Venous thromboembolism in cancer patients – Risk scores and recent randomised controlled trials

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Summary
Cancer patients are at increased risk of developing venous thromboembolism (VTE). Guidelines recommend routine thromboprophylaxis in hospitalised acutely ill cancer patients and in myeloma patients receiving combination treatments including thalidomide or lenalidomide. Currently, thromboprophylaxis is not recommended in cancer outpatients. It is the aim of this review to give an overview of studies that applied scores for the risk assessment of cancer-related VTE. We will also discuss randomised controlled trials (RCTs) that investigated primary thromboprophylaxis in cancer patients. Recently, Khorana et al. published a practical and reproducible risk assessment score that includes clinical and laboratory parameters for the stratification of cancer patients according to their propensity to develop VTE. Patients assigned to the high-risk group are likely to benefit most from primary thromboprophylaxis. This score was validated in prospective and retrospective observational studies. In the Vienna Cancer and Thrombosis Study (CATS) the score was expanded by adding two biomarkers, and the prediction of VTE was considerably improved. In recent RCTs including cancer patients with different malignancies it was shown that thromboprophylaxis is safe and effective. However, VTE incidence rates were low. To date, no data is available from interventional studies applying thromboprophylaxis in cancer patients categorised into high-risk groups on the basis of risk assessment with scores. From the available literature we conclude that risk assessment for VTE is feasible in cancer patients; however, interventional studies to investigate the safety and efficacy of thromboprophylaxis in a high risk cancer population have yet to be performed.

Keywords
Cancer, venous thrombosis, risk assessment, randomised controlled trials

Introduction
In 1865 Armand Trousseau first described the association between cancer and venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE) (1). Since then the relation between cancer and VTE has been studied extensively. To date, it is well established that cancer patients are at increased risk of developing VTE, corresponding to an approximate incidence of one in 200 cancer patients (2–4). However, the true prevalence of VTE is underestimated, because a considerable number of VTE events are asymptomatic and remain undetected. Reported rates of incidentally detected VTE in cancer patients range from 2.6% to 6.8% (5–7). It has also been shown that VTE is among the leading causes of death in cancer patients (8) and that patients who develop VTE during the course of disease have a worse overall survival outcome than those without VTE (9, 10).

In cancer patients with confirmed VTE a significantly higher annual VTE recurrence rate of 21% was found compared to 7% in non-cancer patients in a prospective follow-up study (11). In addition, the risk of bleeding was twice as high in cancer patients with confirmed VTE receiving anticoagulation compared to non-cancer patients. Cancer patients undergoing surgery have a three- to five-fold increased risk of developing VTE compared to non-cancer patients (12).

It has clearly been shown that several patient-, treatment- and tumour-related risk factors contribute to the overall VTE risk related to cancer (13). The identification of cancer patients who might benefit from primary thromboprophylaxis is still a major challenge, as incidence rates of VTE differ widely among the cancer population, and the risk of VTE also has to be weighed against the increased risk of major bleeding.

Guidelines recommend routine thromboprophylaxis in hospitalised acutely ill cancer patients and in cancer patients undergoing major surgery (14, 15). Also cancer outpatients with high-risk multiple myeloma, who receive combination treatments including thalidomide or lenalidomide should receive thromboprophylaxis (16).

The most recent guidelines of the American College of Chest Physicians (ACCP) again recommend against routine thrombosis prophylaxis. This score was validated in prospective and retrospective observational studies. In the Vienna Cancer and Thrombosis Study (CATS) the score was expanded by adding two biomarkers, and the prediction of VTE was considerably improved. In recent RCTs including cancer patients with different malignancies it was shown that thromboprophylaxis is safe and effective. However, VTE incidence rates were low. To date, no data is available from interventional studies applying thromboprophylaxis in cancer patients categorised into high-risk groups on the basis of risk assessment with scores. From the available literature we conclude that risk assessment for VTE is feasible in cancer patients; however, interventional studies to investigate the safety and efficacy of thromboprophylaxis in a high risk cancer population have yet to be performed.

Keywords
Cancer, venous thrombosis, risk assessment, randomised controlled trials

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prophylaxis in outpatients with cancer. However, the ACCP guidelines suggest prophylactic doses of low-molecular-weight heparin (LMWH) or low doses of unfractionated heparin rather than no prophylaxis in outpatients with solid tumours who have additional risk factors for VTE and who are at low risk of bleeding. The mentioned additional risk factors comprise previous venous thromboembolism, immobilisation, hormonal therapy, angiogenesis inhibitors, thalidomide, and lenalidomide – they are, however, not defined more precisely (17). According to these suggestions, a very large number of cancer patients would be eligible for thrombosis prophylaxis, even those with a relatively low absolute risk of thrombosis (e.g. women with breast cancer and hormonal therapy).

