Tumor-Related Venous Thromboembolism (NOAC) as an Alternative Treatment Option in Non-vitamin K Antagonist Oral Anticoagulants

Jan Beyer-Westendorf, Robert Klamroth, Stephan Kreher, Florian Langer, Axel Matzdorff, Hanno Riess

Summary

Background: The risk of venous thromboembolism (VTE) is 4 to 7 times higher in cancer patients than in the normal population. Moreover, cancer patients who take anticoagulants suffer more frequently from hemorrhagic complications and VTE recurrences. Patients often find low-molecular-weight heparin (LMWH) treatment unpleasant; approximately 20% stop taking LMWH during the first six months of treatment.

Methods: Based on a non-systematic literature search, an interdisciplinary group of specialists (hematology, oncology, hemostaseology, and angiology) developed a set of recommendations concerning the treatment of tumor-related thrombosis with non–vitamin K antagonist oral anticoagulants (NOAC).

Results: Patient-, tumor-, and tumor-treatment–related factors and clinical situations were identified that should be considered in therapeutic decision-making in the individual case. NOAC may be an alternative that lessens the rate of VTE recurrence (though at the cost of more hemorrhagic complications), without lessening mortality. Moreover, many factors need to be considered that can limit the utility of NOAC treatment or even make it impossible.

Conclusion: It seems likely that, in future, the treatment of tumor-related VTE will often not involve a single decision to use either NOAC or LMWH, but rather a switching of treatment in either of two directions: from LMWH to NOAC in stable phases of the underlying malignant disease, conferring better quality of life to suitable patients; or from NOAC to LMWH, e.g., in patients suffering from emesis or thrombocytopenia, to whom the greater clinical experience with LMWH, parenteral application, or stepwise dose titration can confer benefits.

Cite this as:


Deep vein thrombosis and pulmonary embolism, collectively referred to as venous thromboembolism (VTE), contribute significantly to morbidity and mortality in cancer patients (1, 2). It is estimated that approximately 20%–30% of all new-onset VTE are cancer-related (2); the absolute risk of VTE (cumulative incidence) in cancer patients is put at 1%–8%. Compared to the healthy population, they have a between four- and seven-fold higher risk of developing VTE as a result of local compression syndromes, immobility, procoagulatory effects of the cancer and cancer treatment, as well as the long-term use of port systems (2). Anticoagulation in VTE further increases the existing risk of bleeding complications in active cancer, making VTE treatment in cancer patients particularly challenging (3, 4). Therefore, this disease is differentiated from general VTE under the term “cancer-associated thrombosis” (CAT). Although there is no precise definition of the term “active cancer,” it is reasonable—according to general clinical understanding as well as the more recent studies conducted on this indication—to include recurrent, locally advanced, or metastatic disease, as well as hematological malignancies without complete remission and cancer treatment carried out within the preceding 6 months, in addition to cancer diagnoses within the previous 6–24 months.

VTE risk depends on tumor entity (higher in the rarer pancreatic, brain, and gastric tumors, as well as in myeloma undergoing immunomodulatory therapy; lower in the significantly more common prostate, cervical, uterine, and breast tumors), local tumor stage, and the extent of metastasis, which applies in particular to the risk of recurrent VTE (relative risk increase due to metastasis of around 1.4) (5).

The improved sensitivity of computed tomography and magnetic resonance imaging increases the percentage of asymptomatic or unexpected VTE events in the setting of cancer follow-up imaging (6). The prevalence of findings of this kind is put at 2%–6% (7), and it is recommended that these incidental findings be treated like symptomatic VTE in cancer patients, since also these findings are clinically relevant (8–11). Nevertheless, in order to avoid overtreatment, it is essential that the severity of VTE (symptomatic versus asymptomatic; pulmonary embolism versus proximal thrombosis versus distal...
thrombosis) be taken into account in all treatment decision-making processes. Against this backdrop, one should also note that the well-documented excess mortality for CAT patients (compared to cancer patients without thrombosis) cannot be explained by the occurrence of fatal pulmonary embolism alone, but may also be the result of a particularly aggressive underlying disease.

