

# Direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism

## What do we know so far?

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### Keywords

malignancy, venous thrombosis, pulmonary embolism, heparins

### Summary

Cancer patients with venous thromboembolism (VTE) are at increased risk for both bleeding and VTE recurrence. Anticoagulation with low-molecular-weight heparin (LMWH) is the standard of care during the initial and long-term treatment phase (i.e. during the first 3–6 months of therapy) based on its overall beneficial safety and efficacy profile compared to vitamin K antagonists (VKAs). The direct oral anticoagulants (DOACs) rivaroxaban, apixaban, edoxaban, and dabigatran are approved for the treatment of acute VTE, and the combined six phase-3 trials have included >1500 patients with active cancer, as defined by variable selection

criteria. Subgroup analyses of these patients, either pooled or separately reported, suggest that DOACs could be a safe and efficacious alternative to VKA therapy for the treatment of cancer-associated VTE. However, the populations of cancer patients included in the DOAC and LMWH trials are not comparable with regard to mortality and VTE risk, and no specific data from direct head-to-head comparisons of DOACs with LMWHs are currently available. The use of DOACs for the management of VTE in cancer is thus not recommended by clinical practice guidelines.

### Schlüsselwörter

Malignom, venöse Thrombose, Lungenembolie, Heparine

### Zusammenfassung

Tumorpatienten mit venöser Thromboembolie (VTE) haben ein erhöhtes Blutungs- und VTE-Rezidivrisiko. In der ersten Behandlungsphase (d.h. in den ersten 3–6 Monaten) ist die Antikoagulation mit niedermolekularem Heparin (NMH) aufgrund des gegenüber Vitamin-K-Antagonisten (VKAs) vorteilhaften Sicherheits- und Wirksamkeitsprofils der Therapiestandard. Die direkten oralen Antikoagulantien (DOAKs) Rivaroxaban, Apixaban, Edoxaban und Dabigatran sind zur VTE-Therapie zugelassen. In die sechs Phase-3-Studien waren zusammen >1500 Patienten mit aktiver Krebserkrankung, definiert durch variable Selektionskriterien, eingeschlossen. Kombinierte und separate Subgruppenanalysen dieser Patienten legen nahe, dass DOAKs eine sichere und wirksame Alternative zu den VKAs in der Therapie der tumorassoziierten VTE darstellen. Allerdings sind die Kohorten an Krebspatienten zwischen den DOAK- und NMH-Studien bezüglich des Mortalitäts- und VTE-Risikos nicht vergleichbar. Zudem sind aktuell keine spezifischen Studiendaten zum direkten Vergleich von DOAKs mit NMHs verfügbar. Der routinemäßige Einsatz von DOAKs zur Therapie der tumorassoziierten VTE wird deshalb in den aktuellen Leitlinien nicht empfohlen.

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### Behandlung der tumorassoziierten venösen Thromboembolie mit direkten oralen Antikoagulantien –

#### Was wissen wir bisher?

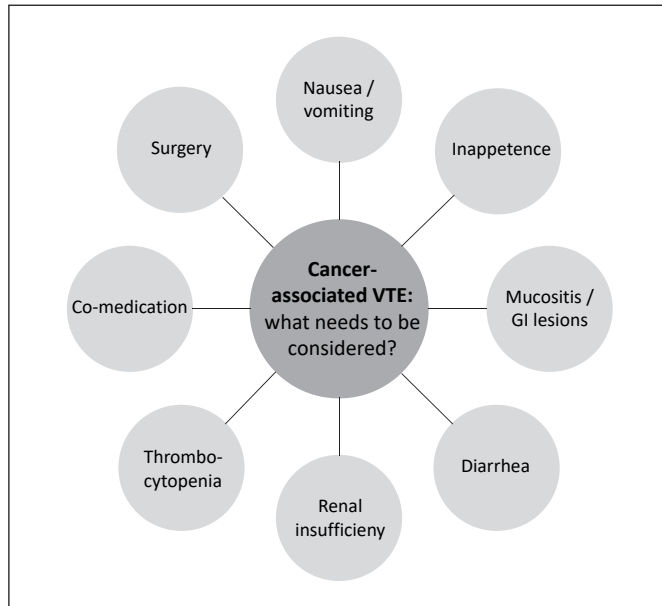
*Hämostaseologie* 2017; 37: 241–255  
<https://doi.org/10.5482/HAMO-16-09-0036>  
received: September 26, 2016  
accepted in revised form: February 1, 2017  
epub ahead of print: May 16, 2017

Venous thromboembolism (VTE), a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of death in patients with cancer (1). Depending on disease-, treatment-, and patient-related risk factors, the incidence of VTE during the first year after diagnosis may approach 20% in certain cancer popu-

lations (2). Symptomatic VTE has a significant impact on morbidity and thus decreases quality of life of affected patients (3). Furthermore, the occurrence of cancer-associated VTE, both symptomatic and asymptomatic, is associated with an unfavorable clinical outcome, because it may not only reflect a highly aggressive

behavior of the underlying malignancy, but also delay or even prevent its efficacious treatment with modern anti-cancer agents (4–6).

During anticoagulant treatment of established VTE, patients with cancer are at increased risk for both bleeding and VTE recurrence compared to patients



**Fig. 1**

Clinical aspects that should be taken into account when approaching a patient with cancer-associated venous thromboembolism. GI: gastrointestinal.

without cancer (7, 8). This dilemma poses a particular challenge to healthcare professionals and underscores the need for safe and efficacious anticoagulants in this specific group of patients. This review will summarize current treatment options for cancer-associated VTE with particular focus on available clinical trial data for the direct oral anticoagulants (DOACs), i.e. the direct factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban, and the direct thrombin inhibitor, dabigatran.

## General considerations

To the best of our knowledge, there is no universal definition of „active cancer“, particularly not in the context of acute VTE. In clinical practice, the term usually refers to a state of malignancy that requires specific anti-cancer therapy, whether or not the patient is actually receiving it. While this definition clearly includes patients with metastatic or recurrent disease, a patient with aggressive non-Hodgkin's lymphoma (NHL), for example, who has finished combination immunochemotherapy three months earlier and is now in complete remission, or a patient with resection of stage-II colorectal cancer five months earlier, would not be classified as having „active cancer“. A broader definition of the term would also include patients receiving

adjuvant chemo-, radio-, or hormonal therapy following surgery for locally advanced (e.g., lymph node-positive) cancer or maintenance therapy after achieving a partial or complete remission of their malignancy.

