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
respondents. Other medical record analyses showed that only 25% to 30% of patients actually received LMWH monotherapy as the first-line VTE treatment. 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.

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 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 and is expanding for the treatment of mechanical heart valves, heart failure, and coronary artery disease. 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 and SELECT-D trial for rivaroxaban versus dalteparin. 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. Several systemic reviews and meta-analyses of clinical trial data also revealed similar efficacy and safety between NOACs and the standard therapy. 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. 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. 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.

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. For edoxaban, the cancer group consisted of both the patients with active cancer and those with a history of cancer regardless of the treatment. 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. 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, 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.\textsuperscript{20,24} Only the dabigatran treatment for 3 to 12 months was also compared to warfarin, showing non-inferiority.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{54}

Conversely, most recent meta-analysis of 9 clinical trials supported the study by Alotaibi \textit{et al}.\textsuperscript{55} Women, compared to men, showed a 35% higher risk of bleedings while maintaining the treatment efficacy with NOACs.\textsuperscript{55} All these analyses had
their own limitations such as no stratification of outcome data and patient characteristics by sex, except one study of apixaban. In addition, there are no recommendations for women specific cancer types or issues in the management of VTE. 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. 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). The pharmacokinetic profiles of factor Xa inhibitors may be affected by body weight, but no compelling evidence on the clinical effect was observed. 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. 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 \( \geq 120 \) kg, and 27% higher with weight \( \leq 50 \) kg, and therefore may not warrant the dose adjustment based on the body weight. 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 \( \leq 60 \) kg; however, the efficacy and safety of edoxaban were

<table>
<thead>
<tr>
<th>Generic Name (Trade Name)</th>
<th>Warfarin (Coumadin)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>Indirect Vitamin K antagonist</td>
<td>Direct thrombin inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
<td>Direct Factor Xa inhibitor</td>
</tr>
<tr>
<td>Food or drug effect</td>
<td>Dietary vit K influence on PD, many drug interactions</td>
<td>Food prolong AUC, T(_{\text{max}}) to 2h, potent P-gp inhibitors/inducers</td>
<td>Food increases AUC, potent CYP3A4 and P-gp inhibitors/inducers</td>
<td>No food effect, potent CYP3A4 and P-gp inhibitors/inducers</td>
<td>No food effect, potent P-gp inhibitors</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>3-5days</td>
<td>1h</td>
<td>2.5-4h</td>
<td>3h</td>
<td>1-2h[5]</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>79-100%</td>
<td>3-7%</td>
<td>80-100%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>99%</td>
<td>35%</td>
<td>95%</td>
<td>87%</td>
<td>40-59%</td>
</tr>
<tr>
<td>Half-life</td>
<td>40h</td>
<td>12-17h</td>
<td>5-9h</td>
<td>8-15h</td>
<td>9-11h</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable (0.5-16 mg OD)</td>
<td>150, 110 mg BID</td>
<td>15, 20 mg OD</td>
<td>2.5, 5 mg BID</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Greater INR response, clearance decrease in patients ( \geq 75 ) y</td>
<td>Cmin increase of 31% in patients ( &gt;65 ) y</td>
<td>AUC increase of 50% in patients ( &gt;65 ) y</td>
<td>AUC increase of 32% in patients ( &gt;65 ) y</td>
<td>None</td>
</tr>
<tr>
<td>Sex</td>
<td>Lower dose required for None female</td>
<td>None</td>
<td>Exposure in females higher by 18%</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>No effect on dose</td>
<td>C(_{\text{min}}) decrease of 20% in patients ( &gt;100 ) kg</td>
<td>Exposure increase of 25% in patients ( &lt;50 ) kg and decrease by 25% in patients ( &gt;120 ) kg</td>
<td>Exposure increase of 30% in patients ( &lt;50 ) kg and decrease by 30% in patients ( &gt;120 ) kg</td>
<td>Exposure increase in patients ( &gt;60 ) kg</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>&gt;90%</td>
<td>&gt;80%</td>
<td>66%</td>
<td>25-27%</td>
<td>50%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2C9, CYP3A4, CYP2C19, CYP1A2</td>
<td>Substrate for P-gp</td>
<td>CYP3A4 CYP2J2 and CYP-independent mechanisms; substrate for P-gp</td>
<td>CYP3A4 CYP2J2, CYP1A2; substrate for P-gp</td>
<td>CYP3A4 (&lt;4%); CYP3A4/5, CYP2J, CYP1A2; substrate for P-gp</td>
</tr>
<tr>
<td>Anticoagulation monitoring</td>
<td>Required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
<td>Not required</td>
</tr>
<tr>
<td>Reversal agents</td>
<td>Vitamin K</td>
<td>Idarucizumab, Arapazine</td>
<td>Andexanet, Arapazine, Arapazine</td>
<td>Andexanet, Arapazine</td>
<td>Andexanet, Arapazine</td>
</tr>
</tbody>
</table>

AUC, area under the curve; C\(_{\text{min}}\), minimum concentration; CYP, cytochrome P450; P-gp, permeability glycoprotein; T\(_{\text{max}}\), time to maximum concentration
maintained with dose reduction in this group.\textsuperscript{32}