**CAT treatment with low-molecular-weight heparin or vitamin K antagonists**

Standard VTE therapy to date included initial treatment with a rapid-onset parenteral anticoagulant (generally low-molecular-weight heparin, LMWH) for ≥ 5 days, followed by 3- to 6-month secondary prevention with vitamin K antagonists (VKA) initiated to overlap with LMWH therapy. The treatment approach in patients with active cancer differs in key aspects from the approach in non-cancer patients. Maintaining the therapeutic international normalized ratio (INR) target range when using VKA can be challenging due to altered pharmacokinetics in cachectic patients, critically impaired liver or kidney function, disease- or treatment-related thrombocytopenia, drug interactions, as well as altered oral bioavailability caused by gastrointestinal infections or treatment-related vomiting. For example, time in the INR therapeutic range (TTR) in patients treated with warfarin in the CLOT and CATCH studies was only 46% and 47%, respectively (12, 13). LMWH, in contrast, exhibit only scant interindividual dose–effect fluctuations and low potential for drug interactions due to their good bioavailability and low plasma protein binding.

Over the previous two decades, studies on both the initial treatment and secondary prevention of cancer-associated VTE have demonstrated the superior clinical benefit–risk profile of LMWH compared to unfractionated heparin (UFH) (14).

A recently published network meta-analysis showed that LMWH resulted in a greater reduction in VTE recurrence risk compared to VKA at comparable rates of bleeding (15). Neither study revealed differences in overall mortality between the two study arms. The interpretation of these data is limited by the fact that they were gathered under standardized conditions and in the context of clinical trial monitoring, meaning that their extrapolation to routine clinical care warrants critical scrutiny.

On the basis of CLOT and CATCH, as well as other smaller studies (Table 1), national and international guidelines on the secondary prevention of cancer-associated VTE primarily recommended LMWH over VKA (11, 19, 20), although the rate of VTE recurrence was 10%–15% and the rate of severe bleeding 2.5%–4% in the most methodologically reliable LMWH studies (12, 13, 21, 22). This means that complications are seen relatively frequently even in the case of guideline-compliant LMWH treatment. The observation period in these studies was 6 months, which is why the evidence for the phase following the extended secondary prevention of 3–6 months currently normally recommended (10, 11) is weak.

The use of LMWH is associated with a number of limitations. The need for continuous subcutaneous administration, the risk of heparin-induced thrombocytopenia, as well as cost considerations could be reasons for the limited treatment compliance under parenteral anticoagulation. In a non-representative survey of German hematologists, oncologists, and angiologists (6% response rate), 76% of respondents reported using LMWH for the initial treatment of VTE, whereas 22% switched to oral anticoagulation with VKA or direct acting non–vitamin K antagonist oral anticoagulants (NOAC) within the first three months of treatment (e1). Only about half of cancer patients were treated with LMWH in the 3–6 months of secondary prevention, and almost 50% of these at only half the therapeutic dose. The reason most frequently given for switching (prematurely) to an oral anticoagulant was patients’ reservations about the subcutaneous administration of LMWH. Real-world data from France and the US confirm insufficient guideline adherence, particularly in the case of continued anticoagulation (23, 24).

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment schedule LMWH</th>
<th>Recurrent VTE LMWH versus VKA</th>
<th>Major bleeding LMWH versus VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTHANOX (17)</td>
<td>146</td>
<td>Dalteparin 200 IU/kg/d for 4 weeks, thereafter 150 IU/kg/d</td>
<td>8.0 vs. 15.8%</td>
<td>5.6 vs. 3.6%</td>
</tr>
<tr>
<td>CLOT (12)</td>
<td>676</td>
<td>Dalteparin 200 IU/kg/d for 4 weeks, thereafter 150 IU/kg/d</td>
<td>8.0 vs. 15.8%</td>
<td>5.6 vs. 3.6%</td>
</tr>
<tr>
<td>ONCENOX (18)</td>
<td>102</td>
<td>Enoxaparin 1 and 1.5 mg/d</td>
<td>6.6 vs. 10%</td>
<td>8.9 vs. 2.9%</td>
</tr>
<tr>
<td>LITE (16)</td>
<td>200</td>
<td>Tinzaparin 175 IU/kg/d</td>
<td>6.0 vs. 10%</td>
<td>7.0 vs. 7.0%</td>
</tr>
<tr>
<td>CATCH (13)</td>
<td>900</td>
<td>Tinzaparin 175 IU/kg/d</td>
<td>6.9 vs. 10%</td>
<td>2.7 vs. 2.4%</td>
</tr>
</tbody>
</table>

