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Bleeding complications during anticoagulant treatment in patients with cancer

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ABSTRACT

Patients with cancer have an increased risk of bleeding complications, of which some are fatal. This risk is influenced by chemotherapy, cancer type and stage, thrombocytopenia, renal function, and previous bleeding. Since many cancer patients receive anticoagulant treatment for prophylaxis or treatment of venous thromboembolism (VTE), bleeding complications are a challenge in clinical practice. This review article focuses on the overall bleeding risk of cancer patients and the risk of major and clinically relevant bleeding associated with anticoagulant treatment, such as vitamin K antagonists, LMWH and the direct oral anticoagulants. It also describes strategies for individual risk assessments.

Introduction

Many patients with cancer receive some form of anticoagulant treatment. This may consist of thromboprophylaxis to prevent the occurrence of venous thromboembolism (VTE) or anticoagulant treatment for acute VTE. Cancer itself is associated with an increased risk of bleeding, for instance due to thrombocytopenia induced by chemotherapy. Furthermore, patients with a malignancy who receive anticoagulant treatment have a higher bleeding risk than patients without cancer. This leads to a challenging situation in clinical practice for physicians who treat cancer patients.

In this article we have summarised the current literature on the relation between bleeding and cancer, especially in patients who receive anticoagulation. We will describe the bleeding risk of the different anticoagulants, including the direct oral anticoagulants.

Bleeding complications in cancer patients without anticoagulation

Data on "spontaneous" bleeding rates in cancer patients are scarce. Most of the available data are derived from randomized trials investigating thromboprophylaxis against placebo, where often patients with bleeding risk are excluded, or VTE treatment studies, where placebo control patients are lacking. Furthermore, epidemiological data on the bleeding risk often lack standardization of bleeding definition.

The overall risk of clinically relevant bleeding in patients with advanced cancer has been estimated to be around 10% [1]. A recent study evaluated the rates of bleeding in more than 25,000 chemotherapy patients with a range of solid tumors using a retrospective analysis of the United States IMPACT health care claims database. In this analysis, chemotherapy patients who developed VTE had an excessive risk of major bleeding (11.0% at 3.5 months and 19.8% at 12 months), but major bleeding complications were also high for chemotherapy patients without VTE (3.8% within 3.5 months and 9.6% within 12 months of starting chemotherapy) [2]. Therefore, the baseline risk of cancer patients seems significantly higher than suggested by the comparatively low rates seen in patients selected for randomized interventional trials.

The manifestation of bleeding in cancer may present as a localized bleeding diathesis as a result of local injury by tumor invasion or as a generalized hemorrhagic diathesis. In addition to the known bleeding risk factors such as age, stroke or impaired renal function, cancer patients exhibit specific risk factors which include

- ulcerating or actively bleeding solid tumors such as gastric, neck or lung cancer [2,3]
- thrombocytopenia [4]
- platelet dysfunction [5]
- acquired von Willebrand syndrome, coagulation factor deficiencies or presence of inhibitors [6,7]
- mucositis [8]
- hyperfibrinolysis in hematologic malignancies or tumor lysis syndrome [9]
- disseminated intravasal coagulation [10]
- cancer surgery [11,12]
- intracerebral metastases [13]
- acute myeloid leukaemia [14]
- hematopoietic stem cell transplantation, especially with graft versus host reaction [15]
- myelosuppressive chemotherapy [2]
- use of VEGF receptor tyrosine-kinase inhibitors [16]

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Table 1
Efficacy and safety of LMWH thromboprophylaxis in outpatients receiving chemotherapy for cancer with increased VTE risks.

