Novel clinical trial data on the treatment of cancer-associated venous thromboembolism with DOACs

M. Voigtlaender[1]; J. Yamamura[2]; F. Langer[1]

[1]II. Medizinische Klinik und Poliklinik, Hubertus Wald Tumorzentrum – Universitäres Cancer Center Hamburg (UCCH), Universitätsklinikum Hamburg-Eppendorf; [2]Klinik und Poliklinik für Diagnostische und Interventionelle Radiologie und Nuklearmedizin, Universitätsklinikum Hamburg-Eppendorf

Keywords

Direct oral anticoagulants, low-molecular-weight heparin, cancer-associated venous thromboembolism, bleeding, gastrointestinal cancer

Summary

Venous thromboembolism (VTE) is a frequent complication in patients with malignancy. Based on an improved safety and efficacy profile compared to vitamin K antagonists (VKA), current guidelines recommend anticoagulation with low-molecular-weight heparin (LMWH) for 3–6 months as the preferred treatment of cancer-associated VTE. Real-world evidence indicates, however, that guideline adherence is poor in clinical practice, a finding most likely explained by the daily subcutaneous injections and relatively high treatment costs associated with LMWH therapy. Although direct oral anticoagulants (DOACs) may be an attractive alternative owing to their ease of administration and favorable pharmacokinetics compared to VKA, the rather small and insufficiently characterized subgroups of cancer patients included in the large phase-3 trials did not allow translation of study findings into daily practice. With HOKUSAI VTE Cancer (edoxaban) and SELECT-D (rivaroxaban) two large prospective, randomized trials, which have compared DOACs with LMWH for the treatment of cancer-associated VTE, are now available. Both studies showed a reduction in recurrent VTE, but an increased risk in (gastrointestinal and urothelial) bleeding. Taking into account patient preferences and tumor characteristics, future treatment of cancer-associated VTE will thus require a high degree of selection and individualization.

Schlüsselwörter

Direkte orale Antikoagulantien, niedermolekulares Heparin, tumorassoziierte venöse Thromboembolie, Blutungen, gastrointestinaler Tumor

Zusammenfassung

Die venöse Thromboembolie (VTE) ist eine häufige Komplikation bei Patienten mit maligner Grunderkrankung. Basierend auf einer verbesserten Wirksamkeit und Sicherheit gegenüber Vitamin K-Antagonisten (VKA) empfehlen aktuelle Leitlinien eine 3- bis 6-monatige Antikoagulation mit niedermolekularem Heparin (NMH) als Standardtherapie der tumorassoziierten VTE. Versorgungsdaten zeigen jedoch eine geringe Leitlinienadhärenz im klinischen Behandlungsalltag, was am ehesten auf die täglichen subkutanen Injektionen und die relativ hohen Therapiekosten zurückzuführen ist. Aufgrund ihres Einnahmemodus und ihrer im Vergleich zu VKA günstigen Pharmakokinetik stellen die direkten oralen Antikoagulantien (DOAKs) zwar eine vielversprechende Alternative dar; die Subgruppen der in die großen Zulassungsstudien eingeschlossenen Krebspatienten waren aber aufgrund ihrer Größe und Tumorcharakteristika nicht geeignet, die bisherigen Studiendaten in den klinischen Alltag zu übertragen. Mit HOKUSAI VTE Cancer (Edoxaban) und SELECT-D (Rivaroxaban) stehen nun die Ergebnisse von zwei prospektiven, randomisierten Studien zur Verfügung, die die Wirksamkeit und Sicherheit von DOAKs im Vergleich zu NMH bei Patienten mit tumorassoziierter VTE untersucht haben. In beiden Studien war die DOAK-Einnahme mit weniger VTE-Rezidiven, jedoch mit einer höheren Rate an (gastrointestinalen und urothelialen) Blutungen assoziiert. Somit wird die zukünftige Therapie der tumorassoziierten VTE unter Berücksichtigung von Patientenpräferenz und Tumorcharakteristika ein hohes Maß an Selektion und Individualisierung erfordern.

Correspondence to:
Prof. Dr. med. Florian Langer
II. Medizinische Klinik und Poliklinik
Hubertus Wald Tumorzentrum – Universitäres Cancer Center Hamburg (UCCH)
Universitätsklinikum Eppendorf
Martinistr. 52, D-20246 Hamburg
Tel. +49 40/7410–52453/-50664
Fax +49 40/7410–55193
E-Mail: langer@uke.de

Neue Studiendaten zur Therapie der tumorassoziierten venösen Thromboembolie mit DOAKs
Phlebologie 2018; 47: 309–317
https://doi.org/10.12687/phleb2450-6-2018
Received: 26. July 2018
Accepted: 15. August 2018

Introduction

Treatment of cancer-associated venous thromboembolism (VTE) is a major challenge in everyday clinical practice. Cancer patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) have not only an increased risk of thromboembolic recurrence on anticoagulation but also a significantly increased risk of bleeding compared to patients without underlying malignant disease (1–3).

Relapsed, locally advanced or metastatic cancer is usually a persistent severe risk factor; accordingly, this results in an indication for long-term, indefinite continuation of the anticoagulation in patients with a history of VTE (▶ Fig. 1 and Ref. 4). Against this background, the safety of anticoagulation therapy is of particular importance in cancer patients.

In patients with cancer-associated VTE, oral anticoagulation with vitamin K antagonists (VKA) has proved impractical due to a high risk of bleeding and recurrence of VTE (1–3). This is mainly attributable to the unfavourable pharmacokinetics with a delayed onset of effect and prolonged wearing off time, the indirect, vitamin K-dependent mechanism of action, and the numerous food and drug interactions, which make a stable adjustment of the International Normalized Ratio (INR) particularly difficult in cancer patients. Based on several prospective randomised studies, national and international guidelines recommend anticoagulation with low-molecular-weight heparin (LMWH) for 3–6 months as the standard treatment for cancer-associated VTE (5). Meta-analyses show that, compared to VKA therapy, LMWH therapy significantly reduces the risk of recurrent VTE in cancer patients by 40–50% without increasing the risk of major bleeds (6–8).

