CAD/PAD=coronary or peripheral artery disease; ACS=acute coronary syndrome; PX=prophylaxis; TX=treatment; HIT=heparin induced thrombocytopenia; SVT=superficial vein thrombosis; PE=pulmonary embolism; PK=pharmacokinetics, Pgp=P-glycoprotein; PCC=prothrombin complex concentrate.

Select-D Trial: Rivaroxaban vs Dalteparin in CAT Treatment

N=406.

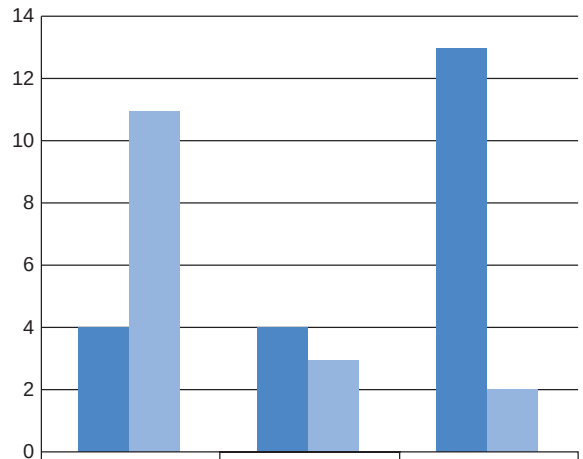
Patients: cancer patients with VTE.

Median age 67years, 53% men, 47% women, 95% white, 38% early/localized disease, 59% metastatic disease, 3% hematologic malignancies, 60% receiving anticancer treatment.

Prospective, randomized, open label, multicenter pilot study.

Study arm: Rivaroxaban 15mg BID x 3 weeks, then 20mg daily for rest of 6 months.

Control arm: Dalteparin 200 IU/kg daily for 1 month, then 150 IU/kg for 5 months.



	Recurrence at 6 mon (%)	Major bleeding (%)	CRNMB (%)
Rivaroxaban	4	4	13
Dalteparin	1	3	2

Young, A, Marshall A, Thirlwall J, 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.

CRNMB = clinically relevant non-major bleeding

CASSINI: Rivaroxaban in CAT prophylaxis

N=841.

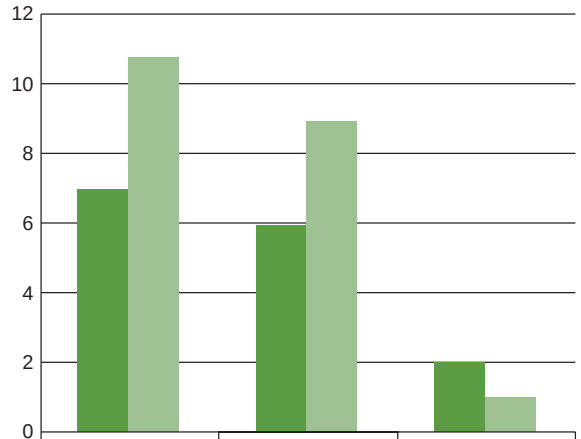
Patients: cancer patients starting cancer treatment who were at higher risk for VTE (Khorana score ≥ 2) with CrCl ≥ 30ml/min, and ECOG PS 0-2.

Prospective, randomized, double-blind, placebo-control trial.

Study arm: rivaroxaban 10mg once daily.

Control arm: placebo once daily.

Study duration: 6 months.



	VTE/VTE death (%) while on treatment	VTE/VTE death (%) at 6 mon	Major Bleeding (%)
Rivaroxaban	6.9	5.95	2
Placebo	10.7	8.79	1

Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med 2019; 380:720-8.

CRNMB = clinically relevant non-major bleeding

AVERT: Apixaban in CAT prophylaxis

N=563

Patients: ambulatory patients with cancer, at higher risk for VTE (Khorana score ≥ 2) who were starting chemotherapy.

