journal of
thrombosis and haemostasis

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Journal:	*Journal of Thrombosis and Haemostasis*
Manuscript ID	JTH-2020-00189.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Key Words:	individual participant data meta-analysis, khorana score, cancer, venous thromboembolism, thromboprophylaxis, GRADE

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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Essentials

- 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 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 a 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.

ABSTRACT

Background: 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.

Objective: To examine the performance of the Khorana score in assessing 6-month VTE risk, and the efficacy and safety of LMWH among high-risk Khorana score patients.

Methods: This individual patient data meta-analysis evaluated (ultra)-low-molecular-weight heparin (LMWH) in patients with solid cancer using data from seven randomized controlled trials.

Results: A total of 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%). 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 cancer types (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 controls (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).

Conclusion: The Khorana score was unable to stratify patients with lung cancer based on their VTE risk. Among those with other cancer types, a high-risk score was associated with a 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.

Keywords: Venous thromboembolism, individual participant data meta-analysis, thromboprophylaxis, heparin, Khorana score, cancer

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 10^9/L (1 point), platelet count ≥350 x 10^9/L (1 point), and body mass index >35 kg/m^2 (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 (Supplementary Table 1). We contacted authors and sponsors of eligible trials by email, fax or telephone, to invite them to share their data. When necessary, we placed data sharing requests through clinicalstudydatarequest.com. Shared data were compared to published results and study authors were contacted to resolve discrepancies. No outstanding issues were inconsistencies were identified. 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 and the GRADEpro app (www.gradepro.org) 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 I^2 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 decision 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 fourteen available randomized studies provided data required to calculate the Khorana score [25–30]; we excluded the other seven studies [31–36] (Supplementary Figure 1). 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 2 summarizes 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 2 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 a substantial proportion of patients were lost to follow-up [28] 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 VTE [28] or absence of central adjudication of outcomes [30].
Supplementary Figure 2 presents results of the risk of bias assessment for the evaluation of the efficacy and safety of thromboprophylaxis. Three studies were not placebo controlled[27,28,30] 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 (I^2=57%, *P*=0.03; Supplementary Figure 3). 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 surgery[27,28,30,38] 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; $P_{interaction}$=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 3 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/m^2 (OR 6.6; 95% CI, 1.2 to 36; $P_{interaction}$=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 4A). The treatment effect of LMWH was not significantly modified by the dichotomous Khorana score ($P_{interaction}$=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 4B) 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 4C). 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, particularly 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 τ^2 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 cancer [40] 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 cancer [44] 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 trial of 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 biomarkers remains to be seen.

ACKNOWLEDGMENTS

The authors would like to thank the research organizations and authors responsible for sharing primary clinical trial data: Sanofi, Novartis Pharma GmbH, Instituto Científico y Tecnológico, University of Navarra, Velindre National Health Service Trust, Charité–Universitätsmedizin Berlin, and Sunnybrook Health Sciences Centre.

Funding: This project is funded by a Knowledge Synthesis grant awarded by the Canadian Institutes for Health Research (grant KRS 126594) to HJS. The Canadian Institutes for Health Research had no role in the design, analysis or interpretation phases of this investigation.

Author contributions: HJS and EAA conceived of the study. HJS obtained funding. The concept and design of this study were generated primarily by NvE, MV, PMB, HRB, MDN, QZ, EAA, and HJS. MDN, SN, MC, MB, DG, GL, FM, GG, AI, JB, LM, IN, MB, JB, GG, SM, NS, MS, CK, TB, IF, OGA, ZS, WA, MM, GB, GZ, AM, BL, RL, JE, KS, CL, RM, SMB, UP, MA, MO, JP, and LK collected data in the original studies. NvE performed the statistical analyses. NvE, PMB, MDN, HRB, HJS, and MV interpreted the data and drafted the manuscript. QZ, EEA, SN, MC, MB, DG, GL, FM, GG, AI, JB, LM, IN, MB, JB, GG, SM, NS, MS, TB, IF, OGA, ZS, WA, MM, GB, GZ, AM, CK, BL, RL, JE, KS, CL, RM, SMB, UP, MA, MO, JP, and LK revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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/m^2 (SD)	25 (5)
>35 kg/m^2, 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 10^9/L, n (%)	784 (24)
Baseline platelet count ≥350 x 10^9/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	Certainty 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

