**The Khorana score for prediction of venous thromboembolism in cancer patients: an individual patient data meta-analysis**

Running title: Prediction of cancer-associated VTE

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**ABSTRACT**

Oncology guidelines suggest using the Khorana score to select ambulatory cancer patients receiving chemotherapy for primary venous thromboembolism (VTE) prevention, but its performance in different cancers remains uncertain. This individual patient data meta-analysis of seven randomized controlled trials that evaluated (ultra)-low-molecular-weight heparin (LMWH) in patients with solid cancer addresses the performance of this score in assessing 6-month VTE risk, and the efficacy and safety of LMWH among patients with a high-risk Khorana score. The 3,293 patients from the control groups with an available Khorana score had lung (n=1,913; 58%), colorectal (n=452; 14%), pancreatic (n=264; 8%), gastric (n=201; 6%), ovarian (n=184; 56%), breast (n=164; 5%), brain (n=84; 3%), or bladder cancer (n=31; 1%). Overall, the 6-month VTE incidence was 9.8% among high-risk Khorana score patients and 6.4% among low-to-intermediate-risk patients (OR 1.6; 95%-CI, 1.1-2.2). The dichotomous Khorana score performed differently in lung cancer patients (OR 1.1; 95%-CI, 0.72-1.7) than in the group with other types of cancer (OR 3.2; 95%-CI, 1.8-5.6; P*interaction*=0.002). Among high-risk patients, LMWH decreased the risk of VTE by 64% compared to placebo or observation (OR 0.36; 95%-CI, 0.22-0.58), without increasing the risk of major bleeding (OR 1.1; 95%-CI, 0.59-2.1). In conclusion, the Khorana score was unable to stratify patients with lung cancer based on their VTE risk, while in the group of patients with other cancer types, a high-risk score was associated with an 3-fold increased risk of VTE compared with a low-to-intermediate risk score. Thromboprophylaxis was effective and safe in patients with a high-risk Khorana score.

**INTRODUCTION**

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), is a frequent and burdensome complication of cancer. Current evidence shows that between 1% and 15% of cancer patients will develop VTE during the course of their disease, depending on cancer type, stage, and treatment.1 With the substantial increase in cancer survival, aging of the cancer population, and the introduction of novel, often thrombogenic cancer therapies,2,3 VTE incidence in cancer patients is likely to rise in the coming years.

International guidelines recommend against routine use of thromboprophylaxis in cancer outpatients, while most recommend or suggest primary prevention for patients at high risk of VTE as assessed by the Khorana score.4–8 This score calculates the risk of VTE from five clinical and laboratory items: type of cancer (0 points for low, 1 point for high, or 2 points for very high-risk), hemoglobin level <10 g/dL or use of erythropoietin stimulating agents (1 point), white blood cell count >11 x 109/L (1 point), platelet count ≥350 x 109/L (1 point), and body mass index >35 kg/m2 (1 point). Patients scoring 0 points are classified as low-risk of developing VTE, those with 1 or 2 point as intermediate-risk, and those scoring 3 or more points as high-risk.

Although several studies have evaluated the Khorana score in mixed cancer populations,9,10 its performance appears to be less robust in studies recruiting single types of cancer.11–13 This has potential implications for the use of the Khorana score in current practice, in which oncologists increasingly specialize in the treatment of only a few or a single cancer type. Treating physicians also need information regarding the risks and benefits of thromboprophylaxis in patients classified as high-risk by the Khorana score, since this is the group often considered for primary prevention of VTE.

By using individual patient data of almost 7,000 patients enrolled in seven randomized studies, we assessed the performance of the Khorana score across different types of cancer and evaluated the efficacy and safety of primary VTE prophylaxis among high-risk cancer patients receiving chemotherapy.

**METHODS**

The present analysis includes individual patient data from multicenter randomized studies of prophylactic parenteral anticoagulants in ambulatory patients with solid cancer. These studies were identified by a systematic search of the literature. The methods are reported in full elsewhere.14 Briefly, a search of EMBASE, MEDLINE, and The Cochrane Library from inception up to January 2017 identified randomized controlled trials comparing unfractionated heparin, (ultra)-low-molecular-weight heparin (LMWH), or fondaparinux with placebo or observation in patients with solid cancer. Authors of thirteen of nineteen studies that met the eligibility criteria provided individual patient data. Studies that had not prospectively collected data on one or more of the Khorana score items were excluded. The present analysis was a pre-specified secondary objective of this collaborative project.14

*Risk of bias and evidence grading*

For the evaluation of the performance of the Khorana score, two authors independently assessed risk of bias for the studies using the Quality In Prognosis Studies (QUIPS) tool.15 Three of six QUIPS items were omitted because they were irrelevant to the research question (study confounding) or irrelevant at a study level because data were aggregated at a patient level (prognostic factor measurement and statistical analysis). For the evaluation of efficacy and safety of thromboprophylaxis, two authors independently assessed risk of bias using the Cochrane Risk of Bias Tool. Reviewers resolved disagreement by discussion. The GRADE framework was used to assess evidence for the prognostic performance of the Khorana score as well as for the efficacy and safety of thromboprophylaxis.16–18

*Outcomes*

The primary outcome was objectively confirmed DVT or PE in the first 6 months of follow-up from randomization, either symptomatic or incidentally detected. The study definitions of VTE, which varied somewhat, were accepted and used in the present analysis. Secondary outcomes included symptomatic VTE, DVT, PE, major bleeding, and all-cause mortality.