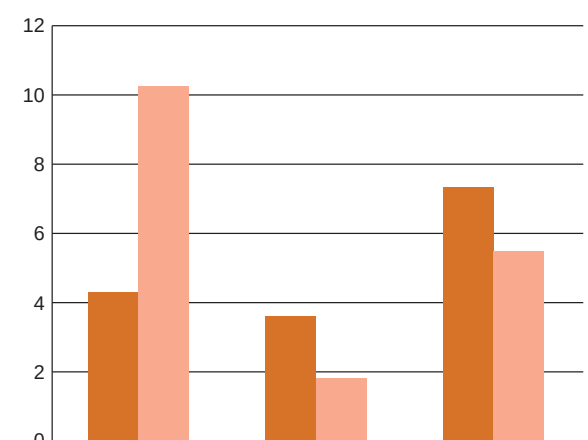
Median age 61yo, 42% male, 95% with CrCl>50ml/min, ECOG PS≥2.

Prospective, randomized, placebo-controlled double-blind trial.

Study arm: Apixaban 2.5mg BID

Control arm: Placebo BID

Study duration: 6 months



	VTE (%)	Major Bleeding (%)	CRNMB (%)
Apixaban	4.2	3.5	7.3
Placebo	10.2	1.8	5.5

Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med. 2019: 380:711-9..

CRNMB = clinically relevant non-major bleeding

ORAL ANTICOAGULANTS

continued from page 9

In addition, 7.3 percent of the apixaban-treated group experienced CRNMB, whereas 5.5 percent of the placebo group did. The authors concluded that apixaban treatment at 2.5 mg BID reduced the risk of VTE in this patient group, but it did result in higher rates of major bleeding and CRNMB. A summary of this trial is presented in the AVERT diagram.

The results of a randomized, controlled trial of apixaban versus dalteparin in the treatment of CAT were recently presented (2018 ASH Annual Meeting, Abstract 421). Patients with active cancer and confirmed VTE were randomized to apixaban 10 mg BID x 7 days then 5 mg BID for the balance of 6 months or dalteparin 200 IU/kg SQ daily x 30 days, then 150 IU/kg SQ daily for the rest of 6 months. Patients were excluded if they had a poor performance status, significant renal or hepatic impairment, treated with a CYP3A4 inducer, or at high risk of bleeding. The results presented showed a difference in the rate of VTE recurrence: 3.4 percent in the apixaban arm and 14.1 percent in the dalteparin group (HR 0.21 (95% CI, 0.09-0.47, p=0.0182). Both groups had similar rates of major and clinically relevant non-major bleeding at 6.2 percent for the apixaban group and 6.3 percet in the dalteparin group. The authors concluded that apixaban treatment was associated with a low bleeding rate and a significantly lower rate of VTE recurrence. The ADAM VTE diagram summarizes this trial.

Edoxaban

Edoxaban is another oral factor Xa inhibitor. It has been approved by the FDA for the treatment of NVAF and treatment of VTE. It has mixed renal and hepatic clearance, and the dose should be adjusted for renal impairment, age >65 years old and low body weight ≤60 kg to reduce the risk of bleeding. Conversely, edoxaban is not recommended for those patients with CrCl >90 mL/min, as it may have lower efficacy. It has not been studied in those with CrCl < 30 mL/min or severe hepatic impairment. **Table 3** details more information about edoxaban.

Edoxaban was studied in a randomized, controlled, open-label non-inferiority trial for the treatment of CAT (*N Engl J Med* 2018;378:615-624). These patients were randomized to either edoxaban 60mg daily or dalteparin 200 IU/kg SQ daily x 1 month, then 150 IU/kg. The edoxaban dose was reduced for those patients with CrCl 30-50 mL/min or who were also taking potent Pgp inhibi-

Continued on page 37

ADAM VTE: Apixaban vs dalteparin in CAT treatment.