Trial	Drug	Comparator	Cancer type	Rate of VTE with prophylaxis	Rates of major bleeding with prophylaxis	NNH (major bleeding) with prophylaxis vs. placebo
PROTECHT [17] (n=1150)	nadroparin	placebo	Solid tumors	2.0%	0.7%	~142
FAMOUS [18] (n=385)	dalteparin	placebo	Solid tumors	2.4%	0.5%	~200
SAVE-ONCO [19] (n=1608)	semuloparin	placebo	Solid tumors	1.2%	1.2%	~1000
Maraveyas [20] (n=119)	dalteparin	placebo	Pancreatic cancer	3.4%	3.4%	~500
PROSPECT-CONKO [21] (n=312)	dalteparin	placebo	Pancreatic cancer	5%	Not reported	Not reported
PRODIGE [22] (n=186)	dalteparin	placebo	glioma	9%	5.1%	~25
Palumbo [23] (n=659)	enoxaparin	VKA or aspirin	myeloma	5.0%	0%	n.a. (active control)
Palumbo [24] (n=342)	enoxaparin	aspirin	myeloma	1.2%	0%	n.a. (active control)
INPACT [25] (n=503)	nadroparin	placebo	Solid tumors	not assessed	4.1%	~166
Klerk [26] (n=302)	nadroparin	placebo	Solid tumors	not assessed	3.0%	~50
Sideras [27]	LMWH	placebo/SOC	Solid tumors	6%	3%	n.a. (active control)

VTE= venous thromboembolism, LMWH= low-molecular weight heparin, VKA= Vitamin-K antagonists, SOC = standard of care, NNH = number needed to harm, n.a. = not applicable

Bleeding in cancer patients who receive thromboprophylaxis

Thromboprophylaxis in cancer patients consists mainly of subcutaneous low-molecular weight heparin (LMWH). Table 1 lists LMWH prophylaxis trials in outpatients receiving chemotherapy for cancer subtypes with increased thromboembolic risk. As indicated, even with LMWH prophylaxis, rates of VTE were around 5 to 10%. On the other hand, rates of major bleedings in these trials were only 0-5%. However, it has to be considered that in these trials patients at high risk for bleeding were excluded. Therefore, bleeding risks outside of clinical trials could be considerably higher which may affect the benefit-risk ratio.

Two recent meta-analyses on the risks and benefit of outpatient thromboprophylaxis during chemotherapy pooled data from 9 randomized trials and 3538 patients [28] and 11 randomized trials and 7805 patients [29], respectively. In these analyses, LMWH significantly reduced the incidence of symptomatic VTE (OR 0.5-0.6) when compared with inactive control. On the other hand, both analyses consistently demonstrated a 60% increase in major bleeding with LMWH. Across trials, rates of major bleedings (of note: different definitions used!) ranged between 0 and 5% (Table 1) and numbers needed to harm ranged between 25 and 1000, clearly indicating the large variability of VTE and bleeding risks between different cancer types and therapies. Based on these and other data, thromboprophylaxis is not generally recommended for outpatients receiving chemotherapy [30,31], but should be considered in high-risk situations such as chemotherapies containing antiangiogenetic agents, if bleeding risk is low [30].

In contrast to ambulatory cancer patients, LMWH prophylaxis is recommended for most hospitalized cancer patients [11,31,32], as these patients are usually immobilized, have central venous catheters and undergo surgery, radiation or intense chemotherapy. All of these factors significantly increase the thromboembolic risks, but many of them are equally associated with bleeding complications. As a consequence, rates, severity and management of bleeding complications are highly variable and a careful risk-benefit evaluation has to be made for every patient.

For non-surgical cancer patients, the benefit of in-hospital thromboprophylaxis has not been studied in detail recently but has been demonstrated in subgroup analyses from several prospective trials such as MEDENOX [33] and CERTIFY [34]. However, non-surgical including cancer patients exhibit significant bleeding risk factors [35] and the indication, type and dosage of in-hospital thromboprophylaxis should reflect the individual risk profile. Current guidelines recommend mechanical prophylaxis over LMWH in patients with increased bleeding risks [31]. While extended VTE prophylaxis may be considered for some cancer patients, the risk of bleeding may outweigh the benefit in the post-discharge phase, since three recent trials demonstrated a significant increase of bleeding risks in post-discharge non-surgical patients [36-38]. Of note, only few patients with active cancer were included in these trials.

After cancer surgery, bleeding complications are also common. In the @RISTOS study [12], which evaluated the efficacy and safety of VTE prophylaxis in 2373 patients undergoing cancer surgery until day 30±5 post discharge the rates of bleeding complications (not classified) was 9% and half of these patients required blood transfusions. Interestingly, in the majority of cases (69.7%), bleeding was considered “expected” by the treating physician and rates of fatal bleeding were low with 0.12%.

