Review Article

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

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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:

Beyer-Westendorf J, Klamroth R, Kreher S, Langer F, Matzdorff A, Riess H: Non-vitamin K antagonist oral anticoagulants (NOAC) as an alternative treatment option in tumor-related venous thromboembolism. *Dtsch Arztebl Int* 2019; 116: 31–8. DOI: 10.3238/arztebl.2019.0031

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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

TABLE 1

Study results for LMWH versus VKA in the treatment of cancer-associated venous thromboembolism*

Study	N	Treatment schedule LMWH	Recurrent VTE LMWH versus VKA	Major bleeding LMWH versus VKA
CANTHANOX (17)	146	Enoxaparin 1.5 mg/d	2.8 vs. 4.0%	7.0 vs. 16.0%
CLOT (12)	676	Dalteparin 200 IU/kg/d for 4 weeks, thereafter 150 IU/kg/d	8.0 vs. 15.8%	5.6 vs. 3.6%
ONCENOX (18)	102	Enoxaparin 1 and 1.5 mg/d	6.6 vs. 10%	8.9 vs. 2.9%
LITE (16)	200	Tinzaparin 175 IU/kg/d	6.0 vs. 10%	7.0 vs. 7.0%
CATCH (13)	900	Tinzaparin 175 IU/kg/d	6.9 vs. 10%	2.7 vs. 2.4%

* Modified from Ay et al. (32)

LMWH, low-molecular-weight heparins; VKA, vitamin K antagonists; VTE, venous thromboembolism

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 2

Overview of the characteristics of the NOAC dabigatran, apixaban, edoxaban, and rivaroxaban ^{*1}

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

^{*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

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 (e2); 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 [0.68; 4.96]) (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 3

Available routine data on the use of NOAC in the treatment of cancer-associated venous thromboembolism*

Study/ first author	N	Study design	Duration	Recurrent VTE	Major bleeding	Mortality
XALIA/ Turpie (e15) Ageno (e16)	Rivaroxaban: 146	Prospective registry	6 Months	3.5%	1.4%	4.8%
Mahe (e17)	Various anticoagulation regimens	Prospective registry	~ 4.5 Months	Breast cancer (n = 938) 5.6% / year (95% CI: [3.8; 8.1] Prostate cancer (n = 629) 6.9% / Year [4.4;10]	4.1% / year [2.7; 5.9] 13% / year [9.2; 17]	31% / year [26; 31] 33% / year [27; 35]
Bott-Kitslaar (e11)	Rivaroxaban: 118	Prospective registry	≥ 3 Months	3.3%	2.5%	31%
McBane (e12)	Rivaroxaban: 135 LMWH: 121	Prospective registry	~ 6.5 Months	Rivaroxaban: 2.8% LMWH: 1.7% (p = 0.45)	Rivaroxaban: 2.2% LMWH: 5.8% (p = 0.20)	Rivaroxaban: 30% LMWH: 41% (p = 0.047)
Mantha (e13)	Rivaroxaban: 200	Prospective cohort study	Prospective registry	4.4% [1.4; 7.4]	2.2% [0.0; 4.2]	17.6% [11.3; 23.0]
Khorana (e19)	Rivaroxaban: 1728	Retrospective data- base analysis	Unknown	Unknown	2.61% / year [1.80; 3.78]	Unknown
Ross (e18)	NOAC: 30 (rivaroxaban in 27) LMWH: 123	Retrospective case analysis	6 Months	NOAC: 3.3% LMWH: 5.7%	NOAC: 13.3% LMWH: 10.6%	Unknown
Pignataro (e14)	Rivaroxaban: 400; (302 [75.5%]) with initial enoxapa- rin pretreatment for a median of 3 days)	Retrospective case analysis	6 Months	3.25%	5.5%	29.2%

*Modified from Beyer-Westendorf; adapted from (28)

LMWH, low-molecular-weight heparins; NOAC, non-vitamin K antagonist oral anticoagulants; VTE, venous thromboembolism; 95% CI, 95% confidence interval

(12.3% versus 6.7%; RR: 2.31 [0.85; 6.28]; number needed to harm: 18) (26).

