

University of Groningen

Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis

Eck, Ruben J.; Bult, Wouter; Wetterslev, Jorn; Gans, Reinold O. B.; Meijer, Karina; Keus, Frederik; van der Horst, Iwan C. C.

Published in:
 Seminars in thrombosis and hemostasis

DOI:
[10.1055/s-0039-1696965](https://doi.org/10.1055/s-0039-1696965)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
 Final author's version (accepted by publisher, after peer review)

Publication date:
 2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Eck, R. J., Bult, W., Wetterslev, J., Gans, R. O. B., Meijer, K., Keus, F., & van der Horst, I. C. C. (2019). Intermediate Dose Low-Molecular-Weight Heparin for Thrombosis Prophylaxis: Systematic Review with Meta-Analysis and Trial Sequential Analysis. *Seminars in thrombosis and hemostasis*, 45(8), 810-824. <https://doi.org/10.1055/s-0039-1696965>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Intermediate dose low-molecular-weight heparin for thrombosis prophylaxis: systematic review with meta-analysis and trial sequential analysis

Authors:

Ruben J. Eck, MD, r.j.eck@umcg.nl

¹ Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Wouter Bult, PhD, w.bult@umcg.nl

² Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands

³ Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Jørn Wetterslev, MD, PhD, joern.wetterslev@ctu.dk

⁴ The Copenhagen Trial Unit (CTU), Center for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark.

Professor Reinold O.B. Gans, MD, PhD, r.o.b.gans@umcg.nl

¹ Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Professor Karina Meijer, MD, PhD, k.meijer@umcg.nl

⁵ Department of Haematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Frederik Keus, MD PhD, f.keus@umcg.nl

³ Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Associate Professor Iwan C.C. van der Horst, MD, PhD, i.c.c.van.der.horst@umcg.nl

³ Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Corresponding author:

Ruben J. Eck, MD

University of Groningen

University Medical Center Groningen

Department of Internal Medicine

Hanzeplein 1

9700 RB Groningen

The Netherlands

Phone: +31 6 42514894

Fax: +31-503619986

Email: r.j.eck@umcg.nl, ruben.eck@hotmail.com

Word count:

Abstract: 274

Manuscript: 3903

Keywords: low-molecular-weight heparin, LMWH, thrombosis, systematic review, meta-analysis

Systematic review registration: PROSPERO CRD42016036951

Running title: Intermediate dose LMWH for thrombosis prophylaxis

ABSTRACT

Background: Different doses of low-molecular-weight heparin (LMWH) are registered and used for thrombosis prophylaxis. We assessed benefits and harms of thrombosis prophylaxis with a predefined intermediate dose LMWH compared to placebo or no treatment in patients at risk of venous thromboembolism (VTE).

Methods: We performed a systematic review with meta-analyses and trial sequential analyses (TSA) following *The Cochrane Handbook for Systematic Reviews of Interventions*. Medline, Cochrane CENTRAL, Web of Science, and Embase were searched up to December 2018. Trials were evaluated for risk of bias and quality of evidence was assessed following the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.

Results: Seventy randomized trials with 34,046 patients were included. Eighteen (26%) had overall low risk of bias. There was a small statistically significant effect of LMWH on all-cause mortality (risk ratio (RR) 0.96; trial sequential analysis-adjusted confidence interval (TSA-adjusted CI) 0.94-0.98) which disappeared in sensitivity analyses excluding ambulatory cancer patients (RR 0.99; TSA-adjusted CI 0.84-1.16). There was moderate quality evidence for a statistically significant beneficial effect on symptomatic VTE (odds ratio (OR) 0.59; TSA-adjusted CI 0.53-0.67; Number Needed to Treat (NNT) 76; 95%CI 60-106) and a statistically significant harmful effect on major bleeding (peto OR 1.66; TSA-adjusted CI 1.31-2.10; Number Needed to Harm (NNH) 212; 95%CI 142-393). There were no significant intervention effects on serious adverse events.

Conclusion: The use of intermediate dose LMWH for thrombosis prophylaxis compared to placebo or no treatment was associated with a small statistically significant reduction of all-cause mortality that disappeared in sensitivity analyses

excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent cause of morbidity and mortality.¹ Commonly recognized risk factors for VTE in acutely ill patients include age, active cancer, previous VTE, thrombophilia, reduced mobility, recent trauma or surgery, heart and/or respiratory failure, stroke, and sepsis.²

The American College of Chest Physicians (ACCP) guidelines recommend the use of mechanical or pharmacological thrombosis prophylaxis for surgical and acutely ill medical patients at high risk of thromboembolism.³ Multiple pharmacological agents such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are available for this indication. Several 'prophylactic doses' are registered for each LMWH type as reflected by differences between authorised summary of product characteristics (SPC) in the United States and Europe, and also by differences in dosing regimens in randomized trials.⁴⁻¹¹ The ACCP guidelines provide no recommendation regarding dose or type of LMWH for thrombosis prophylaxis.

Multiple systematic reviews have evaluated LMWH for thrombosis prophylaxis in specific patient groups, such as oncological patients¹²⁻¹⁴, orthopedic patients^{11,15}, and others.¹⁶⁻¹⁹ While evaluations of risks of bias are vital for any systematic review, these were parsimoniously considered. Further, only one systematic review, in

critically ill patients, used trial sequential analysis (TSA) ¹⁷, while the others did not apply any methods to account for risks of random error.^{12–19} No review evaluated benefits and harms associated with specifically a low or intermediate prophylactic LMWH dose.

Our aim was to perform a systematic review with meta-analyses and TSA of randomized clinical trials (RCTs) according to *The Cochrane Handbook for Systematic Reviews of Interventions* comparing the benefits and harms of a predefined intermediate dose LMWH versus placebo or no treatment in patients at risk of VTE.²⁰

METHODS

This systematic review was conducted according to a prepublished protocol on PROSPERO (CRD42016036951) following recommendations of *The Cochrane Handbook for Systematic Reviews of Interventions* and reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) checklist.^{20,21}

Eligibility criteria

We considered all RCTs for inclusion irrespective of language, blinding, publication status, or sample size. Quasi-randomized trials and observational studies were excluded. Only trials with adult patients at risk for VTE allocated to intermediate dose LMWH, placebo, or no treatment were eligible for inclusion, regardless their underlying illnesses or setting (hospital or outpatient).

Intervention

All trials that evaluated an intermediate dose of LMWH were considered, independent of the type of LMWH or duration of treatment. If different LMWHs or (weight adjusted) doses were used in one trial or even in one patient, we classified the trial according to what was used most frequently. Trials that evaluated ultra-low-molecular-weight heparin were included as well. We a priori defined 'low' and 'intermediate' dose LMWH in our protocol according to the SPCs as approved by the Food and Drug Administration, the European Medicines Agency and national authorities (Table 1 and Suppl. Table 1).⁴⁻¹⁰ The control intervention was either placebo or no treatment.