Although these patients are being treated with specific antineoplastic agents, their cancers may not be considered active from a biological point of view. The broadest definition of the term would include all patients at risk for cancer recurrence, who are not currently receiving any specific anti-cancer therapy, such as the patient with NHL or the patient with colorectal cancer. In this regard, cancer patients are generally considered cured, if at least five years have passed since completion of their treatment, but this time interval may even be longer in certain tumor entities such as breast cancer. These varying definitions of the term „active cancer“ should be kept in mind when interpreting clinical trial findings on cancer-associated VTE.

Treatment of cancer with antineoplastic agents is associated with significant side effects relevant to systemic anticoagulation.

These side effects include, but are not limited to, nausea and vomiting, inappetence, oral and gastrointestinal mucositis, diarrhea, renal insufficiency, and throm-

bocytopenia (► Fig. 1). Some of these side effects may be more important for oral than for parenteral anticoagulants. For instance, vomiting shortly after the intake of an oral anticoagulant raises the question about redosing or omitting the dose, a practical problem that, based on their respective pharmacokinetics and mode of action, is certainly more relevant for DOACs than for vitamin K antagonists (VKAs). In particular, vomiting with or without redosing may have a more pronounced impact on systemic drug levels of DOACs with a once daily regimen (i.e. rivaroxaban, edoxaban) as compared to DOACs with a twice daily regimen (i.e. apixaban, dabigatran) (9).

Lack of appetite could be an issue for patients taking rivaroxaban, because daily doses of 15 or 20 mg require intake of the drug together with food to achieve a sufficiently high oral bioavailability of 80–100% (10). A recent case study indicated that intake of rivaroxaban under fasting conditions resulted in significantly decreased peak plasma levels with insufficient efficacy in the prevention of recurrent VTE (11).

It is currently not clear how gastrointestinal mucositis will affect DOAC absorption. While diarrhea may result in accelerated clearance of the drug or prodrug from the intestines with an overall decreased bioavailability, inflammatory alterations of the intestinal mucosa may cause higher than normal absorption, which is particularly relevant to DOACs with low oral bioavailability (i.e. dabigatran). Toxic esophagitis and gastritis are a concern for patients taking dabigatran, which has been shown to cause dyspepsia in 10–20% of patients due its formulation with a tartaric acid core to lower the gastric pH level (12). Moreover, many patients with active cancer receive proton pump inhibitors that may at least mildly impact on the oral bioavailability of dabigatran (13). Finally, erosive or ulcerative lesions in the context of mucositis or non-resected gastric or colorectal cancer may increase the risk of gastrointestinal bleeding, particularly in patients taking DOACs.

Impairment of renal function is a frequent finding in patients with cancer (14), mainly due to an age-related decline of the

glomerular filtration rate (GFR) in a generally elder patient population. However, several classic cytotoxic drugs such as cisplatin and more modern anti-cancer agents including monoclonal antibodies, small-molecule tyrosine kinase or mTOR inhibitors, and drugs used for androgen deprivation therapy pose a risk of acute kidney injury that is further aggravated by volume depletion in the context of infection, inappetence, or toxic enteritis (15–19). Impairment of renal function is a concern for all anticoagulants, but particularly relevant for drugs with predominantly renal clearance such as dabigatran and fondaparinux (20, 21).

Dabigatran is contraindicated in patients with a GFR of <30 ml/min, and only limited experience exists for the direct oral factor Xa inhibitors in patients with a GFR of 15–30 ml/min (22–27).

Thrombocytopenia is frequently encountered in patients with cancer and may be due to severe systemic infections, the underlying malignancy itself, or its specific therapy with myelotoxic drugs. In clinical practice, therapeutic anticoagulation is considered problematic in most patients with a peripheral platelet count of  $<50 \times 10^9/l$ . Depending on the type and severity of VTE, phase of treatment, and other patient-related risk factors for bleeding, interruption, complete cessation, or continuation of anticoagulation, either at full or reduced intensity, may be reasonable approaches (28). While at least some expert opinions, albeit based on quite limited clinical evidence, exist for the management of thrombocytopenic patients with low-molecular-weight heparin (LMWH) (29), no such recommendations, at least to the best of our knowledge, are currently available for the use of DOACs in patients with cancer-associated VTE.

In addition to these side effects, potential pharmacokinetic interactions between anticoagulants and drugs used for specific anti-cancer therapy or supportive care need to be considered. Although the clinical consequences of these (potential) interactions have not yet been defined, inhibitors of P-glycoprotein and CYP3A4 such as cyclosporine, tamoxifen, and imati-

nib may increase the DOAC level, while inducers of P-glycoprotein and CYP3A4 such as doxorubicin and high-dose dexamethasone may be associated with decreased DOAC plasma levels (29–31).

Finally, patients with active cancer often need to undergo invasive or surgical procedures, such as bone marrow or solid organ biopsies, ascites or lumbar puncture, pleurocentesis, or resection of primary tumors and gross metastases. While interruption of anticoagulation for several days is usually required in patients with an exceedingly high bleeding risk, continuation of anticoagulation may be reasonable in patients with a low-to-moderate bleeding risk. According to our clinical experience, temporary dose adjustments (i.e. reducing the intensity of anticoagulation from a therapeutic to a half-therapeutic or prophylactic dose) are frequently carried out in surgical cancer patients treated with LMWH, although this approach is solely based on empirical evidence. Still, at least in our opinion, much less experience exists with regard to the perioperative management of patients taking DOACs (32). Urgent invasive or surgical procedures are clearly problematic in patients on VKA therapy.

Most of the above aspects are particularly relevant to VKAs (e. g. warfarin, acenocoumarol, phenprocoumon), because these drugs have a narrow therapeutic window, a rather slow onset and decay of action following initiation or interruption of therapy, and significant food and drug interactions requiring routine monitoring of the international normalized ratio (INR) and frequent dose adjustments (33). LMWHs are pharmacologically inert and have a parenteral route of administration, which may offer some advantages over oral anticoagulants in the management of patients with cancer-associated VTE. At least theoretically, however, these drugs harbor the risk of (pseudo)allergic skin reactions and heparin induced thrombocytopenia (HIT), a potentially life-threatening complication of heparin therapy (34, 35). In addition, the need for subcutaneous injections once or twice daily always raises the concern about patient adherence (36).

