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암환자의 정맥혈전색전증 치료를 위한 새로운 경구용 항응고제

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Novel Oral Anticoagulants for the Treatment of Venous Thromboembolism in Cancer Patients

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ABSTRACT

Venous thromboembolism, encompassing deep vein thrombosis and pulmonary embolism, has increased in cancer patients and adversely affects their prognosis. Low-molecular-weight heparins are recommended as efficacious and safe anticoagulation treatment in cancer patients. However, in practice, oral anticoagulation is preferred, especially if longterm or extended treatment is necessary. Novel oral anticoagulants have recently emerged as an alternative to the standard therapy owing to the ease of administration, predictable anticoagulation effect without the need of laboratory monitoring, and fewer drug interactions. These new agents have been shown as effective and safe for the management of cancer-associated thrombosis in ongoing head-to-head comparative trials. Here we review the advances and limitation of current anticoagulant therapies.

KEY WORDS: Novel oral anticoagulant, cancer, venous thromboembolism

Cancer is a major risk factor for venous thromboembolism (VTE), especially in the first few months of diagnosis and at the metastatic stage of disease.[1,2] The VTE risk in cancer patients further increases with surgical procedures, anti-cancer treatments, and the placement of central venous catheters (CVCs) and adversely affects both short-term and long-term prognosis.[3,4] A population-based study showed a poor survival rate in cancer patients with concurrent VTE compared to those without VTE[5] and there were similar results in other registry data.[2,4] The VTE incidence in cancer patients has been increasing over the last decade,[6] probably because of long-term and frequent use of CVCs and newer thrombogenic agents (hormonal or anti-angiogenic therapy) and ageing.[7,8]

Because of increasing incidence of VTE and its adverse effect on clinical outcomes in cancer patients, timely management and prophylaxis of VTE are essential in this population. Based on the favorable therapeutic outcome from several clinical trials, major clinical guidelines recommended low-molecular-weight heparins (LMWHs) for both short-term and long-term (beyond 3 months) treatment of VTE in cancer patients.[9-11] Long-term treatment with LMWHs versus oral anticoagulants (vitamin K antagonists) presented in the updated Cochrane review showed significantly greater reduction in recurrent VTE with LMWHs, but not the bleeding and mortality in cancer patients.[12]

Clinicians prefer oral anticoagulation therapy in the long-term VTE management of cancer patients. In the global survey of oncologists, oral anticoagulation was favored as long-term management after an episode of DVT by up to 80% of

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respondents.[13] Other medical record analyses showed that only 25% to 30% of patients actually received LMWH monotherapy as the first-line VTE treatment.[14,15] Several factors such as low cost, no need for daily injections, the availability of reversal agent, and long history of use in VTE of warfarin-based anticoagulation agents might be taken into consideration in the selection of anticoagulants in cancer.[16,17]

Novel oral anticoagulants (NOACs) have different characteristics compared to warfarin, as listed in Table 1, and they can be administered with fixed dose regimens without routine coagulation monitoring because of specific anticoagulant activities, relatively fast onset/offset of actions, and little food or drug interactions. The efficacy and safety of NOACs for atrial fibrillation (AF) management in general population have been proven to be non-inferior compared to warfarin,[18-20] and these agents have been increasingly used in clinical practice. A cohort study of over 60,000 AF patients showed that NOAC therapy is replacing warfarin for the VTE management[21] and is expanding for the treatment of mechanical heart valves, heart failure, and coronary artery disease.[22] However, these new agents are not popular among oncologists, at least not yet, because of less familiarity and relatively limited data in the VTE treatment for cancer patients.

Therefore, this study aimed to discuss important considerations of four available NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) when used in cancer patients, based on their distinct pharmacological profiles and outcome data of currently available studies compared to the standard therapy.

CLINICAL TRIALS

Randomized trials of NOACs compared to warfarin or LMWH specific to the cancer population have not been reported, except the ongoing study of Hokusai VTE-cancer trial for edoxaban versus dalteparin[23] and SELECT-D trial for rivaroxaban versus dalteparin.[24] A recent subset-analyses of cancer patients in NOAC trials have shown non-inferiority to the standard therapy consisting of enoxaparin followed by dose-adjusted warfarin.[25-28] Several systemic reviews and meta-analyses of clinical trial data also revealed similar efficacy and safety between NOACs and the standard therapy.[29,30] However, the extent of the disease or the status of cancer treatment has not been described in detail and may affect the outcome of anticoagulation therapy. Moreover, these results should be interpreted with caution because of the enrollment of only a small proportion of cancer patients, different definition of active cancer as well as various inclusion criteria for cancer patients (patients with cancer history and patients with new onset of cancer).

As listed in Table 2, the sub-group analyses of dabigatran, rivaroxaban, apixaban, and edoxaban was conducted for only 6.6%, 7.9%, 3.1%, and 2.5% of highly selected cancer patients, respectively.[25-28] Moreover, the definition of active cancer and the diagnosis timing differ among different studies. Active cancer in the dabigatran study was defined as being diagnosed with cancer regardless of tumor status or having received any treatments for cancer within 5 years.[28] The patients diagnosed during the study were later included without considering the possibility of different responses to the VTE treatment. In the rivaroxaban study, cancer treatment or diagnosis at the entry was classified to the active cancer group, and the patients diagnosed with new cancer during the study were also reclassified to that group, but the patients with a short life expectancy were excluded at the entry.[26]

Each subgroup analysis of apixaban and edoxaban trials included different categories of active cancer group in addition to the cancer history group, probably because of a small portion of active cancer patients. The data analysis for apixaban was conducted not only in the active cancer group consisting of patients with ongoing treatment or within the previous 6 months, but also in the cancer history group with no active cancer at baseline.[25,31] For edoxaban, the cancer group consisted of both the patients with active cancer and those with a history of cancer regardless of the treatment.[27,32] Furthermore, apixaban and edoxaban analyses did not include cancer patients in whom long-term LMWH use was anticipated or with the possibility of aggressive or extensive cancer.[33] As a result, cancer patients included were likely less prone to thrombosis. In other words, those studies may not be representative or applicable to all the cancer patients, based on the fact that 67% of the study patients had metastatic diseases and 10% had no baseline disease of cancer in the CLOT trial,[34] a comparison study between LMWH and warfarin in cancer patients.

Given that patients with active cancers is at higher risk of VTE recurrence and bleedings, extended anticoagulation is generally considered; however, the choice of anticoagulant and the optimal length of anticoagulation to prevent recurrent VTE are still under investigation. In general cancer population, the extension studies and their meta-analysis of NOACs (dabigatran for 6 to 36 months, rivaroxaban for 6 or 12 months, and 2 doses of apixaban for 12 months) showed superior efficacy in

reducing VTE or VTE-related death over the placebo; however, the reduction of mortality risk was not statistically significant.[29,34] Only the dabigatran treatment for 3 to 12 months was also compared to warfarin, showing non-inferiority.[36] Unlike the comparison studies of conventional therapy for acute VTE, the extended coagulation with dabigatran, rivaroxaban, and higher dose of apixaban was associated with higher risk of major bleeding or clinically relevant bleeding, compared to the placebo. The post hoc analysis of the edoxaban study evaluating the treatment beyond 3 months also proved their efficacy with less major bleeding than warfarin. Whether the extended treatment with edoxaban or any NOACs can be clinically beneficial in cancer patients is not yet determined.

