Risk of venous thromboembolism and primary prophylaxis in cancer
Should all patients receive thromboprophylaxis?

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Summary
Venous thromboembolism (VTE) is a common complication in patients with cancer that causes significant morbidity and mortality. Several patient-, tumour- and treatment-related risk factors for VTE in cancer patients have been identified. An effective and safe thromboprophylaxis in cancer patients at high risk of VTE is desirable. Recently, the identification of potential biomarkers and the development of risk scoring models for prediction of cancer-associated VTE have been published. Whether primary VTE prophylaxis based on risk assessment through these biomarkers and risk prediction models might be useful, is currently not yet known. However, thromboprophylaxis is clearly indicated in high-risk situations. While VTE prophylaxis is recommended in cancer patients undergoing surgery and in hospitalised patients with acute disease, studies in ambulatory cancer patients are still rare and evidence for primary VTE prophylaxis is currently limited. In this review, risk factors associated with VTE in cancer patients and current approaches of thromboprophylaxis in different settings, specifically in ambulatory cancer patients are subjected to a critical evaluation.

Keywords
Cancer, venous thromboembolism, thromboprophylaxis

In recent years malignant disease has been recognised as important risk condition for venous thrombosis and pulmonary embolism (1). Since these diseases are more or less regarded as an entity, the term venous thromboembolism (VTE) has been coined and will be used in this review, which will specifically address
• risk factors,
• parameters for assessing the individual risk in cancer patients, and
• treatment options to prevent VTE in these patients.

VTE in cancer patients may present with typical clinical symptoms, but is also found in patients without symptoms. The latter may be diagnosed in the course of imaging procedures performed to evaluate a patient’s disease state. Most studies specifically addressing the frequency of VTE in cancer patients chose the symptomatic thrombotic event as index event (2, 3), whereas less frequently specific screening procedures were used to also identify the frequency of asymptomatic VTE (4–7).

Heidrich et al. performed a retrospective and prospective study to determine the frequency of VTE in cancer patients (7). In the retrospective part of the study (409 tumour patients), in which only symptomatic events were recorded, the frequency was only 6.6%, whereas it was 33% in patients prospectively enrolled and screened with duplex sonography and/or venography.

Symptomatic VTE is an independent risk factor for worse prognosis in cancer patients (8, 9).

Whether this is also true for asymptomatic thrombosis is not yet known, but ought to be investigated in future studies.

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Prevention of VTE in cancer patients would be important for various reasons:
1. to prevent fatal pulmonary embolism,
2. to prevent a further deterioration of a cancer patient’s condition and, in consequence,
3. to prevent loss of quality of life during this most sensitive period in life.

In this respect, it has also been shown in several publications that VTE is an independent predictor of increased mortality in cancer patients (10).

Whether prevention of VTE also has an impact on non-thrombosis-related but cancer-related death is yet unclear.

An optimized management regarding the prevention of cancer-associated VTE would include identification of patients with a substantially increased VTE risk and administration of a highly effective and well-tolerated prophylaxis. The risk of thrombosis may also fluctuate during the course of disease in a cancer patient, so knowing about periods with increased risk might also allow better tailoring of thrombosis prophylaxis.

Risk factors for tumour-associated VTE

Conditional and tumour-associated risk factors

Age is a clear risk factor for VTE in persons without malignancy (11) and has been shown to be of some impact in studies of cancer patients (12). However, in the Vienna Cancer and Thrombosis study (CATS) risk of VTE in cancer patients was unrelated to age (13), and this has also been observed by Blom et al. (14). This suggests that age may have some impact on the VTE risk, however, it is not a major risk-determinant and may not be used as a clinically relevant VTE-risk predictor in cancer patients. There neither seems to be an important difference with regard to sex, as women and men with malignancy had similar risks of developing tumour-associated VTE (13, 15, 16). In contrast, a poor performance status poses a cancer patient at a higher risk of thrombosis (17), which can conclusively be explained by the presence of more advanced disease and an increased risk due to immobilisation in patients with poor performance status. Also obesity (BMI > 35) has been demonstrated as a risk condition by Khorana et al (2), however, in our European cancer population included in CATS a BMI of >35 was only rarely observed and was not associated with increased thrombosis risk (unpublished observation). A previous history of VTE was found to be associated with a clearly (almost 8-fold) increased risk in the prospective study published by Mandala et al. (18). Thus, taking into account the history of VTE in a cancer patient could help assess an individual’s thrombosis risk.