*Modified from Ay et al. (32)*

LMWH, low-molecular-weight heparins; VKA, vitamin K antagonists; VTE, venous thromboembolism.
According to a recent US publication, only around one third of cancer patients receive LMWH at 6 months, whereas treatment persistence is almost twice as high for oral anticoagulants (23); besides the pharmacological differences, this might also be due to the high costs of LMWH that patients have to bear in the US health system. A European study showed LMWH discontinuation rates of 21% in the first 6 months, primarily due to LMWH-related side effects (24); also, patients (and physicians) are often reluctant to undertake months of (self-)injections (25), which raises the question of modern oral treatment alternatives.

**CAT treatment with non–vitamin K antagonist oral anticoagulants**

Since 2011, four different NOAC with varying pharmacological characteristics have become established in the treatment of VTE: apixaban, edoxaban, and rivaroxaban act as direct inhibitors of activated factor X, while dabigatran acts as a direct thrombin inhibitor (Table 2).

Large phase-III VTE treatment studies involving over 25 000 VTE patients have been published on these NOAC in recent years, although less than 5% of study participants were classified as cancer patients and even fewer as patients with “active cancer” (e3–e10). For this reason, any subgroup analyses in relation to this are subject to significant uncertainties, which is why dedicated randomized controlled trials (RCT) to compare NOAC versus LMWH in the treatment of CAT are needed. The HOKUSAI VTE Cancer Study (a large international, open, non-inferiority study with >1000 CAT patients) compared edoxaban treatment (initiated after ≥ 5 days of initial LMWH treatment) with 12-month LMWH administration (dalteparin, dosed according to the CLOT schedule [Table 1]) over a 12-month period. The study demonstrated non-inferiority in the combined endpoint of recurrent VTE and major bleeding with a numerically lower rate of VTE recurrence for edoxaban (7.9% versus 11.3%; relative risk [RR]): 0.74; 95% confidence interval: [0.48; 1.06]) and significantly more major bleeding events (6.9% versus 4.0%; RR: 1.77 [1.03; 3.04]) (21). The SELECT-D trial, an open randomized pilot study on 406 CAT patients, reported that rivaroxaban (2 × 15 mg/day for 21 days followed by 1 × 20 mg/day) showed a reduced rate of VTE recurrence (4% versus 11%; RR: 0.43 [0.19; 0.99]) compared to dalteparin (dosed according to the CLOT schedule), but an increased tendency to bleeding (major bleeding 6% versus 4%; RR: 1.83 [1.03; 3.04]) (22). A meta-analysis of these two studies is now available evidencing a tendency toward fewer VTE recurrences for treatment with edoxaban or rivaroxaban compared to dalteparin (5.8% versus 8.8%; RR: 0.65 [0.42; 1.01]; number needed to treat: 33); however, this is at the cost of a significantly increased risk of major bleeding (5.5% versus 3.2%; RR: 1.74 [1.05; 2.88]; number needed to harm: 44) and clinically relevant non-major bleeding