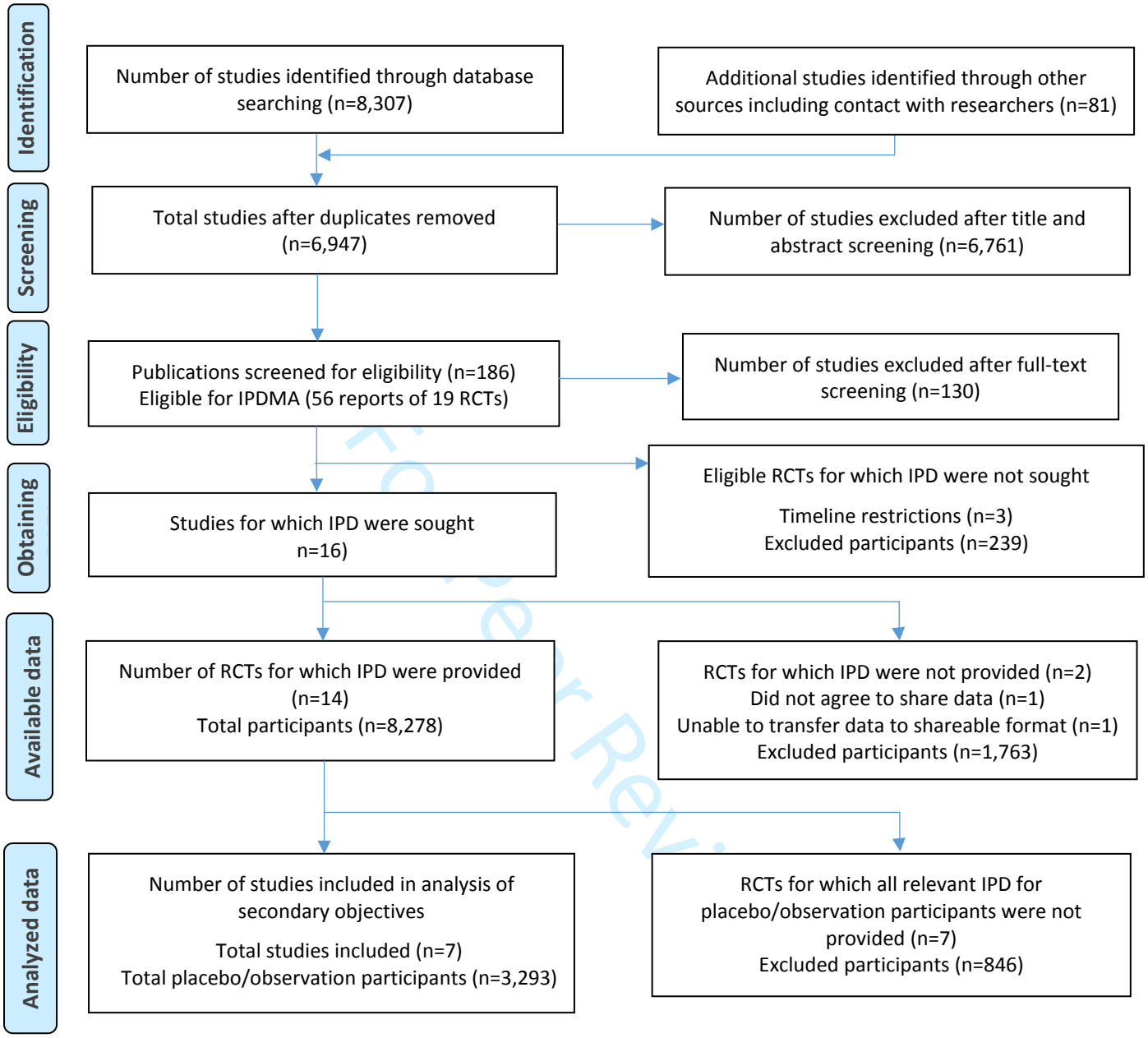
Table 4B. Summary of findings regarding efficacy and safety of thromboprophylaxis in high-risk Khorana score patients

Patient group	Outcomes	No. of participants (studies) Follow-up	Certainty 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 months LMWH group: 25/744 Non-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 months LMWH group: 22/744 Non-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 months LMWH group: 10/318 Non-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 months LMWH group: 17/318 Non-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