*Data synthesis*

The Khorana score was calculated by using baseline data routinely collected in the studies.19 We applied the modifications proposed by Ay and colleagues, wherein primary brain cancer is considered as a ‘very high-risk’ tumor type.10 Patients with a score of 0 points were classified as ‘low-risk’, those with 1 or 2 points as ‘intermediate-risk’, and those with 3 points as ‘high-risk’. The prognostic performance of the Khorana score was evaluated in the patients allocated to the control groups (placebo or observation).

To assess overall discrimination, the area under the receiver operating characteristic (ROC)-curve of the continuous Khorana score for predicting VTE was calculated for each study. Variances were obtained by DeLong’s method, and study estimates were transformed to the logit scale to better approximate underlying assumptions, before they were aggregated in an inverse variance weighted random-effects meta-analysis. Maximum likelihood estimation was adopted and the Knapp-Hartung-Sidik-Jonkman method was used.20 Summary estimates obtained in meta-analysis were presented on the conventional probability scale. Heterogeneity was assessed by calculating the I2 statistic.

We examined the performance of the Khorana score when dichotomized at the conventional positivity threshold of 3 points, in the overall study group and in subgroups defined by tumor type and presence of metastasis. Given recent reports that the Khorana score may perform poorly in lung cancer patients,21 we evaluated the dichotomous score separately in this group and, separately, in the combined group of all other types of cancer.

The proportion of patients with VTE among high-risk patients, the proportion of patients with VTE among low-risk patients, and the odds ratio for the difference between high-risk and low-risk patients along with 95% confidence intervals (CI) were estimated from a multi-level logistic regression model, in which a random effect was modeled for study and the dichotomous score result was added as fixed effect.

Summary odds ratios for risk of VTE, bleeding, and death in patients allocated to LMWH compared to those allocated to control (placebo or observation) were calculated in a multi-level logistic regression model with a random effect for study. The risks of VTE and bleeding associated with LMWH were evaluated separately in patients with a high-risk Khorana score.

Heterogeneity across studies was illustrated by calculating 95% prediction intervals (PI) around the point estimates.22 Such an interval takes the between-study variability into account; it indicates a range for the predicted point estimate in a new study.

*Sensitivity and exploratory analyses*

The predictive performance of the individual Khorana score items was evaluated in a multivariable, multi-level logistic regression model with a random effect modeled for study. Sensitivity analyses were performed in which follow-up was restricted to the first 90 days, since the Khorana score was derived in a study with a median follow-up of 2.5 months, and in which studies enrolling patients during chemotherapy or shortly after surgery were excluded, since blood counts can be affected by chemotherapy and surgery is a well-known risk factor for VTE. The performance of the Khorana score was also assessed using an exploratory high-risk positivity threshold of 2 points, since this cut-off was adopted by several guidelines after publication of two recent trials.23,24

All analyses were based on the intention-to-treat principle. A significance level of 0.05 was used in statistical testing. All analyses were performed with R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org) using the *pROC* v1.8, *lme4* v1.1-12, and *meta* v4.8-1 packages.

*Role of the funding source*

The funding source (Canadian Institutes for Health Research) had no role in the study design, collection, analysis, or interpretation of the data, writing of the report, nor in the submission to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

**RESULTS**

Investigators of seven of thirteen available randomized studies provided data required to calculate the Khorana score;25–30 we excluded the other six studies.31–36 Table 1 presents characteristics of the included studies. Four had a blinded design and three an open-label design. The studies enrolled patients with lung cancer, pancreatic cancer, breast cancer, glioma, or a mixed oncology population, with sample sizes ranging from 39 to 3,212 patients. In all studies, investigators followed patients for at least 6 months. The definition of VTE was similar across the studies, and typically included symptomatic or incidental lower extremity DVT, upper extremity DVT, and fatal or non-fatal PE (Table 1). All studies defined major bleeding in accordance with criteria set by the International Society on Thrombosis and Haemostasis.37 The individual patient dataset comprised 6,832 patients with cancer, randomly allocated to LMWH (n=3,429) or to placebo or observation (n=3,403). Table 2summarizes patient characteristics of patients allocated to placebo or observation. During 6 months of follow-up, 188 patients (5.5%) in the control group developed VTE, of whom 153 (81%) experienced a symptomatic event.

*Risk of bias*

Supplementary Table 1 present results of the risk of bias assessment for the evaluation of the Khorana score in the control groups. One study was judged to be at moderate risk of bias with respect to study participation, because a substantial proportion of eligible patients was not randomized.29 Three studies were judged to be at moderate to high risk of bias regarding study attrition because of a substantial proportion of patients were lost to follow-up28 or because patients were excluded because of a positive baseline VTE screening for thrombosis.25 Two studies were judged to be at moderate risk of bias with respect to outcome measurement because of unclear definitions of VTE28 or absence of central adjudication of outcomes.30

Supplementary Figure 1 presents results of the risk of bias assessment for the evaluation of the efficacy and safety of thromboprophylaxis. Three studies were not placebo controlled27,28,30 and outcomes were not adjudicated in two of these studies.27,28 Data analysts were not blinded in six studies.25,27,29,30 One study was judged to be at high risk of selection and reporting bias.30