Outcomes

All outcomes were graded according to the patients' perspective following the *Grading of Recommendations Assessment, Development and Evaluation (GRADE)* approach (Suppl. Table 2).²² The primary outcome was all-cause mortality at maximum follow-up. Secondary outcomes were serious adverse events (SAE), symptomatic VTE, VTE screening (VTE diagnosed through screening of all patients in the trial), major bleeding, and heparin-induced thrombocytopenia (HIT). SAE was defined as a composite outcome measure summarizing all serious events necessitating an intervention, operation, or prolonged hospital stay according to the *International Council for Harmonisation - good clinical practice guideline*.²³ To assess the balance between thrombosis and bleeding, VTE symptomatic and major bleeding were regarded SAE when they were counted as such by the original trial, but mortality was excluded. VTE included both DVT and PE. A diagnosis of DVT or PE was accepted when confirmed by imaging technique or autopsy. No distinction was

made according to location of DVT. Major bleeding and HIT were registered according to trial criteria, yet HIT required laboratory confirmation.

Search strategy

We searched *the Cochrane Central Register of Controlled Trials (CENTRAL)* in *The Cochrane Library*, *PubMed/MEDLINE*, *EMBASE* and *Web of Science* (Suppl. Table 3). We searched the references of the identified trials and systematic reviews to identify any further relevant trials. Finally, we searched the *World Health Organization trial platform* and *ClinicalTrials.gov* for on-going trials.

Study selection and data extraction

Two authors independently identified trials for inclusion. Any indication for thrombosis prophylaxis was eligible. Trials excluded based on full text were listed with reasons for exclusion. We extracted characteristics of the trials (year of conduct and publication, country, numbers of participating sites and patients enrolled), participants (age, sex, inclusion and exclusion criteria), interventions (type, dose and duration of LMWH), and outcome. Corresponding authors were contacted in case of unclear or missing data. We resolved differences in opinion through discussion.

Bias risk assessment

Two authors independently assessed the risks of bias of the trials according to *The Cochrane Handbook for Systematic Reviews of Interventions*.²⁰ The following risk of bias domains were extracted from each trial: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. Trials were

classified as having overall low risk of bias if all the domains were assessed at low risk. Trials were considered to have overall high risk of bias if one or more of the bias risk domains were assessed as unclear or high risk of bias.²⁴

Statistical analysis

We performed the meta-analyses according to *The Cochrane Handbook for Systematic Reviews of Interventions* using the software package Review Manager 5.3.5.²⁰ The analyses were performed on an intention-to-treat basis whenever possible. For dichotomous variables we calculated risk ratios (RR) with trial sequential analysis-adjusted confidence intervals (TSA-adjusted CI) if there were two or more trials for an outcome. For rare events (<5% in the control group) we calculated odds ratios (OR) or Peto's OR in case of very rare events (<2% in the control group), each with TSA-adjusted CI. TSA-adjusted CI excluding 1 were considered statistically significant. In case of statistical significant RR we calculated Number Needed to Treat (NNT) or Number Needed to Harm (NNH).

We used a fixed-effect and a random-effects model for meta-analysis in the presence of two or more trials included under the outcomes. In case of discrepancy between the two models, we reported the results of both models. Considering the anticipated abundant clinical heterogeneity, we emphasized the random-effects model except if one or two trials dominated the evidence. Heterogeneity was measured by inconsistency (I^2) and diversity (D^2) and explored by the chi-squared test with significance set at p-value of 0.10.^{25,26} We used funnel plots to explore small trial bias if more than ten trials were available.²⁰

Trial sequential analysis

TSA is analogue to the interim analysis in a single randomized trial.²⁷ TSA combines information size estimation for meta-analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta-analysis.^{28–31} This adjusted threshold is more conservative when data are sparse and becomes progressively more lenient as the cumulated sample size approaches the estimated required information size.^{30,32} We performed TSA on all outcomes to account for the risk of type-I error and to provide information on how many more patients need to be included in further trials. Analyses were conducted using TSA software 0.9.5.10 Beta.³³ We performed TSA with an overall type-I error of 5% and a power of 90%. The estimated required information size was calculated using the variance according to the meta-analytic model corresponding to the diversity adjusted information size (DIS), suggested by a relative risk reduction (RRR) of 10%. We calculated the model variance based diversity (D^2) adjusted required information size since the heterogeneity adjustment with I^2 tends to underestimate the required information size.²⁵ The TSA was conducted using the unweighted control event proportion calculated from the actual meta-analyses. For all outcomes, we reported the CI adjusted for sparse data and repetitive testing, which we described as the TSA-adjusted CI.

Sensitivity analysis

Sensitivity TSA was conducted for all outcomes using a RRR suggested by the meta-analysis of the included trials. If D^2 equalled zero we performed a sensitivity TSA using a D^2 of 25%. Additionally, trials evaluating types of LMWH that we were unable to classify as 'low' or 'intermediate' were included in sensitivity analyses.

GRADE

We used GRADE to assess the quality of the body of evidence associated with each outcome.²² The quality measure of a body of evidence considers within-study risk of bias, indirectness, heterogeneity, imprecision, and risk of publication bias.

RESULTS

The search was last updated on December 1st, 2018 and generated 9644 hits (Suppl. Table 4). Screening of reference lists and contacting authors revealed two additional hits. After removing duplicates and screening of titles and abstracts 523 hits remained of which 457 were excluded based on full text. The remaining 66 records reported 70 randomized trials and all fulfilled the eligibility criteria for inclusion.^{34–99}

Characteristics of included studies

Two trials were excluded from analyses for reporting surrogate or unclear outcomes.^{70,93} Two reports were translated (Chinese and French)^{48,95} and six trials were published as abstract only.^{37,68,70,85,92,99} Six trials evaluated types of LMWH which we were unable to classify either as 'low' or 'intermediate' dose; these were excluded from the primary analyses and included in sensitivity analyses as 'LMWH dose undefined' (Suppl. Table 5).^{35,40,48,60,66} Eventually, 70 trials were included in this systematic review and 68 trials contributed data to the meta-analyses. We identified thirteen ongoing randomized trials (Suppl. Table 6).

There were 36 single-center and 34 multicenter trials (Suppl. Table 7). Two trials used a four-arm design and five trials used a three-arm design; all other trials used a two-arm parallel group design. A variety of types of patients were evaluated by the trials, including ambulatory oncological patients (21 trials), surgical patients (15 trials), orthopedic or immobilized patients (20 trials), acutely ill medical patients (6 trials), neurological patients (3 trials) and others such as pregnant women at high risk of VTE or patients with cirrhotic liver disease (6 trials) (Suppl. Table 7). Eight different types of LMWH were evaluated; enoxaparin and dalteparin were most commonly used (Suppl. Table 7). LMWH was compared to placebo (37 trials) or to no intervention (33 trials). Duration of follow-up varied from 7 days to 5 years.