In summary, the exploratory analysis on a small, heterogeneous collection of data cannot propose any definitive conclusion and further studies are required. Moreover, different baseline patient characteristics such as advanced age, end-organ dysfunction, and interacting drugs might have a significant effect on the VTE management in cancer patients.[37] The clinical benefits of NOACs over warfarin for the extended or indefinite treatment are still under investigation. Therefore, potential risks and benefits based on the patient circumstances and pharmacological profiles of individual agent should be carefully and strategically assessed prior to selecting anticoagulation therapy in cancer patients.

AGE AND SEX

The predictable anticoagulant responses of the NOACs enable fixed dose administration without routine laboratory monitoring, thereby offering benefits and convenience for senior patients. Although pharmacokinetic data of some NOACs showed slight change in the elderly patients, as listed in Table 1, special attention should be focused on the effective and safe management of NOAC therapy, especially for those with interfering factors such as renal impairment, comorbidities, and polypharmacy. Several cases of hemorrhagic and gastrointestinal bleeding events associated with dabigatran in the patients over 75 years have been reported, indicating renal dysfunction as a major contributing factor to these circumstances.[38-40] Incidences of intracranial hemorrhage associated with rivaroxaban or apixaban were also reported in the elderly patient with concurrent conditions such as renal impairment, hypertension, and heart failure.[26,41-43]

In contrast, in the meta-analysis of major clinical trials including over 25,000 elderly patients, the risk of major bleeding or embolism associated with dabigatran, rivaroxaban, and apixaban was not higher in the patients ≥75 years, compared to the standard therapy for the VTE treatment.[44] The clinical trial analysis of bleeding related to edoxaban in the elderly patients did not show any increase in bleeding events compared to warfarin.[45] These findings are not surprising because the participants in the included trials might not represent the typical elderly patients in everyday practice with predisposing conditions for bleeding on anticoagulants. The presence of concurrent physical and medical problems such as immobility, malignant disease, and organ dysfunction, particularly renal function and the use of other anticoagulants might be attributed to the anticoagulant-associated bleeding in elderly patients.[46]

NOAC therapy in cancer patients is often interrupted for chemotherapy-induced thrombocytopenia and invasive procedures such as catheter ablation, excisional biopsy, and surgical treatment of cancer.[47,48] In addition, more variability and unpredictability of anticoagulant effects should be expected and cautioned with NOACs in older cancer patients, not only because of their dependence on renal function (particularly dabigatran) and potential interactions with many cancer therapies but also modified pharmacokinetic properties of anticoagulant drugs in these groups.[49]

Previously, sex-related differences have been reported in anticoagulated patients with VKAs as well as in healthy subjects, with a trend toward increased bleedings in women.[50,51] In the study of standard anticoagulation therapy including heparins, women had fewer recurrences of deep vein thrombosis and more bleeding than men undergoing anticoagulation therapy.[52] For NOACs, the sex differences in pharmacokinetic profiles do not exist, as listed in Table 1. The relationship between sex and the anticoagulant effects was analyzed in several meta-analyses, presenting mixed results. In a sex-based meta-analysis of NOAC trials (except edoxaban) for acute or extended VTE treatment, similar treatment efficacy but a 21% higher risk of bleeding was reported in women with no clear explanation.[53] In contrast, the following meta-analysis of 13 trials including all the NOACs showed similar clinical benefits as the standard therapy in acute VTE treatment with no difference between sex but higher increase in bleeding risks in men in the extended treatment: risk ratio 4.97 versus 1.33.[54]

Conversely, most recent meta-analysis of 9 clinical trials supported the study by Alotaibi *et al.*[53] Women, compared to men, showed a 35% higher risk of bleedings while maintaining the treatment efficacy with NOACs.[55] All these analyses had

Table 1. Pharmacologic characteristics of warfarin and novel oral anticoagulants. [32,38-40,120,124-125]

Generic Name (Trade Name)	Warfarin (Coumadin)	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
Drug class	Indirect Vitamin K antagonist	Direct thrombin inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor	Direct Factor Xa inhibitor
Food or drug effect	Dietary vit K influence on PD, many drug interactions	Food prolong T_{max} to 2h, potent P-gp inhibitors/inducers	Food increases AUC, potent CYP3A4 and P-gp inhibitors/inducers	No food effect, potent CYP3A4 and P-gp inhibitors/inducers	No food effect, potent P-gp inhibitors
Time to peak effect	3-5days	1h	2.5-4h	3h	1-2h(s)
Bioavailability	79-100%	3-7%	80-100%	50%	62%
Protein binding	99%	35%	95%	87%	40-59%
Half-life	40h	12-17h	5-9h	8-15h	9-11h
Dosing	Variable (0.5-16 mg OD)	150, 110 mg BID	15, 20 mg OD	2.5, 5 mg BID	
Age	Greater INR response, clearance decrease in patients ≥65 y	Cmin increase of 31% in patients ≥75 y	AUC increase of 50% in patients >65 y	AUC increase of 32% in patients >65 y	None
Sex	Lower dose required for female	None	None	Exposure in females higher by 18%	None
Body weight	No effect on dose	C_{min} decrease of 20% in patients >100 kg	Exposure increase of 25% in patients <50 Kg and decrease by 25% in patients >120 kg	Exposure increase of 30% in patients <50 kg and decrease by 30% in patients >120 kg	Exposure increase in patients 60 kg
Renal elimination	>90%	>80%	66%	25-27%	50%
Metabolism	CYP2C9, CYP3A4, CYP2C19, CYP1A2	Substrate for P-gp	CYP3A4 CYP2J2 and CYP-independent mechanisms; substrate for P-gp	CYP3A4/5, CYP2J2, CYP1A2; substrate for P-gp	CYP3A4 (<4%); substrate for P-gp
Anticoagulation monitoring	Required	Not required	Not required	Not required	Not required
Reversal agents	Vitamin K	Idarucizumab, Arapazine	Andexanet, Arapazine	Andexanet, Arapazine	Andexanet, Arapazine

AUC, area under the curve; C_{min}, minimum concentration; CYP, cytochrome P450; P-gp, permeability glycoprotein; T_{max}, time to maximum concentration

their own limitations such as no stratification of outcome data and patient characteristics by sex, except one study of apixaban.[56] In addition, there are no recommendations for women specific cancer types or issues in the management of VTE.[57] Until more definite information is obtained, dosage adjustments to reduce the bleeding risk in women with NOACs do not seem necessary.

