

# New Oral Anticoagulants Open New Horizons for Cancer Patients with Venous Thromboembolism

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**Abstract:** Venous thromboembolism (VTE) is associated with increased morbidity and mortality, decreased quality of life, and higher economic burden in patients with cancer. Currently, the treatment of VTE in patients with cancer is particularly challenging. For many years, low molecular weight heparin (LMWHs) has been the standard for the treatment of cancer-associated VTE. Recently, the introduction of new oral anticoagulants (NOACs) may offer an oral anticoagulant option for some patients with cancer-associated thrombosis (CAT) as a growing body of literature supports the use of NOACs in the setting of CAT. With the use of NOAC as a new option in the management of CAT, clinicians now face several choices for the individual cancer patient with VTE. We need a more in-depth understanding of the drug properties, efficacy and safety, economic analysis that allows us to choose the most appropriate treatment for each patient. In the review, we will present an overview of CAT management, discuss the available evidence, economic costs for NOACs in the treatment of CAT, and seek to provide the best range of treatments for cancer patients.

**Keywords:** new oral anticoagulants, low molecular weight heparin, venous thromboembolism, cancer-associated thrombosis, anticoagulants

## Introduction

Venous thromboembolic (VTE) disease is a continuing global health burden, particularly in cancer patients.<sup>1-4</sup> The incidence of cancer-associated thrombosis (CAT) continues to rise over the years.<sup>5</sup> It is also recognised that anticoagulant treatment is important in this growing population. Vitamin K antagonists (VKAs) have been for a long time the only option for oral anticoagulation. Low molecular weight heparins (LMWHs) have been shown to be superior to VKAs<sup>6-11</sup> and recommended by guidelines as the standard of treatment for CAT in the last few years.<sup>12-14</sup> However, the treatment with LMWHs still has limitations like an inconvenience for patients and costly for health care systems.<sup>15</sup> The introduction of new oral anticoagulants (NOACs) has remodeled the antithrombotic therapy of choice, with a tendency of widening the range of indications. Taking into account the positive results of the studies so far, NOACs have been included in current guidelines as important alternatives to LMWHs for the treatment of VTE in suitable patients with cancer, but further studies are expected. Herein, in the present review, we have discussed recent evidence and their potential clinical and economic impact to will further our understanding of the optimal antithrombotic approach to the management of VTE in this patient population.

## Burden of Venous Thromboembolism in Patients with Cancer

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer and is termed as cancer-associated thrombosis (CAT). Patients with cancer have a four to sevenfold increased risk of VTE compared with patients without cancer.<sup>16</sup> The factors that are responsible for the increase of risk basically include cancer type and anticancer-associated treatment.<sup>17-21</sup> The highest incidence rate of 42% (OR 2.55; 95% CI 2.10–3.09) ( $p < 0.001$ ) was observed in patients with pancreatic cancer.<sup>22</sup>

Chemotherapy in anticancer-associated treatment is an independent risk factor for CAT. The annual incidence of chemotherapy-related VTE is about 11%, and this rate may rise to 20% with the use of different chemotherapy medicines.<sup>23</sup> Data from a recent study indicated that the risk of VTE in cancer patients is increasing steadily and is ninefold higher than in the general population.<sup>24</sup> The incidence of CAT may have changed in the past decade,<sup>6</sup> which is associated with 4–20% among different cancers.<sup>25</sup> However, of all cancer patients, only 15% develop symptomatic VTE, while up to 50% have evidence of asymptomatic DVT/PE and as many as 50% have VTE at autopsy, with VTE being the second-leading cause of death after cancer progression.<sup>2,26</sup>