Fondaparinux, a synthetic pentasaccharide, is generally well tolerated and does not cause HIT, but no robust clinical trial data for the (long-term) treatment of cancer-associated VTE are available for this specific indirect factor Xa inhibitor (37).

In our opinion, all of these considerations should be taken into account when approaching a patient with cancer-associated VTE in clinical practice.

## Current standard of care

The „classical“ treatment of acute VTE involves initial parenteral anticoagulation with LMWH or fondaparinux at therapeutic dosages followed by a VKA at daily dosages adjusted to maintain the INR between 2.0 and 3.0. Parenteral anticoagulation is carried out for at least five days and must only be stopped when the INR values are stable within the therapeutic range. This treatment regimen has been associated with unsatisfying safety and efficacy results in patients with cancer-associated VTE (8, 38). In the study by Prandoni et al. (2002), more than 10% of cancer patients experienced recurrent VTE during the first two months of treatment with the VKA, warfarin, as compared to less than 5% of patients without cancer (7). Similarly, the risk of bleeding was also increased in the cancer cohort, particularly during the initial treatment phase, indicating that the concept of overlapping anticoagulation with individual titration of VKA dosages is problematic in this particular patient population.

Based on these and other observations, the CLOT trial investigated the safety and efficacy of six months of anticoagulation with the LMWH, dalteparin, in comparison to VKA therapy (► Tab. 1) (39). Patients with active cancer and symptomatic proximal DVT, PE, or both (n=676) were randomized to receive dalteparin at a dose of 200 IU/kg body weight once daily for the first month followed by a reduced dose of approximately 150 IU/kg for the next five months (LMWH group) or dalteparin at 200 IU/kg for five to seven days followed by one of the VKAs, warfarin or acenocoumarol, with a target INR of 2.5

**Tab. 1** Study details and major results of randomized controlled trials on low-molecular-weight heparin (LMWH) for the treatment of acute venous thromboembolism (VTE) in cancer patients.

	<b>CANTHANOX (47)</b>	<b>CLOT (39)</b>	<b>ONCENOX (48)</b>	<b>LITE (46)</b>	<b>CATCH (40)</b>
<b>cancer definition</b>	any solid or hematologic malignancy, active or in remission but with ongoing antitumor treatment	any active cancer (other than basal-cell or squamous-cell carcinoma of the skin), determined by diagnosis or treatment in the preceding 6 months or by recurrent or metastatic disease	any active cancer, determined by histological confirmation, measurable disease, elevated tumor markers or metastatic disease, without the possibility of curative intent surgery	cancer without further specification	any active cancer (other than basal-cell carcinoma or non-melanoma skin cancer), determined by diagnosis or treatment in the preceding 6 months, recurrent, locally advanced, or metastatic disease, or hematological malignancy not in complete remission
<b>index VTE</b>	acute deep vein thrombosis and/or pulmonary embolism	acute symptomatic proximal deep vein thrombosis and/or pulmonary embolism	acute non-catheter-associated VTE	acute proximal deep vein thrombosis (optionally with pulmonary embolism)	acute symptomatic proximal deep vein thrombosis and/or pulmonary embolism
<b>treatment</b>	enoxaparin 1.5 mg/kg OD vs. enoxaparin 1.5 mg/kg OD for ≥ 4 days followed by warfarin	dalteparin 200 IU/kg OD for 1 month followed by dalteparin 150 IU/kg OD vs. dalteparin 200 IU/kg OD for 5–7 days followed by warfarin or acenocoumarol	enoxaparin 1.0 mg/kg BID for 5 days followed by 1 mg/kg OD or 1.5 mg/kg OD vs. enoxaparin 1.0 mg/kg BID for ≥ 5 days followed by warfarin	tinzaparin 175 IU/kg OD vs. UFH for ≥ 6 days followed by warfarin	tinzaparin 175 IU/kg OD vs. tinzaparin 175 IU/kg OD for 5–10 days followed by warfarin
<b>duration of treatment</b>	3 months	6 months	6 months	3 months	6 months
<b>time of recruitment</b>	1995–1999	1999–2001	2001–2002	1994–2003*	2010–2013
<b>no. of patients</b>	146	676	102	200	900
	<b>enoxaparin</b>	<b>dalteparin</b>	<b>enoxaparin (1.0 mg/kg)</b>	<b>tinzaparin</b>	<b>tinzaparin</b>
	<b>VKA</b>	<b>VKA</b>	<b>enoxaparin (1.5 mg/kg)</b>	<b>VKA</b>	<b>VKA</b>
<b>recurrent VTE at the end of treatment</b>	2/67 (3.0%)	27/336 (8.0%)	2/29 (6.9%)	6/100 (6%)	31/449 (6.9%)
<b>major bleeding</b>	5/71 (7%)	19/338 (6%)	2/31 (6.5%)	7/100 (7%)	12/449 (2.7%)
<b>mortality at the end of treatment</b>	8/71 (11.3%)	130/336 (39%)	7/31 (22.6%)**	20/100 (20%)	150/449 (33.4%)
		<b>HR (95% CI)</b>			<b>HR (95% CI)</b>
		0.48 (0.30–0.77)	3/30 (10%)	10/100 (10%)	45/451 (10.0%)
		12/335 (4%)	1/34 (2.9%)	7/100 (7%)	11/451 (2.4%)
		136/336 (41%)	11/34 (32.4%)**	19/100 (19%)	138/451 (30.6%)
			(41.7%)**		(0.85–1.36)

Data are presented as n (%) or HR (95% CI). BID: twice a day; CI confidence interval; HR: hazard ratio; OD: once a day; VKA: vitamin K-antagonist

\*2003 refers to the completion of follow-up.

\*\*Mortality rate refers to the end of follow-up, i.e. 1 month after 6 months of treatment.

(therapeutic range, 2.0–3.0) for six months (VKA group). In the CLOT trial, active cancer was defined as any cancer (other than basal-cell or squamous-cell carcinoma of the skin) diagnosed or treated within the preceding six months, or by recurrent or metastatic disease.