Bias risk assessment

Random sequence generation was assessed as low risk of bias in 39 trials (54%); allocation concealment in 41 trials (59%); blinding of participants and personnel in 31 trials (44%); blinding of outcome assessors in 38 trials (54%); incomplete outcome data in 49 trials (70%), and selective outcome reporting in 50 trials (71%). A total of 18 trials (26%) were classified as having an overall low risk of bias (Table 2).

Outcomes

For each outcome, the pooled intervention effects with TSA-adjusted CI were calculated, first for the trials with overall low risk of bias, second for all trials irrespective their risk of bias. Further, a priori defined subgroup effects were specified. Detailed data are available for each outcome in the supplementary appendix.

Primary outcome

All-cause mortality at maximum follow-up

Thirty-seven randomized trials with 24,732 patients reported all-cause mortality, with follow-up varying from 7 days to 5 years (Fig 1). Overall mortality proportions were 18.6% in the LMWH group and 19.2% in the control group. The pooled intervention effect estimate of all RCTs suggested an overall beneficial effect in TSA (RR 0.96; TSA-adjusted CI 0.94 to 0.98; I^2 0%; D^2 0%; Table 3) and conventional meta-analysis (RR 0.94; CI 0.90 to 0.98; I^2 12%; Table 3). Control event rates varied from 0.8% (orthopedics) to 76.6% (ambulatory cancer patients) and the overall effect estimate was primarily driven (83.4%) by the subgroup of ambulatory cancer patients receiving LMWH as anticancer treatment (Fig 1). We conducted a sensitivity analysis excluding this subgroup. When considering the remaining twenty-nine trials, TSA was not associated with a lower risk of all-cause mortality in the trials with low risk of bias (RR 1.00; TSA-adjusted CI 0.76 to 1.31; I^2 0%; D^2 0%; Table 3) or in all trials regardless of bias risk (RR 0.99; TSA-adjusted CI 0.84 to 1.16; I^2 0%; D^2 0%; Table 3). Results from conventional meta-analyses and sensitivity analyses confirmed the above results and subgroup analyses on LMWH type, length of intervention period, and length of follow-up showed no statistically significant tests of interaction.

Secondary outcomes

Serious adverse events

Sixteen randomized trials with 10,670 patients reported data on SAE. The incidence of SAE was 4.8% in the LMWH group and 4.2% in the control group. In the trials with overall low risk of bias, 5.4% of the required information size was accrued with low statistical heterogeneity, and no statistically significant intervention effect was found

(RR 1.21; TSA-adjusted CI 0.42 to 3.45; I^2 0%; D^2 0%; Table 3). All conventional and sensitivity analyses confirmed the absence of a significant intervention effect on SAE (Table 3). Subgroup analyses showed no statistically significant tests of interaction.

Symptomatic venous thromboembolism

Thirty-six randomized trials with 24,195 patients reported data on symptomatic venous thromboembolism (Fig 2). The incidence of symptomatic VTE was 1.6% in the LMWH group and 2.9% in the control group. TSA could not be conducted when only including trials with overall low risk of bias since less than 5% of the required information size was accrued. When considering all trials approximately 18.3% of the required information size was reached and a statistically significant beneficial intervention effects was found (OR 0.59; TSA-adjusted CI 0.53 to 0.67; I^2 0%; D^2 0%; NNT 76; 95% CI 60-106; Table 3; Fig 3). These results were confirmed in two out of three sensitivity TSA's and in the conventional analyses of all trials (Table 3).

Subgroup analyses showed no significant tests of interaction.

Major bleeding

Fifty-seven randomized trials with 28,182 patients reported data on major bleeding (Fig 4). The incidence of major bleeding was 1.2% in the LMWH group and 0.7% in the control group. TSA could not be conducted since less than 5% of the required information size was accrued (all trials and overall low risk of bias). Conventional analyses of the trials with overall low risk of bias showed no statistically significant increase in major bleeding (Peto OR 1.35; 95% CI 0.81 to 2.26; I^2 3%; Table 3).

When considering all trials regardless of bias risk, sensitivity TSA with RRR estimated by the meta-analysis found a statistically significant harmful intervention

effect (Peto OR 1.66; TSA-adjusted CI 1.31 to 2.10; I^2 0%; D^2 0%; NNH 212; 95% CI 142 to 393; Table 3; Fig 5) which was confirmed by conventional meta-analysis (Peto OR 1.66; 95% CI 1.30 to 2.12; I^2 20%; Table 3). No subgroup differences were detected.

Venous thromboembolism screening

Forty-two randomized trials with 13,963 patients reported data on VTE screening. The incidence of VTE screening was 6.3% in the LMWH group and 12.0% in the control group. In the TSA of trials with overall low risk of bias, 5.1% of the required information size was accrued, with moderate statistical heterogeneity, and no statistically significant intervention effect was found (RR 0.57; TSA-adjusted CI 0.14 to 2.32; I^2 52%; D^2 54%; Table 3). The sensitivity TSA with RRR estimated by the meta-analysis found that LMWH was associated with a statistically significant beneficial intervention effect (RR 0.57; TSA-adjusted CI 0.39 to 0.82; I^2 52%, D^2 54%; Table 3). When considering all trials a statistically significant beneficial effect was found (RR 0.52; TSA-adjusted CI 0.44 to 0.61; I^2 0%; D^2 0%; NNT 18; 95% CI 15 to 21; Table 3), confirmed by all conventional meta-analyses and sensitivity analyses. Subgroup analyses based on the duration of the interventions showed a statistically significant test of interaction ($p=0.02$), indicating a larger beneficial intervention effect in the subgroup of trials treating patients for less than 30 days (RR 0.47; CI 0.42 to 0.53; I^2 0%) compared to the subgroup of trials treating patients for more than 30 days (RR 0.66; CI 0.51 to 0.84; I^2 15%, Suppl. Fig 5c).

Heparin-induced thrombocytopenia

Thirteen randomized trials with 10,340 patients reported data on heparin-induced thrombocytopenia, but no objective laboratory HIT confirmation was reported so we were unable to perform analyses.

Small trial bias

Funnel plots showed no clear arguments for small trial bias in all but one outcome (Suppl. Figure 6a-e). The funnel plot of 'VTE screening' was asymmetric, possibly indicating publication bias.

GRADE approach

The quality of the evidence was assessed as low to moderate for all outcomes based on risk of bias limitations, inconsistency, imprecision and other considerations (Suppl. Table 8).

DISCUSSION

We evaluated the benefits and harms of intermediate dose LMWH for thrombosis prophylaxis in patients at risk for VTE. We included 70 RCTs with 34,046 randomized patients of which 18 trials (26%) had overall low risk of bias. Analyses indicated that compared to placebo or no treatment intermediate dose LMWH was associated with a small decrease in mortality which disappeared in a sensitivity analysis excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding.