VTE has a significant negative impact on the quality of life in patients with cancer, which is associated with a variety of poor consequences including an increased risk of VTE recurrence, major bleeding, and early mortality.<sup>5,26–31</sup> It has long been observed that thromboembolism represents a major cause of death among patients with cancer after the malignancy itself.<sup>5,31,32</sup> The occurrence of VTE has been reported to increase the likelihood of death for cancer patients by 2- to 6-fold.<sup>4,5,28,33</sup> A large-scale survey revealed that in-hospital mortality was observed in 5.5% of cancer patients without a VTE diagnosis, whereas in 15.0% of those with VTE, including 19.4% with a pulmonary embolism, in the United States.<sup>34</sup> Moreover, when cancer patients develop VTE, they have a significantly increased risk of VTE recurrence and bleeding with a threefold higher risk of recurrent VTE, and a twofold higher risk of anticoagulation-associated bleeding compared to patients without cancer.<sup>35</sup> Furthermore, recurrent VTE is associated with a higher risk for a range of VTE-related complications, including venous ulcers, pulmonary hypertension, and venous insufficiency, which has a broader impact on the patient's quality of life.<sup>36</sup> For these reasons, VTE may lead to otherwise unnecessary hospitalizations and increased annual health care costs.<sup>3,37</sup> Several qualitative studies have explored patients' experiences of cancer-associated thrombosis, with consistent reports of VTE causing considerable distress to patients with cancer and their families.<sup>38–40</sup>

VTE events place a substantial economic burden on the healthcare system that is further amplified among patients with cancer. Compared to cancer patients without VTE, cancer patients with VTE have been shown to have three times as many all-cause hospitalizations, more days spent in the hospital, and a significantly higher number of outpatient visits.<sup>3</sup> Mean total hospitalization costs were 2.5-times (\$17,089) higher among cancer patients with VTE compared to patients without VTE and accounted for 62% of the VTE-related total healthcare costs.<sup>41</sup> Total (all-cause) health care costs were about 80% higher in cancer patients with VTE (mean unadjusted cost of \$74,959 per patient) in comparison with matched cancer patients without VTE (\$41,691)<sup>42</sup> and remain significantly higher for years after the index VTE event.<sup>43</sup> Using claims data, Khorana et al found that cancer patients with VTE incurred significantly higher total healthcare costs compared to cancer patients without VTE (\$74,959 vs \$41,691 per patient over the 12-month follow-up period;  $p < 0.0001$ ).<sup>3</sup> Furthermore, in a real-world study, cancer patients with recurrent VTE incurred nearly twice the total healthcare costs relative to cancer patients without recurrent VTE, of which nearly 75% of the increased cost was associated with VTE recurrence.<sup>44</sup>

## Evolution from Traditional Anticoagulants to NOACs for CAT

Tailoring anticoagulation with the optimal agents in patients with cancer is of utmost importance due to dismal prognosis and higher healthcare costs. Historically, vitamin K antagonists (VKAs) were the mainstay of therapy for VTE in patients with cancer.<sup>45</sup> However, published studies showed that the use of VKAs for CAT is associated with a higher risk for both recurrence and bleeding compared with the general population. Patients with cancer had a threefold to fourfold higher risk for VTE recurrence with VKAs treatment and a sixfold higher risk for anticoagulant-associated bleeding compared with non-cancer patients.<sup>46,47</sup> Furthermore, the management of VKAs is further complicated by frequent blood test monitoring and numerous drug-drug and drug-food interactions.<sup>48</sup>

Low molecular weight heparins (LMWHs) were the first available alternatives to VKAs in the past few years, which represent a more effective and stable pharmacological approach to CAT treatment. The anticoagulant effect of LMWHs is due to the inhibition of the final common pathway of the coagulation cascade by activation of antithrombin III, which promotes the inactivation factors Xa and IIa.<sup>49</sup> Compared with VKAs, the major advantages of LMWHs are their independence from gut absorption, fewer drug-drug interactions, and similar or lower rates of VTE recurrence bleeding in cancer patients.<sup>6,10,50</sup>