Recurrent symptomatic VTE occurred in 8.0% (27/336) of evaluable patients in the LMWH group and 15.8% (53/336) of evaluable patients in the VKA group, with a hazard ratio (HR) of 0.48 (95% confidence interval [CI] 0.30–0.77,  $p=0.002$ ). Probabilities of recurrent VTE at six months were 9 and 17% in the LMWH and VKA group, respectively. Major bleeding occurred in 6% (19/338) of the patients in the LMWH group and 4% (12/335) of the patients in the VKA group ( $p=0.27$ ). Rates of any bleeding were 14% (LMWH) and 19% (VKA), respectively ( $p=0.09$ ). Mortality rates at six months were 39% in the LMWH group and 41% in the VKA group ( $p=0.53$ ). In the CLOT trial, long-term treatment with dalteparin was thus superior to VKA therapy in the prevention of recurrent symptomatic VTE without an increased risk of major or any bleeding.

Patients in the CLOT trial had been recruited between May 1999 and October 2001, raising the question of whether the study's outcome findings were still applicable to the management of hematology and oncology patients 10–15 years later. The CATCH trial therefore investigated the safety and efficacy of the LMWH, tinzaparin, in comparison to the VKA, warfarin, in a more contemporary treatment environment (►Tab. 1) (40). Between August 2010 and November 2013, a total of 900 patients with active cancer and acute symptomatic DVT, PE, or both were randomized to receive tinzaparin at a dose of 175 IU/kg once daily for six months (LMWH group) or warfarin (target INR, 2.0–3.0) for six months with overlapping tinzaparin at 175 IU/kg for the first five to ten days (VKA group). In the CATCH trial, active cancer was defined by histologically or cytologically confirmed malignancy (other than basal-cell carcinoma of the skin or non-melanoma skin cancer) that met any of the following criteria: diagnosis or treatment within the previous six months; recurrent, regionally advanced, or meta-

static disease; or hematological malignancy not in complete remission.

The primary efficacy outcome of recurrent VTE, a composite of symptomatic DVT, symptomatic nonfatal PE, fatal PE, and incidental proximal DVT or PE, occurred in 6.9% (31/449) of patients in the LMWH group and 10.0% (45/451) of patients in the VKA group, with a HR of 0.65 (95% CI 0.41–1.03,  $p=0.07$ ). Probabilities of recurrent VTE at six months were 7.2 and 10.5% in the LMWH and VKA group, respectively. Major bleeding occurred in 2.7% (12/449) of the patients in the LMWH group and 2.4% (11/451) of the patients in the VKA group ( $p=0.77$ ). Rates of clinically relevant non-major bleeding (CRNMB) were 10.9% (LMWH) and 15.3% (VKA), respectively ( $p=0.004$ ), while any bleeding occurred in 25.4% (LMWH) and 24.4% (VKA) of patients, respectively. Mortality rates at six months were 33.4% in the LMWH group and 30.6% in the VKA group ( $p=0.54$ ). In the CATCH trial, long-term treatment with full-dose tinzaparin, as compared with warfarin, thus reduced the risk of recurrent VTE by 35%, albeit this effect was not statistically significant, without increasing the risk of major bleeding and at a lower risk of CRNMB.

Although from a strictly scientific, evidence-based perspective CATCH did not meet its primary objective (i.e. the demonstration that tinzaparin is superior to warfarin in the prevention of recurrent VTE in patients with active cancer), the study's findings are perceived as a confirmation of current clinical practice guidelines recommending LMWH over VKA for the initial and long-term treatment of cancer-associated VTE (i.e. during the first 3–6 months of anticoagulation) (41–45). This perception is primarily based on the fact that the clinically important and pre-specified secondary efficacy outcome of symptomatic recurrent proximal DVT was significantly reduced by tinzaparin therapy, with a HR of 0.48 (95% CI 0.24–0.96;  $p=0.04$ ), and that patients benefited from LMWH treatment with regard to recurrent VTE in the likewise pre-specified per protocol analysis, with a HR of 0.62 (HR 0.38–1.00,  $p=0.05$ ) (40). In addition, other smaller studies such as LITE (tinzaparin) and ONCENOX and

CANTHANOX (both with enoxaparin) have yielded results consistent with a favorable safety and efficacy profile of LMWH over VKA for the treatment of cancer-associated VTE (Table 1) (46–48).

## Clinical trial data on DOACs on cancer-associated VTE

### Rivaroxaban

Detailed data on the safety and efficacy of oral rivaroxaban for the treatment of symptomatic VTE in patients with cancer included in the EINSTEIN-DVT/-PE trials were published in 2014 (►Tab. 2) (49). The pooled analysis of the two trials comprised a total of 8281 and 8246 patients for the intention-to-treat efficacy and safety analysis, respectively. Of these patients, 469 reported a diagnosis of cancer in their medical history only, while 462 patients had active cancer at study inclusion, and 193 patients received a diagnosis of cancer during the study.

Active cancer at study inclusion was defined as any cancer, including basal-cell or squamous-cell carcinoma of the skin, diagnosed or treated within six months before enrolment, or recurrent or metastatic cancer. Active cancer during the study was defined as a new diagnosis of cancer or recurrence of cancer after randomization. A history of cancer was defined as any cancer not meeting the criteria for active cancer (i.e. a cancer that had been diagnosed and treated >6 months before the onset of VTE and that was either cured or in remission at the time of enrolment). Thus, three different cohorts of cancer patients comprising 1124 patients (13.6%) were analyzed in comparison to the 7157 patients (86.4%) without known cancer. Treatment duration in the EINSTEIN-DVT/-PE studies was 3, 6, or 12 months.

- In patients with a history of cancer, the VTE recurrence rate was 2% in both treatment arms and not different from the VTE recurrence rate in patients without known cancer. In addition, there was no difference in the safety outcomes major bleeding (occurring in up to 2% of patients) and clinically relevant bleeding (occurring in 9–11% of patients) between patients with a history of cancer and those without known

**Tab. 2** Major results of the cancer subgroup analyses of the EINSTEIN-DVT/-PE phase-3 clinical trials on rivaroxaban for the treatment of acute venous thromboembolism (VTE). Treatment: rivaroxaban 15 mg twice a day for 21 days followed by 20 mg once daily vs. enoxaparin 1 mg/kg twice a day for  $\geq 5$  days followed by warfarin or acenocoumarol. Treatment duration: 3, 6 or 12 months (49).