Dose adjustment for NOACs based on the body weight may not be warrants, 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.\textsuperscript{63}

**RENALE 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.\textsuperscript{64} Renal excretion is the major route of elimination for \textasciitilde50\% of all the cancer therapeutic agents, and any reduction in renal clearance can accumulate potentially toxic drugs or metabolites.\textsuperscript{65} Thus, the dosage of drugs with renal clearance should be adjusted in proportion to the renal function in cancer patients.\textsuperscript{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, dabigatran and it predominantly (\textasciitilde80\%) 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).\textsuperscript{57,68} The underweight older patients with renal insufficiency were particularly at high risk of bleeding associated with dabigatran,\textsuperscript{40,69} and therefore the initial and periodic assessment of renal function is recommended in this population.\textsuperscript{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.\textsuperscript{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),\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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,\textsuperscript{79} a similar result to those of prior meta-analyses.\textsuperscript{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.\textsuperscript{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 \\geq\ 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
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.\textsuperscript{83} 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).\textsuperscript{62}

Based on the aforementioned studies of each NOAC agent and recent meta-analysis of clinical trials,\textsuperscript{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,\textsuperscript{83} major NOAC trials excluded all the patients with

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### Table 2. Sub-analyses of cancer patients in clinical trials regarding novel oral anticoagulants for the treatment of venous thromboembolism.\textsuperscript{23-27, 30-32}

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

*The efficacy outcome was recurrent symptomatic VTE or VTE-related death  
**The safety outcome was major or clinically relevant non-major bleeding (CRNM)
active or chronic liver disease as well as any evidence of hepatic impairment on baseline laboratory values. All the NOACs, with the exception of dabigatran, undergo hepatic metabolism via cytochrome (CYP) P450 enzymes with different degrees, 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).

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. 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. 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. 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.

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. 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. Several cases reporting life-threatening hepatotoxicity associated with rivaroxaban or dabigatran are quite alarming 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.

Absorption of NOACs is dependent on the permeability glycoprotein (P-gp) efflux transporters in many tissues and can be modulated by drugs or foods. 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; therefore, potential pharmacokinetic interactions involving P-gp are restricted to absorption across the intestinal wall. 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%).

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>
<thead>
<tr>
<th>Table 3. Drugs which have a possible interactions with NOACs by P-gp and CYP3A4 systems.</th>
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<tr>
<td><strong>P-glycoprotein</strong></td>
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<tr>
<td><strong>Substrate</strong></td>
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<tr>
<td>Dalbigratran</td>
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<tr>
<td>Rivaroxaban</td>
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<td>Apixaban</td>
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<td>Edoxaban</td>
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<td><strong>Oncology drugs</strong></td>
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<tr>
<td>Bendamustine</td>
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<td>Crizotinib</td>
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<td>Daunorubicin</td>
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<td>Docetaxel</td>
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<td>Etoposide</td>
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<td>Imatinib</td>
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<td>Paclitaxel</td>
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<td>Vinorelbine</td>
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<td><strong>Antiarrhythmics</strong></td>
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<td>Diltiazem</td>
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<td>Quinidine</td>
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<td>Verapamil</td>
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<td><strong>Antiemetics</strong></td>
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<td>Ondansetron</td>
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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. Quinidine and verapamil increased the AUC of edoxaban by 76.7% and 52.7%, respectively. Based on these pharmacokinetic interactions, quinidine use was prohibited while on dabigatran, and a reduced dose (30 mg daily) of edoxaban was administered to the patients taking strong P-gp inhibitors in a clinical study. According to an in vivo study of P-gp transporter, the clinical impact of P-gp inhibitory effects on edoxaban seems uncertain at present. 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.

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

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Carbamazepine</th>
<th>Carbamazepine Phenobarbital Phenytoin</th>
<th>Carbamazepine Felbamate Oxcarbamazepine Phenobarbital Phenytoin Primidone Topiramate</th>
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<tbody>
<tr>
<td>Antimicrobials</td>
<td>Amoxicillin</td>
<td>Atazanavir Clarithromycin Erythromycin Fosamprenavir Indinavir Itraconazole Ketoconazole Lopinavir Neoral Nevirapine Ritonavir Saquinavir Tetracycline</td>
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<tr>
<td>Immune-modulators</td>
<td>Cyclosporine Dexamethasone Tacrolimus</td>
<td>Cyclosporine Dexamethasone Tacrolimus</td>
<td>Cyclosporine Dexamethasone Tacrolimus</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Cimetidine Colchicine Domperidone Loperamide Fexofenadine Ranitidine</td>
<td>Atorvastatin Bromocriptine Modafinil Ethanol St John’s wort</td>
<td>Grapefruit Milk-thistle</td>
</tr>
</tbody>
</table>

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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 P-gp are also likely to be additive. Although with very little involvement of CYP metabolism, the AUC of dabigatran and P-gp are also likely to be additive. Although with very little involvement of CYP metabolism, the AUC of dabigatran and P-gp are also likely to be additive. Although with very little involvement of CYP metabolism, the AUC of dabigatran and P-gp are also likely to be additive. Although with very little involvement of CYP metabolism, the AUC of dabigatran

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 aprepiant 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.\(^{113,114}\) Although 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{126}

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.

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