In this context, however, it is important to note that the improved efficacy of LMWH compared to VKA is essentially based on the results of the CLOT study, in which a six-month anticoagulation with dalteparin reduced the risk of VTE recurrence from 17% in the VKA arm to 9% in the LMWH arm, corresponding to a relative risk reduction of 52% (P=0.002) (9). No other LMWH study on its own, including the to date largest CATCH trial (tinzaparin vs. warfarin) (10), has demonstrated a superior efficacy of LMWH over VKA. As a result, the evidence is assessed differently in the guidelines. While the North American ACCP guideline on VTE therapy in cancer patients advises the use of LMWH instead of VKA with a grade 2B recommendation (11), the ITAC-CME guideline has a preference for therapy with LMWH over VKA with a grade 1A recommendation (12).

Real-world data demonstrate that implementation of guideline recommendations in everyday clinical practice is poor. In the United States, for example, a large proportion of oncological VTE patients are still treated with VKA, which significantly improves the persistence with therapy compared to parenteral anticoagulation with LMWH (13,14). A study by Khorana et al. revealed a median duration of treatment of 3.3 months in the LMWH cohort and 7.9 months in the VKA cohort (14). After six months, 63% of LMWH patients had already discontinued the initially prescribed therapy, whereas this was the case in only 39% of VKA patients. A similar pattern is seen in Germany. In a survey of haematologists/oncologists, angiologists and phlebologists, only 55% of physicians reported abstaining from the use of oral anticoagulants during the phase of secondary prophylaxis of cancer-associated VTE (i.e. during the first 3–6 months) (15). Although higher costs of LMWH therapy and, particularly in the US, reimbursement aspects are possible reasons for the insufficient adherence to guidelines, consideration must also be given to the daily subcutaneous injections with painful haematoma formation and negative effects on the quality of life of oncological patients in addition to a fear of needles and a known heparin allergy or heparin-induced thrombocytopenia (HIT).

Particular mention should also be made of reports claiming that oral VKA therapy of cancer patients with VTE appears to be sufficiently effective and safe when supervised at specialised facilities aiming at the optimal adjustment of the INR (16, 17). Against this background, the market launch of direct oral anticoagulants (DOACs) led to the hope of offering patients with cancer-associated VTE a safe and effective treatment option that would combine the advantages of VKA (oral tablet intake and lower treatment costs) with those of LMWH (predictable pharmacokinetics with fast onset and a short wearing off time, and few food/drug interactions). Exploratory subgroup analyses of cancer patients included in the large approval studies have shown that DOACs may be a useful alternative to VKA in the treatment of cancer-associated VTE (18). However, the subgroups of oncological patients, each accounting for only 5–6 % of the total study population, were not comparable to the cancer patients from the large LMWH studies CLOT and CATCH with respect to severity and prognosis of the cancer. Accordingly, the transferability of the post hoc

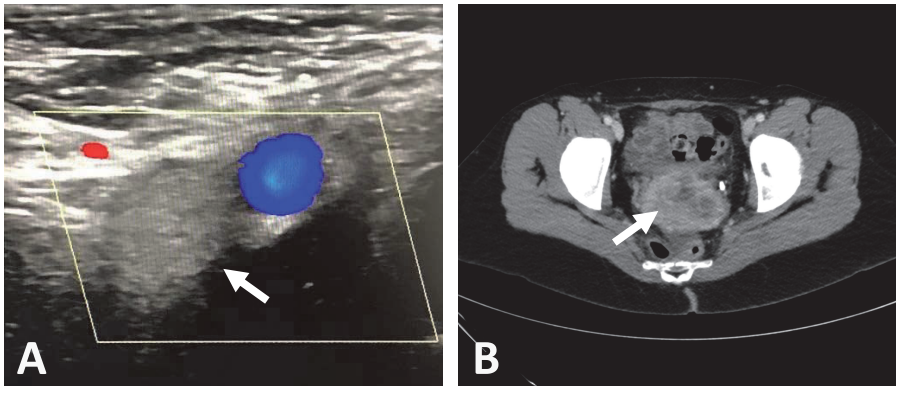

Fig. 1 Extended leg/pelvic vein thrombosis associated with cervical carcinoma: **A** The image shows an occluding thrombus in the left external iliac vein (arrow). **B** The 41-year-old female patient with squamous cell carcinoma of the cervix with an initially locally advanced tumour stage FIGO IVa (cT2b, pN1) (arrow). Only a few weeks after completion of a curatively intended combined chemoradiotherapy, pleural and mediastinal lymph node metastases were diagnosed.

analyses into daily clinical practice had to be questioned in spite of a promising indirect comparison (7, 18).

Meanwhile, the results of two prospective, randomised studies on the use of DOACs in patients with cancer-associated VTE are available, which require a closer examination against the background of the current guideline recommendations.

HOKUSAI VTE Cancer

At the end of 2017, the results of the HOKUSAI VTE cancer study were published (19). This was a prospective, randomised, open-label blinded endpoint evaluation study (PROBE design) that included adult patients with acute VTE and active cancer or cancer diagnosed in the previous two years (20). Active cancer was assumed if at least one of the following three criteria was met:

- Tumour diagnosis or therapy in the previous 6 months
- Recurrent, locally advanced or metastatic tumour stage
- Haematological neoplasia in incomplete remission

Basal or squamous cell carcinomas of the skin were not considered. Hence, the definition of active cancer in HOKUSAI VTE Cancer was comparable to that of the two large LMWH studies CLOT and CATCH (▶ Table 1). In addition to symptomatic VTE, patients could also exhibit an unexpectedly detected, incidental proximal DVT or PE in segmental or larger pulmonary arteries.