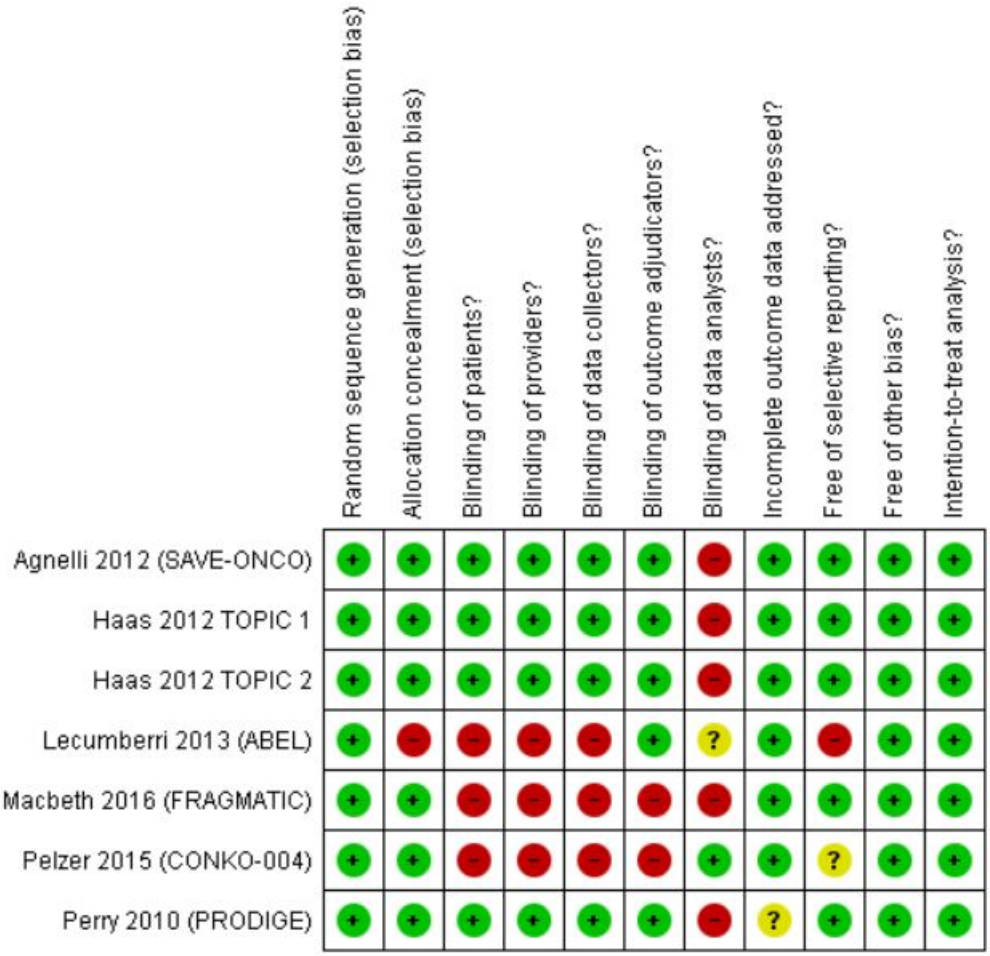
Heparin use in oncologic patients IPDMA

Supplementary Figure 1. PRISMA-IPD study selection flow chart



Heparin use in oncologic patients IPDMA

Supplementary Figure 2. Risk of bias summary for venous thromboembolism and major bleeding

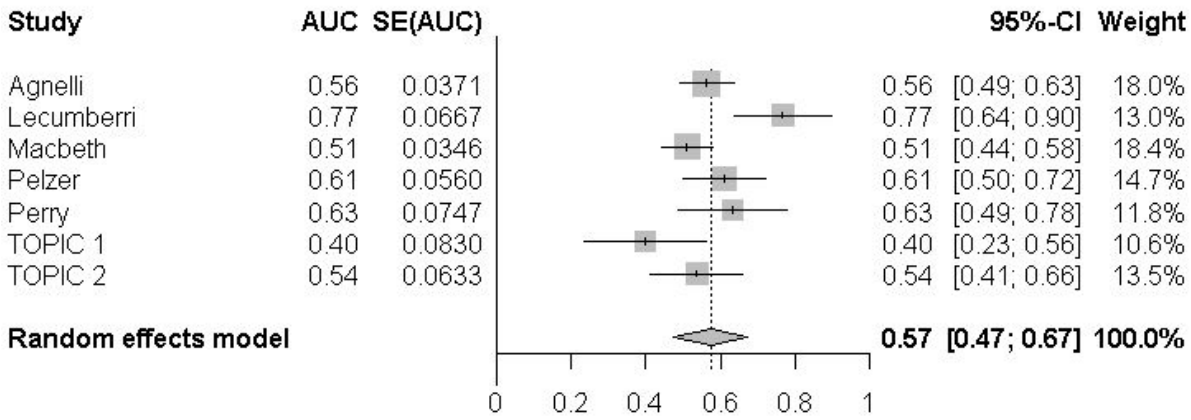


Judgements about each methodological quality item for each included study.

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

Heparin use in oncologic patients IPDMA

Supplementary Figure 3. 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: I^2=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]

Heparin use in oncologic patients IPDMA

Supplementary Table 1. Electronic search strategy for

Database	Strategy
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19

Supplementary Table 2. 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 3. 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 10^9/L	1.3 (1.00-1.8)	0.050
Platelet count ≥350 x 10^9/L	0.88 (0.67-1.2)	0.37
Body mass index >35 kg/m^2	1.6 (0.97-2.6)	0.067

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

Heparin use in oncologic patients IPDMA

Supplementary Table 4A. 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.

Heparin use in oncologic patients IPDMA

Supplementary Table 4B. 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

Heparin use in oncologic patients IPDMA

Supplementary Table 4C. 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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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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Essentials

- 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 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 a~~n~~ 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.

ABSTRACT

Background: 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.

Objective: To examine the performance of the Khorana score in assessing 6-month VTE risk, and the efficacy and safety of LMWH among high-risk Khorana score patients.

Methods: This individual patient data meta-analysis evaluated (ultra)-low-molecular-weight heparin (LMWH) in patients with solid cancer using data from seven randomized controlled trials.

Results: A total of 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%). 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 cancer types (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 controls (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).

Conclusion: The Khorana score was unable to stratify patients with lung cancer based on their VTE risk. Among those with other cancer types, a high-risk score was associated with a 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.