*Khorana score prognostic performance*

Among the 3,293 patients allocated to placebo or observation in whom the Khorana score could be calculated, the summary area under the ROC-curve of the continuous Khorana score was 0.57 (95% CI, 0.47 to 0.66) with evidence of between-study heterogeneity (I2=57%, *P*=0.03; Supplementary Figure 2). The Khorana score classified 402 patients (12%) as ‘low-risk’, 2,121 (62%) as ‘intermediate-risk’, and 770 (23%) as ‘high-risk’. The score proved unavailable in 110 patients (3.2%) due to missing data. The 6-month cumulative VTE incidence was 4.1% among low-risk patients (95% CI, 1.9 to 8.4), 6.8% among intermediate-risk patients (95% CI, 4.5 to 10), and 10% among the high-risk patients (95% CI, 6.7 to 15). The odds ratio for the relative difference between low-to-intermediate patients and high-risk patients was 1.6 (95% CI, 1.1 to 2.2; 95% PI, 0.29 to 8.6; *P*=0.006). The sensitivity analysis restricted to the four studies that did not enroll patients prior to chemotherapy or shortly after surgery27,28,30,38 yielded comparable results: OR 1.5 (95% CI, 1.01 to 2.1; 95% PI, 0.24 to 9.1; *P*=0.04). In a sensitivity analysis of VTE during the first 90 days, the incidence was 5.7% (95% CI, 3.7 to 8.6) among patients with a high-risk Khorana score compared with 4.1% (95% CI, 2.8 to 6.0) in those with a low-to-intermediate risk score, yielding a similar OR of 1.4 (95% CI, 0.95 to 2.1; 95% PI, 0.32 to 6.2; *P*=0.09).

For the outcomes of symptomatic VTE, DVT, and PE the odds ratios for the relative difference between patients with a low-to-intermediate Khorana score and those with a high-risk score were 1.4 (95% CI, 0.98 to 1.9; 95% PI, 0.18 to 10; *P*=0.07), 1.5 (95% CI, 0.92 to 2..4; 95% PI, 0.16 to 14; *P*=0.11), and 1.7 (95% CI, 1.1 to 2.6; 95% PI, 0.29 to 9.8; *P*=0.02), respectively.

Table 3 presents the association between the Khorana score and VTE occurrence for various types of cancer and for patients with metastatic cancer. A high-risk Khorana score was significantly associated with VTE in pancreatic cancer patients (OR 2.2; 95% CI, 1.02 to 4.9), but not in other individual tumor types. The OR was not homogenous across the various types of cancer (Tarone test *P*=0.013) and there was evidence of a significantly different performance of the Khorana score in lung cancer (OR 1.1; 95% CI, 0.72 to 1.7; 95% PI, 0.61 to 2.0) compared to other types of cancer (OR 3.2; 95% CI, 1.8 to 5.6; 95% PI, 0.36 to 28; *Pinteraction*=0.002). Table 4A shows the summary of findings regarding the prognostic performance of the Khorana score overall, in lung cancer patients, and in those with other types of cancer than lung cancer.

When applying the exploratory positivity threshold of 2 points, the overall incidence of VTE was 7.9% (95% CI, 5.1 to 12) in high-risk Khorana score patients and 6.7% (95% CI, 4.2 to 11) in low-risk Khorana score patients, corresponding to an OR of 1.2 (95% CI, 0.85 to 1.7; 95% PI, 0.21 to 6.9; *P*=0.31).

Supplementary Table 2 presents results of the multivariable analysis of the Khorana score items. Only high-risk tumor type (OR 1.8; 95% CI, 1.05 to 3.1) and very high-risk tumor type (OR 2.4; 95% CI, 1.4 to 4.4) were significantly associated with VTE. Interaction terms between tumor risk category and the other score items were not statistically significant, except for the interaction between very high-risk tumor type and body mass index over 35 kg/m2 (OR 6.6; 95% CI, 1.2 to 36; *Pinteraction*=0.029).

*Efficacy and safety of low-molecular-weight heparin in patients with high risk Khorana score*

Among the 1,514 patients classified as high-risk by the Khorana score (≥3 points), the 6-month VTE risk was 3.7% (95% CI, 2.1 to 6.4) among LMWH recipients and 9.8% (95% CI, 6.3 to 15) among those not receiving LMWH, corresponding to an OR of 0.36 (95% CI, 0.22 to 0.58; 95% PI, 0.07 to 1.9; *P*<0.001; Supplementary Table 3A). The treatment effect of LMWH was not significantly modified by the dichotomous Khorana score (*Pinteraction*=0.16). In patients with a high-risk Khorana score, LMWH was not associated with a significantly increased risk of major bleeding (OR, 1.1; 95% CI, 0.59 to 2.1; 95% PI, 0.07 to 16; *P*=0.77; Supplementary Table 3B) nor with a significantly different mortality (OR, 0.82; 95% CI, 0.66 to 1.01; PI, 0.20 to 3.3; *P*=0.06; Supplementary Table 3C). Table 4B shows the summary of findings regarding the efficacy and safety of LMWH in high-risk patients. In the sensitivity analysis applying the exploratory positivity threshold of 2 points, LMWH was associated with a 53% reduction in the risk of VTE (OR, 0.47; 95% CI, 0.34 to 0.65; *P*<0.001) and a similar risk of major bleeding (OR, 1.04; 95% CI, 0.68 to 1.6; *P*=0.85) compared to observation or placebo.