Patients received either dalteparin according to the CLOT protocol (1 x 200 IU anti-Xa/kg SC per day for 30 days followed by 1 x 150 IU anti-Xa/kg SC per day) or edoxaban 1 x 60 mg/day subsequent to a therapeutically dosed parenteral anticoagulation with LMWH for at least five days. The edoxaban dose was reduced to 1 x 30 mg/day according to the usual criteria: creatinine clearance of 30–50 ml/min, body weight ≤ 60 kg or concomitant therapy with a strong P-glycoprotein inhibitor. Randomisation of patients was stratified according to the risk of bleeding and the need for dose reduction of edoxaban. The intended treatment duration of all patients was at least six months, but whenever possible twelve months. The combined primary study endpoint was the first occurrence of recurrent VTE or major bleeds over the twelve-month observation period. The study was designed for non-inferiority.

Of the 1,050 randomised patients, 522 received edoxaban, 524 dalteparin, and four patients received no study medication. The mean age was 64 years in both groups. About two-thirds of the patients had an index event consisting of symptomatic VTE or PE with or without concomitant DVT respectively. Active cancer was present in 98% and a metastatic tumour stage in 53% of the patients. The median duration of treatment in the dalteparin arm was 184 days, which was approximately one month shorter than in the edoxaban arm (211 days). This difference was statistically significant (P = 0.0143). 38.3% of the patients treated with edoxaban and 29.4% of the patients treated with dalteparin received treatment for the entire twelve months or until the end of the study (▶ Fig. 2).

With respect to the included malignancies, 11% of the patients had a haematological neoplasia. The most common solid tumour entities were colorectal, hepatobiliary, gynaecological, bronchial, pancreatic and breast carcinomas as well as tumours of the urogenital and upper gastrointestinal (GI) tract.

The combined primary study endpoint of recurrent VTE and major bleeds over the twelve-month observation period occurred in 12.8% of patients in the edoxaban group and in 13.5% of patients in the dalteparin group, corresponding to a hazard ratio (HR) of 0.97 (95% confidence interval [CI] 0.70–1.36; P = 0.006 for non-inferiority). Consistent results were observed when considering only the first six months or only the patients receiving treatment according to protocol. Both sub-analyses were pre-specified. Hence, HOKUSAI VTE Cancer achieved the primary study objective, showing that edoxaban administered orally to patients with cancer-associated VTE is not inferior to parenteral anticoagulation with dalteparin in terms of net clinical benefit.

When the components of the primary endpoint are considered individually, VTE recurrences, particularly symptomatic events and isolated DVTs, were less common in the edoxaban group than in the dalteparin group (6.5% vs. 10.3%). In contrast, major bleeds, especially those of the upper GI tract, were more common in the edoxaban group than in the dalteparin group (6.3% vs. 3.2%).

All VTE recurrences and bleeding events over the twelve-month observation period were analysed as secondary study endpoints. In this analysis too, VTE recurrences were at 7.9% numerically less frequent in the edoxaban arm than in the dalteparin arm (11.3%), corresponding to an HR of 0.71 (95% CI 0.48–1.06; P = 0.09). The reduced rate of recurrent VTE was mainly due to a lower number of recurrent DVTs in the edoxaban group (HR 0.56; 95% CI 0.32–0.97), while the number of re-

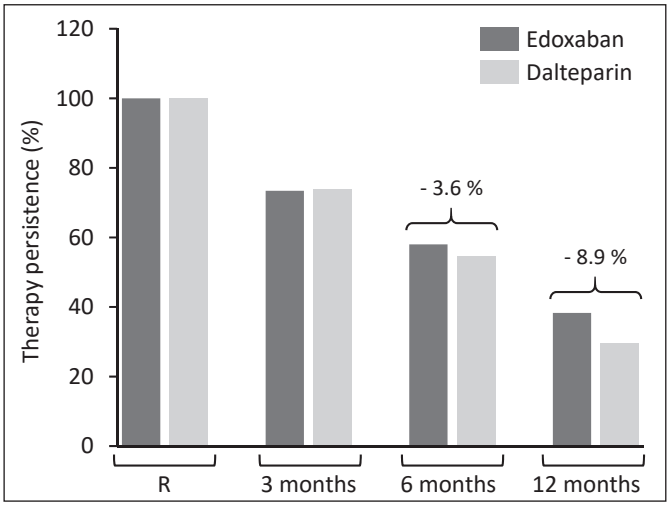

Fig. 2 Persistence with therapy in HOKUSAI VTE Cancer: proportion of patients in the edoxaban and dalteparin arm still receiving the assigned study medication at the respective timepoint (R = randomisation). Data from Raskob et al. (19).

Tab. 1 Randomised controlled trials comparing LMWH to VKA and DOACs in the therapy of cancer-associated VTE. *LMWH* = low molecular weight heparin; *VKA* = vitamin K antagonist; *DOAC* = direct oral anticoagulant; *VTE* = venous thromboembolism; *DVT* = deep vein thrombosis; *PE* = pulmonary embolism; *SD* = standard deviation; *HR* = hazard ratio; *95% CI* = 95% confidence interval. [a]Except for basaliomas and non-melanoma skin cancer. [b]Active cancer was present in 1,024 out of a total of 1,046 included patients (98%). [c]Dose reduction to edoxaban 30 mg/day if creatinine clearance 30–50 ml/min, body weight ≤ 60 kg or concomitant intake of strong P-glycoprotein inhibitors. [d]Temporal dose reduction of dalteparin if platelets < 100 x 10^9/L. [e]Interruption of therapy if thrombocytes < 50 x 10^9/L and dose adjustment or treatment interruption in case of impaired renal function. [f]Temporal dose adjustment or treatment interruption in case of thrombocytopenia or significantly impaired renal function. [g]Tumour therapy within the last 4 weeks prior to study enrolment. [h]In 6 patients, DVT was present in addition to incidental PE.