Our findings on mortality are in line with results from previous systematic reviews.^{13–}

¹⁷ The overall effect estimate obtained by pooling all RCTs did suggest lower mortality associated with intermediate dose LMWH. However, we decided *post hoc* to do a sensitivity analysis excluding eight RCTs that assessed ambulatory cancer patients who received LMWH as adjuvant to their cancer treatment from the primary outcome analysis as this subgroup had a substantially higher control event rate of mortality of 76.6%, contributed 83.4% weight and was the main driving force for the overall pooled effect estimate and its significance. Although in any meta-analysis a certain amount of clinical heterogeneity is unavoidable, the observed differences in control event rates suggest potentially relevant clinical differences between patient populations. For this reason we deemed it inappropriate to rely solely on the overall pooled effect estimate as this could lead to spurious inferences about the effect on mortality in other subgroups with fewer observed events. This decision was primarily based on clinical considerations as we observed low statistical heterogeneity and subgroup analyses showed no statistically significant tests of interaction.

Robustness of conclusions was evaluated by several additional analyses. We conducted our main analysis with TSA of all outcomes based on an a priori hypothesized 10% RRR as specified in our protocol. Sensitivity analyses with meta-analytic estimates of trials with overall low risk of bias suggested a 41% RRR for symptomatic VTE and a 35% RRI for major bleeding. Although even this low risk of bias RRR estimate may still be overestimated, the a priori specified 10% RRR for the TSA used in our analyses may have been too conservative and alternatively one could probably base the conclusions on the TSA anticipating the RRR estimated from the trials with low risk of bias. Further, in subgroup analyses the bias effect seems

limited since the meta-analytic point-estimates are rather similar across all outcomes regardless of the bias risks of the trials, suggesting that we may rely on the more precise estimates derived from all the trials. These sensitivity and subgroup analyses strengthen the conclusion of a beneficial intervention effect on VTE but also indicate a harmful effect on major bleeding. The NNT for preventing one case of symptomatic VTE is 76 compared to a NNH of 212 for major bleeding, which suggests the balance favors the intervention. As we did not detect any significant subgroup differences we cannot make inferences about the benefit to harm ratio in specific patient populations.

The main strength of this review is its systematic approach according to *The Cochrane Handbook for Systematic Reviews of Interventions*, following a previously published protocol with assessment of the risks of systematic and random errors, and, most important, incorporation of error risks in the primary analyses and conclusions.²⁰ We systematically explored the associations between bias risks and intervention effects in all outcomes, while previous reviews did not incorporate the bias risks in their results and conclusions.^{11,14,15,17}

This systematic review is, however, associated with important limitations. We provided a comprehensive overview of the effects of intermediate dose LMWH in all patient populations. As we wished to evaluate the overall effect of intermediate dose LMWH in patients at increased risk for VTE we deliberately included all types of patients. Generally statistical heterogeneity was low, but obviously clinical heterogeneity of patients, including control event rates, durations of interventions and follow-up was substantial. For reasons described above we made a deviation from

our protocol and decided post hoc, in a sensitivity analysis, to exclude trials which assessed overall mortality in ambulatory cancer patients receiving LMWH as an anticancer treatment from the primary outcome analysis. We did include these trials as planned in analyses of the other outcomes since they also provide data on VTE or major bleeding events.

Second, we included both VTE and major bleeding in our definition of SAE to evaluate the balance between thrombosis and bleeding. While we excluded mortality, our outcome SAE by definition included double counts of VTE and bleeding events since these were also considered separately. Most trial reports were unclear about the definitions and the numbers of SAE and we were often unable to distinguish whether VTE or major bleeding had been incorporated in the SAE counts. This made a direct evaluation of the balance between thrombosis and bleeding impossible. Third, we accepted all events of VTE proven by objective testing, but we did not make a distinction according to DVT location (i.e. distal versus proximal or lower versus upper extremity). This may have contributed to heterogeneity in our VTE outcome definition. However, many of the original trial reports did not provide details on DVT locations, which prevented such detailed evaluations.

Conclusions

The use of intermediate dose LMWH for thrombosis prophylaxis compared to placebo or no treatment was associated with a small statistically significant reduction of all-cause mortality, which however disappeared in a sensitivity analysis excluding trials that evaluated LMWH for anticancer treatment. Intermediate dose LMWH provides benefits in terms of VTE prevention while it increases major bleeding, as

suggested by consistent effects in a broad range of populations estimated by randomized trials with overall low risks of systematic and random errors.

AUTHORSHIP DETAILS

Authors' contributions:

R.J. Eck, W. Bult and F. Keus had full access to all data in the study and take responsibility for integrity and accuracy of data analysis. All authors contributed to study concept and design. R.J. Eck and W. Bult contributed to acquisition of data. R.J. Eck, J. Wetterslev and F. Keus did the statistical analysis and interpreted the data. J. Wetterslev, R.O.B. Gans, K. Meijer, F. Keus and I.C.C. van der Horst provided directions and intellectual content. R.J. Eck and F. Keus drafted the manuscript with critical revisions from all authors. The final version of this manuscript has been read and approved by all authors.

ACKNOWLEDGEMENTS

Acknowledgements: We thank dr. Ruohan Wu for his assistance with translating and analysing two Chinese articles.

Potential conflicts of interest disclosure

K. Meijer reports grants from Bayer, Sanquin, and Pfizer; speaker fees from Bayer, Sanquin, Boehringer Ingelheim, BMS, and Aspen; and consulting fees from Uniqure. J. Wetterslev is a member of the task force at the Copenhagen Trial Unit to develop theory and software of Trial Sequential Analysis. R.J. Eck, W. Bult, R.O.B. Gans, F. Keus and I.C.C. van der Horst report no conflicts of interest.

Ethics committee approval: No ethics committee approval was required

Funding: There was no funding source for this study

References

1. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:3-14.
2. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. A systematic review. *Thromb Haemost*. 2017;117:801-808.
3. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:7S-47S.
4. Food and Drug Administration (United States). Drug approval reports. www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 7, 2019.
5. Medicines & Healthcare products Regulatory Agency (United Kingdom). Summary of Product Characteristics. <http://www.mhra.gov.uk/spc-pil/>. Accessed July 31, 2017.
6. Health Products Regulatory Authority (Ireland). Summary of Product Characteristics. www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine. Accessed February 7, 2019.
7. Italian Medicines Agency (Italy). Summary of Product Characteristics. www.agenziafarmaco.gov.it/en. Accessed February 7, 2019.
8. National Agency for the Safety of Medicine and Health Products (France).