Keywords: Venous thromboembolism, individual participant data meta-analysis, thromboprophylaxis, heparin, Khorana score, cancer

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 10^9/L (1 point), platelet count ≥350 x 10^9/L (1 point), and body mass index >35 kg/m^2 (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 (Supplementary Table 1). We contacted authors and sponsors of eligible trials by email, fax or telephone, to invite them to share their data. When necessary, we placed data sharing requests through clinicalstudydatarequest.com. Shared data were compared to published results and study authors were contacted to resolve discrepancies. No outstanding issues were inconsistencies were identified. 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 and the GRADEpro app (www.gradepro.org) 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 I^2 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~~ decision 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 fourteen available randomized studies provided data required to calculate the Khorana score [25–30]; we excluded the other seven studies [31–36] (Supplementary Figure 1). 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 2 summarizes 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 2 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-up [28] 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 VTE [28] or absence of central adjudication of outcomes [30]. Supplementary Figure 2 presents results of the risk of bias assessment for the evaluation of the efficacy and safety of thromboprophylaxis. Three studies were not placebo controlled[27,28,30] 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 (I^2=57%, *P*=0.03; Supplementary Figure 3). 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 surgery[27,28,30,38] 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; $P_{interaction}$=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 3 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/m^2 (OR 6.6; 95% CI, 1.2 to 36; $P_{interaction}$=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 4A). The treatment effect of LMWH was not significantly modified by the dichotomous Khorana score ($P_{interaction}$=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 4B) 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 4C). 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, particularly 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 τ^2 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 cancer [40] 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 cancer [44] 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 trial ~~enrolling~~ of 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.

ACKNOWLEDGMENTS

The authors would like to thank the research organizations and authors responsible for sharing primary clinical trial data: Sanofi, Novartis Pharma GmbH, Instituto Científico y Tecnológico, University of Navarra, Velindre National Health Service Trust, Charité–Universitätsmedizin Berlin, and Sunnybrook Health Sciences Centre.

Funding: This project is funded by a Knowledge Synthesis grant awarded by the Canadian Institutes for Health Research (grant KRS 126594) to HJS. The Canadian Institutes for Health Research had no role in the design, analysis or interpretation phases of this investigation.

Author contributions: HJS and EAA conceived of the study. HJS obtained funding. The concept and design of this study were generated primarily by NvE, MV, PMB, HRB, MDN, QZ, EAA, and HJS. MDN, SN, MC, MB, DG, GL, FM, GG, AI, JB, LM, IN, MB, JB, GG, SM, NS, MS, CK, TB, IF, OGA, ZS, WA, MM, GB, GZ, AM, BL, RL, JE, KS, CL, RM, SMB, UP, MA, MO, JP, and LK collected data in the original studies. NvE performed the statistical analyses. NvE, PMB, MDN, HRB, HJS, and MV interpreted the data and drafted the manuscript. QZ, EEA, SN, MC, MB, DG, GL, FM, GG, AI, JB, LM, IN, MB, JB, GG, SM, NS, MS, TB, IF, OGA, ZS, WA, MM, GB, GZ, AM, CK, BL, RL, JE, KS, CL, RM, SMB, UP, MA, MO, JP, and LK revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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/m^2 (SD)	25 (5)
>35 kg/m^2, 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 10^9/L, n (%)	784 (24)
Baseline platelet count ≥350 x 10^9/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~~ Certainty 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