In the 619 patients with types of cancer other than lung cancer, a high-risk Khorana score corresponded to a 6-month VTE incidence of 3.3% (95% CI, 1.4 to 7.7) among LMWH recipients and 13% (95% CI, 6.8 to 24) among those not receiving LMWH (OR, 0.23; 95% CI, 0.11 to 0.46; 95% PI, 0.02 to 2.3; *P*<0.001). There was no difference in major bleeding (OR 1.2, 95% CI, 0.56 to 2.5; 95% PI, 0.04 to 37; *P*=0.67). In the sensitivity analysis using the positivity threshold of 2 points, LMWH was associated with an OR of 0.34 for VTE (95% CI, 0.20 to 0.58; *P*<0.001) and 1.4 for major bleeding (95% CI, 0.74 to 2.7; *P*=0.29). Table 5B shows the summary of findings regarding the efficacy and safety of thromboprophylaxis in patients with a high-risk Khorana score, separately for all cancer types and those with non-lung cancer.

**DISCUSSION**

In this large individual patient data meta-analysis, the overall discriminatory performance of the Khorana score was suboptimal. Overall, patients with solid cancer receiving chemotherapy who had a high-risk Khorana score (≥3 points) had a 1.6-fold higher 6-month VTE incidence compared to patients with a low-to-intermediate risk score, corresponding to an absolute risk difference of 3.4%. Discrimination of the score appeared inconsistent across cancer types, with poor performance in lung cancer patients and good performance in the combined group of those with other types of cancer. Among cancer patients with a high-risk Khorana score, LMWH in prophylactic doses reduced the risk of VTE at 6 months by two-thirds, compared to placebo or observation, with no increase in major bleeding.

A strength of the present study is that it combines patient-level data of almost 7,000 patients, enabling robust evaluation of the Khorana score as well as of the effectiveness and safety of LMWH among those with a high-risk score. Data were collected in seven high-quality randomized controlled trials which succeeded in limiting loss to follow-up. A limitation is that only eight types of cancer could be evaluated, and the group of non-lung cancer patients was heterogeneous. Some of the subgroup analyses, particulary in patients with bladder or brain cancer, were based on small numbers of patients and events obtained from only one trial, limiting the precision of the estimates. Similarly, no events were observed in patients with ovarian cancer or breast cancer patients with a high-risk Khorana score. Although the definition of VTE was similar across the studies, it was not identical. For example, incidentally detected VTE was not always included in the outcome and the definition of DVT varied. Since logistic regression rather than survival analysis was used to estimate the VTE risk at 6 months, our absolute risk estimates may have been conservative, although loss to follow-up was minimal in most studies. As reflected by the wide prediction intervals, substantial between-study heterogeneity was observed in the evaluations of the Khorana score. This was most likely due to the differences in cancer types across studies, since τ2 of the random effect decreased to 0 when type of cancer was added to the model (data not shown). The prediction intervals need to be interpreted with caution though, since the number of studies was small. The search was performed in 2017, but to the best of our knowledge no new trials evaluating LMWH in patients with active cancer have been published, only in the adjuvant treatment setting.

Our findings are largely in line with other reports, in which results about the performance of the Khorana score have been conflicting. Some studies of mixed oncology populations,9,10 germ cell tumors,39 and colorectal cancer40 confirmed the discriminative performance of the Khorana score, whereas other studies including patients with different types of cancer,41 pancreatic cancer,11,42 hepatocellular carcinoma,43 urothelial cell cancer,12 or lung cancer44 did not. The same conclusion was drawn in a recent systematic review and meta-analysis on the performance of the Khorana score;45 the overall odds ratio between low-to-intermediate and high-risk patients was 1.8, while it ranged from 1.0 in lung cancer patients to 3.0 in those with urogenital cancer. This heterogeneous performance of the score may reflect the different natural history of VTE across various cancer types and patient populations, as well as differences in design between the original cohort study and subsequent studies, including the present analysis.

Although the Khorana score has been introduced as a pan-cancer risk assessment tool, the present analysis challenges that concept. Clinically significant differences in the discriminatory performance of the Khorana score across cancer types were observed. Most patients included in this individual patient data meta-analysis had lung cancer, and in this subgroup in particular, moderate quality evidence suggests that the Khorana score is not discriminatory as reflected by the odds ratio of 1.1. In contrast, when aggregating data of all patients diagnosed with cancers other than lung cancer, moderate quality evidence suggests that a high-risk Khorana score is associated with a clinically and statistically significant 3-fold higher risk of VTE. Differences in baseline risk across cancer types are a likely explanation for this effect modification, supported by the results of the multivariable analysis, in which the predictive performance of the Khorana score appeared to be driven by the item ‘tumor type’, while the other items were only weakly associated with the development of VTE. This illustrates that clinicians should be cautious if applying the Khorana score as a universal risk assessment tool.