It is difficult to estimate the current impact of LMWH prophylaxis in surgical cancer patients, since placebo-controlled trials in this population have been obsolete for at least two decades (Table 2). However, the VTE risk in this population is excessively high and can be significantly reduced by pharmacological interventions. Therefore, the benefit of LMWH prophylaxis by far outweighs the potential increase in bleeding risk and current guidelines, therefore, strongly recommend thromboprophylaxis [11,43].

Bleeding in cancer patients who receive therapeutic anticoagulant treatment

In patients with cancer the most common reason to use anticoagulant treatment is acute VTE [43]. Although guidelines recommend long-term treatment with LMWH for acute VTE in cancer patients, many patients still receive VKA. A recent international survey among medical specialists analysed the preferences for long-term anticoagulant treatment for VTE in cancer patients [44]. LMWH was indicated as the first choice for the long-term treatment by 82% of the respondents, of whom 60% used full therapeutic doses and 40% chose a dose reduction. When continuing anticoagulants beyond six months, 44% of respondents preferred LMWH, 10% VKA, while the remaining 45% chose per individual patient for either LMWH or VKA. So, in clinical practice both LMWH and VKA are prescribed for cancer and VTE, and the dose of LMWH varies from full-therapeutic to supra-prophylactic. Furthermore, many clinicians experience

Table 2
Efficacy and safety of LMWH thromboprophylaxis in hospitalized cancer patients

Trial	Drug	Comparator	Cancer type	Rate of VTE with prophylaxis	Rates of major bleeding with prophylaxis	NNH (major bleeding) with prophylaxis vs. placebo
Sakon [39] (n=164)	enoxaparin	IPC	Abdominal cancer surgery	1.2%	4.6%	~50
Simonneau [40] (n=1288)	nadroparin	enoxaparin	colorectal cancer surgery	12.6-15.9%	7.3-11.5%	n.a. (active control)
ENOXACAN [41] (n=631)	enoxaparin	UFH	Abdominal/pelvic cancer surgery	14.7-18.2%	4.1%	n.a. (active control)
ENOXACAN-II [42] (n=332)	enoxaparin 28d	enoxaparin 6-10d	Abdominal/pelvic cancer surgery	5-12%	1.2%	n.a. (active control)
MEDENOX [33] cancer subgroup (n=118)	enoxaparin	placebo	Acutely ill medical patients with active cancer	9.7%	Not reported	Not reported
CERTIFY [34] cancer subgroup (n=274)	certoparin	UFH 5000 t.i.d.	Acutely ill medical patients with active cancer	4.5%	0.75%	n.a. (active control)

VTE= venous thromboembolism, UFH= unfractionated heparin, IPC= intermittent pneumatic compression, NNH = number needed to harm, n.a. = not applicable

bleeding complications of anticoagulant treatment in cancer patients: Bleeding as side effect was reported by 19% of the respondents for LMWH and 79% for VKA [44].

Vitamin K antagonists

As earlier mentioned, bleeding risk is increased in patients with cancer, and this is further enhanced by anticoagulant treatment. Three studies, published about a decade ago, analysed the bleeding risk of cancer patients who were treated with VKA for acute VTE. The first study was a retrospective analysis of two randomized controlled trials, with a total of 1421 patients with acute VTE, of whom 262 patients had a malignancy [45]. Malignancies were commonly located in the genitourinary tract (29%), the gastrointestinal tract (19%), and in the breast (15%). The mean age of patients with a malignancy was 66 years and 18% had a pulmonary embolism, compared to 59 years and 19% in the VTE patients without cancer, respectively. Half of the patients were male. Mean duration with VKA was 73 and 82 days in the cancer and non-cancer group, respectively. A total of 12 (0.8%) major bleedings occurred, 7 (2.7%) in patients with cancer. The overall incidence of major bleeding was 13.3 per 100 patient-years (95% CI, 5.4-27.5) for patients with malignancy and 2.1 per 100 patient-years (95% CI, 0.7-5.0) for patients without malignancy (rate ratio, 6.2; 95% CI, 2.0 to 19.7). In the second, prospective cohort study, 842 patients with acute DVT were analysed, of which 181 (21%) patients had cancer, most often genitourinary (26%), gastrointestinal (20%), and breast (15%) [46]. Patients with cancer had a mean age of 64 years compared to 60 years in the non-cancer patients. Half of the patients were male. The median duration of anticoagulation was 224 days (range, 4-360 days) in patients with cancer and 90 days (range, 3-360 days) in those without. Major bleeding occurred in 17 of the 181 (9.4%) patients with cancer (15.7/100 patient-years), and in 23 of the 661 (3.5%) patients without cancer (8.6/100 patient-years) (hazard ratio 2.2, 95% CI 1.2-4.1). Among patients with cancer, the frequency of major bleeding per 100 patient-years was 42.8, 19.1, and 3.4 in patients with extensive, moderately extensive, and less-severe cancer, respectively. The third study analysed 833 patients with VKA, 95 with cancer [47]. Most patients were treated for less than 6 months. Major bleeding occurred in 5.4% of the cancer patients and in 0.9% of the non-cancer patients. Taken together, these three studies, the largest cohort studies of patients with cancer and VTE treated with VKA, show a 2-6 fold increased risk of VKA-related major bleeding of cancer patients as compared to patients without cancer. Notably, in all these studies the number of patients with major bleeding events was low, which affects the precise estimation of the bleeding rate and makes analysis of risk factors for bleeding, such as chemotherapy and cancer site, difficult.