	LMWH vs. VKA		DOAC vs. LMWH	
	CLOT (Lee et al. 2003 [9])	**CATCH (Lee et al. 2015 [10])**	**HOKUSAI VTE Cancer (Raskob et al. 2018 [19])**	**SELECT-D (Young et al. 2018 [21])**
Inclusion criteria				
Cancer	Any cancer[a] diagnosed and/or treated within the last 6 months prior to study enrolment, and any cancer with a relapse or metastatic spread at study enrolment	Any cancer[a] diagnosed and/or treated within the last 6 months prior to study enrolment, any locally advanced or metastatic cancer with a relapse at study enrolment, and any haematological neoplasia not in complete remission	Any active cancer or cancer diagnosed within the last two years prior to study enrolment[a]; active cancer defined as cancer diagnosed and/or treated within the last 6 months prior to study enrolment, any relapsed, locally advanced or metastatic cancer at study enrolment, and any haematological neoplasia not in complete remission[b]	Any cancer[a] diagnosed and/or treated within the last 6 months prior to study enrolment, and any cancer with a relapse or metastatic spread at study enrolment, and any haematological neoplasia not in complete remission
Index VTE	Newly diagnosed symptomatic proximal DVT and/or PE	Newly diagnosed symptomatic proximal DVT and/or PE	Newly diagnosed symptomatic or incidental proximal DVT and/or PE	Symptomatic proximal DVT and/or symptomatic or incidental PE
Study arms	Dalteparin 200 IU/kg (maximum 18,000 IU/day) for 1 month, then 150 IU/kg vs. VKA (INR target range 2–3) initially overlapping with Dalteparin 200 IU/kg for 5–7 days	Tinzaparin 175 IU/kg vs. VKA (INR target range 2–3) initially overlapping with tinzaparin 175 IU/kg for 5–10 days	LMWH at a therapeutic dose for ≥ 5 days, then edoxaban 60 mg/day[c] vs. dalteparin 200 IU/kg (maximum 18,000 IU/day) for 30 days, then 150 IU/kgd	Rivaroxaban 2 x 15 mg/day for 3 weeks, then 20 mg/day[e] vs. dalteparin 200 IU/kg (maximum 18,000 IU/day) for 30 days, then 150 IU/kg[f]
Duration of therapy	6 months	6 months	6–12 months	6 months
Time of recruitment	1999–2001	2010–2013	2015–2016	2013–2016
Number of patients	676	900	1,046	406
Age (years), mean ± SD or median (range)	62 ± 12 / 63 ± 13	59.7 ± 12.7 / 58.8 ± 12.5	64.3 ± 11 / 63.7 ± 11.7	67 (22–87)
ECOG stage, number (percent)				
0–1	428 (63)	691 (77)	792 (76)	304 (76)
2	240 (36)	209 (23)	247 (24)	95 (24)
3	8 (1)			
Haematological neoplasia, number (percent)	70 (10)	94 (10)	111 (11)	31 (8)
Metastatic cancer, number (percent)	455 (67)	492 (55)	554 (53)	236 (58)

Tab. Continued.

	LMWH vs. VKA						DOAC vs. LMWH					
	CLOT (Lee et al. 2003 [9])			CATCH (Lee et al. 2015 [10])			HOKUSAI VTE Cancer (Raskob et al. 2018 [19])			SELECT-D (Young et al. 2018 [21])		
Tumour therapy at study inclusion, number (percent)	525 (78)			476 (53)			757 (72)[g]			282 (69)		
Incidental index VTE, number (percent)							340 (33)			213 (52)[h]		
	Dalteparin (n=336)	VKA (n=336)	HR (95% CI)	Tinzaparin (n=449)	VKA (n=451)	HR (95%-CI)	Edoxaban (n=522)	Dalteparin (n=524)	HR (95%-CI)	Rivaroxaban (n=203)	Dalteparin (n=203)	HR (95%-CI)
VTE recurrence, number (percent)	27 (8)	53 (16)	0.48 (0.30–0.77)	31 (7)	45 (10)	0.65 (0.41–1.03)	41 (8)	59 (11)	0.71 (0.48–1.06)	8 (4)	18 (9)	0.43 (0.19–0.99)
Major bleeds, number (percent)	19 (6)	12 (4)		12 (3)	11 (2)	0,89 (0.40–1.99)	36 (7)	21 (4)	1.77 (1.03–3.04)	11 (5)	6 (3)	1.83 (0.68–4.96)
Clinically relevant non-severe bleeding, number (percent)				49 (11)	69 (15)	0.58 (0.40–0.84)	76 (15)	58 (11)	58 (11)	25 (12)	7 (3)	3.76 (1.63–8.69)
Overall mortality, number (percent)	130 (39)	136 (41)		150 (33)	138 (31)	1.08 (0.85–1.36)	206 (40)	192 (37)	192 (37)	48 (24)	56 (28)	

current PEs was comparable between the treatment groups (HR 1.00; 95% CI 0.59–1.69). With regard to the secondary safety endpoints, significantly more major bleeding events were observed on anticoagulation with edoxaban (6.9%) than on anticoagulation with dalteparin (4.0%), corresponding to an HR of 1.77 (95% CI 1.03–3.04; P=0.04). The combination of major and clinically relevant non-major bleeding was also more frequent in the edoxaban arm than in the dalteparin arm (18.6% vs. 13.9%), while overall mortality was comparable in both treatment groups at 39.5% and 36.6%.