In cancer outpatients, it remains to be determined who is at high risk of VTE and likely to benefit from primary thromboprophylaxis. In addition, an effective thromboprophylaxis should not only reduce the incidence of VTE, but also mortality. Most cases of cancer-related VTE now occur in the outpatient setting (18).

A novel and promising approach is the stratification of patients according to their risk of thrombosis, applying risk assessment models (RAMs) that include clinical parameters and biomarkers. In 2005 Kucher et al. presented a RAM for VTE in hospitalised patients (19). Eight common risk factors were incorporated in this model including cancer. A computer-alert program was used to encourage the use of thromboprophylaxis in hospitalised patients who were at high risk of VTE according to the RAM. In this randomised controlled trial (RCT) the risk of DVT and PE was reduced by 41% in the intervention group. In another study that included hospitalised patients the Kucher model was modified and termed the Padua Prediction Score (20). Also this RAM clearly discriminated between patients at high and low risk of VTE. Since these RAMs did not specifically address cancer patients, the validity for cancer patients remains unclear.

Similar RAMs might be useful for predicting the bleeding risk in anticoagulated cancer patients, as the effectiveness of such models was evidenced in anticoagulated patients with atrial fibrillation (21). However, currently no RAMs for prediction of the bleeding risk in anticoagulated cancer patients are published yet, therefore we only investigated RAMs for VTE. As clear guidelines exist for acutely ill hospitalised cancer patients and those undergoing surgery we focused on the overall cancer population. Most patients included in studies that established RAMs were outpatients, however, not exclusively, as the observation periods also included periods when patients were admitted to hospital.

This review consists of two parts. In part 1, we will present available data from studies that applied RAMs for the prediction of VTE in cancer patients. In part 2 we will focus on RCTs that investigated primary thromboprophylaxis in cancer outpatients.

Risk assessment models for cancer-related VTE

The stratification of cancer patients according to their risk of VTE is a novel and promising approach for identifying cancer patients who might benefit from primary thromboprophylaxis. First, Khorana et al. published a RAM in 2008 (which we will refer to as “Khorana score”) for the prediction of symptomatic cancer-related VTE using baseline clinical and laboratory variables, which were determined prior to the initiation of chemotherapy (22). Meanwhile, this score has been independently validated in a number of studies and was also expanded by the addition of biomarkers. Moreover, Palumbo et al. published a RAM, based on expert recommendation statements, for the prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma patients (16). In this part of the review we will present and discuss clinical data from studies that applied RAMs, mainly the Khorana score, for the stratification of cancer patients according to their VTE risk.

The Khorana VTE risk assessment score

The Khorana score was developed in a study population of 4,066 cancer patients who were enrolled in the “Awareness of Neutropenia in Chemotherapy” (ANC) Study Group Registry and started a new chemotherapy regimen. The median observation period was 2.5 months. The risk score included the following parameters that were predictive of VTE in univariate analysis: primary site of cancer, pre-chemotherapy platelet count of 350 $\times 10^9$ /L or more, haemoglobin level less than 10 g/dl and/or use of erythropoiesis-stimulating agents, pre-chemotherapy leucocyte count of more than 11 $\times 10^9$/l, and a body mass index of 35 kg/m² or more. Numerical values (0–2) were assigned to each covariate (Table 1). Patients were stratified into three discrete categories according to numerical scores that corresponded to the risk of developing VTE (Table 2). In the derivation and validation cohort the rates of VTE were 0.8% and 0.3% in the low-risk group (score = 0), 1.8% and 2% in the intermediate-risk group (score = 1–2), and 7.1% and 6.7% in the high-risk group (score ≥ 3). Khorana et al. con-

<table>
<thead>
<tr>
<th>Khorana VTE Risk Assessment Score (13)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>site of cancer: very high risk: stomach, pancreas</td>
<td>2</td>
</tr>
<tr>
<td>high risk: lung, lymphoma, gynaecologic, bladder, testicular</td>
<td>1</td>
</tr>
<tr>
<td>platelet count $\geq 350 \times 10^9$ /L</td>
<td>1</td>
</tr>
<tr>
<td>haemoglobin and/or use of erythropoiesis-stimulating agents (ESAs) $&lt; 10$ g/dl</td>
<td>1</td>
</tr>
<tr>
<td>leucocyte count $&gt; 11 \times 10^9$ /L</td>
<td>1</td>
</tr>
<tr>
<td>body mass index $\geq 35$ kg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