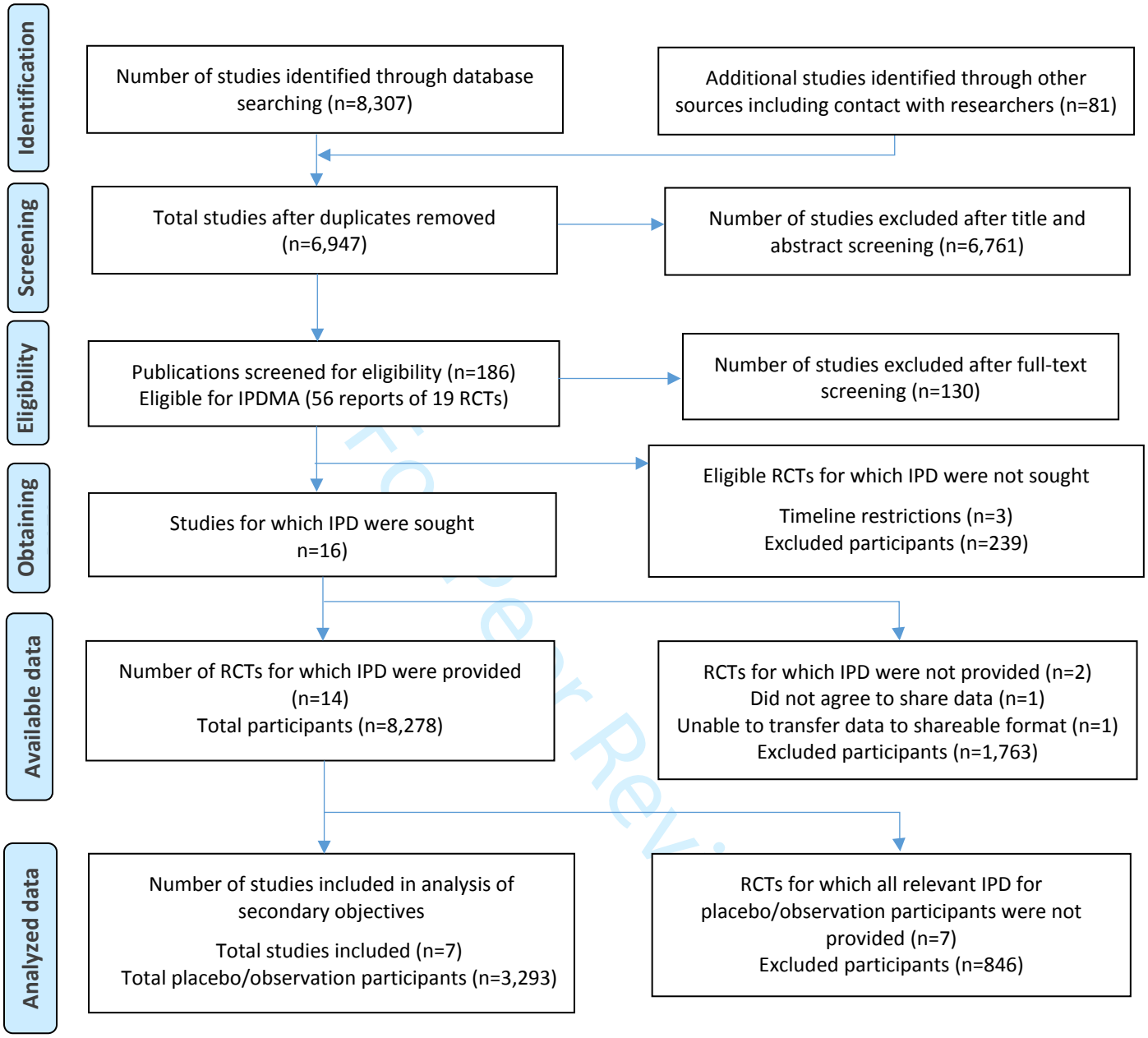
Table 4B. Summary of findings regarding efficacy and safety of thromboprophylaxis in high-risk Khorana score patients

Patient group	Outcomes	No. of participants (studies) Follow-up	~~Quality~~ Certainty 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 months LMWH group: 25/744 Non-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 months LMWH group: 22/744 Non-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 months LMWH group: 10/318 Non-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 months LMWH group: 17/318 Non-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