LMWH

Four randomised controlled trials (RCT) assessed the efficacy and bleeding risk of treatment with LMWH compared to VKA in patients with active cancer [48-51]. These studies varied from 101 to 673 patients with acute VTE and cancer. In all four studies a therapeutic dose of LMWH was given, 1-1.5 mg/kg enoxaparin for three months [48], tinzaparin 175 aXa/kg for 6 months [49], dalteparin 200 mg/kg for one month followed by 150 mg/kg for 5 months [50], and enoxaparin 1.5 mg/kg for three months [51]. In all studies, VKA, most often warfarin, was the comparator treatment arm, with a target INR of 2 to 3. The incidence of major bleeding varied in the four RCTs, but was not significantly different in either study. A total of 576 patients were treated with LMWH and 544 with VKA. 37 (6.4%) major bleeding events occurred with LMWH and 32 (5.9%) with VKA (pooled HR 1.05, 95% CI 0.53-2.10) (Figure 1a) [52]. The risk of minor bleeding was 16% with LMWH and 17.3% with VKA (pooled HR 0.85, 95% CI 0.53-1.35) (Figure 1b) [52]. Mortality rate was also not different between LMWH and VKA. In conclusion, based on four RCTs with over 1000 patients with cancer and VTE, major bleeding risk is around 6%, and not different between LMWH or VKA, when they are treated for 3-6 months, which is essentially the same as the bleeding rate of VKA in the cohort studies. Further data on bleeding risk in cancer patients with acute VTE is expected from the large Comparison of Acute Treatments in Cancer Haemostasis (CATCH; NCT01130025), a multinational, Phase III, open-label, randomised controlled trial comparing tinzaparin 175 IU/kg once daily for 6 months with warfarin, which recently has completed the inclusion of 900 patients [53].

In the RIETE registry, 3805 patients with cancer and acute VTE were analysed for bleeding complications. [54]. In this observational registry, 49% of the patients were treated with LMWH and 43% with VKA. In the first three months of anticoagulant treatment, a major bleeding occurred in 156 (4.1%) of the patients. 109 patients had a bleeding in the first month of treatment. 47% of the patients had a gastrointestinal bleeding, 19% genitourinary, and 8% had a cerebral bleeding. No less than 29% of these patients died due to the bleeding. Most