BODY WEIGHT

There is no specific clinical implication with NOACs for the patients with extreme body weight. Moreover, NOAC trials included only a small portion of patients with extreme body weight.[58] Based on limited data, trough concentration of dabigatran decreased by 20% in the patients over 100 kg, but its bioavailability did not show variations in the obese or underweight patients (Table 1).[32,59] The pharmacokinetic profiles of factor Xa inhibitors may be affected by body weight, but no compelling evidence on the clinical effect was observed.[58] A study to assess the effect of extreme body weight on the rivaroxaban effect did not report any clinical relevance, and therefore dose adjustment is not required.[60] A study for apixaban also found only modest change with the exposure to apixaban in healthy subjects with extreme body weight; 23% lower with weight ≥120 kg, and 27% higher with weight ≤50 kg, and therefore may not warrant the dose adjustment based on the body weight.[61]

Edoxaban is the first NOAC to address and recommend dose reductions for the VTE patients with low body weight along with renal dysfunction or drug interactions. The exposure of edoxaban may increase in the patients with a body weight ≤60 kg[62]; however, the efficacy and safety of edoxaban were

maintained with dose reduction in this group.[32)]

Dose adjustment for NOACs based on the body weight may not be warranted, according to the data currently available. However, a combination of additional factors such as older age and renal dysfunction for bleeding might lead to dose adjustment of any anticoagulants including NOACs in underweight patients, representing common clinical pictures of cancer patients.[63)]

RENAL FUNCTION

Renal functions of cancer patients are often deteriorated for a variety of reasons such as advanced age, chronic comorbidities (diabetes, renal disease, hypertension, and cardiovascular disease), tumor infiltration, and the use of several nephrotoxic agents including chemotherapeutic drugs, analgesics, radiopharmaceuticals, contrast dyes, and injectable bisphosphonates.[64)] Renal excretion is the major route of elimination for ~50% of all the cancer therapeutic agents, and any reduction in renal clearance can accumulate potentially toxic drugs or metabolites.[65)] Thus, the dosage of drugs with renal clearance should be adjusted in proportion to the renal function in cancer patients.[66)]

Renal excretion is a major contributor to the clearance of dabigatran and to a lesser degree, rivaroxaban, edoxaban, and apixaban in the order (Table 1). As such, the risk of drug accumulation and bleeding increases with various degrees of renal dysfunction. After oral administration, dabigatran etexilate is converted to its active form, dabigatrana and it predominantly (>80%) undergoes renal excretion. The impairment of renal function significantly increased the elimination half-life and the exposure of dabigatran in parallel with the increase in the risk of bleeding; approximately 3-fold increase (30-50 mL/min) in the dabigatran exposure in creatinine clearance was reported (CrCl).[67,68)] The underweight older patients with renal insufficiency were particularly at high risk of bleeding associated with dabigatran,[40,69)] and therefore the initial and periodic assessment of renal function is recommended in this population.[70)] In addition, dose modification in accordance with renal function as well as patient's other bleeding risk may provide a better clinical outcome: for example, 110 mg dabigatran for the patients over 75 years with CrCl in the range 30-50 mL/min.[69)]

The degree of renal excretion also affects anticoagulant effects via factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). The overall effect of renal impairment on rivaroxaban pharmacokinetics seems moderate with no need for dose adjustment (1.5-fold increase in CrCl, 30-50 mL/min),[71,72)] as is expected by the pharmacokinetic data that 66% of the dose administered is eliminated via the kidney, in which 36% as unchanged drug and 30% as inactive metabolites.[73)] A registry data showed that 22% of major bleeding events associated with rivaroxaban occurred in the patients with a CrCl of <50 mL/min, but rarely required any intensive care.[74)] The pharmacovigilance study of the patients treated with rivaroxaban demonstrated bleeding complications at a rate of 2.86%, and majority of them had comorbidities such as hypertension, coronary artery disease, heart failure, and renal disease.[75)] In the patients with severe renal dysfunction of CrCl (15-30 mL/min), 10 mg daily dose of rivaroxaban reached the similar plasma level of 20 mg without compromising efficacy.[71)] Overall, a reduced dose of rivaroxaban with close assessment of renal function is advisable for the patients with severe renal impairment (CrCl, 15-30 mL/min).

Apixaban seems to be the preferred agent in the view of pharmacokinetic data of the lowest portion (25-27%) of renal excretion.[76)] The apixaban exposure showed a minor increase in the area under the curve (AUC) for the patients with moderate renal impairment (29% higher AUC in CrCl 40 mL/min).[77)] The post-analysis of the clinical trial showed that apixaban was superior to warfarin in reducing major bleeding across all the degrees of renal function including CrCl of <50 mL/min.[78)] A recent meta-analysis of the clinical trials to evaluate the risk of bleeding also concluded that the use of apixaban in the patients with CrCl <50 mL/min is safe,[79)] a similar result to those of prior meta-analyses.[44,80)]

The Hokusai-VTE trial for edoxaban, the newest of NOACs, was designed to address the concerns of high risk of bleeding for the patients with renal impairments.[81)] Based on the exposure-response modeling, half doses of edoxaban were administered to the patients with renal dysfunction, and a trend favoring edoxaban was maintained without any significant interaction between the renal function and anticoagulation effect. Interestingly, a 30 mg daily dose of edoxaban administered to the patients with normal renal function (CrCl ≥80 mL/min) showed significantly worse outcome compared to warfarin. This was explained by a higher renal elimination of edoxaban in the patients with normal renal function and is now included as part of its warning label. Complementary to the clinical trials, bleeding rates among the patients with severe renal impairment treated

Table 2. Sub-analyses of cancer patients in clinical trials regarding novel oral anticoagulants for the treatment of venous thromboembolism.[25-27, 30-32]

Drugs	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trial name	RE-COVER I, RE-COVER II	EINSTEIN-DVT, EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Study design	Randomized, double-blind, non-inferiority, parallel group	Randomized, open-label, event-driven, non-inferiority, parallel group	Randomized, double-blind, parallel group	Randomized, double-blind, non-inferiority, parallel group
Dosage	150 mg BID for 6 months, after enoxaparin or UFH for 5 days	15 mg BID for 3 weeks followed by 20 mg OD for 3, 6, or 12 months (pre-specified), optional parenteral anticoagulation (max 48h)	10 mg BID for 7 days followed by 5 mg BID for 6 months, optional parenteral anticoagulation (max 36h)	60 mg OD (30 mg if CrCl 30-50 mL/min, bodyweight <60 kg or P-gp inhibitors) for 3 to 12 months (flexible), after enoxaparin or UFH for 5 days
Comparator	Warfarin (INR 2-3)	Enoxaparin 1mg/kg BID ≥5days and warfarin or acenocoumarol (INR 2-3)	Enoxaparin 1 mg/kg BID ≥5days and warfarin (INR 2-3)	Warfarin (INR 2-3)
Active cancer patients, (N, % of total patients)	335 (6.6%) vs. 4772 no cancer [221 with cancer at baseline and 114 new cancer during the study]	655 (7.9%), vs. 7157 no cancer [462 cancer at baseline and 193 new cancer during the study, 469 cancer history]	169 (3.1%) vs 4861 no cancer [365 cancer history without active cancer at baseline]	208 (2.5%) vs. 7521 no cancer [563 cancer history]
Definition of active cancer	Diagnosis within 5 years at baseline	Cancer diagnosis or receiving treatment at baseline or new cancer during the study	Cancer diagnosis or treatment within the past 6 months (cancer history defines a diagnosis >6 month previously and no current treatment)	
Efficacy outcome*	Cancer at baseline; HR 0.74 (0.2-2.7), new cancer during the study; HR 0.63 (0.2-2.0)	Active cancer; HR 0.67 (0.35-1.30)	Active cancer; HR 0.56 (0.13-2.37) Any cancer including cancer history; HR 0.30 (0.11-0.82)	Any cancer including cancer history; HR 0.53 (0.28-1.00),
Safety outcome**	Cancer at baseline Major bleeding HR 1.23 (0.28-5.5), New cancer Major bleeding HR 0.43 (0.08-2.3)	Major bleeding; HR 0.42 (0.18-0.99) Major bleeding or CRNM; HR 0.80 (0.54-1.20)	Major bleeding HR 0.32 (0.09-0.16) Major bleeding or CRNM; HR 0.47 (0.29-0.75)	Major bleeding or CRNM HR 0.64 (0.45-0.92)
Conclusions	Dabigatran provided similar clinical benefit as warfarin	Net clinical benefit was more favorable in rivaroxaban patients	Apixaban is a convenient option for cancer	Edoxaban is as effective as warfarin and is associated with less clinically relevant bleeding.