- Summary of Product Characteristics. www.anism.sante.fr/Produits-de-sante/Medicaments. Accessed February 7, 2019.
9. Federal Institute for Drugs and Medical Devices (Germany). Summary of Product Characteristics. www.bfarm.de/DE/Home/home_node.html. Accessed January 31, 2016.
 10. Medicines Evaluation Board (The Netherlands). Summary of Product Characteristics. www.geneesmiddeleninformatiebank.nl/nl/. Accessed February 7, 2019.
 11. Laporte S, Chapelle C, Bertoletti L, et al. Indirect comparison meta-analysis of two enoxaparin regimens in patients undergoing major orthopaedic surgery. Impact on the interpretation of thromboprophylactic effects of new anticoagulant drugs. *Thromb Haemost.* 2014;112:503-510.
 12. Kahale LA, Tsoiakian IG, Hakoum MB, et al. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database Syst Rev.* 2018.
 13. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane database Syst Rev.* 2016;12:CD008500.
 14. Sanford D, Naidu A, Alizadeh N, Lazo-Langner A. The effect of low molecular weight heparin on survival in cancer patients: an updated systematic review and meta-analysis of randomized trials. *J Thromb Haemost.* 2014;12:1076-1085.
 15. Chapelle C, Rosencher N, Jacques Zufferey P, Mismetti P, Cucherat M, Laporte S. Prevention of venous thromboembolic events with low-molecular-

- weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials. *Arthroscopy*. 2014;30:987-996.
16. Alikhan R, Bedenis R, Cohen AT. Heparin for the prevention of venous thromboembolism in acutely ill medical patients (excluding stroke and myocardial infarction). *Cochrane database Syst Rev*. 2014;5:CD003747.
 17. Beitland S, Sandven I, Kjaervik LK, Sandset PM, Sunde K, Eken T. Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med*. 2015;41:1209-1219.
 18. Brotman DJ, Shihab HM, Prakasa KR, et al. Pharmacologic and mechanical strategies for preventing venous thromboembolism after bariatric surgery: a systematic review and meta-analysis. *JAMA Surg*. 2013;148:675-686.
 19. Bain E, Wilson A, Tooher R, Gates S, Davis L-J, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. *Cochrane database Syst Rev*. 2014;2:CD001689.
 20. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011.
 21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
 22. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is “quality of evidence” and why is it important to clinicians? *BMJ*. 2008;336:995-998.

23. International Conference on Harmonisation Expert Working Group.
International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, ed. ICH harmonised tripartite guideline; guideline for good clinical practice.
www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.
Published 1997.
24. Savovic J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med*. 2012;157:429-438.
25. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86.
26. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
27. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol*. 2017;17:1-18.
28. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials*. 1997;18:580-586.
29. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet*. 1998;351:47-52.
30. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random

- error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol.* 2009;38:287-298.
31. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol.* 2008;61:64-75.
 32. Thorlund K, Devereaux PJ, Wetterslev J, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? *Int J Epidemiol.* 2009;38:276-286.
 33. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. Software for Trial Sequential Analysis (TSA) version 0.9.5.5 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research.
 34. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med.* 1998;339:80-85.
 35. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med.* 2012;366:601-609.
 36. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: Two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. *J Orthop Sci.* 2008;13:442-451.
 37. Le Gagneux F, Steg A, Le Guillou N, Gagneux. Subcutaneous enoxaparine (Lovenox) versus placebo for preventing deep vein thrombosis (DVT) after

- transurethral prostatectomy (TUP) [abstract]. *Thromb Haemost.* 1987;58:116.
38. Gates S, Brocklehurst P, Ayers S, Bowler U. Thromboprophylaxis and pregnancy: two randomized controlled pilot trials that used low-molecular-weight heparin. *Am J Obstet Gynecol.* 2004;191:1296-1303.
 39. Goel DP, Buckley R, deVries G, Abelseth G, Ni A, Gray R. Prophylaxis of deep-vein thrombosis in fractures below the knee: a prospective randomised controlled trial. *J Bone Joint Surg Br.* 2009;91:388-394.
 40. Haas SK, Freund M, Heigener D, et al. Low-Molecular-Weight Heparin Versus Placebo for the Prevention of Venous Thromboembolism in Metastatic Breast Cancer or Stage III/IV Lung Cancer. *Clin Appl Thromb Hemost.* 2012;18:159-165.
 41. Halim TA, Chhabra HS, Arora M, Kumar S. Pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury: an Indian perspective. *Spinal Cord.* 2014;52:547-550.
 42. Ho YH, Seow-Choen F, Leong A, Eu KW, Nyam D, Teoh MK. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. *Dis Colon Rectum.* 1999;42:196-203.
 43. Intiyanaravut T, Thongpulsawasdi N, Sinthuvanich N, Teavirat S, Kunopart M. Enoxaparin versus no anticoagulation prophylaxis after total knee arthroplasty in Thai patients: A randomized controlled trial. *J Med Assoc Thai.* 2017;100:42-49.
 44. Dahan R, Houlbert D, Caulin C, et al. Prevention of Deep Vein Thrombosis in

- Elderly Medical In-Patients by a Low Molecular Weight Heparin: A Randomized Double-Blind Trial. *Haemostasis*. 1986;16:159-164.
45. Dar TI, Wani KA, Ashraf M, et al. Low molecular weight heparin in prophylaxis of deep vein thrombosis in Asian general surgical patients: A Kashmir experience. *Indian J Crit Care Med*. 2012;16:71.
 46. Ahuja RB, Bansal P, Pradhan GS, Subberwal M. An analysis of deep vein thrombosis in burn patients (part II): A randomized and controlled study of thrombo-prophylaxis with low molecular weight heparin. *Burns*. 2016;42:1693-1698.
 47. Ek L, Gezelius E, Bergman B, et al. Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: The RASTEN trial. *Ann Oncol*. 2018;29:398-404.
 48. Elias A, Milandre L, Lagrange G, et al. Prevention of deep venous thrombosis of the leg by a very low molecular weight heparin fraction (CY 222) in patients with hemiplegia following cerebral infarction: a randomized pilot study (30 patients)]. *La Rev Med interne*. 1989;11:95-98.
 49. Jorgensen P, Knudsen JB, Broeng L, et al. The thromboprophylactic effect of a Low-Molecular-Weight Heparin (Fragmin) in Hip Fracture Surgery. A Placebo-Controlled Study. *Clin Orthop Relat Res*. 1992:95-100.
 50. Jung YJ, Seo HS, Park CH, et al. Venous Thromboembolism Incidence and Prophylaxis Use After Gastrectomy Among Korean Patients With Gastric Adenocarcinoma. *JAMA Surg*. 2018;153:939-946.
 51. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin,

- therapy with dalteparin, and survival in advanced cancer: The fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol.* 2004;22:1944-1948.
52. Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann J-F. Low-Molecular-Weight Heparin and Mortality in Acutely Ill Medical Patients. *N Engl J Med.* 2011;365:2463-2472.
 53. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, et al. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. *Int Angiol.* 1996;15:162-168.
 54. Karthaus M, Kretschmar A, Kroning H, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol.* 2005;17:289-296.
 55. Khorana AA, Francis CW, Kuderer NM, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: A randomized trial. *Thromb Res.* 2017;151:89-95.
 56. Kim SM, Moon YW, Lim SJ, Kim DW, Park YS. Effect of oral factor Xa inhibitor and low-molecular-weight heparin on surgical complications following total hip arthroplasty. *Thromb Haemost.* 2016;115:600-607.
 57. Alalaf SK, Jawad AK, Jawad RK, Ali MS, Al Tawil NG. Bemiparin for thromboprophylaxis after benign gynecologic surgery: A randomized clinical trial. *J Thromb Haemost.* 2015;13:2161-2167.