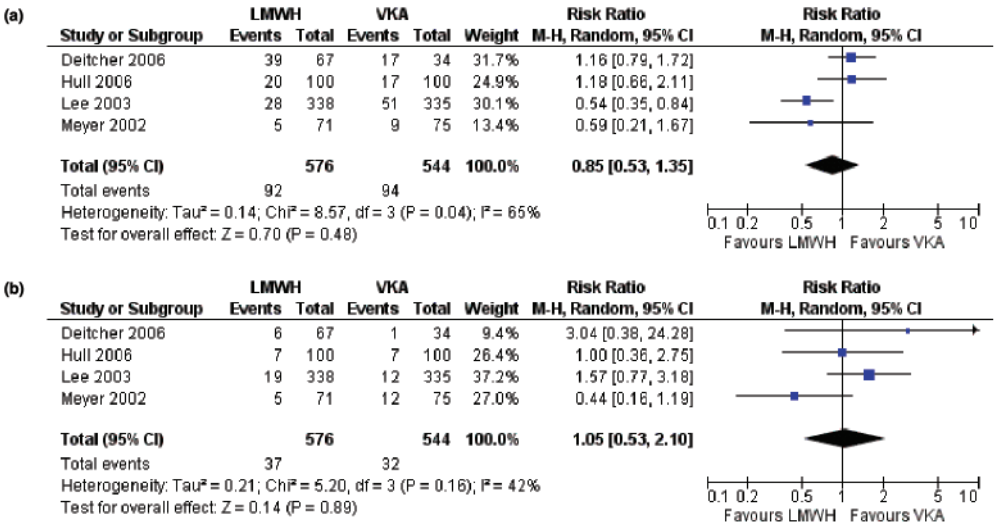

Fig. 1. Pooled analysis of the bleeding risk of LMWH and VKA in patients with cancer [52]. (a) Minor bleeding. (b) Major bleeding.

patients with a major bleeding had metastases. Although direct comparison between LMWH and VKA is difficult in this registry, and is likely subject to differences in patient characteristics, VKA seemed to be associated with less bleeding than LMWH: of the patients with major bleeding, 47% used long-term LMWH and 29% VKA. It is not clear from the study whether bleeding events during initial treatment with LMWH were included in the VKA treatment arm. There was also no information on specific cancer treatment.

Recently, the long-term safety of dalteparin was assessed in the single arm Daltecan study in patients with cancer and acute VTE [55]. The regimen of dalteparin dose followed the Clot study: dalteparin 200 IU/kg daily subcutaneously for 1 month, followed by 150 IU/kg daily for subsequent 11 months. 334 patients with VTE and active cancer were treated with dalteparin, of whom 185 (55.4%) completed six months of therapy and 109 (33%) completed 12 months. 92% of the patients had solid tumors, with lung (16.8%), breast (9.3%), or pancreas (9.3%). The overall major bleeding rate during one year treatment was 10.2%. The highest major bleeding rate occurred in the first month of dalteparin therapy at 3.6%, with a frequency declining to 1.1% during months 2-6, and 0.7% over months 7-12, with no statistically significant difference in rates between months 2-6 and 7-12 (p=0.39). 154 patients died, two due a fatal bleeding. This large study shows that the risk of major bleeding with LMWH in cancer patients with VTE is 10% per year, and prolonged therapy beyond 6 months seems associated with a decrease in bleeding compared to the initial period of therapy.

Direct oral anticoagulants

There are no large studies with the direct oral anticoagulants (DOAC) in cancer patients with VTE. In the phase II apixaban study, 125 non-VTE patients with advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian or prostate cancers, cancer of unknown origin, myeloma or selected lymphomas, were randomized to 5 mg, 10 mg or 20 mg once daily of apixaban or placebo in a double-blind manner for 12 weeks [56]. Two (2.2%) patients on apixaban had a major bleeding and four (4.3%) patients suffered from clinically relevant non-major bleeding, so 6.5% of the patients had a clinically relevant bleeding (CRB) (combination of major and clinically relevant non-major bleeding). The study was too small to assess the relation between bleeding and dose of apixaban.

Today, phase III studies in acute VTE have been published for four different DOACs: the direct thrombin inhibitor dabigatran [57], and the direct factor Xa inhibitors rivaroxaban [58,59], apixaban [60], and edoxaban [61]. In all these studies a DOAC was compared to VKA, most often warfarin, with a target INR of 2-3. Patients with active cancer could be included in these studies, but at the discretion of the treating physician. Although the percentage of cancer patients in these trials is relatively limited, important information on major and clinically relevant non-major bleeding can be retrieved. In the two RECOVER studies, all patients received initial LMWH treatment for at least 5 days, followed by 6 months of either dabigatran 150 mg bd or warfarin. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment, any treatment for cancer within 5 years before enrolment or recurrent or metastatic cancer [62]. A total of 5107 patients was included, of whom 357 (7%) had cancer. Patients were treated for 6 months. 6/159 (3.8%) of the cancer patients randomised to dabigatran 150 mg bd and 7/152 (4.6%) on warfarin developed a major bleeding (HR 0.60; 95% CI 0.36-0.99). CRB occurred in 23 of the 159 (14.5%) of the patients with dabigatran and in 20/152 (13.2%) patients with warfarin (HR 1.12; 95% CI 0.59-2.13). The bleeding rate was clearly higher in cancer patients compared to non-cancer patients in both treatment groups (major bleeding 0.8% and 1.4%, CRB 3.7% and 7.3%, with dabigatran and warfarin, respectively). No bleeding rates of cancer patients are published so far for the dabigatran extension studies.