*The efficacy outcome was recurrent symptomatic VTE or VTE-related death
**The safety outcome was major or clinically relevant non-major bleeding (CRNM)

with a 15 mg dose edoxaban (CrCl 15-30 mL/min) were similar to the patients with CrCl ≥50 mL/min treated with a 30 mg or 60 mg dose.[82] This study indicated that edoxaban with 50% dose reduction can be safely given to the patients with moderate renal dysfunction (CrCl 30-50 mL/min).[62]

Based on the aforementioned studies of each NOAC agent and recent meta-analysis of clinical trials,[44] severe renal impairment appears to be a limiting factor with NOACs in the cancer patients, and apixaban or edoxaban with dose adjustment could be the most considerable option for the patients with renal impairment (no less than CrCl 30 mL/min).

HEPATIC FUNCTION

Since the withdrawal of ximelagatran, the initial oral thrombin inhibitor, from the market because of severe liver toxicity,[83] major NOAC trials excluded all the patients with

active or chronic liver disease as well as any evidence of hepatic impairment on baseline laboratory values.[59] All the NOACs, with the exception of dabigatran, undergo hepatic metabolism via cytochrome (CYP) P450 enzymes with different degrees[84]; therefore, hepatic impairment can affect coagulation by decreased hepatic clearance of the drugs as well as generation of clotting factors. In a review on the pharmacological properties of NOACs in the patients with liver impairments, there were increases in the AUC of rivaroxaban and apixaban, whereas decreases in those of edoxaban and dabigatran in liver function of Child Pugh classification (Child Pugh) B.[85]

The pharmacokinetic data of rivaroxaban in healthy population showed that ~50% of rivaroxaban dose was eliminated via hepatic biotransformation by both CYP-dependent mechanisms and non-CYP mediated hydrolysis.[86] Moderate hepatic impairment increased the AUC and peak concentration of rivaroxaban by 2.3- and 1.3-fold, respectively. Rivaroxaban is contraindicated in the cases of coagulopathy associated with liver disease and risk of clinically relevant bleeding, including cirrhosis, according to manufacture (Child Pugh B and C). The pharmacokinetic data of apixaban were not substantially altered in the patients with mild to moderate hepatic impairment.[76] According to package insert, apixaban is advised to use with caution in the cases of mild to moderate hepatic impairment or elevated liver enzymes (above 2 times the normal) or bilirubin levels 1.5 times of the normal level. However, it is contraindicated in the patients with high risk of bleeding such as hepatic disease associated with coagulopathy and cirrhosis (Child Pugh C).

In contrast, moderate hepatic impairment does not affect dabigatran pharmacokinetics or anticoagulant activity of dabigatran; therefore, dose adjustment is not required.[87] The administration of dabigatran is considered safe for the patients with moderate hepatic impairment but not for the patients with elevated liver enzymes (above 2 times the normal) and is contraindicated in the cases of hepatic impairment expected to have any impact on patient survival, according to the package insert. The use of edoxaban is also not restricted for the patients with hepatic impairment but is advised with care for the patients with severe hepatic impairment.[85]

As much as their increased risk of bleeding in hepatic impairments, the risk of liver injury associated with NOACs was concerned in a recent systemic review although in a similar degree to other drugs including warfarin.[88] An analysis of NOAC trials in 152,116 patients reported a similar risk of drug-induced liver injury indicated by liver enzyme elevations above 3 times the normal with the total bilirubin above 2 times the normal, compared to the control (LMWH, VKA or placebo); 2.1% taking dabigatran versus 2.7% in control groups. Moreover, hepatotoxic instances during NOAC trials were generally mild and self-limited, resolving completely within a few weeks of discontinuation or even without stopping therapy.[89,90] Several cases reporting life-threatening hepatotoxicity associated with rivaroxaban or dabigatran are quite alarming,[91] and most of the affected patients also had concurrent drugs or diseases. Because hepatotoxicity seems to appear at therapeutic doses of any NOACs, rapid withdrawal of the drug in signs of hepatic injury is recommended, considering its severity.

Liver injury occurs in cancer patients because of infiltration of tumor tissues and/or the use of certain hepatotoxic chemotherapeutic agents, especially with a high dose. Given conservative exclusion criteria for the clinical trials and post-marketing cases of hepatotoxicity associated with NOACs, these agents should be withheld in the cases of active liver disease or abnormal liver function tests at baseline. In addition, patients should be informed about possible symptoms of hepatotoxicity while using NOACs, especially with hepatotoxic chemotherapeutic agents.

INTERACTIONS WITH CANCER THERAPEUTIC AGENTS

The minimal interactions of NOACs with other commonly used drugs were considered as one of the advantages over warfarin, but the unexpected drug responses due to drug interactions, have been increasingly reported, particularly in the patients with organ dysfunction. Drug interactions should be anticipated when NOACs are administered with any drugs that strongly modulates their pharmacokinetic activities. Table 3 lists the NOACs and drugs with possible drug interactions with NOACs by P-gp and CYP3A4 systems.[92-94]

Absorption of NOACs is dependent on the permeability glycoprotein (P-gp) efflux transporters in many tissues and can be modulated by drugs or foods.[95] Dabigatran etexilate (not dabigatran) is absorbed through the intestinal P-gp transporter and undergoes esterase-mediated hydrolysis in the plasma and liver without being much affected by CYP3A4 activity[96]; therefore, potential pharmacokinetic interactions involving P-gp are restricted to absorption across the intestinal wall.[97] The

other factor Xa inhibitors, rivaroxaban and apixaban, are the substrates of both P-gp and CYP3A4. In contrast, edoxaban serves as a substrate of P-gp transporter and is minimally metabolized via CYP3A4 (<4%).[32]

Theoretically, the serum levels of NOACs can be altered by the concomitant use of P-gp modulators (amiodarone, quinidine, verapamil, dronedarone, etc.), and therefore potential adverse effects are anticipated. As expected, the

Table 3. Drugs which have a possible interactions with NOACs by P-gp and CYP3A4 systems.[92-112]