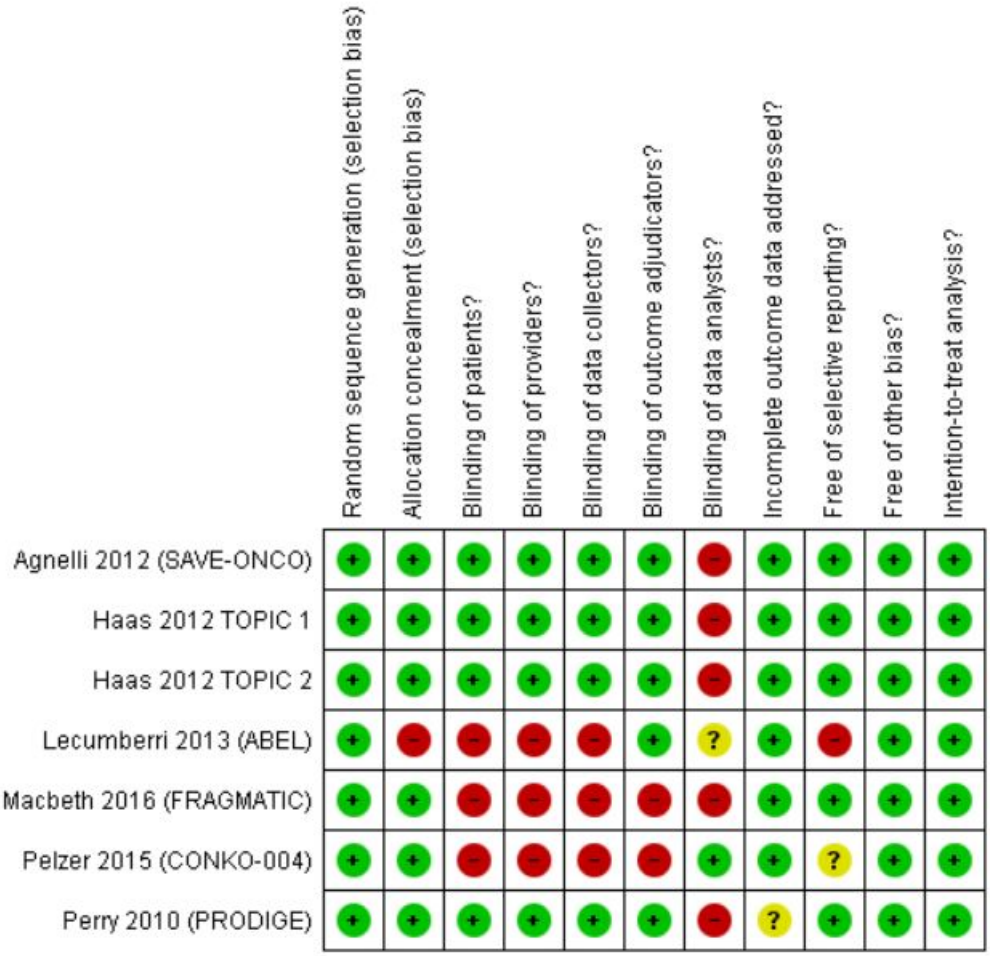
Heparin use in oncologic patients IPDMA

Supplementary Figure 1. PRISMA-IPD study selection flow chart



Heparin use in oncologic patients IPDMA

Supplementary Figure 2. Risk of bias summary for venous thromboembolism and major bleeding



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]

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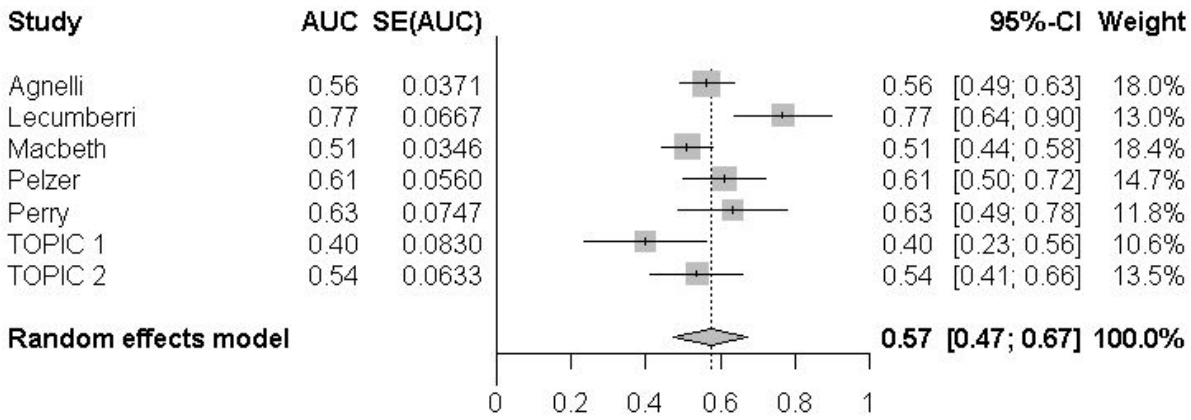
Supplementary Figure 3. Forest plot of areas under the receiver operating characteristics curves



Forest plot displays area under receiver operating characteristic curves after transformation from logit scale. Heterogeneity: I^2=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]

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Supplementary Table 1. Electronic search strategy for

Database	Strategy
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19

Supplementary Table 2. 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

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Supplementary Table 3. 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 10^9/L	1.3 (1.00-1.8)	0.050
Platelet count ≥350 x 10^9/L	0.88 (0.67-1.2)	0.37
Body mass index >35 kg/m^2	1.6 (0.97-2.6)	0.067

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

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Supplementary Table 4A. 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.

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Supplementary Table 4B. 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

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Supplementary Table 4C. 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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PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	3
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	4
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	4
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	4,5
Identifying studies -	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers	4,5

information sources		and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, SUP
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	4, 5
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	5
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	5, 6
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	5
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	5
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	5,6