Rivaroxaban was analysed in the two Einstein studies [58,59]. In the Einstein-DVT study, 118/1731 (6.8%) patients with cancer were randomised to rivaroxaban 15 mg bd for three weeks, followed by 20 mg od, and 89/1718 (5.2%) cancer patients to VKA [58]. All patients had acute DVT of the legs and were treated for 3-12 months. Major bleeding rate in cancer patients is not specified in the article. CRB rate was 17/118 (14.4%) for rivaroxaban, and 14/88 (15.9%) for VKA (HR 0.91, 95% CI 0.42-1.94). This bleeding rate was 7.6% in the patients without cancer in both groups. No bleeding rates for cancer patients are published for the Einstein-extension study. The design of the Einstein-PE study in patients with acute PE was similar to the Einstein-DVT study [59]. 114/2419 (4.7%) patients with cancer were randomised to rivaroxaban and 109/2413 (4.5%) cancer patients to VKA. Major bleeding rate in cancer patients was again not specified in the article. CRB rate of the two studies was 14/114

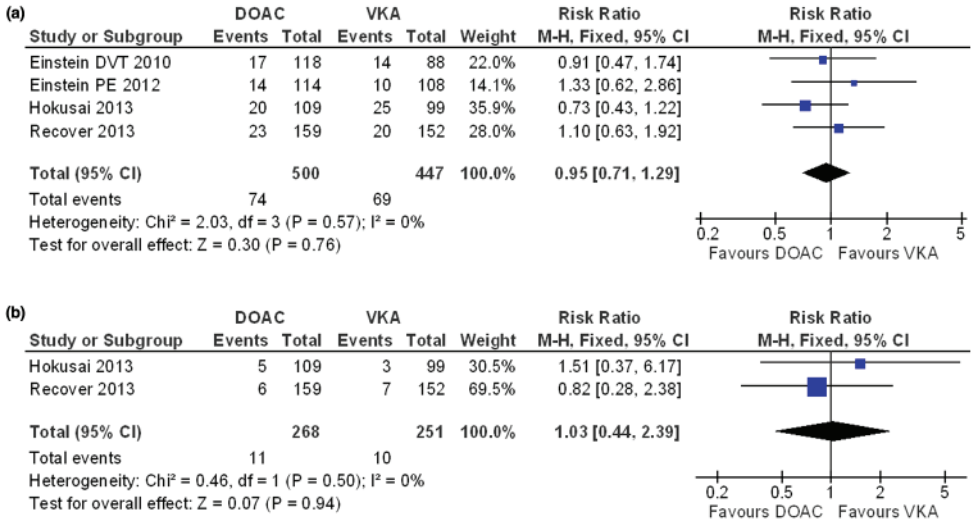

Fig. 2. Pooled analysis of the bleeding risk of DOAC and VKA in patients with cancer. (a) Clinically relevant bleeding. (b) Major bleeding.

(12.3%) for rivaroxaban, and 10/108 (9.3%) for VKA (HR 1.32, 95% CI 0.57-3.11). These rates were 10.2% and 11.5% for rivaroxaban and VKA, respectively, in the patients without cancer.