	P-glycoprotein			**CYP3A4**		
	Substrate	Induction	Inhibition	Substrate	Induction	Inhibition
NOACs	Dabigatran Rivaroxaban Apixaban Edoxaban			Rivaroxaban Apixaban Edoxaban (<4%)		
Oncology drugs	Bendamustine Crizotinib Daunorubicin Docetaxel Doxorubicin Etoposide Idarubicin Imatinib Irinotecan Lapatinib Mitomycin C Nilotinib Paclitaxel Vemurafenib Vinblastine Vincristine	Doxorubicin Vinblastine	Abiraterone Crizotinib Enzlutamide Imatinib Lapatinib Nilotinib Sunitinib Tamoxifen Vandetanib	Abiraterone Busulfan Crizotinib Cyclophosphamide Dasatinib Docetaxel Doxorubicin Enzalutamide Erlotinib Etoposide Flutamide Fulvestrant Gefitinib Ifosfamide Imatinib Irinotecan Lapatinib Letrozole Nilotinib Paclitaxel Sorafenib Sunitinib Tamoxifen Vandetanib Vemurafenib Vinblastine Vincristine Vinorelbine	Enzalutamide Paclitaxel Vemurafenib	Abiraterone Anastozole Bicalutamide Cinorelbine Crizotinib Cyclophosphamide Dasatinib Docetaxeletoposide Doxorubicin Enzalutamide Idarubicin Ifosfamide Imatinib Lapatinib Lomustine Nilotinib Tamoxifen Vinblastine Vincristine
Analgesics	Morphine	Morphine	Meperidine Methadone Morphine	Codeine Hydrocodone Oxycodone Fentanyl Methadone Acetaminophen		Fentanyl Methadone Acetaminophen
Antiarrythmics	Diltiazem Quinidine Verapamil	Verapamil	Amiodarone Diltiazem* Dronedarone Propafenone Quinidine Verapamil	Amiodarone Dronedarone Quinidine Verapamil		Amiodarone Diltiazem Dronedarone Verapamil
Antiemetics	Ondansetron			Aprepitant Fosaprepitant Ondansetron Palonosetron	Aprepitant Fosaprepitant	Aprepitant Fosaprepitant

Table 3. Drugs which have a possible interactions with NOACs by P-gp and CYP3A4 systems (continued).

Antiepileptics			Carbamazepine	Carbamazepine Phenobarbital Phenytoin	Cambamazepine Felbamate Oxcarbamazepine Phenobarbital Phenytoin Primidone Topiramate	
Antimicrobials	Amprenavir Erythromycin Indinavir Itrazonazole Nelfinavir Saquinavir Tetracycline	Amprenavir Clotrimazole Indinavir Nelfinavir Nevirapine Rifabutine Rifampicin Ritonavir Saquinavir	Atazanavir Clarithromycin Efavirenz Erythromycin Fosamprenavir Indinavir Itraconazole Ketoconazole Lopinavir Nelfinavir Ritonavir Saquinavir	Clarithromycin Darunavir Efavirenz Erythromycin Etavirine Fosamprenavir Indinavir Itraconazole Ketoconazole Mefloquin Nelfinavir Nevirapine Rifabutin Ritonavir Saquinavir	Efavirenz Etravirine Nevirapin Rifabutine Rifampicin	Atazanavir Ciprofloxacin Clarithromycin Darunavir Doxycycline Efavirenz Erythromycin Fluconazole Fosamprenavir Indinavir Isoniazide Itraconazole Ketoconazole Lopinavir Miconazole Nelfinavir Nevirapin Posaconazole Ritonavir Roxithromycin Saquinavir Voriconazole
Immune-modulators	Cyclosporine Dexamethasone Everolimus Sirolimus Tacrolimus Temsirolimus	Dexamethasone	Cyclosporin Dexamethasone Tacrolimus	Cyclosporine Dexamethasone Everolimus Methylprednisolone Prednisolone Prednisone Sirolimuc Temsirolimus	Dexamethasone Prednisone	Cyclosporin Dexamethasone Methylprednisolone Tacrolimus
Miscellaneous	Cimetidine Colchicine Domperidone Loperamide Fexofenadine Ranitidine	St. John's wort	Atorvastatin Bromocriptine		Modafinil Ethanol St John's wort	Grapefurit Milk-thistle

AUC of dabigatran increased by 53% and 2.4-fold when given with quinidine and immediate-release verapamil by their strong inhibitions of P-gp transporters, respectively.[32,98] Quinidine and verapamil increased the AUC of edoxaban by 76.7% and 52.7%, respectively.[99] Based on these pharmacokinetic interactions, quinidine use was prohibited while on dabigatran,[90] and a reduced dose (30 mg daily) of edoxaban was administered to the patients taking strong P-gp inhibitors in a clinical study.[32] According to an *in vivo* study of P-gp transporter, the clinical impact of P-gp inhibitory effects on edoxaban seems uncertain at present.[100] Besides P-gp modulation by concurrent drugs, alterations in P-gp expression and function by genetic variations in *ABCB1* (*MDR1*), encoding for P-gp, was speculated for their relation to drug bioavailability and response. A genome-wide association analysis in dabigatran study showed an association between genetic polymorphism and dabigatran exposure, but further study is needed to determine the clinical effect of genetic factors to P-gp dependent drugs including NOACs.[101]

However, in the case of both impaired renal function and P-

gp inhibition, adverse effects could increase with greater effect on dabigatran or edoxaban pharmacokinetics. In a few case reports of the elderly patients taking concomitant dabigatran and P-gp inhibitors (amiodarone and dronedarone), major hemorrhagic events occurred in relation to high levels of dabigatran through the impairment of renal clearance and P-gp-mediated uptake.[39,102)]

Potential drug interactions involving hepatic metabolism and P-gp are also likely to be additive. Although with very little involvement of CYP metabolism, the AUC of dabigatran and edoxaban increased by 153% and 87%, respectively, by strong dual P-gp/CYP3A4 inhibitor, ketoconazole[98,103)] and only 7% and 9.5% by digoxin, with minimal clinical importance.[99,104)] Besides being substrates of P-gp, rivaroxaban and apixaban (33% and 25%, respectively) are metabolized via CYP 3A4 pathways to varying degrees,[58)] indicating a concern for drug interactions with inhibitors or inducers of both systems. The pharmacokinetic data showed that rivaroxaban AUC increased by 1.3-fold and 2.6-fold with a moderate dual inhibitor (erythromycin) and a strong dual inhibitor (ketoconazole), respectively. The apixaban exposure also showed increase by approximately 1.4-fold and 2-fold with co-administration of a moderate inhibitor (diltiazem) and a strong inhibitor (ketoconazole), respectively.[105)] There were no clinically significant interactions of rivaroxaban or apixaban with a P-gp inhibitor, digoxin.[98)]

Conversely, the AUC of rivaroxaban and apixaban decreased by 50% and 54%, respectively, when used with a strong dual P-gp/CYP3A4 inducer, rifampicin.[106,107)] When administrated with rifampicin, the AUC of dabigatran and edoxaban also reduced by 67% and 34%, respectively.[108,109)] The relevant case of interference with rivaroxaban's clinical efficacy by metabolic inducers was recently reported and alerted.[106)] The sub-therapeutic concentration of rivaroxaban for the patients taking rifampicin together led to fatal embolism, which was linked to the interaction of rivaroxaban with rifampicin.