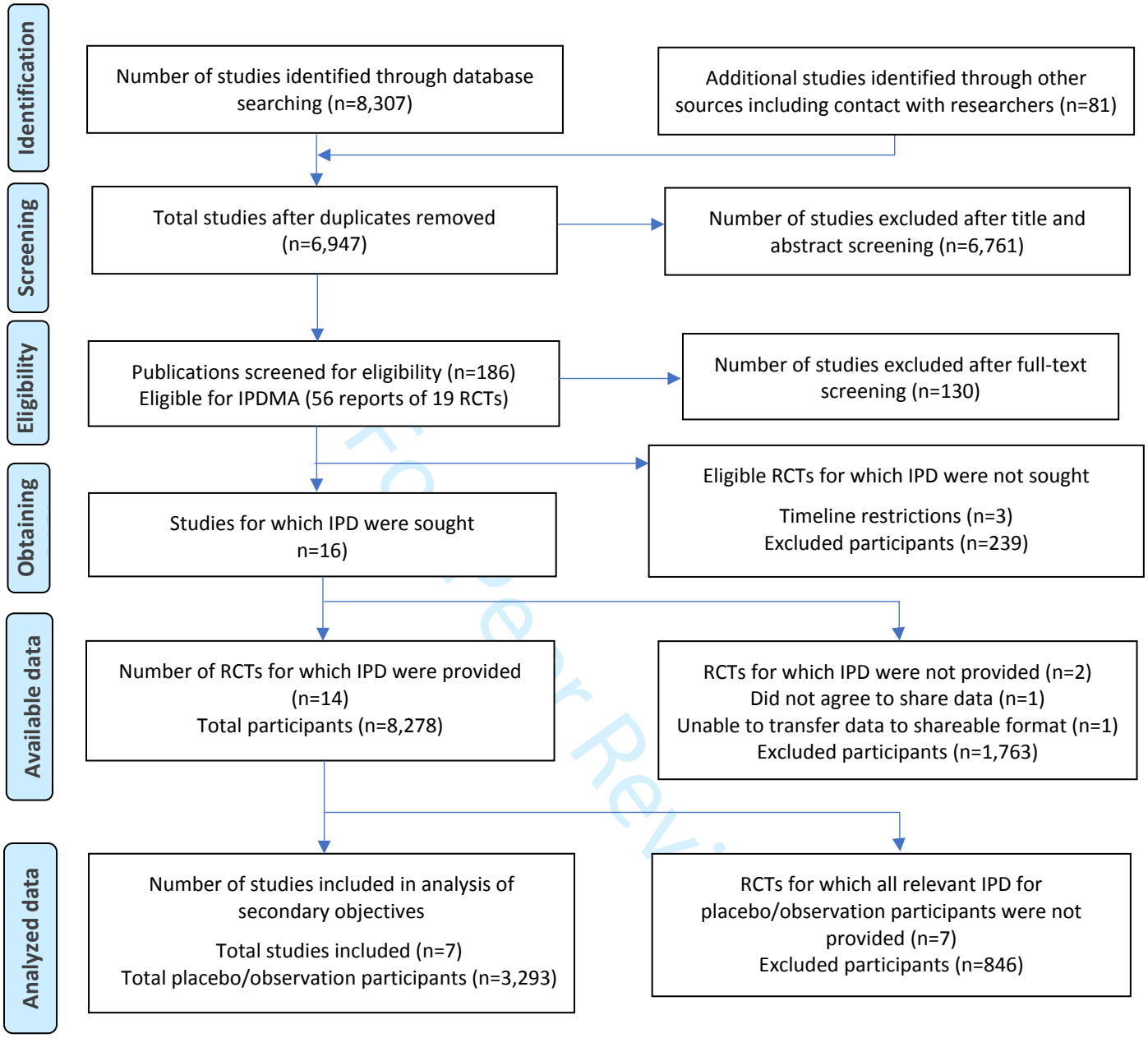
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	5, 6
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	5, 6
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	5, 6
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	6, 7
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	Sp fig 1, 7
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Table 1
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	5

Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Figure 2, pg 7,8
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Sp 3
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	Pg 8,9, 10 table 3, 4
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Figure 2, pg 7,8
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	Pg 9, 10
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	Table 4, pg 10, 11
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	pg 10, 11
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	Pg 11, 12
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	Pg 12
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	14