	VTE or VTE-related death			major bleeding			mortality		
	riva-roxaban	VKA	HR (95% CI)	riva-roxaban	VKA	HR (95% CI)	riva-roxaban	VKA	HR (95% CI)
<b>active cancer at study inclusion (n=462)*</b>	6/258 (2%)	8/204 (4%)	0.62 (0.21–1.79)	5/257 (2%)	8/202 (4%)	0.47 (0.15–1.45)	38/257 (15%)	36/202 (18%)	0.82 (0.52–1.30)
<b>history of cancer (n=469)*</b>	5/233 (2%)	5/236 (2%)	0.98 (0.28–3.43)	1/231 (<1%)	4/236 (2%)	0.23 (0.03–2.06)	5/231 (2%)	4/236 (2%)	1.12 (0.30–4.22)
<b>diagnosis of cancer during the study (n=193)*</b>	10/96 (10%)	12/97 (12%)	0.80 (0.34–1.88)	3/96 (3%)	7/96 (7%)	0.33 (0.08–1.31)	20/96 (21%)	17/96 (18%)	1.30 (0.67–2.52)
<b>no cancer (n=7157)</b>	65/3563 (2%)	70/3594 (2%)	0.93 (0.66–1.30)	31/3546 (1%)	53/3582 (1%)	0.58 (0.37–0.91)	33/3546 (1%)	42/3582 (1%)	0.77 (0.49–1.22)

Data are presented as n (%) or HR (95% CI). CI: confidence interval; VTE: venous thromboembolism; VKA: vitamin K-antagonist; HR: hazard ratio.

\*Active cancer at study inclusion was defined as any cancer, including basal-cell or squamous-cell carcinoma of the skin, diagnosed or treated within the past 6 months or recurrent or metastatic cancer. A history of cancer was defined as any cancer not meeting the criteria for active cancer. Active cancer during the study was defined as a new diagnosis or recurrence of cancer after randomisation.

cancer, irrespective of treatment assignment.

- In patients with active cancer at baseline, rates of VTE recurrence and major bleeding were 2% in patients receiving rivaroxaban and 4% in patients receiving VKA. Clinically relevant bleeding occurred in 12% (rivaroxaban) and 13% (VKA) of patients.
- In patients diagnosed with cancer during the study, recurrent VTE occurred in 10% of patients receiving rivaroxaban and in 12% of patients receiving VKA. Rates of major bleeding (3 vs. 7%) and clinically relevant bleeding (19 vs. 23%) were numerically lower in the rivaroxaban group than in the VKA group.

In none of the three cancer subgroups, safety and efficacy outcomes were significantly different between patients receiving rivaroxaban and those receiving VKA, suggesting that anticoagulation with rivaroxaban is a feasible treatment option in patients with cancer-associated VTE. It has to be mentioned, however, that only the VTE recurrence rates in patients diagnosed with cancer during the study (10–12%) were in a magnitude comparable to the VTE recurrence rates observed in the CATCH (7–10%) and CLOT (9–16%)

study populations (39, 40). Furthermore, the mortality rates in patients with active cancer at baseline or a diagnosis of cancer during the study were only 15–21% in EINSTEIN-DVT/-PE, whereas mortality rates of 30–33% and 39–41% were observed in CATCH and CLOT, respectively, indicating that different populations of cancer patients were included in the rivaroxaban and the two pivotal LMWH trials. While only 19–25% of the cancer patients included in EINSTEIN-DVT/-PE had recurrent or metastatic disease, advanced cancer was present in 55 and 67% of the patients included in CATCH and CLOT, respectively.

### Apixaban

Safety and efficacy data for apixaban in the treatment of acute VTE in patients with cancer included in the AMPLIFY trial were published in 2015 (► Tab. 3) (50). In AMPLIFY, 5395 patients were randomized to receive either apixaban or enoxaparin/VKA. At baseline, active cancer was present in 169 patients (3.1%), while 365 patients (6.8%) reported a history of cancer. Active cancer was defined as any cancer that was diagnosed or treated within the past six months. A history of cancer was defined as cancer diagnosed >6 months

before and not receiving any treatment, including surgery, radiation, chemotherapy, or hormonal therapy, at enrolment. The remaining 4861 patients (90.1%) had neither active cancer nor a history of cancer at study inclusion. This cohort, however, included 25 patients who were diagnosed with cancer during the study. Treatment duration in the AMPLIFY study was six months.

In the evaluable patients with either active or a history of cancer, the primary efficacy outcome of recurrent symptomatic VTE or VTE-related death occurred in 1.9% of patients receiving apixaban and in 6.3% of patients receiving VKA, with a RR of 0.30 (95% CI 0.11–0.82). The composite safety outcome of major bleeding and CRNMB was observed in 8.1 and 17.4% of patients in the apixaban and VKA group, respectively (RR 0.47, 95% CI 0.29–0.75). Consistent findings were found in the subgroup of patients with a history of cancer, with VTE/VTE-related death occurring in 1.1 and 6.3% (RR 0.17, 95% CI 0.04–0.78) and major bleeding/CRNMB occurring in 6.0 and 15.1% (RR 0.40, 95% CI 0.20–0.78) of patients in the apixaban and VKA group, respectively. In the subgroup of patients with active cancer at study inclusion, the safety (12.6 vs. 22.5%) and efficacy (3.7 vs. 6.4%) outcomes also occurred less fre-

**Tab. 3** Major results of the cancer subgroup analyses of the AMPLIFY phase-3 clinical trial on apixaban for the treatment of acute venous thromboembolism (VTE). Treatment: apixaban 10 mg twice a day for 7 days followed by 5 mg twice a day vs. enoxaparin 1 mg/kg twice a day for  $\geq 5$  days followed by warfarin. Treatment duration: 6 months (50).

	VTE or VTE-related death			major bleeding			mortality*		
	apixaban	VKA	HR (95% CI)	apixaban	VKA	HR (95% CI)	apixaban	VKA	HR (95% CI)
active cancer at study inclusion (n=169)**	3/81 (3.7%)	5/78 (6.4%)	0.56 (0.13–2.37)	2/87 (2.3%)	4/80 (5.0%)	0.45 (0.08–2.46)	6.0%	7.7%	
history of cancer (n=365)**	2/179 (1.1%)	11/175 (6.3%)	0.17 (0.04–0.78)	1/184 (0.5%)	5/179 (2.8%)	0.20 (0.02–1.65)	1.1%	2.9%	
diagnosis of cancer during the study (n=25)**	0/13 (0%)	4/12 (33.3%)		1/13 (7.7%)	1/12 (8.3%)				
no cancer (n=4861)***	54/2349 (2.3%)	55/2382 (2.3%)	0.99 (0.69–1.44)	12/2405 (0.5%)	40/2430 (1.7%)	0.30 (0.16–0.58)			

Data are presented as n (%) or HR (95% CI). CI: confidence interval; VTE: venous thromboembolism; VKA: vitamin K-antagonist; HR: hazard ratio.