Thromboprophylaxis effectively prevents VTE in patients with solid cancer. Overall, LMWH approximately halves the risk of VTE, while not resulting in an important increase in major bleeding.46 The present study provides high certainty evidence that LMWH is also safe and effective in patients classified as high-risk by the Khorana score. When using the Khorana score for risk stratification in patients with cancer originating outside the lungs and treating only high-risk patients, our analysis suggests that as few as 10 such patients need to receive LMWH for 6 months to prevent one VTE event. However, for a small group of patients who may be averse to daily self-injection of LMWH for at least 6 months, the burden may still not be perceived worth the anticipated desirable health outcomes. Direct oral anticoagulants have the potential to ameliorate this. A recently completed randomized placebo-controlled trial showed that apixaban in prophylactic doses effectively reduces the risk of venous thromboembolism in cancer patients with a Khorana score of 2 points or higher, with a number needed to treat of 17.23 Similarly, rivaroxaban thromboprophylaxis was associated with a non-significant 2.8% absolute VTE risk reduction in a placebo-controlled enrolling cancer patients with a Khorana score of at least 2 points.24 In both trials, the risk of major bleeding was two-fold increased in the direct oral anticoagulant groups with a corresponding number needed to harm of 50 to 100. Our analysis, though, does not support the use of a 2-point positivity threshold to select patients for thromboprophylaxis, since the risk of VTE was not significantly higher in patients with 2 or more points compared to those with 0 or 1 point. Also, the number needed to treat for LMWH increased from 10 to 17 in the non-lung cancer patients when applying this threshold.

The present analysis supports the use of the Khorana score to select patients with other types of cancer than lung cancer for thromboprophylaxis. About one of every five non-lung cancer patients had a high-risk Khorana score, and these patients had a three-fold higher risk of VTE when compared to patients with a low-to-intermediate-risk score resulting in a 10% absolute risk over the 6-month study period. Importantly, thromboprophylaxis appeared to be very effective and safe in preventing VTE in this high-risk group. At the same time, this analysis highlights the limited sensitivity of the Khorana score. That is, while the risk is significantly elevated in cancer patients with a high Khorana score, the majority of VTE events still occur in the (much larger) low-risk group. This calls for development of risk prediction tools that are either designed for a single type of cancer, by including cancer-specific risk factors for VTE, or a new or updated pan-cancer prediction tool with actionable performance across a broad range of tumor types. A variety of prediction tools for cancer-associated VTE aimed at improving risk stratification have already been proposed, but none of these has been widely adopted because they rely on the addition of tests not routinely used in clinical practice, perform only modestly better than the Khorana score, or are in need of external validation.47–50 There is significant room for improvement in evaluating the risk of VTE in patients with solid cancer who receive chemotherapy, but whether this will involve the addition of further parameters to pre-existing risk stratification tools or the evaluation of novel new biomarkers remains to be seen.

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Declaration of interests: NvE has received advisory board honoraria from Bayer, LEO Pharma, and Daiichi Sankyo. DG has been a consultant or received research funding from Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Daiichi-Sankyo, Janssen, Pfizer and Portola. SN is on the advisory boards for Leo Pharma, Pfizer, Bristol Meyers Squibb and Bayer. He has received honoraria for Leo Pharma, Pfizer and Boheringer Ingelheim, and has received grants from Leo Pharma and Pfizer. GG has been a consultant for Pfizer on trial design and has also received free drugs from Pfizer for cancer related trials under the UK National Cancer Research Institute. MDN has received consulting fees from Bayer Health Care and Grifols. SM has received consulting fees from Portola. MS has received research funding from Portola and has consulted for Daiichi-Sankyo, Boehringer, Pfizer and Janssen Healthcare. AM has received an advisory board honoraria for Leo Pharma and Bayer. WA has accepted consulting fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Meyers Squibb, Daiichi-Sankyo and Italfarmaco. WA has also received research support from Bayer. MAC reports receiving fees for participation in Data Safety Monitoring committees from Bayer and Daiichi, fees for advisory boards or educational material preparation/presentation from Shionogi, Portola, Octapharma, Bayer, Pfizer, Alexion, and Boerhringer Ingelheim, Institutional funding from Bayer and Leo Pharma and personal stock ownership in Alnylam. None of the other authors report any conflicts of interest.

**Table 1. Study characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Design | Inclusion period | Patients | Experimental treatment | Randomized patients | Patients in control group | Follow-up | Definition of VTE |
| Agnelli (2012)26 | Double-blind | June 2008-November 2010 | Locally advanced or metastatic cancer of lung, pancreas, stomach, colon, bladder, or ovary | Semuloparin 20 mg od during chemotherapy | 3,212 | 1,604 | 12 months | Adjudicated symptomatic DVT of lower or upper extremities, non-fatal PE, or VTE-related death |
| Haas (2005) 25 | Double-blind | Apr 1999-Nov 2004 | Metastatic breast cancer | Certoparin 3,000 IU od for 6 months | 353 | 178 | 6 months | Objectively confirmed symptomatic or asymptomatic distal or proximal DVT, symptomatic PE, upper extremity DVT, or superficial thrombosis if requiring treatment |
| Haas (2012)25 | Double-blind | Apr 1999-Nov 2004 | Stage III or IV non-small cell lung cancer  | Certoparin 3,000 IU od for 6 months | 547 | 273 | 6 months | Objectively confirmed symptomatic or asymptomatic distal or proximal DVT, symptomatic PE, UEDVT, superficial thrombosis if requiring treatment |
| Lecumberri (2013)30 | Open-label | Oct 2005-Jan 2010 | Limited disease small cell lung cancer | Bemiparin 3,500 IU od for 26 weeks or until disease progression | 39 | 18 | Until death | Objectively confirmed symptomatic VTE |
| Macbeth (2015)27 | Open-label | Sep 2007-Dec 2011 | Lung cancer | Dalteparin 5,000 IU od for 24 weeks | 2,202 | 1,101 | Until death | Objectively confirmed DVT of upper or lower extremities, arterial thromboembolic events, or PE |
| Pelzer (2015)28 | Open-label | Apr 2004-Jan 2009 | Pancreatic cancer | Weight-adjusted enoxaparin (1mg/kg) for 3 months, followed by 40 mg od until disease progression | 312 | 152 | 18 months | Objectively confirmed symptomatic VTE |
| Perry (2010)29 | Double-blind | Oct 2002-May 2006 | WHO grade 3 or 4 glioma | Dalteparin 5,000 IU od for at least 6 months | 186 | 87 | 12 months | Adjudicated symptomatic proximal lower extremity DVT or PE |