Among the tumour-associated risk factors the tumour entity turned out to be of major importance. It is now widely accepted that several tumour types bear a very high risk of VTE; namely
- tumours of the pancreas (16), brain (19) and stomach (16), for which incidence rates of 10–20% were found, followed by
- tumours of the bladder, uterus, kidney, lung and colon (14, 16).

Lower incidence rates were found for breast and prostate cancer (14). Even in patients with dermatologic tumours, such as melanoma, the risk of thrombosis was substantial (20).

Besides the tumour entity also the stage is of major importance with regard to the risk of thrombosis. Patients with metastatic disease have a higher risk than those with regional disease (16). In the Californian registry the risk of thrombosis was 0.2 – 4.2 in various tumour entities after one year in patients with local disease, whereas it was 0.9 – 20 in those with metastatic disease. In addition, also the histology type is relevant for the occurrence of VTE. Patients with adenocarcinoma of the lung had a 2-fold higher risk (10-fold versus 5-fold) compared to patients with a tumour histology of squamous cell cancer (21).

Impact of anticancer treatment on VTE risk

Certain anti-cancer treatments seem to increase the risk of VTE in cancer patients. In an epidemiologic study performed in Olmsted County over a period of approximately 25 years the risk for VTE in patients with malignancy and chemotherapy was clearly higher in comparison to patients without chemotherapy (11). Similarly, this was found in a large cohort study from the Netherlands (22). Already much earlier, an increased risk was observed in women who underwent chemotherapy for treatment of advanced breast carcinoma, specifically when also tamoxifen was used.

In women with a combination of chemotherapy and tamoxifen the risk was more than twice as high in comparison to chemotherapy or tamoxifen alone (23).

There are a number of other anti-tumour agents that are associated with an elevated VTE-risk; this is the case for thalidomide and lenalidomide, particularly in combination with dexamethasone and chemotherapy in multiple myeloma and lymphoma (24–26). Bevacizumab, an antiangiogenic agent, was shown to increase the risk of thrombosis by about 30% (27) but also for bleeding there was an approximately 2-fold risk (28).

The peri- and post-surgical period is a well known classical risk situation for venous thrombosis and pulmonary embolism, not only in non-cancer patients, but even more in cancer patients (29). In the latter, thrombosis prophylaxis is recommended in the peri- and postoperative period, at least as long as the patient is hospitalised (30, 31). Several studies have investigated a prolonged thrombosis prophylaxis in cancer patients. In a recent meta-analysis (32) the positive effect of extended thrombosis prophylaxis was found. The authors suggested a prolonged thrombosis prophylaxis to be superior to mere inpatient-prophylaxis in patients undergoing major abdominal and pelvic surgery with a risk ratio (RR) of 0.44 (CI 95% confidence interval CI 0.28–0.7). However, data from a systematic review on extended perioperative thromboprophylaxis in patients with cancer were more critically interpreted by another group (33). Although a reduction in the risk of asymptomatic VTE is evident, there was no decrease in mortality after three months. The authors of the latter review state that more and better quality evidence is needed to justify extended regimens.
Biomarkers as VTE risk indicators in cancer patients

In contrast to patients without cancer, in whom biomarkers have not been found useful for predicting VTE, the situation might be different for cancer patients. The overall risk of VTE is much higher in cancer patients than in healthy persons, which makes it easier to study biomarkers as potential VTE predictors in the cancer patient group.

For the first time Khorana et al. showed that patients with an increased platelet count have a higher risk than those with normal platelet levels (34); a higher risk was also observed in anaemic patients and those with elevated leukocyte counts. Khorana used this observation to create a model for a more precise prediction of VTE in the individual patient. It will be discussed later in this review. Thrombocytosis, leukocytosis and anaemia are most probably due to a subclinical inflammatory state, which is also demonstrated by elevated levels of the C-reactive protein (CRP), even in cancer patients without bacterial infection (35, 36).