In a pre-specified analysis, major bleeding events were classified into four categories according to their medical urgency. A major bleeding event was present if at least one of the following criteria was met:

- Fatal outcome
- Transfusion of two or more units of packed red blood cells
- Decrease in the haemoglobin value by ≥ 2 g/dl
- Bleeding at a critical site (e.g., retroperitoneal, intracranial, intraocular or intraarticular bleeding)

Major bleeds of category 4 were those resulting in death prior to or immediately after hospitalisation, while major bleeds of category 3 consisted of a medical emergency (e.g. GI bleeding with haemodynamic instability or intracranial bleeding with neurological symptoms). Major bleeds of category 1 were not associated with any medical emergency, whereas major bleeds of category 2 could not be assigned to any other category. Category 3 or 4 major bleeds occurred in 2.3% (12/522) of patients treated with edoxaban and in 2.5% (13/524) of patients treated with dalteparin. Since category 1 bleeding events were not observed, the increase in major bleeds in the edoxaban group was mainly due to category 2 bleeding, which occurred in 24/522 (4.6%) vs. 8/524 (1.5%) patients. An analysis of the safety component of the primary study endpoint shows that this consisted primarily of upper GI bleedings.

Patient randomisation in HOKUSAI VTE Cancer was stratified according to the risk of bleeding. For this purpose, the following six risk factors were defined in advance:

- Surgical intervention ≤ 2 weeks earlier
- Intake of platelet inhibitors
- Primary brain tumour or brain metastases
- Locally advanced or metastatic cancer
- GI or urothelial tumour either in situ or diagnosed ≤ 6 months earlier
- Therapy with the VEGF antibody bevacizumab ≤ 6 weeks earlier

At the time of randomisation, only 17.6% of the patients in both groups had no bleeding risk, while the remaining 82.4% of patients had at least one of the six risk factors listed. A subgroup analysis shows that

patients with GI tumours taking edoxaban had a significantly higher risk of major bleeds than those receiving therapy with dalteparin (▶ Fig. 3): Major bleeds occurred in 18/136 (13.2%) patients treated with edoxaban and in 3/125 (2.4%) patients treated with dalteparin (P = 0.017).

Regarding the secondary efficacy and safety endpoints, patients without a risk of bleeding at the time of randomisation appear to benefit from treatment with edoxaban. In these patients, the VTE recurrence rate (edoxaban vs. dalteparin) was 3.3% vs. 13.0%, and the rate for major bleeds was 4.3% vs. 5.4%. In contrast, efficacy in patients with at least one bleeding risk factor at the time of randomisation was comparable between both treatment arms (8.8% vs. 10.9%), with numerically more events of major bleeds in the edoxaban group (7.4% vs. 3.7%). It should be noted, however, that this is at best an exploratory, hypothesis-generating analysis as the risk of bleeding at the time of randomisation had no significant effect on either the efficacy (P for interaction 0.064) or the safety endpoint (P for interaction 0.165).

SELECT-D

The results of the SELECT-D study are available this year in full text, in which the LMWH dalteparin administered according to the CLOT protocol was compared with the direct oral factor Xa inhibitor rivaroxaban (2 x 15 mg/day for three weeks followed by 1 x 20 mg/day for a total of six months) in patients with cancer-associated VTE (21). This was a prospective, randomised, open-label pilot study at 58 centres in the United Kingdom and Northern Ireland. The primary study objective was to determine the rate of VTE recurrence in patients receiving anticoagulation with rivaroxaban as a basis for a subsequent definitive phase-3 study. Following initial randomisation (dalteparin vs. rivaroxaban), the study envisaged a second randomisation after six months: patients with PE as index event or a relevant residual thrombosis were to receive either placebo or rivaroxaban 1 x 20 mg/day for a further six months in a blinded fashion. So far, only the results for the first part of the study are available.

Originally, the aim of the SELECT-D trial was to include 530 patients with active cancer and symptomatic proximal DVT, symptomatic PE or incidental PE. Because of slow recruitment, the number of cases was corrected during the study to 400 patients (200 patients per treatment arm). Randomisation was stratified according to tumour stage, platelet count (≤ 350 vs. > 350 x 10^9/L), type of VTE (symptomatic vs. incidental PE), and thrombogenicity of the primary tumour (high vs. low risk of recurrent VTE). SELECT-D allowed therapeutic anticoagulation for 96 hours prior to study inclusion, while concomitant therapy with strong inhibitors or inducers of CYP3A4 or P-glycoprotein was not allowed.

A total of 406 patients (203 patients per treatment arm) were included in the study between September 2013 and December 2016. The median age was 67 years in both groups. 58% of the patients in each group had a metastatic tumour stage and slightly more than half had incidental PE as the index event. Similar to HOKUSAI VTE Cancer, about 90% of the patients in SELECT-D had a solid tumour and only