Abbreviations: DVT, deep vein thrombosis; IU, international units; od, once daily; PE, pulmonary embolism; VTE, venous thromboembolism; WHO, World Health Organization.
Patients in the control groups were used in the analysis on the performance of the Khorana score.

**Table 2. Baseline characteristics**

|  |  |
| --- | --- |
|  | Placebo / observation(N=3,293) |
| Mean age, years (SD) | 61 (10) |
| Male sex, n (%) | 1,927 (59) |
| Body mass index |  |
|  Mean, kg/m2 (SD) | 25 (5) |
|  >35 kg/m2, n (%) | 153 (4.6) |
| Cancer type, n (%) |  |
|  Lung | 1,913 (58) |
|  Colorectal | 452 (14) |
|  Pancreatic | 264 (8.0) |
|  Stomach | 201 (6.1) |
|  Ovarian | 184 (5.6) |
|  Breast | 164 (5.0) |
|  Brain | 84 (2.6) |
|  Bladder | 31 (0.9) |
| Metastatic disease, n (%) | 2,253 (68) |
| Chemotherapy, n (%) | 3,076 (93) |
| WHO performance status, n (%) |  |
|  0 | 1,053 (32) |
|  1 | 1,592 (48) |
|  ≥2 | 320 (9.7) |
| Use of erythropoietin stimulating agents, n (%) | 142 (4.3) |
| Baseline hemoglobin <10 g/dL, n (%) | 233 (7.1) |
| Baseline leukocyte count >11 x 109/L, n (%) | 784 (24) |
| Baseline platelet count ≥350 x 109/L, n (%) | 1,117 (34) |
| Khorana score, n (%) |  |
|  0 points | 402 (12) |
|  1 point | 1,033 (31) |
|  2 points | 1,088 (33) |
|  ≥3 points | 770 (23) |

Abbreviations: SD, standard deviation.

**Table 3. Association between dichotomous Khorana score and venous thromboembolism**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Proportion high-risk% (95% CI) | VTE in high-risk patients% (95% CI) | VTE in low-to-intermediate risk patients% (95% CI) | Odds ratio VTE high-risk vs low-to-intermediate-risk(95% CI) |
| Overall (N=3,293)(7 studies) | 18(5.2-46) | 9.9(6.4-15) | 6.4(4.2-9.7) | 1.6(1.1-2.2) |
| Lung cancer(N=1,913)(4 studies) | 22(18-27) | 6.6(4.7-9.2) | 6.0(4.9-7.4) | 1.1(0.72-1.7) |
| Colorectal cancer(N=452)(1 study) | 1.8(0.9-3.5) | 13(1.7-54) | 1.8(0.9-3.6) | 7.8(0.86-71) |
| Pancreatic cancer(N=264)(2 studies) | 51(36-66) | 16(11-23) | 7.9(4.3-14) | 2.2(1.02-4.9) |
| Gastric cancer(N=201)(1 study) | 42(35-49) | 2.4(0.60-9.0) | 1.7(0.4-6.6) | 1.4(0.19-10) |
| Ovarian cancer(N=184)(1 study) | 13(8.4-18) | 0 | 0 | NA |
| Breast cancer(N=164)(1 study) | 0 | NA | 3.1(1.3-7.0) | NA |
| Brain cancer(N=84)(1 study) | 50(39-61) | 21(12-36) | 7.1(2.3-20) | 3.5(0.89-14) |
| Bladder cancer(N=31)(1 study) | 23(11-40) | 14(2.0-58) | 8.3(2.1-28) | 1.8(0.14-24) |
| Other types than lung cancer (N=1,380)(4 studies) | 13(0.9-72) | 12(6.8-22) | 4.3(2.3-8.0) | 3.2(1.8-5.6) |
| Metastatic cancer(N=2,253)(5 studies) | 14(2.4-53) | 9.5(6.0-15) | 5.1(3.3-7.8) | 1.9(1.3-2.9) |

Analysis restricted to patients in the placebo / observation groups.

Abbreviations: CI, confidence interval; NA, not available; VTE, venous thromboembolism.