The two largest studies, CLOT (Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy) and CATCH (Comparison of Acute Treatments in Cancer Haemostasis) studies, investigated the safety and efficacy of LMWHs compared with VKAs in patients with cancer-associated VTE. In 2003, the CLOT trial (Randomised Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer), which was a large randomized clinical trial comparing VKAs to an LMWHs in 672 cancer patients, demonstrated that LMWHs dalteparin was associated with significantly lower rates of recurrent VTE with no increased risk of major bleeding when compared to warfarin.<sup>6</sup> In the CLOT study, 336 patients received dalteparin 200 international units (IU) per kilogram of body weight once daily (maximum 18,000 IU per day) for 1 month followed by 150 IU per kilogram once daily for 5 months. 336 patients received VKAs for six months after initial anticoagulation with dalteparin 200 IU/kg for 5 to 7 days.<sup>6</sup> The results of the multinational CLOT trial showed that the rates of recurrent VTE were 8% (27/336) and 16% (53/336) in the dalteparin and VKAs groups, corresponding to a hazard ratio (HR) of 0.48 (95% confidence interval (CI): 0.30–0.77,  $p = 0.002$ ). Furthermore, there was no significant difference in major bleeding with rates of 6% in the dalteparin group and 4% in the VKAs arm ( $p=0.27$ ). Thus, this led to LMWHs being the first-line treatment for CAT and is still widely used. Subsequently, this recommendation was supported by the more contemporary CATCH trial published in 2015, which was the largest trial to compare LMWHs with VKAs.<sup>10</sup> In 900 cancer patients with cancer-associated VTE, 6-month treatment with LMWHs tinzaparin nonsignificantly reduced the primary efficacy outcome of recurrent VTE and did not affect major bleeding compared with the VKAs warfarin. The rates for recurrent VTE were not statistically significant with 31/449 (7%) patients receiving tinzaparin and 45/451 (10%) patients on warfarin ( $p=0.07$ ), corresponding to a nonsignificant risk reduction with an HR of 0.65 (95% CI: 0.41–1.03). Rates of major bleeding were found at 2.7% in the tinzaparin arm and 2.4% in the warfarin arm ( $p=0.77$ ), while clinically relevant nonmajor bleeding (CRNMB) was statistically significant with 49 (10.9%) patients in the tinzaparin group compared to 69 (15.3%) in the warfarin group ( $p=0.004$ ). As for LMWHs vs VKAs, meta-analyses and retrospective studies confirmed the superiority of LMWHs over conventional treatment in reducing recurrences, reinforcing the use of LMWHs over VKAs for the treatment of CAT. A meta-analysis including six randomized controlled trials comparing LMWHs with VKAs reported an overall reduction in risk of recurrent VTE with LMWHs (odds ratio (OR): 0.55; 95% CI: 0.40–0.75) with no increased risk in bleeding (relative risk (RR): 1.10; 95% CI: 0.71–1.69).<sup>51</sup> And one retrospective study<sup>52</sup> found that LMWHs were more efficacious in the treatment of cancer-associated VTE with similar bleeding risk compared with VKAs.

Although effective and safe, LMWHs treatment has practical limitations, including the daily subcutaneous injections and associated costs, which may limit long-term adherence in some patients. Daily subcutaneous injections that can lead to pain, bruising, and hematomas, may have an impact on the patient's quality of life.<sup>53,54</sup> An additional limitation is the high cost of LMWHs therapy relative to VKAs.<sup>55</sup> Thus, the compliance of treatment with LMWHs is low in patients with cancer-associated VTE. However, real-world data suggest that patient compliance with LMWHs is only 37% still on therapy at 6 months (vs 61% of patients prescribed oral agents).<sup>56</sup> As a result, safer and more convenient new agents have been sought for patients with cancer who have VTE.

New oral anticoagulants (NOACs) represent a convenient and effective treatment option, which have certainly changed the landscape of anticoagulation in specific patient populations affected by cancer. Three of these molecules (namely, apixaban, edoxaban, and rivaroxaban) target activated factor X, and one molecule (ie, dabigatran) is directed against activated factor II, thrombin. In this study, the wording NOACs refer to apixaban, rivaroxaban, and edoxaban—except for dabigatran, which has not been specifically studied in a randomized trial in patients with cancer-associated VTE. They offer many advantages over VKAs, including predictable pharmacokinetics and pharmacodynamics, rapid onset and offset of action, short half-life, wide therapeutic window, few drug-drug and drug-food interactions, and no need for laboratory monitoring.<sup>57</sup> In addition, unlike LMWHs, NOACs are administered orally, are cheaper than LMWHs,<sup>58</sup> and therefore an attractive potential alternative to traditional anticoagulants for the treatment of CAT.