Drug interactions involving hepatic metabolism and drug clearance of the chemotherapeutic agents are the major mechanism of clinically significant reactions reported in literature.[110)] Several cancer therapeutic agents are the substrates for the CYP system or have relevant interactions with CYP3A4 and/or P-gp: cyclophosphamide, ifosfamide, vinca alkaloids, etoposide, paclitaxel, certain hormonal agents, and tyrosine kinase inhibitors.[94)] Antiemetic drugs such as aprepitant and fosaprepitant may inhibit or induce CYP3A4 enzyme activity, and analgesics such as acetaminophen, fentanyl, and methadone are also CYP3A4 inhibitors.[93)] Therefore, the use of these agents in combination with NOACs could alter their serum levels and affect their responses.[94,111)] Cancer patients are potentially at higher risk of complications not only because of multiple medications, but also the altered drug absorption, distribution, and excretion from their clinical conditions such as mucositis, edema, malnutrition, and organ dysfunction.[112)]

REVERSAL AGENTS

Despite the rapid offset of action due to drug's short half-lives, specific reversal agents of the NOACs would be beneficial to manage cancer patients who undergo emergent interventions and experience life-threatening bleedings. Non-specific prohemostatic therapies, such as fresh frozen plasma, prothrombin complex concentrate (PCC), activated PCC (aPCC) or recombinant activated factor VII (rFVIIa) are often recommended in the current guidelines to reverse the anticoagulant effect of the NOACs for the patients with intracranial or other serious bleeding,[113,114)] albeit their clinical efficacy is unproven.[115,116)] In fact, the efficacy of these agents has been confirmed only in animal models or healthy human volunteers, not in the clinical trials assessing the actual effect for NOAC-associated bleeding.[117,118)] Moreover, the use of these reversal agents in the case of a catastrophic events may offer little clinical benefit according to current experience and literature.[119)]

Recently, idarucizumab, a humanized antibody fragment directed against dabigatran, received the accelerated approval for the use in patients during emergency situations, based on the efficacy demonstrated in healthy volunteers. Idarucizumab selectively neutralizes the anticoagulant activity of dabigatran within minutes with no effect on thrombin.[120)] Several studies evaluating idarucizumab in terms of pharmacological reversal of dabigatran anticoagulation and clinical resolution of bleeding have shown preliminary but promising results in volunteers of varying ages and renal function.[121-123)] Because of the lack of control group and small size of study population, the evidence of clinical improvement with the use of idarucizumab compared to non-specific reversal agents is not obtained, especially in the specialized population including those with cancer. Whether this novel agent will improve the safety of patients treated with dabigatran in current practice

will have to be demonstrated in a larger, randomized controlled study.

Andexanet alfa for reversing the anticoagulant effects of factor Xa inhibitors and arapazine for reversing both factor Xa inhibitors and factor IIa inhibitors are currently under development and not yet registered for clinical use.[124,125)]

At present, the mainstay of management of patients receiving NOAC with major bleeding should be supportive care and urgent referral for surgical or mechanical intervention, following the immediate withdrawal of the offending agents.[126,127)] In addition, it is important to point out that clinical prognosis is highly dependent on patient's coexisting medical conditions as well as the overall management such as rapid diagnosis, supportive care, and easy access to antidote administration.[128)] Taking the little data on reversal strategy into consideration, proactive monitoring of patients during therapy for bleeding complications may be warranted, especially for high-risk groups.

CONCLUSION

Several aspects of NOACs such as easy administration, predictable effect without need for monitoring, and a few drug interactions have been favored in choosing an anticoagulant in the VTE management, especially for the long-term or extended period. The clinical outcomes of NOAC therapy were promising in the general population. In cancer patients, the current data recommends LMWH monotherapy as the initial treatment for acute VTE, but there is no guideline for the extended treatment. Although LMWH therapy was superior to warfarin, neither warfarin nor LMWH therapy has been compared to NOACs in pre-defined cancer patients. Based on limited data, NOACs were found to be non-inferior than heparin followed by warfarin in cancer patients, without adjusting for type of VTE and type/stage of cancer. Moreover, the data is not compared to LMWH monotherapy, which is the current standard of care in cancer patients.

For the moment, LMWH therapy seems to be the standard treatment for VTE in the cancer patients. However, for long-term VTE treatment, the cost of LMWH and the need for daily injections can be burdensome and decrease patient's quality of life as well as adherence to the treatment. NOACs are attractive alternatives for oncologists as well as for cancer patients. When there are no serious organ dysfunction or drug interactions with concurrent therapy, each NOAC agent may play its own role in managing VTE for cancer patients.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Blom JW, Doggen CJ, Osanto S, *et al*. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293(3):715-22.
2. Chew HK, Wun T, Harvey D, *et al*. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med 2006;166(4):458-64.
3. Rickles FR, Levine M, Edwards RL. Hemostatic alterations in cancer patients. Cancer Metastasis Rev 1992;11(3-4):237-48.
4. Khorana AA. Venous thromboembolism and prognosis in cancer. Thromb Res 2010;125(6):490-3.
5. Sorensen HT, Mellemkjaer L, Olsen JH, *et al*. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343(25):1846-50.
6. Timp JF, Braekkan SK, Versteeg HH, *et al*. Epidemiology of cancer-associated venous thrombosis. Blood 2013;122(10):1712-23.
7. Falanga A and Marchetti M. Anticancer treatment and thrombosis. Thromb Res 2012;129(3):353-9.
8. Hawbaker S. Venous thromboembolism in the cancer population: pathology, risk, and prevention. J Adv Pract Oncol 2012;3(1):23.
9. Farge D, Debourdeau P, Beckers M, *et al*. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. J Thromb Haemostasis 2013;11(11):56-70.
10. Lyman GH, Khorana AA, Kuderer NM, *et al*. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31(17):2189-204.
11. Mandala M, Falanga A, Roila F. *et al*. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(suppl6):vi85-vi92.
12. Akl EA, Kahale L, Barba M, *et al*. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2014;7:1-70.
13. Kakkar AK, Levine M, Pinedo H, *et al*. Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist 2003;8(4):381-8.
14. Delate T, Witt DM, Ritzwoller D, *et al*. Outpatient use of low molecular weight heparin monotherapy for first-line treatment of venous thromboembolism in advanced cancer. Oncologist 2012;17(3):419-27.
15. Imberti D, Agnelli G, Ageno W, *et al*. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. Haematologica 2008;93(2):273-8.
16. Kearon C, Kahn SR, Agnelli G, *et al*. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(suppl6):454s-545s.
17. Rahme E, Feugère G, Sirois C, *et al*. Anticoagulant use in patients with cancer associated venous thromboembolism: A retrospective cohort study. Thromb Res 2013;131(3):210-7.