\*Mortality rate given at 3 months.

\*\*Active cancer at study inclusion was defined as any cancer diagnosed or treated within the past 6 months. A history of cancer was defined as any cancer diagnosed  $>6$  months before and not receiving any treatment at study inclusion. Active cancer during the study was captured through adverse event reporting.

\*\*\*Including 25 patients with cancer diagnosed during the study.

quently in patients receiving apixaban than in patients receiving VKA, but these differences were not statistically significant with 95% CIs of the RR crossing the 1.0 border.

In patients with neither active nor a history of cancer, both regimens were similarly effective, with a rate of VTE/VTE-related death of 2.3% in both treatment arms, while patients receiving apixaban experienced significantly less major bleeding/CRNMB than patients receiving VKA (3.9 vs. 8.9%), with a RR of 0.43 (95% CI 0.34–0.55). Only 25 patients received a diagnosis of cancer after treatment assignment, as identified by adverse event reporting: 13 in the apixaban group and 12 in the VKA group. Recurrent VTE occurred in 0/13 and 4/12 of the patients and major bleeding/CRNMB in 1/13 and 2/12 of the patients, respectively.

Reported mortality rates at three months were 6–8% in patients with active cancer and 1–3% in patients with a history of cancer. Thus, similar to the EINSTEIN-DVT/PE trials, patients in AMPLIFY likely had less aggressive cancers than patients in the two pivotal LMWH trials. In contrast to the findings of the rivaroxaban trials, however, the findings of AMPLIFY suggest that not only patients with active cancer, but also those with a history of

cancer are at increased risk of VTE recurrence and bleeding during VKA therapy.

### Edoxaban

Detailed safety and efficacy data for edoxaban in the treatment of patients with acute VTE and cancer were published in 2016 (►Tab. 4) (51). Of the 8240 patients included in the modified intention-to-treat and safety analyses of the HOKUSAI-VTE trial, 771 patients (9.4%) reported any history of cancer at enrolment. According to a pre-specified procedure, these patients were categorized as having active cancer based on the clinical judgement of the local investigator. In a post-hoc analysis, all patients with a history of cancer were reviewed by an independent physician blinded to treatment assignment. In this analysis, active cancer was defined as either the presence of solid measurable cancer (other than non-melanoma skin cancer) or hematological malignancy not in remission. Treatment duration in the HOKUSAI-VTE study was 3–12 months. Patients in the edoxaban group received initial parenteral anticoagulation with unfractionated heparin (UFH) or LMWH for  $\geq 5$  days.

In patients with no cancer either at study inclusion or during follow-up

(n=7287), the VTE recurrence rate was 3% in patients receiving edoxaban and 3% in patients receiving VKA, with a HR of 1.03 (95% CI 0.78–1.36). Clinically relevant bleeding (major or non-major) occurred less frequently in the edoxaban (8%) than in the VKA group (9%), with a HR of 0.83 (95% CI 0.71–0.97).

In the group of patients with any history of cancer (n=771), VTE recurrence rates were 4 and 7% in patients receiving edoxaban and VKA, respectively (HR 0.53, 95% CI 0.28–1.00) with major bleeding or CRNMB occurring in 12% (edoxaban) and 19% (VKA) of patients (HR 0.64, 95% CI 0.45–0.92). Identical VTE recurrence rates of 4% (edoxaban) and 7% (VKA) were found in the pre-specified subgroup of patients with active cancer (n=208), while major bleeding/CRNMB occurred more frequently in both the edoxaban (18%) and VKA (25%) treatment arm. Overall similar rates of the safety and efficacy endpoints were found in the 162 patients classified as having active cancer in the post-hoc analysis. Of note, VTE recurrence rates were 17% (edoxaban) and 20% (VKA) in the 175 patients who received a diagnosis of cancer during the study.

In patients with any history of cancer (n=771), mortality rates were 10–11% during the overall study period of

**Tab. 4** This sentence should read as follows: Major results of the cancer subgroup analyses of the HOKUSAI phase-3 clinical trial on edoxaban for the treatment of acute venous thromboembolism (VTE). Treatment: enoxaparin or unfractionated heparin (UFH) for  $\geq 5$  days followed by edoxaban 60 mg once daily vs. enoxaparin or UFH for  $\geq 5$  days followed by warfarin. Treatment duration: 3–12 months (51).

	VTE or VTE -related death			major bleeding			mortality		
	edoxaban	VKA	HR (95% CI)	edoxaban	VKA	HR (95% CI)	edoxaban	VKA	HR (95% CI)
<b>active cancer at study inclusion (n=208)*,**</b>	4/109 (4%)	7/99 (7%)	0.55 (0.16–1.85)	5/109 (5%)	3/99 (3%)	1.52 (0.36–6.43)	31/109 (28%)	26/99 (26%)	
<b>any history of cancer (n=771)*</b>	14/378 (4%)	28/393 (7%)	0.53 (0.28–1.00)	10/378 (3%)	13/393 (3%)	0.80 (0.35–1.83)	40/378 (11%)	40/393 (10%)	
<b>diagnosis of cancer during the study (n=175)*</b>	13/78 (17%)	19/97 (20%)	0.73 (0.36–1.49)						
<b>no cancer (n=7287)</b>	103/3658 (3%)	99/3629 (3%)	1.03 (0.78–1.36)	39/3658 (1%)	48/3629 (1%)	0.80 (0.53–1.22)			

Data are presented as n (%) or HR (95% CI). CI: confidence interval; VTE: venous thromboembolism; VKA: vitamin K-antagonist; HR: hazard ratio.

\*Any history of cancer is not further defined, but includes patients with active cancer at study enrolment. Pre-specified definition of active cancer was based on the clinical judgment of the investigator at the time of enrolment. Post-hoc, all patients with any history of cancer were categorised to the presence or absence of active cancer by an independent physician. Here, active cancer was defined as either the presence of solid measurable cancer, other than non-melanoma skin cancer, or hematological malignancy not in remission. There is no further description of active cancer diagnosed during follow-up.