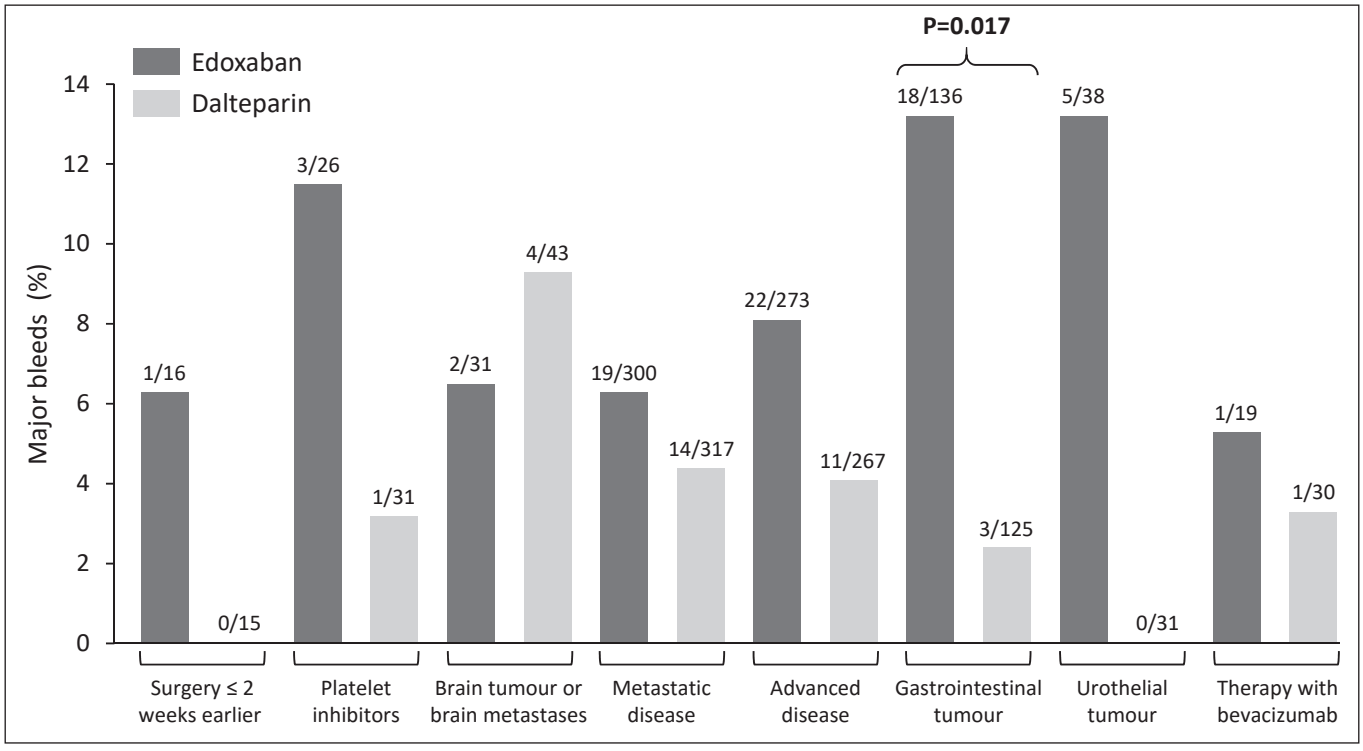

Fig. 3 Subgroup analysis of the frequency of major bleeds in HOKUSAI VTE Cancer. The figure shows the proportion of patients with major bleeds in the edoxaban and dalteparin arm as a function of the presence of a pre-specified risk factor. The analysis is based on the safety population (all randomised patients who received at least one dose of the study medication). The P value indicates a significant interaction between the risk factor "gastrointestinal tumour" and the occurrence of major bleeds as a function of the assigned therapy. Data from Raskob et al. (19).

about 10% had haematological neoplasia (e.g. CLL, myeloma or lymphoma). The median duration of treatment was 5.8 months in the dalteparin group and 5.9 months in the rivaroxaban group. The share of patients who reported at least one missed dose was slightly higher for DOAC (27%) than for LMWH (22%).

Over the six-month treatment period, recurrence of VTE was observed in 8 patients of the rivaroxaban group and in 18 patients of the dalteparin group, corresponding to a cumulative VTE recurrence rate (rivaroxaban vs. dalteparin) of 4% (95% CI 2–9%) vs. 11% (95% CI 7–16%) and a HR of 0.43 (95% CI 0.19–0.99). With regard to VTE recurrence events, particularly fewer DVTs (3 vs. 7) and fewer incidental PEs (1 vs. 6) were observed in the rivaroxaban group. Predictive risk factors for VTE recurrence were location of the primary tumour (HR 5.6 for gastric/pancreatic carcinoma and HR 2.7 for lymphoma, gynaecological malignancies or pulmonary/bladder carcinoma vs. other tumours) and the type of index VTE (HR 2.8 for symptomatic VTE vs. incidental PE).

Major bleeds occurred in 11 patients in the rivaroxaban group and in 6 patients in the dalteparin group, corresponding to a cumulative bleeding rate (rivaroxaban vs. dalteparin) of 6% (95% CI 3–11%) vs. 4% (95% CI 2–8%) and HR of 1.83 (95% CI 0.68–4.96). The major bleeds consisted mainly of bleeding from the upper or lower GI tract. Particularly patients with (gastro)oesophageal tumours had an increased risk of bleeding when taking rivaroxaban. In these patients, major bleeds were observed in 1/19 (5%) patients of the dalteparin group and in 4/11 (36%) patients of the rivaroxaban group. Based on an interim analysis after the first 220 patients, patients with these tumour localisations were excluded from further recruitment.

The cumulative rate for clinically relevant non-major bleeding was 4% (7 events) in the dalteparin group and 13% (25 events) in the rivaroxaban group, corresponding to a HR of 3.76 (95% CI 1.63–8.69). These events consisted mainly of GI or urothelial bleeds. In terms of overall survival, there was no difference between the treatment groups, with 70% (dalteparin) and 75% (rivaroxaban).

In the SELECT-D trial, a total of 143 patients had a tumour in the area of the oesophagus, gastroesophageal junction stomach, colon or rectum. More clinically relevant bleedings were observed in the rivaroxaban than in the dalteparin group in this subgroup of patients with GI tumours (▶ Fig. 4).