18. Dogliotti A, Paolasso E, Giugliano RP. Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. Clin Cardiol 2013;36(2):61-7.
19. Larsen TB, Skjoth F, Nielsen PB, *et al*. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. Br Med J 2016;353:1-9.
20. Ruff CT, Giugliano RP, Braunwald E, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383(9921):955-62.
21. Wharin C and Tagalakis V. Management of venous thromboembolism in cancer patients and the role of the new oral anticoagulants. Blood Rev 2014;28(1):1-8.
22. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. Arterioscler. Thromb Vasc Biol 2015; 35(5):1056-65.
23. van Es N, Di Nisio M, Bleker SM, *et al*. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. Thromb Haemost 2015;114(6):1268-76.
24. Young A, Phillips J, Hancocks H, *et al*. Anticoagulation therapy in selected cancer patients at risk of recurrence of venous thromboembolism. Thromb Res 2016;140(suppl1):S172-3.
25. Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thromb Haemost 2015;13(12):2187-91.
26. Prins MH, Lensing AW, Brighton TA, *et al*. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1(1):e37-46.
27. Raskob GE, van Es N, Segers A, *et al*. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. Lancet Haematol. 2016;3(8):e379-87.
28. Schulman S, Goldhaber SZ, Kearon C, *et al*. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. Thromb Haemost 2015;114(1):150-7.
29. Sardar P, Chatterjee S, Mukherjee D. Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials. Drugs 2013;73(11):1171-82.
30. Vedovati MC, Germini F, Agnelli G, *et al*. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest 2015;147(2):475-83.
31. Raskob G, Buller H, Prins M, *et al*. Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study--methodological implications for clinical trials. J Thromb Haemost 2013;11(7):1287-94.
32. Bounameaux H and Camm AJ. Edoxaban: an update on the new oral direct factor Xa inhibitor. Drugs 2014;74(11):1209-31.
33. Dobesh PP and Fanikos J. New oral anticoagulants for the treatment of venous thromboembolism: understanding differences and similarities. Drugs 2014;74(17):2015-32.
34. Lee AYY, Levine MN, Baker RI, *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(2):146-53.
35. Becattini C and Agnelli G. Treatment of venous thromboembolism with new anticoagulant agents. J Am Coll Cardiol 2016;67(16):1941-55.
36. Schulman S, Kearon C, Kakkar AK, *et al*. Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism. N Engl J Med 2013;368(8):709-18.
37. Piatek C, O'Connell CL, Liebman HA. Treating venous thromboembolism in patients with cancer. Expert Rev Hematol 2012;5(2):201-9.
38. Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. N Engl J Med 2012;366(9):864-6.
39. King AE, Szarlej DK, Rincon F. Dabigatran-associated intracranial hemorrhage: literature review and institutional experience. Neurohospitalist 2015;5(4):234-44.
40. Wychowski MK and Kouides PA. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. Ann Pharmacother 2012;46(4):e10.
41. Çaliskan F, Akdemir HU, Nurata H, *et al*. Rivaroxaban-induced severe diffuse intracerebral hemorrhage. Am J Emerg Med 2015;33(3):e471.
42. Kato T, Kimura M, Inoko M. Cerebral infarction accompanied by cerebral bleeding in patients receiving apixaban. BMJ Case Rep 2015;2015. doi: 10.1136/bcr-2014-208965.
43. Molina M, Hillard VH, Fekete R. Intracranial hemorrhage in patient treated with rivaroxaban. Hematol Rep 2014;6(1):5283.
44. Sardar P, Chatterjee S, Chaudhari S, *et al*. New oral anticoagulants in elderly adults: evidence from a meta-Analysis of randomized trials. J Am Geriatr Soc 2014;62(5):857-64.
45. Kato ET, Giugliano RP, Ruff CT, *et al*. Efficacy and safety of edoxaban for the management of elderly patients with atrial fibrillation: ENGAGE AF-TIMI 48. Circulation 2014;130(suppl2): A16612.
46. Shoeb M and Fang MC. Assessing Bleeding Risk in Patients Taking Anticoagulants. J Thromb Thrombolysis 2013;35(3):312-9.
47. Faraoni D, Levy JH, Albaladejo P, *et al*. Updates in the perioperative and emergency management of non-vitamin K antagonist oral anticoagulants. Crit Care 2015;19(1):1-6.
48. Prandoni P. Treatment of patients with acute deep vein thrombosis and/or pulmonary embolism: efficacy and safety of non-VKA oral anticoagulants in selected populations. Thromb Res 2014;134(2): 227-33.
49. Bertoletti L, Ollier E, Duvillard C, *et al*. Direct oral anticoagulants: current indications and unmet needs in the treatment of venous thromboembolism. Pharmacol Res 2016, doi: 10.1016/j.phrs.2016.06.023.
50. Mauer AC, Khazanov NA, Levenkova N, *et al*. Impact of sex, age, race, ethnicity and aspirin use on bleeding symptoms in healthy adults. J Thromb Haemost 2011;9(1):100-8.
51. Takach LS, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis. J Thromb Haemost 2014;12(5):595-605.
52. Blanco-Molina A, Enea I, Gadelha T, *et al*. Sex differences in patients receiving anticoagulant therapy for venous thromboembolism. Medicine 2014;93(17):309-17.
53. Alotaibi GS, Almodaimegh H, McMurtry MS, *et al*. Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism? A sex-based meta-analysis. Thromb Res 2013; 132(2):185-9.
54. Dentali F, Sironi AP, Gianni M, *et al*. Gender difference in efficacy and safety of nonvitamin K antagonist oral anticoagulants in patients with nonvalvular atrial fibrillation or venous thromboembolism: a systematic review and a meta-analysis of the literature. Semin Thromb Hemost 2015;41(17):774-87.
55. Loffredo L, Violi F, Perri L. Sex related differences in patients with acute venous thromboembolism treated with new oral anticoagulants. A meta-analysis of the interventional trials. Int J Cardiol 2016;212:255-8.
56. Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of

acute venous thromboembolism. N Engl J Med 2013;369:799-808.
57. Bauersachs RM. Guidelines for the management of cancer and thrombosis - Special aspects in women. Thromb Res 2015;135:S16-22.
58. Burnett AE, Mahan CE, Vazquez SR, *et al*. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis 2016;41(1):206-32.
59. Pokorney SD, Sherwood MW, Becker RC. Clinical strategies for selecting oral anticoagulants in patients with atrial fibrillation. J Thromb Thrombolysis 2013;36(2):163-74.
60. Kubitza D, Becka M, Zuehlsdorf M, *et al*. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;47(2):218-26.
61. Upreti VV, Wang J, Barrett YC, *et al*. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013;76(6):908-16.
62. Lip GY and Agnelli G. Edoxaban: a focused review of its clinical pharmacology. Eur Heart J 2014;35(28):1844-55.
63. Macedo AF, Bell J, McCarron C, *et al*. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. Thromb Res 2015;136(2):250-60.
64. Aapro M and Launay-Vacher V. Importance of monitoring renal function in patients with cancer. Cancer Treat Rev 2012;38(3):235-40.
65. Launay-Vacher V, Oudard S, Janus N, *et al*. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management. Cancer 2007;110(6):1376-84.
66. Lichtman SM, Wildiers H, Launay-Vacher V, *et al*. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 2007;43(1):14-34.
67. Reilly PA, Lehr T, Haertter S, *et al*. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63(4):321-8.
68. Stangier J, Rathgen K, Stähle H, *et al*. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. Clin Pharmacokinet 2010;49(4):259-68.
69. Safouris A, Triantafyllou N, Parissis J, *et al*. The case for dosing dabigatran: how tailoring dose to patient renal function, weight and age could improve the benefit–risk ratio. Ther Adv Neurol Disord 2015;8(6):245-54.
70. Hughes S, Szeki I, Nash MJ, *et al*. Anticoagulation in chronic kidney disease patients—the practical aspects. Clin Kidney J 2014;7(5):442-9.
71. Kubitza D, Becka M, Mueck W, *et al*. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2010;70(5):703-12.
72. Wasserlauf G, Grandi SM, Filion KB, *et al*. Meta-analysis of rivaroxaban and bleeding risk. Am J Cardiol 2013;112(3):454-60.
73. Weinz C, Schwarz T, Kubitza D, *et al*. Metabolism and excretion of rivaroxaban, an oral, direct factor Xa inhibitor, in rats, dogs, and humans. Drug Metab Dispos 2009;37(5):1056-64.
74. Beyer-Westendorf J, Förster K, Pannach S, *et al*. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood 2014;124(6):955-62.
75. Tamayo S, Frank Peacock W, Patel M, *et al*. Characterizing major bleeding in patients with nonvalvular atrial fibrillation: a pharmacovigilance study of 27 467 patients taking rivaroxaban. Clin Cardiol 2015;38(2):63-8.
76. Raghavan N, Frost CE, Yu Z, *et al*. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos 2009;37(1):74-81.
77. Chang M, Yu Z, Shenker A, *et al*. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. J Clin Pharmacol 2016;56(5):637-45.
78. Hohnloser SH, Hijazi Z, Thomas L, *et al*. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 2012;33(22):2821-30.
79. Pathak R, Pandit A, Karmacharya P, *et al*. Meta-analysis on risk of bleeding with apixaban in patients with renal impairment. Am J Cardiol 2015;115(3):323-7.
80. Harel Z, Sholzberg M, Shah PS, *et al*. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. J Am Soc Nephrol 2014;25(3):431-42.
81. Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093-104.
82. Koretsune Y, Yamashita T, Yasaka M. Evaluation of edoxaban in patients with atrial fibrillation and severe renal impairment. Eur Heart J 2013;34(suppl1):520.
83. Agnelli G, Eriksson BI, Cohen AT, *et al*. Safety assessment of new antithrombotic agents: Lessons from the EXTEND study on ximelagatran. Thromb Res 2009;123(3):488-97.
84. Mekaj YH, Mekaj AY, Duci SB, *et al*. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manage 2015;11:967-77.
85. Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. Clin Pharmacokinet 2013;52:243-54.
86. Mueck W, Stampfuss J, Kubitza D, *et al*. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 2014;53(1):1-16.
87. Stangier J, Stahle H, Rathgen K, *et al*. Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, are not affected by moderate hepatic impairment. J Clin Pharmacol 2008;48(12):1411-9.
88. Caldeira D, Barra M, Santos AT, *et al*. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart 2014;100:550-6.
89. Schulman S, Kearon C, Kakkar AK, *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361(24):2342-52.
90. Connolly SJ, Ezekowitz MD, Yusuf S, *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-51.
91. Liakoni E, Rätz Bravo AE, Krähenbühl S. Hepatotoxicity of New Oral Anticoagulants (NOACs). Drug Saf 2015;38(8):711-20.
92. Kim RB. Drugs as P-glycoprotein substrates, inhibitors, and inducers. Drug Metab Rev 2002;34(1-2):47-54.
93. Samer CF, Lorenzini KI, Rollason V, *et al*. Applications of CYP450 Testing in the Clinical Setting. Mol Diagn Ther 2013;17(3):165-84.
94. Short NJ and Connors JM. New oral anticoagulants and the cancer patient. Oncologist 2014;19(1):82-93.
95. Stöllberger C and Finsterer J. Relevance of P-glycoprotein in stroke prevention with dabigatran, rivaroxaban, and apixaban. Herz 2015;40(2):140-5.