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

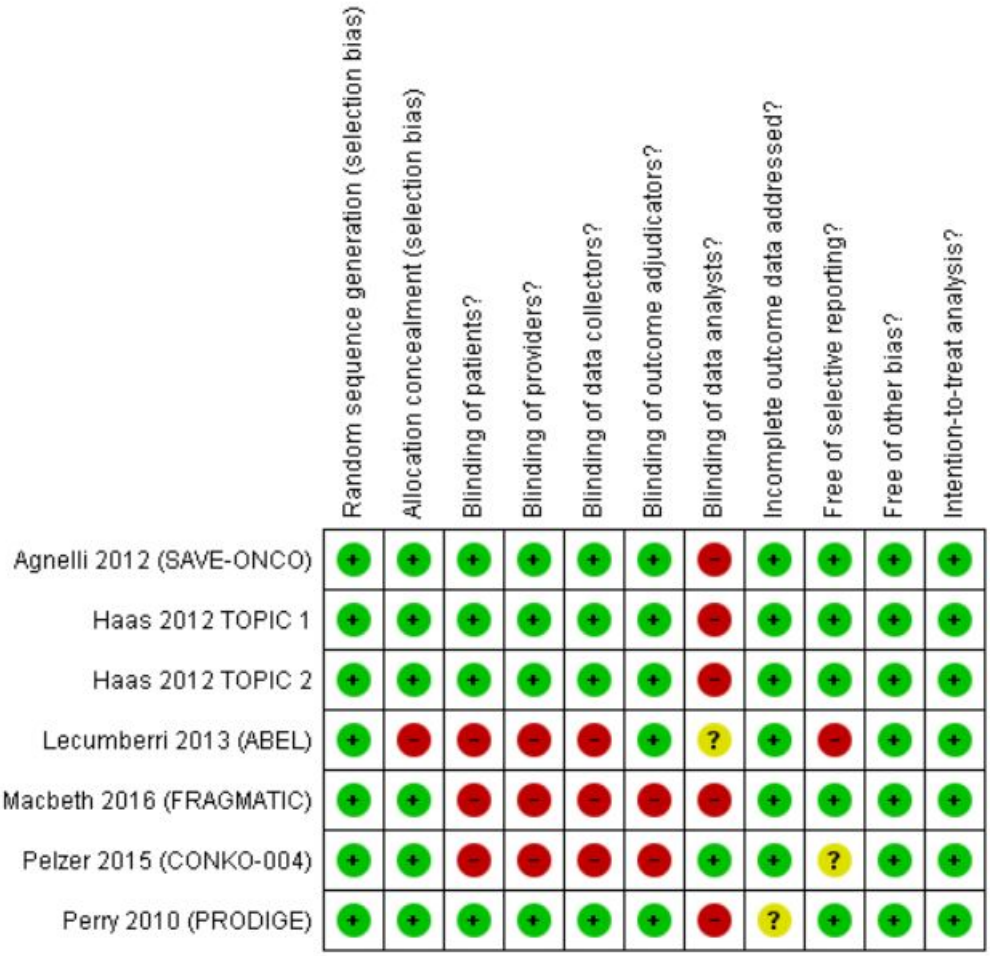
Heparin use in oncologic patients IPDMA

Supplementary Figure 1. PRISMA-IPD study selection flow chart



Heparin use in oncologic patients IPDMA

Supplementary Figure 2. Risk of bias summary for venous thromboembolism and major bleeding

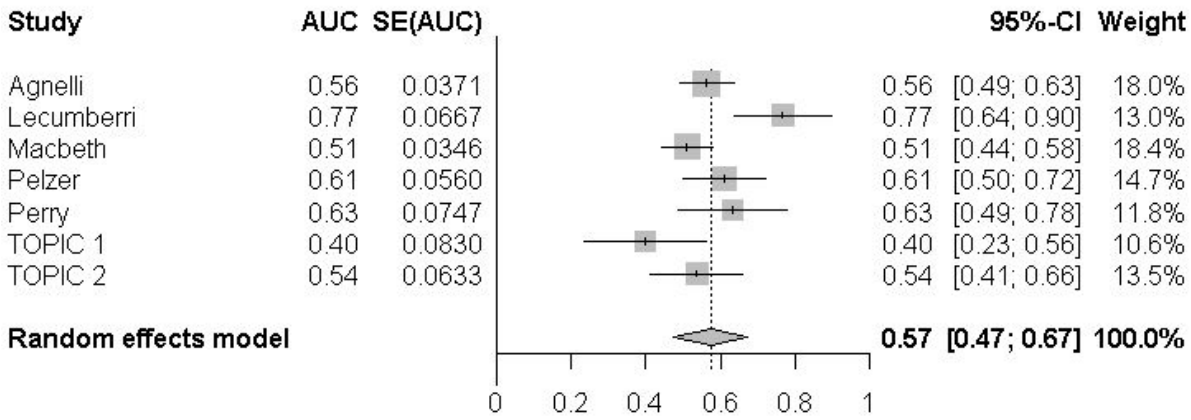


Judgements about each methodological quality item for each included study.

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

Heparin use in oncologic patients IPDMA

Supplementary Figure 3. 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: I^2=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]

Heparin use in oncologic patients IPDMA

Supplementary Table 1. Electronic search strategy for

Database	Strategy
MEDLINE	#1 Heparin/ #2 Heparin.tw #3 Heparin, Low-Molecular-Weight/ #4 (LMWH OR low molecular weight heparin OR nadroparin OR fraxiparin OR enoxaparin OR clexane OR lovenox OR dalteparin OR fragmin OR ardeparin OR normiflo OR tinzaparin OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR orgaran).tw #5 1 OR 2 OR 3 OR 4 #6 Coumarins/ #7 Warfarin/ #8 (warfarin OR coumadin OR acenocumarol OR phenprocumon OR 4-hydroxicoumarins OR oral anticoagulant OR vitamin K antagonist OR VKA).tw #9 6 OR 7 OR 8 #10 (fondaparinux OR Arixtra).tw #11 (ximelagatran OR Exanta).tw #12 (Pradaxa or Dabigatran or rivaroxaban or Xarelto or apixaban).tw. #13 5 OR 9 OR 10 OR 11 OR 12 #14 Neoplasms/ #15 (malignan$ OR neoplasm$ OR cancer OR carcinoma$ OR adenocarcinoma OR tumour OR tumor).tw #16 14 OR 15 #17 clinical trial.pt. OR random:.tw. OR tu.xs. #18 animals/ NOT human/ #19 17 NOT 18 #20 13 AND 16 AND 19

Supplementary Table 2. 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 3. Multivariable analysis of Khorana score items

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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 10^9/L	1.3 (1.00-1.8)	0.050
Platelet count ≥350 x 10^9/L	0.88 (0.67-1.2)	0.37
Body mass index >35 kg/m^2	1.6 (0.97-2.6)	0.067

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

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Supplementary Table 4A. 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.

Heparin use in oncologic patients IPDMA

Supplementary Table 4B. 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

Heparin use in oncologic patients IPDMA

Supplementary Table 4C. 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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