In the Amplify study, patients with acute VTE were randomized to apixaban 5 mg bd or LMWH sc followed by warfarin [60]. 2.5-2.8% of the included patients had active cancer. No bleeding results are published for this subgroup of patients. Finally, in the Hokusai study, edoxaban 60 mg od, or 30 mg od (patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg) was compared with warfarin for 3-12 months therapy in 8292 patients with acute VTE [61]. All patients received initial LMWH treatment for at least 5 days. Patients with active cancer in whom long-term treatment with LMWH was anticipated were excluded, but patients with a history of cancer or with active cancer were eligible if long-term LMWH treatment was not planned due to availability, physician judgment or patient preference. A total of 771 cancer patients (9.3%) were enrolled (208 with active cancer and 563 with a history of cancer) [63]. Among patients with active cancer, CRB occurred in 20 of the 109 patients (18.3%) with edoxaban (5 patients with major, 4.6%) and 25 of the 99 patients (25.3%) with warfarin (3 patients with major, 3.0%) (hazard ratio 0.72, 95% CI 0.40-1.30). In all 771 patients with cancer (active and previous), CRB occurred in 47 patients (12.4%) with edoxaban (10 patients with major bleeding, 2.6%) and 74 patients (18.8%) with warfarin (13 patients with major bleeding, 3.3%) (HR 0.64, 95% CI 0.45-0.92). In the non-cancer patients, CRB occurred in 280 of 3658 patients (7.7%) who received edoxaban (39 patients with major, 1.1%) and in 330 of 3629 patients (9.1%) given warfarin (48 patients with major, 1.3%) (HR 0.83, 95% CI 0.71 - 0.97).

Based on the results of the major bleeding rate and rate for clinically relevant bleeding in patients with DOACs or VKA, we performed a pooled analysis, for which Review Manager (RevMan; version 5.2 for Windows; Oxford, England; The Cochrane Collaboration, 2003) was used. Hazard ratio and 95%CI were calculated for each study, and results were compared using a fixed-effects model. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study. Figure 2a shows the results for CRB. Four studies could be analysed, with 500 cancer patients treated with a DOAC and 447 with VKA. 74 (14.8%) patients had a CRB with a DOAC compared to 69 (15.4%) patients using VKA, resulting in a HR of 0.95 (95% CI 0.71-1.29). There was no statistical heterogeneity between the studies (I^2=0%). For major bleeding (Figure 2b), only two studies could be assessed, with 268 cancer patients treated with a DOAC and 251 with VKA. Major bleeding occurred in 11 (4.1%) patients with DOACs and 10 (3.98%) patients with VKA (HR 1.03, 95% CI 0.44-2.39), again without statistical heterogeneity (I^2=0%). These results suggest that the bleeding risk is equal between VKA and DOACs in patients with active cancer and VTE. It is important to acknowledge that in these trials patients with renal insufficiency and cancer patients with an indication for long-term treatment with LMWH were excluded. This is reflected by the clearly lower rate of major bleeding in these trials compared to the LMWH studies. Studies with DOACs in cancer patients with acute VTE, should be performed, preferably with LMWH as the comparator. This would also elucidate potential differences in the bleeding patterns between the different anticoagulants.

Can we identify cancer patients starting or using anticoagulants who are at risk for bleeding?

Since patients with cancer have an increased risk of bleeding, identification of high-risk patients is important, especially when anticoagulant treatment is started. As aforementioned, the risk of bleeding in cancer is influenced by many factors, such as cancer type, chemotherapy, surgical interventions, and thrombocytopenia. In the Riete registry, a multivariate analysis of 156 patients with major bleeding events showed that recent bleeding (<30 days prior to the thromboembolic event) and creatinin clearance <30 ml/min doubled the risk of major bleeding. Also immobility ≥4 days and metastatic disease increased the major bleeding risk [54].

No bleeding score that assesses the risk of bleeding in patients with cancer has been developed, so an individualized approach of the bleeding risk should be performed before anticoagulant prophylaxis or treatment is started. In patients with severe renal insufficiency, recent bleeding, or platelet count <$50x10^9$/l, LMWH dose may be tapered, or in the case of thrombocytopenia, platelet transfusion may be used.

Conclusion

Patients with cancer have an increased risk of major bleeding, which is further enhanced by anticoagulation. Although data on bleeding rates in cancer patients are scarce, major bleeding occurs in around 10% of cancer patients, and is influenced by cancer type

and stage, renal function, previous bleeding, thrombocytopenia and chemotherapy. Notably, the rate of major bleeding with thromboprophylaxis in trials is underreported and comparison with placebo is absent. For anticoagulant treatment in patients with acute VTE, major bleeding rate with LMWH is similar to VKA, around 6%. Based on post-hoc analyses of the large DOAC studies in patients with acute VTE, major and clinically relevant bleeding seem equal between DOACs and VKA in cancer patients, but evidence is insufficient to prescribe DOACs to cancer patients with VTE.

Conflict of interest statement

The authors declare no competing financial interests

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