\*\*Data for patients with active cancer according to the post-hoc classification: recurrent VTE in 2/85 patients (2%) in the edoxaban group vs. 7/77 patients (9%) in the VKA group, HR 0.30 (95% CI 0.06–1.51); major bleeding in 4/85 patients (5%) vs. 2/77 (3%), HR 1.67 (CI 0.34 – 8.11); mortality in 26/85 patients (31%) and 24/77 (31%).

12 months, while mortality rates were 26–28% and 31% in the subgroup of patients with active cancer, as defined by the pre-specified categorization and in the post-hoc analysis, respectively.

## Dabigatran

Safety and efficacy results for dabigatran in the treatment of patients with symptomatic VTE and cancer were published in 2015 (►Tab. 5) (52). The two phase-3 studies, RE-COVER I and II, included 335 patients with cancer, either active at enrolment (n=221) or diagnosed during the study (n=114), comprising 6.6% of the total study population. Active cancer was defined as a diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within five years before enrolment, any treatment for cancer within five years, or recurrent or metastatic cancer. Diagnosis of cancer during the study was captured through adverse event reporting. Treatment duration in the RE-COVER I/II studies was six months.

Patients in the dabigatran group received initial parenteral coagulation with UFH, LMWH, or fondaparinux for  $\geq 5$  days.

Compared to patients without cancer (n=4772), the primary efficacy endpoint of recurrent VTE or VTE-related death occurred more frequently in patients with cancer at any time, with a HR of 3.3 (95% CI 2.1–5.3), and more frequently in patients diagnosed with cancer during the study than in patients with active cancer at study inclusion (HR 2.6, 95% CI 1.1–6.2). The risk of bleeding was also significantly increased in patients with cancer at any time compared to patients without cancer, with a HR of 4.1 (95% CI 2.2–7.5) for major bleeding and a HR of 1.5 (95% CI 1.2–2.0) for any bleeding. No difference was found for any of the safety and efficacy outcomes between patients receiving dabigatran and those receiving VKA.

Although the definition of cancer was highly variable, some interesting conclusions can be drawn from the DOAC trials.

Except for the pooled analysis of the EINSTEIN-DVT-PE studies, patients with a history of cancer appeared to have a higher risk of recurrent VTE than patients without cancer. The highest rates of recurrent VTE, however, were observed in patients diagnosed with cancer during the study, although robust data for these patients were only available for the rivaroxaban, edoxaban, and dabigatran trials.

## Meta-analyses of DOACs in cancer-associated VTE

In 2014, van Es et al. (53) published a review of the six phase-3 clinical trials on DOACs for the treatment of acute VTE. In the combined study population, about 6% of patients (n=1565) had a known malignancy at baseline. In this subgroup of cancer patients, the risk of recurrent VTE was significantly lower in patients receiving DOACs than in patients receiving VKAs (RR 0.57, 95% CI 0.36–0.91, p=0.02), while there was no difference in the risk of major bleeding (RR 0.77, 95% CI



**Tab. 5** This sentence should read as follows: Major results of the cancer subgroup analyses of the RE-COVER I/II phase-3 clinical trials on dabigatran for the treatment of acute venous thromboembolism (VTE). Treatment: low-molecular-weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux for  $\geq 5$  days followed by dabigatran 150 mg twice a day vs. LMWH, UFH or fondaparinux for  $\geq 5$  days followed by warfarin. Treatment duration: 6 months (52).

	VTE or VTE-related death			major bleeding			mortality		
	dabigatran	VKA	HR (95% CI)	dabigatran	VKA	HR (95% CI)	dabigatran	VKA	HR (95% CI)
<b>active cancer at study inclusion (n=221)*</b>	4/114 (3.5%)	5/107 (4.7%)	0.74 (0.20–2.70)	4/105 (3.8%)	3/100 (3.0%)	1.23 (0.28–5.5)	16/114 (14%)	16/107 (15%)	0.93 (0.47–1.86)
<b>history of cancer (n=?)*</b>									
<b>diagnosis of cancer during the study (n=114)*</b>	5/59 (8.5%)	7/55 (13.0%)	0.63 (0.20–2.00)	2/54 (3.7%)	4/52 (7.7%)	0.43 (0.08–2.3)	10/59 (16.9%)	7/55 (12.7%)	1.24 (0.47–3.26)
<b>no cancer (n=4,772)</b>	51/2380 (2.1%)	43/2392 (1.8%)	1.19 (0.79–1.79)	18/2297 (0.8%)	33/2310 (1.4%)	0.55 (0.31–0.97)	15/2380 (0.6%)	17/2392 (0.7%)	0.89 (0.44–1.77)

Data are presented as n (%) or HR (95% CI). CI: confidence interval; VTE: venous thromboembolism; VKA: vitamin K-antagonist; HR: hazard ratio.

\*Active cancer at study inclusion was defined as any cancer, other than basal-cell or squamous-cell carcinoma of the skin, diagnosed or treated within the last 5 years, or recurrent or metastatic cancer. There is no information on patients with a history of cancer. Active cancer during the study was captured through adverse event reporting.

0.44–1.33,  $p=0.35$ ). Of note, in patients receiving VKAs, the rates of recurrent VTE (5.9 vs. 2.5%) and major bleeding (3.7 vs. 1.6%) were higher in patients with cancer at baseline as compared to patients without known malignancy, a finding also observed in patients receiving DOACs: 3.4 vs. 2.4% (recurrent VTE) and 2.9 vs. 1.0% (major bleeding). These findings confirm that cancer patients are generally at higher risk for recurrent VTE and major bleeding than patients without cancer (7, 8). However, the VTE recurrence rate in the combined VKA group of the DOAC trials (5.9%) is still considerably lower than the VTE recurrence rates in the VKA groups of the CLOT (15.8%) and CATCH trial (10.0%) (39, 40).

In the same year, a second meta-analysis, in which the patients of the AMPLIFY trial (apixaban) were not considered, reported the clinical outcomes of 973 patients with active cancer that were included in the remaining five DOAC trials and comprised 5.1% of the total study population (54). In this cancer subgroup, the RR of recurrent VTE was 0.66 in patients receiving DOACs when compared to patients receiving VKAs (95% CI 0.38–1.17), while the RR of major bleeding and CRNMB was 0.94 (95% CI 0.70–1.28).

Taken together, these findings and those from four other (semi-)systematic reviews and meta-analyses using the same phase-3 clinical trial data indicate that DOACs were at least as safe and efficacious as VKAs in the treatment of cancer-associated VTE (55–58).