### Table 2

**Overview of the characteristics of the NOAC dabigatran, apixaban, edoxaban, and rivaroxaban**

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Mode of action</th>
<th>Dose interval</th>
<th>Pharmacokinetics/ pharmacodynamics</th>
<th>Time to maximum plasma concentration</th>
<th>Half-life</th>
<th>Elimination (following oral administration)</th>
<th>Effect of food on bioavailability</th>
<th>Drug interactions</th>
<th>Published multicenter RCT on the treatment of cancer-associated VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibition</td>
<td>2 × daily</td>
<td>Dose-proportional (10–400 mg 3 × daily)</td>
<td>1.25–1.5 h</td>
<td>12–17 h</td>
<td>Renal: &gt;80%</td>
<td>No effect</td>
<td>Relevant for strong P-GP inhibitors or inducers</td>
<td>–</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibition</td>
<td>2 × daily</td>
<td>Dose-proportional (2.5–25 mg 3 × daily)</td>
<td>3–4 h</td>
<td>8–15 h</td>
<td>Renal: 24.5–28.8%</td>
<td>No effect</td>
<td>Relevant for strong CYP3A4 and/or P-GP inhibitors or inducers</td>
<td>–</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Direct factor Xa inhibition</td>
<td>1 × daily</td>
<td>Dose-proportional (10–150 mg)</td>
<td>1–3.5 h</td>
<td>9–10 h</td>
<td>Renal: 35%; Biliary/intestinal: 62%; Metabolism: &lt;29%</td>
<td>Minimal effect</td>
<td>Relevant for strong P-GP inhibitors or inducers</td>
<td>HOKUSAI VTE Cancer (21)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibition</td>
<td>1 × daily</td>
<td>Dose-proportional (5–30 mg 3 × daily)</td>
<td>2–4 h</td>
<td>6–9 h</td>
<td>Renal: 36%; Fecal: 7%</td>
<td>Increased bioavailability in higher dosages when taken with food</td>
<td>Relevant for strong CYP3A4 and/or P-GP inhibitors or inducers</td>
<td>SELECT-D (22)</td>
</tr>
</tbody>
</table>

*1 Adapted from (30); *2 healthy subjects, various dosages
CYP3A4, cytochrome P450 3A4; NOAC, non–vitamin K antagonist oral anticoagulants; P-GP, glycoprotein; RCT, randomized controlled trial; VTE, venous thromboembolism
There were no differences in mortality between the two treatment options (25.9% versus 24.9%; RR: 1.03 [0.85; 1.26]). We would like to point out that the observed trend toward a reduction in VTE with edoxaban or rivaroxaban may be more clinically relevant than the increased risk of bleeding with this treatment. Since the recurrence of VTE under therapeutic anticoagulation often results in a further intensification of anticoagulation (combined with a further rise in the risk of bleeding), and since it is not uncommon for the required complete and intensive anticoagulation to delay tumor resection or chemotherapy, it is essential that thromboembolic complications are prevented in order to carry out cancer treatment as planned. In contrast, the statistically significantly increased risk of bleeding caused by edoxaban and rivaroxaban appears to be limited to mostly readily manageable mucous membrane bleeding and thus, from a clinical perspective, is associated with significantly fewer complications. For example, a detailed evaluation performed as part of the HOKUSAI VTE Cancer study showed that the rate of life-threatening bleeding was roughly the same in the two treatment arms (12/522 or 2.3% with edoxaban and 13/524 or 2.5% with dalteparin), while the difference in severe, non-life-threatening bleeding events with edoxaban was primarily observed in patients with gastrointestinal tumors, mainly due to bleeding in the upper gastrointestinal tract (21, 27).

In addition to the data from the above-mentioned RCTs, numerous investigations show that NOAC have long been used in the routine treatment of CAT patients (e11–e19). Table 3 lists examples of currently published routine data, as well as the rates of VTE recurrence and major bleeding under NOAC, which are generally comparable with the study data (28).

Based on all these scientific and clinical data, the first guidelines have listed edoxaban and—with methodological limitations—rivaroxaban as equivalent treatment alternatives to LMWH treatment in CAT patients (10, 29).

Which patients could benefit from NOAC and when?