58. Kiudelis M, Gerbutavicius R, Gerbutaviciene R, et al. A combinative effect of low-molecular-weight heparin and intermittent pneumatic compression device for thrombosis prevention during laparoscopic fundoplication. *Medicina (Kaunas)*. 2010;46:18-23.
59. Klerk CPWW, Smorenburg SM, Otten H-M, et al. The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy. *J Clin Oncol*. 2005;23:2130-2135.
60. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet*. 1995;346:459-461.
61. Lapidus LJ, Ponzer S, Elvin A, et al. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: A randomized placebo-controlled, double-blind study. *Acta Orthop*. 2007;78:528-535.
62. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of Deep Vein Thrombosis after major knee Surgery - A Randomized, Double-Blind Trial Comparing a Low molecular Weight Heparin Fragment (Enoxaparin) to Placebo. *Thromb Haemost*. 1995;67:417-423.
63. Lecumberri R, Lopez Vivanco G, Font A, et al. Adjuvant therapy with bemiparin in patients with limited-stage small cell lung cancer: results from the ABEL study. *Thromb Res*. 2013;132:666-670.
64. Lederle FA, Sacks JM, Fiore L, et al. The prophylaxis of medical patients for thromboembolism pilot study. *Am J Med*. 2006;119:54-59.
65. Leizorovicz A, Cohen AT, Turpie AGG, Olsson C-G, Vaitkus PT, Goldhaber SZ.

- Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients. *Circulation*. 2004;110:874-879.
66. Levine MN, Gent M, Hirsh J, et al. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery. *Arch Intern Med*. 1996;156:851-856.
67. Macbeth F, Noble S, Evans J, et al. Randomized Phase III Trial of Standard Therapy Plus Low Molecular Weight Heparin in Patients With Lung Cancer: FRAGMATIC Trial. *J Clin Oncol*. 2016;34:488-494.
68. AlGahtani FH, Al-Dohami H, Abo-Harbesh S, Al-Gader A, Aleem A. Thromboembolism prophylaxis after cesarean section (PRO-CS) trial [abstract]. *Thromb Res*. 2015;135:S71.
69. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J Cancer*. 2012;48:1283-1292.
70. Maurer PF, Schurch L V, Shahin O, Gasser TC. Thromboprophylaxis with Dalteparine for transurethral surgery, a double-blind placebo-controlled randomised study [abstract]. *J Urol*. 2009;181:700-701.
71. Meyer G, Besse B, Doubre H, et al. Anti-tumour effect of low molecular weight heparin in localised lung cancer: A phase III clinical trial. *Eur Respir J*. 2018;52:1801220.
72. Michot M, Conen D, Holtz D, et al. Prevention of deep-vein thrombosis in

- ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low-molecular weight heparin. *Arthroscopy*. 2002;18:257-263.
73. Modesto-Alapont M, Nauffal-Manzur D, Ansotegui-Barrera E, et al. Can home prophylaxis for venous thromboembolism reduce mortality rates in patients with chronic obstructive pulmonary disease? *Arch Bronconeumol*. 2006;42:130-134.
74. Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: Outcomes from the CONKO-004 trial. *J Clin Oncol*. 2015;33:2028-2034.
75. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost*. 2010;8:1959-1965.
76. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. *Haemostasis*. 1989;19:245-250.
77. Rodger MA, Phillips P, Kahn SR, James AH, Konkle BA. Low-molecular-weight heparin to prevent postpartum venous thromboembolism a pilot randomised placebo-controlled trial. *Thromb Haemost*. 2015;113:212-216.
78. Rodger MA, Phillips P, Kahn SR, et al. Low molecular weight heparin to prevent postpartum venous thromboembolism: A pilot study to assess the feasibility of a randomized, open-label trial. *Thromb Res*. 2016;142:17-20.
79. Altinbas M, Coskun HS, Er O, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung

- cancer. *J Thromb Haemost.* 2004;2:1266-1271.
80. Samama CM, Clergue F, Barre J, et al. Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. *Br J Anaesth.* 1997;78:660-665.
 81. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med.* 1999;341:793-800.
 82. Sang CQ, Zhao N, Zhang J, et al. Different combination strategies for prophylaxis of venous thromboembolism in patients: A prospective multicenter randomized controlled study. *Sci Rep.* 2018;8:8277.
 83. Selby R, Geerts WH, Kreder HJ, et al. A Double-Blind, Randomized Controlled Trial of the Prevention of Clinically Important Venous Thromboembolism After Isolated Lower Leg Fractures. *J Orthop Trauma.* 2015;29:224-230.
 84. Sideras K, Schaefer PL, Okuno SH, et al. Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. *Mayo Clin Proc.* 2006;81:758-767.
 85. Sourmelis S, Patoulis G, Tzortzis G. Prevention of deep vein thrombosis with low molecular weight heparin in fractures of the hip. *J Bone Joint Surg Br.* 1995;77:173.
 86. Torholm C, Broeng L, Jorgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *J Bone Joint Surg Br.* 1991;73:434-438.

87. Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med.* 1986;315:925-929.
88. Verso M, Agnelli G, Bertoglio S, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: A double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol.* 2005;23:4057-4062.
89. Villa E, Camma C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology.* 2012;143:1253-1254.
90. Cesarone MR, Belcaro G, Nicolaidis AN, et al. Venous thrombosis from air travel: the LONFLIT3 study--prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. *Angiology.* 2002;53:1-6.
91. van Doormaal FF, Di Nisio M, Otten H-M, Richel DJ, Prins M, Buller HR. Randomized Trial of the Effect of the Low Molecular Weight Heparin Nadroparin on Survival in Patients With Cancer. *J Clin Oncol.* 2011;29:2071-2076.
92. Vadhan-Raj S, Zhou X, Varadhachary GR, et al. Randomized Controlled Trial Of Dalteparin For Primary Thromboprophylaxis For Venous Thromboembolism (VTE) In Patients With Advanced Pancreatic Cancer (APC): Risk Factors Predictive Of VTE [abstract]. *Blood.* 2013;122.
93. Wang Y, Qiu H, He X, Sun X. Prevention of venous thromboembolism after