N=287

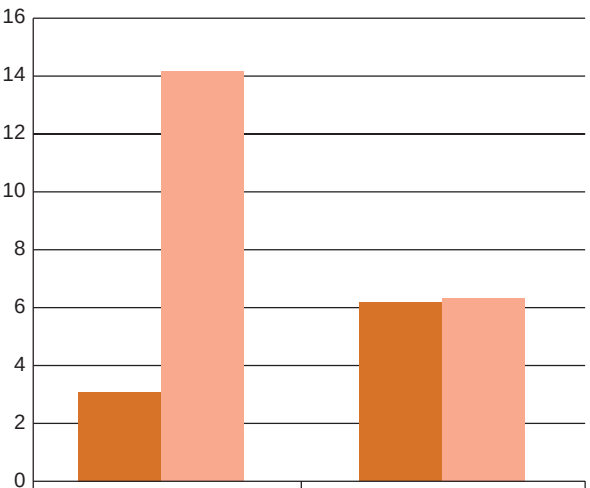
Patients: those with active cancer and confirmed VTE, ECOG PS 0-2, CrCl ≥30ml/min, ALT/AST ≤ 3x ULN.

Randomized, controlled trial.

Study arm: Apixaban 10mg BID x 7 days, then 5mg BID.

Control arm: Dalteparin 200 IU/kg SQ daily x 30 days, then 150 IU/kg SQ daily.

Study duration: 6 months



	VTE recurrence (%)	Major Bleeding + CRNMB
Apixaban	3.4	6.2
Dalteparin	14.1	6.3

CRNMB = clinically relevant non-major bleeding

McBane RD, Wysokinski WE, Le-Rademacher J, et al. Apixaban, dalteparin in active cancer associated venous thromboembolism, the ADAM VTE trial. ASH annual meeting #421, 2018.

Hokusai VTE Cancer: Edoxaban vs dalteparin in CAT treatment.

N=1046.

Patients: those with active cancer, median age 64yo, 52% male, 53% metastatic disease, ECOG PS 0-2.

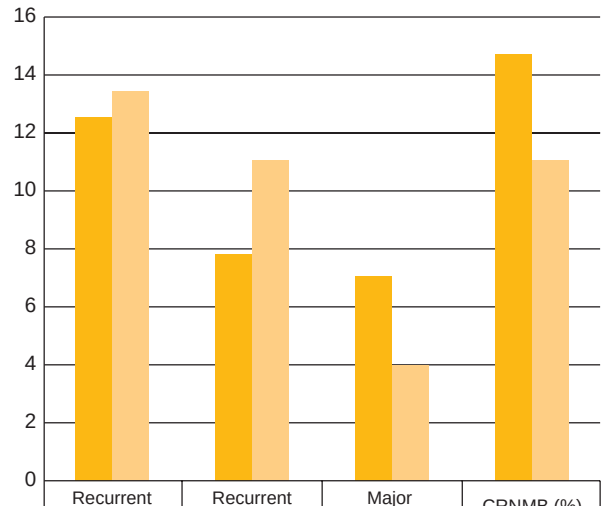
Randomized, open-label, controlled, non-inferiority trial.

Study arm: Edoxaban 60mg daily (except if CrCl 30-50ml/min or potent Pgp inhibitors: 30mg daily)

Control arm: Dalteparin 200 IU/kg SQ daily x 30 days, then 150 IU/kg SQ daily.

Treatment length: 6-12 months

Primary outcome determined at 12 months: recurrent VTE or major bleeding.



	Recurrent VTE or MB (%)	Recurrent VTE (%)	Major Bleeding (%)	CRNMB (%)
Edoxaban	12.8	7.9	6.9	14.6
Dalteparin	13.5	11.3	4	11.1

MB = major bleeding
CRNMB = clinically relevant non-major bleeding

Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Eng J Med 2018; 378:615-24.