*In the Vienna Cancer and Thrombosis Study brain tumours (high-grade glioma) were allocated to the “very high risk” sites of cancer.
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Table 2: Comparison of the Khorana VTE risk score applied in four observational studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Khorana et al.* (22)</th>
<th>Ay et al. (24)</th>
<th>Moore et al. (30)</th>
<th>Mandala et al. (31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>prospective</td>
<td>prospective</td>
<td>retrospective</td>
<td>prospective</td>
</tr>
<tr>
<td></td>
<td>prior to initiation of a new chemotherapy (CHT) regimen</td>
<td>without and with various treatments during observation period</td>
<td>treated with cisplatin-based CHT, at least 4 weeks of follow-up after first cisplatin dose</td>
<td>enrolled and treated in phase I studies investigating the toxicity of a new drug or of a new combination of drugs</td>
</tr>
<tr>
<td>Total number of patients, n</td>
<td>1365</td>
<td>819</td>
<td>932</td>
<td>1412</td>
</tr>
<tr>
<td>Median age at study entry, years</td>
<td>not given</td>
<td>62</td>
<td>60</td>
<td>not given</td>
</tr>
<tr>
<td>Median observation period</td>
<td>2.5 months</td>
<td>6 months</td>
<td>not given**</td>
<td>2 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>VTE rate</th>
<th>Patients (n)</th>
<th>VTE rate</th>
<th>Patients (n)</th>
<th>VTE + arterial TE rate</th>
<th>Patients (n)</th>
<th>VTE rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk group (score 0)</td>
<td>374</td>
<td>0.3%</td>
<td>276</td>
<td>1.5%</td>
<td>224</td>
<td>13%</td>
<td>525</td>
</tr>
<tr>
<td>Intermediate risk group (score 1–2)</td>
<td>842</td>
<td>2.0%</td>
<td>229</td>
<td>score 1: 3.8%</td>
<td>538</td>
<td>17.1%</td>
<td>825</td>
</tr>
<tr>
<td>High risk group: (score ≥3)</td>
<td>149</td>
<td>6.7%</td>
<td>93</td>
<td>17.7%</td>
<td>170</td>
<td>28.2%</td>
<td>62</td>
</tr>
<tr>
<td>C statistic</td>
<td>0.70</td>
<td>not given</td>
<td>0.65</td>
<td>not given</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Each study included patients with various cancer sites. * VTE rates of the validation cohort are given. ** 54% of patients developed arterial or venous thromboembolism within 50 days.

Validation of the Khorana risk assessment score

In a subsequent study that was performed in the framework of the Vienna Cancer and Thrombosis Study (CATS), Ay et al. independently validated the Khorana score in a group of 819 patients with different malignancies (24). The Vienna CATS is an ongoing prospective observational study that investigates the association of biomarkers and laboratory parameters (determined at study inclusion) with the occurrence of VTE during a follow-up period of two years. Remarkably, CATS has contributed a wealth of information regarding the identification of variables predictive of cancer-related VTE, since elevated levels of sP-selectin (25), factor VIII (26), D-dimer and prothrombin fragment F1 + F2 (27), peak thrombin generation (28), and high thrombocyte count (29) were shown to indicate an increased propensity for the development of VTE in cancer patients.

Applying the Khorana score to the CATS cohort, the cumulative probability of VTE after six months was 1.5% in 276 patients with score 0, 3.8% in 229 patients with score 1, 9.6% in 221 patients with score 2, and 17.7% in 93 patients with score ≥3 (Table 2). Ay et al. concluded from their study that the Khorana score was reproducible because sensitivity and specificity of the score were comparable in their own and in Khorana’s original study. Remarkably, VTE rates were higher in the CATS cohort than in the ANC Study Group Registry (7.4% vs. 2.1%), which was most probably due to the longer follow-up time of six months in the CATS cohort and a higher proportion of patients with high-risk cancer sites, such as brain, gastric and pancreatic tumours.