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 4

NOAC in cancer-associated venous thromboembolism: potential risk factors

Risk factors	Comments
Cancer with high risk of bleeding	There are established cancer situations known to be at high risk for bleeding : AML, ALL, gastrointestinal tumors, urothelial tumors, glioma and brain metastases, pancreatic carcinoma, ulcerating tumors
Mucositis, mechanical swallowing disorders	Mucositis (e.g., following radiotherapy, in the setting of fluoropyrimidine use, MTX): increased risk of bleeding, plus NOAC absorption unclear ; mechanical swallowing disorders (e.g., tumors of the mouth/throat, tumors of the upper gastrointestinal tract): NOAC absorption unclear
Nausea, vomiting, diarrhea, long-term opioid therapy	Nausea/vomiting are common side effects of cancer treatments: NOAC uptake and absorption unclear ; opioids slow down peristalsis and absorption: NOAC absorption unclear ; diarrhea (e.g., also under tyrosine kinase inhibitors), short bowel syndrome, fistulas, peritoneal carcinosis: NOAC absorption unclear
Clinically relevant renal impairment	Apixaban, edoxaban, and rivaroxaban are no longer recommended from a creatinine clearance of <15 mL/min, dabigatran is contraindicated from a creatinine clearance of <30 mL/min. Age, pre-existing chronic lesions, underlying malignancy (e.g., myeloma), side effects of cancer therapy (e.g., cisplatin) and adjuvant treatment (e.g., antibiotics), as well as treatment complications (tumor lysis, infection, sepsis), among many others, can cause either acute or chronic renal impairment: NOAC elimination possibly impaired; risk of build-up and increased risk of bleeding
Pharmacological interaction between NOAC and cancer treatment	Interactions (based on various mechanisms) with NOAC are potentially possible (e.g., dexamethasone, tamoxifen, vinca alkaloids, tyrosine kinase inhibitors, and many more), whereby there are scant data on clinical relevance and the potential need for NOAC dose adjustment. The most important possibilities for interaction with the different NOAC relate to the inhibition or induction of CYP3A4 and/or P-GP. An interaction check is recommended (e.g., www.drugs.com/drug_interactions.html or [33, 34]): attenuation or amplification of the NOAC effect is possible depending on the interaction
Severe thrombocytopenia	Thrombocytopenia frequently occurs in patients with hematological disorders, intensive, hypoplasia/aplasia-inducing chemotherapy (e.g., leukemia, myeloma, lymphoma), as well as in solid tumors with high-dose or dose-dense treatments. Anticoagulation is to be viewed critically in the case of thrombocytopenia <50 000/μl and no evidence of bleeding. There are recommendations on heparin dosage in the case of thrombocytopenia (35); there are no recommendations on dose adjustment for NOAC: increased risk of bleeding
Lack of health literacy	Patients should be capable of grasping the indication for anticoagulation and integrating it in the sometimes complex cancer treatment plan. The patient has been informed about the symptoms of recurrent VTE and the risk of bleeding and is able to organize help in the case of complications

ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; CYP3A4, cytochrome P450 3A4; MTX, methotrexate; NOAC, non-vitamin K antagonist oral anticoagulants; P-GP, P-glycoprotein; VTE, venous thromboembolism

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

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—conferring 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.

Acknowledgments

In addition to the six named authors, Prof. Dr. med. Rupert Bauersachs (Angiology, Darmstadt Hospital, Germany) and Prof. Dr. med. Ulrich Hoffmann (Angiology, University Hospital Munich, Germany) played a significant role in the consensus-finding process and preparation of this manuscript.

Conflict of interest statement

Dr Beyer-Westendorf received fees for lectures and/or consultancy activities from LEO Pharma, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Daiichi Sankyo, and Portola, and was reimbursed for travel expenses and participation fees by LEO Pharma, Bayer, and Daiichi Sankyo. He received fees (third-party account) for conducting commissioned clinical trials from LEO Pharma, Bayer, Pfizer, Boehringer Ingelheim, Janssen, Daiichi Sankyo, and Portola.

Dr Beyer-Westendorf received consultancy fees from LEO Pharma, Bayer, Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, and Boehringer Ingelheim, as well as participation fees and travel expense reimbursement from LEO Pharma, Bayer, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo.

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.

Dr Kreher received consultancy fees from Daiichi Sankyo, Bayer, and LEO Pharma. Participation fees and travel expenses were reimbursed to him by Bayer and LEO Pharma, while he received lecture fees from Bayer, LEO Pharma, and Daiichi Sankyo.

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. Matzdorff 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.

Prof. Riess received fees for consultancy activities and lectures from Aspen, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, LEO Pharma, and Pfizer.

Manuscript received on 17 April 2018, revised version accepted on 19 November 2018.

Translated from the original German by Christine Schaefer-Tsorpatzidis.