A relevant proportion of patients with CAT do not receive long-term LMWH treatment (e1, e2, e12, e15). The main reason for this could be improved patient acceptance of oral anticoagulants, which results in better long-term treatment compliance. If one looks in the registries at the CAT patients treated with LMWH or

<table>
<thead>
<tr>
<th>Study/first author</th>
<th>N</th>
<th>Study design</th>
<th>Duration</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>XALIA/Turpie (e15)</td>
<td>146</td>
<td>Rivaroxaban: Prospective registry</td>
<td>6 Months</td>
<td>3.5%</td>
<td>1.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Mahe (e17)</td>
<td>Various anticoagulation regimens</td>
<td>Prospective registry</td>
<td>~4.5 Months</td>
<td>Breast cancer (n = 938) 5.6% / year (95% CI: [3.8; 8.1])</td>
<td>4.1% / year [2.7; 5.9]</td>
<td>31% / year [26; 31]</td>
</tr>
<tr>
<td>Bott-Kitslaar (e11)</td>
<td>Rivaroxaban: 118</td>
<td>Prospective registry</td>
<td>≥3 Months</td>
<td>Prostate cancer (n = 629) 6.9% / Year [4.4;10]</td>
<td>13% / year [9.2; 17]</td>
<td>33% / year [27; 35]</td>
</tr>
<tr>
<td>McBane (e12)</td>
<td>Rivaroxaban: 135</td>
<td>Prospective registry</td>
<td>~6.5 Months</td>
<td>Rivaroxaban: 2.8% LMWH: 1.7% (p = 0.45)</td>
<td>Rivaroxaban: 2.2% LMWH: 5.8% (p = 0.20)</td>
<td>Rivaroxaban: 30% LMWH: 41% (p = 0.047)</td>
</tr>
<tr>
<td>Mantha (e13)</td>
<td>Rivaroxaban: 200</td>
<td>Prospective cohort study</td>
<td>Prospective registry</td>
<td>NOAC: 3.3% LMWH: 5.7%</td>
<td>NOAC: 13.3% LMWH: 10.6%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Khorana (e19)</td>
<td>Rivaroxaban: 1728</td>
<td>Retrospective database analysis</td>
<td>Unknown</td>
<td>Unknown</td>
<td>2.61% / year [1.80; 3.78]</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ross (e18)</td>
<td>NOAC: 30 (rivaroxaban in 27)</td>
<td>Retrospective case analysis</td>
<td>6 Months</td>
<td>NOAC: 3.3% LMWH: 5.7%</td>
<td>NOAC: 13.3% LMWH: 10.6%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pignataro (e14)</td>
<td>Rivaroxaban: 400; (302 [75.5%]) with initial enoxaparin pretreatment for a median of 3 days</td>
<td>Retrospective case analysis</td>
<td>6 Months</td>
<td>NOAC: 3.25%</td>
<td>5.5%</td>
<td>29.2%</td>
</tr>
</tbody>
</table>

*Modified from Beyer-Westendorf; adapted from (28)
LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism; 95% CI, 95% confidence interval.
NOAC, one sees a marked difference in the underlying tumor entities, suggesting that not only patient factors such as age or kidney function, but also tumor entity and stage appear to influence the choice of anticoagulation. Since oral anticoagulants (including VKA that are inferior to LMWH) showed a lower discontinuation rate in studies compared to LMWH, one can assume that the prescription of a NOAC results in a relevant improvement in treatment compliance in many patients with cancer-associated VTE (21); this could be of considerable relevance in the future given the prolonged treatment duration recommended in guidelines.

However, in view of the increased risk of bleeding with NOAC, the decision on their use in CAT patients should be made by the treating physician on the basis of an appropriate risk–benefit assessment. The use of edoxaban or rivaroxaban particularly in patients with stable cancer and an overall low risk of bleeding seems worthy of consideration (e.g., stable patients with metastatic breast or prostate cancer and well-controlled tumor activity, patients with low-grade lymphoma or chronic lymphatic leukemia, etc.). In contrast, NOAC should be used with restraint if a high risk of bleeding is anticipated. This applies most notably in:

- Patients with tumor entities or sites of tumor metastasis at critical risk for bleeding (for example, locally advanced gastric cancer, colorectal cancer, brain tumors, advanced lung cancer with endobronchial tumor infiltration, advanced bladder cancer, etc.)
- Patients with disease characterized by high cancer dynamics (e.g., high-grade lymphoma) and requiring prompt cancer-specific measures (chemotherapy, radiotherapy, surgery, etc.), as in acute hematological malignancies (acute myeloid leukemia, acute lymphatic leukemia)
- Patients with (or expected to develop) impaired hematopoiesis (critical thrombocytopenia).