Soluble P-selectin

Another novel biomarker, soluble P-selectin (sP-selectin), was described in 2007 to be associated with VTE in non-cancer patients (37). P-selectin is an adhesion molecule and is found in alpha granules of platelets and Weibel-Palade bodies of endothelial cells. P-selectin is expressed on the cell surface upon activation and mediates leukocyte rolling and the adhesion of leukocytes to stimulated endothelial cells and platelets (38). When we studied sP-selectin in patients included in CATS we found a 2.6-fold increased risk [hazard ratio (HR), 95% CI 1.4–4.9] for development of symptomatic VTE (3).

D-dimer, F1+2

It is known that cancer patients have an activated clotting system, which has been investigated through determination of D-dimer levels (39–41). As D-dimer is known to be predictive of recurrence of thrombosis in patients who have a history of spontaneous thrombosis and who have quit anticoagulation, it could be suggested that elevated D-dimer and/or elevation of prothrombin fragment F1+2 (F1+2) could also help identify patients with malignancy at an increased risk of VTE.

D-dimer and F1+2 are markers of coagulation activation and subsequent fibrinolysis.

F1+2 is released, when factor Xa cleaves prothrombin to thrombin, and D-dimer is the degradation product of cross-linked fibrin. In CATS D-dimer was measured in 821 patients of whom 62 developed VTE during the course of disease. D-dimer was significantly higher in cancer patients with VTE in comparison to those without VTE during the observation period (13). In a multivariable Cox proportional hazard model, which included elevated D-dimer, elevated F1+2, surgery, radiotherapy, chemotherapy, sex and age, the hazard ratio for elevated D-dimer was 1.8 and for elevated F1+2 it was 2.0. When elevated D-dimer and F1+2 were combined, this revealed an odds ratio of 3.6 (95% CI, 1.4–9.5). Patients with both, elevated D-dimer and elevated F1+2, had a probability of developing VTE after 6 months of 15.2% in comparison to those with non-elevated D-dimer and F1+2 (5%). The cutoff for D-dimer and F1+2 was predefined as the 75th percentile of the levels of the total CATS study population.

FVIII

Another biomarker that has been extensively studied in CATS is clotting factor VIII (FVIII). A deficiency in FVIII leads to a bleeding tendency that is known as hemophilia A and is severe, when FVIII is <1%. On the other hand, an elevation of FVIII is associated with an increased risk of venous thrombosis – this was first shown in the Leiden thrombophilia study (42). Elevation of FVIII was also found to be associated with an increased risk of recurrence in patients with a history of VTE, but without cancer (43).

When we studied data on 840 prospectively followed patients from the CATS cohort, the cumulative probability of VTE after six months was 14% in patients with elevated FVIII levels and only 4% in those with normal levels. Interestingly, the association was strongest in younger patients (44). In 40-year-old patients a 2-fold VTE risk per FVIII increase of 20% with an odds ratio of 2.0 (95% CI, 1.5–2.7) was observed. The association was still present, but attenuated in older patients. The elevation of FVIII might reflect the overall inflammatory condition of patients with cancer.

CRP

For this reason we were also interested in studying CRP levels and in assessing their predictive potential for VTE in cancer patients (36). Indeed, in univariate analysis elevated CRP as a metric variable per double increase was associated with VTE with a HR of 1.2 (95% CI, 1.1–1.3; p 0.048). However, in multivariable analysis including chemotherapy, surgery and radiotherapy, metastases, cancer sites and sP-selectin, the association with VTE was no longer observed (HR 1.0; 95% CI, 0.9–1.2). It can therefore be concluded that elevated CRP levels are not independently associated with VTE. In the same publication Kanz et al., however, showed that CRP was strongly associated with survival: a double increase in CRP led to a hazard ratio for death of 1.3 (95% CI, 1.2–1.3) in multivariable analysis. The cumulative survival after 12 months was only 43% in patients with CRP levels above the 75th percentile of the CATS population, but 82% in those below the 75th percentile. The same behaviour was found in each studied cancer entity, such as breast, lung, stomach, colorectal, pancreas, prostate and various other tumours. This result is in line with other published data on CRP levels in cancer patients.

Microparticles

Only very recently the first study was published that prospectively evaluated circulating procoagulant microparticles as predictive parameter for VTE in a large number of cancer patients (45). It was somewhat unexpected that the quantitative determination of microparticles by using an ELISA-based method was not predic-
tive, although microparticles were higher in cancer patients than in healthy controls. The potential of microparticles for predicting VTE in patients with malignancy is extensively reviewed by Thaler et al. in this issue (Hämostaseologie 2012; 32: 127–131).