Meta-analysis HOKUSAI VTE Cancer and SELECT-D

In a meta-analysis, the results of the HOKUSAI VTE Cancer and SELECT-D studies were summarised taking the first six months of therapy into account (22). This analysis revealed a strong trend in favour of the two factor Xa inhibitors (HR 0.65; 95% CI 0.42–1.01) compared to dalteparin in preventing VTE recurrence associated with a significant increase of major bleeds (HR 1.74; 95% CI 1.05–2.88). Clinically relevant non-severe bleeding was also more frequent in patients taking DOAC than in those receiving LMWH therapy, with an HR of 2.31 (95% CI 0.85–6.28), while after six months there was no difference in total mortality between the treatment groups (DOAC vs. LMWH) (HR 1.03; 95% CI 0.85–1.26).

Discussion and conclusion for practice

Although the dosing regimens of edoxaban and rivaroxaban are fundamentally different, the first two large randomised DOAC studies HOKUSAI VTE Cancer and SELECT-D show consistent results. According to these studies, although intake of DOACs is associated with improved efficacy, at the same time it also bears an increased risk of bleeding. These conflicting efficacy and safety data make it difficult to integrate the study results in daily clinical practice.

Despite the previous comments on the need for an optimal adjustment of the INR, the improved efficacy of LMWH over VKA is well established and forms the base for the current guideline recommendations. Nevertheless, the rate of VTE recurrence in patients with active cancer receiving LMWH therapy is still graded as unacceptably high. In CLOT, the rate of VTE recurrence in patients receiving dalteparin was 8.0% (27/336) after six months; in the HO-

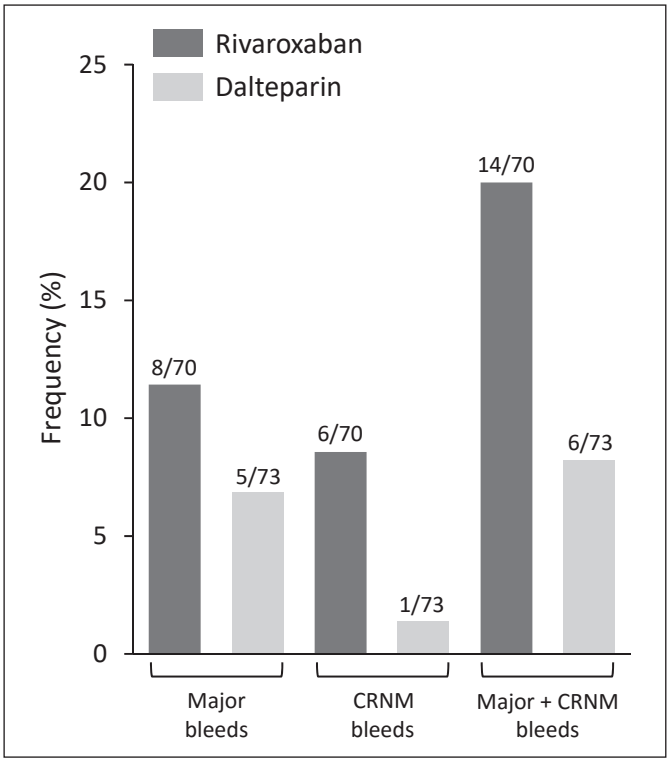

Fig. 4 Frequency of clinically relevant bleeding in patients with gastrointestinal tumours in SELECT-D. Shown is the frequency of major and clinically relevant non-major (CRNM) bleeding in patients who at the timepoint of randomisation suffered from a tumour in the region of the oesophagus or the gastroesophageal junction (n=30), the stomach (n=11) or the colon/rectum (n=102). Data from Young et al. (21).

KUSAI VTE Cancer study it was 8.8% (46/524), and in the SELECT-D study 8.9% (18/208). These consistent event rates in the dalteparin arms show that the studies of the included cancer patients are comparable, even though there are almost 15 years between the recruitment of the CLOT study and that of the two DOAC studies (▶ Table 1).

The reduction of the dalteparin dose to 75–80% of the initial dose after 30 days is cited as a possible explanation for the improved efficacy of DOACs. This raises the question of whether a comparison of edoxaban with tinzaparin, administered according to the CATCH protocol at a therapeutic dose throughout the six months, would have led to similar results. However, a closer look at the timing of VTE recurrence in HOKUSAI VTE Cancer shows that the event curves for this secondary efficacy endpoint diverge no earlier than after > 90 days, although the risk of thromboembolic recurrence in cancer patients is known to be increased particularly in the first 1–2 months after the onset of the index VTE (1–3). In HOKUSAI VTE Cancer, the proportion of patients with < 3 months of therapy is almost identical between the two treatment arms, with 26.6% (edoxaban) and 26.1% (dalteparin). Only thereafter does the dalteparin group show a higher dropout rate (▶ Fig. 2). The inconvenience of drug administration as a reason for permanent treatment discontinuation was reported more than three times more often in the dalteparin group (14.9%) than in the edoxaban group (4.0%). Hence, lower persistence with therapy could, in principle, be considered as the cause of the reduced efficacy of LMWH therapy in the HOKUSAI VTE Cancer study. According to this interpretation, DOAC intake would be more efficient, but not necessarily more effective than subcutaneous LMWH injections. Or put another way: the reduced rate of VTE recurrence in patients receiving edoxaban is based more on an easier-to-implement treatment concept than on an improved pharmacodynamic effect. Another reason, however, could be the required adjustment of the dalteparin dose for platelet values of 50–100 x 10^9/L, while the administration of edoxaban at the standard dose was allowed up to a platelet count of 50 x 10^9/L.

It is interesting to note that in the HOKUSAI VTE Cancer study the event curves for the secondary safety endpoint "major bleeds" already diverge after only about ten days. By that time, the majority of patients in the edoxaban arm had already been switched to the DOAC: the median duration of the initial LMWH therapy was five days.