# Evidence for the Use of NOACs in Cancer Patients

## Evidence from Randomized Clinical Trials

Initial evidence from analysis of cancer patient subgroups included in the landmark NOACs trials, which focused on the general patient population,<sup>59–64</sup> showed that the efficacy and safety of NOACs were similar to those found in the general population.<sup>64–69</sup> Subsequently, randomized clinical trials (RCTs) specifically focusing on VTE cancer patients have confirmed previous observations related to the efficacy of NOACs in the treatment of CAT, and have further provided safety of NOACs in the cancer setting. Four head-to-head randomized clinical trials have been conducted, including HOKUSAI VTE Cancer (edoxaban),<sup>70</sup> SELECT-D (rivaroxaban),<sup>53</sup> and ADAM VTE<sup>71</sup> and Caravaggio (apixaban).<sup>72</sup> NOACs, in particular the Factor Xa direct inhibitors apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily), rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily), and edoxaban (60 mg daily after at least 5 days of LMWHs therapy), have been compared with LMWHs as suggested by the CLOT study (dalteparin 200 IU/kg for 1 month, followed by dalteparin 150 IU/kg) for CAT in four RCTs. In each study, patients were followed for at least 6 months. The primary endpoint in the SELECT-D and CARAVAGGIO studies was recurrent VTE, in the ADAM VTE was major bleeding, while the Hokusai-VTE Cancer study chose a combined endpoint of recurrent VTE and major bleeding. In all three studies, major bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria in three studies. The European Medicines Agency definition was used in the Caravaggio study<sup>73</sup> and includes all the ISTH criteria for major bleeding and bleeding requiring surgical intervention. Specifics of study and the conclusions of outcome are in Table 1.

The Hokusai-VTE Cancer study showed an incidence of the primary composite outcome (recurrent VTE or major bleeding) of 12.8% in the edoxaban arm and 13.5% in the dalteparin arm (HR: 0.97, 95% CI: 0.70–1.36,  $p=0.006$  for non-inferiority).<sup>70</sup> Recurrent VTE was lower in the edoxaban group compared to the dalteparin group (7.9% vs 11.3%; HR: 0.71, 95% CI: 0.48–1.06,  $P=0.09$ ), but major bleeding was significantly increased with edoxaban compared to dalteparin (6.9% vs 4.0%; HR: 1.77; 95% CI: 1.03–3.04,  $P=0.04$ ) driven by higher bleeding rates in patients with gastrointestinal cancers (13.2% vs 2.4%).<sup>70</sup> The second published trial was the SELECT-D study.<sup>53</sup> The primary outcome of VTE recurrence rate was 4% with rivaroxaban and 11% with dalteparin (HR, 0.43; 95% CI: 0.19–0.99) with a rate of major bleeding of 6% for rivaroxaban and 4% for dalteparin (HR: 1.83, 95% CI: 0.68 to 4.96) and rates of CRNMB of