At a later time point, the Khorana score was also applied by Moore et al. in a retrospective analysis of 952 cancer patients treated with cisplatin-based chemotherapy (30). In this study the incidence rates of venous and arterial thromboembolic events were given together and the term thromboembolism (TE) was coined for both. A high TE event rate of 18.1% was found. TE events included DVT alone (49.7%), PE alone (25.4%), DVT plus PE (13.6%), arterial TE alone (8.3%), and DVT plus arterial TE (3.0%). In groups categorised according to the Khorana score the incidence of TE was 13% in the low-risk group, 17.1% in the inter...
mediate-risk group and 28.2% in the high-risk group (Table 2). It has to be considered that the comparability of this study with other studies (that only investigated VTE) is hampered because Moore et al. did not provide data on VTE rates separated from arterial TE rates. Moore et al. suggested that the high TE rate may be due to the fact that their study population, which consisted only of cisplatin-exposed patients, was at a higher thrombosis risk than the general cancer population.

Only recently, Mandala et al. applied the Khorana score in a study that included 1,415 patients enrolled and treated in phase I trials conducted by the South Europe New Drugs Organization (SENDO) Foundation (31). In these phase I trials, all adverse events of patients who received experimental anticanic agents were reported. Also in Mandala’s study the incidence of VTE increased with the number of present risk factors according to the Khorana score, namely from 1.5% in the low-risk group, to 4.8% in the intermediate-risk group, to 12.9% in the high-risk group during a median follow-up period of two months (Table 2). Mandala et al. concluded that most probably the patients in the high-risk group would benefit from thromboprophylaxis. In addition, they argued that in future phase I studies VTE incidence rates should likewise be reported, as the VTE incidence was not negligible in the high-risk group.

Recently, the Khorana score was also used in a retrospective analysis of the SAVE-ONCO study, as yet the largest RCT investigating primary thromboprophylaxis in cancer patients (currently published only in abstract form) (32). Patients were randomised either to the ultra-low-molecular-weight-heparin (ULMWH) semuloparin (20 mg, once daily) or placebo. In Table 3 VTE and bleeding rates according to the Khorana score are given for the verum and placebo group. In patients receiving semuloparin, VTE rates were comparably low in the various risk groups. In patients receiving placebo, VTE rates were 1.3%, 3.5% and 5.4%, respectively. Thus, the treatment effect was primarily seen in the higher risk groups of the Khorana score. No increased incidence of clinically relevant bleeding was present in patients receiving semuloparin compared to placebo. In the RCT section of this review we will discuss the SAVE-ONCO study in detail.

Moreover, in a retrospective analysis of the PROTECHT (Phrophaxis of Thromboembolism during Chemotherapy) study, patients were also categorised according to the Khorana score (33). In this study, 1,150 cancer patients were randomised either to nadroparin or placebo. Unfortunately, in this study no information was given on VTE rates in risk groups categorised according to the Khorana score.

The Vienna VTE risk assessment score

After performing additional analyses in the CATS cohort, the Khorana score was expanded by adding two predictive biomarkers, namely sP-selectin and D-dimer (24). In the Vienna VTE assessment score, the predictability of VTE was considerably improved, as for example patients with a score ≥ 5 (30 of 819 patients) had a significantly higher cumulative probability of developing VTE of 35%. Information on VTE incidence rates in the expanded Khorana score and on the positive and negative predictive value according to each score is given in Table 4.

Risk assessment of the Myeloma Working Group for the prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma patients

Thalidomide and lenalidomide are two structurally similar but functionally different drugs that per se do not increase the risk of VTE in myeloma patients (16). However, the combination of thalidomide with dexamethasone, melphalan, melphalan/prednisol, doxorubicin/dexamethasone or multiagent chemotherapies, and the combination of lenalidomide with dexamethasone or cyclophosphamide, respectively, are associated with high VTE incidence.
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VTE Risk Assessment Score of the Myeloma Working Group for myeloma patients treated with thalidomide or lenalidomide (16)

<table>
<thead>
<tr>
<th>Individual risk factors:</th>
<th>Body mass index ≥ 30 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous VTE</td>
</tr>
<tr>
<td></td>
<td>Central venous catheter or pacemaker</td>
</tr>
<tr>
<td>Associated disease (cardiac disease, chronic renal disease, diabetes, acute infection, immobilisation)</td>
<td></td>
</tr>
<tr>
<td>Surgery (general surgery, any anaesthesia, trauma)</td>
<td></td>
</tr>
<tr>
<td>Medications (erythropoietin)</td>
<td></td>
</tr>
<tr>
<td>Blood clotting disorders</td>
<td></td>
</tr>
<tr>
<td>Myeloma-related risk factors:</td>
<td>Diagnosis</td>
</tr>
<tr>
<td></td>
<td>Hyperviscosity</td>
</tr>
<tr>
<td>Myeloma therapy:</td>
<td>High dose dexamethasone (480 mg/month), doxorubicin, multiagent chemotherapy</td>
</tr>
<tr>
<td></td>
<td>LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2–3)</td>
</tr>
</tbody>
</table>

Table 5: The VTE Risk Assessment Score of the Myeloma Working Group for myeloma patients treated with thalidomide or lenalidomide.