From these observations, the recommended action for daily practice in a patient with cancer-associated VTE and at least one of the six bleeding risk factors would be to perform the anticoagulation over the first 4–12 weeks first with LMWH and to monitor the patient with particular care with regard to any symptoms of bleeding. With good tolerability, the switch to edoxaban would then be possible, especially since the duration of the initial LMWH therapy in the HOKUSAI VTE Cancer study was at the discretion of the study investigator. While patients with no risk of bleeding benefit from the improved persistence with oral therapy, long-term LMWH therapy is an effective and safe option for patients at risk of bleeding, provided that they are convinced of the benefits of parenteral drug administration and adhere to it consistently (23).

In the SELECT-D study, the reduced rate of VTE recurrence in patients taking rivaroxaban cannot be attributed to a higher treatment dropout rate in the LMWH group, as the median duration of treatment was comparable between both treatment arms. This leads to the hypothesis that high-dose therapeutic anticoagulation with the direct oral factor Xa inhibitor over the first three weeks resulted in a particularly effective and sustained control of the paraneoplastic coagulation processes. It is important to note that especially this initial phase of therapy was not associated with a dramatic increase in major bleeds.

Similar to HOKUSAI VTE Cancer, SELECT-D patients with tumours of the upper or lower GI tract had an increased risk of bleeding when taking DOACs (▶ Figs. 3 and 4).

In this regard, a possible source of bleeding may be either the intraluminally growing tumours themselves or therapy-induced mucosal lesions in the GI tract, e.g. toxic mucositis after treatment with 5-fluorouracil. Based on current knowledge, these patients appear to be unsuitable for DOAC therapy, just as patients with urothelial carcinoma of the bladder. In the SELECT-D study, 6/10 (60%) patients with the latter tumour entity experienced clinically relevant bleeding while taking rivaroxaban, whereas this was observed in 1/4 (25%) patients in the dalteparin group. In HOKUSAI VTE Cancer, major bleeds (edoxaban vs. dalteparin) occurred in 5/38 (13%) vs. 0/31 (0%) patients with urothelial tumours (▶ Fig. 2).

HOKUSAI VTE Cancer and SELECT-D demonstrate that oral anticoagulation with edoxaban or rivaroxaban is an alternative to guideline-compliant LMWH therapy in patients with cancer-associated VTE. This conclusion is supported by several smaller observational studies (22). However, careful selection under consideration of patient preference and specific tumour characteristics is necessary in order to translate the respective advantages and disadvantages of oral and parenteral anticoagulants into an optimal clinical net benefit in terms of individualised therapy.

Conflict of interest

MV received travel reimbursements from Bristol-Myers Squibb and LEO Pharma. JY declared no conflict of interest. FL received consultancy and/or lecturing fees and travel reimbursements from the following companies: Aspen, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma, Pfizer and Sanofi.

Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

References

1. Levitan N, Dowlati A, Remick SC et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999; 78(5): 285–291.
2. Prandoni P, Lensing AW, Piccioli A et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients

with cancer and venous thrombosis. Blood 2002; 100(10): 3484–3488.
3. Monreal M, Falgá C, Valdés M et al. Riete Investigators. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2006 Sep;4(9):1950–1956.
4. Bauersachs R. [Prolonged Secondary Prevention After Venous Thromboembolism]. Dtsch Med Wochenschr 2018; 143(3): 137–142.
5. Lee AYY. Overview of VTE treatment in cancer according to clinical guidelines. Thromb Res 2018; 164(Suppl 1): S162–S167.
6. Carrier M, Cameron C, Delluc A, Castellucci L, Khorana AA, Lee AY. Efficacy and safety of anticoagulant therapy for the treatment of acute cancer-associated thrombosis: a systematic review and meta-analysis. Thromb Res 2014; 134(6): 1214–1219.
7. Posch F, Konigsbrugge O, Zielinski C, Pabinger I, Ay C. Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants. Thromb Res 2015; 136(3): 582–589.
8. Kahale LA, Hakoum MB, Tsolakian IG et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. Cochrane Database Syst Rev 2018; 6: CD006650.
9. 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(2): 146–153.
10. Lee AY, 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(7): 677–686.
11. Kearon C, Akl EA, Ornelas J et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149(2): 315–352.
12. Farge D, Bounameaux H, Brenner B et al.Inter national clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol 2016; 17(10): e452-e466.
13. Khorana AA, Yannicelli D, McCrae KR et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 2016; 145: 51–53.
14. Khorana AA, McCrae KR, 15.Milentijevic D et al. 18. Current practice patterns and patient persistence with anticoagulant treatments for cancer associated thrombosis. 20. Res Pract Thromb Haemost 2017; 1: 14–22.
15. 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(4): 194–201.
16. Bona RD, Sivjee KY, Hickey AD, Wallace DM, Wajcs SB. The efficacy and safety of oral anticoagulation in patients with cancer. Thromb Haemost 1995; 74(4): 1055–1058.
17. Marshall AL, Campigotto F, Neuberg D, Rowe B, Connors JM. Recurrence of Venous Thromboembolism in Patients With Cancer Treated With Warfarin. Clin Appl Thromb Hemost 2015; 21(7): 632–638.
18. Voigtlaender M, Langer F. Direct oral anticoagulants for the treatment of cancer-associated venous thromboembolism. What do we know so far? Hamostaseologie 2017; 37(4): 241–255.
19. Raskob GE, van Es N, Verhamme P, et al. Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018; 378(7): 615–624.
20. van Es N, Di Nisio M, Bleker SM, et al. Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study. Thromb Haemost 2015; 114(6): 1268–1276.
21. 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(20): 2017–202322..
22. 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 (Epub ahead of print)
23. Voigtlaender M, Langer F. A case-based practical approach to the management of cancer-associated venous thromboembolism. Vasa 2018; 47(2): 77–89.