**Table 1** Clinical Study to Evaluate the Efficacy and Safety of NOACs in CAT Treatment

Clinical Study	Hokusai-VTE Cancer <sup>70</sup>	SELECT-D <sup>53</sup>	ADAM VTE <sup>71</sup>	Caravaggio <sup>72</sup>
Study design	Edoxaban vs LMWHs	Rivaroxaban vs LMWHs	Apixaban vs LMWHs	Apixaban vs LMWHs
Number of patients	522/524	203/203	145/142	576/579
Key inclusion criteria	≥18 years of age with cancer (active or diagnosed within 2 y) <sup>a</sup> and acute VTE	≥18 years of age, active cancer <sup>c</sup> +acute VTE	≥18 years of age, with active cancer <sup>b</sup> + acute VTE	≥18 years of age with cancer (active or diagnosed within 2 y) <sup>c</sup>
NOACs	Edoxaban 60 mg QD after LMWHs for 5 days <sup>c</sup>	Rivaroxaban 15 mg BID × 3 weeks → 20 mg QD	Apixaban 10 mg BID × 7 days → 5 mg BID	Apixaban 10 mg BID × 7 days → 5 mg BID
Dalteparin	200 IU/kg QD × 1 month → 150 IU/kg QD	200 IU/kg QD × 1 month → 150 IU/kg QD	200 IU/kg QD × 1 month → 150 IU/kg QD	200 IU/kg QD × 1 month → 150 IU/kg QD
Treatment duration	6–12 months	6 months	6 months	6 months
Primary outcomes	Composite of recurrent VTE and major bleeding defined according to the ISTH criteria	Recurrent VTE and other sites of thrombosis	Major bleeding defined according to the ISTH criteria	Recurrent VTE and major bleeding defined according to the ISTH criteria
Major Conclusions	Recurrent VTE 7.9% vs 11.3%, Major bleeding 6.9% vs 4.0%	Recurrent VTE 11% vs 4.0%, Major bleeding 4.0% vs 6.0%	Recurrent VTE 0.7% vs 6.3%, Major bleeding 0.0% vs 1.4%	Recurrent VTE 5.6% vs 7.9%, Major bleeding 3.8% vs 4.0%

**Notes:** <sup>a</sup>Active cancer defined as diagnosed within 6 mo, treatment within 6 mo, recurrent/metastatic cancer, hematologic cancer not in complete remission. <sup>b</sup>Active cancer defined as any evidence of cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior 6 mo. <sup>c</sup>Or 30 mg 1 ×/d, if (i) body weight <60 kg, (ii) creatinine clearance of 30–50 mL/min, or (iii) concomitant therapy with a potent P-glycoprotein inhibitor.

13% and 4%, respectively (HR: 3.76, 95% CI: 1.63 to 8.69).<sup>53</sup> As in the Hokusai-VTE Cancer study, it was observed that the risk of major bleeding with rivaroxaban was higher in patients with malignancies of the gastrointestinal tract. The results of the ADAM VTE Trial found that NOACs treatment for cancer patients reduced the incidence of major bleeding and recurrent VTE compared with LMWHs. No patients on apixaban suffered a major bleeding complication compared to 1.4% of patients receiving LMWHs.<sup>71</sup> The secondary outcome of the VTE recurrence rate was 0.7% in the apixaban group and 6.3% in the dalteparin group (HR: 0.099, 95% CI: 0.013–0.780,  $P=0.0281$ ).<sup>71</sup> The recently published CARAVAGGIO study confirmed recurrent VTE was 5.6% in the apixaban group and 7.9% in the dalteparin group (HR: 0.63, 95% CI: 0.37 to 1.07,  $P<0.001$  for non-inferiority).<sup>72</sup> Major bleeding rates were 3.8% in apixaban group and 4.0% in dalteparin group (HR: 0.82, 95% CI: 0.40 to 1.69,  $P=0.60$ ). CRNMB rates were 9.0% with apixaban and 6.0% with dalteparin (HR: 1.42, 95% CI: 0.88 to 2.30).<sup>72</sup>

The above four trials suggest that NOACs had a significantly lower risk of recurrent VTE, without a significantly higher likelihood of major bleeding than when treated with dalteparin. However, the overall heterogeneity contribution for major bleeding was mainly related to the apixaban studies. Hokusai VTE Cancer and SELECT-D reported an increased risk of major bleeding with NOACs compared with dalteparin in patients with gastrointestinal cancer. In contrast, bleeding rates were very low with both apixaban and dalteparin in the ADAM VTE trial, and in the Caravaggio trial, bleeding rates were similar in the apixaban and dalteparin arms. Given the absence of a direct head-to-head comparison of the different NOACs, the differences in safety profiles should be regarded with caution.