**Table 4A. Summary of findings regarding prognostic performance of the Khorana score**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient group** | **Outcomes** | **No. of participants (studies)Follow-up** | **Quality of evidence** **(GRADE)** | **Relative effect (95% CI)** | **Risk with low or intermediate risk Khorana score** | **Risk with high-risk Khorana score** | **Summary** |
| All patients | Venous thromboembolism | 3,293(7 studies)6 months | **Low**due to risk of bias and a combination of inconsistency and imprecision | OR 1.6 (1.1 to 2.2) | 64 per 1,000 | 99 per 1,000 | Low quality evidence suggests that a high risk Khorana score is associated with a moderately increased 6-month risk of venous thromboembolism in patients with solid cancer |
| Lung cancer patients | Venous thromboembolism | 1,913(4 studies)6 months | **Moderate**due to risk of bias | OR 1.1(0.72 to 1.7) | 60 per 1,000 | 66 per 1,000 | Moderate quality evidence suggests that a high risk Khorana score is not associated with an increased 6-month risk of venous thromboembolism in patients with lung cancer |
| Non-lung cancer patients | Venous thromboembolism | 1,380(4 studies)6 months | **Moderate**due to risk of bias | OR 3.2(1.8 to 5.6) | 43 per 1,000 | 125 per 1,000 | Moderate quality evidence suggests that a high risk Khorana score is associated with a substantially increased 6-month risk of venous thromboembolism in patients with cancer other than lung cancer |

**Table 4B. Summary of findings regarding efficacy and safety of thromboprophylaxis in high-risk Khorana score patients**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient group** | **Outcomes** | **No. of participants (studies)Follow-up** | **Quality of evidence** **(GRADE)** | **Relative effect (95% CI)** | **Risk without thromboprophylaxis** | **Risk difference with thromboprophylaxis** | **Summary** |
| Cancer patients with high-risk Khorana score | Venous thromboembolism | 1,514(7 studies)6 monthsLMWH group: 25/744Non-LMWH group: 66/770 | **High** | OR 0.36(0.22 to 0.58) | 98 per 1,000 | 60 per 1,000 fewer(34 to 76 per 1,000 fewer) | Among cancer patients with a high risk Khorana score, high quality evidence suggests that prophylactic (ultra)-low-molecular-weight heparin significantly reduces the 6-month risk of venous thromboembolism |
|  | Major bleeding | 1,514(7 studies)6 monthsLMWH group: 22/744Non-LMWH group: 19/770 | **Moderate**due to imprecision | OR 1.1 (0.59 to 2.1) | 20 per 1,000 | 2 per 1,000 more(-13 to 48 per 1,000 more) | Among cancer patients with a high risk Khorana score, moderate quality evidence suggests that prophylactic (ultra)-low-molecular-weight heparin does not increase the 6-month risk of major bleeding |
| Non-lung cancer patients with high-risk Khorana score | Venous thromboembolism | 619(4 studies)6 monthsLMWH group: 10/318Non-LMWH group: 35/301  | **High** | OR 0.23(0.11 to 0.46) | 130 per 1,000 | 97 per 1,000 fewer(53 to 116 per 1,000 fewer) | Among patients with cancer other than lung cancer a high risk Khorana score, high quality evidence suggests that prophylactic (ultra)-low-molecular-weight heparin does not increase the 6-month risk of venous thromboembolism |
|  | Major bleeding | 619(4 studies)6 monthsLMWH group: 17/318Non-LMWH group: 13/301 | **Moderate**due to imprecision | OR 1.2 (0.56 to 2.5) | 21 per 1,000 | 4 per 1,000 more(-17 to 122 per 1,000 more) | Among patients with cancer other than lung cancer a high risk Khorana score, moderate quality evidence suggests that prophylactic (ultra)-low-molecular-weight heparin does not increase the 6-month risk of major bleeding |

**Supplementary Figure 1. Risk of bias summary for venous thromboembolism and major bleeding**

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Judgements about each methodological quality item for each included study.

Studies: Agnelli (2012)26, TOPIC-1 (2005)25, TOPIC-2 (2012)25, Lecumberri (2013)30, Macbeth (2015)27, Pelzer (2015)28, Perry (2010)29

**Supplementary Figure 2. Forest plot of areas under the receiver operating characteristics curves**



Forest plot displays area under receiver operating characteristic curves after transformation from logit scale. Heterogeneity: I2=57%, *P*=0.03. Studies: Agnelli (2012)26, TOPIC-1 (2005)25, TOPIC-2 (2012)25, Lecumberri (2013)30, Macbeth (2015)27, Pelzer (2015)28, Perry (2010)29

**Supplementary Table 1. Results of risk of bias assessment in the control group using QUIPS tool**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Study participation** | **Study attrition** | **Outcome measurement** |
| Agnelli (2012) | Low risk | Low risk | Low risk |
| Haas (2005) | Low risk | High risk | Low risk |
| Haas (2012) | Low risk | High risk | Low risk |
| Lecumberri (2013) | Low risk | Unclear risk | Moderate risk |
| Macbeth (2015)  | Low risk | Low risk | Low risk |
| Pelzer (2015)  | Low risk | Moderate risk | Moderate risk |
| Perry (2010)  | Moderate risk | Low risk | Low risk |

**Supplementary Table 2. Multivariable analysis of Khorana score items**

|  |  |  |
| --- | --- | --- |
| **Khorana score item** | **Adjusted odds ratio****(95% CI)** | **P-value** |
| High-risk tumor type (vs low risk) | 1.8 (1.05-3.1) | 0.032 |
| Very high-risk tumor type (vs low risk) | 2.4 (1.4-4.4) | 0.003 |
| Hemoglobin <10 g/dL or ESA use | 1.01 (0.68-1.5) | 0.97 |
| White blood cell count >11 x 109/L | 1.3 (1.00-1.8) | 0.050 |
| Platelet count ≥350 x 109/L | 0.88 (0.67-1.2) | 0.37 |
| Body mass index >35 kg/m2 | 1.6 (0.97-2.6) | 0.067 |

Abbreviations: CI, confidence interval; ESA, erythropoietin stimulating agent.