- resection of primary liver cancer with low molecular weight heparin and its association with P-selectin , lysosomal granule glycoprotein , platelet activating factor and plasma D-dimer. *Eur Rev Med Pharmacol Sci.* 2018;22:4657-4662.
94. Warwick D, Bannister GC, Glew D, et al. Perioperative low-molecular-weight heparin. Is it effective and safe? *J Bone Joint Surg Br.* 1995;77:715-719.
 95. Xia X, Tan Y, Sun Y, et al. Enoxaparin for the prevention of post surgical pulmonary embolism. *Zhongguo wei zhong bing ji jiu yi xue (Chinese Crit care Med.* 2011;23:661-664.
 96. Zwicker JI, Liebman HA, Bauer KA, et al. Prediction and prevention of thromboembolic events with enoxaparin in cancer patients with elevated tissue factor-bearing microparticles: a randomized-controlled phase II trial (the Microtec study). *Br J Haematol.* 2013;160:530-537.
 97. Chin PL, Amin MS, Yang KY, Yeo SJ, Lo NN. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial. *J Orthop Surg (Hong Kong).* 2009;17:1-5.
 98. Christensen TD, Vad H, Pedersen S, et al. Coagulation profile in patients undergoing video-assisted thoracoscopic lobectomy: A randomized, controlled trial. *PLoS One.* 2017;12:e0171809.
 99. Conte GF, Aravena PC, Fardella PD, et al. Prophylaxis of Venous Thrombosis (VT) Associated with Central Venous Catheter (CVC) with Low Molecular Weight Heparin (LMWH) in Hematologic Malignancies [abstract]. *Blood.* 2003;102:Suppl. 122B.

Fig 1. Forest plot of all-cause mortality

Fig 1 caption: Forest plot of all-cause mortality at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to population, including ambulatory cancer patients receiving LMWH for anticancer treatment. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals

Fig 2. Forest plot of VTE symptomatic

Fig 2 caption: Forest plot of VTE symptomatic at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to the population type. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals

Fig 3. Trial sequential analysis of VTE symptomatic

Fig 3 caption: Trial sequential analysis of VTE symptomatic at maximal follow-up of LMWH compared to placebo or no treatment in patients at risk for VTE. The required information size of 132,001 patients was calculated using the predefined $\alpha=0.05$ (two sided), $\beta=0.10$ (power 90%), $D^2=0\%$, an anticipated relative risk reduction of 10% and an event proportion of 2.86% in the control arm. The cumulative Z-curve is constructed using a random effects model, and each cumulative Z-value is calculated after inclusion of a new trial (as represented by black dots). The dotted horizontal lines represent the conventional naïve boundaries for benefit (positive, $Z = +1.96$) or harm (negative, $Z = -1.96$). The etched lines represent the trial sequential boundaries for benefit (positive), harm (negative), or futility (middle triangular area). The

cumulative Z-curve crosses the TSA boundary for benefit, indicating future trials are very unlikely to change conclusions.

Fig 4. Forest plot of major bleeding

Fig 4 caption: Forest plot of major bleeding at maximal follow-up of LMWH prophylaxis compared to placebo or no treatment in patients at risk for VTE, stratified according to the population type. *Size of the squares* reflects the weight of the trial in the pooled analysis. *Horizontal bars* represent 95% confidence intervals.

Fig 5. Trial sequential analysis of major bleeding

Fig 5 caption: Trial sequential analysis of major bleeding at maximal follow-up of LMWH compared to placebo or no treatment in patients at risk for VTE. The required information size of 42,077 patients was calculated using the predefined $\alpha=0.05$ (two sided), $\beta=0.10$ (power 90%), $D^2=0\%$, an anticipated relative risk reduction of -35% (as anticipated by the low risk of bias trials) and an event proportion of 0.7% in the control arm. The cumulative z-curve, constructed using a random-effects model, crosses the TSA boundary for harm, indicating future trials are very unlikely to change conclusions. Please refer to the caption of Fig. 3 for further explanation of the TSA graphic.

Table 1. Classification of low and intermediate dose prophylactic ranges

	A priori defined prophylaxis dose limits		Dose as used in included trials
	Low dose	Intermediate dose	
Nadroparin (Fraxiparine)	< 5700 IU	≥ 5700 IU	5700 - 7600 IU ^a
Dalteparin (Fragmin)	< 5000 IU	≥ 5000 IU	5000 IU ^b
Enoxaparin (Lovenox)	< 40 mg	≥ 40 mg	40 mg - 1 mg/kg
Tinzaparin (Innohep)	< 4500 IU	≥ 4500 IU	4500 IU ^c
Parnaparin (Fluxum)	< 4250 IU	≥ 4250 IU	Not used
Bemiparin (Zibor)	< 3500 IU	≥ 3500 IU	3500 IU
Reviparin (Clivarin)	< 3436 IU	≥ 3436 IU	Not used

Table 1 footnote: IU: International Units; mg: milligrams; ^a one study by van Doormaal et al⁹¹ used weight-dependent doses up to 15.200 IU intended as prophylaxis; ^b one study by Maraveyas et al⁶⁹ used 200 IU/kg intended as prophylaxis; ^c one study by Meyer et al⁷¹ used 100 IU/kg intended as prophylaxis

Table 2. Risk of bias assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Agnelli 1998	Low	Low	Low	Low	Low	Low
Agnelli 2012	Low	Low	Low	Low	Low	Low
Ahuja 2016	Low	Unclear	High	Unclear	Unclear	Low
Alalaf 2015	Low	Low	High	Unclear	Low	Low
AlGahtani 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Altinbas 2004	Unclear	Unclear	High	Low	Low	Unclear
Cesarone 2002	Unclear	Unclear	Unclear	Unclear	high	Low
Chin 2009	Unclear	Unclear	Unclear	Low	Unclear	High
Christensen 2017	Low	High	High	Unclear	High	Low
Conte 2003	Unclear	Unclear	Low	Unclear	Unclear	Low
Dahan 1986	Unclear	Unclear	Low	Unclear	Low	Low
Dar 2012	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Ek 2018	Low	Low	High	Unclear	Low	Low
Elias 1990	Unclear	Unclear	High	Unclear	Low	Low
Fuji 2008a	Unclear	Unclear	Unclear	Low	High	Low
Fuji 2008b	Unclear	Unclear	Unclear	Low	High	Low
Gagneux 1987	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gates 2004a	Low	Low	Low	Low	Low	Low
Gates 2004b	Low	Low	Low	Low	Low	Low
Goel 2009	Low	Low	Low	Low	Low	Low
Haas 2012a	Low	Low	Low	Low	Low	Low
Haas 2012b	Low	Low	Low	Low	Low	Low
Halim 2014	Low	Low	High	Low	Low	High
Ho 1999	Unclear	Low	High	Low	High	Low
Intiyaravut 2017	Unclear	Low	High	Low	Unclear	Low
Jorgensen 1992	Unclear	Unclear	Low	Unclear	Low	Low
Jung 2018	Low	Low	High	Unclear	Low	High
Kakkar 2004	Low	Low	Low	Low	Low	Low
Kakkar 2011	Low	Low	Low	Low	Low	Low
Kalodiki 1993	Unclear	Low	Low	Low	Unclear	Low
Karthus 2006	Low	Low	Low	Low	Low	Low
Khorana 2017	Low	Low	High	Low	Low	Low
Kim 2016	Low	Low	Low	Low	High	High
Kiudelis 2010	Unclear	Unclear	High	Unclear	Low	High