## Evidence from Meta-Analyses and Observational Studies

The validity and generalizability of the efficacy of NOACs compared with dalteparin in the treatment of VTE in cancer patients are strengthened by meta-analysis. Within the previous evidence-based analysis, Vedovati et al<sup>74</sup> conducted a meta-analysis of randomized studies with NOACs assessing the safety and efficacy of NOACs in patients with thrombosis and cancer. In recent years, a meta-analysis of four randomized controlled studies (2894 patients) comparing apixaban, edoxaban, or rivaroxaban with dalteparin shows that cancer-associated VTE who were treated with NOACs had a significantly lower risk of recurrent VTE, without a significantly higher likelihood of major bleeding than when treated with dalteparin.<sup>75</sup> Another meta-analysis found that NOACs significantly reduced VTE recurrence (RR: 0.59, 95% CI: 0.48–0.73) compared with conventional therapy. Results were similar in the LMWHs and VKAs subgroups.<sup>76</sup> NOACs had a higher, though the nonsignificant, risk of major bleeding compared with LMWHs (RR: 1.33, 95% CI: 0.94–1.89) lower risk of major bleeding compared with VKAs (RR: 0.60, 95% CI: 0.39–0.93).<sup>76</sup>

Although RCTs provide the highest level of clinical evidence, applying the results of RCTs to assessments of clinical effectiveness in real-world practice may be challenging. Emerging real-world studies have recently been published, describing initial experiences in the cancer population. A real-world study evaluating NOACs (including rivaroxaban, apixaban, edoxaban, or dabigatran) vs LMWHs enoxaparin for cancer-associated VTE showed that the groups had a similar risk of VTE recurrence (HR: 0.62, 95% CI: 0.39–1.01,  $P=0.05$ ) and major bleeding (HR: 0.80, 95% CI: 0.52–1.24,  $P=0.32$ ) at 12 months of follow-up. However, taking NOACs was associated with a significantly lower risk of gastrointestinal bleeding compared with receiving enoxaparin (10 patients (1.9%) vs 41 patients (7.1%), HR: 0.29, 95% CI: 0.15–0.59,  $P<0.001$ ).<sup>77</sup> Findings for both primary outcomes were consistent with competing risk analyses (recurrent VTE: HR: 0.68, 95% CI: 0.45–1.01,  $P=0.05$ ; major bleeding: HR: 0.77, 95% CI: 0.51–1.16,  $P=0.21$ ).<sup>77</sup> This cohort study found that in real-world practice, among Asian patients with cancer-associated VTE, the use of NOACs was associated with a similar risk for recurrent VTE or major bleeding compared with the use of the LMWHs enoxaparin. Nonetheless, the use of NOACs was associated with a significantly lower rate of gastrointestinal bleeding.<sup>77</sup> In a large retrospective study comparing outcomes in patients with cancer treated with rivaroxaban or standard treatment, the overall VTE recurrence was significantly lower by 28% in patients treated with rivaroxaban versus LMWHs. Major bleeding rates were similar in patients taking rivaroxaban in comparison with patients receiving LMWHs.<sup>78</sup> Smaller retrospective studies reported similar results with NOACs in comparison with LMWHs in patients with cancer.<sup>79–82</sup>



## Ongoing Studies

Several ongoing studies are evaluating NOACs versus LMWHs for the treatment of cancer-associated VTE. The Comparing Oral and Injectable Blood Thinners to Prevent and Treat Blood Clots in Patients with Cancer (CANVAS; NCT02744092) trial is a 940-patient study with the primary objective of evaluating comparing NOACs therapy (rivaroxaban, apixaban, edoxaban, or dabigatran, by investigator's choice) with LMWHs with or without a transition to warfarin.<sup>83</sup> The primary outcome in CANVAS is VTE recurrence; secondary outcomes include major bleeding, health-related quality of life, and the burden of anticoagulant therapy. The CASTA-DIVA (NCT02746185)<sup>84</sup> study (rivaroxaban vs dalteparin) for the treatment of CAT has primary outcomes of recurrent VTE, major bleeding, and clinically relevant nonmajor bleeding and mortality. The API-CAT trial (NCT03692065) is comparing the efficacy and safety of two doses of apixaban for the extended treatment of VTE in cancer patients (breast, prostate, and colon-rectum);<sup>85</sup> the EVEExtended study compares the safety of two doses of apixaban for the extended treatment of cancer patients with VTE; and other studies such as COSIMO37 (NCT027426239), a prospective cohort study (patient-reported outcomes with rivaroxaban: a noninterventional study), and Conko-011 (NCT02583191) evaluating rivaroxaban versus LMWHs with patient-reported treatment satisfaction as the primary outcome.<sup>85</sup> These clinical trials will provide further evidence for the use of these agents in patients with cancer and will help to clarify remaining the questions.