96. Stangier J and Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009;15(suppl1):9S-16S.
97. Hellwig T and Gulseth M. Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants. Ann Pharmacother 2013;47(11):1478-87.
98. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis 2011;31(3):326-43.
99. Mendell J, Zahir H, Matsushima N, *et al*. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. Am J Cardiovasc Drugs 2013;13(5):331-42.
100. Mikkaichi T, Yoshigae Y, Masumoto H, *et al*. Edoxaban transport via P-glycoprotein is a key factor for the drug's disposition. Drug Metab Dispos 2014;42(4):520-8.
101. Pare G, Eriksson N, Lehr T, *et al*. Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013;127: 1402-12.
102. Legrand M, Mateo J, Aribaud A, *et al*. The use of dabigatran in elderly patients. Arch Intern Med 2011;171(14):1285-6.
103. Parasrampuria DA and Truitt KE. Pharmacokinetics and Pharmacodynamics of Edoxaban, a Non-Vitamin K Antagonist Oral Anticoagulant that Inhibits Clotting Factor Xa. Clin Pharmacokinet 2016; 55(6):641-55.
104. Stangier J, Stähle H, Rathgen K, *et al*. No interaction of the oral direct thrombin inhibitor dabigatran etexilate and digoxin. J Thromb Haemost 2007;5(suppl2):W672.
105. Frost CE, Byon W, Song Y, *et al*. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Br J Clin Pharmacol 2015;79(5):838-46.
106. Altena R, van Roon E, Folkeringa R, *et al*. Clinical challenges related to novel oral anticoagulants: drug-drug interactions and monitoring. Haematologica 2014;99(2):e26-e27.
107. Vakkalagadda B, Frost C, Byon W, *et al*. Effect of rifampin on the pharmacokinetics of apixaban, an oral direct inhibitor of factor Xa. Am J Cardiovasc Drugs 2016;16(2):119-27.
108. Härtter S, Koenen-Bergmann M, Sharma A, *et al*. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. Br J Clin Pharmacol 2012;74(3):490-500.
109. Mendell J, Chen S, He L, *et al*. The effect of rifampin on the pharmacokinetics of edoxaban in healthy adults. Clin Drug Invest 2015;35(7):447-53.
110. Lam MS and Ignoffo RJ. A guide to clinically relevant drug interactions in oncology. J Oncol Pharm Pract 2003;9(2-3):45-85.
111. Mavrakanas T, Samer CF, Fontana P, *et al*. Direct oral anticoagulants: efficacy and safety in patient subgroups. Swiss Med Wkly 2015; 145:w14081.
112. Riechelmann RP and Del Giglio A. Drug interactions in oncology: how common are they? Ann Oncol 2009;. doi: 10.1093/annonc/mdp369.
113. Holbrook A, Schulman S, Witt DM, *et al*. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141(suppl2):e152S-84S.
114. Steiner T, Böhm M, Dichgans M, *et al*. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. Clin Res Cardiol 2013;102(6):399-412.
115. Eerenberg ES, Kamphuisen PW, Sijpkens MK, *et al*. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124(14):1573-9.
116. Marlu R, Hodaj E, Paris A, *et al*. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. Thromb Haemost 2012;108(2):217-24.
117. Sarich TC, Seltzer JH, Berkowitz SD, *et al*. Novel oral anticoagulants and reversal agents: Considerations for clinical development. Am Heart J 2015;169(6):751-7.
118. Suryanarayan D and Schulman S. Potential antidotes for reversal of old and new oral anticoagulants. Thromb Res 2014;133:S158-66.
119. Lazo-Langner A, Lang ES, Douketis J. Clinical review: Clinical management of new oral anticoagulants: a structured review with emphasis on the reversal of bleeding complications. Crit Care 2013;17(3):230.
120. Schiele F, van Ryn J, Newsome C, *et al*. A specific antidote for dabigatran: functional and structural characterization. Blood 2013;121(18): 3554-62.
121. Glund S, Stangier J, Schmohl M, *et al*. A specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in healthy male volunteers. Circulation 2013;128(suppl22):A17765.
122. Glund S, Stangier J, Schmohl M, *et al*. Idarucizumab, a specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in elderly and renally impaired subjects. Blood 2014;124(21):344.
123. Pollack CVJ, Reilly PA, Eikelboom J, *et al* Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373(6):511-20.
124. Schwarb H and Tsakiris DA. New direct oral anticoagulants (DOAC) and their use today. Dent J 2016;4(1):5.
125. Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. J Thromb Thrombolysis 2015;39(3):395-402.
126. Hu TY, Vaidya VR, Asirvatham SJ.Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexan*et al*fa, and idarucizumab. Vasc Health Risk Manage 2016;12:35.
127. Siegal DM, Curnutte JT, Connolly SJ, *et al*. Andexan*et al*fa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373(25): 2413-24.
128. Bauer KA. Targeted anti-anticoagulants. N Engl J Med 2015;373(6): 569-71.