References

- Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH: Thromboembolism is a leading cause of death in cancer patients receiving out-patient chemotherapy. *J Thromb Haemost* 2007; 5: 632–4.
- Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC: Epidemiology of cancer-associated venous thrombosis. *Blood* 2013; 122: 1712–23.
- Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR: Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000; 18: 3078–83.
- Lyman GH, Eckert L, Wang Y, Wang H, Cohen A: Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist* 2013; 18: 1321–9.
- Louzada ML, Majeed H, Dao V, Wells PS: Risk of recurrent venous thromboembolism according to malignancy characteristics in patients with cancer-associated thrombosis: a systematic review of observational and intervention studies. *Blood Coagul Fibrinolysis* 2011; 22: 86–91.
- Carrier M, Righini M, Wells PS, et al.: Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost* 2010; 8: 1716–22.
- Douma RA, Kok MG, Verbeke LM, Kamphuisen PW, Buller HR: Incidental venous thromboembolism in cancer patients: prevalence and consequence. *Thromb Res* 2010; 125: e306–9.
- Dentali F, Agno W, Giorgi Pierfranceschi M, et al.: Prognostic relevance of an asymptomatic venous thromboembolism in patients with cancer. *J Thromb Haemost* 2011; 9: 1081–3.
- Lyman GH, Khorana AA, Kuderer NM, et al.: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; 31: 2189–204.
- National Comprehensive Cancer Network: Cancer-associated venous thromboembolic disease, Version 1.2018. www.nccn.org/professionals/physician_gls/default.aspx#supportive (last accessed on 21 August 2018).
- Kearon C, Akl EA, Comerota AJ, et al.: Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141(2 Suppl): e419S–96S.
- Lee AY, Levine MN, Baker RI, et al.: Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349: 146–53.
- Lee AYY, Kamphuisen PW, Meyer G, et al.: Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015; 314: 677–86.
- Hakoum MB, Kahale LA, Tzolakis IG, et al.: Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev* 2018; 1: CD006649.
- Vedovati MC, Giustozzi M, Bonitta G, Agnelli G, Becattini C: Efficacy and safety of anticoagulant agents in patients with venous thromboembolism and cancer: a network meta-analysis. *Thromb Res* 2018; 170: 175–80.
- Hull RD, Pineo GF, Brant RF, et al.: Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006; 119: 1062–72.
- Meyer G, Marjanovic Z, Valcke J, et al.: Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002; 162: 1729–35.
- Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J: Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost* 2006; 12: 389–96.
- Lyman GH, Bohlke K, Khorana AA, et al.: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol* 2015; 33: 654–6.
- Hach-Wunderle V (Leitlinienkoordination): Diagnostik und Therapie der Venenthrombose und der Lungenembolie. S2-Leitlinie; AWMF-Leitlinienregister 065/002, 2015: www.awmf.org/uploads/tx_szleitlinien/065-002l_S2k_VTE_2016-01.pdf (last accessed 2 December 2018).
- Raskob GE, van Es N, Verhamme P, et al.: Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018; 378: 615–24.
- Young AM, Marshall A, Thirlwall J, et al.: Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018; 36: 2017–23.
- Khorana AA, Yannicelli D, McKrae KR, et al.: Evaluation of US prescription patterns: are treatment guidelines for cancer-associated venous thromboembolism being followed? *Thromb Res* 2016; 145: 51–3.
- Mahé I, Puget H, Buzzi JC, et al.: Adherence to treatment guidelines for cancer-associated thrombosis: a French hospital-based cohort study. *Support Care Cancer* 2016; 24: 3369–77.
- Mahé I, Chidiac J, Helfer H, Noble S: Factors influencing adherence to clinical guidelines in the management of cancer-associated thrombosis. *J Thromb Haemost* 2016; 14: 2107–13.
- Li A, Garcia DA, Lyman GH, Carrier M: Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. *Thromb Res* 2018; pii: S0049–3848.
- Kraaijpoel N, Di Nisio M, Mulder FI, et al.: Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the hokusai VTE cancer study. *Thromb Haemost* 2018; 118: 1439–49.

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 8.8% 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.

28. Beyer-Westendorf J: What have we learned from real-world NOAC studies in venous thromboembolism treatment? *Thromb Res* 2018; 163: 83–91.
29. Khorana AA, Noble S, Lee AYY, et al.: Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018; 16: 1891–4.
30. Riess H, Ay C, Bauersachs R, et al.: Use of direct oral anticoagulants in patients with cancer: practical considerations for the management of patients with nausea or vomiting. *The Oncologist* 2018; 23: 822–39.
31. Khorana AA, Vadhan-Raj S, Kuderer NM, et al.: Rivaroxaban for preventing venous thromboembolism in high-risk ambulatory patients with cancer: rationale and design of the CASSINI trial. *Thromb Haemost* 2017; 117: 2135–45.
32. Ay C, Kamphuisen PW, Agnelli G: Antithrombotic therapy for prophylaxis and treatment of venous thromboembolism in patients with cancer: review of the literature on current practice and emerging options. *ESMO Open* 2017; 2: e000188.
33. Lee AY, Bauersachs R, Janas MS, et al.: CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. *BMC Cancer* 2013; 13: 284.
34. Short NJ, Connors JM: New oral anticoagulants and the cancer patient. *Oncologist* 2014; 19: 82–93.
35. Farge D, Debourdeau P, Beckers M, et al.: International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost* 2013; 11: 56–70.