## Current Clinical Guidelines

Treatment of VTE in cancer patients represents a continuing clinical challenge. Evidence-based guidelines from professional organizations have provided treatment recommendations for the management of CAT. Major guidelines include the American College of CHEST Physicians (CHEST), National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and European Society of Cardiology (ESC).<sup>14,15,86–88</sup> Nearly a decade of several international guidelines has given preference to NOACs over LMWHs in selected patients with cancer-associated VTE.<sup>89</sup> Most recently, the National Comprehensive Cancer Network (NCCN) guidelines indicate that are preferred or acceptable for particular cancer patients without gastric or gastroesophageal lesions.<sup>90</sup> The use of NOACs was also entered as an alternative treatment for CAT in the recent the American Society of Clinical Oncology (ASCO) guidelines.<sup>91</sup> However, guidelines caution about their use in patients with Gastrointestinal (GI) and genitourinary (GU) malignancies due to the higher risk of bleeding until more experience is accrued to inform clinical practice. In the future, NOACs may become even more prominent in further CAT guidelines. Unfortunately, during the last decade, half of the patients with CAT fail to receive guideline-concordant therapy.<sup>92</sup> As treatment options for CAT expand, further efforts are needed to understand the factors associated with anticoagulant use in a non-trial setting to close the gap between ideal and actual care.

## Cost-Effectiveness

Economic evaluation has gained widespread application in many areas of clinical research as health care costs consume an increasing proportion of the gross domestic product (GDP). In particular, health economics help address the clinical decision-making process. Although we were not trained in economics, and as physicians, we care about patients' well-being and not about costs, economic issues impinge on our clinical practice on daily, and should help patients explore resources that may facilitate receiving the best anticoagulant for their particular situation.

The cost-effectiveness studies comparing NOACs with LMWHs in patients with cancer will provide perspective regarding the selection of NOACs for the treatment of CAT. The cost-effectiveness and budget impact of rivaroxaban compared with dalteparin in patients with cancer at risk of recurrent VTE in the Netherlands found that the use of rivaroxaban instead of dalteparin can save over €10 million per year, primarily driven by the difference in drug costs.<sup>93</sup> An economic comparison of edoxaban and LMWHs in the Brazilian population showed Edoxaban represents a cost-saving alternative to LMWHs for the management of CAT.<sup>94</sup> Furthermore, Li et al found that rivaroxaban or edoxaban as compared to dalteparin is cost saving from a payer's perspective for the treatment of CAT.<sup>95</sup> Other studies showed that edoxaban, when compared to LMWHs, was a cost-effective treatment for six months in cancer patients in the United States.<sup>96</sup> The study from the perspective of the Chinese healthcare system, which compared the cost-effectiveness of