**Thrombin generation**

Another biomarker, thrombin generation, was recently described. Thrombin plays a central role in coagulation and the measurement of thrombin generation is a method that allows, at least to some extent, the global measurement of the haemostatic potential (46). Thrombin generation has been shown to be predictive of primary and recurrent VTE (47, 48) and could thus also be a promising marker for predicting future venous thrombosis or pulmonary embolism in cancer patients.

Indeed, patients with a peak thrombin generation above the 75th percentile of the cancer population included in CATS proved to have a twofold (HR 2.1, 95%CI 1.3–3.3) increased risk of VTE during their course of disease (49).

Other parameters measured in the thrombin generation assay, such as lag phase, time to peak and velocity index, were also significantly different in cancer patients with VTE compared to those without, whereas the area under the curve was not different. The cumulative probability for development of VTE after 6 months was 11% in patients with increased and 4% in those without increased peak thrombin generation.

**Risk assessment models**

In 2008 Khorana et al. described a risk assessment model for prediction of the VTE risk in ambulatory cancer patients who had to undergo chemotherapy (2). Based on an observational study he defined important risk predictors (Tab. 1).

Numbers are summarized and this score is then used for individualised risk assessment. In the validation cohort of 1365 patients the incidence of VTE after a median of 2.5 months was

- 0.8 in patients with a low risk score of 0,
- 1.8 in patients with an intermediate risk score of 1–2 and
- 7.1% in those with a score of ≥3.

The major advantage of this score is that its assessment is easy to perform, as these clinical and laboratory parameters are known in each cancer patient prior to the beginning of chemotherapy.

An interventional study that is presently under way will show, whether this score is also useful with regard to decisions on prophylactic treatment. In this ongoing study a low molecular weight heparin is used for prophylaxis.

The mentioned model was independently validated in another patient cohort, namely in patients from the Vienna CATS (50). Indeed, it turned out that this score is also applicable in unselected cancer patients with and without chemotherapy and other treatments, such as radiotherapy or surgery. Furthermore, compared to the initial study of Khorana et al., patients in CATS were studied for a longer period of time. After an observation period of six months the incidence of VTE was

- 1.5 in patients with a score of 0,
- 3.8% in those with a score of 1,
- 9.4% in patients with a score of 2 and
- 17.7% in those with a score ≥3.

The authors from the latter study developed another risk model that additionally includes two biomarkers, D-Dimer and sP-selectin. Both parameters had previously been shown to be significantly associated with an increased VTE risk and are relatively easy to determine. One point each was added for an increased level of either D-dimer or sP-selectin. Thus, a patient can have a risk score of a minimum of 0 and a maximum of 8. The study revealed a strong association of the risk score and the occurrence of VTE: In the expanded risk model that evaluated the occurrence of VTE in 819 patients, the cumulative VTE probability after 6 months in patients with the highest score (≥5, n = 30) was 35.0%, and 10.3% in those with an intermediate score (score 3, n = 130), as opposed to only 1.0% in patients with score 0 (n = 200). Patients with the highest score had an almost 26-fold increased risk of VTE compared to those with the lowest score: HR 25.9 (8.0–84.6). It is also interesting to mention that the numbers of patients in the low risk groups was high, whereas it was relatively low in the high risk groups.

This approach could, in addition to the risk model proposed by Khorana et al. help to design targeted thrombosis prophylaxis for ambulatory cancer patients and thus reduce costs for the health insurance system and inconvenience for patients, as a large number of them would be assigned to a group not needing thrombosis prophylaxis.

**Primary thrombosis prophylaxis in ambulatory cancer patients**

Whereas a number of studies have been performed in cancer patients undergoing surgery and in hospitalised patients with acute disease, and prophylaxis peri- and postoperatively and in acutely ill patients is well established (30), studies in ambulatory cancer patients are still rare.