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► **Supplementary material**

For eReferences please refer to:
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CLINICAL SNAPSHOT

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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Conflict of interest statement: The authors declare that no conflict of interest exists.

Translated from the original German by David Roseveare

Cite this as: Schneider KN, Gosheger G, Liem D: Progressive prominent swelling over the acromioclavicular joint. *Dtsch Arztebl Int* 2019; 116: 38. DOI: 10.3238/arztebl.2019.0038

Supplementary material to:

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

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

Dtsch Arztebl Int 2019; 116: 31–8. DOI: 10.3238/arztebl.2019.0031

eReferences

- e1. Matzdorff A, Ledig B, Stuecker M, Riess H: Practice patterns for prophylaxis and treatment of venous thromboembolism in German cancer patients. *Oncol Res Treat* 2016; 39: 194–201.
- e2. van der Wall SJ, Klok FA, den Exter PL, et al.: Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice. *J Thromb Haemost* 2017; 15: 74–9.
- e3. Goldhaber SZ, Schellong S, Kakkar A, et al.: Treatment of acute pulmonary embolism with dabigatran versus warfarin. A pooled analysis of data from RE-COVER and RE-COVER II. *Thromb Haemost* 2016; 116: 714–21.
- e4. Schulman S, Goldhaber SZ, Kearon C, et al.: Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015; 114: 150–7.
- e5. Prins MH, Lensing AW, Bauersachs R, et al.: Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; 11: 21.
- e6. Prins M, Lensing A, Brighton T, et al.: Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol* 2014; 1: e37–46.
- e7. Agnelli G, Buller HR, Cohen A, et al.: Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; 369: 799–808.
- e8. Agnelli G, Buller HR, Cohen A, et al.: Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost* 2015; 13: 2187–91.
- e9. Buller HR, Decousus H, Grosso MA, et al.: Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; 369: 1406–15.
- e10. Raskob GE, van Es N, Segers A, et al.: Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol* 2016; 3: e379–87.
- e11. Bott-Kitslaar DM, Saadiq RA, McBane RD, et al.: Efficacy and safety of rivaroxaban in patients with venous thromboembolism and active malignancy: a single-center registry. *Am J Med* 2016; 129: 615–9.
- e12. McBane RD, Simmons B, Saadiq R, et al.: Rivaroxaban compared to low molecular weight heparin in treatment of malignancy associated venous thromboembolism. *Am Coll Cardiol* 2016; 67: 2257.
- e13. Mantha S, Laube E, Miao Y, et al.: Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. *J Thromb Thrombolysis* 2017; 43: 166–71.
- e14. Pignataro BS, Nishinari K, Cavalcante RN, et al.: Oral rivaroxaban for the treatment of symptomatic venous thromboembolism in 400 patients with active cancer: a single-center experience. *Clin Appl Thromb Hemost* 2017; 23: 883–7.
- e15. Turpie AGG, Mantovani LG, Haas S, et al.: Subgroup analysis of patients with cancer in xalia—a non-interventional study of rivaroxaban in routine treatment of deep vein thrombosis. *Blood* 2016; 128: 1438.
- e16. Ageno W, Mantovani LG, Haas S, et al.: Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016; 3: e12–21.
- e17. Mahe I, Chidiac J, Bertoletti L, et al.: The clinical course of venous thromboembolism may differ according to cancer site. *Am J Med* 2017; 130: 337–47.
- e18. Ross JA, Miller MM, Rojas Hernandez CM: Comparative effectiveness and safety of direct oral anticoagulants (DOACs) versus conventional anticoagulation for the treatment of cancer-related venous thromboembolism: a retrospective analysis. *Thromb Res* 2017; 150: 86–9.
- e19. Khorana AA, Peacock F, Tamayo SG, et al.: Major bleeding events among cancer and non-cancer patients taking rivaroxaban for venous thromboembolism treatment in a department of defense health system cohort. *Blood* 2016; 128: 1447.