Table 3: Edoxaban

MOA	Factor Xa inhibitor
FDA-approved uses	NVAF, DVT/PE
Off-label uses	CAT TX
Dose/Administration	NVAF: 60mg daily. (decreased efficacy if Cr>95 mL/min) DVT/PE: if >60 kg: 60 mg daily; if ≤60 kg: 30 mg daily CAT TX: 60 mg daily (following 5 days of dalteparin) (30mg daily if CrCl <30 mL/min or < 60 kg) *(N Engl J Med* 2018;378:615-624) May take without regards to meals
PK	Half-life 10-14 hrs, renal clearance ~50%, hepatic metabolism via CYP3A4 to active metabolites, time to peak 1-2hrs. Substrate of Pgp.
Important drug interactions	Pgp inhibitors and inducers
Dosage adjustments	NVAF or DVT/PE: CrCl> 95 mL/min: use is not recommended. CrCl 15-50 mL/min: 30 mg daily. CrCl <15 mL/min: not recommended. (Those with CrCl <30 mL/min were excluded from trials.) If ≥ 65 years old, dose should be reduced if CrCl 30-50 mL/min; avoid use if CrCl <30 mL/min. Not recommended in those with severe hepatic impairment.
Tests to detect presence of drug	PT, Antifactor Xa assay
Reversal agent	Andexanet alfa

Definitions: DOAC=direct (non-vitamin K) oral anticoagulant; NVAF=non-valvular atrial fibrillation; VTE=venous thromboembolism; CAT=cancer associated thrombosis; CAD/PAD=coronary or peripheral artery disease; ACS=acute coronary syndrome; PX=prophylaxis; TX=treatment; HIT=heparin induced thrombocytopenia; SVT=superficial vein thrombosis; PE=pulmonary embolism; PK=pharmacokinetics, Pgp=P-glycoprotein; PCC=prothrombin complex concentrate.

Table 4: Potential Drug Interactions

Strong Inhibitors of Pgp	Clarithromycin, conivaptan, intraconazole, HIV protease inhibitors, ketoconazole
Other Inhibitors of Pgp	Amiodarone, atorvastatin, carvedilol, cyclosporine, diltiazem, doxazosin, dronedarone, erythromycin, felodipine, lapatinib, PPIs, paroxetine, sertraline, simvastatin, tacrolimus, tamoxifen, verapamil, voriconazole
Pgp Inducers	Carbamazepine, dexamethasone, doxorubicin, phenobarbital, phenytoin, rifampin, spironolactone, St John Wort, trazodone, some HIV medications
Strong CYP3A4 Inhibitors	Clarithromycin, diltiazem, itraconazole, idelalisib, ketoconazole, posaconazole, voriconazole
Moderate CYP3A4 Inhibitors	Aprepitant, cimetidine, ciprofloxacin, cyclosporine, drondedarone, erythromycin, fluconazole, imatinib, verapamil
CYP3A4 Inducers	Bosentan, carbamazepine, enzalutamide, mitotane, modafinil, phenytoin, rifampin, St John Wort

tors. The treatment length in both arms was 6-12 months, but the primary outcome was determined at the end of 12 months, even if treatment had ended earlier. The primary outcome was a combination of both recurrent VTE and major bleeding. This outcome was reached in 12.8 percent of those treated with edoxaban and 13.5 percent treated with dalteparin (HR 0.9; 95% CI, 0.7-1.36). Edoxaban showed a roughly similar rate of recurrent VTE at 7.9 percent versus 11.3 percent with dalteparin (HR 0.71; 95% CI, 0.48-1.06; p=0.09). The rate of major bleeding was higher at 6.9 percent with edoxaban and 4.0 percent with dalteparin (HR 1.77; 95% CI, 1.03-3.04; p=0.04). The rate of CRNMB was similar. As this was a non-inferiority trial, the authors concluded that edoxaban treatment was not inferior to dalteparin, with a slightly higher rate of major bleeding. The results of this trial are displayed in the Hokusai VTE Cancer diagram.

As oral factor Xa inhibitors, the preferred agent to reverse the anticoagulation in urgent or emergent situations is andexanet alfa, although prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa might be used. All of these agents have shorter half-lives than warfarin, and in less serious situations holding the medication might be sufficient. All of these agents can have clinically significant drug-drug interactions with Pgp and/or CYP3A4 inhibitors and inducers. It is very important to check for interactions with the patient's specific concomitant medications. **Table 4** lists some of the more common Pgp/CYP3A4 inducers and inhibitors.

In summary, these recently presented or published trials give important information regarding the use of oral factor Xa inhibitors in the prevention or treatment of cancer-associated thromboembolism. OT