Recent randomised controlled trials investigating thromboprophylaxis in cancer patients

Recent RCTs have shown that primary thromboprophylaxis is feasible and safe in cancer outpatients. However, in most of these RCTs VTE rates were low. For example, in the PROTECHT study the primary outcome measure was the composite of symptomatic venous and arterial TE events during a median treatment period of approximately four months in cancer outpatients (38). Only 2% of patients in the treatment group (receiving the LMWH nadroparin) and 3.9% in the placebo group developed a venous or arterial TE event; the rates of VTE were 1.4% and 2.9%, respectively. The SAVE-ONCO study as yet the largest RCT investigating primary thromboprophylaxis (with the new ULMWH semuloparin) including 3,212 cancer outpatients with locally advanced or metastatic tumours prior to initiation of chemotherapy (38). In this study 1.2% of patients in the treatment group and 3.4% in the placebo group developed VTE during a median treatment period of approximately 3.5 months. Although in both studies the reduction in VTE incidence was statistically significant, it may be questionable, whether a VTE risk of 3–4% warrants thromboprophylaxis. In the PROTECHT study only 1.9% of patients benefited from thromboprophylaxis, corresponding to a number-needed-to-treat (NNT) of 53 patients to avoid one venous or arterial TE event. In the SAVE-ONCO study 2.2% of patients benefited from thromboprophylaxis, corresponding to a NNT of 45 patients. Another important point is that in the PROTECHT and the SAVE-ONCO study no influence of thromboprophylaxis on overall survival was found. It needs to be mentioned that both studies included a broad range of malignancies and no risk stratification identifying patients at high risk of VTE was performed. However, in a recent analysis of the SAVE-ONCO study, which is present in the RAM section of this review, patients were retrospectively categorised according to the Khorana score (Table 3).

Evidence indicates that the type of cancer is a particularly important risk factor for the development of VTE (10). Recently two RCTs were performed that included only patients with pancreatic cancer, one of the most prothrombotic malignancies with VTE incidence rates ranging from 17–57% (39–41). Maraveyas et al. investigated gemcitabine versus gemcitabine plus dalteparin (LMWH) in full therapeutic dose for 12 weeks in patients with advanced pancreatic cancer (40). The VTE incidence rate was 23% in the control and 3.4% in the treatment arm. No increased risk of bleeding was found. In the CONKO-004 study, the second RCT that included only patients with pancreatic cancer (currently published only in abstract form [41]), the LMWH enoxaparin was...
added to chemotherapy for a period of 12 weeks (41). In the observation arm 14.5% of patients developed VTE versus 5.0% in the treatment arm. Also in this study the risk of severe bleedings was not increased. Results from these two RCTs indicate that thromboprophylaxis is effective and safe in pancreatic cancer patients. At least in this patient group primary thromboprophylaxis may be justified in the outpatient setting without additional risk stratification. To the best of our knowledge, it remains to be investigated in specifically designed RCTs, whether this also applies to other high-risk cancer sites (e.g. brain tumours).

Conclusions and future directions

A growing body of evidence indicates that risk assessment for VTE with scoring models allows the identification of cancer patients at high risk of VTE. Consistently, the Khorana risk assessment score has been validated in recent retrospective and prospective observational trials. Cancer patients stratified into high-risk groups according to the Khorana score are likely to benefit from primary thromboprophylaxis. Recent data also suggest that in pancreatic cancer patients primary thromboprophylaxis might be justified without previous risk stratification, because of the high VTE risk associated with the cancer site per se.

To date, there is no consensus how long patients should receive thromboprophylaxis. The VTE risk seems to be particularly high in the first few months, but some patients may need indefinite thromboprophylaxis. Future interventional trials should investigate the benefit of primary thromboprophylaxis for patients categorised into high-risk groups through risk assessment scores. The prognostic value of regular risk assessment during the course of disease is not known yet and should also be investigated in future studies.

Conflicts of interest

J. Thaler and C. Ay declare no conflicts of interest. I. Pabinger has received honoraries for lectures from Pfizer, Sanofi Aventis, Boehringer-Ingelheim and Bayer.

References