Interestingly, one of the latter studies also performed an indirect network comparison between DOACs and LMWH (58). According to this analysis, DOACs and LMWH had comparable efficacy (RR 1.08, 95% CI 0.59–1.95;  $p=0.81$ ) with a non-significant RR towards improved safety with DOACs (RR 0.67, 95% CI 0.31–1.46;  $p=0.31$ ).

### Ongoing specific DOAC trials on cancer-associated VTE

#### HOKUSAI-VTE CANCER

HOKUSAI-VTE CANCER (ClinicalTrials.gov ID, NCT02073682) is a currently enrolling study aimed to demonstrate the non-inferiority of a 12-month course of LMWH/edoxaban compared with dalteparin for the prevention of the combined outcome of recurrent VTE or major bleeding in patients with cancer-associated VTE (59). If non-inferiority is established, edoxaban will be compared with dalteparin

for superiority. The trial is a prospective, randomized, open-label phase-4 study with blinded endpoint evaluation (PROBE design) including patients with symptomatic or incidental proximal DVT or PE who either have active cancer or have received a diagnosis of cancer within the preceding two years. Active cancer is defined by any of the following criteria:

- diagnosis of cancer within the preceding six months;
- recurrent, locally advanced, or metastatic cancer;
- current cancer therapy or cancer therapy within the preceding six months; or
- hematological malignancy that is not in complete remission.

Approximately 1000 patients will be randomized in a 1:1 fashion to receive either dalteparin according to the CLOT protocol (200 IU/kg for 30 days followed by 150 IU/kg) or LMWH at a therapeutic dose for at least five days followed by edoxaban at the standard dose of 60 mg per day for a total of 12 months. Dose adjustment to edoxaban 30 mg per day will be carried out in patients with a body weight of  $\leq 60$  kg, a creatinine clearance of 30–50 ml/min, or concomitant use of P-glycoprotein inhibitors.

Some aspects of the HOKUSAI-VTE CANCER study warrant further discussion. First, cancer patients with incidentally (or unexpectedly) diagnosed VTE are included, because previous studies have suggested that these patients have a recurrence and mortality rate similar to that of cancer patients with symptomatic VTE (60).

Second, treatment duration in both arms is 12 months. This decision is based on findings from the DALTECAN study according to which continued anticoagulation with dalteparin beyond six months is safe and efficacious in patients with symptomatic cancer-associated VTE (61).

Third, the duration of initial parenteral anticoagulation in the LMWH/edoxaban arm is up to the discretion of the investigator. It is thus not mandatory to switch from therapeutic LMWH to edoxaban after five days of treatment, which could be particularly relevant to patients considered at high risk for VTE recurrence.

Finally, the primary study outcome is a combination of recurrent VTE (i.e. new symptomatic DVT or PE, new incidental proximal DVT of the legs or incidental PE in segmental or more proximal pulmonary arteries, and fatal PE including unexplained death for which PE cannot be ruled out) and major bleeding, thus reflecting the net clinical benefit considered particularly relevant for this high-risk population.

### Other DOAC trials

While HOKUSAI-VTE CANCER is sponsored by the pharmaceutical industry (Daiichi-Sankyo), several investigator-initiated studies, either currently recruiting or planned, address the role of DOACs in cancer-associated VTE using a prospective, randomized trial design.

- For instance, NCT02583191 (CONKO\_011) is an open-label study by the German Working Group of Medical Oncology (AIO-Studien-gGmbH) that compares rivaroxaban with the current standard of care, LMWH. Primary outcome measure is patient-reported treatment satisfaction after four weeks of treatment.
- A French study (NCT02746185) will use a PROBE design to compare riva-

roxaban with dalteparin for the prevention of recurrent or worsening VTE during three months of treatment.

- NCT02585713 is a currently recruiting open-label study in the United States (US) comparing apixaban with LMWH. Primary outcome measure is the occurrence of major bleeding, including fatal bleeding, during the first week of treatment.
- The also US-based CANVAS study (NCT02744092) will compare various treatment strategies, including all four DOACs and LMWH +/- warfarin, with regard to the cumulative VTE recurrence rate after six months of treatment.

Collectively, these studies will provide important information on the safety, efficacy, and perceived treatment satisfaction of DOACs for the treatment of cancer-associated VTE.

## Concluding remarks

The management of cancer-associated VTE remains a challenge, because hematology and oncology patients are at increased risk for both bleeding and VTE recurrence. During initial and long-term treatment (i.e. during the first 3–6 months), anticoagulation with LMWH is the standard of care based on its overall favorable safety and efficacy profile over VKAs. Although a substantial number of cancer patients had been included in the six phase-3 DOAC trials on the treatment of symptomatic VTE, these patients have not yet been sufficiently characterized (e.g. with regard to tumor type and stage or concomitant anti-cancer therapy) to allow a meaningful comparison with the two pivotal LMWH trials, CATCH and CLOT. Overall rates of VTE recurrence and mortality, however, indicate that different populations of cancer patients had been included in the DOAC and LMWH trials.

In this regard, it has to be mentioned that variable inclusion and exclusion criteria for the definition of „active cancer“ were used in the DOAC trials and that participating study centers were generally recommended not to include cancer patients for whom LMWH was considered the ap-

propriate treatment and to exclude patients with a life expectancy of less than 3–6 months.

Furthermore, post-hoc statistical analyses of safety and efficacy endpoints in cancer patients treated with VKA compared to those treated with DOACs are problematic, since only in the RE-COVER studies randomization was stratified according to the presence or absence of active cancer, and there are no reports available demonstrating the balancing of important patient characteristics in these subgroups.

Finally, treatment durations in the DOAC trials were highly variable, and caution is therefore warranted when comparing the event rates of safety and efficacy endpoints between the various cancer subgroups.

In conclusion, currently available subgroup analyses, either pooled or separately reported, suggest that anticoagulation with DOACs could be a safe and efficacious alternative to VKA therapy for the treatment of cancer-associated VTE. However, only the results of currently ongoing prospective, randomized trials with a direct head-to-head comparison of DOACs with LMWH will show, if clinical practice guidelines recommending anticoagulation with LMWH as the treatment of choice need to be revised.

### Conflicts of interest

MV has received travel support from Bristol-Myers Squibb and LEO Pharma. FL has received lecture fees, honoraria for consultancy, and/or travel support from Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, LEO Pharma, Pfizer, and Sanofi.

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