**Supplementary Table 3A. Venous thromboembolism for each Khorana score per included study during 6-month follow-up**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **0 points** | **1 point** | **2 points** | **3 points** | **4 points** | **5 points** |
|  | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** |
|  | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** | **No VTE** | **VTE** |
| Agnelli (2012)  | 292 | 5 | 308 | 2 | 451 | 18 | 480 | 8 | 490 | 16 | 479 | 5 | 205 | 13 | 208 | 5 | 58 | 1 | 59 | 2 | 4 | 0 | 6 | 0 |
| Haas (2005)  | 100 | 5 | 107 | 4 | 53 | 1 | 35 | 1 | 5 | 0 | 12 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haas (2012)  | 0 | 0 | 0 | 0 | 113 | 8 | 120 | 5 | 80 | 7 | 92 | 5 | 42 | 5 | 32 | 1 | 7 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Lecumberri (2013)  | 0 | 0 | 0 | 0 | 7 | 3 | 9 | 0 | 6 | 0 | 9 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Macbeth (2015)  | 0 | 0 | 0 | 0 | 355 | 24 | 401 | 13 | 363 | 24 | 374 | 15 | 256 | 19 | 222 | 11 | 25 | 2 | 32 | 0 | 0 | 0 | 0 | 0 |
| Pelzer (2015)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 51 | 4 | 47 | 2 | 55 | 13 | 72 | 2 | 14 | 4 | 25 | 0 | 3 | 0 | 5 | 1 |
| Perry (2010)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 39 | 3 | 39 | 6 | 26 | 8 | 36 | 3 | 7 | 0 | 8 | 0 | 0 | 1 | 0 | 0 |

Abbreviations: O/P, observation/placebo groupVTE, venous thromboembolism.

**Supplementary Table 3B. Major bleeding for each Khorana score per included study during 6-month follow-up**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **0 points** | **1 point** | **2 points** | **3 points** | **4 points** | **5 points** |
|  | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** |
|  | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** |
| Agnelli (2012)  | 295 | 2 | 309 | 1 | 464 | 5 | 479 | 9 | 500 | 6 | 479 | 5 | 216 | 2 | 210 | 3 | 57 | 2 | 61 | 0 | 3 | 1 | 5 | 1 |
| Haas (2005) | 105 | 0 | 108 | 3 | 54 | 0 | 36 | 0 | 5 | 0 | 13 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haas (2012)  | 0 | 0 | 0 | 0 | 119 | 2 | 123 | 2 | 82 | 5 | 90 | 7 | 47 | 0 | 32 | 1 | 7 | 0 | 11 | 0 | 0 | 0 | 0 | 0 |
| Lecumberri (2013)  | 0 | 0 | 0 | 0 | 10 | 0 | 9 | 0 | 6 | 0 | 9 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Macbeth (2015)  | 0 | 0 | 0 | 0 | 375 | 4 | 405 | 9 | 377 | 10 | 384 | 5 | 272 | 3 | 229 | 4 | 27 | 0 | 32 | 0 | 0 | 0 | 0 | 0 |
| Pelzer (2015)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 55 | 0 | 49 | 0 | 60 | 8 | 65 | 9 | 16 | 2 | 22 | 3 | 3 | 0 | 5 | 1 |
| Perry (2010)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 42 | 0 | 42 | 3 | 34 | 0 | 39 | 0 | 7 | 0 | 8 | 0 | 1 | 0 | 0 | 0 |

**Supplementary Table 3C. All-cause mortality for each Khorana score per included study during 6-month follow-up**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **0 points** | **1 point** | **2 points** | **3 points** | **4 points** | **5 points** |
|  | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** | **O/P** | **Intervention** |
|  | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** | **No MB** | **MB** |
| Agnelli (2012)  | 274 | 23 | 282 | 28 | 392 | 77 | 404 | 84 | 375 | 131 | 376 | 117 | 135 | 83 | 154 | 59 | 34 | 25 | 41 | 20 | 1 | 3 | 4 | 2 |
| Haas (2005)  | 98 | 7 | 98 | 13 | 47 | 7 | 33 | 3 | 5 | 0 | 9 | 4 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haas (2012)  | 0 | 0 | 0 | 0 | 90 | 31 | 92 | 33 | 65 | 22 | 66 | 31 | 28 | 19 | 25 | 8 | 3 | 4 | 8 | 3 | 0 | 0 | 0 | 0 |
| Lecumberri (2013)  | 0 | 0 | 0 | 0 | 9 | 1 | 9 | 0 | 5 | 1 | 8 | 1 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Macbeth (2015)  | 0 | 0 | 0 | 0 | 315 | 64 | 345 | 69 | 268 | 119 | 278 | 111 | 164 | 111 | 140 | 93 | 14 | 13 | 17 | 15 | 0 | 0 | 0 | 0 |
| Pelzer (2015)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 31 | 24 | 35 | 14 | 48 | 20 | 54 | 20 | 15 | 3 | 15 | 10 | 2 | 1 | 2 | 4 |
| Perry (2010)  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 37 | 5 | 37 | 8 | 31 | 3 | 32 | 7 | 5 | 2 | 7 | 1 | 0 | 1 | 0 | 0 |

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