Other factors, such as dysphagia and mucositis, nausea, vomiting, critical organ failure, drug interactions, and many more, can affect the NOAC level and result in hazardous over- or underdosing (30).

Table 4 lists suitability criteria and risk factors that need to be taken into consideration when deciding on

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**TABLE 4**

<table>
<thead>
<tr>
<th>NOAC in cancer-associated venous thromboembolism: potential risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factors</strong></td>
</tr>
<tr>
<td>Cancer with high risk of bleeding</td>
</tr>
<tr>
<td>Mucositis, mechanical swallowing disorders</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, long-term opioid therapy</td>
</tr>
<tr>
<td>Clinically relevant renal impairment</td>
</tr>
<tr>
<td>Pharmacological interaction between NOAC and cancer treatment</td>
</tr>
<tr>
<td>Severe thrombocytopenia</td>
</tr>
<tr>
<td>Lack of health literacy</td>
</tr>
</tbody>
</table>

ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; CYP3A4, cytochrome P450 3A4; MTX, methotrexate; NOAK, non–vitamin K antagonist oral anticoagulants; P-GP, P-glycoprotein; VTE, venous thromboembolism.
the use of a NOAC. Until more clinical experience has been gained with these drugs, we recommend that parenteral treatment be preferred in patients that do not fulfill these general suitability criteria, particularly in the first weeks following the diagnosis of CAT. If a NOAC is to be used nonetheless in these patient groups, we recommend using edoxaban or rivaroxaban (based on the available evidence) and close clinical monitoring (e.g., once a week for 4 weeks and every 4–12 weeks thereafter for the duration of anticoagulation) for bleeding or symptoms of recurrent VTE. The patient should be able to recognize these symptoms in the home environment and contact their treating physician in the case of their onset. Due to the increased risk of recurrent VTE in cancer patients, prompt initial ultrasound follow-up (within 2 weeks of diagnosis) is always advisable in deep vein thrombosis (DVT). Similarly, clinical follow-up within 2 weeks of diagnosis is recommended in patients with cancer-associated pulmonary embolism (PE) without DVT, which should be supplemented by echocardiography (to exclude right ventricular strain) and CT angiography (to exclude renewed PE and investigate differential diagnoses) only in the case of new chest or cardiopulmonary symptoms. Further follow-up (imaging or clinical VTE monitoring, determining the duration of anticoagulation) should be guided by the particular features of the individual case.

**Practical guide for NOAC use: patient selection, information, and follow-up**

The following recommendations on initiating NOAC treatment in cancer patients are made on the basis of the hitherto available data, experience with CAT patients, as well as clinical and pharmacological considerations:

- CAT patients should be fully informed (and this documented in their record) about the risk of progressive or recurrent thromboembolism and the increased risk of bleeding due to underlying disease, cancer treatment, and anticoagulation
- Instructions should be provided on how to respond in the case of further VTE symptoms, bleeding, or other complications such as vomiting, diarrhea, impaired diuresis, or severe inflammation
- Treatment alternatives—NOAC versus LMWH—should be explained to the patient, as well as the fact that adjustments may be necessary depending on the course of the underlying disease and treatment
- Absolute and relative contraindications and interaction risks should be determined (cf product information for the respective NOAC, as well as Table 3)
- Detailed consideration of NOAC selection and dosage (currently there only is evidence for therapeutic dosages of edoxaban and rivaroxaban), whereby it must be borne in mind that edoxaban is only approved for patients that have received 5-day initial treatment with LMWH

- The co-treating/follow-up physician should be informed about the reasons the treatment was selected, possible problems (potential for interactions, bleeding), and about the reasons for switching from NOAC to LMWH if such a switch occurred
- Although determinations of NOAC function and level are not routinely recommended, they should be considered in the case of suspected over- or underdosing and relevant drug interactions
- A near-term appointment should be arranged to follow-up VTE in order to identify possible treatment complications and to eliminate/clarify possible misunderstandings
- The treatment decision and duration should be regularly re-evaluated depending on disease course and patient-specific factors (tumor dynamics, tumor-specific treatments, general condition of the patient, laboratory values, concomitant medication, etc.), whereby the intervals between these re-evaluations should not exceed 3–6 months for patients with active cancer.