Klerk 2005	Low	Low	Low	Low	Low	Low
Kock 1995	Unclear	Unclear	High	Unclear	Low	Low
Lapidus 2007	Unclear	Low	Low	Unclear	Low	Low
Leclerc 1992	Low	Low	Low	Low	Low	Low
Lecumberri 2013	Low	Low	High	High	Low	Low
Lederle 2006	Low	Low	Low	Low	Low	Low
Leizorovicz 2004	Unclear	Unclear	Low	Low	High	Low
Levine 1996	Low	Low	Low	Low	Low	Low
Macbeth 2016	Low	Low	High	Unclear	Low	Low
Maraveyas 2012	Low	Low	High	High	Low	Low
Maurer 2009	Unclear	Unclear	Unclear	Unclear	Unclear	High
Meyer 2017	Low	Low	High	Low	Low	High
Michot 2002	Unclear	Low	High	Low	Low	Low
Modesto-Alapont 2006	Low	Low	High	Unclear	Low	Low
Pelzer 2015	Low	Low	High	High	Low	Low
Perry 2010	Low	Low	Low	Low	Low	Low
Prins 1989	Unclear	Unclear	Low	Unclear	Low	Low
Rodger 2015	Low	Low	Low	Low	Low	Unclear
Rodger 2016	Low	Low	High	Low	Low	Unclear
Samama 1997	Low	Low	Low	Low	Low	Low
Samama 1999	Unclear	Low	Low	Low	Low	Low
Sang 2018	Low	Unclear	High	Unclear	Low	High
Selby 2015	Low	Low	Low	Low	Low	Low
Sideras 2006	Low	Low	High	Unclear	Low	Low
Sourmelis 1995a	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Sourmelis 1995b	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Torholm 1991	Unclear	Unclear	Low	Unclear	Low	Low
Turpie 1986	Unclear	Unclear	Low	Low	Low	Low
Vadhan-Raj 2013	Unclear	Unclear	High	Unclear	Low	Low
van Doormaal 2011	Unclear	Low	High	Low	Low	Low
Verso 2005	Low	Low	Low	Low	Low	Low
Villa 2012	Low	Low	High	Low	Low	Low
Wang 2018	Unclear	Unclear	High	High	Unclear	High
Warwick 1995	Unclear	Unclear	High	Low	Unclear	High
Xia 2011	Low	Unclear	Unclear	Unclear	Low	High
Zwicker 2013	Unclear	Unclear	High	Unclear	Low	Low

Table 2 footnote: Review of authors' judgements about each risk of bias domain for each included study.

Table 3. Outcomes: results from conventional meta-analyses and trial sequential analyses

Outcome	Included trials	Trials (patients)	Conventional analysis^a	Main analysis TSA^a <i>RRR 10%, β 90%, D^2 model variance based</i>	Sensitivity TSA^a <i>RRR based on low risk trials, β 90%, D^2 model variance based</i>	Sensitivity TSA^a <i>RRR 10%, β 90%, D^2 25%</i>
Mortality						
Including 'LMWH for anticancer treatment'	Low bias risk	10 (10,770)	RR 0.92 (0.86 to 0.98)	RR 0.92 (0.83 to 1.01)	RR 0.92 (0.81 to 1.04)	RR 0.92 (0.82 to 1.03)
Excluding 'LMWH for anticancer treatment'	Low bias risk	8 (10,083)	RR 1.00 (0.89 to 1.13)	RR 1.00 (0.76 to 1.31)	Not performed (RRR 0%)	RR 1.00 (0.73 to 1.37)
Including 'LMWH for anticancer treatment'	All	37 (24,732)	RR 0.94 (0.90 to 0.98)	RR 0.96 (0.94 to 0.98)	RR 0.96 (0.94 to 0.99)	RR 0.96 (0.94 to 0.99)
Excluding 'LMWH for anticancer treatment'	All	29 (20,288)	RR 0.99 (0.90 to 1.10)	RR 0.99 (0.84 to 1.16)	Insufficient data (<5% of DIS)	RR 0.99 (0.82 to 1.19)
SAE						
	Low bias risk	4 (8,741)	RR 1.21 (0.93 to 1.56)	RR 1.21 (0.42 to 3.45)	RR 1.21 (0.68 to 2.14)	Insufficient data (<5% of DIS)
	All	16 (10,670)	RR 1.16 (0.99 to 1.37)	RR 1.16 (0.60 to 2.23)	RR 1.16 (0.91 to 1.47)	RR 1.16 (0.60 to 2.23)
VTE symptomatic						
	Low bias risk	11 (10,759)	Peto OR 0.59 (0.39 to 0.91) ^b	Insufficient data (<5% of DIS) ^b	Peto OR 0.59 (0.30 to 1.18) ^b	Insufficient data (<5% of DIS) ^b
	All	36 (24,195)	OR 0.58 (0.46 to 0.73)	OR 0.59 (0.53 to 0.67)	OR 0.59 (0.48 to 0.73)	OR 0.59 (0.27 to 1.29)
Major bleeding						
	Low bias risk	14 (11,631)	Peto OR 1.35 (0.81 to 2.26) ^b	Insufficient data (<5% of DIS) ^b	Peto OR 1.35 (0.17 to 10.85) ^b	Insufficient data (<5% of DIS) ^b
	All	57 (28,182)	Peto OR 1.66 (1.30 to 2.12) ^b	Insufficient data (<5% of DIS) ^b	Peto OR 1.66 (1.31 to 2.10) ^b	Insufficient data (<5% of DIS) ^b
VTE screening						
	Low bias risk	6 (1,737)	RR 0.57 (0.40 to 0.80)	RR 0.57 (0.14 to 2.32)	RR 0.57 (0.39 to 0.82)	Not performed ($D^2 > 25\%$)
	All	42 (13,963)	RR 0.50 (0.44 to 0.57)	RR 0.52 (0.44 to 0.61)	RR 0.52 (0.46 to 0.58)	RR 0.52 (0.43 to 0.62)

Table 3 footnote: β : power; D^2 : diversity; DIS: diversity adjusted information size; OR: odds ratio; RR: relative risk; RRR: relative risk reduction; SAE: serious adverse events; TSA: trial sequential analysis; ^a Small discrepancies of the intervention effect estimates between the traditional RevMan meta-analyses and the TSA adjusted results may occur due to different pooling methods (for example the inclusion of zero-event trials in TSA analyses); ^b Fixed-effect model