**Table 2** Cost-Effectiveness Analyses

Country	Drugs	Results	Conclusion
Netherlands <sup>93</sup>	Rivaroxaban vs LMWH	Rivaroxaban were cost- saving while also slightly improving the patient's health.	Treatment with rivaroxaban is economically dominant over dalteparin in patients with cancer at risk for recurrent VTE in the Netherlands.
Brasilia <sup>94</sup>	Edoxaban vs LMWH	Edoxaban was associated with an incremental cost difference of \$16,654.27 and an incremental QALY difference of 3.2. The estimated ICER is \$5204.46 and represented cost saved per QALY lost, in favor of edoxaban.	Edoxaban represents a cost-saving alternative to LMWH for the management of CAT.
The US <sup>95</sup>	NOACs (Edoxaban+ Rivaroxaban) vs LMWH	DOAC versus dalteparin was associated with an incremental cost reduction of \$24,129 with an incremental QALY reduction of 0.04.	Rivaroxaban or edoxaban as compared to dalteparin is cost saving from a payer's perspective for the treatment of CAT.
The US <sup>96</sup>	Edoxaban vs LMWH	Edoxaban has similar quality-adjusted life years and significantly lower cost vs LMWH.	Edoxaban remains the most cost-effective anticoagulation strategy when compared to the LMWH.
China <sup>97</sup>	NOACs (Edoxaban +Rivaroxaban +Apixaban) vs LMWH	Treatment with DOACs would result in a large reduction in cost but a small reduction in QALYs compared with LMWHs over a 5-year time frame.	As compared to LMWHs, NOACs can be a cost-saving anticoagulant choice for the treatment of CAT in the general oncology population and gastrointestinal malignancy population.

using NOACs and LMWHs for treating CAT, showed that NOACs can be a cost-saving anticoagulant choice.<sup>97</sup> The 6-month cost of NOACs was \$ 654.65 with 0.40 quality adjusted life-years (QALYs) while the 6-month cost of LMWHs was \$USD 1,719.31 with 0.37 QALYs. Similarly, treatment with NOACs had a lower cost (\$USD 657.85 vs \$USD 1,716.56) and more health benefits (0.40 QALYs vs 0.37 QALYs) than treatment with LMWHs in a subgroup of patients with gastrointestinal malignancy. The study found treatment with NOACs would result in a large reduction in cost (\$USD 1,447.22 vs \$USD 3,374.70) but a small reduction in QALYs (3.07 QALYs vs 3.09 QALYs) compared with LMWHs over a 5-year time frame, resulting in an ICER of \$USD 112,895.50/QALYs. The results of the cost-effectiveness analysis in different countries are summarized in Table 2.

These findings may provide a better understanding of VTE treatment-related utilization of healthcare resources and corresponding costs in patients with cancer. Nevertheless, in the existing literature, there is limited information on the healthcare resource use and costs associated with anticoagulants in patients with cancer. However, cost-effectiveness may depend heavily on country-specific health system organizations and economics. We should encourage other countries to conduct a similar reflection and to think about the respect of the good practice recommendations to optimize the public healthcare expenditure in this group of population.

## Conclusion

VTE is a common and serious complication among patients with cancer, resulting in a substantial clinical and economic burden in the oncology setting. Cancer patients are at greater risk for VTE compared with patients without cancer. VTE is associated with higher morbidity, mortality, and rates of recurrent VTE as well as bleeding rates, all leading to increased healthcare costs and decreased quality of life. Consequently, anticoagulant therapy is essential and should take into consideration the potential of clinical benefit and economic costs for the management of VTE in patients with cancer.

Adding further complexity to the management of CAT, the emergence of NOACs challenges the concept of traditional anticoagulants as the standard of care. These products are considered appealing alternatives as they have practical advantages providing great opportunities to improve the quality of life. Gegard studies of NOACs in recent years illustrated that NOACs are at least as safe and effective as initial LMWHs followed by vitamin K antagonists for the treatment of cancer-associated VTE. Given the potentially favorable features of NOACs in the setting of active cancer treatment and the suggestion of better efficacy of NOACs with similar safety in studies for the treatment of VTE, NOACs

have recently been added to clinical practice guidelines as alternative treatment in particular patients with cancer. While the majority of clinical recommendations discuss LMWHs as the standard of treatment for several years in cancer patients with VTE, more recent guidelines also increasingly consider NOACs as an alternative option in selected patients with cancer. The guidelines also advise caution with using NOACs in patients with GI and GU malignancies, and further research of their safety profile is still needed.

In modern healthcare, the economic sustainability of any treatment has gained paramount importance and we cannot just turn away when we are faced with cost-effectiveness issues. The knowledge of the economic impact of VTE in cancer patients would allow us to choose the most appropriate treatment in this group of the population. In the future, NOACs may become the best treatment approach in this specific population.

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