**Conclusion**

The factor Xa inhibitors edoxaban and rivaroxaban now represent evidence-based oral treatment alternatives that are comparable in terms of their efficacy and safety balance to LMWH for the treatment of cancer-associated VTE, but which can also confer additional benefits on patients and treating physicians by virtue of their oral administration (and significantly lower cost). In order to achieve this, however, the limitations of oral anticoagulation in these high-risk patients need to be precisely determined and considered. One can assume for the future that the treatment of cancer-associated VTE in many patients will not be a “NOAC versus LMWH” decision, but that most CAT patients will undergo a change in their anticoagulation: from LMWH to NOAC—confering better quality of life to suitable patients, i.e. patients with stable cancer and low complication risk; from NOAC to LMWH—in the case of vomiting, diarrhea, bleeding complications, hospitalization, sepsis, or thrombocytopenia, when the greater clinical experience with LMWH, parenteral administration, or the option of gradual dose adjustments can confer benefits.

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Dr Klamroth received consultancy fees from Bayer, Daiichi Sankyo, and Leo Pharma. He received lecture fees from LEO Pharma, Bayer, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Boehringer Ingelheim, and Sanofi. For conducting commissioned clinical studies, he received fees (third-party account) from LEO Pharma and Bayer.

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Dr Langer received fees for consultancy activities and lectures, as well as reimbursement for participation fees and travel expenses from Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma, Pfizer, and Sanofi. He received fees from Bayer for conducting clinical trials.

Prof. Matzdorf owns shares in Bayer. He received consultancy fees from Bayer, Daiichi Sankyo, LEO Pharma, Novartis, Bristol-Myers Squibb, and Pfizer. He was reimbursed for lecture and participation fees by LEO Pharma, and received travel expense reimbursement from LEO Pharma, Daiichi Sankyo, and Bayer. He also received fees (third-party account) from LEO Pharma for conducting commissioned clinical trials.

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References


Key messages

- Cancer patients with thromboembolism are at high risk for recurrent VTE (approximately 10%/year) and major bleeding complications (approximately 6%/year).

- Although the standard treatment with low-molecular-weight heparin (LMWH) hitherto recommended in guidelines is superior to vitamin-K antagonists, it is not tolerated by many cancer patients for prolonged periods, leading to a treatment discontinuation rate of around 20% in the first 6 months.

- According to recent data from randomized controlled trials, the non–vitamin K antagonist oral anticoagulants (NOAC) edoxaban and rivaroxaban appear to be safe and effective treatment alternatives for many of these patients.

- A meta-analysis of the two studies showed edoxaban/rivaroxaban (E/R) to result in a reduction in recurrent VTE compared to LMWH (5.8% for E/R versus 6.8% for LMWH), but also an increase in major (5.5% versus 3.2%) and clinically relevant bleeding complications (12.3% versus 6.7%), due primarily to an increase in gastrointestinal bleeding.


Progressive Prominent Swelling Over the Acromioclavicular Joint

An 81-year-old man (no relevant medical history, no medications) reported a progressive, mobile swelling over the acromioclavicular (AC) joint, present for several months. Sonographic examination confirmed the liquid nature of the mass. Three aspirations of the content by the patient’s family physician before eventual referral to the hospital were successful only in the very short term: just a few hours later, the swelling was as large as before. The patient suffered no pain during normal daily activity, but was bothered by the appearance of the lesion and above all by the difficulty he experienced in getting dressed and in wearing his rucksack. Magnetic resonance imaging showed advanced osteoarthritis of the AC joint with a prominent AC joint cyst and the characteristic geyser sign. Because of the clinical symptoms the patient was treated with arthroscopic resection of the AC joint and open resection of the AC joint cyst. Six months later the skin and operation scar showed no signs of inflammation. No recurrence was reported.

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Non-vitamin K Antagonist Oral Anticoagulants (NOAC) as an Alternative Treatment Option in Tumor-Related Venous Thromboembolism

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eReferences