The first study was performed by Levine et al. (51). They randomized patients with metastatic breast carcinoma to receive either low dose warfarin or placebo. In those treated with warfarin there were less events of deep vein thrombosis, the frequency of pulmonary embolism was equal and survival was not different in the two groups.
In a multicenter study, patients with glioblastoma were included and received either prophylaxis with 5000 Units dalteparin or placebo (52). The study was terminated prematurely because of expiration of study medication. Although a reduction in VTE events was seen, there was also an increase in cerebral bleedings and, to date, the importance of anticoagulation for this patient group is still uncertain.

In a study by an Italian group 3800 units of nadroparin were compared to placebo in a double-blind randomized trial on primary prophylaxis in cancer patients (53). Patients with advanced stage carcinoma received treatment for as long as they were on chemotherapy and for a maximum of four months, two thirds were randomized for nadroparin and one third for placebo. A high number of patients (n = 1150) were included in the primary efficacy evaluation, and the primary study outcome was the composite of symptomatic venous and arterial thromboembolism: 769 patients were included in the nadroparin arm and 381 patients in the placebo group. In total, 15 (2.0%) patients treated with nadroparin and 15 (3.9%) patients on placebo experienced a thromboembolic event, this difference was borderline statistically significant. Of the 30 thrombotic events there were just 6 arterial thromboses, the other events were either deep vein thrombosis or pulmonary embolism. With regard to bleeding complication there was no difference, overall bleeding was rare, 5 (0.7%) of the patients in the nadroparin group and no patient in the placebo group had a major bleeding. Interestingly, the difference between the groups with regard to thromboembolic event was mainly present in patients with lung carcinoma, gastrointestinal carcinoma and other types, but not in patients with pancreatic carcinoma. Several conclusions can be drawn from this important study: The overall risk of thrombosis was not very high in these patients with various tumours. Furthermore, it is possible to decrease the risk by administration of prophylactic doses of low molecular weight heparin, while the efficacy of prophylactic doses differs with regard to the various tumour groups. A prophylactic dose might be sufficient to protect patients with lung or gastrointestinal carcinoma, whereas it might be too low in patients with pancreatic tumour.

Another approach to thrombosis prophylaxis was chosen by a German group. The investigators included only patients with advanced pancreatic carcinoma in this controlled open-label trial, the design is already published (54). The investigators used a higher dose of enoxaparin (1mg/kg) in the first 3 months and then reduced enoxaparin to a prophylactic dose (40 mg). The study was presented at several congresses, however is not yet published as a full manuscript. Preliminary data show a statistically significant reduction in VTE without an increase in the bleeding risk and no substantial change of survival (55). In the FRAGEM study, which is another study that was performed in patients with pancreatic cancer, a therapeutic dose of dalteparin was used. Also this study is not yet published as a full manuscript. Reports from congresses seem to be very promising as for a reduction in the VTE-risk. There was no increase in bleeding and an improvement of survival. However, before definitive conclusions can be drawn, the full publication of these two trials should be awaited.

Conclusions

The presented conclusions will mainly focus on primary prophylaxis in ambulatory cancer patients. There is no doubt about the increased risk of VTE in cancer patients. However, the risk is highly variable with incidence rates between less than 1% and higher than 20% during the first 3–6 months after diagnosis. The tumour entity seems to be the most important risk determinant, however, there are multiple other risk factors that have to be taken into account, such as:

- stage,
- biomarkers and
- effects of antineoplastic treatment.

It has also been convincingly shown that VTE is an independent predictor of increased mortality in cancer patients. Thus, the main aim of VTE prophylaxis in these patients is to prevent a complication, namely VTE, during the course of disease, which could in consequence also result in an improved survival.

Efficacy needs to be balanced against safety, tolerance of treatment-related side effects and inconveniences that may result from long term application of low molecular weight heparin.

With the introduction of new anticoagulants this balance could be different. Since the overall VTE risk of most ambulatory cancer patients is low, an approach to generally recommend thrombosis prophylaxis is not acceptable to date. At present, data on the effect of prophylaxis in pancreatic cancer patients are promising, however, as already stated above, full publications have to be awaited. In patients with other cancer entities, risk assessment models might be a very good approach to individual risk assessment and tailored prophylaxis – however, also in these patients results from properly designed trials have to be awaited.

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Conflict of interest

C. Ay declares that he has no conflicts of interest. I. Pabinger declares that she received honoraries for lectures from Pfizer, Sanofi Aventis, Boehringer-Ingelheim, Bayer.

References


